The effects of mechanical vibration on Class II orthopaedic appliance therapy at different stages of skeletal maturity

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STATEMENT OF ORIGINALITY

I, Lam Linda Cheng, do solemnly and sincerely declare that the intellectual content of this thesis is the product of my own work, and that all assistance received in preparing this thesis and all sources have been acknowledged. The work presented has not been submitted, either in whole or in part, for any degree at this, or any other University.

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ABSTRACT

Mechanical vibration has been utilised in medicine for decades as a non-pharmacological therapy aimed at enhancing bone integrity, muscle coordination, joint function, and pain management. Its use has been broadened to dentistry in recent years to minimise alveolar bone loss and reduce patient discomfort from orofacial pain, orthodontic therapy and local anaesthetic administration. There was a heightened interest at one stage with the use of commercially available mechanical vibration devices to accelerate tooth movement, with the intent of shortening orthodontic treatment time. This popularity has faded due to conflicting research results and further robust randomised controlled trials are required to validate its use in orthodontics. Nevertheless, the success achieved through the use of mechanical vibration in orthopaedic medicine has inspired its clinical application to dentofacial orthopaedics, which to date has not been explored. Class II functional appliance therapy is a type of dentofacial orthopaedics used to improve mandibular retrusion during the peak pubertal growth stage.

The purpose of the present study was to evaluate and compare the effects of intraoral mechanical vibration stimulation during Class II functional appliance therapy. It was understood that the effects of functional appliance therapy varied with different maturity. Therefore, the scope of the current study has extended to compare these effects between treatment initiated during the peak pubertal growth stage and the late adolescence stage. Fifty-five patients aged between 11 and 18 years who attended the Department of Orthodontics, Sydney Dental Hospital, Sydney Local Health District for orthodontic treatment were randomised into four different groups. The two positive control groups consisted of subjects who underwent Class II functional appliance therapy, with one group comprising subjects at the peak pubertal growth stage and the other at the late adolescent stage. The two treatment groups received Class II functional appliance therapy with concomitant intraoral mechanical

vibration stimulated by a commercially available device, VPro5. One of the treatment groups consisted of subjects at the peak pubertal growth stage, and the other involved subjects at the late adolescent stage. Cone beam computed tomography (CBCT) records were taken before treatment and immediately after Class II functional appliance removal. Cephalometric and three-dimensional airway analysis were performed utilising these CBCT records. All groups showed correction of skeletal Class II malocclusion by maxillary incisor retraction, mandibular incisor proclination and varying degree of maxillary retrusion and mandibular protrusion. The results revealed an increase in dental compensation and a reduction in skeletal efficacy when mechanical vibration was used as an adjunct to Class II functional appliance therapy during the late-adolescent stage. In contrast, there may be some benefit to vibration stimulation in provoking more substantial skeletal effects of Class II functional appliance therapy during the peak-pubertal stage; however, a larger sample size investigation is necessary to confirm this. Additionally, intraoral mechanical vibration has been shown to enhance upper airway dimensions during Class II functional appliance therapy, as both experimental groups displayed greater airway volumetric changes during treatment, particularly in the oropharynx.

It is postulated that intraoral mechanical vibration may not have exerted sufficient stimulation on the mandibular and condylar structures to elicit a strong skeletal response, resulting in similar changes reflected in cephalometric analysis in the peak-pubertal groups. In the late-adolescence groups, mechanical vibration induced a stronger dental response, leading to lesser skeletal correction. Therefore, the use of intraoral mechanical vibration with Class II functional appliance therapy is not recommended during the post-pubertal period. Despite this, the use of mechanical vibration was beneficial in ensuring airway patency, which is paramount in patients with sleep disordered breathing. This served as a valuable prompt to pursue further research in its use in sleep medicine.

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AUTHOR ATTRIBUTION STATEMENT

A modified and condensed version of Chapters 2 and 3 of this thesis will be submitted to the American Journal of Orthodontics and Dentofacial Orthopedics. I have designed the study, analysed the data and will be writing the drafts of the manuscripts.

In addition to the authorship attribution statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

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GENERATIVE AI STATEMENT

The generative AI tools used in this thesis were solely for the purpose of spelling grammatical checks (via in-built Microsoft Word spellcheck and Grammarly) and reference and citation (via EndNote).

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ABBREVIATION

SDB	Sleep disordered breathing
TMD	Temporomandibular joint disorder
LMHF	Low magnitude and high frequency
GH	Growth hormone
GHR	Growth hormone receptor
95%CI	95% confidence interval
GRADE	Grading of Recommendations Assessment, Development and Evaluation
OHRQoL	Oral Health Related Quality of Life
MD	Mean difference
RCT	Randomised controlled trial
Forsus FRD	Forsus fatigue resistance device
CMA	Carriere motion appliance
IZCG	Infrazygomatic miniscrew anchored CMA
EXG	Essix-anchored CMA
3D CBCT	Three-dimensional cone beam computed tomography
EMG	Electromyography
TADs	Temporary anchorage devices
MCPP	Modified C-palatal plate
SNA	Sella to Nasion to A Point
ANB	B Point to Nasion to A Point
CAT	Clear aligner therapy
CA	Clear aligner
SNB	Sella to Nasion to B Point
TMJ	Temporomandibular joint
MRI	Magnetic resonance imaging
Pg/Olp	Pogonion to occlusal plane perpendicular
BSSO	Bilateral sagittal split osteotomy
TB	Twin Block
MARA	Mandibular Anterior Repositing Appliance
N-ANS	Nasion to Anterior Nasal Spine
SN- Pog	Sella to nasion to pogonion
IGF-1	Insulin growth factor 1
OASIS	Oral Aesthetic Subjective Impact Scale
OHQoL	Oral Health Quality of Life
Ihh	Indian hedgehog
FGF8	Fibroblast growth factor 8
VEGF	Vascular endothelial growth factor
PTHrP	Parathyroid hormone-related peptide
BMAL1	Brain and muscle arnt-like 1
MCC	Mandibular condylar cartilage

3D	Three dimensional
OSAS	Obstructive sleep apnoea syndrome
PSG	Polysomnography
2D	Two-dimensional
ODI	Oxygen desaturation index
MEP	Maximum expiratory pressure
ATB	Aesthetic Twin Block
FR-2	Functional Regulator-2
Co-Gn	Condylion to Gnathion (mandibular length)
SN-MP	Sella nasion line to mandibular plane line angle
ANS-Me	Anterior nasal spine to menton
OJ	Overjet
OB	Overbite
SN-GoGn	sella nasion line to gonion gnathion line angle
Invisalign® MA	Invisalign® Mandibular Advancement
FMA	Functional mandibular advancer
L1-MP	Lower incisor to mandibular plane angle
L1-NB	Lower incisor to nasion to B-point line
Ar-Go	Articulare to Gonion
SN-PP	Sella to Nasion to Palatal Plane line angle
LAFH	Lower anterior facial height
Xi-CF-PTV	Xilion to Centre Facial to Pterygoid true vertical plane angle
CCT	Clinical controlled trial
Olp	Occlusal plane perpendicular
CBCT	Cone beam computed tomography
HTH®	Hanks telescoping Herbst®
S-Go	Sella to Gonion
BMI	Body mass index
NREM	Non-rapid eye movement
REM	Rapid eye movement
SBD	Sleep-related breathing disorders
SDSC	Sleep Disturbance Scale for Children
AHI	Apnoea Hypopnea Index
CT	Computed tomography
MDCT	Multidetector computed tomography
DICOM	Digital Imaging and Communications in Medicine
MCA	Minimal cross-sectional area
HU	Hounsfield units
AI	Artificial intelligence
RDI	Respiratory disturbance index
MP	Mandibular plane
SN	Sella to Nasion line
OSA	Obstructive sleep apnoea

NSBa	Nasion to Sella to Basion
ML-NSL	Mandibular line to Nasion to Sella line
Me-Go-Ar	Menton to gonion to articulare
MP-H	Mandibular plane to hyoid bone
MAD	Mandibular advancement device
RME	Rapid maxillary expansion
MARPE	Miniscrew-assisted rapid palatal expansion
DO	Distraction osteogenesis
SARME	Surgically assisted maxillary expansion
MMA	Maxillomandibular advancement surgery
ESS	Epworth sleepiness scale
CCW	Counterclockwise
HA	Hydroxyapatite
OCN	Osteocalcin
BSP	Bone sialoprotein
OPN	Osteopontin
BMP	Bone morphogenetic protein
FSS	Fluid shear stress
MMP	Matrix metalloprotinases
M-CSF	Macrophage colony-stimulating factor
RANKL	Receptor activator of nuclear factor-κβ ligand
PTH	Parathyroid hormone
PGE2	Prostaglandin E2
OPG	Osteoprotegerin
Cx43	Connexon 43
Wnt	Wingless-related integration sites
NO	Nitric oxide
FGF-23	Fibroblast growth factor-23
TNF	Tumour necrosis factor
IL-6	Interleukin-6
miRNA	microRNA
RANK	Receptor activator of nuclear factor κ
GPCR	G protein-coupled receptor
IP3	Inositol 1,4,5-trisphosphate
cAMP	Cyclic adenosine monophosphate
ECM	Extracellular matrix
PDM	Preosteoblast-derived matrix
YAP	Yes-associated protein
TAZ	Transcriptional activator with PDZ-binding motif
Ca^{2+}	Calcium
Piezo 1	Piezo type mechanosensitive ion channel component 1
MSC	Mesenchymal stem cell
ATP	Adenosine triphosphate

AGTR1	Angiotensin II receptor 1
BDKRB2	Bradykinin receptor B2
Runx2	Runt-related transcription factor 2
FAK	Focal adhesion kinase
LIF	Leukemia inhibitory factor
MENK	Methionine enkephalin
MGF	Mechano-growth factor
H_2S	Hydrogen sulphide
CSE	Cystathionine gamma-lyase
SOD1	Superoxide dismutase
BMSC	Bone marrow stem cell
IGF	Insulin growth factors
TGF	Transforming growth factors
FGF	Fibroblast growth factors
Cbfa	Core-binding factor alpha
WBV	Whole body vibration
WBVT	Whole body vibration training
G6PD	Glucose 6-phosphate dehydrogenase
BSAP	Bone specific alkaline phosphatase
P1NP	Procollagen type 1 N-terminal propeptides
CTX1	Bone resorption C terminal telopeptide of type 1 collagen
BMD	Bone mineral density
WMD	Weighted mean difference
COPD	Chronic obstructive pulmonary disease
HbA1c	Glycosylated haemoglobin
DM2	Type 2 diabetes mellitus
OIIRR	Orthodontically-induced inflammatory root resorption
HFV	High frequency vibration
BIC	Bone to implant contact
BV/TV	*Bone* volume relative to tissue volume

Chapter 1: Effects of Mechanical Vibration on Class II Orthopaedic Appliance Therapy at Different Stages of Skeletal Maturity - Literature Review

1.0 INTRODUCTION

Class II malocclusion is the most common orthodontic problem found in Caucasians, with a global prevalence of 23%.[1] The most common expression of Class II malocclusion is Class II division 1 malocclusion on a skeletal 2 base with mandibular retrusion. Treatment of such malocclusion is essential as it could lead to detrimental sequelae such as trauma,[2,3] reduced self-esteem,[4] and possibly sleep disordered breathing (SDB)[5,6] and temporomandibular joint disorder (TMD).[7]

There is a myriad of treatment modalities for Class II division 1 malocclusion with mandibular retrusion. The determining factors for the type of treatment are the severity of the problem and the patient's skeletal age. Growth modification with functional appliance therapy is used to improve the skeletal discrepancy in a growing individual. When the growth of the mandible has slowed or ceased, the alternative treatment for the skeletal discrepancy is orthognathic surgery. However, due to the high cost and the inherent risk of surgery, patients may opt to camouflage the underlying skeletal discrepancy by merely correcting the malocclusion with fixed orthodontic appliance treatment. However, if the skeletal discrepancy is too severe to camouflage, the occlusion may be left in an unsatisfactory position. Many studies have investigated the use of functional appliances in adolescence with minimal pubertal growth potential or even in adults, aiming to minimise the skeletal discrepancy as much as possible and camouflage what cannot be achieved with fixed appliance orthodontics. The results showed that the majority of the corrections were conducive to dentoalveolar changes, but interestingly, minor skeletal alterations were also observed.[8]

The biological theory behind functional appliance therapy involves inducing tension in the mandibular condylar cartilage through the anterior propulsion of the mandible. This tension

initiates an anabolic response in chondrocytes[9] and results in condylar cartilage growth, which subsequently leads to endochondral ossification and bone growth. Simultaneously, there is bone remodelling at the glenoid fossa, therefore, maintaining the temporomandibular joint integrity.[10,11] A previous animal study explored the use of mechanical stimulation to enhance condylar cartilage growth and found profound results, concluding that low-magnitude, high-frequency (LMHF) stimuli could induce osteogenesis.[12]

Functional appliance therapy has also been used to improve the airway volume and minimise the occurrence of SDB. Advancement of the mandible brings the posterior soft tissue and hyoid bone anteriorly, thereby increasing the sagittal airway dimension in some individuals.[13,14] This was evident in many two-dimensional and three-dimensional airway analytical studies.[15-17] Early intervention may help to enlarge the airway and decrease the potential risk of SDB later in life.

This literature review aimed to explore the treatment for Class II Division 1 malocclusion with skeletal 2 mandibular retrusion discrepancy, the impact of treatment on the airway, and how mechanical stimulation could potentially enhance mandibular and condylar growth in these patients.

2.0 CLASS II MALOCCLUSION

2.1 Definition and Classification

In 1899, Angle[18] defined normal occlusion as "mesio-buccal cusp of the upper first molar is received in the sulcus between the mesial and distal buccal cusps of the lower, the slight overhanging of the upper teeth bringing the buccal cusps of the bicuspids and molars of the lower jaw into the mesio-distal sulci of their antagonists, while the upper centrals, laterals, and cuspids overlap the lower about one-third the length of their crowns." He then further described Class II malocclusion as "relative mesio-distal relations of the dental arches abnormal; all the lower teeth occluding distal to normal, producing very marked inharmony in the incisive region and in the facial lines." Later in 1907, Angle[19] revised the definition taking into account the skeletal structure and stated as follow: "when from any cause the lower first molars lock distally to normal with the upper first molars on their eruption to the extent of more than one-half the width of one cusp on each side, it must necessarily follow that every succeeding permanent tooth to erupt must also occlude abnormally, all the lower teeth being forced into positions of distal occlusion, thereby causing more or less retrusion, or lack of development , or both, of the entire lower jaw."

There were several dental and skeletal expressions of Class II malocclusion. From the dental aspect, there are two types of Class II malocclusion differentiated by the inclination of upper incisors. Class II division 1 malocclusion denotes proclined upper incisors, hence an increased overjet. Class II division 2 malocclusion is characterised by retroclined upper incisors and is often accompanied by an increased overbite. This review will focus on Class II division 1 malocclusions.

Skeletally speaking, Class II malocclusion can be expressed in Class I skeletal structure, i.e. normal maxillomandibular relationship or in Class II skeletal structure, i.e. maxillary protrusion and or mandibular retrusion. The most common skeletal form of Class II skeletal relationship is mandibular retrusion.[20] Fisk *et al*.[21] categorised six different types of morphological variation of Class II skeletal relationship: (1) maxilla and teeth are anteriorly placed with respect to cranial base, (2) maxillary base is normal while the upper teeth are anteriorly positioned, (3) mandible and normal in size but posteriorly positioned, (4) mandible is underdevelopment, (5) the lower dentition are posteriorly placed, (6) various combination of the above.

Skeletal Class II is generally presented as a convex facial profile. Additionally, Class II malocclusion is often associated with abnormal perioral function. The lower lip may be trapped behind the proclined upper incisors in front of the lower incisors, which could exacerbate the overjet. Active orbicularis oris and mentalis muscles are frequently observed in Class II division 2 patients, resulting in upright and lingually inclined incisors.

2.2 Prevalence

Class II malocclusion is one of the most common orthodontic problems, and a recent systematic review showed that the global distribution of Class II malocclusion in mixed dentition and permanent dentition was 23.11±14.94% and 19.56±13.76%, respectively.[1] The overall global prevalence ranged from 1.6% (Nigeria) to 63% (Belgium), with the highest prevalence of Class II malocclusion found in Caucasians for both mixed and permanent dentition.

2.3 Aetiology

Current research recognised that a combination of genetic, environmental and functional factors plays a significant role in the development of dental arches and occlusion.[22] Understanding the aetiological factors enables clinicians to plan treatment appropriately and gain a deeper understanding of the prognosis for treatment. The success of treatment depends on the contribution of genes and environmental factors to the malocclusion. The greater the genetic contribution to malocclusion, the lower the success rate of orthodontic and orthopaedic treatment.[23]

2.3.1 Genetic Factors

There are at least 19 genes that are found to be associated with Class II malocclusion.[24] George *et al*.[23] discovered a positive correlation between specific genes and skeletal Class II malocclusion, including FGFR2, MSX1, MATN1, MYN1, MYOH1, ACTN3, GHR, KAT6B, HDAC4 and AJUBA. Multiple muscle-related genes and pathways have also been identified, which aligns with Moss's[25] "Functional Matrix Hypothesis" that the muscular units surrounding the skeleton played an essential role in the development of skeletal structure and malocclusion.[24]

Growth hormones (GH) stimulate osteoblasts and play a critical role in regulating the linear and angular growth and development of craniofacial structures.[26] The growth hormone receptor (GHR) is a binding protein that supports GH activity. Several variables, including development, diet, hormones, and tissue-specific factors, regulate the expression of the GHR gene. In addition, there are diverse effects of GH in different ethnic groups. Growth modification treatment can successfully treat maxillo-mandibular discrepancies by modulating

the growth of the skeletal bases of the upper and lower jaws. However, if the skeletal discrepancy is due to genetic factors, the success of growth modification treatment can be uncertain. GHR gene polymorphism has an inhibitory effect on mandibular morphogenesis, affecting mandibular height (ramal height) more than mandibular body length.

A systematic review and meta-analysis on the heritability of dental arches and occlusal characteristics found that dental arch dimensions had a high heritability, whereas occlusal parameters demonstrated moderate to low heritability.[27] The high heritability of dental arch dimensions, such as arch width, arch length, and palatal depth, indicates that the genetic influence on the skeletal component was more substantial than on the dental component. In fact, the heritability coefficients for buccal segment relationship and overjet were 0.32 (95% confidence interval (95% CI), 0.15-0.49) and 0.25 (95% CI, 0.04-0.46), respectively, which were considered low. The overall certainty of the evidence was also low, according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.

2.3.2 Environmental Factors

2.3.2.1 Oral habits

Persistent thumb, digit, or pacifier sucking has a significant impact on the development of malocclusion due to the imbalance of force created around the dentition, as proposed in the equilibrium theory by Proffit.[28] Frequent occlusal problems associated with thumb, digit, or pacifier sucking included open bite, increased overjet, and crossbite.[29,30] Stahl *et al*.[31] showed a decrease in oral habits in deciduous dentition to mixed dentition, from 40.2% to 26.1%.

2.3.2.2 Functional Factors

Nasal obstruction in non-human primates can lead to changes in lip and tongue posture, as well as differences in the recruitment and electromyographic activity of the genioglossus, geniohyoid, digastric, temporalis, and median and lateral pterygoid muscles.[32] The subsequent effects included tongue protrusion, lip elevation and lowering and advancement of the mandible as an effort to maintain airway patency. Consequently, the imbalanced forces exerted on the dentition resulted in the development of Class II open bite malocclusion. Similarly, in human adult experiments, nasal obstruction caused head extension and lowering of the mandible.[33] Additionally, there was a decrease in muscular activity of the post-cervical and anterior temporalis muscles, and an increase in activity of the suprahyoid muscles. Head extension was shown to be associated with Class II malocclusion.[34] Enlarged adenoids and tonsils in children can interfere with normal breathing, which may lead to an anterior, inferior tongue posture and a retrognathic and posteriorly inclined mandible.[35,36] Additionally, there was an increase in the anterior facial height, extension of the head and lowering of the hyoid bone, which promoted mouth breathing, especially at nighttime.

A contemporary concept that the lack of or shorter breastfeeding duration is a cause of skeletal Class II, anterior open bite, and posterior crossbite development has been under scrutiny. This notion is based on functional matrix theory, in which, during breastfeeding, the child positions the tongue correctly by squeezing the nipple against the palate.[37] This leads to lip tone development and protruding mandibular movements which is in contrast to bottle feeding. Therefore, it is hypothesised that the lack of breastfeeding could lead to mandibular underdevelopment.[38-40] Of course, many reputable studies have refuted this theory as breastfeeding is often for the first year or the first few years of a child's life, which would have minimal impact on mandibular development.[41-43] However, Luz *et al*.[42] found that a short

period of breastfeeding (<6 months) could lead to increased non-nutritive sucking habits, and these non-nutritive sucking habits correlated with Class II malocclusion.

2.4 Reason for Treatment

Most patients with a Class II malocclusion seek orthodontic treatment for both aesthetic and functional improvements. Increased overjet and unfavourable facial profile could lower self-esteem and acceptance of self-image.[4] In fact, a systematic review by Göranson *et al*.[44] found that malocclusions in adolescents have a negative impact on oral health-related quality of life (OHRQoL). The more severe the malocclusion, the lower the OHRQoL. Increased overjet with incompetent lips predisposes patients to dental trauma.[3] Children with severe overjet were 1.81 (12 years old with overjet >5mm) to 3.37 times (0-6 years old with overjet ≥3mm) more likely to suffer from dental trauma.[2]

In recent years, severe mandibular retrusion has been found to be associated with a smaller airway volume, particularly in the velopharynx and oropharynx.[45-47] This was confirmed by a recent systematic review on the differences in upper airway volume in various craniofacial patterns.[48] Class II patients documented a reduction in airway volume (pooled mean difference (MD) = -2256.06 mm^2, 95% CI: -3201.61 mm^2 to -1310.51 mm^2) when compared with Class I patients and constriction mainly localised at the oropharynx. This study also analysed the airway in different vertical skeletal patterns and revealed that hyperdivergent patients had smaller airway volumes than hypodivergent patients (pooled MD = -1957.6 mm^2, 95% CI: -3063.3 mm^2 to -851.8 mm^2). In addition, Rodrigues *et al*.[49] conducted a systematic review and meta-analysis on the impact of skeletal Class II and Class III on pharyngeal airway

dimensions and discovered that Class II skeletal malocclusion had significantly smaller airway volume and area measurements when compared with Class III skeletal malocclusion.

Malocclusion, to some extent, has an impact on dentofacial development and oral health and function,[50-52] and some specific malocclusions are associated with TMD.[53,54] Identifying malocclusion that poses a high risk of TMD could assist orthodontists in providing intervention before the development of TMD and being mindful of the treatment plan and orthodontic mechanics that could predispose patients to TMD. The latest meta-analysis by Huang *et al*.[7] evaluated the prevalence of TMD in patients with malocclusion and discovered that TMD prevalence were higher in females (mean=44%, 95% CI:24%-64%), adults (mean=42%, 95% CI:24%-56%), Class II (mean=40%, 95% CI:32%-49%), openbite (mean=42%, 95% CI:24%-59%), increased overjet (mean=40%, 95% CI:36%-44%) and crossbite (mean=37%, 95% CI:27%-48%). It was suggested that Class II malocclusion, increased overjet, open bite, or cross bite should be treated early to prevent the development of TMD. However, it is essential to note that this meta-analysis exhibited significant heterogeneity (I^2 = 98.1%), indicating that the current evidence has limitations and further studies are necessary to draw convincing conclusions.

2.5 Treatment of Class II Malocclusion

Management of Class II malocclusion depends on the patient's skeletal age, the severity of malocclusion, appliance compliance and personal preferences.[55] There are generally three main categories of orthodontic treatment: growth modification, camouflage, and orthognathic surgery. Growth modification, as the name suggests, utilises the growth potential of the patient to improve skeletal relationship. Camouflage treatment can be carried out at any age, involving

the achievement of good occlusion through orthodontic tooth movement, which masks the underlying mild to moderate skeletal discrepancy. Orthognathic surgery is usually carried out in a non-growing individual who has a severe skeletal discrepancy that requires surgical movement of the jaw to optimise the facial aesthetics. The timing of growth modification is crucial, as it determines the extent of skeletal correction that can be achieved, ultimately leading to improved occlusion and facial aesthetics.

2.5.1 Treatment in Growing Individuals

Growth modification with functional appliance, also referred to as orthopaedic appliance, is an ideal treatment for growing individuals suffering from skeletal Class II malocclusion with mandibular retrusion. A functional appliance helps to protrude the mandible into a forward position, causing the muscles and soft tissues to stretch, with forces transmitted to the skeletal and dental structures. The resultant skeletal bone growth and tooth movement will improve the skeletal discrepancy and the occlusion. Details on growth modification with functional appliance will be discussed in the later part of this literature review.

There are also other therapies that are effective during growth and designed to correct specific Class II malocclusion problems, such as headgear, elastics, molar distalisation appliance, and even maxillary expansion. In certain circumstances, camouflage with extraction therapy is applicable to a growing individual with a dental Class II malocclusion on a mild skeletal class II base.

2.5.1.1 Headgear

Headgear is an extraoral traction therapy that aims to distalise the upper dentition, reinforce anchorage or induce an orthopaedic effect in Class II malocclusion. Meta-analyses disclosed that headgear can potentially restrict sagittal maxillary growth, distalise maxillary molars and reduce overjet.[56-58] In recent times, Ghislanzoni *et al*.[59] explored the role of headgear compliance on treatment outcome via a randomised controlled trial (RCT). Forty patients were randomly assigned to either the experimental or control group. The control group received no treatment, while the experimental group wore cervical headgear attached to the first permanent molar for 12 hours per day over a period of 9 months. The headgear was equipped with an electronic temperature and force-sensitive module that recorded data every 15 minutes. The compliance rate throughout the 9-month treatment was 55%. The average molar distalisation in the experimental group was 1.2 ± 1.0 mm, which was significantly different from the control group's average of 0.2 ± 0.5 mm of mesialisation. There was also a significant increase in arch depth (average of 1.3 ± 2.3 mm) in the experimental group, which was logical, as the molars were distalised to a similar degree. Distal tipping of 3.4 ° ± 3.6 ° was observed in the treatment group, which was significantly different from the mesial tipping of 0.6 ° ± 2.3 ° found in the control group. This occurred because the force applied was below the centre of resistance. As teeth were distalised into the broader part of the maxilla, the interpremolar distance was also significantly increased. However, the intermolar distance was similar between the two groups. The amount of molar distalisation was correlated considerably with the compliance rate.

The timing of headgear treatment can impact the overall effect. Early headgear treatment can lead to larger and wider dental arches, potentially reducing the need for future complex orthodontic treatment.[60,61] However, it often results in a two-phase treatment and a longer mean total treatment time.[62] Hannula *et al*.[63] presented a long-term study comparing dental

arch changes from 7 to 18 years between early cervical headgear treatment and late cervical headgear treatment. The outcomes of the study aligned with a previous study, which found that early cervical headgear treatment (i.e., after eruption of the first permanent molars) resulted in more favourable changes, such as a longer maxillary dental arch, compared to late cervical headgear treatment (i.e., approximately 18 months after early treatment). In addition, the final length and width of the maxillary arch were achieved earlier in the early treatment group, and the gained length was more stable in the long term. This could be due to the development of the second permanent molar in the late group. During early treatment, the second molar crowns are mineralising, while during late treatment, the second molar roots were developing, which probably gave more hindrance during first molar distalisation. One intriguing finding from this study was that more patients in the late treatment group required permanent tooth extraction in the second phase of treatment compared with the early treatment group. Therefore, early headgear treatment is a viable treatment for a quarter to half unit Class II malocclusion with dental crowding.

2.5.1.2 Fixed Appliance with Class II Intermaxillary Elastics

Mild to moderate Class II malocclusion can also be corrected with Class II intermaxillary elastics mechanics in growing patients.[20] Similar to a removable functional appliance, such as Twin Block, the success of treatment depends on patient compliance. It has been shown that Class II elastics had a similar dentoalveolar effect to a functional appliance, accompanied by some skeletal effects.[64] The dentoalveolar effects include upward forward movement of the mandibular first molars, proclination of lower incisors, and retroclination of upper incisors. In terms of skeletal impacts, there is forward movement and backward rotation of the mandible.[65-68] Condylar remodelling has been shown in animal studies.[69]

Several comparative studies have been conducted to evaluate the effects of Class II elastics in comparison to functional appliances. When comparing Class II elastics with the Forsus fatigue resistance device (Forsus FRD), there was a 0.8 mm significantly greater mean molar correction and 1.1mm significantly more mesial lower molar movement with Forsus FRD.[70] There was also a greater average clockwise rotation of the occlusal plane in patients with Forsus FRD.[70,71] According to the meta-analysis by Matthaios *et al*.,[72] the overjet correction was significantly better with Forsus FRD when compared with Class II elastics (pooled MD = -0.41 mm, 95% CI: -1.18 mm, 0.35 mm, p=0.01; I^2=0%) Additionally, there was more lower incisor inclination with Forsus FRD than with Class II elastics (pooled MD = 1.03°, 95% CI: 0.11°, 1.96°, p=0.03; I^2=0%). However, the differences did not seem clinically significant. Therefore, Class II elastics treatment can be considered similar to the use of Forsus FRD in correcting Class II malocclusion in growing children.

How do Class II elastics fare against other functional appliances, such as the Herbst? Most research studies have shown promising results following functional orthopaedic appliance therapy; however, these effects have been found to reverse during the second phase of treatment, and the outcome has been reported to be comparable to that of fixed appliances with Class II elastics alone.[73,74] Nelson *et al*.[75] compared the long-term effects of Begg full fixed appliance therapy with an isolated Herbst functional appliance. Following the active appliance phase, both methods showed very similar maxillary restriction. However, in the Begg group, there was significantly less anterior positioning of the mandible and a greater increase in lower facial height and maxillary plane angle. During the follow-up period of about 6.0 to 9.9 years, there was a relapse in overjet with proclination of upper incisors, increased maxillary and mandibular prognathism. Overall, most of the measured parameters were similar between the two groups, with the exception that the Begg group exhibited greater maxillary prognathism

and increased lower facial height. The less maxillary prognathism in the Herbst group could be attributed to the use of an activator during the retention phase. Interestingly, the increased mandibular plane angle during fixed appliance had returned to normal post-treatment. Therefore, authors have concluded that the outcome of treatment of a Class II malocclusion was similar regardless of which orthodontic devices were used. It is important to note that only male subjects were recruited in this study.

There is an interesting systematic review that compared the effects of Herbst and Class II elastics using three-dimensional cone-beam computed tomography (3D CBCT).[72] This review showed a greater increase in left mandibular length (Co-Gn) (pooled MD = 1.47 mm, 95% CI: 0.16 mm, 2.79 mm, p=0.03; I^2=0%) and in right ramus height (pooled MD = 1.61 mm, 95% CI: 0.43 mm, 2.78 mm, p=0.007; I^2=0%). However, the quality of evidence was considered low because there were only two eligible studies in this meta-analysis, and one of them was a small sample-size pilot study.

2.5.1.3 Carriere Motion Appliance

Carriere Motion Appliance (CMA) is a Class II distalising appliance that was invented by Luis Carriere in 2004.[76] The appliance aims to correct the Class II molar relationship before full fixed orthodontic treatment by distalising the posterior segment (canines to molars) using Class II elastics off the appliance, pitting against appropriate mandibular anchorage units such as a lower lingual holding arch or a clear retainer and a molar attachment for elastics to hook on. The appliance features a lever arm inserted as a ball and socket joint on the posterior bonding pad. (Figure 1) The author claimed that the ball and socket joint would prevent molar tipping and de-rotation during distalisation. To determine the dental and skeletal effects of CMA,

Barakat *et al.*[77] performed a systematic review and meta-analysis, finding no significant skeletal effect achieved by CMA. In terms of dentoalveolar change, there was a substantial increase in lower incisor proclination (pooled MD = -0.69°, 95% CI: -1.14°, -0.24; P<0.003; I^2=0%). Despite this, the qualitative evaluation showed CMA was able to correct the molar relationship with minimal molar tipping and rotation. CMA was effective in decreasing overjet and increasing overbite, but at the expense of upper canine extrusion, which did not align with Luis Carriere's proposition. Later, Ghozy *et al.*[78] performed an RCT to compare the dentoskeletal effects of infrazygomatic miniscrew anchored CMA (IZCG) with conventional Essix-anchored CMA (EXG). The results of this trial showed no significant difference in the average treatment period to obtain a Class I molar relationship (6.3 months for IZCG and 5.9 months for EXG). IZCG had no skeletal effect, whereas EXG had significant skeletal improvement. Because no Class II elastics were used for IZCG, there was no significant lower incisor proclination nor lower molar extrusion. The dental effects of IZCG were maxillary canine and molar intrusion.

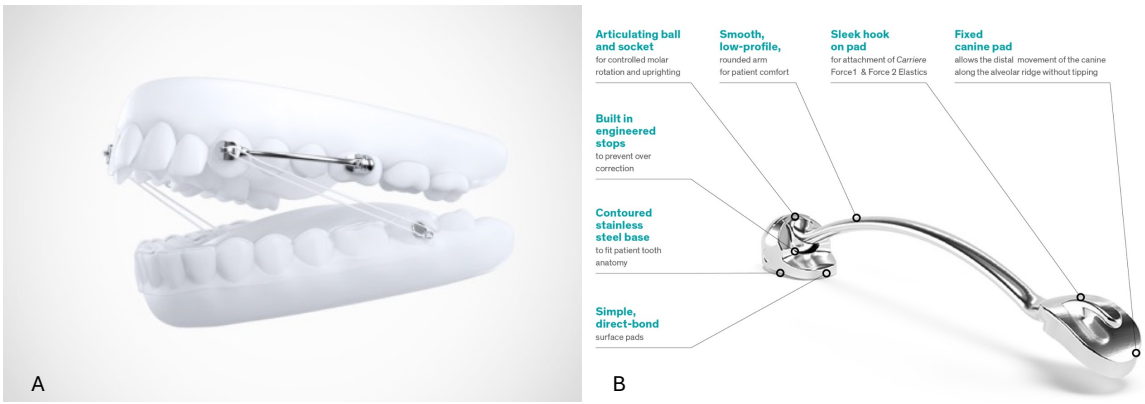


Figure 1 - Carrier Motion 3D (A) Intraoral view with elastics (B) Features of Carrier Motion 3D (obtained from https://henryscheinortho.com/brands-and-products/motion-3d/motion-3d-class-ii-appliance/)

As for soft tissue changes, Mohamed *et al*.[79] found through their 3D CBCT study that the lower lip retracted from the aesthetic line, with an increase in the nasolabial angle and soft tissue convexity angle. A retrospective study with a small sample size (n = 20) using 3D CBCT has shown a significant increase in airway volume and a minimal increase in cross-sectional area following CMA.[80] However, be cautious when interpreting the results of this study, as it lacked an untreated control group and subjects were post-pubertal patients (14 to 30 years old) with no history of airway problems. There was also a significant increase in the electromyographic (EMG) activity of the masseter and temporalis muscles following CMA.[81] This study was considered biased, as it consisted of only nine female subjects. All in all, further prospective RCTs with a reasonable sample size and long-term follow-up are required to draw meaningful conclusions regarding the beneficial effects of CMA.

2.5.1.4 Molar Distalisation

Camouflage treatment of Class II division 1 malocclusion usually entails premolar extraction. Disadvantages of premolar extractions include compromised profile aesthetics, adjacent alveolar injury associated with extraction and reopening of the extraction space during retention. The alternative to extraction camouflage treatment is the non-extraction approach, which involves upper dentition distalisation. This can be achieved by various appliances, such as headgear, distal jet, Jasper Jumper, and pendulum.[82,83] The disadvantages of these appliances include poor compliance (for headgear), poor aesthetics (for headgear), undesirable extrusion and protrusion of anterior teeth, and distal tipping and rotation, as well as extrusion of upper first molars.[82,84,85]

A Cochrane Database Systematic Review was conducted to assess the effects of upper first molar distalisation in children and adolescents with intraoral and extraoral appliances.[83] The

review stated that the degree and direction of molar movement, as well as the loss of anterior anchorage, varied with the type of appliance. The mean molar distal movement was 2.20 mm for the intraoral appliance and 1.04 mm for the headgear. There was a statistically significant difference between the two types of appliances (pooled MD = -1.45 mm, 95% CI: -2.74 mm, -0.15 mm, p=0.03; I^2=73%) favouring intraoral appliances. On the other hand, headgear appeared to be advantageous, resulting in less loss of anterior anchorage. This was indicated by the statistically significant differences in mean mesial upper incisor movement (pooled MD = 1.82 mm, 95% CI: 1.39 mm, 2.24 mm, p<0.00001; I^2=0%) and overjet (pooled MD = 1.64 mm, 95% CI: 1.26 mm, 2.02 mm, p<0.00001; I^2=15%) favouring headgear treatment.

Temporary anchorage devices (TADs) have been introduced to provide absolute anchorage during molar distalisation, aiming to minimise side effects such as molar extrusion. TADs for molar distalisation can be placed buccally and palatally in the inter-radicular spaces, the palatal vault, and the infrazygomatic region. A recent systematic review conducted by Owayda *et al*.[86] has shown maximum upper molar distalisation of 4.2 mm, 5.4 mm, and 5 mm with the use of TADs, palatal plates, and infra-zygomatic TADs, respectively, as anchorage. This was almost twice as much as cervical headgear, which recorded a maximum of 2.5 mm of molar distalisation in this review.[86] The molars were distally tipped and intruded, with a reduction of overjet, and retroclination of upper incisors. This impacted the facial soft tissue, showing an increased nasolabial angle and lip retraction. However, TADs supported distalisation did not induce skeletal effects or changes in airway space. Unfortunately, the authors described the overall certainty of evidence as low to very low. Further well-designed, high-quality RCTs are required to determine the effect of maxillary distalisation with different appliances.

Raghis *et al*.[87] conducted a meta-analysis on molar distalisation with Modified C-Palatal plates (MCPP) and inter-radicular miniscrews. The greatest significant distal movement of upper molar was from MCPP adults (pooled MD = 4.00 mm, 95% CI: 3.42 mm, 4.58 mm; P<0.0001; I^2=89%), followed by MCPP in adolescents (pooled MD = 3.54 mm, 95% CI: 2.91 mm, 4.17 mm; P<0.00001; I^2=68%) and inter-radicular miniscrews (pooled MD = 2.44 mm, 95% CI: 1.68 mm, 3.19 mm; P<0.00001; I^2=90%). The mean distal tipping of upper molar was more pronounced in MCPP adult (pooled MD = 3.17°, 95% CI: 2.77°, 3.58°; P<0.00001; I^2=0%°), followed by inter-radicular miniscrews (pooled MD = 2.91°, 95% CI: 1.06°, 4.76°; P<0.002; I^2=83%°) then MCPP adolescents (pooled MD = 1.61°, 95% CI: 1.05°, 2.17°; P<0.00001; I^2=0%). There was a significant intrusion with MCPP adult group and inter-radicular miniscrews, and a slight, non-significant extrusion with the MCPP adolescent group. This could be due to the counteracting downward growth of the maxilla in adolescents. The upper incisors were retracted similarly across three groups, but there was significantly less retroclination and extrusion in the inter-radicular miniscrew group.

An interesting finding from this meta-analysis was that there were positive skeletal changes in Sella to Nasion to A point (SNA) angle and A point to Nasion to B point (ANB) angle for the MCPP adult and adolescent groups, characterised by a reduction of around 1°. There was also significant mandibular plane downward rotation indicated by increased mandibular plane angle with MCPP adolescents (pooled MD = -1.29°, 95% CI: -2.38°, -0.20°; P=0.02; I^2=92%°) showing almost double the change of MCPP adults (pooled MD = -0.66°, 95% CI: -1.02°, -0.30°; P=0.0003; I^2=46%). Once again, this could be due to the growth effect of adolescents. Comparable upper and lower lip retraction was evident across the three groups, with the MCPP adult group having a significantly greater increase in nasolabial angle (pooled MD = -6.06°, 95% CI: -7.66°, -4.46°; P<0.00001; I^2=72%°) than the other two groups. Shoaib *et al*.[88]assessed

the post-treatment change and found significantly greater dental relapse in the MCPP adolescent group compared with the MCPP adult group (mean mesial molar movement of 2.94 mm vs 0.41 mm, respectively). This resulted in a net mean change of 0.60 mm for MCPP adolescents and 3.59 mm for MCPP adults, respectively. For inter-radicular miniscrews, there was an average mesial movement of 0.64 mm, resulting in a mean net change of 1.8 mm. Therefore, it seemed that the best way to distalise the molar is MCPP in adults. In this study, Raghis *et al*.[87] also compared MCPP with headgear and showed significantly more distal upper molar movement, less upper molar extrusion, and less upper molar distal tipping, as well as a greater reduction in the Sella to Nasion to A Point (SNA) angle with MCPP. Patient compliance and the limitation of cervical headgear control attributed to this difference.[89]

Further to this, Ceratti *et al*.[90] carried out a systematic review and meta-analysis to explore whether the location, number of TADs, and appliance design of different miniscrew-supported maxillary molar distalisation appliances have an impact on their effectiveness. The study found the amount of distalisation of the upper first molar did not vary with TADs location nor the number of TADs (3-TAD supported vs 2-TAD supported) but the side effect of distal tipping in palatal appliance was greater in non-rigid design (pooled MD = 9.84^{o}, 95% CI: 8.08^{o}, 11.60; P<0.0001; I^2=60%^{o}) compared with rigid design (pooled MD = 1.97^{o}, 95% CI: 1.01^{o}, 2.92; P<0.0001; I^2=71%^{o}). Distal tipping and intrusion were higher in zygomatic TADs, but not significantly more, when compared with other areas, i.e., palatal or buccal. The amounts of distalisation for palatal, buccal, and zygomatic TADs were 3.74 mm, 3.23 mm, and 3.68 mm, respectively. On the scale of a first molar tooth, this is probably half the cusp width. Therefore, molar distalisation cases should only be attempted when the molar discrepancy is half-unit Class II.

As mentioned earlier, one of the side effects of molar distalisation is tipping and extrusion of the molar. This could lead to bite opening and clockwise rotation of the lower jaw, which potentially exacerbates the Class II malocclusion. In the last few decades, clear aligner therapy (CAT) has become more common, and with the continuous enhancement of this technology, 2-3 mm upper molar bodily distal movement has become achievable.[91-94] As mesiodistal tipping was minimised during molar distalisation with clear aligners (CAs), lower facial height changes were also minimal.[91] This was illustrated by a randomised prospective clinical trial that compared the vertical effects of the pendulum appliance with CAs during Class II malocclusion treatment.[95] In this trial, the pendulum appliance had a significantly greater increase in anterior facial vertical parameters and greater maxillary and mandibular molar extrusion compared with CAT. Therefore, CAT is a better molar distalisation method than pendulum appliance showing minimal side effects.

2.5.1.5 Maxillary Expansion

Posterior transverse discrepancy usually accompanies Class II malocclusion and expresses as a narrow maxilla skeletally and or dentally.[96-99] This may not be evident on centric occlusion as the mandible is retruded and occluding the wider posterior part of the maxilla. When patients are asked to occlude anteriorly to the ideal bite, crossbite may be evident. Maxillary expansion is commonly used to address the transverse discrepancy issues, but McNamara[85,100] has found that when the transverse discrepancy was resolved, there was spontaneous correction of the Class II malocclusion. He referenced the "foot to the shoe" analogy, which originated from Korbit[101] and Reichenbach *et al*.,[102] to describe the relationship between the maxilla and mandible.[44] The "shoe" is the maxilla, and if it is too narrow, the "foot", which is the mandible, would not fit in. If the "shoe" is wide enough, the "foot" would slide forward into the "shoe". Many studies[103-105] have been carried out to contest this theory. A recent systematic review and

meta-analysis have shown slight but significant improvements in overjet (pooled MD = -0.36 mm, 95% CI: -0.69 mm, -0.02 mm) and molar relationship (pooled MD = 1.50 mm, 95% CI: 0.69 mm, 1.61 mm).[106] However, there was no evidence of improvement in sagittal skeletal parameters with maxillary expansion. Similar to this review, Kotarska *et al*.[107] conducted an earlier systematic review and showed although there was a small body of moderate quality evidence for statically and clinically favourable changes in Sella to Nasion to B point (SNB) and ANB angles, the lack of control groups indicated the changes could be contributed mainly by normal growth. Therefore, more quality RCTs were recommended to assess the use of maxillary expansion in the treatment of Class II malocclusion.

2.5.2 Treatment in late adolescence and adults

2.5.2.1 Camouflage Treatment

Camouflage treatment involving premolar extraction is the most common correction therapy for Class II division 1 malocclusion with mild to moderate skeletal discrepancy in late adolescence and adulthood. It allows correction of overjet and masks the slight underlying skeletal discrepancy. Class II extraction camouflage treatment usually involves the extraction of two upper premolars or four premolars, one from each quadrant. Controversy still exists regarding whether premolar extraction can lead to a flattened facial profile, resulting in undesirable facial aesthetics. However, extraction is not always undesirable, as it can result in facial profile aesthetic improvement and periodontal health preservation in the right cases. Many factors must be considered when implementing extraction treatment, including vertical dimension outcomes, treatment stability, arch widths, perioral soft tissues, and facial profile.[108,109] For example, extraction treatment may be preferred in cases with a Class II open bite malocclusion and moderate to severe crowding. The difficulty lies in managing borderline

extraction cases. Moon *et al.*[110] performed a systematic review and meta-analysis comparing the soft tissue profile change in patients with and without extraction. The analysis found no significant difference in soft tissue parameters between extraction and non-extraction patients. Therefore, both treatments were comparable in borderline extraction cases.

Premolar extraction treatment enables maxillary anterior teeth retraction and normalisation of overjet. The effect of premolar extraction on soft tissue profile included lip retraction, which could be detrimental in retrusive profile cases but favourable in protrusive profile cases.[111,112] This is illustrated by an RCT that evaluated and compared the lip profile changes of patients with Class II division 1 malocclusion following premolar extraction treatment with a fixed functional appliance, Forsus FRD.[113] Premolar extraction subjects exhibited a significant increase in the nasolabial angle, greater retraction of the upper lip and lower lip, a significant increase in upper and lower lip thickness, a significant improvement in upper lip strain, and a substantial improvement in the soft tissue profile. The authors concluded that premolar extraction therapy represented a superior treatment approach over Forsus FRD for Class II patients exhibiting moderate skeletal discrepancies, increased overjet, protruded maxillary incisors, and protruded lips. This modality results in more significant improvements in the soft tissue profile and lip relationship. However, it should be noted that premolar extraction treatment involved in this study utilised implant-supported en-masse retraction of maxillary anterior teeth. Therefore, the results could be different if conventional anchorage were to be used.

Class II elastics are frequently used as part of camouflage extraction treatment for Class II malocclusion. The force vector of Class II elastics can create side effects, such as extrusion of the molar and upper anterior teeth, which could potentially increase the anterior facial height

and worsen the skeletal Class II relationship and the resultant facial profile. The worst-case scenario would increase the patient's risk to TMD. To minimise such side effects, micro-implants have been used to provide anchorage control. However, evidence on the use of micro-implants in vertical control has been controversial, with some researchers reporting favourable outcomes with counter-clockwise rotation of the mandible,[114-116] and others finding that it could induce more molar extrusion.[117-119] Hence, a systematic review was conducted to evaluate the effectiveness of micro-implants used in vertical control during orthodontic extraction treatment in adults and post-pubertal adolescents with Class II malocclusion.[120] From this analysis, the use of micro-implant had better decrease in mandibular plane angle (MD=-1.15°; 95% CI=-1.67° to -0.63°, P<0.0001, I^2=96%) and better intrusion of the upper molar (MD=-1.45 mm; 95% CI=-2.02 mm to -0.89 mm, P<0.00001, I^2=98%). The findings concluded that micro-implant was more effective in vertical control than conventional anchorage during orthodontic extraction treatment of Class II adults and post-pubertal adolescents.

Class II elastic wear during orthodontic treatment has been shown to improve the balance of masticatory muscle activity. A two-centre RCT conducted by Nalamliang and Thongudompo[121] compared adults who wore Class II elastics full-time with those who did not during orthodontic treatment. Surface electromyography scores revealed better balance of masticatory muscle activity and improved masticatory performance following three months of Class II elastic wear. This could be due to an improvement in the contact area when the Class II buccal segment was normalised to a Class I segment, which provided a better balance of occlusion. Unfortunately, this experiment failed to show significantly more areas of occlusal contact and near contact in the experimental group compared with the control group. It was also unable to identify significant differences in occlusal contact or near contact throughout the treatment. Perhaps another reason for improving masticatory muscle activity is the anterior

movement of the mandible, which consequently changes the dimensions of the masticatory muscles, resulting in an alteration of masticatory muscle activity.

Camouflage with non-extraction treatment has gained popularity recently and is reserved for minor skeletal and moderate dental discrepancies, as well as some Class II borderline surgery cases. Due to the high cost and surgical risks, some researchers have explored the use of functional appliances to promote repositioning of the mandible, with the hope of inducing temporomandibular joint (TMJ) remodelling as a result.[122-126] Fixed functional appliances, such as the Herbst appliance and Forsus FRD, have been used to correct Class II malocclusion in adults.[8,125,127,128] The outcome of the research was controversial, with some claiming dentoskeletal changes[127,129] and others showing solely dentoalveolar effects.[122,123] An animal study by McNamara *et al*.[130] has demonstrated that the Herbst appliance induced a stimulatory effect on the adult Rhesus monkey's TMJ through condylar growth and glenoid fossa remodelling. This was translated into a human model, where Ruf and Pancherz[126] discovered, via their magnetic resonance imaging (MRI) study, that similar condylar growth and glenoid fossa remodelling changes were evident following Herbst therapy in adults and adolescents. Ruf and her team further investigated and compared the effects of orthognathic surgery and orthopaedic therapy using the Herbst appliance, finding both treatments successfully corrected the Class II malocclusion with profile improvement.[8] However, the skeletal effect was greater in the surgical group (Overjet = 63%, Molar correction = 80%) when compared to the Herbst appliance group (Overjet = 13%, Molar correction = 22%). Interestingly, the mandibular plane angle was reduced in the Herbst group and increased in the surgery group. This could be due to inadequate overlap between two bony fragments at the time of surgery, muscular reattachment and adaptation at the gonion area, and the generally adaptive processes of soft tissue, tendons, and muscles in response to jaw displacement and possible condylar resorption

following surgery. In terms of facial profile, there was a greater reduction of facial convexity in the surgery group than in the Herbst group. The authors suggested the use of advancement genioplasty to improve chin projection as an adjunct to Herbst treatment. This would be less financially burdensome and less risky than mandibular sagittal split osteotomy.[131]

In contrast, a systematic review by Gonzalez Espinosa *et al*.[10] reported that the effects were mainly of a dentoalveolar nature. Meta-analysis showed minor but significant change in SNB (pooled MD = 0.87º, 95% CI: 0.08º, 1.66º), ANB (pooled MD = -0.82º, 95% CI: -1.24º, 0.04º) and pogonion to occlusal plane perpendicular (Pg/Olp) (2.3 mm to 1.2 mm (P<0.001)). The Herbst appliance was the only appliance in the study that reported a minor forward movement of the mandible. In fact, the effects obtained by mandibular propulsion in non-growing individuals were similar to those using Class II elastics. The analysis was limited by the lack of facial profile data, a key factor for deciding orthodontic camouflage against orthognathic surgical options.

There has been an increasing number of adults seeking orthodontic treatment in recent years, and appliance aesthetics is a high priority for these patients. Invisalign® was one of the first generations of CAs that was introduced in 1997. Molar distalisation with Invisalign® has been shown to be effective in adult patients by Saif *et al*.,[132] who recorded a mean distalisation movement of approximately 2.6 mm. However, it came at a cost, resulting in the loss of anterior anchorage and causing the upper incisors and lateral incisors to flare to a lesser extent. The author suggested using Class II elastics during molar distalisation to counteract the reactive anchorage loss. In contrast, Patterson *et al*.[133] have proven that there was no significant difference in overjet and molar relationship in adult Class II malocclusion patients between

pretreatment and following Invisalign® treatment. Therefore, it was concluded that Invisalign® failed to achieve substantial Class II correction or significantly reduce overjet.

2.5.2.2 Orthognathic Surgery

Combined orthodontic and orthognathic surgery treatment is the preferred treatment for moderate to severe adult skeletal class II deformities. Apart from achieving skeletal, dental, and functional outcomes, orthognathic surgery also offers psychological benefits, including heightened self-esteem and self-confidence.[134] The most commonly performed surgical procedure for Class II skeletal mandibular retrusion is the bilateral sagittal split osteotomy (BSSO). During this procedure, the proximal (anterior) portion of the split is repositioned anteriorly and secured with rigid fixation using plates and screws. The difficulty in placing fixation is to ensure the condyle is in its proper place because the anatomy allows it to move in three dimensions.[135,136] If this was not done properly, one of the worst post-surgery complications may arise, i.e. condylar resorption.[137] Fortunately, the human body is remarkably adaptable, especially in cases of mild to moderate displacement. Condylar remodelling occurs in response to forces and stresses applied to the TMJ, enabling it to maintain morphological, functional, and occlusal balance.[138] A recent systematic review confirmed that patients without TMD underwent a natural adaptive process of the mandibular condyle following orthognathic surgery. There was a reduction in bone density, accompanied by morphological reshaping of the condyle through bone apposition. However, incorrect condylar positioning during surgery can also lead to anterior open bites and TMD, which makes post-operative orthodontics challenging.

Class II mandibular advancement surgery is considered highly stable with <10% of significant posttreatment change.[139] The success of orthognathic surgery also depends on patient

satisfaction. A systematic review evaluated the satisfaction levels of adult patients following orthognathic treatment and indicated that Class III surgical patients acquired higher satisfaction than Class II surgical patients.[140] Additionally, bimaxillary surgery generally yielded better outcomes. Specifically for Class II surgery, Espeland *et al*.[141] reported a satisfactory rate of 83% three years post-surgery.

Due to the invasive nature and financial burden associated with orthognathic surgery, patients may opt for orthodontic camouflage as an alternative. However, as skeletal discrepancy becomes more severe, camouflage treatment may not produce an aesthetically pleasing outcome, especially when a profile change is required. A systematic review and meta-analysis have been conducted to compare the dental, skeletal and aesthetic outcomes between orthodontic camouflage and orthodontic-surgical treatment in patients with skeletal Class II malocclusion with mandibular retrusion.[142] Although overjet and overbite showed significantly better improvement with orthognathic surgery, the pre-treatment overjet and overbite were substantially more severe in the orthognathic surgery patients. This could have dichotomous views. One explanation could be that orthognathic surgery had a superior outcome, as it helped to reduce a larger pre-existing overjet and overbite to a greater degree. On the other hand, as it had a larger pre-existing overjet and overbite, it would be expected that the correction should be larger to normalise the overjet and overbite. Upon close examination, the pretreatment mean differences for overjet and overbite were -0.56 mm and -0.21 mm, respectively. The mean differences for changes in overjet and overbite were -0.64 mm and -0.33 mm, respectively. This indicated that although there was a difference in the pre-treatment overjet and overbite, the treatment changes could overcome this difference and had further favourable effects. This concluded that orthognathic surgery was, in fact, more effective. There was also a mean difference of 1.04º reduction in ANB with orthognathic surgery, which was not statistically

significant but could be considered clinically important in some individuals. However, this extra reduction should be weighed against the risks of surgical complications, such as a bad split (2.3%), postoperative infection (9.6%), removal of osteosynthesis material (11.2%), and neurosensory disturbances in the lower lip (33.9%).[143]

2.6 Growth Modification with Functional Appliance

Functional Appliances are orthopaedic devices designed to encourage or redirect growth in a favourable direction by inducing sagittal and vertical changes in the maxilla and mandible.[144] Essentially, this sagittal and vertical change eliminates the barrier, which is primarily due to malocclusion or surrounding soft tissue pressure, and optimises the growth of the mandible, restoring normal occlusion. Functional appliance also provides restraint to the maxilla and upper dentition, as well as mesialisation of the lower dentition.

The design of functional appliances is widely variable, ranging from removable to fixed to hybrid (a mixture of removable and fixed). They can be constructed with acrylic and/or metal. The modes of action for each type of functional appliance are similar yet distinct.

Removable functional appliances are made of acrylic and are bulky and loose in the mouth, which can temporarily impair speech. This is difficult for patients to wear, leading to poor patient cooperation. Patient compliance is a crucial factor that significantly influences the success of functional appliance therapy. Research has shown that the discontinuation rates of Twin Block (TB) range from 9% to 33%.[145,146] Some examples of removable functional appliances are the bionator, activator, functional regulator, and TB.

Non-compliance functional appliances, also called fixed functional appliances, are cemented on patient's dentition, which can overcome the reliance on patient cooperation. Fixed functional appliances, therefore, are frequently used in patients who are at the peak of pubertal growth or have just passed pubertal growth, as patient compliance is ultimately crucial to the success of treatment. Some examples of fixed functional appliances include the Herbst, Jasper Jumper, PowerScope and Mandibular Anterior Repositioning Appliance (MARA).

2.6.1 Timing of Growth Modification Treatment

Growth modification treatment is also referred to as functional appliance therapy or orthopaedic appliance therapy. Generally, growth modification treatment for Class II malocclusion is most effective, stable and least deleterious during the pubertal growth spurt. However, early treatment for Class II malocclusion may be indicated for specific reasons such as risk of incisal trauma due to increased overjet, development of improper swallowing patterns, incompetent lip function, psychological concerns and SDB.

Several studies have proven the effectiveness of treatment in early mixed dentition; however,[147,148] most RCTs have shown that the most effective skeletal changes occur from treatment during late mixed or early permanent dentition.[73] This was due to the alignment of the peak growth velocity of the mandible with the pubertal peak growth and the timing of optimal occlusion obtained at the end of treatment in the permanent dentition, which contributes to long-term stability of this change. In fact, Hagg and Pancher[149] found that condylar growth was twice as much in patients treated during the pubertal peak as in patients treated three years before and after the peak.

Frye *et al.*[150] compared the effect of fixed functional appliance treatment before and after the pubertal growth peak. There were more vertical changes documented in younger patients (female younger than 12 years old and male younger than 14 years old), with a significant increase in both anterior and posterior facial height. A substantial difference in Nasion to Anterior Nasal Spine (N-ANS) was also observed between the two groups. There was a greater change in mandibular advancement (SNB, Sella to Nasion to Pogonion (SN-Pog)) among older patients from the initial to the end of treatment. However, this change was not significantly different from that of younger patients. In terms of dental changes, there was no significant difference between the groups. The proportion of skeletal effects in the younger group was 35% in younger patients and 19% in older patients. This study also found that the soft tissue did not follow the skeletal changes.

Data from a 2015 systematic review and meta-analysis showed fixed functional treatment resulted in better total mandibular elongation in pubertal patients (MD=1.95 mm; 95% CI=1.47 mm to 2.44 mm, P<0.00001, I^2=0%) when compared with post-pubertal patients (MD=-1.73 mm; 95% CI=-2.60 mm, -0.86 mm, P<0.0001).[151] A similar group of investigators also conducted a systematic review and meta-analysis comparing the treatment effects of removable functional appliances in pre-pubertal and pubertal Class II patients.[152] The findings also suggested that the skeletal effect was greater when functional appliance was used during pubertal period with greater increased in total mandibular length (MD=2.91 mm; 95% CI=2.04 mm, 3.79 mm, P<0.00001, I^2=48%) than pre-pubertal period (MD=0.95 mm; 95% CI=0.38 mm, 1.51 mm, P=0.001, I^2=49%). Similarly, there was greater mandibular ramal height increase in the pubertal group (MD=2.18 mm; 95% CI=1.51 mm, -2.86 mm, P<0.00001, I^2=0%) compared with pre-pubertal studies (MD=0.00mm; 95% CI=-0.52 mm, 0.53 mm, P=0.99, I^2=0%). The authors offered substantial evidence for this view. Previous reports have

shown that insulin growth factor 1 (IGF-1) is one of the key factors that promote chondrogenesis of condylar cartilage.[153] The serum level of IGF-1 was significantly greater in pubertal subjects than in pre-pubertal subjects;[154,155] therefore, it justified the increased mandibular total length and ramal height during the pubertal period.

The use of reliable biological indicators helps to detect the pubertal spurt in mandibular growth.[149,156-159] These indicators include age, secondary sexual characteristics, stature height changes, skeletal maturation index from hand-wrist x-rays and cervical maturation index from lateral radiographs. The latter seems to be a popular indicator for orthodontists, as the cervical spine is visible on the lateral cephalogram, a routine radiograph taken at the time of consultation. O'Reilly and Yanniello[160] established a relationship between cervical vertebral maturation (CVM) stages (Figure 2) and mandibular growth changes by evaluating annual lateral cephalograms of 13 girls. Statistically significant increases in mandibular length, corpus length and ramus height were found to be associated with specific maturational stages in cervical vertebral, i.e. stages one to three.

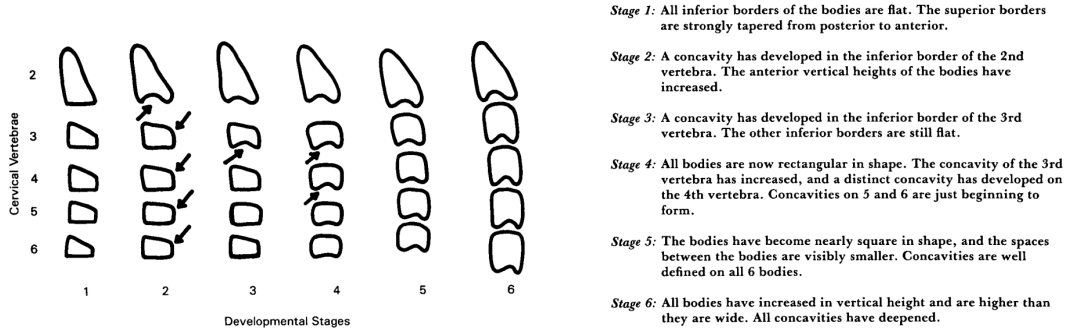
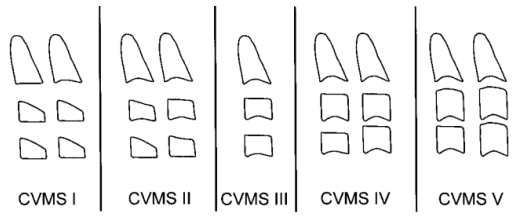


Figure 2 - Stages of cervical vertebral maturation[160]

Later, Franchi *et al.*[161] indicated that CVM stages 3 and 4 coincided with the pubertal peak in both mandibular growth and body height. However, this CVM system relies on changes in C2 to C6 and may not always be fully visible on a lateral cephalogram. Baccetti *et al.*[162] improved this CVM method by focusing only on C2 to C4, which are usually visible on a lateral cephalogram. This new system is called the cervical vertebral maturation stage (CVMS). (Figure 3) The peak mandibular growth occurs within one year after CVMS and within one or two years before CVMS III. This means that CVMS II is the ideal stage to begin functional appliance therapy.



Cervical Vertebral Maturation Stage (CVMS)	Description
I	The lower borders of C2 to C4 are flat, except a concavity at the lower border of C2 in almost half of the cases. The bodies of both C3 and C4 are trapezoid in shape. Peak mandibular growth will occur not earlier than one year after this stage.
II	Concavities at the lower borders of both C2 and C3 are present. The bodies of C3 and C4 may be either trapezoid or rectangular horizontal in shape. The peak in mandibular growth will occur within one year after this stage.
III	Concavities at the lower borders of C2 to C4 now are present. The bodies of both C3 and C4 are rectangular horizontal in shape. The peak in mandibular growth has occurred within one or two years before this stage.
IV	Concavities at the lower borders of C2 to C4 are still present. At least one of the bodies of C3 and C4 is squared in shape. If not squared, the body of the other cervical vertebra still is rectangular horizontal. The peak in mandibular growth has occurred not later than one year before this stage.
V	Concavities at the lower borders of C2 to C4 are still evident. At least one of the bodies of C3 and C4 is rectangular vertical in shape. If not rectangular vertical, the body of the other cervical vertebra is squared. The peak in mandibular growth has occurred not later than two years before this stage.

Figure 3 - The diagram shows morphological features in the bodies of C2, C3 and C4 for the improved CVM stages. The table provides a detailed description of each stage, along with its associated mandibular growth status.[162]

2.6.2 One-Phase vs Two-Phases Treatment

A vast body of quality research has been carried out to compare the effectiveness of early versus late orthopaedic treatment. The controversy lies in the issue of timing: whether to treat early with two separate phases or wait until the appropriate time and carry out functional appliance therapy and full fixed orthodontic appliance therapy in one phase. The two phases involved

functional appliance therapy when the patient is around seven to ten years old, followed by a second phase of full fixed orthodontic appliances once the permanent dentition is established. Several RCTs were conducted in the 1990s and early 2000s to assess the effectiveness of early functional treatment. The findings were quite similar, showing that early treatment corrected the incisal relationship with both skeletal and dentoalveolar contributions to the changes. The proportion of skeletal contribution differed for different orthopaedic appliances used. However, when comparing the outcomes between two-phase treatment and single-phase treatment in adolescence, it was found that early treatment had no benefit, with outcomes being very similar between the two types of treatment. The difference was the efficiency of treatment. Early treatment did not reduce the phase two treatment time and did not decrease the proportion of complex treatment involved in the adolescent phase. Therefore, the decision for early treatment should be based on individual need.

The validity of these RCTs has been questioned. Darendeliler[163] questioned whether Class II malocclusion could be due to either or both maxillary protrusion and mandibular retrusion. The selection criteria of an increased overjet or an ANB of more than 4^{o} did not define the aetiology of the Class II malocclusion for that particular individual. Blanket treatment carried out during these trials may not address the cause of the problem; hence, the results should be interpreted with caution. O'Brien *et al.*[164] also criticised these RCTs as they were carried out in a single dental school with one to four operators, and the patients were screened and offered incentives to cooperate with treatment, which did not reflect the "real" world situation. The team overcame these challenges by conducting an RCT involving 14 hospital-based orthodontic specialists. The results of this trial indicated that the substantial improvement in overjet was mainly due to dentoalveolar correction, with a small element of favourable skeletal

change. This meant that early functional appliance treatment did not impact the Class II skeletal pattern to a clinically significant level.

Mandall *et al.*[165] sought to determine the effect of treatment timing on clinical and psychological outcomes with TB therapy through a multicentre, two-arm parallel RCT. One group of subjects was treated immediately (Group ITG), and another group was treated 18 months later (Group LTG). The study found no clinically significant differences in the treatment effect between the two groups. Additionally, Group LTG was not disadvantaged psychologically, as indicated by the results from both questionnaires: the Oral Aesthetic Subjective Impact Scale (OASIS) and the Oral Health Quality of Life (OHQoL).

2.6.3 Treatment Duration of Functional Appliance

The determination of treatment time for a functional appliance depends on the time required for condylar remodelling and bone formation. Previously, Pancherz[166] suggested Herbst treatment to be six to eight months, and ideally, finished treatment during the permanent dentition stage so that interdigitation can be obtained to minimise relapse. Later, Chayanupatku *et al.*[167] advocated maintaining the mandible in the advanced position for a more extended period to allow the newly developed bone matrix to transform into a more stable Type 1 collagen matrix. This process would help ensure normal mandibular growth once the appliance is removed, Therefore, Chayanupatkul *et al.*[167] and Hagg *et al.*[168] recommended that the duration of mandibular advancement should be twice the typical period of five to seven month period for sufficient maturation of newly formed bone, leading to improved clinical outcomes with extended treatment times.

2.6.4 Effects of Functional Appliance

The dental and skeletal effects are similar across different types of functional appliances; however, the magnitude of these effects varies. Generally, it increases mandibular length, restricts forward growth of the maxilla, promotes growth in the condyle, and causes mesialisation of the lower dentition and distalisation of the upper dentition. The soft tissue that follows the skeletal change can be quite variable; however, there is usually an advancement of the lower lip and chin point, along with an improvement in facial profile.[169,170]

2.6.4.1 Animal studies

Animal studies provide a better understanding of how functional appliances induce chondrogenesis and osteogenesis at the cellular and even molecular levels. Rats have similar histological features in their TMJ to human TMJ, despite some morphological differences, and are therefore widely used in functional appliance therapy research.[171] Based on the findings from animal studies, human clinical trials can be justified, and therefore, animal research is paramount.

Functional appliance propels the mandible in a forward position, which creates tension at the mandibular condylar cartilage. When mechanical loading, i.e., tension, is too strong, cell proliferation is inhibited.[172] On the other hand, if the loading is optimal, anabolic response in chondrocytes is activated.[9] In the condylar cartilage of developing rats, mandibular advancement devices enhance the expression of collagen-binding integrins, IGF-I and IGF-II, and promote cell proliferation.[173,174] The transmission of mechanical force to the cells is via transmembrane receptors called integrins.[172,175] It was understood, through animal studies, that Indian Hedgehog (Ihh) was a transcription factor that controls chondrocyte proliferation and

differentiation.[176] Hence, mandibular growth during functional appliance treatment can be indicated by the expression levels of Ihh.[9]

Condylar cartilage is a framework onto which new bone will form. Type II collagen is responsible for this matrix, and research has shown that there is an increase in Type II collagen following the forward position of the mandible.[177] Apart from Type II collagen, Shen et al[178] discovered a significant increase in Type X collagen and maturation of chondrocytes in rats subjected to functional therapy using a bite-jumping device. Hypertrophic chondrocytes synthesised Type X collagen to allow bone matrix deposition and calcification. Type X collagen forms a highly resorbable framework for bone matrix deposition, offering support as the cartilage degrades.[179] Similarly, Rabie *et al.*[180] found that forward mandibular position accelerated and enhanced chondrocyte differentiation and cartilage formation.

Additionally, fibroblast growth factor 8 (FGF-8) helps control bone formation by regulating the proliferation of mesenchyme and chondrocyte cells. As a result, the condyle develops via endochondral ossification, whereas the glenoid fossa undergoes intramembranous ossification. Endochondral ossification involves the process of creating and resorbing the cartilage matrix.[181] Mesenchymal cells differentiate into chondrocytes during endochondral ossification and are responsible for secreting cartilaginous matrix. As chondrocyte cells become hypertrophic, the matrix undergoes remodelling and calcification. For cartilage to be converted to bone during endochondral ossification, new blood vessels have to establish in the area to deliver blood and several non-differentiated mesenchymal cells to the site. These cells convert into osteoprogenitor cells, which subsequently become osteoblasts, thereby generating new bone. When neovascularisation is established, the cartilage is resorbed. Vascular endothelial growth factor (VEGF) is an important molecular regulator of neovascularisation

that is expressed and upregulated in the condyles of growing rats during anterior mandibular displacement.[182,183] The level of VEGF can be measured and used as an indicator of new bone formation. It is proven that its expression is increased with mechanical strain.[184,185] Therefore, elevated levels of VEGF, Type X collagen, Type II collagen, and Ihh would be a great indication of new bone growth.

Through animal studies, it was determined that the effect of mandibular anterior displacement on the mandible was dependent on the duration of application and the degree of protrusion provided by the appliance. Rabie and Al-Kalaly[178] investigated the effect of 2 mm and 4 mm mandibular advancement on condylar growth at different duration (3, 7, 14, 21 and 30 days) by measuring the new bone formation quantitatively with computer-assisted analysing system and levels of mRNA expression of growth markers via molecular analysis utilising real-time reverse transcription-polymerase chain reaction. There was significantly more newly formed bone in the 4 mm group when compared with the 2 mm and control groups at 21 and 30 days of the experiment. The total amount of newly formed condylar bone was significantly increased on days 14, 21, and 30 compared to the control group, with the highest amount being reached on day 30. There was also elevated expression of growth markers such as Ihh, parathyroid hormone-related peptide (PTHrP) and Type II collagen. It can be concluded that the amount of mandibular growth achieved with the functional appliance is related to the duration of treatment and the amount of advancement exerted.

The growth of the mandibular condyle has also been shown to be associated with the circadian rhythm. Oudet *et al.*[186] studied and compared the growth rate of condylar cartilage in rats with functional appliances during rest and wake periods. The functional appliance significantly increased the growth rate of the condylar cartilage, with a greater induction during the rest

period. This could be explained by Yu *et al.*,[187] who investigated the role of the brain and muscle arnt-like 1 (BMAL1) circadian regulator in postnatal growth of mandibular condylar cartilages (MCC). The transcription factor BMAL1 is the core driver of the circadian pacemaking in mammals.[188] BMAL1 was shown to control osteogenic differentiation and osteoclast differentiation in the mandible.[189] Similarly, Yu *et al.*[187]have shown that BMAL1 is critical to chondrogenesis and endochondral ossification of MCC. This implied that the growth of MCC was related to the circadian rhythm.

2.6.4.2 Human Studies

2.6.4.2.1 Dental and Skeletal Changes

The effect of functional appliance therapy in correcting Class II skeletal abnormalities includes growth of the mandible and remodelling of the glenoid fossa.[190,191] The remodelling of the TMJ involves bone deposition on the roof of the glenoid fossa and the posterior aspect of the mandibular condylar head.[10,11] Consequently, studies have claimed that the glenoid fossa relocated in inferior and anterior directions following functional appliance therapy.[191-193] Cephalometric effects of functional appliance therapy include a small reduction of the SNA angle, a slight increase of the SNB angle and a moderate decrease of the ANB angle, indicating restraint of maxillary growth and promotion of mandibular growth, resulting in an improvement of the maxillomandibular relationship.[194] In terms of dentoalveolar changes, there is a reduction of overjet due to retroclination of upper incisors and proclination of lower incisors and molar correction to Class I relationship. The degree of change differs with various types of functional appliances, which will be discussed later.

2.6.4.2.2 Profile Changes

Correcting a Class II skeletal profile characterised by mandibular retrusion usually requires increasing the anterior projection of the chin. There are three mechanisms to achieve this: lengthening of the mandible, repositioning of the glenoid fossa and counterclockwise rotation of the mandible. Even so, this could not be easy to obtain because for the mandible to come forward, the vertical growth of the condyles must exceed the vertical growth of the maxillary corpus and maxillary and mandibular dentoalveolar processes.[195,196] According to Bjork and Skieller,[197] mandibular total rotation was a combination of matrix and intramatrix rotation, and perhaps the degree of this inherent rotation plays a vital role in the amount of anterior projection of the chin following Class II orthopaedic treatment. This was highlighted by LaHaye *et al.*,[198] who compared the chin projection following different types of Class II treatment in vertical patients and reported no difference in chin projection improvement when compared with untreated controls. This indicates that the patients with backward rotation were less likely to respond favourably in terms of profile aesthetics following orthopaedic treatment.

The elimination of overjet facilitates the enhancement of perioral muscular tonicity and posture following the use of a functional appliance.[199] Consequently, the lower lip position, thickness and mentolabial angle improved. The upper lip was also positioned backwards in relation to the E plane.[200] This was reiterated in a recent systematic review, which showed that the upper lip moved backwards (pooled MD = -1.93 mm, 95% CI: -2.37 mm, -1.50 mm; I^2=63%) following TB treatment compared with the untreated control.[201] On the other hand, the Herbst appliance produced the most significant lower lip protrusion compared to the untreated control (4.3±3.1 mm vs 2.1±3.4 mm, p=0.030).[202] This was followed by Forsus FRD (1.1±3.68 mm) and activator (1.91±7.97 mm).[203] In terms of chin position, there were inconsistent findings across different studies, with some showing chin advancement with TB (MD = 5.45±3.80 mm,

p<0.001), Forsus FRD (MD = 2.322±0.676 mm, p=0.003), and activator (MD = 3.982±0.676 mm, p<0.000).

In terms of facial convexity, most studies have shown a significant increase in the facial convexity angle,[200,204] mentolabial angle,[200,204,205] and Z-angle following functional appliance therapy.[205,206] The nasolabial angle also seemed to have significantly increased following Twinbock treatment when compared with untreated control (pooled MD = 5.75^{o}, 95% CI: 4.57^{o}, 6.93^{o}; I^2=70%).

All in all, soft tissue changes appeared to follow the dentoalveolar and skeletal changes induced by the functional appliance; however, the degree of change did not correlate with the changes in each other.[207] Twin block treatment appeared to have a greater effect on the upper lip, pogonion projection, and facial convexity, while Herbst treatment seemed to have a more pronounced change on the lower lip.[200]

When profile changes from functional appliances were assessed in a non-cephalometric scale, Luyten *et al.*[169] revealed that all studies in the systematic review reported an improvement in aesthetic scores after treatment. Improvement seemed to be gender-dependent, with female patients tending to show more improvement in their profiles. Additionally, malocclusion was found to be a factor, with the more severe the malocclusion, the better the improvement in the profiles.[208] The upper and lower lip proportions changed significantly, with the proportion of Class II patients having normal upper and lower lip improved from 40% to 70% and 23% to 75%, respectively. Similarly, the proportion of Class II patients with normal chin projection increased from 23% to 72% after treatment.

Emerging digital technologies enable the three-dimensional (3D) assessment of facial profiles via laser surface scanning, stereophotogrammetry, geometric morphometrics, non-rigid surface registration, and mesh technology. Luyten *et al*.[170] reported the results of a systematic analysis on 3D profile assessment, finding that following functional appliance therapy, there was a downward and forward movement of the mandible, as well as improvements in sulcus inferior position, lower lip posture, and chin projection. Facial height and facial depth have also increased significantly during treatment.

2.6.4.2.3 Airway Changes

When the mandible is in a retruded position, the tongue and soft palate would also be placed posteriorly, which could partially block the upper airway.[209] With the use of a functional appliance that brings the retruded mandible anteriorly, the associated soft tissue and muscles can be drawn forward, thereby improving airway patency. Therefore, functional appliances can be considered for Class II growing patients with obstructive sleep apnoea syndrome (OSAS). This would allow for the correction of skeletal discrepancies and eliminate adaptive changes in the upper airway.

Oral appliances have been considered a low-cost, relatively comfortable form of therapy to relieve symptoms of OSAS. In fact, the early use of functional appliances would be beneficial for children with SDB, as it can decrease the future risk of OSAS by enlarging airway dimensions, reducing the potential for airway collapse, and thus improving airway muscle tone.[15] Many previous studies have shown improvement in posterior airway passage dimensions after functional appliance therapy in children[210-216] and oral appliance therapy in adults. Maspero *et al*.[217] compared the airway dimension changes following the Andresen appliance, a type of functional appliance, with those of untreated control patients and found

improvement in airway dimension. There was a significant difference in the changes between the two groups in the posterior airway space, mandibular plane to hyoid bone distance, distance from tip of soft palate to middle pharyngeal wall and distance from vallecula to lower pharyngeal wall. This increase could be due to the forward position of the tongue induced by the anterior position of the mandible with the appliance. In fact, the follow-up polysomnography (PSG) showed improved breathing parameters compared with the control group. Similarly, Schutz *et al*.[215] documented a pronounced increase in posterior airway space by 3.2 mm and a reduction in airway resistance in teenagers with a retrognathic mandible who have undergone Herbst appliance therapy.

Three-dimensional cone beam computed tomography (3D CBCT) enables volumetric measurement of the airway, overcoming the inadequacies of two-dimensional (2D) lateral cephalometric analysis. Most 3D studies have shown that functional appliance therapy has an insignificant effect on the nasopharynx but a significant increase in oropharyngeal volume. This was reflected in the recent 3D CBCT study, which investigated volumetric airway changes following Herbst appliance therapy compared with a group without an appliance. The results showed that Herbst appliance therapy significantly increased the oropharynx volume by 30%, and the mean oropharynx volume was considerably larger than that of the group with no appliance. It was suggested that the anterior repositioning of the mandible changes the position of the hyoid bone, tongue and associated musculature, improving the patency of the airways.[218]

The next question is whether one type of functional appliance produces better airway improvement than another. Arora *et al*.[219] compared the airway changes following the use of Herbst and AdvanSync appliances, both of which are fixed functional appliances. Herbst seemed to offer better improvement at the retropalatal oropharyngeal airway, with a difference

of 1.12 mm (95% CI: 0.133 mm, 2.107 mm, p=0.027). Both appliances showed airway improvement at the nasopharynx (Herbst: 2.12±1.73 mm and AdvanSync: 1.89±2.08 mm), oropharynx (Herbst: 2.33±1.71 mm and AdvanSync: 1.21±1.36 mm), and hypopharynx (Herbst: 1.57±2.79 mm and AdvanSync: 1.53±1.40 mm) levels by the end of treatment. Radwan *et al.*[220] compared the effect of TB on SDB with a control group that had fixed orthodontic appliance therapy. TB had significantly better improvement in the oropharynx volume (MD= TB: 3.14 cc and control: -1.44 cc), maximum area (MD= TB: 76.8 mm^2 and control: 6.19 mm^2), minimal area (MD= TB: 52.99 mm^2 and control: 27.34 mm^2) and average area (ME= TB: 50.97mm^2 and control: 15.44 mm^2). Most importantly, TB therapy showed significantly better improvement in sleep respiratory indicators, such as the oxygen desaturation index (ODI) and maximum expiratory pressure (MEP), compared with the control group. Mandibular advancement induced by TB resulted in a forward movement of the hyoid bone and the tongue, which could better increase the oropharyngeal airway.[221,222]

2.6.4.2.4 Temporomandibular Joint Changes

Temporomandibular joint disorder (TMD) is a condition that affects the TMJ apparatus and the surrounding muscles. Functional appliances displace the mandible anteriorly, which could alter the disc-condyle relationship and induce TMD.[223] Previous studies have documented the following symptoms during functional appliance therapy: TMJ capsular pain upon palpation, TMJ sounds, and muscle pain upon palpation.[224,225] Whether functional appliance therapy causes TMD is still a topic of controversy. Some animal research studies have shown no TMJ symptoms,[226] while other studies suggest that functional appliance therapy causes TMDs through disruption of occlusion,[227-229] and some studies have shown a return of the condyle-glenoid fossa relationship following treatment.[230] This controversy prompted the need for a systematic review and meta-analysis, which was recently conducted by Ding *et al.*[223] The

results showed that 3.3% of patients reported TMJ symptoms following functional mandibular advancement in adolescents; however, these symptoms resolved during the follow-up period. The reported symptoms included TMJ noises, TMJ pain and oral facial pain, but no TMJ dysfunction. 1.8% of cases reported osteoarthritic changes or deviation in condyle form, but none reported TMJ dysfunction. 4.9% had disc displacement, but all returned to normal position at one-year follow-up. The development of TMD was not dependent on the amount of forward mandibular advancement. Therefore, it could be concluded that functional appliance therapy is relatively safe and only causes TMJ symptoms and temporal TMJ disc changes in a small proportion of patients.

2.6.5 Types of Functional Appliance

2.6.5.1 Removable Functional Appliances

2.6.5.1.1 Twin Block

Twin Block (TB) is one of the most popular functional appliances used to treat Class II malocclusion, especially in younger children. (Figure 4) TB is a tissue borne removable appliance that differs from others in that it is composed of maxillary and mandibular components, allowing patients to eat with it in and enhancing wear time.

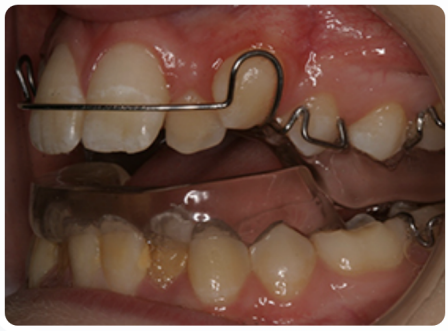


Figure 4 - Twin Block (Courtesy of British Orthodontic Society: https://bos.org.uk/museum-and-archive/appliances-and-equipment/functional-appliances/clarks-twin-block/)

TB has been shown to exert dental and skeletal effects, which include an increase in mandibular length, an increase in facial height, and the eruption of upper and lower molars. O'Brien *et al.*[164] reported the skeletal contribution to overjet and molar corrections as 27% and 41%, respectively, during the transition dentition stage. On the other hand, Baysal and Uysal[231] reported much higher skeletal contributions to overjet and molar correction, at 70% and 71.5%, respectively, with their subjects' mean age around 13 years old. There were debatable results for the maxillary restraining effect with TB therapy, with some studies showing restriction[164,232-235] and some did not.[145,236] The increase in facial height was partly attributed to the passive eruption that occurred when the acrylic blocks were trimmed during TB treatment in deep bite cases. It was also partly contributed by mandibular protrusion during TB therapy and the resultant ramal height development.[231,232] The condyles moved anteriorly following TB appliance therapy, leading to a decrease in the anterior joint space and an increase in the posterior joint space.[237] According to the meta-analysis by Li *et al.*,[237] the anteroposterior diameters of the condyles (pooled MD = 0.63 mm, 95% CI: 0.30 mm, 0.97 mm; $P<0.0002$; $I^2=4\%$) and condylar height (pooled MD = 0.94 mm, 95% CI: 0.78 mm, 1.09 mm; $P<0.00001$; $I^2=0\%$) increased following TB treatment.

The shortcomings of TB include proclination of lower incisors, speech impediment and patient compliance. Efforts are made to alter the design of the original TB to minimise the proclination of lower incisors. These include acrylic capping of the lower incisors,[238] increasing the number of anterior ball clasps,[239] and relieving the lingual acrylic with an inbuilt labial bow.[240] A contemporary modified TB called the Aesthetic Twin Block (ATB) has been designed to overcome these adverse effects, providing a more aesthetically pleasing appearance and

hopefully enhancing patient compliance. (Figure 5) ATB is made from clear, vacuum-formed hard plates, similar to clear aligners, with clear acrylic bite ramps.[241] A recent RCT compared the dentoskeletal effects of ATB with conventional Twin Block (CTB) in the treatment of skeletal Class II malocclusion.[241] This study reported that ATB had significant favourable changes in ANB (2.72°±1.54° for ATB vs 1.72°±1.41° for CTB) and SNB (-2.70°±-0.84° for ATB vs -1.92°±0.81° for CTB) angles, indicating that ATB had better skeletal relationship improvement. Dentally, there was significantly less retraction of upper incisors (-2.00°±2.02° for ATB vs -4.18°±3.34° for CTB) and proclination of lower incisors (1.34°±2.08° for ATB vs 3.88°±2.47° for CTB), which denoted less dental compensation. Interestingly, there was significantly less change in the Jarabak ratio (0.84±1.44% for ATB vs -0.65±1.37% for CTB) in the ATB group, implying that ATB had better vertical control.

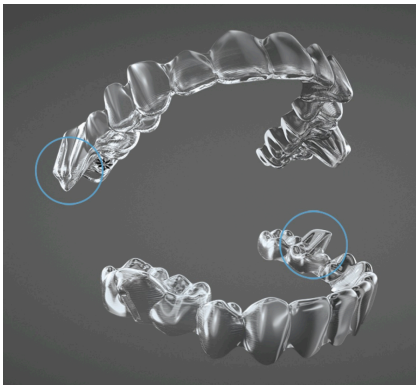


Figure 5 - Example of an Aesthetic Twin Block by Invisalign® (Courtesy of Invisalign®: https://www.invisalign.com/provider/align-digital-platform/mandibular-advancement)

Speech impediment is one of the factors influencing compliance with removable appliances. Shahbodaghi *et al.*[242] carried out an RCT to compare the speech effect between ATB and CTB. The study's results showed that both appliances had some impact on speech, but ATB had less speech distortion immediately after insertion. This could be due to the more streamlined design with ATB. Additionally, articulation structures were adapted more quickly with ATB than with

CTB. This is crucial, as the initial adaptation would foster positive patient cooperation from the start of treatment.

The removable nature of TB gives rise to the issues of wear time and patient compliance, which are crucial for treatment effectiveness. There are heat sensors, such as TheraMon® (Handelsagentur Gschladt, Hargelsberg, Austria), that could be placed in the appliance to monitor patient compliance. The sensors track compliance by recording how long the appliance remains at intraoral temperature. To overcome the compliance issue, Frilund *et al.*[243] attempted to distinguish whether a 6-week or 4-week check-up interval has an impact on wear time. The outcome of the study showed no statistically significant difference in overjet reduction and total wear time between 6-weekly and 4-weekly check-up intervals. This meant that frequent patient visits for check-ups did not enhance the treatment effect. In fact, the mean wear time was about six to seven hours per day when clinicians instructed patients to wear it for 12 hours a day.

How does TB fare against other functional appliances? A systematic review scrutinised the differences in skeletal and dental effects between Forsus FRD and TB in growing individuals, which showed that both appliances were effective in Class II correction.[244] However, TB offered better outcomes in ANB (MD=-1.34^{o}; 95% CI -1.03^{o},-1.65^{o}; $p<0.00001$; $I^2=92\%$) and SNB (MD=1.32^{o}; 95% CI 1.67^{o}, 0.97^{o}; $p<0.00001$; $I^2=86\%$) correction.

2.6.5.1.2 Functional Regulator (Frankel Appliance)

Frankel developed the Functional Regulator (Figure 6) to produce 3D changes in Class II malocclusion during the mixed and early permanent dentition stages.[245] It is a tissue-borne removable appliance that utilises acrylic vestibular shields to eliminate unwanted muscular

forces that would otherwise restrict skeletal and dental development. It has been documented that a 4-6 mm increase in maxillary arch width and a 2-4 mm increase in mandibular arch width are typically observed in Functional Regulator-2 (FR-2).[246,247] The lower labial and lingual shields anteriorly repositioned the mandible. Unfortunately, there was conflicting evidence on the effects of functional regulators due to the nature of the treated sample and controls, the various designs of the appliance and disparity in treatment techniques.

Figure 6 - Frankel Function Regulator (Courtesy of British Orthodontic Society: https://bos.org.uk/museum-and-archive/appliances-and-equipment/functional-appliances/frankel-function-regulator/)

2.6.5.1.3 Activator

Activator (Figure 7) is a one-piece acrylic removable functional appliance designed firstly by Andreasen in 1909 to improve the retrognathic mandible in Class II malocclusion.[245,248] He first treated his daughter with this appliance, calling it a "Biofunctional Retainer" to be worn at night. Later, he collaborated with Haupl, who together named the appliance an activator. Because the appliance is one-piece, speech and functional activity would be impeded. The effects of the activator are similar to those of other removable functional appliances.

Xie *et al*.[249] carried out a systematic review and meta-analysis to illustrate the effects of activator treatment in patients with skeletal Class II malocclusion compared with the untreated control group. In terms of skeletal effects, there seemed to be a restricted growth of maxilla as indicated by a statistically significant reduction of SNA (pooled MD = -0.52°, 95% CI: -0.78°, -0.27°; P<0.0001; I^2=64%) and enhanced growth of mandible which was indicated by a statistically significant increase in SNB (pooled MD = 0.80°, 95% CI: 0.47°, 1.14°; P<0.00001; I^2=77%) and Condylion to Gnathion (Co-Gn) (pooled MD = 3.02 mm, 95% CI: 1.89 mm, 4.14 mm; P<0.00001; I^2=77%). As a result, the maxillomandibular discrepancy has improved as shown in a reduction of ANB (pooled MD = -1.44°, 95% CI: -1.77°, -1.10°; P<0.00001; I^2=81%). There seemed to be an increase of anterior facial height as indicated by significant increase in sella nasion line to mandibular plane line angle (SN-MP) (pooled MD = 0.98°, 95% CI: 0.63°, 1.33°; P<0.00001; I^2=0%) and anterior nasal spine to menton (ANS-Me) (pooled MD = 1.50 mm, 95% CI: 0.53 mm, 2.47 mm; P=0.002; I^2=81%). In terms of dental effect, activator is effective in reducing overjet (OJ) (pooled MD = -5.46 mm, 95% CI: -6.05 mm, -4.88 mm; P<0.00001; I^2=77%) and overbite (OB) (pooled MD = -2.01 mm, 95% CI: -2.80 mm, -1.23 mm; P<0.00001; I^2=92%). The OJ correction was partly attributed to significant retroclination of upper incisors (pooled MD = -6.22°, 95% CI: -9.05°, -3.40°; P<0.0001; I^2=87%) and significant proclination of lower incisors (pooled MD = 1.73°, 95% CI: 0.85°, 2.61°; P=0.0001; I^2=70%). Upper lip retracted significantly from E-line when compared with

untreated control (pooled MD = -1.50°, 95% CI: -1.98°, -1.02°; P<0.00001; I^2=0%). The changes in the lower lip were similar in the activator and untreated control groups.

2.6.5.1.4 Clear Aligners

Orthodontic clear aligners (CAs) have gained significant interest in recent years due to their ability to treat a wider variety of cases and the expanded spectrum of orthodontic tooth movement compared to years ago. Due to its clarity and smoothness, CAs offer patients a form of orthodontic treatment that is both aesthetically pleasing and comfortable to wear. However, due to the removable nature, wear compliance becomes problematic, especially in children and adolescents. Several aligner brands have introduced aligners to provide early orthodontic intervention for conditions such as posterior crossbite and Class II dentoskeletal discrepancies.[250,251] Align Technology™ (Invisalign® Mandibular Advancement), Angel Align™ (A6) and Smartee™ (S8-SGTB) have incorporated mandibular advancement features into their clear aligners, providing an invisible alternative to traditional functional appliances and allowing for tooth alignment during the growth modification stage. Several clinical studies have been conducted to investigate the effects of these novel aligners. There was a significant improvement in sagittal and vertical skeletal relationship (increased SNB 2.14±2.02°, decreased ANB -1.53±1.46°, decreased sella nasion line to gonion gnathion line angle (SN-GoGn) -1.11±1.93°), dental relationships (reduced OJ -3.80±2.24 mm) and reduction in upper lip protrusion (-0.95±1.66 mm) according to Sadek and Awad.[252] Unlike TB, there was no significant change in lower incisor angle, indicating that Invisalign® Mandibular Advancement (Invisalign® MA) provided greater control of the lower incisors. However, this study lacked an untreated control group, which raises questions about the actual degree of treatment change. Yu *et al*.[253] agreed with this in a meta-analysis, which found better lower incisor control when comparing CAs with conventional functional appliances as reflected in significant difference

found in the parameter lower incisor angle (pooled MD = -2.50°, 95% CI: -3.99°, -1.01°; P<0.0010; I^2=65%). However, the mandibular length (Co-Gn) was significantly less in the clear aligner (CA) group when compared with the conventional functional appliance by a mean of 1.10mm (pooled MD = 1.10 mm, 95% CI: -1.60 mm, -0.60 mm; P<0.0001; I^2=0%).[253]

In terms of airway changes, Yue *et al*.[254] carried out a retrospective comparison of the upper airway and hyoid bone position between TB and Invisalign® MA. Both TB and Invisalign® MA showed increased oropharynx and hypopharynx volumes and minimal cross-sectional areas. However, Invisalign® MA had a significantly greater increase in minimal cross-sectional area at the hypopharynx when compared with TB. Both appliances also promoted a similar amount of anterior downward movement of the hyoid bone, which potentially opens the upper airway. Wu *et al*.[255] compared the skeletal and dentoalveolar effects of Invisalign® MA with those of Van Beek activator, Herbst, and TB. The Van Beek activator had the highest proportion of skeletal correction (OJ 74.73%), while Invisalign® MA had the lowest (OJ 48.91%). Unfortunately, most studies to date have been retrospective and lacked a control group without treatment. Further RCTs with larger sample sizes would be more meaningful in determining the effectiveness of CA mandibular advancement as a tool for growth modification.

2.6.5.2 Fixed Functional Appliance

2.6.5.2.1 Functional Mandibular Advancer

In 2002, Kinzinger *et al*.[256] introduced the functional mandibular advancer (FMA), a fixed functional appliance similar to the Herbst appliance. Unlike the Herbst appliance, which utilises a pin and tube system or telescopic arms to propel the lower jaw forward, FMA uses 60° incline planes and a protrusive bar instead. (Figure 7) The developer claimed that the FMA

has a more vertical inter-gnathic force vector and a shorter lever arm than the Herbst appliance. Kumar *et al*.[257] performed a systematic review and meta-analysis on the effectiveness of FMA in treating patients with Class II malocclusion. The skeletal and dentoalveolar changes were similar to those of other functional appliances, except for a significantly greater reduction of ANB angle (pooled MD = 1.00º, 95% CI: 1.34º, -0.65; P<0.00001; I^2=0%) when compared with other functional appliances.

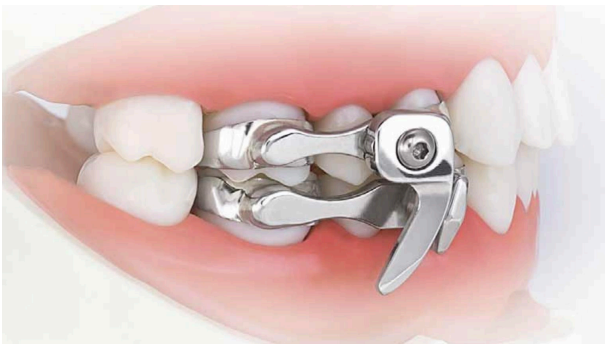


Figure 7 - Fixed Functional Appliance (Courtesy of Forestadent catalogue: https://www.afridentco.com/wp-content/uploads/2021/08/Forestadent-Functional-Mandibular-Advancer-FMA.pdf)

2.6.5.2.2 Forsus Fatigue Resistance Device (Forsus FRD)

Forsus FRD is a semi-rigid fixed functional appliance that can be attached to a fixed orthodontic appliance. (Figure 8) Instead of the telescopic arms in a Herbst appliance, the propulsion of the mandible is initiated with a nickel-titanium coil spring. There is no laboratory procedure involved, and it can all be assembled chair-side, which is an advantage of this appliance. The spring is attached to the headgear tube on the upper molar and connected to the lower wire distal to the mandibular canine bracket. Due to this configuration, breakages of the lower canine bracket frequently occur, but these can be overcome by altering the design through the application of a spring on a jig auxiliary to the arch wire or by placing a gable bend on the pin part of the apparatus. The treatment time is typically 6.2 months, and the effect is primarily dentoalveolar.[258]

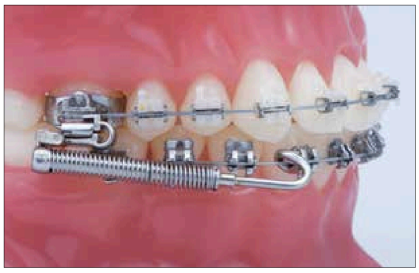


Figure 8 - Forsus FRD (Courtesy from 3M™ catalogue: https://multimedia.3m.com/mws/media/823065O/forsus-fatigue-resistant-device-treatment-guide.pdf)

One of the problems with a fixed functional appliance is that it is mounted on the teeth; therefore, it exerts more dentoalveolar effects, i.e. side effects. To improve the skeletal correction of Forsus FRD, skeletal anchorage has been used to minimise dental side effects. Eissa *et al*.[259] performed a meta-analysis and systematic review aimed at analysing the skeletal and dental effects of skeletally anchored Forsus FRD in Class II treatment. The outcome of this meta-analysis showed skeletally anchored Forsus FRD had significantly favourable correction in SNA (pooled MD = -0.26º, 95% CI: -0.50º, -0.02º; P=0.03; I^2=0%), significantly more increase in SN-MP angle (pooled MD = 0.53º, 95% CI: 0.06º, 1.00º; P-0.03; I^2=0%), significantly less lower incisor proclination as depicted in lower incisor to mandibular plane angle (L1-MP) (pooled MD = -2.12º, 95% CI: -4.96º, -2.12º; P<0.00001; I^2=53%) and significantly less lower incisor protrusion reflected in lower incisor to nasion to B-point line (L1-NB) (pooled MD = -1.05 mm, 95% CI: -1.42 mm, -0.68 mm; P<0.00001; I^2=70%). This meant that skeletally anchored Forsus FRD could minimise the side effect of lower incisor proclination and provided better "headgear" effect when compared with Forsus FRD attached to a fixed appliance only. It is essential to note that the duration of Forsus FRD treatment in these studies ranged from 4.8 to 6.5 months, which may not be sufficient to induce condylar growth or mandibular changes.

2.6.5.2.3 Herbst Appliance

The Herbst appliance has been around for over a century and was developed by Emil Herbst in the early 1900s. The popularity was regained in the late 1970s following the extensive research studies led by Hans Pancherz and his team.[260] There were many variations and designs of the Herbst appliance, but essentially, it consisted of bilateral telescopic arms attached to upper and lower metal and/or acrylic frameworks, which were cemented onto the teeth. (Figure 9)

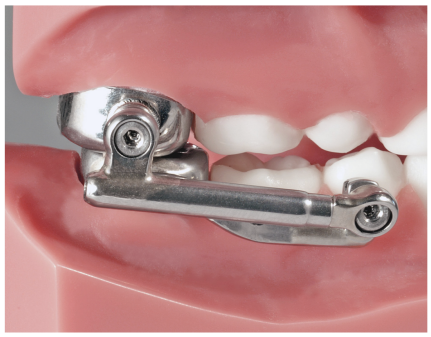


Figure 9 - Hanks telescoping herbst® appliance (Courtesy of American Orthodontics: https://www.americanortho.com/products/fixed-and-functional/fixed-and-functional-hth/)

The purpose of the telescopic arm was to posture the mandible in an anterior position during occlusion and function. Unlike the TB appliance, patient compliance is not an issue with the Herbst appliance because the appliance is cemented onto the dentition. However, the cost of fabrication and high breakage rate in earlier designs have been reported as disadvantages.[146,261] The complications associated with Herbst appliance included lower splint breakage, band or crown fracture, screw loosening, rod distortion, pivot breakage and soft tissue injuries.[262] Silva *et al*.[261] recorded an average of 2.5 complications per patient, regardless of the design of the Herbst appliance. There was variability in the frequency of complications recorded in the literature, with a range from 60% to 86%.[263] Moro *et al*.[263] reported that the more contemporary and streamlined cantilever bite jumping Herbst seemed to have fewer complications, with 33% of patients having no complications and an average of 1.1 complications per patient.

2.6.5.2.3.1 Treatment Timing for Herbst Appliance

As previously mentioned, regarding the timing of treatment, there is no evidence to suggest that early Class II treatment is more effective than treatment performed during the pubertal growth peak. This was reiterated in a prospective clinical study explored by de Almeida *et al*.[264] on the effect of early Herbst treatment, with a historical untreated control sample group used to eliminate the impact of normal growth and development. Interestingly, the results showed that there were primarily dentoalveolar changes, namely upper incisor retraction and retroclination and lower incisor proclination. There was also a significant increase in mandibular posterior dentoalveolar height and restriction in vertical development of the upper molar. In terms of skeletal changes, there was no maxillary changes but modest and statistically significant mandibular lengthening, indicated by significantly increased Co-Gn (Herbst 4.8±3.5 mm Control 3.2±3.4 mm), Articulare to Gonion (Ar-Go) (Herbst 2.9±2.2 mm Control 1.5±1.8 mm) and SNB angle (Herbst 0.5±1.3^{o} Control -0.1±1.3^{o}). However, this degree of increase in mandibular length was less than that observed in adolescent Herbst patients in other studies when natural growth was taken into consideration.[260,265,266] Moreover, there was no significant vertical change, as indicated by both anterior and posterior facial heights and the mandibular plane.

2.6.5.2.3.2 Effects of Herbst Appliance Therapy

The effects of Herbst on the skeletal structures were reportedly minimal restraint of maxillary growth and a significant increase in mandibular length, ranging from 2.0 mm[265] to 3.5 mm[266] depending on the treatment period. There was also remodelling of the TMJ, namely bone apposition on the roof of the glenoid fossa and the posterior aspect of the condylar head.[10,11]

There was a tendency for clockwise rotation of the palatal plane (Sella to Nasion to Palatal plane line angle (SN-PP)) noted during Herbst therapy compared with the control group, which did not adversely affect lower anterior facial height (LAFH).[267-269] The vertical changes were different with the different designs of Herbst. The banded Herbst has been reported to favour the increase of LAFH.[260,265]

The dentoalveolar effects of the Herbst appliance included distal movement of the upper dentition and anterior movement of the lower dentition. Class II molar correction came mainly from maxillary molar distalisation and mandibular molar mesialisation, whereas the majority of overjet correction was obtained by proclination of lower incisors. Pancherz[105] reported that 57% of molar correction and 44% of overjet correction were dentoalveolar origin. Franchi *et al.*[270] showed a lower dentoalveolar component, accounting for one-third of the overjet reduction, with the acrylic-splint Herbst. However, posttreatment relapse generally occurred in the dentoalveolar component, as well as with catch-up growth of the maxilla.[271-274] One year post-treatment results showed that the dentoalveolar effect in the aforementioned study by Franchi *et al*.[270] had relapsed in 53.3% of cases, all of which were from the lower incisor. The molar correction was relapsed in 82.5% of cases, mainly due to mesial movement of the upper molar.

There seems to be a gender difference in terms of Herbst treatment. A retrospective study conducted by Manfredi *et al*.[275] investigated the treatment effect of the Herbst appliance in growing children, taking into consideration the normal growth effect in an untreated norm group of European descent (Bhatia-Leighton standard). The study showed that male subjects exhibited remarkable mandibular forward repositioning without altering the gonial angle, as expressed in the ANB and Xi-CF-PTV (Xilion to Centre Facial to Pterygoid true vertical plane

angle) angles. On the other hand, female subjects showed a significant increase in mandibular ramal height and a significant reduction in ANB.

A systematic review by Yang *et al*.[276] reviewed 12 clinical controlled trials (CCTs) that investigated the effectiveness of the Herbst appliance for Class II correction. The meta-analysis discovered a significant increase in SNB (pooled MD = 1.06°, 95% CI: 0.53°, 1.60°), decrease in SNA (pooled MD = -0.56°, 95% CI: -0.99°, -0.14°) and ANB (pooled MD = -1.08°, 95% CI: -2.16°, -0.00°) which indicated anterior mandibular movement and restriction of maxillary anterior growth. There was also a significant increase in Pg/OLp (pooled MD = 1.45 mm, 95% CI: 0.43 mm, 2.47 mm) and Co-Gn (pooled MD = 1.76 mm, 95% CI: 1.27 mm, 2.26 mm), which signified mandibular growth in length and condylar growth. Additionally, there was an insignificant change in the mandibular plane angle, which could be beneficial for patients with vertical growth tendencies. However, authors warned that the results of this review should be interpreted with caution due to the substantial heterogeneity for measurements such as SNA, SNB and ANB. Furthermore, some studies reviewed did not include an untreated control group and functional appliance treatment was performed during the peak growth velocity. Therefore, the increase in mandibular length could partly be due to normal growth and development. Nevertheless, the Herbst appliance was effective in reducing the OJ, OB, and molar discrepancy, likely due to both skeletal and largely dentoalveolar changes, with minimal vertical variations.

The types of Herbst design underwent subgroup analysis, which revealed differing effects. The banded Herbst had significant changes in SNA, SNB and Pg/OLp. Splinted Herbst had substantial changes in SNA, ANB, OB, and A-point to occlusal plane perpendicular (OLp). As for crowned Herbst, a significant change was detected in Pg/OLp. Other factors that

significantly affected the effectiveness included treatment duration, as measured by Pg/OLp and molar relationship. Publication bias was detected in measurements of SNA, mandibular plane angle, and A point to OLp.

A systematic review was dedicated solely to crown or banded Herbst, which only included studies with a Class II malocclusion and a nontreated control group. Out of the original 80 articles searched, Barnett *et al*.[277] culled based on strict criteria and obtained three prospective clinical trials to base this review on. Due to the heterogeneity of the methodology, a meta-analysis could not be performed using the received data. This review concluded that there were both skeletal and dentoalveolar effects associated with the crown or banded Herbst appliance. There was minimal maxillary effect and significant mandibular change of approximately 2-3 mm. However, the type of mandibular change was not clear, and it could be attributed to either mandibular posturing or mandibular lengthening. The dentoalveolar changes included maxillary incisal retroclination and a significant mandibular incisal proclination. The maxillary molar displayed statistically significant intrusion, albeit in small quantity, accompanied by distalisation. In contrast, the mandibular molar moved anteriorly with extrusion. The intrusion of the maxillary molar could be responsible for this extrusion.

A similar review, carried out by Flores-Mir *et al*.,[278] focused on the effect of acrylic-splint Herbst appliances, which also included three studies in the final analysis. The result showed significant changes in posterior facial height, LAFH, maxillary sagittal position, maxillary first molar position and increased mandibular dimensions. Similar to the crown or banded Herbst, there was significant proclination of the lower incisors. In contrast, the vertical skeletal dimensions associated with acrylic-splint Herbst were different from those of crown or banded

Herbst, most likely due to the presence of an interocclusal acrylic layer. Long-term studies have been recommended to investigate whether this change is temporary or long-lasting.

In recent years, 3D imaging has become more readily available with the introduction of low-radiation cone beam computed tomography (CBCT). The advantage of 3D imaging is that blurred, overlapped structures in a 2D lateral cephalogram, such as the mandibular condyle, can be visualised with clarity in the 3D reconstructed image, as it allows for sectioning and rotation. One study assessed the mandibular skeletal effects following Herbst appliance therapy by utilising the geometric morphometric technique with CBCT images.[279] There were approximately 1.5-2 mm greater condylar changes and 0.5 mm greater pogonion changes that occurred during Herbst treatment. This effect was stabilised even after the fixed appliance therapy that followed the Herbst treatment. Taking into consideration of the untreated control growth, 40-50% of patients exceeded condylar growth by more than 1.5 mm, and 85-100% of patients showed significant condylar change of more than 0.5 mm; however, the changes at the pogonion were not different.

2.6.5.2.3.3 Herbst and TMD

Herbst appliance therapy has been documented to be associated with TMD, with conflicting views. Some studies have reported an increased incidence of TMD following Herbst treatment, while others have found no association or even shown improvement in TMD.[280-283] The mandibular protrusion from the Herbst appliance altered the jaw joint by stretching the disc and tensing the surrounding muscles, which could lead to joint inflammation, muscle strain, and instability. The TMD symptoms Herbst patient reported included pain in the TMJ, muscle pain and limited jaw movement. A recent meta-analysis found no difference in TMD

prevalence between patients before and after Herbst therapy.[284] This meant that Herbst is not a factor that can cause or exacerbate TMD symptoms.

2.6.5.2.3.4 Mode of Activation

Stepwise mandibular advancement involved activating the device in small increments, or bite jumping, meaning activating the device to the ideal bite position from the start of treatment. Some studies suggest that stepwise mandibular advancement has advantages in producing skeletal effects or enhancing condylar growth, with the least side effects, particularly in lower incisor proclination.[124,285-287] It was also reported that oral muscular adaptation was better with incremental advancement, resulting in more favourable long-term stability.[288] Additionally, due to the smaller activation, the occurrence of appliance breakages was less compared to one-step bite jumping.[289]

Extensive animal studies have been conducted by the team at the University of Hong Kong regarding stepwise mandibular advancement. The initial advancement was found to be crucial, as more favourable bone formation was observed with 4 mm initial advancement compared to 2 mm initial advancement.[178] The team found that the 4 mm activation significantly increased the production of Type II collagen, the main component of cartilage in the mandibular condyle.[124,178] The subsequent incremental activation produced more replicating cells in the condyle and the glenoid fossa. A 2 mm bi-monthly activation was suggested to be the optimal activation in maximising the replicating cells.[130,290,291] Additionally, Hägg *et al*.[292] reported greater condylar growth adaptation with stepwise advancement when compared with bite jumping advancement.

To investigate whether stepwise mandibular advancement has a more significant skeletal effect than bite-jumping advancement in a clinical setting, Knosel *et al.*[293] conducted a systematic review and meta-analysis of previously published literature. There was indeed a statistically significant advantage in parameters such as ANB (pooled MD = -0.95°, 95% CI: -1.80°, -0.10°, I^2=72%) and SNB (pooled MD = 0.20°, 95% CI: -0.47°, -1.00°, I^2=38%), meaning more mandibular improvement. However, the evidence was considered low, and the difference was not considered clinically significant. There was also evidence that stepwise advancement produced less undesirable lower incisor proclination (pooled MD = -1.59°, 95% CI: -3.98°, 0.80°, I^2=0%). Upon closer inspection of the data obtained for this, only two studies were included, and both have a polarised view. Aras *et al*.[285] found no difference in the L1-MP angle, and Amuk *et al*.[294] found less proclination with bite jumping compared to incremental advancement. This discrepancy could be attributed to the skeletal maturity difference between the two studies, as well as the design of the Herbst appliance. In Amuk *et al*.,[294] the subjects were composed of late adolescents and young adults, whereas pre-pubertal and peak pubertal patients were recruited in the Aras *et al*.[285] study. Aras *et al*.[285] showed a picture of the Herbst design, and the lower lingual bar was designed away from the lower incisors, indicating less pressure on the lower anterior teeth.

2.6.5.2.3.5 Treatment Effect Comparison between Herbst and Other Functional Appliances

2.6.5.2.3.5.1 Herbst vs Frankel

Although there was a statistically significant difference in midface length between Herbst and FR-2, the magnitude difference was not considered clinically significant (about 0.5 mm). Significantly greater distal and superior movements of the upper incisors were evident in Herbst when compared with FR-2. Additionally, the lower molars and incisors moved more

mesially with the Herbst appliance than with the FR-2 and control groups. Due to the proclination of lower incisors, the incisors were more intruded in the Herbst group. Conversely, the lower molars extruded more in the FR-2 group than in the Herbst and control groups. In terms of skeletal changes, the mandibular length increased significantly more with both appliance groups than with the control group. There was more vertical facial development in the FR-2 group compared to the Herbst and control groups. Based on these results, McNamara *et al*.[267] concluded that Herbst, being a tooth-borne appliance, created a more dentoalveolar effect than the tissue-borne appliance FR-2. Both appliances produced similar skeletal effects.

2.6.5.2.3.5.2 Herbst vs TB

Many studies have been conducted to investigate whether TB is better than Herbst and vice versa. However, no consensus was found. Schaefer *et al*.[295] claimed TB was better at correcting molar relationships and sagittal maxillomandibular discrepancies. O'Brien *et al*.[146] considered Herbst as a treatment alternative to TB due to the high compliance level. Baysal and Uysal[231] compared the TB and Herbst appliances with a control group and found that both appliances were effective in correcting Class II malocclusions. In this study, TB produced more skeletal effects (70% for overjet correction and 71.5% for molar correction), primarily due to mandibular lengthening. On the other hand, overjet and molar correction with the Herbst appliance were largely dentoalveolar (70.9% for overjet correction and 63.3% for molar correction). This was considerably more than previously reported by Pancherz of 47% for overjet correction and 54% for molar correction. This could be due to the design of the research study, where Baysal and Uysa[231] gave subjects removable appliances for both groups (a monoblock for Herbst and a modified Hawley with an anterior inclined plane) to wear for an additional 4-6 months. In the Herbst group, the monoblock was trimmed to allow for occlusal settling. The final radiographs were taken when good cuspal interdigitation was achieved.

Therefore, additional tooth movement would have occurred during the settling time, contributing to the differing results from other studies. Baysal and Uysal[200] also analysed the soft tissue changes in the same subjects and found that both TB and Herbst significantly improved soft tissue convexity and H angle. There was a significant reduction in the mentolabial angle with the TB group compared to the Herbst and Control groups. The soft tissue changes in the lower lip and pogonion were more pronounced in the TB group when compared with the Herbst group, which correlated with the skeletal changes.

The latest RCT that compared Hanks telescoping Herbst (HTH) and TB showed that the former has more efficient and predictable overjet reduction than TB, but requires more routine and emergency visits.[296] In addition, there was a greater likelihood of treatment discontinuation and deterioration in OHRQoL with TB. This reiterated the findings from a previous multicentre RCT in the United Kingdom by O'Brien *et al*.,[146] in which patients who had TB reported changes in speech and sleep patterns and felt embarrassed about their appliance, and it influenced their relationship with family. In this trial, there were no differences in the skeletal effects of treatment between the two appliances; however, HTH exhibited greater mandibular molar advancement and mandibular incisor protrusion than TB.

In a recent meta-analysis that compared the skeletal and dentoalveolar effect of TB with Herbst showed statistically significant greater increase in mandibular body length (Go-Gn) (pooled MD = 1.44 mm, 95% CI: 0.93 mm, 1.96 mm $p<0.001$ $I^2=0.0\%$), but more lower incisor proclination (pooled MD = 2.64°, 95% CI: 2.09°, 3.19° $p<0.001$ $I^2=0.0\%$) and extrusion (pooled MD = 0.76 mm, 95% CI: 0.22 mm, 1.31 mm $p=0.006$ $I^2=0.0\%$) and less facial convexity change (pooled MD = -1.89°, 95% CI: -3.12°, -0.66° $p=0.003$ $I^2=0.0\%$) with Herbst. On the other hand, TB had more increased in posterior facial height, Sella to Gonion (S-Go) reduction

(pooled MD = -1.23 mm, 95% CI: -2.08 mm, -0.38 mm p=0.005 I2=48.3%), and more retroclination of upper incisor inclination (pooled MD = 2.24°, 95% CI: 2.25°, 4.43° p<0.001 I^2=75.7%). Both appliances were considered effective in treating Class II malocclusion, and the differential effects allow clinicians to determine which appliance is better suited for each patient type.

Lastly, a systematic review by Cozza *et al.*[297] compared different types of functional appliances and found the Herbst appliance to be the most effective, followed by the TB appliance. However, the study claimed both appliances have their shortcomings.[146] TB being removable nature, patient compliance plays a huge role in treatment success. On the other hand, the Herbst appliance has been reported to have a high rate of breakages, which require additional appointments and clinical chair time for repairs.

2.6.5.3 Skeletal Anchored Functional Appliances

Conflicting results have been deduced from previous studies on the enhancement of skeletal outcome with the use of skeletal anchored functional appliances, with some showing promising results[298,299] and others disproving this effect.[300,301] A systematic review by Elkordy *et al.*[302] showed no statistically significant differences in skeletal effect between skeletal-anchored functional appliances and conventional functional appliances. However, there was statically significant reduction of upper incisor (pooled MD = -1.43°, 95% CI: -2.59°, -0.27°; P<0.02; I^2=88%) and lower incisor (pooled MD = -1.04°, 95% CI: -1.57°, -0.51°; P<0.0001; I^2=20%) proclination. Remarkably, miniplate anchorage appeared to produce more skeletal effects compared to miniscrew-supported functional appliances. One reason could be that indirect anchorage was used with miniscrews, and direct anchorage was used with miniplates.

2.6.5.3.1 Miniplates with Forsus FRD

The most common unwanted effects of functional appliance therapy are excessive proclination of the lower incisors. Therefore, several authors have suggested the use of skeletal anchorage (miniplates or miniscrews) in the mandible, aiming to induce a more significant skeletal effect with minimal proclination of the lower incisors.[300,303] Unal *et al*.[304] used Forsus FRD in combination with skeletal miniplates that were inserted in the mandibular symphysis during the peak of pubertal growth. There was significant improvement in skeletal structures with maxillary restriction and mandibular protraction. The overjet correction was approximately 74% skeletal component. Unlike other functional appliance therapies, there was significant retroclination of both upper and lower incisors (-10.86±4.57º and -4.23±2.40º, respectively). This was substantially greater than the aforementioned systematic review by Elkordy *et al*.[302] The greater retroclination of the upper incisors could be due to the distalisation of the upper dentition being pitted against the skeletal miniplates. The retroclination of the lower incisor could be due to the trapping effect of retruded upper incisors and the lower lip pressure. The facial convexity has increased, accompanied by an increase in SN-MP, anterior facial height, and posterior facial height. In addition, there was a high success rate of the miniplates (91.5%). Unfortunately, a control group was not used in this study; therefore, it did not negate the growth changes.

2.6.5.3.2 Herbst & TADs

Speaking specifically for skeletal anchored Herbst, Al-Dboush *et al*.[305] showed through their systematic review that there was minimal anchorage loss and enhanced skeletal effects. However, the evidence was considered to have a very low level of confidence. The studies included in this review had variable appliance designs and numbers of miniscrews placed. Nevertheless, the meta-analysis showed statistically significant reduction of mandibular incisor

inclination (pooled MD = -5.49°, 95% CI: -7.36°, -3.63°; P<0.001; I^2=23%) and less molar distalisation (pooled MD = 1.50°, 95% CI: 0.64°, 2.36 °; P<0.0006; I^2=0%) when compared to matched control treated with acrylic splint Herbst. In terms of skeletal effect, mandibular bone base length was longer with TAD supported Herbst (pooled MD = 2.22 mm, 95% CI: 0.02 mm, 3.61 mm; P<0.002; I^2=40%) leading to a decrease in maxillomandibular discrepancy (pooled MD = -2.02°, 95% CI: -3.32°, -0.73°; P<0.002; I^2=53%) when compared with Herbst alone.

2.6.5.3.3 Skeletal anchorage mandibular advancement appliance (aka bi-maxillary skeletal anchorage devices (BMSADs)

In recent years, there has been a growing popularity in incorporating skeletal anchorage with functional appliances or intermaxillary elastics, which aim to minimise dental side effects and optimise skeletal correction as forces are focused directly on the bone. A systematic review by Alhammadi *et al*.,[306] which included four studies, showed that all sagittal skeletal parameters improved favourably; however, the change was only statistically significant compared to the untreated control groups, but not statistically significant compared to the treated control groups. This meant that BMSADs produced similar results to conventional functional appliances. In terms of vertical skeletal relation, only Al-Dumaini *et al*.[307] showed a statistically significantly greater counterclockwise mandibular rotation (2.25±0.95°) in the study group compared to the untreated control group. In terms of dentoalveolar changes, Al-Dumaini et al.[307] showed statistically significant retroclination of the upper incisors (-1.15±0.94°) compared to the untreated control, whereas Ozbilek *et al*.[308] showed statistically significant proclination (4.60±2.40°) than the treated control (-2.33±1.87°). Intermaxillary elastics were used in conjunction with the skeletal plates, and the treated controls were treated with a monoblock. Statistically significant retroclination of lower incisors was found in two studies using intermaxillary elastics compared with comparative and untreated control groups. There was a

statistically significant proclination in one study compared with the untreated control group. In terms of OJ, there was no statistically significant reduction in the two studies that were compared with their respective treated control groups. These inconclusive results suggest the need for further RCTs to establish the effectiveness of adding skeletal anchorage to functional appliances.

Regarding facial soft tissue changes with skeletally anchored Herbst, Brandão *et al*.[309] performed an RCT that compared the facial soft tissue changes in adolescents treated with TB, Herbst and skeletally anchored Herbst. There was no statistically significant difference among the three appliances tested. Skeletally anchored Herbst showed significant anterior movement in the lower lip and sulcus inferioris relative to the vertical reference line and substantial reductions in H angle and upper lip to the E plane during treatment.

2.6.6 Stability of Functional Appliance

Several factors, including occlusion, soft tissue and muscle forces, and craniofacial growth with aging, may influence the outcome of a functional appliance. Typically, functional appliance therapy followed by fixed orthodontic treatment can improve the stability of orthopaedic correction, as a stable occlusion with good interdigitation is likely to preserve the corrected Class I occlusion. A literature review by Moro *et al*.[263] outlined that long-term skeletal corrections seem to be stable with functional appliance therapy. There appeared to be some relapse in Class II molars and OJ due to a combination of tooth movement and unfavourable post-treatment maxillomandibular growth patterns, especially in cases with poor interdigitated occlusion.

Bock *et al*.[310] performed a systematic review and meta-analysis on the stability of Class II fixed functional appliance therapy and realised that all but one eligible study was associated with the use of a Herbst appliance. Meta-analysis discovered post-treatment relapse in the following parameters: ANB (0.2 mm, 12.4% relapse), Wits appraisal (0.5 mm, 19.5% relapse), molar relationship (1.2 mm, 21.8% relapse), soft tissue profile convexity excluding nose (<0.1°, 1.0% relapse), OJ (1.8 mm, 26.2% relapse) and OB (1.4 mm, 44.7% relapse). Although the degree of relapse was statistically significant for some parameters, it was deemed clinically insignificant. Therefore, the Herbst appliance produces relatively good dentoskeletal stability.

Jacobsone *et al.*[311] investigated the treatment changes using a crown Herbst appliance and followed up one year after treatment via a prospective clinical study. Unlike some long-term studies of functional appliances, the subjects in this study, who were reviewed at a one-year follow-up, did not have fixed appliances. Therefore, the results reflected the sole effect of the Herbst appliance. During the active phase of treatment, skeletal changes occurred, including an increase in mandibular length, a decrease in the ANB angle, and restriction of vertical growth of the posterior maxilla. The dentoalveolar changes were distal tipping and movement of maxillary molars, proclination of the lower incisors and retroclination of upper incisors. At the end of the follow-up period, there was a marked rebound of dentoalveolar changes such as incisor uprighting, leading to the reoccurrence of OJ and OB. The upper molar was also uprighted, but the lower jaw has moved forward to maintain the Class I buccal relationship. Interestingly, this study excluded 21 patients who had relapse after initial treatment and only subjects who remained in stable Class I occlusion were analysed. This could be responsible for the lack of skeletal changes reported in this paper. Nevertheless, the skeletal component of molar correction increased from 27% during treatment to 34% throughout the treatment and retention period. This was very similar to many previous studies.

TB appliance therapy also seemed to have an acceptable level of stability. Oliver *et al*.[312] evaluated the stability of TB appliance therapy followed by fixed appliances 12 months post-treatment. The study discovered a relapse of 0.67 mm and 0.06 mm in the OJ and molar relationships, respectively. The magnitude of relapse is negligible in clinical significance. Interestingly, there was weak evidence that the treatment-induced change in OJ was linked with OJ relapse. This seems quite logical, as the further the tooth moves, the more susceptible it is to relapse.

3.0 AIRWAY

3.1 Pharynx (Upper Airway)

The pharynx is a muscular organ that performs the essential functions of breathing, swallowing, and speech.[313] It is a pliable tubular structure that is demarcated from the base of the skull to the level of the cricoid cartilage, which then extends continuously with the cervical oesophagus. The wall of the pharynx consists of five layers: mucosa, submucosa, pharyngobasilar fascia, muscles, and buccopharyngeal fascia.[314] All of these are soft tissue, which makes the pharynx a highly collapsible tube that enables the unique function of both breathing and swallowing. There are two types of muscles found in the pharynx, longitudinal and circular, which are respectively in charge of elevation of the larynx and propulsion of the food bolus inferiorly during swallowing. The muscles and fascia of the pharynx are inserted to the surrounding bones and cartilages, including the medial pterygoid plates, the hyoid bone, the thyroid cartilage, and the cricoid cartilage. The pharynx is partitioned into three sections according to the anatomical level: nasopharynx, oropharynx and the hypopharynx.

The nasopharynx is the superior section responsible for respiratory function. The nasopharynx communicates anteriorly with the nasal cavity via the choanae. It extends craniocaudally from the cranial base to the level of the hard palate just superior to the soft palate. The nasopharynx contains the entrance to the Eustachian tube, which leads to the middle ear. Adenoids or pharyngeal tonsils are lymphoid tissue that can be found on the roof and posterior wall of the nasopharynx, forming the Waldeyer's ring.[315,316] Enlargement of adenoids is more common in young children as adenoid tissues tend to regress after puberty.[313,317] The increased size of adenoids and tonsils can contribute to the constriction of the nasopharynx, leading to breathing problems and potentially obstructive sleep apnoea (OSA).

The oropharynx is the middle section of the pharynx that allows the passage of both air and food. It extends superiorly from the junction of the soft and hard palate and inferiorly to the level of the hyoid bone and epiglottis, usually around the 3rd cervical vertebra. Typically, the oropharynx has an elliptical cross-sectional shape, wider at the transverse dimension.[318] The position of the surrounding anatomical structures, such as the tongue and mandible, can impact the patency of the oropharynx. Similarly to the nasopharynx, there are tonsillar tissues that can be found in multiple sites throughout the oropharynx, namely at the base of the tongue and at the posterior tonsillar fossae. The oropharyngeal wall thickness can be influenced by the body mass index (BMI), age and gender. Obese individuals are found to have significantly thicker walls than non-obese patients.[319] Additionally, the wall thickness tends to decrease above the age of 60 years, and thicker walls are typically found in men compared to women.

The hypopharynx, the inferior section of the pharynx, serves as a crucial connection between the larynx and the oesophagus, functioning as a passageway for both food and air. It journeys from the level of the hyoid bone to the oesophagus at the level of the lower border of the cricoid cartilage and the 6th cervical vertebra.[313,320] There is a gender-related difference in the transverse diameter of the hypopharynx, with males displaying a wider tube than females, possibly due to the larger size of the thyroid cartilage in men.[321] The hypopharynx has three subsections: pyriform sinuses, posterior hypopharyngeal wall and post-cricoid region. The pyriform sinuses are pear-shaped recesses that are responsible for speech production, and the other sections assist in making food its way down to the oesophagus.

3.2 Growth and Airway

Longitudinal studies of Chinese children demonstrated that the transverse dimension growth spurt of the nasopharynx occurred between 8 and 10 years of age. In contrast, the peak growth of the sagittal dimension of the nasopharynx took place between 12 and 13 years of age.[322] The pharyngeal airway growth will continue at a slower pace well into adulthood.[323,324] In earlier studies, a restriction in the nasopharyngeal area was observed during the pre- and early school years due to adenoid hypertrophy, followed by an increase in the nasopharyngeal airway during pre- and early adolescence due to adenoid involution.[323,324] Jean *et al.*[324] have shown a steady rise in nasopharynx dimension with age, and from 13 years old onwards, males exhibited significantly larger airway dimensions than females. This concurred with a retrospective MRI study that described a steady growth of nasopharyngeal and oropharyngeal width from age one to eleven years.[325] In addition, Preston *et al.*[326] found a gender difference in the growth pattern of the bony nasopharynx, with growth velocity slowed two years earlier in girls (12 years old) than in boys (14 years old). In contrast, AlKawari *et al.*[327] found no difference in airway dimension between subjects less than 16 years of age and more than 16 years of age. However, results should be interpreted with caution, as there was no specification on the age range for subjects under 16 years old, and from previous understandings, it is known that peak growth occurs around 12-13 years old.

3.3 Sleep Disordered Breathing (SDB)

Deformation of the pharyngeal airway can cause disturbed breathing function, which commonly occurs during sleep due to postural changes and relaxation of the dilator muscles of the pharynx. Miyamoto *et al.*[328] investigated the mandibular posture during different phases of sleep in healthy adults. The results showed the mandible opened progressively with the

depth of non-rapid eye movement (NREM) sleep stage and was even wider in rapid eye movement (REM) sleep. The mouth opening could predispose an individual to SDB as inferior-posterior movement of the mandible and the tongue would reduce the pharyngeal diameter and create resistance to the airway.[329,330] Interestingly, Miyamoto *et al*.[328] found no difference in mouth opening between supine sleep and lateral recumbent position.

Sleep disordered breathing (SDB) encompasses a broad range of sleep-related conditions characterised by increased upper airway resistance, loud snoring, significant reduction in airflow (hypopnoea), and complete cessation of airflow (apnoea).[331] Aetiologies for SDB include OSAS, central sleep apnoea, sleep-related hypoventilation and sleep-related hypoxemia disorder.[332]

3.3.1 Obstructive Sleep Apnoea Syndrome

Obstructive Sleep Apnoea Syndrome (OSAS) is one of the most common sleep-related breathing disorders (SBDs), characterised by repeated episodes of partial or complete upper airway obstruction during sleep. It affects between 2% and 4% of the adult population[333] and 1.0% and 2.2% of children.[334-337] The predisposing factors included obesity, especially in the cervical area,[338] increasing age, male sex and anatomical abnormalities of the craniofacial region and upper airway.[339] Retrognathia, leading to the narrowing of the pharyngeal airway space and collapse of the airway during respiration due to reduced muscle tone while sleeping, is a central pathogenesis of OSAS.[340] On the other hand, the most common aetiology of OSAS in children is adenotonsillar hypertrophy.[341,342]

OSAS symptoms expressed by children are similar but different from those of adults; both populations exhibit snoring, daytime fatigue and sleepiness, and a lack of concentration.[333]

Children also tend to display nocturnal enuresis, irritability and other behavioural and neurocognitive changes.[343,344] These changes often manifest as poor academic performance and social adjustment problems.[345]

Undiagnosed or untreated OSAS could lead to substantial harmful health consequences. Short-term effects include the development of intermittent hypoxia, unstable blood pressure, irregular heart rhythm, and increased intrathoracic pressure.[346] These acute problems can manifest into long-term sequelae such as hypertension and cardiovascular morbidities,[346] a decrease in mood,[347] cognitive function[348] and quality of life and ultimately premature death.[349]

3.3.2 Diagnostic Procedures for OSAS

There are many techniques used to diagnose OSAS. The Berlin questionnaire, which asks patients about various risk factors for OSAS, is currently the most widely used tool for identifying this condition.[350] There are also other questionnaires that serve as a diagnostic tool to determine if further testing is required. These include the Sleep Disturbance Scale for Children (SDSC)[351] and the Epworth Sleepiness Scale,[352] which is designed for adult patients. Recently, smartphone applications have also been launched for the screening of OSAS.[353,354]

Polysomnography (PSG) is a gold-standard diagnostic tool that monitors neurological and cardiorespiratory parameters using sensors, allowing it to detect interruptions in ventilation and arousals caused by airway obstruction.[355] It comprises an assessment of the electroencephalogram, electrocardiogram, electrooculogram, airflow, chin electromyogram, oxygen saturation, and heart rate. Due to the high cost and inconvenience of this test for patients, alternative screening methods have been developed. Portable PSG has proven to be

an effective and more affordable initial screening option for OSAS, offering greater convenience for patients.[356]

One of the measured outcomes from PSG is Apnoea Hypopnoea Index (AHI). AHI is used to assess the severity of OSAS. The index measures the average number of apnoea and hyponoea episodes lasting longer than 10 seconds per hour of sleep.[357] Apnoeas are defined as a greater than 90% drop in the airflow (thermal sensor signal) in the presence of continued respiratory effort lasting at least 10 seconds.[357] Hyponoea is defined as a 30% or greater drop in the nasal pressure signal lasting for at least 10 seconds, associated with arousal or 4% or greater oxygen desaturation. Patients with an AHI of 5 or more are diagnosed with OSAS. The American Academy of Sleep Medicine classifies the severity of OSA as mild (AHI = 5-15), moderate (AHI = 16-30), and severe (AHI > 30).[333]

3.4 Upper Airway Image Assessment

Although PSG is the standard diagnostic test for OSAS, the precise location of the obstruction affecting airflow cannot be detected by this investigation. Nasopharyngoscopy is a valuable tool for assessing the level, degree, and shape of upper airway obstruction and can be easily performed in awake subjects.[358] Imaging modalities such as x-ray cephalometry, videofluoroscopy, computed tomography (CT) scanning and MRI have been used to detect the obstruction site and other structural abnormalities.[359] Recently, dynamic imaging modalities such as cine MRI, CBCT, and functional imaging have also been introduced for upper airway analysis.[359-361]

CBCT provides a 3D assessment of the upper airway with high spatial resolution, clearly defining the soft tissues and airway space.[362,363] This has become a more widely used imaging technique because the radiation exposure is significantly lower and less costly than that of conventional CT. Yamashina *et al*.[364] reported that air space measurements on CBCT were reasonably accurate when compared with multidetector computed tomography (MDCT). In addition, unlike cephalometric radiography, which provides linear and angular measurements, CBCT eliminates the overlap of structure in 2D radiography and provides 3D imagery that allows volumetric calculation of the airway space. Each sliced image is stored as Digital Imaging and Communications in Medicine (DICOM) files, which can be used with various software for reconstruction, visualisation, and analysis.

Numerous studies have been conducted to compare CBCT with other techniques for assessing the airway. For example, Tsolakis *et al.*[365] compared CBCT with acoustic reflection in calculating airway volumes and the minimal cross-sectional area. The results showed no differences in determining the minimal cross-sectional (MCA) pharyngeal area between the two methods, and there was also a high correlation in pharyngeal volume between CBCT and acoustic reflection.

There are some shortcomings regarding the use of CBCT for airway assessment. Some CBCT scans are taken with a machine that allows patients to sit down, and the head position can be controlled with a chin cup and head support. However, SBD, as the name suggests, occurs while the patient is sleeping in supine position. Therefore, airway images obtained with this type of machine do not accurately depict the airway during sleep. In addition, the gravitational effect of soft tissues in the airway, such as the soft palate, epiglottis and oesophagus, differs in supine and sitting positions.[366] In fact, a study by Camacho *et al*.[367] found a reduction in airway

obstruction from 32.3% to 75.9% in OSA patients when they are in the supine position compared with when they are in the upright position. This problem can be surmounted, as there are CBCT machines that can capture images while the patient is in a supine position. However, the head position cannot be standardised with this type of machine because patient can easily over- or under-extend or rotate their head on the head cushion. Muto *et al*.[368] have shown that the head posture (cranio-cervical inclination) can influence the pharyngeal airway space. A change of 10^{o} in cranio-cervical inclination could result in a 4 mm change in the posterior airway space. Apart from head posture, respiration and tongue position can also produce image distortion.[369] Therefore, meticulous instructions are required when taking images of the airway during supine CBCT. To obtain optimal CBCT quality, Scarfe and Farman[370] suggested asking the patient to remain still, avoid swallowing, and hold their breath during the scan.

3.4.1 Two-Dimensional vs Three-Dimensional Imaging

There are conflicting views on the association between 2D and 3D measurements during airway assessment. Martins *et al*.[371] analysed 250 CBCTs to investigate the correlation between 2D linear and spatial data and 3D volumetric measurements using the Dolphin imaging program. The study found a positive correlation in the sagittal areas of the nasopharynx and oropharynx, with their respective volumes (Pearson coefficients of 0.734 to 0.893), and the most constricted area in the oropharynx was associated with the oropharynx volume (Pearson coefficients of 0.899 for males and 0.811 for females). This contradicts Lenza *et al*.,[362] who showed a weak correlation between most of the 2D and 3D measurements and concluded that single linear measurements did not accurately depict the morphology of the airway, suggesting that 3D analysis would be a more effective method for assisting airway diagnosis.

3.4.2 Computer Software for Airway Analysis

Currently, several computer software programs are available to analyse airway dimension. The process of software analysis involves 3D reconstruction from volumetric data obtained from CBCT, followed by segmentation of the airway, which can be performed either manually or semi-automatically. The manual approach is rather time-consuming because segmentation is performed by an operator identifying the airway on each and every slice of the CBCT image, and the software then combines all slices to form a 3D volume. On the other hand, the semi-automatic approach is much faster and clinically practical because the computer utilises the differences in density values, also known as grey levels or thresholds, to delineate the airway and the surrounding soft tissues. The manual method is deemed more accurate when analysing the tortuous anatomy of the airway, as the semi-automated segmentation does not delineate the airway slice by slice, and the measurement is subject to the threshold chosen.

Density values or grey levels are measured in Hounsfield units (HU). In terms of grey levels, the operator can use either a fixed threshold protocol, which involves a single threshold for all patients, or an interactive threshold protocol, where the operator selects different thresholds for each patient's image. The advantage of having a fixed threshold is reproducibility. A few studies have investigated the most accurate threshold value for airway volume quantification, with variable results ranging from 25HU to 73HU. This wide variation was mainly due to the difference in the airway model used and the CBCT scan protocol.

Recently, Dolphin Imaging introduced a semi-automatic airway segmentation function that enables fast computations of airway volume and minimal airway cross-sectional area. The volume of the airway can be calculated by planting seed points in the airway image, choosing

the appropriate density values and with a single press of a button, the information on the airway volume and MCA will be available. It also provides a volume colour map that shows the volume at each level of the pharynx. The use of Artificial Intelligence (AI) in dentistry has taken off in recent years. Fully automated segmentation, which relies on the application of AI, has been invented and could potentially replace manual and semi-automated systems in the future. However, at the present moment, AI relies on sophisticated computer and software equipment, which is not practical in the current clinical setting. The semi-automatic method is currently the most efficient tool.

3.4.3 Accuracy, Reliability and Reproducibility of Information

A systematic review published by Guijarro-Martinez and Swennen[369] has revealed that 3D analysis of the upper airway with CBCT can be achieved accurately and reliably. Strikingly, the paper showed the availability of 18 different software systems for 3D volumetric analysis of the upper airway. One of the difficulties in this meta-analysis was the variation in anatomical demarcations of different airway sections and the thresholds used by research papers. (Table 1) As a result, authors encountered significant difficulties in comparing the volumetric analyses of the airways among papers.

Region	Limits
Nasal airway	***Anterior limit:*** ANS (frontal plane perpendicular to the FH plane passing through ANS) ***Posterior limit:*** PNS (frontal plane perpendicular to the FH plane passing through PNS)
Oral airway	***Anterior limit:*** Incisive canal and midline of the upper incisors ***Posterior limit:*** not reported
Nasopharynx	***Superior limit:*** * Last slice before fusion of the nasal septum with the posterior wall of the pharynx * Intersection of the line PNS-So (midpoint of the sella-basion line) and the posterior wall of

	the pharynx * Soft tissue contour of the posterior pharyngeal wall extending from the superior aspect of the pterygomaxillary fissure * Plane perpendicular to the plane through PNS at the height of the pterygomaxillary fissure * Highest point of the nasopharynx, coinciding with the posterior choanae * Posterior nasal plane (frontal plane perpendicular to the FH plane passing through PNS) ***Inferior limit:*** * Palatal plane (ANS-PNS) extended to the posterior wall of the pharynx * Plane including the PNS and the lower medial border of the 1st cervical vertebra * Plane including the PNS and basion * Plane parallel to the FH plane passing through PNS
Oropharynx	***Superior limit:*** inferior limit of the nasopharynx. ***Inferior limit:*** * Plane parallel to the palatal plane that passes through the most anteroinferior point of the 2nd cervical vertebra * Plane parallel to the FH plane that passes through the most anteroinferior point of the 2nd cervical vertebra * Horizontal line through the superior point of the epiglottis * Horizontal line through the base of the epiglottis * Plane tangent to the most caudal medial projection of the 3rd cervical vertebra perpendicular to the sagittal plane * Plane extending from the most anteroinferior point on the body of the 3rd cervical vertebra to the base of the epiglottis * Plane parallel to the FH plane passing through the superior margin of the epiglottis
Hypopharynx	***Superior limit:*** inferior limit of the oropharynx ***Inferior limit:*** Plane connecting the entrance to the oesophagus to the body of the hyoid bone and left and right greater horns of the hyoid

Table 1- Anatomical limits of the upper airway adopted from Guijarro-Martinez and Swennen[369] (FH: Frankfort horizontal, ANS: anterior nasal spine, PNS: posterior nasal spine)

Most of the research studies have shown that Dolphin imaging is highly reproducible and reliable.[372-375] However, in terms of accuracy, the literature shows bipolar evidence. This could

be due to the method or software that was used when investigating the differences. Some studies compared one imaging software against another using a human model, while others utilised a wax or acrylic airway model, in which the volume of the model can be manually measured and served as the gold standard. Consequently, some studies[376,377] found significant differences between Dolphin imaging and programs such as Mimics that utilised manual segmentation. However, according to Garcia-Uso *et al*.,[376] the results were statistically different but clinically insignificant.

Weissheimer *et al*.[373] compared the accuracy and reliability of six imaging software programs on images from growing patients and an acrylic oropharynx model, which serves as the gold standard. The six imaging software were Mimics (Materialise, Leuven, Belgium), ITK-Snap (www.itksnap.org), OsiriX (Pixmeo, Geneva, Switzerland), Dolphin3D (Dolphin Imaging & Management solutions, Chatsworth, California), InVivo Dental (Anatomage, San Jose, California) and Ondemand3D (CyberMed, Seoul, Korea). The studies demonstrated high reliability for all programs, with an error rate of less than 2% using Mimics, Dophin3D, OsiriX, and ITK-Snap under the interactive threshold protocol, when compared with the gold standard. The remaining two software programs, InVivo Dental and OnDemand3D, exhibited errors greater than 5%. On the other hand, when the fixed threshold protocol was used, the programs InVivo Dental, Mimics, Ondemand3D, OsiriX and ITK-Snap all underestimated the acrylic model volume by 11%. The results of this part of the study highlighted the importance of the interactive threshold protocol when calculating oropharynx volume using computer software, which reinforced the findings of Lenza *et al*.,[362] who found error generation when a single threshold value was used, particularly during volume analysis. However, the interactive threshold protocol relies on human vision to differentiate airway boundaries; therefore, the

accuracy and reliability of the results can be subject to factors such as lighting, fatigue, grayscale ability, and visual acuity.[378]

Furthermore, El and Palomo[375] compared three commercially available DICOM viewers (Dolphin3D, InVivo, and OnDemand3D) with a manual segmentation program called OrthoSegment. The results showed high reliability for all programs. The highest correlation was found between OrthoSegment and Dolphin3D for the oropharynx. The nasal passage volume was more variable due to its intricate anatomy. Although there was high reliability and correlation, the accuracy of the software was considered doubtful because a statistically significant difference was found in the volumetric measurement among software programs.

Additionally, Torres *et al*.[379] investigated the reliability and validity of software InVivo versus Dolphin 3D. The two systems showed statistically significant differences in locating the MCA in the nasopharynx and the volume of the oropharynx. The difference in localisation of the minimal area in a cross-section was due to the technique used in the software system. Dolphin 3D measures the minimal area in cross-section parallel to the axial slices, whereas Invivo measures the actual minimal area in a cross-section of the pharyngeal airway. Additionally, the Dolphin 3D system tended to overestimate airway volume measurements. This was also deduced in Lo Giudice *et al*.'s[377] investigation, in which five commercial software programs were compared against manual segmentation with Mimics. On the other hand, Invivo was found to underestimate the airway volume. Interestingly, there was a strong correlation between the software systems. The author suggested utilising these software systems in assessing volumetric changes between two timepoints.

3.5 Airway and Craniofacial Morphology

The relationship between airway obstruction and craniofacial patterns has been documented for more than a century, beginning with Angle[380] reported a narrow upper airway in children with a retruded mandible in 1907. This was followed by the vast research carried out by Linder-Aronson and the team on adenoids and craniofacial structure. Linder-Aronson[381] has found distinct facial features associated with adenoid problems and mouth breathing. The term "adenoid facies" was used to describe an individual who had a long history of mouth breathing, characterised by facial features such as a flattened nose, small and poorly developed nostrils, a mouth held open, a short upper lip, a voluminous and pouting lower lip, and a vacant facial expression. However, the question remains as to whether the craniofacial features are a result of an adenoid or breathing problem, or whether the deformed craniofacial features create an environment conducive to adenoid or breathing difficulties.

Studies have demonstrated an improvement in craniofacial morphology following successful treatment of the airway problem.[381-384] Guilleminault *et al*.[385] have extensively examined the effect of adenotonsillectomy on the airway. This study compared the outcomes of adeno-tonsillectomy followed by orthodontics with orthodontic treatment followed by adeno-tonsillectomy and revealed that both groups displayed improvement in AHI and respiratory disturbance index (RDI).

Numerous studies have demonstrated a significant influence of the maxillomandibular complex position, tongue volume, palatine and adenoid size on the size of the upper airway.[386] The majority of this evidence was reflected in OSAS studies. Most associated craniofacial abnormalities with OSAS are mandibular deficiency, maxillary hypoplasia, inferior position of

hyoid bone, a narrowed posterior air space, a greater flexion of the cranial base and elongation of soft palate.[387,388]

A meta-analysis conducted by Flores-Mir *et al*.[6] examined clinical studies on the craniofacial morphological characteristics of non-syndromic and untreated minors with OSAS. The results showed that cephalometric variables, such as the mandibular plane (MP) to sella nasion line (SN) angle (SN-MP), SNB, and ANB, were significantly different from those of the control groups in the normative growth centre data. This meant that patients with craniofacial morphology characterised by a retrusive chin, a steep mandibular plane, a vertical direction of growth, and a tendency towards Class II malocclusion were more prone to OSAS. However, the debate over whether the craniofacial factor is a result of OSAS or the cause of OSAS remains a mystery. Therefore, the craniofacial morphologies could serve as a "red flag" for OSAS.

Katyal *et al*.[389] assessed craniofacial and upper airway morphology in children with primary snoring and OSAS via a systematic review and found that OSAS subjects had an increased ANB due to a decreased SNB, which confirmed the findings of Flores-Mir *et al*.[6] However, the difference was only 1.64^{o} which was deemed to be marginally clinically significant. This study also shows a reduced sagittal width of the airway at the level of the posterior nasal spine and superiorly at the level of the adenoidal mass in patients with OSAS. The mandibular angle showed a trend towards hyperdivergence but with significant heterogeneity, indicating the inconclusiveness of this result.

Additionally, Neelapu *et al*.[390] performed a systematic review and meta-analysis of craniofacial and upper airway morphology in adult obstructive sleep apnoea (OSA) patients, which revealed

substantial evidence that adult OSA patients have a reduced pharyngeal airway space, an inferiorly placed hyoid bone, and increased anterior facial height. Authors also pointed out that the inferiorly placed hyoid bone could increase the chance of pharyngeal airway collapse.

A more recent systematic review by Finke *et al*.[5] had very similar results, indicating that mandibular retrusion and vertical growth directions were risk factors for OSAS. This study reviewed research on both children and adults, which differed from that of Flores-Mir *et al*.[6] This systematic review identified nine craniofacial measurements that may have a potential influence on patients with OSA compared to control groups. These were decreased nasion to sella to basion (NSBa) angle in males only, increased ANB angle, increased mandibular line to nasion to sella line (ML-NSL) angle, obtuse menton to gonion to articulare (Me-Go-Ar) angle, shorter SN distance, longer nasion to anterior nasal spine (N-ANS) distance, higher mandibular plane to hyoid bone (MP-H) distance, longer uvula length in adults and increased uvula thickness. Out of all nine factors, the MP-H, uvula length, and uvula thickness showed the highest relevance. Interestingly, this study also disclosed an increased BMI associated with OSAS, which reiterated that obesity is one of the risk factors for OSAS. The author concluded that craniofacial anomalies can be a risk factor or an indicator of OSAS, which could serve as a screening method for diagnosing OSAS.

3.6 Airway Changes with Orthodontic and Orthognathic Therapy

Evidence from the aforementioned systematic reviews has indicated that skeletal Class II malocclusion with mandibular deficiency and increased anterior facial height are considered risk factors for OSAS.[391] Treatment aimed at improving the skeletal Class II relationship, such as Class II functional therapy and mandibular surgery, may enhance airway patency and reduce

the risk of SBD. Conversely, orthognathic surgical treatment, such as maxillary impaction or mandibular setback, can potentially compromise the airway and should be carefully considered when treating patients who are at risk of SBD.

3.6.1 Extraction Treatment

Orthodontic treatment often involves the extraction of four premolars to improve the facial profile for bimaxillary protrusive patients. This could also be a treatment alternative in camouflaging the underlying skeletal discrepancy. Removal of teeth results in a reduction in arch length, which inevitably leads to encroachment of tongue space. Some research speculated that this could suppress the tongue and reduce the airway space. However, the debate persists due to the heterogeneity of the evaluation methodology, as highlighted in a systematic review by Hu *et al*.[392] This review suggested that extensive retraction of anterior teeth in adults could result in upper airway constriction. Conversely, mesial movement of the molar could potentially increase the posterior space for the tongue and increase the upper airway dimension.

Recently, a retrospective study by Fang *et al*.[393] evaluated the benefits of four premolar extractions in orthodontic treatment by examining airway changes on CBCT images with three sagittal skeletal relationships. Following extraction treatment, significant positive airway changes were found in Class I skeletal relationships, with an increased upper area of the oropharyngeal airway and an increased vertical distance of the pharyngeal airway. Similarly, the Class II skeletal relationship group showed improvement in the vertical distance of the pharyngeal airway. However, there was a significant decrease in airway space, especially the oropharyngeal minimal axial area, for the Class III skeletal treatment group. Therefore, when

planning for camouflage Class III treatment, serious consideration must be taken for extractions, especially in high-risk SBD patients.

In contrast, AlKawari *et al*.[327] assessed the airway sagittal dimension changes in Class II skeletal patients with upper first premolar extraction and in Class III skeletal patients with lower first premolar extraction, and found increased nasopharynx measurements in both groups. The authors concluded that a positive airway outcome was achieved with the removal of two premolars as a camouflage treatment, and this approach may be considered for Class III skeletal patients who require extraction.

3.6.2 Orthopaedic Treatment

The benefits of orthopaedic treatment on OSAS, especially in paediatric patients, have been widely documented. The most recent systematic review by Gorikapudi *et al*.[14] reported promising improvements in OSAS symptoms, such as AHI, nasal resistance, sleep parameters, and upper airway dimensions, in paediatric populations treated orthodontically and orthopaedically. The concept behind airway changes with Class II functional appliance therapy is based on the anterior movement of the mandible, which pulls the posterior soft tissue away from the airway through soft tissue adaptation, thereby increasing the volume or anteroposterior dimension of the airway. Early intervention may help to enlarge the airway and decrease the potential risk of OSAS in future.

3.6.2.1 Functional Appliance Therapy

Xiang *et al*.[15] conducted a systematic review on changes in airway dimensions following the use of functional appliances in growing skeletal Class II patients and revealed a significant

increase in oropharyngeal dimensions in the treatment group, with small heterogeneity among the analysed studies. However, none of the studies included in this analysis were RCTs, but they claimed to be well-designed and of high quality.

In 2009, Haskell *et al*.[394] utilised CBCT imaging to quantify the difference in upper respiratory airway dimensions and volume with and without a mandibular advancement device (MAD). The results revealed an average increase in oropharyngeal volume of approximately 2,800 mm^3 with the use of a MAD. It was later demonstrated in a systematic review by AlQahtani *et al*.[17] that orthopaedic functional appliances used in Class II skeletal malocclusion treatment have a positive impact on the volume of the oropharyngeal airway. In fact, this review demonstrated that removable appliance treatment resulted in a greater increase in oropharyngeal volume. This could be due to the age difference, in which removable appliances were generally used in younger children compared to fixed functional appliances, which were used when most deciduous teeth had been exfoliated. The highest amount of oropharyngeal volume increase was from MARA, followed by TB and Herbst. In the same year, Li *et al*.[13] published a systematic review on the same topic. They found that although functional appliances could increase airway volume and the MCA of the airway in growing Class II patients, the evidence was considered weak according to the GRADE system. There was also weak evidence that the anteroposterior position of the hyoid bone could be affected by functional appliances. The studies included in this review reported patients without airway problems or abnormalities. Therefore, this cannot be extrapolated to patients with OSAS. This weak evidence was also documented by Bidjan *et al*.,[395] in which the systematic review found lower quality of evidence due to methodological issues.

The latest systematic review, which appraised CBCT studies related to functional appliance treatment and the airway, documented a significant increase in upper airway volume following functional appliance therapy compared with untreated controls.[396] Most studies that were analysed also displayed a significant improvement in airway MCA. One study mentioned in the paper explained that the effect was due to the anterior repositioning of the mandible from a functional appliance, which led to forward rotation of the mandible and anterior positioning of the hyoid bone. As a result, the airway was enlarged. This was opposite to where the posterior positioning of the pogonion and the hyoid bone was found to be associated with OSAS symptoms.

When the success of Class II skeletal malocclusion treatment with a functional appliance was measured by the improvement of OSA parameters, Bernardes *et al*.[397] showed significant improvements in AHI and OSA-18 questionnaire results. The author suggested that early correction of mandibular retrusion could facilitate early adaptive changes in the upper airway and decrease the likelihood of developing OSA in adulthood. Therefore, airway examination should be an integral part of the examination, especially in skeletal class II malocclusion with a retrognathic mandible.

Despite the promising results from the aforementioned studies, the Cochrane review on oral appliances and functional orthopaedic appliances for OSA children found insufficient data to support or refute the effectiveness of these treatments for OSA in children. [398] This was due to inconsistency across outcome measures and time points.

3.6.2.2 Maxillary Expansion

The improvement of SDB symptoms following orthopaedic expansion has been a topic of controversy for many years, primarily due to the differences in study design and conflicting results. In the early years, Warren *et al.*[399] exhibited a 45% increase in nasal cross-sectional area following rapid maxillary expansion (RME). Villa and colleagues [400,401]have carried out two clinical studies that examined the effects of RME on OSA parameters and the stability of these effects in the long term. The prospective clinical trial demonstrated a significant improvement in OSA symptoms, including habitual snoring, daytime sleepiness, and tiredness, as well as oral breathing, following RME. In addition, the average AHI decreased from 5.8±6.8 to 2.7±3.5 in 5 months and further reduced to 1.5±1.6 by 12 months post-expansion. Similarly, a significant reduction in the arousal index and obstructive hyponea index was documented. These improvements were maintained for up to 36 months post-treatment.[401] These results resonated with another research group, Pirelli *et al*.,[402,403] in which notable improvements were observed in the reduction of AHI from an average of 12.2 events per hour to less than one event per hour for all subjects. There was also a mean increase of the nasal pyriform opening of 1.3±0.3mm. These improvements were sustained over 12 years. The subjects in Pirelli *et al*.'s studies were free from adenotonsillar hypertrophy, which allowed for the effects to be attributed purely to RME, and the shrinking of adenoid and tonsillar tissue due to growth did not play a part.[402,403]

Pirelli *et al.*[404] further compared the size of the airway on CBCT following RME treatment and found a significant increase in total upper airway volume, nasal volume, nasopharynx volume, and oropharynx volume. These volume increases were accompanied by improvement of AHI and oxygen saturation level (Nadir SPO_2). In contrast, a systematic review by Abdalla and Sonnesen[396] analysed CBCT studies related to airway change following RME treatment. Most

studies showed no significant effect of RME on upper airway volume compared to the control. However, some studies have shown a significant increase in nasopharyngeal volume.

Miniscrew-Assisted Rapid Palatal Expansion (MARPE) has become more popular in recent years, as it is effective in correcting posterior crossbite with a lower tendency for molar buccal tipping and bony dehiscence. As the expander is anchored to the bony maxilla, greater transverse skeletal effects would be expected and the associated enlargement of the airway dimension. A systematic review by Abu Arqub *et al*.[405] on the impact of MARPE and the airway showed insignificant airway volumetric changes, concluding a doubtful effect of MARPE as a treatment modality for improving the airway. There was a short-term, significant change in muscle strength, nasal resistance, and airflow favouring MARPE over conventional RPE, but the evidence was considered low to moderate.

3.6.3 Orthognathic Surgery

3.6.3.1 Distraction Osteogenesis

Patients with severe maxillomandibular abnormalities could benefit from having distraction osteogenesis (DO) for skeletal discrepancy and respiratory problems. Motamedian *et al*.[406] assessed the impact of DO with Le Fort osteotomies on the upper airway volume. This systematic review showed a significantly increased airway dimension following maxillary Le Fort DO, but this increase did not improve the AHI for OSA patients. The results from the meta-analysis had a lower level of evidence due to the design of the included studies; therefore, further standardised investigations are required to confirm the positive effect of DO on airway and OSA.

3.6.3.2 Class II Surgery

Theoretically, similar to Class II functional appliance therapy, mandibular advancement surgery can increase the pharyngeal airway by changing the position of the mandible and hyoid bone, with subsequent effects on the genioglossus and hypoglossus muscles.[407] This increase in airway volume was confirmed by a recent systematic review using CBCT, which evaluated airway changes following different types of orthognathic surgery.[408] Some researchers have reported the long-term stability of this enlargement of the pharyngeal airway to be unstable over time,[409,410] but Goncalves *et al*.[411] reported otherwise. A more recent systematic review revealed that, regardless of the type of surgery, the airway tends to relapse back towards its initial state, even 6 years after surgery.[412] This could be due to the gradual return of the hyoid bone to its preoperative position. Shokri *et al*.[413] also showed moderate evidence to support long-term significant change in upper airway volume following mandibular advancement surgery.

3.6.3.3 Class III Surgery

Class III skeletal discrepancy can be expressed as maxillary retrognathia and/or mandibular prognathia. The corresponding surgery for correcting such disharmony entails combinations of Le Fort advancement, Le Fort impaction, and BSSO setback. As previously mentioned, mandibular setback may lead to constriction of the oropharynx due to encroachment of the tongue space. This was confirmed by a systematic review of CBCT studies by Steegman *et al*.[408] and Christovam *et al*.,[414] which showed a general pattern of reduction in airway volume after BSSO setback surgery. On the other hand, isolated maxillary advancement surgery results in an increase in airway volume in the total airway and oropharynx. In terms of bimaxillary surgery for Class III treatment, He *et al*.[51] compared the literature regarding airway dimensions

following bimaxillary surgery with those following isolated mandibular setback surgery. It was found that bimaxillary surgery resulted in a lesser decrease in the upper airway MCA, nasopharynx volume, and total upper airway volume. Recently, Wei *et al*.[415] performed a systematic review on the development of OSA after orthognathic surgery in skeletal Class III patients. The results showed that the incidences of OSA were considerably low after Le Fort I impaction and BSSO setback, as well as after BSSO setback as a single surgery and Le Fort I advancement and BSSO setback, which were 19.2%, 8.57%, and 0.7%, respectively. However, no evidence could confirm that orthognathic surgery was the culprit for postoperative SBD because OSA is a multifactorial disease and obesity and age also play an essential role. This was reiterated by a systematic review by Canellas *et al*.,[416] which did not find evidence of postoperative sleep apnoea after mandibular setback surgery but suggested that there would be a higher chance of developing OSA if a large amount of mandibular setback were performed in an obese patient.

3.6.3.4 Maxillary Impaction Surgery

Vertical maxillary excess (VME), as the name suggests, is a form of maxillary deformity where the maxilla has excessive vertical development and often presents clinically as a long face and gummy smile. The surgery procedure involved in correcting VME entails a Le Fort I osteotomy, and the loose maxillary complex is repositioned superiorly by impaction to reduce the vertical dimension. As a result of this procedure, the nasal cavity dimension is reduced. Interestingly, research has shown conflicting results in the nasal function following Le Fort I impaction.[417-419] Therefore, Young *et al*.[420] carried out a systematic review to discern whether maxillary impaction surgery had a negative impact on the nasal airway. Following the literature search of 7517 studies, ten studies were included in the meta-analysis. The results showed

enhanced nasal airflow and reduced nasal resistance, despite a decrease in nasal cavity volume and an MCA of the nasal cavity.

3.6.3.5 Surgically Assisted Maxillary Expansion (SARME)

A systematic review by Buck *et al*.[421] showed weak evidence of an association between the SARME effect and oropharyngeal volume due to the high-risk bias identified in the studies investigated. However, a substantial increase in short-term nasal cavity volume was found.

3.6.3.6 Maxillomandibular Advancement Surgery (MMA)

The retrusion of the maxilla and mandible compresses the upper airway, making the individual prone to SDB. Maxillomandibular advancement (MMA) surgery has been successfully reported as the treatment choice for improvement of OSAS. Giralt-Hernando *et al.*[422] showed, via meta-regression analysis, that MMA surgery significantly enlarged both the pharyngeal airway volume and pharyngeal airway space, accompanied by a reduction in AHI to below 20. The difference between the averages of upper airway volume pre- and post-surgery was reported as 7.86 cm^3 [95% CI (6.22 cm^3, 9.49 cm^3)] by Rosario *et al*.[423] Similarly, Christovam *et al*.[414] showed in their meta-analysis that there was moderate evidence of a significant increase in MCA (124.13 mm^2) and total airway volume (7,416.1 mm^3).

John *et al*.[424] reported 100% surgical success of MMA surgery in patients with OSA when outcome was measured by AHI and RDI. In addition, the preoperative severity of OSA significantly influences the outcome of MMA surgery, with a strong positive correlation between pre-surgical AHI and the percentage change post-surgery. This was further confirmed by a meta-analysis by Rojo-Sanchis *et al*.[425] , who found a significant increase in upper airway

volume and oxygen saturation, and a decrease in AHI, RDI, and Epworth Sleepiness Scale (ESS) score, indicating an improvement in biological sense and quality of life. However, only the increase in upper airway volume showed very consistent results across the literature reviewed. Counterclockwise (CCW) rotation MMA procedures are generally used to improve profile aesthetics, giving a more pronounced chin projection.[426,427] Louro *et al.*[428] analysed the literature associated with MMA and CCW rotation and found a significant increase in upper airway space and area. Many researchers have indicated that mandibular advancement surgery leads to an increase in the middle airway space, while MMA surgery results in an expansion of both the upper and middle airway spaces.[411,426]

4.0 MECHANICAL VIBRATION

4.1 Bone

There are two types of bone: cortical bone and cancellous bone. Cortical bone is the hard protective shell with osteons arranged in concentric rings called lamellae, in which resided cells that play a crucial role in bone formation and remodelling.[429] There are blood vessels, lymphatic vessels, and nerve fibres in the centre of each osteon, which is known as the Haversian canal. Cancellous bone is constructed in a unique way that the trabeculae pattern follows the lines of stress to provide maximum strength. Between the trabecular pores lies the red bone marrow, where hematopoietic stem cells reside.[430] The composition of bone, by weight, includes 60% inorganic minerals, 30% organic components and 10% water.[431] The inorganic material consists mainly of hydroxyapatite (HA) ($Ca_{10}(PO_4)_6OH_2$). Bone contains a matrix that helps support its spatial structure and the cells that comprise it. The matrix contains approximately 90% collagen, mainly type I, and non-collagenous proteins, such as osteocalcin (OCN), bone sialoprotein (BSP), osteopontin (OPN), and bone morphogenetic proteins (BMP), among others. The matrix provides the framework for HA deposition and matrix mineralisation, which contributes to the stiffness and resistance of the bone structure. The bone also contains other minerals such as bicarbonate, sodium, potassium, citrate, magnesium, carbonate, fluorite, zinc, barium, and strontium, which contribute to its strength.[432] In addition, several soluble and adhesion molecules in the bone matrix regulate the bioactivity of bone cells and participate in bone remodelling and metabolism. The structure of the bone matrix can absorb and transform mechanical loadings into the cells in the form of compressive stress, tensile strain or fluid shear stress (FSS).[433]

4.2 Bone Adaptation

Mechanical stimuli play a crucial role in maintaining skeletal integrity and bone mass. Frost[434,435] in 1987 and later with an update in 2003, proposed a concept called the mechanostat to define bone adaptation modes when subjected to different degrees of strain. This theory suggested mechanical usage windows and assigned a minimal effective strain for each window. (Figure 10) According to this theory, there is a threshold for disuse mode remodelling (MESr =50-100με) below which bone is removed and weakened. In the modelling region (MESm=1000-1500με), mechanically controlled modelling begins and could increase if strains exceed this upper limit. Further increase of strain would lead to microdamage, which occurs at approximately 30,000 (MESp), and bone can fracture at 25,000 (Fx). Exercises such as walking, jogging, and cycling fall within the physiological and overuse window, which can induce mechanically controlled modelling and are considered beneficial in maintaining good bone health.

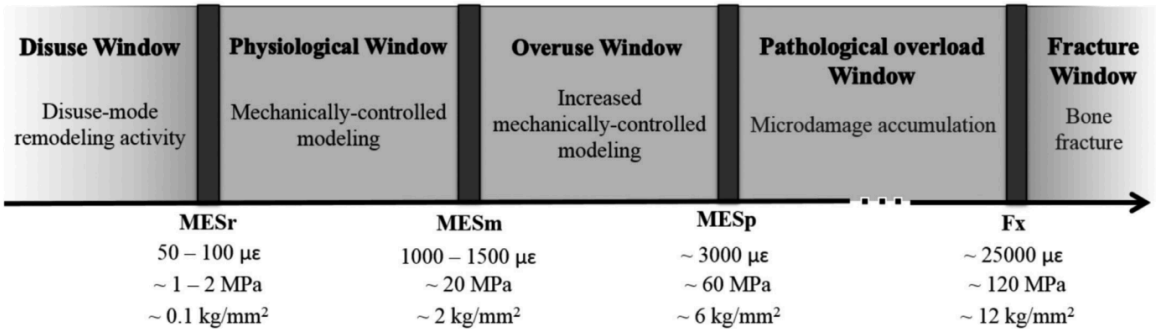


Figure 10 - Mechanical usage window defined by Frost's mechanostat theory of bone adaptation to strain from Rosa et al.[436] (Minimum effective strain (MES) for remodelling (MESr), modelling (MESm), microdamage (MESp) and fracture (Fx))

Bone adaptation is of utmost importance in maintaining skeletal mass and architecture during growth and development, particularly in response to changing mechanical environments. Turner[437] established three rules that control bone adaptation to mechanical stimuli:

1. Bone is sensitive to dynamic rather than static loading
2. Prolonged load duration has a diminishing effect on further bone adaptation
3. Bone cells are less responsive to routine loading signals and are more responsive to abnormal mechanical stimuli.

4.2.1 Dynamic Loading

Dynamic strains, not static strains, are crucial in bone adaptation. This was demonstrated by Hert *et al*.[438] through an animal study, which found increased bone formation in rabbits subjected to intermittent loading. The frequency of stimulation is a significant element in bone adaptation.[439] In fact, Rubin *et al*.[440] claimed that the strain magnitude and strain rate of bone are related. For example, cortical bone mass could be maintained by applying 800με peak-induced loads at a frequency of 3 Hz for 600 seconds per day. However, a lesser load at 200 with strain applied at a higher frequency of 30 Hz also helped maintain cortical bone. This suggests that low-amplitude, high-frequency postural strains resulting from muscular contractions may be as effective as, or even more effective than, high-amplitude, low-frequency strains associated with locomotion in maintaining bone mass. This concept was reiterated by Bacabac *et al*.,[441] who claimed that low-magnitude, high-frequency mechanical stimuli were as stimulatory as high-amplitude, low-frequency stimuli. Numerous studies have demonstrated that both frequency and strain rate are crucial determinants of bone adaptation.[442,443]

4.2.2 Load Duration

Bone mass increase is not proportional to the duration of skeletal loading. In fact, bone mass increases with load duration until a point when bone formation response saturates as loading duration lengthens. This phenomenon is known as diminishing returns.[444,445] (Figure 11)

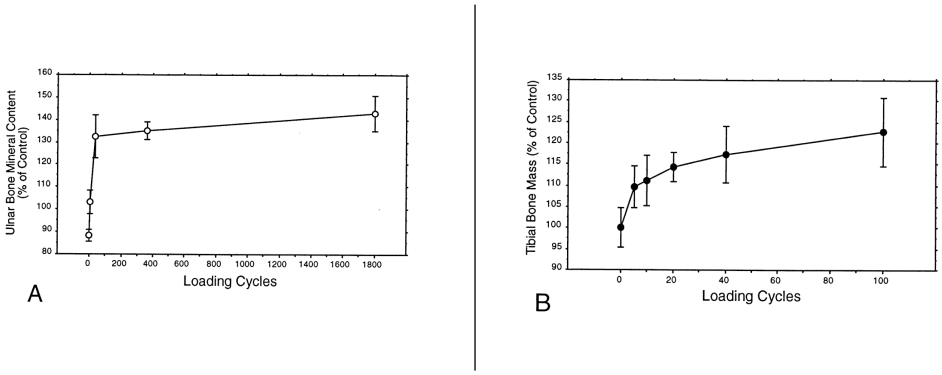


Figure 11 - Two graphs illustrating the phenomenon of diminishing returns, i.e. increased duration of skeletal loading does not yield proportional increases in bone mass. (A) Rubin and Lanyon[444] applied load to the rooster ulna, and when the load duration passed 36 cycles/day, no further increase in bone mass (B). Umemura et al.[445] trained rats to jump various numbers of times per day and found that five jumps per day were sufficient to increase bone mass, but further increases gave diminishing returns.

4.2.3 Routine vs Abnormal Loads

Bone cells can become accustomed to routine load from daily activities such as walking or running. This is because osteoblasts can alter the cytoskeleton and establish a new biological balance that readily adapts to the predominant mechanical loading. Therefore, an unusual mechanical stimulus is required to initiate the bone adaptation process again.

4.3 Bone Remodelling

According to Wolff's Law, bone can adapt to new loads through bone remodelling, a complex biological and cellular process.[446] Bone remodelling involves the balance of bone deposition by osteoblasts and bone resorption by osteoclasts, as well as the precise signalling by the cytokines involved.[447] The effects of mechanical loading depend on the type and magnitude of stimulation and the health of the host, which encompasses factors such as age, sex, disease, and physical activity.[448,449] Excessive loading can dampen osteogenic functions while promoting overactivation of osteoclasts.[448] Vascularisation in the bone plays a crucial role in bone remodelling, as it supplies nutrients to the newly formed bone. This was evident from Nguyen *et al*.,[450] who found that angiogenesis promoted osteogenesis and facilitated bone maturation. Mechanical loading affects bone vascularisation, which, as stated before, is critical for nutrient supply, waste exchange and long-term stability of bone.[451]

A typical remodelling process takes about 120 days, and there are six phases:[452]

1. Quiescence phase: A layer of bone lining cells over a thin collagenous membrane covers the bone surface.
2. Activation phase: Mechanical stresses are transmitted to endosteal lining cells by osteocytes via the lacunar-canalicular network. Matrix metalloproteinases (MMPs) secreted by osteoblasts result in retraction of bone lining cells and the elimination of the collagenous membrane covering the bone's surface.
3. Resorption phase: Osteoclasts develop ruffled membranes and resorb the bone, forming pits and lacunae. Some will immigrate, and some will undergo apoptosis.
4. Reversal phase: Macrophages eliminate the debris of osteoclasts from the pits, and osteoblast progenitors travel to the resorption pit.

5. Early and late formation phases: Active osteoblasts produce osteoid, followed by osteoid mineralisation.
6. Quiescence phase: osteoblasts undergo apoptosis or differentiate into bone lining cells or osteocytes.

4.3.1 Cells Involved in Bone Remodelling

Osteoblasts, osteoclasts, osteocytes and bone lining cells are the main cell types involved in bone remodelling.

4.3.1.1 Osteoblasts

Osteoblasts are derived from mesenchymal stem cells, bone lining cells and chondrocytes that are responsible for bone formation through the production of bone matrices with high type I collagen content.[446,453,454] It is sensitive to mechanical loading and responds by proliferation, extracellular matrix synthesis, and secretion and expression of cytokines.[455] Osteoblasts also play a crucial role in regulating hematopoietic stem cells.[456]

4.3.1.2 Osteoclasts

Osteoclasts originate from monocytic cells of the hematopoietic stem cell lineage in the bone marrow.[457] They are large, multi-nucleated cells, and their development is influenced by several factors, including macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor-κB ligand (RANKL) secreted from osteoblastic lineage cells and stromal cells.[458,459] Osteoclasts participate in bone remodelling by secreting high levels of matrix metalloproteinase, cathepsin K, hydrochloric acid and other enzymes.[460] Once the bone

matrix is dissolved, the Vβ3 integrin receptor is no longer activated, and osteoclasts undergo apoptosis.[461] Osteoclasts are surrounded by fluid in the lacunar-canicular matrix, and when mechanical loading is detected, an exchange of metabolic and biochemical signalling molecules occurs, generating a flow-based mechanical stimulus.[462] Depending on the magnitude and duration of FSS, the function of osteoclasts varies. Physiological FSS loading would inhibit osteoclast differentiation, whereas higher FSS loading would increase osteoclast formation.[463] Osteoclasts are also responsible for regulating hematopoiesis and angiogenesis.[464]

4.3.1.3 Bone Lining Cells

Bone Lining cells are quiescent osteoblasts, and as the name suggests, they cover the bone surface to inhibit bone resorption by forming a barrier between the bone matrix and osteoclasts.[457] These cells help regulate osteoblastic and osteoclastic activity when the bone requires remodelling.[465] Bone lining cells respond to signalling molecules such as parathyroid hormone (PTH) and prostaglandin E2 (PGE2) via surface receptors, and as a result, uncover the unmineralised osteoid, exposing the mineralised underlying bone matrix for osteoclasts to initiate bone resorption. Bone lining cells participate in bone remodelling by communicating with osteocytes, deep inside the bone matrix, through gap junctions. They also produce RANKL and Osteoprotegerin (OPG), which are essential in osteoclast formation.

4.3.1.4 Osteocytes

Osteocytes, which are previously osteoblast cells, reside between lamellae in cortical bone and serve as sensors for mechanical loading. It helps to convert external mechanical forces into biochemical responses, a process known as mechano-transduction, to coordinate the bone

remodelling process. Osteocytes react to bone deformation or its effects, including shear stress due to load-induced fluid flow, electric field caused by generated streaming potentials and hydrostatic pressure.[466-468]

Osteocytes have a dendritic morphology in the lacunae, and their cytoplasmic processes traverse canaliculi, forming the osteocyte lacunar-canalicular system.[469,470] These processes join with adjacent osteocytic processes, other osteoblasts and bone lining cells via gap junctions such as Connexin 43 (Cx43). Communication between processes is via the exchange of small molecules or by the flow of interstitial fluid between osteocyte processes and canaliculi. Due to this unique communication within the lacunar-canalicular system, mechanical loading is detected, and cellular responses are initiated. Therefore, osteocytes act as mechanosensors to assist in adaptation and remodelling to daily mechanical forces. To illustrate, excessive loading causes osteocytes to upregulate or downregulate signals such as BMPs, wingless-related integration sites (Wnts), PGE2 and nitric oxide (NO), thereby manipulating the differentiation, activation, and recruitment of osteoblasts or osteoclasts.[471] Nitric oxide is responsible for stimulating bone formation by promoting osteoblast differentiation and inhibiting osteoclast formation. It also maintains the viability of osteocytes and boosts PGE2.[472] PGE2 has two significant effects on osteoblasts. It stimulates osteogenic function in osteoblasts and recruits and promotes differentiation of precursor cells to increase the production of pre-osteoblasts. Osteocytes have an additional role in regulating phosphate and vitamin D homeostasis by producing fibroblast growth factor-23 (FGF-23).[473] Moreover, osteocytes release sclerostin, which lowers the bone formation rate.[474]

Apoptotic osteocytes are found in bones that are either unloaded or subjected to excessive mechanical strain.[475,476] This promotes osteoclast differentiation and initiates localised bone

resorption. OPG may serve as a decoy receptor for RANKL in osteocytes, thereby inhibiting osteoclast recruitment and/or formation.[477] Alternatively, osteocytes may produce molecular signals, such as osteoclast chemotactic factor and high mobility group box 1 protein, to attract osteoclast precursors and stimulate osteoclast development.[478] This upregulates the expression of RANKL, tumour necrosis factor (TNF) and interleukin-6 (IL-6) and declines OPG expression. Furthermore, there is an elevation of VEGF and RANKL evident in overloaded rat bones, which influences angiogenesis and potentially osteoclast precursor recruitment and osteoclast differentiation.[479]

4.3.2 Regulators

Multifactorial regulators are responsible for modulating the activity of osteogenic cells and bone formation subject to mechanical stimuli. These included hormones or cytokines (PTH,[480] glucocorticoid,[481] follistatin-like 3[482]), cytoskeletal proteins (microtubule actin crosslinking factor 1,[483] Cx43[484]), signalling pathways (Wnt signalling[485,486]) and microRNAs (miRNAs).

4.3.2.1 Hormones or Cytokines

Apart from mechanical stimuli, the rate of bone remodelling also depends on the levels of PTH, oestrogen, and glucocorticoids, which mediate cytokine production. For instance, estrogen helps prevent bone resorption by decreasing the secretion of RANKL and the expression of TRPV5 (a non-selective calcium ion channel), while also stimulating the production of osteoblastic OPG.[487,488] Physical exercise lowers the secretion of proinflammatory cytokines (like IL-1, IL-6, and TNF-α), which can promote bone resorption, while also enhancing the production of protective cytokines (such as IL-10, IL-2, IL-12, and IL-4) via OPG/RANKL/RANK-independent pathways.[489-491]

4.3.2.2 Wnt Signalling

4.3.2.2.1 Sclerostin (regulation of bone formation by osteocytes)

Sclerostin is a potent bone formation inhibitor that is secreted by osteocytes and is a product of the SOST gene.[492-494] It is regulated by stimuli such as PTH and mechanical stress. High mechanical strain resulted in a reduction in sclerostin-positive osteocytes, thereby releasing Wnt signalling, which is associated with higher bone formation on adjacent periosteal surfaces.[495] On the other hand, SOST gene and sclerostin expression are high in unloaded bones.

4.3.2.2.2 RANKL and OPG (regulation of bone resorption by osteocytes)

RANKL is produced or secreted by osteocytes directly or via the process of osteocyte apoptosis indirectly. Initiation of osteoclast development occurs when there is direct contact of membrane-bound RANKL expressed in the osteocytic dendrites with receptor activator of nuclear factor κ (RANK) expressed in osteoclast precursors.[496] Activation of the PTH receptor in osteocytes of transgenic mice was shown to be associated with increased RANKL expression, leading to enhanced bone resorption.[497-499] Osteocytes can also secrete OPG, which competes with RANKL for its receptor, RANK, on osteoclast precursors, thereby inhibiting bone resorption. The Wnt/ß-catenin pathway regulates this OPG secretion. Osteocytes are also a source of secreted M-CSF in bone. Therefore, osteocytes have the potential to regulate bone resorption through both direct and indirect mechanisms, influencing osteoclast differentiation and function under physiological and pathological conditions.[500]

4.3.2.3 miRNAs

miRNAs are short, non-coding RNAs that play a crucial role in various physiological and pathological processes, including cell differentiation, proliferation, apoptosis, and cancer development.[501-503] In particular, miR503-5p[504] and miR-103a[505] are sensitive to different mechanical stimuli when regulating osteogenic cell differentiation and bone formation.

4.3.3 Mechanosensation and Mechanotransduction

The bone matrix can transmit and transform mechanical loadings into bone cells in the form of compressive stress, tensile strain, and FSS, etc.[433] Osteocytes are mechanosensory cells of the bone. Mechanical stress displaces fluid flow through the canalicular space and deforms the dendritic processes of osteocytes, leading to strain within the cell processes of osteocytes. These mechanical strains are converted into cellular signals by osteocytes through the production of signalling molecules that are responsible for modulating the activities of osteoblasts and osteoclasts.[506]

Mechanoreceptors are required to detect external mechanical signals and are in direct contact with the external environment. Mechanosensitive structures are responsive to changes in intermediate cellular structures, such as the cell membrane and intracellular plasm movement, to detect mechanical signals from tension, pressure and FSS. Mechanosensitive structures include cell surface proteins or membrane structures, such as focal adhesions, ion channels, connexons, G protein-coupled receptors (GPCRs), and primary cilia. Once the mechanical signal is sensed, these structures change their conformation or activity in response to the mechanical stimuli, activating downstream signalling pathways and guiding cell behaviours.

4.3.3.1 Mechanoreceptors

Extracellular matrix transmembrane receptors, such as integrins and CD44 receptors, are responsible for converting mechanical stimuli into intracellular signals in osteocytes. These receptors are located on the osteocyte membrane and are attached to both the extracellular matrix and the cytoskeleton.[507,508] Intracellular signal transduction pathways, such as intracellular Calcium (Ca^{2+}), inositol 1,4,5-trisphosphate (IP3) or cyclic adenosine monophosphate (cAMP) dependent pathways, are involved with other mechanosensitive cells.

4.3.3.2 Mechanosensitive Structures

4.3.3.2.1 Extracellular matrix

The extracellular matrix (ECM) plays an important role in osteocyte behaviour. A compact preosteoblast-derived matrix (PDM) can promote the maturation of osteoblasts. On the other hand, the overactivation of osteoclasts is attributed to loose PDM.[509] Osteocytes on a more mineralised bone matrix tend to pull more than those on a softer matrix, resulting in increased tension on stress-bearing elements, such as F-actin.[510] F-actin acts as a mechanosensory, mechanotransduction effector and primary regulator of YAP (Yes-associated protein) and TAZ (transcriptional activator with PDZ-binding motif).[511]

4.3.3.2.2 Focal Adhesion

Focal contacts formed by focal adhesion kinase, integrins, cadherins and other ECM and cytoskeletal proteins act as direct mechanical linkers between the ECM and the cell. They are the connectors that enable the transmission of mechanical stimuli from the ECM to the cytoskeleton.

4.3.3.2.3 Ion channels (PIEZO, TRPV4 and P2X7)

Ion channels in the bone cell membrane are strain-sensitive systems that respond to various stimuli, including ligand binding, voltage changes, stretching, and fluid shearing, through cellular ion fluxes. PIEZO1/2 are cation channels that are responsive to mechanical loading and lead to Ca^{2+} influx in osteoblasts, resulting in coordinated activation of NFATc1, YAP1 and β-catenin.[512] As a consequence, bone formation is promoted by the activation of osteoblasts and osteocytes, and this process also mediates angiogenesis.[513] PIEZO1 has also been shown to regulate osteoblast-osteoclast homeostasis.[514] TRP4 are non-selective cation channels that play a significant role in regulating bone metabolism, influencing bone strength and potentially predicting the risk of fractures.[494] It can mediate mechanical stimuli in osteocytes, chondrocytes and epithelial cells. FSS activates TRPV4 to increase calcium concentrations in the cellular plasma, thereby accelerating collagen deposition and mineralisation.[515,516] In addition, it mediated oscillatory FSS and laminar shear stress-induced calcium signalling and osteogenic gene expression in bone marrow stromal cells. The PIEZO1 detects high-intensity mechanical stimuli, while TRPV4 is mechanosensitive to lower intensity stimuli.[517] TRPV4 is also expressed in osteoclasts and activates NFATc1 signalling to regulate terminal differentiation through Ca^{2+} influx.[518,519] Activated P2X7 on osteoblasts and osteocytes results in PGE2 release, which mediates the balance of osteoblast and osteoclast activity.[520] Piezo type mechanosensitive ion channel component 1 (Piezo1) in endothelial cells senses mechanical stimulation in osteoblasts and osteocytes.

4.3.3.2.4 Primary cilium

The primary cilium is a microtubule-based, antenna-like sensory organelle that protrudes from osteocytes, osteoblasts, and mesenchymal stem cells (MSCs), designed to perceive mechanical

stimuli.[521] In osteocytes, it senses extracellular fluid pulses generated by physical activity. When the cilia bend, mechanosensitive ion channels such as TRPV4 are activated, resulting in Ca^{2+} influx, membrane depolarisation and nerve fibre activation. The cell then undergoes mechanical stimulation.[522] Research has shown that the flow-induced cilia response leads to increased Cox-2 gene expression and PGE2 release, which are essential chemical mediators in the mechanotransduction process, as well as an increase in the OPG/RANKL ratio.[436] The longer the primary cilium, the more sensitive the osteocytes and the more release of adenosine triphosphate (ATP) and NO by osteocytes.[523] Periosteal osteochondroprogenitors can perceive FSS via primary cilia and differentiate into osteoblasts.[524]

4.3.3.2.5 Connexon 43 (Cx43)

Connexon 43 (Cx43) is a gap junction protein that is found in humans' and rodents' osteoblasts, osteocytes and osteoclasts.[525] It acts as an intercellular communication between neighbouring cells in response to extracellular stimuli. Cx43 facilitates the transportation of small molecules, such as Ca^{2+}, cAMP, and PGE2, which prevent osteocyte apoptosis and stimulate osteoblastic differentiation and periosteal bone remodelling. FSS causes an increased Cx43 expression on the osteocyte cell membrane, leading to the formation of hemichannels. This then assists PGE2 release and intercellular gap junction construction.[526-529] An interesting observation is that mechanical stretching of osteoblasts promotes the phosphorylation level of Cx43 without affecting its mRNA expression.[530] However, Cx43 is unable to sense mechanical stress independently. It requires interaction with the conformationally activated integrin α5β1 (C-terminal) to open the Cx43 hemichannel.[531]

4.3.3.2.6 G protein-coupled receptors (GPCRs)

Several specific GPCRs, such as Angiotensin II receptor 1 (AGTR1), bradykinin receptor B2 (BDKRB2), and GPR68, can sense mechanical forces.[532] Consequently, the activated GPCRs can induce signalling events, including an increase in intracellular calcium concentrations via PLC-IP3 and DAG pathways.[533]

4.3.3.3 Mechanotransduction Pathways

There are four steps involved in converting physical load to biochemical signals, which in effect change the morphology and function of cells, gene expression and ECM synthesis:[534-536]

1. Mechnocoupling
2. Biomechanical coupling
3. Transmission of signals from the sensor cells to the effector cells
4. Responses of the effect cells.

Receptors (cadherins and integrins), mechanosensors, and nuclear cue factors are involved in mechanotransduction, resulting in alterations of protein and gene expression profiles. It has been found that both age and gender can affect the mechanotransduction process. Age is an inhibitory factor for bone formation, and men have less mechano-responsiveness than women.[536,537] There are numerous pathways involved in intracellular mechanotransduction and corresponding functional responses, which include the cytoskeleton, RhoA/ROCK, YAP/TAZ, etc.[457]

4.3.3.3.1 Cytoskeleton

The cytoskeleton is composed of the nuclear skeleton, cytoplasmic skeleton, cell membrane skeleton, cross-linking factors, and extracellular matrix, together forming a fibrous framework that provides morphology and connections to all mechanosensitive components. F-actin is one of the main cytoskeletal elements that can sense and transmit mechanical stimuli in osteocytes.[510]

4.3.3.3.2 Ras homolog gene family member A /Rho-associated coiled-coil kinase (RhoA/ROCK)

RhoA/ROCK are small GTPases that transduce information through signalling pathways by transforming between their active GTP-bound and inactive GDP-bound states. The RhoA signalling pathway is essential for mechanotransduction, as it controls the response of the actin cytoskeleton to mechanical forces. Upstream signals from various receptors, such as GPCRs, integrins, and growth factor receptors (TGF-βR), regulate the activation and deactivation of RhoA. Through a GEF-dependent mechanism, mechanical stimuli, such as FSS, can activate small RhoA and interact with its effector (Rho-associated protein kinase family, ROCK 1 and 2). This also phosphorylates myosin phosphatase, resulting in the contraction of the actin cytoskeleton by activating myosin light chain. RhoA/ROCK2 regulates the osteogenic differentiation of C3H10T1/2 cells and MSCs. In addition, under oscillatory fluid flow conditions, RhoA/ROCK2 has additive effects on Runt-related transcription factor 2 (Runx2) expression, leading to osteoblast differentiation.

4.3.3.3.3 Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ)

Yes-associated protein (YAP) and its homolog TAZ play a significant role in the formation of the peri-lacunar/canalicular network, osteocyte-mediated mechanotransduction, regulation of osteoblastic and osteoclastic activities of osteocytes and bone remodelling.[538] They also have complex functions in bone formation, also known as osteogenesis. TAZ is generally regarded as a transcriptional coactivator that interacts with Runx2, acting as a key regulator of osteoblastogenesis.[539] In contrast, YAP inhibits Runx2 activity in ROS 17/2.8 osteoblast-like cells, regulating osteoblastogenesis through Wnt/β-catenin signalling both in vitro and in vivo.[540,541] In summary, YAP/TAZ promotes osteogenic activity in fully differentiated osteoblasts and osteocytes while hindering stem cells from committing to the osteoblastic lineage.

4.3.3.3.4 Wnt/ GSK3ß/β-catenin signalling pathway

Wnt/β-catenin signalling plays a crucial role in osteocyte mechanotransduction. β-catenin is a key mediator of mechanotransduction and an essential regulator of canonical Wnt3α pathway activation. Its activity is regulated by mechanical loading and unloading through the activation of nitric oxide, focal adhesion kinase (FAK), and Akt signalling pathways. Mechanical loading significantly increases N-terminal phosphorylation of GSK-3β and β-catenin expression. The GSK3β/β-catenin signals are linked to bone formation in sites under tensile forces in orthodontic tooth movement.[542] Strength and power training can enhance the expression of Wnt-related genes in humans, while mechanical strain prompts MSCs to shift from adipogenic to osteogenic differentiation by retaining β-catenin in the nucleus. Leukemia inhibitory factor (LIF) secreted by osteoclasts inhibits sclerostin and[543] promotes bone formation by activating

the Wnt/β-catenin signalling pathway, which plays a role in suppressing bone resorption during mechanical stimulation. β-catenin regulates the process of bone remodelling by increasing the expression of OPG, a direct gene target of the β-catenin/TCF complex and a decoy receptor of RANKL, thereby regulating osteoclastogenesis.[544] Dkk1 and Dkk2 are inhibitors of Wnt canonical signalling, which is responsible for full osteoblastic differentiation.[545,546]

4.4 Cell response to different mechanical stimulation

Mechanical stress is generally transmitted via gap junctions, and osteocytes will release signalling factors that activate bone remodelling.[547-549] Compressive loads affect osteoclast activity, and it is force-dependent. Osteoclast differentiation occurs in a low-oxygen environment.[550] Compressive force stimulates osteocytes, reducing the expression of methionine enkephalin (MENK), a neuropeptide that induces apoptosis of osteocytes and bone resorption.[551] Mechanical loads also induce alternative splicing of the Igf1 gene, which in turn leads to the generation of mechano-growth factor (MGF). MGF can regulate osteoblasts in vitro, affecting their proliferation, migration, and differentiation, and plays a critical role in bone remodelling.[552] In addition, mechanical stimulation can change calcium concentration, ATP levels and soluble factor release, which in turn stimulate cell activity in bone.[553] Hydrogen sulphide (H_2S), a gaseous signalling molecule produced by cystathionine gamma-lyase (CSE), is another mediator induced by mechanical loading. H_2S promotes osteoclast differentiation and activation, and encourages the production of anti-inflammatory cytokines, initiating bone resorption.[554] miRNAs are essential components in the bone remodelling process when mechanical force is present. The exact mechanism is unclear, but some antisense miRNAs (anti-miR-503, anti-miR-103 and anti-miR-195) can induce the expression of RunX2 and promote osteoblast differentiation. miR-29 appears to promote osteoclast differentiation.[555,556] Compressive forces can stimulate specific cell populations, such as RAW264.7, when exposed

to RANKL signalling, they encourage the formation of polynuclear giant cells similar to osteoclasts.[557]

Cyclic stretch promotes the differentiation of bone marrow-derived mesenchymal stem cells into osteogenic cells and induces the upregulation of intracellular enzymes such as superoxide dismutase 1 (SOD1), via activation of the AMPK-SIRT1 pathway. SIRT1 act as a mechanosensitive element in the regulation of reactive oxygen species inside the cell and the antioxidant defence system against the mechanical stretch. Mechanical cyclic stretches activate the expression of the p21 protein, which enhances osteogenic differentiation through a well-defined TWIST/E2A/p21 axis.[558]

4.5 Growth Plates

The mandible is frequently considered as a long bone bent into a horseshoe shape. At the condyle, cartilages share similar structure, composition and properties with the growth plate of the long bone. Bone growth longitudinally by chondrocytes synthesising cartilage at the growth plate and subsequently transformed into bone by endochondral ossification. The growth plate is avascular and aneural, with chondrocytes embedded in an extracellular matrix. The chondrocytes are smaller and flatter at the epiphyseal end and larger and rounder towards the metaphysis. There are three distinct zones of chondrocyte differentiation in the growth plate: reserve, proliferative, and hypertrophic zones. Longitudinal growth of bones is an outcome of a complex interaction between cell division (proliferation), cell enlargement (hypertrophy), extracellular matrix synthesis and controlled degradation.[559-562] Chondrocytes start at the reserve zone and undergo proliferation in the proliferative zone, followed by enlargement in the hypertrophic zone, and eventually undergo apoptosis as they undergo

calcification. Longitudinal bone growth can be controlled by modifying the number of growth plate chondrocytes in the proliferative zone, their rate of proliferation, the amount of chondrocytic hypertrophy and the controlled synthesis and degradation of matrix throughout the growth plate. Once the bone has grown to adult size, it undergoes continuous bone remodelling and turnover.

4.5.1 Growth Plate Mechanobiology

Mechanical loading, or lack of, can modify the way bone grows and remodels. As stated previously, according to Wolff's law, bone adapts to its mechanical environment, meaning that increased intermittent stress results in bone deposition, while reduced intermittent stress results in bone resorption. In contrast, biomechanical response to mechanical stimuli associated with immature bone growth can be described by the Hueter-Volkmann 'law' in which sustained additional compression loading results in bone growth suppression, whereas reduced mechanical loading accelerates immature bone growth.[563] The growth plate is sensitive to compression because it is embedded within stiff bone tissue.

Sustained compressive loading affects both proliferative and hypertrophic zones, as well as cellular shape, by reducing the number and proportion of proliferating chondrocytes and the extent of chondrocyte hypertrophy.[560,564,565] As a result, the proliferative and hypertrophic zone in the growth plate becomes thinner. On the contrary, a reduction in sustained pressure or distraction of the growth plate leads to thickening of the growth plate (proliferative and hypertrophic zones) and disruption of chondrocyte columns.[564-566] The thickening of the growth plate is due to enhanced chondrocytic proliferation, resulting in increased chondrocyte number, height, and volume.[564-567]

Several animal studies have reported a narrowing of protein expression of type II collagen and type X collagen in animals subjected to sustained stress.[568,569] There was in vitro evidence that a sustained compressive load could lead to reduced gene expression and distribution of type II and type X collagen in the hypertrophic zone of rat tibial growth plates.[570] However, *in vivo* animal studies showed contrasting results.[568,569,571] In terms of dynamic loading, *in vivo* studies confirmed no changes in Type II and Type X collagens, both at the gene and protein levels, following intermittent cyclic or exercise-oriented compressive loading of rat ulnar or cranial base growth plates.[572-574] Vascular endothelial growth factor (VEGF) is a regulator of chondrogenesis and is increased in rat ulnar growth plates when subjected to cyclic compression within physiological loading ranges.[573]

Mechanical loading also affects the osteogenesis within the growth plate. Alkaline phosphatase activity, mRNA expression, and protein level of OPN were found to be upregulated in growth plates subjected to sustained compression, resulting in accelerated ossification.[568,569] Osteopontin (OPN) was also found to be upregulated in the hypertrophic zone and at the bone cartilage interface, indicating premature mineralisation of these regions.[568] The same study also found downregulation of gene expression of matrix Gla protein, a marker of cartilage and bone calcification, in compact bone, and upregulation in trabecular bone.[569] In terms of intermittent cyclic loading, there was more intense osteonectin expression in the rat femoral growth plate, suggesting a higher mineralisation rate.[574] Ohashi *et al*.[573] found fewer and irregular capillaries in rat ulnar growth plates when exposed to intermittent cyclic compression, which indicated slower ossification.

4.6 Articulating Cartilage

Articular cartilage, found in joints, is a unique load-bearing connective tissue that absorbs and distributes mechanical loads evenly across the underlying bone surface. The difficulty lies in the fact that cartilage tissues are difficult to repair when they are damaged. Chondrocytes are specialised cells that make up the cartilage and are multifunctional, e.g., matrix synthesis and matrix degradation.[575] These cells are responsible for the growth and maintenance of cartilaginous tissue through regulated cell proliferation, growth, synthesis of extracellular matrix proteins, production and activation of matrix-degrading enzymes, and, in some cases, matrix calcification and cell death.

4.6.1 Mechanical Loading of Cartilage

Mechanical loading can prevent cartilage degradation, encourage subchondral bone metabolism, enhance osteoblast activity, and inhibit excessive osteoclast activation. [567,576,577] This activity does not compensate for deficient mineralisation or harmful morphological changes already present in the bone.[578]

Wnt is involved in the formation and metabolism of cartilage and bone, and β-catenin dependent signals are the main transduction pathway for Wnt that is responsible for the differentiation of chondrocytes. This was illustrated by Hou *et al*.[579] and Zhang *et al*.,[580] who showed that low-magnitude vibration causes mechanotransduction, resulting in Wnt signalling, which mediates transcriptional regulation in osteogenic responses in osteoblasts. Hou *et al*.,[581] later, investigated the effect of LMHF vibration on bone marrow stem cells (BMSCs) and found that LMHF vibration promoted BMSCs chondrogenic differentiation, characterised by the

heightened expression of chondrogenesis-related proteins such as Aggrecan, Sox9, and BMP-7. This, in turn, inhibits hypertrophy during chondrogenic differentiation.

4.7 Condylar Cartilage

Condylar cartilage is a secondary cartilage with the exclusive capability to undergo adaptive remodelling in response to external stimuli such as mechanical loading, mandibular repositioning or articulatory functions.[582,583] This adaptive remodelling nature serves as the basis for orthopaedic functional appliance therapy.

Chondrocytes in condylar cartilage are different from those found in epiphyseal cartilage. It is present throughout postnatal life and maintains its morphological and biosynthetic features.[584] The histology of condylar cartilage is arranged as a unique zone-like packing of chondrocytes in different forms.[585] There are five zones: articular, resting, proliferative, hypertrophic and erosive zones. The superficial surface coverage of the articular surface is the articular fibrous layer, containing densely packed collagenous fibres and fibroblasts. A layer of mesenchymal cells resides deep to the layer of fibrous tissue.[586] Below the articular zone is the resting zone, where reserve cartilage cells, which are small in size and have less chondroid matrix, reside. These cartilage cells have a high nuclei-to-cytoplasm ratio, which indicates high mitotic potential.[585] The next layer is the proliferative zone, which contains mature cartilage with a rich intercellular cartilaginous matrix. The large cartilage cells are embedded non-uniformly in lacunae surrounded by a clear zone. The hypertrophic zone follows the proliferative zone, and as the name suggests, highly mature hypertrophic chondrocytes are found in this zone, indicating the termination of chondrogenesis. There is also a high density of collagen fibres in the intercellular matrix, which is continuous with the osteoid matrix underneath. Usually, the

first sign of calcification of cartilage can be seen in this layer. Some cartilage cells would start to degenerate and have a pyknotic appearance.[587] The last erosive zone contains degenerated cartilage, which represents the beginning of osteogenesis.[588-590] The broken-down cartilaginous spicules undergo calcification with hydroxyapatite crystals. There is an invasion of blood vessels in this zone. The newly formed bone trabecular pattern is random in nature.[591]

Animal experiments have shown that when the mandible is advanced anteriorly, the mesenchymal cells in the articular layer are stretched and reoriented towards the pull, resulting in an increased mesenchyme population and enhanced differentiation into chondrocytes, which contributes to the adaptive remodelling process.[192,592] The regeneration of chondrogenesis leads to endochondral ossification.[593]

Endochondral ossification is a multi-step process from cellular differentiation to the establishment and controlled resorption of the cartilaginous matrix, with the final step involving the replacement of the avascular cartilage template by highly vascularised bone tissue. During this final step, hypertrophic chondrocytes secrete a calcified cartilaginous matrix and angiogenic stimulators, which enable capillary invasion and angiogenesis. This process is also known as neovascularisation, which allows for the vast recruitment of cell types involved in cartilage resorption and bone deposition. It also provides signals required for normal morphogenesis.[594]

The transition from chondrogenesis to osteogenesis can be depicted by the presence of Type II and Type X collagen and the invasion of new vasculature.[589,595] Type II collagen is a major collagenous framework of cartilage.[180] Hypertrophic chondrocytes synthesise type X collagen, and new vasculature in erosive cartilage produces osteogenic progenitor cells and indicates the

beginning of osteogenesis.[589] Shen *et al.*[596] have shown that following mandibular reposition, the experimental group exhibited greater Type X collagen and capillary endothelium than the untreated natural growth group. This indicated that both natural growth and mandibular protrusion displayed a conversion of chondrogenesis to osteogenesis, but this transition was more intense when the mandible was subjected to repositioning. This adaptive change occurs not only in growing animals but also in mature rats. This was proven by two animal investigations by Xiong *et al*.[597,598] in which adult rats were subjected to mandibular advancement, the condylar cartilage showed proliferation of mesenchymal cells and greater expression of Type X collagen and VEGF. Type X collagen serves as a target for capillary invasion and angiogenesis.[599] As mentioned earlier, neovascularisation is essential in cartilage resorption and bone deposition which is indicative of transition of cartilage to bone. VEGF has myriad roles in bone remodelling which include mitogenic and chemotactic action on endothelial cells, indirect induction of osteoblasts proliferation and differentiation and coordinator of chondrocyte death, chondroclast function, extracellular matrix remodelling, angiogenesis and bone formation in growth plate.[600]

Consequently, the proliferating layer and chondroblast layers were thickened and new bone was formed. The increased expression of Type II collagen and Type X collagen seemed to indicate that "dormant" endochondral ossification in mature animal was reactivated in the posterior condyle following mandibular advancement.[226] The new bone formation was characterised by thinner trabecular thickness, more trabecular number, increased trabecular space and greater bone density.[597]

Chondrocytes undergo progressive maturation with phenotypic and morphologic changes during chondrogenesis. Various growth factors regulate chondrogenesis which aim to provide

signals for the regulation of cell proliferation, differentiation and maturation.[601] These factors include insulin-like growth factors (IGF), transforming growth factors (TGF), fibroblast growth factors (FGF), BMPs, PTHrP and members of the hedgehog (Ihh) and Wnt gene families. These factors are transduced within the developing mesenchymal cells, causing a change in gene expression mediated by transcription factors such as the Sox family and core-binding factor alpha (Cbfa).

Mandibular advancement elicits a series of molecular responses in condylar cartilage that are induced by enhanced signalling of growth factors.[602] Upregulation of IGF, FGF-2 and their receptors enhanced the proliferative activity of condylar cartilage.[603] Elevated level of Sox9 is associated with chondrocyte differentiation, which is essential for cartilage matrix formation.[180] Increased expression of VEGF indicated neovascularisation, which precedes osteogenesis.[183] Higher levels of PTHrP expression indicate chondrocyte hypertrophy, marking the transition from chondrogenesis to osteogenesis.[602] An elevated level of Type X collagen has also been explicitly observed in hypertrophic cartilage, which is the terminal stage of chondrocyte maturation. Type X collagen also provides an easily resorbed fabric for the deposition of bone matrix and regulates the calcification process during endochondral ossification. [604]

During adaptive remodelling of condylar cartilage, the proliferative zone becomes thickened, indicating chondrogenesis.[605] When chondrogenesis transitions to osteogenesis, the hypertrophic and erosive zones become thinner because new bone has replaced these zones.

4.8 Vibratory Mechanical Stimulation

Whole body vibration (WBV) of LMHF has been utilised to enhance bone formation and bone healing.[606-608] It can also regulate the synthesis of DNA and protein oligosaccharides, particularly in chondrocytes, and initiate the formation of cartilage.[609,610]

The vibration stress-induced response differs from the response to FSS, which is a rate-dependent response, i.e., linear with frequency.[441] Bacabac *et al*.[611] have shown that the release of NO was positively correlated with the cube of the vibration frequency. In addition, the nucleus appeared to vibrate within the cytoplasm, indicating that vibration stimulation directly stimulates the cell nucleus.[611]

4.8.1 Whole-body Vibration Training

Whole-body vibration training (WBVT) has been recently used as an exercise therapy for osteoarthritis and osteoporosis, aiming to improve bone integrity and muscle coordination to optimise joint function.[612,613] Unlike pharmacological treatment or surgical procedures, mechanical vibration therapy is non-invasive and can be localised. The effect of WBVT on bone and cartilage can be appreciated through research studies on osteoarthritis, osteoporosis, osteopenia, etc. The lack of muscle dynamics due to aging, bed rest, microgravity, or paralysis will suppress osteoblastic activity, resulting in a net loss of bone tissue.[614]

In 2022, osteoporosis and low bone mass affected more than 3.4% of people in Australia.[615] The common pharmacologic therapy for osteoporosis aims to inhibit bone resorption. Medications that increase bone formation, such as parathyroid hormone, fluoride, and insulin-like growth factor, are ideal but rare, with significant disadvantages.[614] Mechanical vibration

has been introduced as a non-invasive alternative treatment for improving bone dynamics and has been proven to be effective in animal studies.[616]

Animal research by Rubin *et al*.[614] investigates the use of LMHF mechanical stimuli on rats with hind legs that were disused. The results revealed that mechanical stimuli with WBV (10 minutes a day at 90 Hz and 0.25 g) in disused animals maintained bone remodelling dynamics similar to those of the long-term weight-bearing controls. This study also suggested that low-level persistent strain is vital in maintaining bone tissue health when subjects are immobilised by space flight, bed rest, or paralysis.

Evidence has shown that extremely low-magnitude (<10 microstrain) mechanical signals at high frequency can stimulate bone formation. Qin et al.[617] discovered that vibrational loads induced at 30 Hz can be osteogenic. In addition, 30Hz sinusoidal WBV of only 0.1g stimulated significant new trabecular bone formation in epiphyses of weight-bearing bones of normal standing animals.[618]

WBV can promote the differentiation[619] and proliferation of osteoblasts and increase the expression of related genes.[620] Ota *et al*.[621] discovered that a vibration acceleration of 5.0 m/s^2 and a frequency of 60 Hz are the most effective conditions for promoting osteogenic differentiation. It increased the expression of Runx2, COL-1 and other osteogenic markers. Another study examined the effect of vibration with a lower frequency of 45 Hz on primary osteoblast culture, showing increased expression of ALP, BMP-2, and OPG, with reduced expression of sclerin.[622] Furthermore, the upregulation of COL-1, OPN, and OCN was found in MC3T3-E1 osteoblasts when subjected to low-intensity (0.25g) and high-frequency (35Hz) vibration.[623] Mechanical vibration promotes expression of Wnt signalling genes and proteins

such as Wnt3a, low-density lipoprotein receptor-associated protein 6 and β-catenin, which activate the Wnt signalling pathway leading to osteoblast formation.[622] In addition, the primary cilia respond to low-intensity, high-frequency vibrations by undergoing morphological changes through microtubule movement, which then translates into signals to osteoblasts.[624]

The magnitude and frequency of the vibration exert different effects on bone and cartilage. Wang *et al*.[625] found that WBTV with a low magnitude and a 20 Hz frequency could improve bone microstructure, increase bone turnover, delay cartilage degeneration, and enhance limb function in rabbits with knee osteoarthritis (KOA). On the other hand, LMHF vibration accelerated articular cartilage degeneration and promoted epiphyseal bone formation in a rat KOA model.[626] At a molecular level, Tossige-Gomes *et al*.[627] have shown that WBVT can decrease the proliferation of CD4+ T cells, indicating that T-cell-mediated immunity is modulated and disease progression has been minimised or slowed in elderly KOA patients. In terms of plasma soluble TNF-α receptors 1 and 2, Simao *et al*.[628] found reduced expression in KOA patients who underwent 12 weeks of WBVT, along with squat exercises. Wang *et al*.[629] investigated the effect of WBVT on IL-1β in KOA patients and found WBVT effectively reduced the erosion of the knee joint cartilage in early KOA by decreasing the expression of IL-1β, HIF-2α and MMP-13 and promoting the expression of COK2A1. The effect was also found to be frequency-dependent, with lower frequencies exhibiting better effects.

4.8.2 Vibration on Craniofacial Sutures

There are many functions of craniofacial sutures. It acts similarly to joints, in which it absorbs and transmits mechanical stresses. It also allows longitudinal growth of craniofacial bones. Sutures respond to tensile forces by anabolic changes, including increased sutural width,

angiogenesis, and bone apposition.[630] In contrast, bone resorption is associated with compression force at the suture.[631] However, recent studies investigated the effect of oscillatory mechanical stimuli on sutural growth and found that anabolic sutural responses occur at both compression and tensile sites.[632,633] Oscillatory mechanical stimuli promote sutural cell proliferation in vivo, as evident in an increased number of sutural cells when the pre-maxillary and nasofrontal sutures were subjected to small doses of oscillatory strain. This resulted in an increase in sutural width. Several genes and transcription factors have been identified as being expressed during sutural growth, including the upregulation of FGF-2,[634] Egr-1 mRNA,[635] BMP-4, and Cbfa1/Osf-2.[636] Stimulation of these gene expressions led to an increase in protein synthesis, such as Type II collagen,[637-640] alkaline phosphatase, and glucose 6-phosphate dehydrogenase (G6PD).[641]

4.8.3 Vibration on Human Chondrocytes in Vitro

Chondrocytes are the only cellular component in cartilage and responsible for synthesising extracellular matrix proteins, e.g. collagen II, proteoglycans, fibronectin and etc.[642] Similar to bone, mechanical stimulation can affect chondrocytes and alters biological processes such as proliferation, cell adhesion, differentiation and signal transduction.[643,644] In addition, mechanical intervention induces reorganisation of human chondrocytes cytoskeleton prior to forming three-dimensional aggregates.[623,645,646] When investigating the long term effect of vibration on chondrocytes, it was found that there was a reduction of osteopontin protein and a decrease in PSMD4 and TBX15 gene expression which suggested a positive effects on human chondrocytes.[647] The effects of vibration seems to vary according to the application frequencies. This was evident in a study on the effect of low-magnitude vibration at different frequencies on bone and cartilage in rabbits with knee osteoarthritis.[648] WBV at 10Hz and 20Hz showed reduced cartilage resorption, increased cartilage formation, and delayed cartilage

degradation. On the other hand, higher frequencies of 30 and 40 Hz induced worsening of limb function, shrinkage of cartilage volume, and cartilage resorption. Lützenberg *et al*.[642] examined the effect of vibration on chondrocytes in vitro and discovered no significant morphological changes; however, they observed significant changes in the fibronectin content of chondrocytes, and the cells began to secrete fibronectin into the extracellular space between adjacent cells. There were also significant changes in gene expression of VCL, PXN, ANXA1, ANXA2, BAX and BCL2 mRNAs. The NF-κB p65 protein was downregulated, indicating that vibration has a cell-protective effect on human chondrocytes.

4.8.4 Vibration on Condylar Cartilage

Bone responds to mechanical stimuli, even at extremely low levels, with high frequency.[606,614,649,650] Condylar cartilage has a distinctive capability to react to changes in mechanical loading.[605] Sriram *et al*.[12] investigated condylar cartilage remodelling in mice subjected to WBVT. There were 40 female 12-week-old C3H mice and the experimental group was subjected to 30-Hz pulses (approximately 5με) for 20 minutes a day, 5 days a week, for 28 days. Upon Micro-CT investigation with osmium tetroxide staining on the specimen, a decreased condylar cartilage volume and an increase in trabecular bone pattern and trabecular number in experimental animals were revealed when compared with sham controls. This indicated that LMHF stimuli induced osteogenesis. Interestingly, this change was similar to the adaptive modelling of condylar cartilage during mandibular advancement orthopaedic appliance therapy.[226,596,597]

4.8.5 Applications of Vibration in Medicine

WBVT machines have been utilised for weight loss, enhancing body strength, and treating specific medical conditions.[651] However, the outcome of the effectiveness has always been inconsistent. This could be due to the variety of training machines used, the type of vibration applied (vertical or rotational), the body posture (standing or with knee flex), and the frequency and magnitude of vibration used in various research studies. WBV has been documented to induce favourable changes in hormone levels, strength, power, muscle mass, muscle electrical activity, jumping ability, balance, psychophysical health, and cortical activation.[652] Different vibration frequencies can exert different biological effects. Vibration <20Hz is generally used for muscle relaxation and reduction of spasticity,[653,654] and vibration between 20Hz and 30Hz can improve gait balance.[655] A vibration frequency of 20 Hz is considered a safe level for humans, as some essential human organs resonate between 5 Hz and 20 Hz.[656] However, cells in the long bones are more sensitive to higher frequencies (>60 Hz) than lower frequencies (<45 Hz). This was evident in some rat studies, which have shown that at a higher frequency of 90Hz, bone formation occurred to a greater extent and halted the detrimental effects that resulted from a disused intervertebral disc.[657,658] At the cellular level, mesenchymal progenitor cells subjected to 100 Hz have an increased cell proliferation rate compared to cells exposed to 30 Hz vibration.[659] Similarly, macrophages were more efficient at 100 Hz than at 30 Hz.[660] In terms of vibration amplitude, there is no linear relationship with the cellular output. An example from an animal study is that when the acceleration magnitude increases from 0.1g to 0.3g, the cellular efficacy decreases. When the acceleration increases to 1.0g, the cellular output is restored to a 0.1g level.[661] The effect of vibration therapy duration follows a different relationship. The effect will increase as the duration increases up to a point of saturation, beyond which any further increase in duration will exert the same effect.[444,662,663]

There are many physiological mechanisms associated with the use of WBVT. Firstly, vibration creates rapid muscle contractions, which activate both voluntary and involuntary muscle fibres, leading to greater muscle engagement during exercise.[664] In addition, WBVT improve muscle performance by boosting the involvement and synchronisation of motor units, leading to motor learning and neural adaptations.[665,666] Moreover, vibration therapy has been shown to elevate growth hormone levels and diminish cortisol levels.[667,668] Furthermore, mechanical stress on bone stimulates the bone remodelling process via osteogenesis. Lastly, muscle strength and proprioception are heightened by activating muscle proprioceptors and expanding the myocyte content.

Osteoporosis is a progressive bone disease characterised by reduced bone mineral density, leading to deterioration of bone microarchitecture.[669-671] Generally, as men and women age, the levels of estrogen and testosterone are reduced by sex hormone-binding globulin, and this reduction is more pronounced in women, as estrogen production declines after menopause.[672] This regression in estrogen augmented bone apoptosis by reducing osteoblast production of osteoprotegerin and increasing RANKL.[673] Pharmacological interventions such as anti-osteoporotic drugs, hormones and supplements can be costly and have long-term adverse effects.[674] Therefore, the research focus has shifted to non-pharmacological therapies, such as exercise and WBV stimulation. Exercise has been found to promote osteogenesis, which initiates bone growth by modifying bone tissue architecture, increasing peak bone mass, reducing the risk of fractures and delaying the onset of osteoporosis, thereby slowing down the decline in bone mineral density.[675,676] WBVT is performed with patients either standing upright with or without their knees flexed on a vibration platform. WBV produces strains and modulates muscular force contractions that have been shown to improve bone density, muscle architecture, and function.[663,677-679]

WBVT has been discovered to be effective in preventing bone loss in post-menopausal women.[680] This was confirmed by a recent systematic review and meta-analysis carried out by DadeMatthews *et al*.,[681] who examined 30 eligible studies on WBV and bone health. There was improvement of bone density after WBV in healthy (Hedges' g=0.10; p=0.01, 95%CI=0.02, 0.17) and postmenopausal women (Hedges' g=0.09; p=0.02, 95%CI=0.01, 0.18). However, there was no significant effect on either bone formation biomarkers (bone-specific alkaline phosphatase (BSAP), serum osteocalcin and procollagen type 1 N-terminal propeptides (P1NP)) or bone resorption biomarkers (bone resorption C-terminal telopeptide of type 1 collagen CTX1). In an earlier systematic review and meta-analysis, Harijanto *et al.*[682] investigated the concurrent effects of WBV on both bone and muscle health. It was reported that WBV did not have significant synergistic effects on bone mineral density in the hip and lumbar spine, lean muscle mass, and sit-to-stand time outcomes when compared to the control with no WBV. This was due to some studies that were reviewed, which included patients on pharmacological treatment or an exercise regimen, while others excluded patients with osteoporosis. Moreover, different WBV regimes and modes were employed in various studies, which contributed to the limitations of this systematic review. The most recent systematic review examining the therapeutic effects of WBV on postmenopausal women with osteoporosis provided a broader picture, focusing on skeletal, muscle, and fat parameters.[683] The meta-analysis showed that WBV can significantly increase lumbar spine bone mineral density (BMD) (weighted mean difference (WMD)=0.018; 95%CI: 0.004 to 0.032; P=0.011), femoral neck BMD (WMD=0.005; 95%CI:0.001 to 0.011; P=0.0493) and reduce pain degree (WMD=-0.786; 95%CI:-1.300 to -0.272; P=0.0027). There was no significant effect on patients' muscle mass (WMD=0.547; 95%CI: -1.104 to 2.199; P=0.5158) and fat mass (WMD=0.530; 95%CI: -2.389 to 3.448; P=0.7222). Interestingly, when the studies were

stratified by follow-up period, a significant difference was observed at the six-month follow-up. Still, no significant difference was observed at the 12-month follow-up. This could be due to physiological adaptation to mechanical stimuli.[684]

WBV not only improves musculoskeletal health, but it also has physiological benefits in enhancing neuromuscular performance parameters.[685] Although the recent systematic review concluded that there was low certainty of evidence regarding the use of WBV training machines in improving neuromuscular activity in healthy individuals, the authors have shown that most studies have indicated that WBV increases muscular EMG activity, especially in the pelvic and lower limbs.[686] In addition, the higher the frequency and/or magnitude of WBV, the stronger the EMG activity. WBV has been used to improve muscular activity in individuals who cannot exercise, such as those suffering from severe chronic obstructive pulmonary disease (COPD).[687,688] Cunha *et al*.[689] found in their systematic review that four out of seven studies showed that WBV increases muscle power in COPD patients, suggesting that WBV can be a practical alternative therapeutic option for patients with low tolerance to physical exercise.

WBV has also been investigated for controlling glycaemic levels in patients with type 2 diabetes mellitus (DM2). This is because these patients may acquire physical disabilities and comorbidities, which make adhering to routine aerobic exercise challenging for them. Regular exercise enhances glucose uptake in active muscles, leading to improved insulin sensitivity in individuals with diabetes. There are controversial findings regarding the effect of WBV on glycaemic levels. A systematic review and meta-analysis conducted by Fabregat-Fernández *et al*.[690] assessed the impact of WBV intervention on blood glucose levels and glycosylated haemoglobin (HbA1c) levels in patients with DM2. It was discovered that two-thirds of the studies analysed showed a decreased fasting blood glucose after the use of WBV, but only one-

third of the studies reported a decrease in HbA1c. It also appeared that 12 weeks of WBV intervention were necessary to improve white blood cells and HbA1c levels in patients with DM2. When examining the frequency of WBV, the positive effect was more pronounced when starting at a low frequency and gradually increasing the frequency.

Stroke patients can also benefit from WBV therapy, which significantly reduces motor impairment and enhances motor function. This therapy is even more effective when combined with rehabilitation.[691] Vibration therapy stimulates muscle activity through the excitation of the tonic vibration reflex, which activates efferent Ia nerve fibres, leading to α-motor neuron excitation to generate muscle fibre strength and induce motor function performance.[692,693] Lu *et al*.[691] have shown through their systematic review and meta-analysis that vibration therapy has significantly decreased upper extremity motor impairment, and this improvement was greater with concurrent standard rehabilitation. Similarly, the use of vibration therapy significantly increased upper extremity motor function and improved disability indices.

Knee osteoarthritis is a chronic deterioration of the condylar cartilage due to wear and tear.[694] Patient with knee osteoarthritis complains of knee pain, swelling, limited mobility, stiffness and functional impairment, which impact their daily lives.[695,696] Vibration therapy has been used as an adjunct to conventional rehabilitation in patients who have suffered from knee osteoarthritis. It has been shown that WBVT, combined with conventional rehabilitation, significantly reduces pain and enhances physical function in patients with knee osteoarthritis.[697] The pain reduction seemed to be more effective with high-frequency vibration training. This result is paramount, as the willingness of an individual to commit to rehabilitation or even daily routines hinges on the pain level experienced and functional mobility.

4.8.6 Application of Vibration in Dentistry

Vibration has been used widely in various fields of dentistry. Mechanical vibration can stimulate reduced alveolar bone loss where teeth are missing or in patients with osteoporosis, to help preserve and treat that alveolar bone loss.[698-700] It has also been suggested to minimise patient discomfort from orofacial pain,[701-703] orthodontic therapy and local anaesthetic administration. A systematic review on the use of vibration therapy during local anaesthetic administration showed a reduced perception of anxiety and pain related to the injection. It was assisted by the noise of the vibrational device, which distracted the patient during the injection.

4.8.6.1 Orthodontics

Several animal studies have shown that mechanical vibration can accelerate the rate of tooth movement with no adverse effects on the periodontal tissues.[704-706] The rationale behind this is based on the two proposed theories of orthodontic tooth movement: piezoelectric theory and pressure-tension theory. According to piezo-electric theory, when a force is applied to the tooth, the alveolar bone bends and generates an electric charge, which initiates an osteogenic response.[707] By applying fast intermittent force, such as mechanical vibration, stress-induced piezoelectric charges are induced, stimulating an osteogenic response.[708,709] The pressure tension theory highlights the change in blood flow through the periodontal ligament, which activates cellular responses through chemical mediators, favouring osteogenesis on the tension side and bone resorption on the pressure side. Laboratory studies have confirmed that vibratory stimulation can activate the receptor activator of NF-κB and its ligand (RANK/RANKL) signalling pathway, leading to osteoclast formation and enhanced bone remodelling.[704]

There are two commercially available intraoral vibration devices on the market: AcceleDent (OrthoAccel Technologies Inc., Bellaire, Texas) and VPro5 (Propel Orthodontics, Ossining, New York). AcceleDent was recommended for use 20 minutes a day, whereas VPro5 was recommended for use 5 minutes a day. Each device emits different vibration frequencies, with AcceleDent being a low-frequency device (30 Hz) and VPro5 being a high-frequency device (120 Hz). The effect of these commercially available vibration devices has been studied clinically, but the results have been inconsistent and inconclusive.[710-712] This could be due to the stock standard mouthpiece that accompanies the commercially produced vibration device being too stiff and unable to accommodate the crookedness of the teeth, which consequently cannot deliver the same vibration stimulation to all teeth. Discrepancies among results could also be due to variations in vibration protocols, orthodontic mechanics and measured outcome. Some research studies utilised electric toothbrushes to induce vibratory stimulations, which probably have inconsistent vibration frequencies. However, the electric toothbrush seemed to be a good research idea as it incorporates the tooth cleaning capacity with orthodontic tooth movement acceleration.

4.8.6.1.1 Low Frequency Vibratory Stimulation

From early research on the impact of low-frequency devices used in conjunction with orthodontic appliances, promising results have been observed, especially in animal models[704] and clinical studies,[713,714] particularly with aligners. However, as more human research studies have been carried out, the evidence seems to point in the opposite direction.[715-717] Favourable results with aligners could be due to the better seating of clear aligners to occlusion, which allows for more accurate tracking and faster progress of the aligners.[718] However, there seemed to be no biological response associated with the shortened treatment time.

The effectiveness of a lower frequency device has been questioned, and studies have shown that high-frequency vibration is more effective in accelerating tooth movement compared to low-frequency vibration.[706,718] This was further validated by the most recent Cochrane review[719] that examined the effectiveness of non-surgical adjunctive interventions for accelerating tooth movement. The vibrational studies included in the review utilised a vibrational device that emits a vibrational frequency below 60 Hz. The review showed that light vibrational forces did not increase the rate of tooth movement or shorten the orthodontic treatment time, regardless of whether fixed orthodontic appliances or removable aligner orthodontic therapy was used. In terms of secondary outcomes, such as pain, occlusal outcome, and orthodontically induced inflammatory root resorption (OIIRR), there was also no difference between the vibratory group and the control group.

4.8.6.1.2 High Frequency Vibratory Stimulation

Perhaps high-frequency vibration may paint a different picture of accelerated tooth movement. The physiological effects of high-frequency vibration (HFV) on dental tissues have been investigated using animal and human models. It has been found that HFV boosts osteoclastic (via NF-κB activation) and osteoblastic activities, increasing bone density and enhancing bone remodelling.[698,700,705,706,720-725] It also has an additive effect on the PGE2 and RANKL levels of periodontal ligament cells.[721] In addition, HFV encourages the differentiation of human periodontal cells by upregulating Col-I, Runx2, and Osterix growth factors.[722] An *in vitro* study carried out by Judex *et al*.[620] compared the cellular responses in osteoblasts, fibroblasts, and osteoclasts using two vibrating devices: VPro5 (120 Hz, 0.41 g) and AcceleDent (30 Hz, 0.24 g). The results of this experiment showed that HFV from VPro 5 elicited a greater response, i.e., increased cell proliferation and gene expression, in osteoblasts and fibroblasts.

Interestingly, the osteoclastic response was equally effective with both appliances. A recent systematic review assessed both human and animal *in vivo* studies on the exposure to high (>30Hz) and low (30Hz) frequency mechanical vibrations during accelerated orthodontic tooth movement.[726] Although the literature analysed has conflicting views on both high- and low-frequency stimulation, the authors indicated that HFV was preferable to low-frequency vibration, as most studies, both *in vivo* and clinical, showed that high-frequency vibration increased aligner change, tooth movement and space closure with fixed appliances.

Currently, there have been limited systematic reviews and RCTs regarding HFV and accelerated tooth movement in humans. A split-mouth design experiment was carried out by Leethanakul *et al*.,[727] which utilised a high-frequency electric toothbrush (125 Hz) to exert vibratory stimuli on the canine being distalised. The experimental side was randomised, with the contralateral side serving as control. The results showed enhanced IL-1β secretion in the pressured side of the gingival crevicular fluid, accompanied by accelerated tooth movement. The heightened IL-1β level indicated osteoclast fusion and activation, which regulated alveolar bone remodelling.[728] Later, Shipley[724] performed a pilot study on the effect of a high-frequency acceleration device in conjunction with CAs. The preliminary study reported a significant decrease in the time required, and patients who required refinement aligners were also significantly fewer in number. In fact, no refinements were needed by patients who used high-frequency acceleration devices. This project had a few biases associated with it. Firstly, there was a gender bias as there was unequal sex distribution that could not be corrected statistically. Additionally, the author has disclosed that the research project was financially supported by Propel Orthodontics, and the author has served as a consultant for Propel Orthodontics in the past. Therefore, further robust RCTs are required to prove the effectiveness of the HFV device when used to accelerate tooth movement. Shipley *et al*.[723] further investigated the effect of

HFV on bone density following orthodontic treatment. This study was built on the premise that previous animal studies have shown minimal bone loss or even restoration of bone density in diseased rats (osteoporosis) when subjected to WBV. Improved bone density in the alveolar bone may improve the prognosis of retention following orthodontic treatment. The results of this study indeed revealed that HFV resulted in a significant change in bone density following aligner therapy. In addition, this gain in bone density resulted in significantly higher bone density compared to the control group. This meant that HFV has a promising potential in supporting occlusal stability and preventing orthodontic relapse.

Interestingly, HFV demonstrated a paradoxical biological effect, especially in orthodontic tooth movement.[706] HFV appears to have a significant anabolic effect in healthy tissues or those in a repair phase, particularly when inflammatory mediators are at low levels.[699,729-731] On the other hand, HFV intensifies inflammation at elevated levels of inflammatory mediators, which initiates a catabolic effect.[732,733] Therefore, during orthodontic tooth movement, with significant inflammatory mediators in the periodontal ligament, osteoclastic effects are favoured, leading to accelerated tooth movement. In the absence of orthodontic force and inflammation, HFV can induce an anabolic effect, which could potentially increase the stability and retention of orthodontic results. Below is a table obtained from Alikhani *et al*.,[706] which summarises the possible anabolic and catabolic effects of HFV and its application in orthodontics.

	Anabolic Effect	Catabolic Effect
Method of application	Directly on teeth in the target area, or indirectly on adjacent teeth close to the target area	Directly on tooth or teeth that are moving
Initial state of tissue	Physiologic condition	Inflammatory condition

Target tissue	Bone	Periodontal ligament
Responding cells	Osteocytes and Osteoblasts	Osteoclasts
Resulting effect	Bone formation (Load-independent)	Bone resorption (Load-dependent)
Extension of effect	Gradient effect with highest response on bone surrounding target tooth and extending to adjacent bone	No gradient effect, effective only on target tooth exposed to orthodontic forces with no effect on adjacent teeth
Potential clinical uses	– Preservation of alveolar bone after extractions – Bone regeneration after periodontal disease – Enhance Implant and graft integration – Increased bone formation after Orthopedic treatment – Improved retention after Orthodontic treatment – Increased bone formation after Orthognathic Surgery	– Accelerated tooth movement – Increase in magnitude of movement (distance) – Differential anchorage – Increase in magnitude of Orthopedic correction – Reduced bone density around target tooth to facilitate different types of tooth movement – Reduced necrotic (hyalinized) area in response to static Orthodontic forces – Possible increased frontal resorption

Table 2 - Anabolic and catabolic effects of HFV and their possible applications in orthodontic treatment (adopted from Alikhani et al.[706]

Compliance is another factor that impacts the effectiveness of vibrational stimulation in orthodontic treatment. Miles & Pandi[718] found that the vibration device compliance reduced progressively over the observation period, from a median of 83.0% at the beginning to a median of 51.0% at the end of the 12.5-month evaluation period.

4.8.6.1.3 Orthodontically Induced Inflammatory Root Resorption (OIIRR)

Root resorption is an unavoidable side effect of orthodontic tooth movement. Many studies have been carried out to investigate the use of a vibratory device in minimising OIIRR. DiBiase *et al.*[734] assessed the influence of light vibrational forces, exerted by AcceleDent, on the

severity of OIIRR by measuring root length reduction in the upper central incisors using periapical radiographs. At the end of the alignment stages, there was no statistically significant difference in root length between the control and experimental groups. This was further confirmed by a micro-CT study that quantitatively measured the differences in root resorption crater volume between the control group and the vibration group, both of which had buccally directed orthodontic forces of 150g applied for 12 weeks, showing no significant differences between the groups.[735] In this study, the Oral-B HummingBird device exerted the vibration with a modified tip. The vibration frequency was documented as 50 Hz and applied for 10 minutes per day for 12 weeks. More recently, in an animal model, Mayama *et al.*[736] carried out a split-mouth study examining whether high-frequency vibratory stimuli have a positive effect on orthodontic tooth movement and OIIRR. Although the vibratory group showed significantly faster tooth movement, there was no statistically significant difference in the degree of OIIRR between the control and experimental groups. The vibration frequency used in this study was 102.2 ± 2.6 Hz.

4.8.6.2 Periodontics

Mechanical vibration has been used to maintain periodontal health by improving the activity of periodontal fibroblasts, promoting the differentiation of periodontal stem cells, and supporting alveolar bone height.[737] Fibroblasts are essential repair cells for soft tissue injury.[738] Judex *et al*.[620] found an increased secretion of FGF2 and CTGF in fibroblasts when subject to 30Hz and 120Hz vibration. The effects were 30-40% higher with 120Hz. This showed that fibroblastic activities were more sensitive to HFV. Benjakul *et al.*[721] discovered that LMHF promoted the osteogenic differentiation of periodontal ligament stem cells by increasing the expression of PGE2, RANKL, and sRANKL. This helped promote bone remodelling. Lastly, Alikhani *et al*.[700,720] found that HFV can stimulate bone formation in healthy alveolar bone.

There was also accelerated bone healing and alveolar bone preservation at the tooth extraction site.

Osteoporosis can also manifest in oral tissue as periodontal disease,[739] reduced alveolar bone, [740] tooth loss,[741,742] and decreased dental implant integration and stability.[743] Pharmacological therapy has been used to treat osteoporosis, but long-term use can result in osteonecrosis.[720,744] Mechanical vibration is one of the non-invasive treatment alternatives. As mentioned earlier, evidence has shown that HFV has an osteogenic effect on healthy alveolar bone and preserves alveolar bone structure after tooth extraction.[699,700] The question is whether it would have a similar effect on osteoporotic alveolar bone. Alikhani *et al*.[698] carried out an animal experiment to investigate this and found promising results. The results demonstrated that animals exposed to HFV had higher osteoblast activity and lower osteoclast activity. This was indicated by elevated levels of RunX2, Foxo1, Osterix and Wnt signalling factors. The reduced osteoclastic activity was indicated by the downregulation of RANK/RANKL and Sclerostin levels. This study also showed that the HFV remedy is a localised therapy, as the osteogenic effect dissipates when it is further away from the point of application.

4.8.6.3 Pain Control

Another application of vibration devices that has been suggested in the dental field is pain control, especially during orthodontic treatment. The biological rationale behind it is that vibration may increase vascularity and limit ischaemia, which may prevent or relieve inflammation and pain.[745] Musawi and Kadhu[746] evaluated different methods for reducing pain associated with debonding the orthodontic brackets. This RCT demonstrated that HFV could significantly enhance patient comfort during the orthodontic debonding procedure, particularly in the more sensitive anterior dental region. However, a Cochrane review by Fleming *et al*.[745]

has found that low-quality short-term data showed no difference in pain levels during orthodontic therapy between the control group and the group that received vibratory stimulation. When long-term assessment was carried out, Lobre *et al*.[747] found that the mean pain was lower during the second and fourth months in the vibratory group compared with the control group. However, Lobre *et al*.'s[747] study was considered to have a high risk of bias according to the Cochrane review. All in all, the current evidence for the use of vibrational devices in reducing orthodontic pain is of very low quality, and firm conclusions cannot be made.

4.8.6.4 Dental Implants

As vibration has a positive effect on osteogenesis and bone remodelling, it has been suggested as an augmented treatment to enhance the osteointegration and stability of dental implants. Patients who suffer from bone metabolic diseases, such as osteoporosis, are prone to dental implant failures due to poor bone mass and poor healing.[748-751] Ye *et al*.[752] carried out a systematic review on vibration stimulation and implant osseointegration in animals. Although the evidence was considered of medium and low quality, the systematic review and meta-analysis have shown that LMHF vibration improve bone-to-implant contact (BIC) and peri-implant bone volume relative to tissue volume (BV/TV). Whole body vibration in the rat model appeared to show better BV/TV than direct loading vibration. LMHF vibration may play a role in enhancing osseointegration, particularly for patients with osteoporosis.

5.0 SUMMARY

Mandibular retrusion is the most common skeletal discrepancy associated with Class II division 1 malocclusion, particularly in the Caucasian population. Aetiological factors are a combination of genetic and environmental factors, including oral habits and airway obstruction. Most patients with Class II malocclusion seek orthodontic treatment for aesthetic and functional improvement. Unfavourable facial aesthetics associated with Class II malocclusion include increased overjet, lack of chin projection, and a convex profile, which have a negative impact on self-image acceptance and lower self-esteem. Increased overjet, together with incompetent lips, predisposes patients to dental trauma. Mandibular retrusion is also associated with reduced upper airway volume, which increases the risk of sleep-disordered breathing. Temporomandibular joint disorder has been found to be higher in patients with Class II malocclusion. Considering all these issues, treatment of Class II at the optimal time is paramount to prevent the propagation of complicated health issues.

The preferred choice of Class II division 1 malocclusion with mandibular retrusion treatment modalities depends on the severity and growth status of the patient. The skeletal discrepancy can be corrected in two ways. Firstly, functional appliance therapy is used to improve mandibular skeletal discrepancies as a growth modification treatment in growing individuals. For mature patients who have minimal to no pubertal growth potential and moderate to severe Class II malocclusion, orthognathic surgery is recommended to correct the underlying skeletal discrepancy. When the malocclusion is mild to moderate, the underlying skeletal discrepancy can be masked with camouflage orthodontic treatment. Sometimes, a genioplasty could be employed when the patient matures to improve the deficient chin projection.

Functional appliance therapy is built on the premise that the orthopaedic appliance positions the mandible anteriorly, stretching the muscles and soft tissues that exert tension on the bone. As a result, the condylar cartilage cells are stimulated, and consequently, the growth of mandibular bone occurs. The biological foundation for functional appliances can be appreciated through the understanding of condylar cartilage mechanobiology. Condylar cartilage is a secondary cartilage that undergoes adaptive remodelling in response to external stimuli. It is arranged as a unique, zone-like packing of chondrocytes in various forms, representing different stages of chondrogenesis and its transition to osteogenesis. When the mandible is advanced anteriorly, the mesenchymal cells in the articular layer are stretched and reoriented towards the pull, resulting in an increased mesenchymal population and enhanced differentiation into chondrocytes, which contributes to the adaptive remodelling process.

Aside from mandibular growth, a small increment of anterior maxillary growth restraint has also been evident, resulting from functional appliance therapy. Generally, the skeletal component of Class II malocclusion accounts for approximately 40%. The remainder are from dental corrections, mainly due to distalisation of the upper teeth and mesialisation of the lower teeth. Proclination of lower anterior teeth can be an unwanted side effect of functional appliances. Many researchers have investigated methods to control this undesirable proclination, and with the advent of skeletal anchorage technology, mini-plates or mini-implants have been incorporated with functional appliances to control these side effects.

There is evidence of soft tissue improvement resulting from functional appliance therapy. Profile enhancement involves improving chin projection and lip position, specifically retraction of the protruding upper lip. There is also an increase in facial convexity, mentolabial angle, and Z-angle.

As mentioned earlier, the effectiveness of functional appliance therapy largely depends on the patient's growth status. Evidence has shown that skeletal correction with a functional appliance is best performed when the patient is actively growing. However, fixed functional appliances have been used in late adolescents and even adults to induce dentoalveolar changes during camouflage treatment. This has an advantage over the use of elastics due to the non-compliant nature of the fixed functional appliance. In fact, due to the invasive nature and financial burden of orthognathic surgery, the use of fixed functional appliances in camouflage treatment has been considered as a treatment alternative in borderline Class II surgical cases.

There has been an increasing awareness of sleep-disordered breathing in recent years. Deformation or obstruction of the pharyngeal airway could lead to sleep-disordered breathing. Postural change and relaxation of dilator muscles of the pharynx during sleep lead to an increase in airway resistance. This could be exacerbated by retro-position of either or both maxilla and mandible. As functional appliance therapy promotes anterior positioning of the mandible, the hyoid bone, and associated muscles, this helps maintain the patency of the upper airway. In fact, functional appliance therapy produces positive changes in the posterior airway, specifically increased oropharynx volume and MCA of the airway.

Mechanical vibration has been widely used in the medical field to enhance bone integrity. This is based on the principle that mechanical stimulation promotes differentiation and proliferation of osteoblasts. Similarly, mechanical vibration of a certain frequency has a positive effect on human chondrocytes. Currently, animal models have shown that WBV at 10-20Hz decreases cartilage resorption and increases cartilage formation. Mechanical stimulation has also extended its use in dentistry to reduce pain, accelerate tooth movement, maintain periodontal

health, and preserve and treat alveolar bone loss. The clinical use of vibration therapy in dentistry comes in two modes: high frequency and low frequency, which can lead to different biological responses. Low-frequency vibration appears to be efficacious in animal models, and HFV has been shown to be effective in accelerating orthodontic tooth movement in humans. In 2009, Sriram *et al.*[12] explored the effect of LMHF vibration on the condylar cartilage of mice. The results revealed a significant decrease in the volume of condylar cartilage and a significant increase in bone histomorphometric parameters, suggesting an enhancement of adaptive remodelling of the condylar cartilage. However, since then, no study has been reported that simulates the use of mechanical vibration in humans to induce condylar changes in a clinical setting. With the advent of commercially available intraoral vibration devices, application of mechanical vibration at the dentoalveolar level can be easily achieved clinically, but question remains whether the mechanical vibration at the dentoalveolar level can be transmitted to the mandibular condyle and induce positive change. Therefore, the scope of research concerning the application of mechanical vibration in clinical orthodontics, beyond its role in accelerating tooth movement, has been re-established and merits further in-depth investigation.

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Chapter 2: Effects of Mechanical Vibration on Class II Orthopaedic Appliance Therapy at Different Stages of Skeletal Maturity – Cephalometric Study

1.0 Introduction

Functional appliance therapy is effective in treating patients with Class II division 1 malocclusion and mandibular retrusion during the active growth phase. However, the skeletal effects of functional appliance therapy are controversial and diminish as patients mature into the late adolescent stage.[1,2] From then on, orthognathic surgery would be required to induce optimal skeletal changes, but this could be costly and accompanied by surgical risks. In recent years, fixed functional appliance therapy has been implemented in young adults to camouflage the underlying Class II jaw discrepancy. The overjet and molar corrections were predominantly dentoalveolar in nature, with skeletal component contributions of 22-37% and 25-27%, respectively.[3,4]

Mechanical vibration has been utilised for many years in the medical field to stimulate the activity of bone and cartilage cells. It has also been extended to dentistry and used for alveolar bone maintenance, pain reduction, and accelerated orthodontic tooth movement. The question remains whether mechanical vibration has a positive adjunctive role in enhancing skeletal changes during functional appliance therapy.

Almost 20 years ago, the Department of Orthodontics at the University of Sydney began a series of research on the biological response of craniofacial structures to mechanical vibration. The initial research was a preliminary animal study, which demonstrated a positive effect of pulsed electromagnetic field vibration during orthodontic tooth movement.[5] The tooth movement was significantly more under pulsed electromagnetic field vibration stimulation. Thereafter, the team decided to investigate the effect of mechanical vibration on the healing of mice's cranial bone. Utilising micro-CT investigation, it was found that low-magnitude, high-frequency (LMHF) mechanical vibration assisted in the healing capacity of non-weight-

bearing cranial bones.[6] From the results of this experiment, interest was extended to the influence of mechanical vibration on condylar cartilage. In a mouse model, LMHF mechanical vibration was induced through a whole-body vibration platform.[7] The condylar cartilage was segmented using micro-CT with the aid of a special stain, which enables the quantitative measurement of the condylar cartilage volume. The results indicated a significant decrease in condylar cartilage volume and a significant increase in bone histomorphometric parameters, suggesting an enhancement of adaptive remodelling of the condylar cartilage. Years following, the team diverted the application of mechanical vibration to prevent orthodontically induced root resorption, with both animal and human studies failing to show any significant benefit.[8,9] With the advent of a commercially available intraoral mechanical vibration device, the team now refocused and translated the animal research conducted on mice regarding the adaptive remodelling of condylar cartilage into a practical application in a day-to-day clinical setting.

Therefore, the scope of the present investigation focused on the dental, skeletal, and facial soft tissue changes associated with functional appliance therapy, with and without the concomitant use of a commercially available intraoral mechanical vibration device, during both the peak pubertal growth period and the post-peak pubertal growth period.

2.0 Aims

The primary aim of the current investigation was to measure and compare the dental, skeletal and soft tissue effects of Class II functional appliance therapy with and without simultaneous mechanical stimulation. The secondary aim was to determine if these effects varied by skeletal maturity, specifically during the peak-pubertal and post-pubertal stages.

2.1 Significance of the Aims

This study investigated the impact of mechanical vibration on the dental, skeletal and facial soft tissue effects of Class II functional appliance therapy at different skeletal maturities. Literature suggests that functional appliance therapies are most effective when performed while there is still growth potential, especially during the peak pubertal growth stage. However, some patients may seek treatment later in life due to financial, family, or personal reasons and may miss the ideal treatment period or approach the end of their growth potential. As a result, these patients may face the option of orthognathic surgery to achieve skeletal correction, which could be costly and have comorbidities. To date, no study has investigated the use of mechanical vibration to enhance the dentoskeletal outcomes of a functional appliance. The results of this study may shed light on whether patients nearing the end of their growth can still be treated orthopaedically with a functional appliance when a commercially available mechanical vibration device is used concurrently, thereby avoiding the need for orthognathic surgery.

3.0 Null Hypothesis

1. There were no statistically significant differences in dental, skeletal, and facial soft tissue effects between Class II functional appliance therapy with and without concomitant mechanical vibration.
2. There were no statistically significant differences in dental, skeletal and facial soft tissue effects between Class II functional appliance therapy with concomitant use of mechanical vibration between the two different skeletal maturity statuses.

4.0 Method and Materials

4.1 Trial Design and Ethics

This was a prospective, randomised, placebo controlled clinical trial. Ethics approval was obtained from the Research Ethics and Governance office at the Royal Prince Alfred Hospital before the commencement of the study. (Ethics approval number HREC/16/RPAH/681).

4.2 Subjects

Selection of subjects was from the orthodontic waiting list at the Sydney Dental Hospital, who met the following inclusion and exclusion criteria.

The inclusion criteria for this trial included:

1. Class II division 1 malocclusion;
2. Overjet of at least 6 mm;
3. ANB angle of 3.5^{o} or greater;
4. Permanent dentition;
5. No previous orthopaedic and orthodontic treatment;
6. Cervical growth stage of 2 to 5.

The exclusion criteria for this trial are as follows:

1. Congenital syndromes;
2. Obvious asymmetry;
3. Temporomandibular joint disorder signs and symptoms.

A total of 118 patients from the orthodontic waiting list were screened, and 59 subjects met the inclusion and exclusion criteria. All these patients would require Class II functional appliance therapy as part of their treatment, regardless of their participation in this research. The chief investigator (LC) invited these potential subjects to participate in the study and explained, both verbally and through written information sheets, the aims and design of the investigation to them and their parents or guardians. The subjects and or their parents or guardians were given at least two weeks to consider their involvement. Fifty-five subjects were enrolled in the study, and all subjects and their guardians provided both verbal and written consent.

Of the original sample, one patient terminated treatment early at five months because of treatment refusal. One patient did not have a complete record, and three patients were not occluding during the radiographic examination; therefore, accurate analysis could not be carried out, and these patients were excluded from the study. These four dropouts resulted in a final sample of 50 subjects for statistical analysis. (Figure 1)

4.3 Groups

Fifty-five patients aged 11 to 18 years who were enrolled in the study were randomly allocated into four different groups by independent clinicians (AP, OD, NG) who did not participate in the clinical treatment or data analysis. There were two placebo control groups and two experimental groups. The placebo control groups consisted of subjects who received Class II functional appliance therapy. One placebo control group was at the peak pubertal growth phase (Group FA-Y), as indicated by cervical vertebrae maturation stage (CVS) 2 to 4, and the other placebo control group was at the post-peak pubertal growth phase (Group FA-M), as indicated by CVS 5. The experimental groups included subjects who received Class II functional appliance therapy with concomitant mechanical vibration stimulation. One experimental group

was in the peak pubertal growth phase (Group Vib-FA-Y), as indicated by CVS 2 to 4, and the other experimental group was in the post-peak pubertal growth phase (Group Vib-FA-M), as indicated by CVS 5. Chronological age and secondary sexual characteristics, such as the onset of menses in females and evidence of facial hair and voice changes in males, were also used to determine the growth status of subjects when CVS ambiguity occurred.

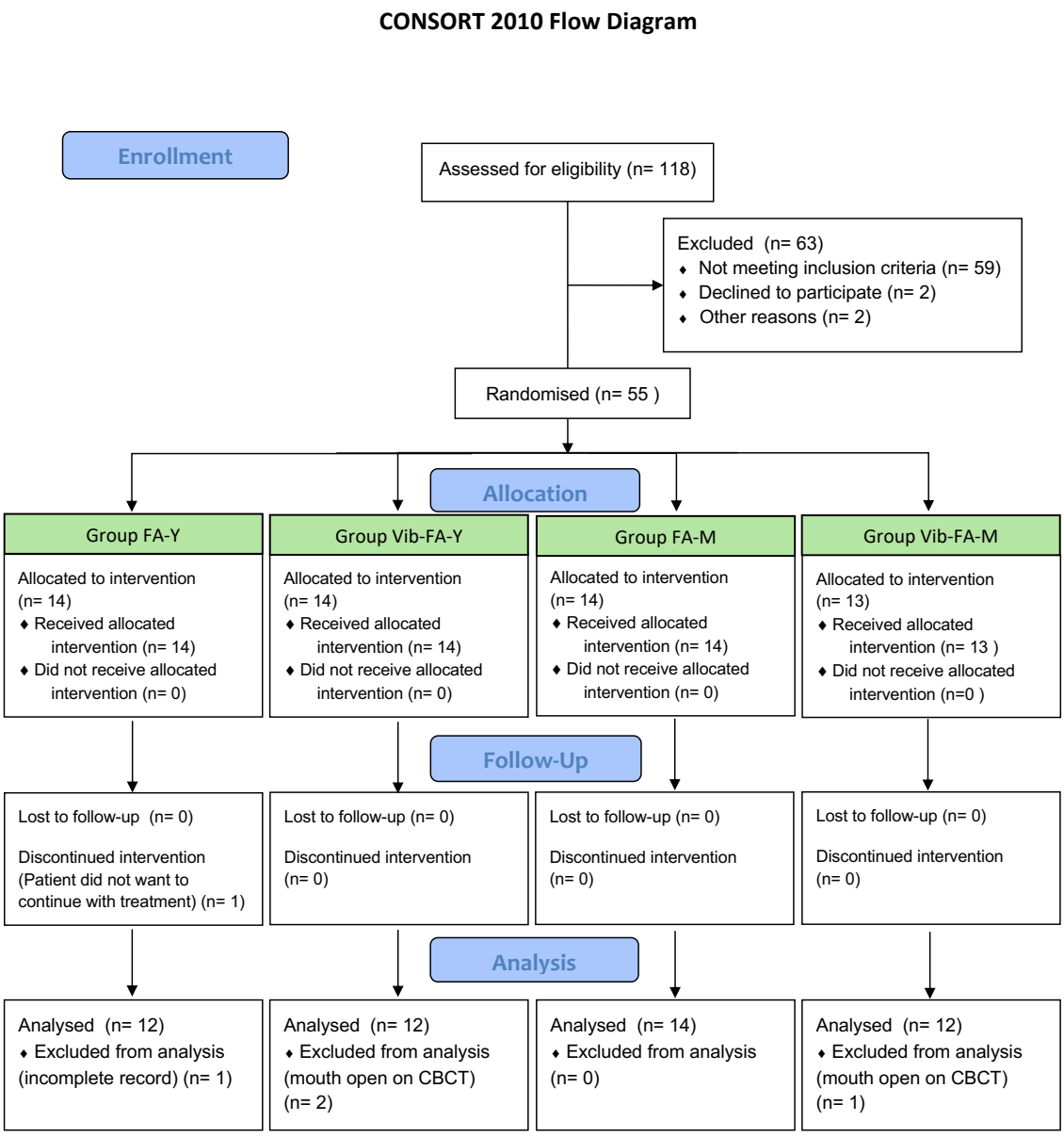

Figure 12 - CONSORT 2010 flow diagram illustrating movement of participants from enrolment to analysis

4.4 Sample Size Calculation

The sample size for the groups was calculated using Harvard University's ARDS Network (https://hedwig.mgh.harvard.edu/sample_size/js/js_parallel_quant.html) based on a significance level of 0.05 and a power of 80 per cent to detect a clinically meaningful difference of 1° (±0.5°) for the ANB angle changes among the groups. The power analysis indicated that 12 patients were required in each group. It was intended to recruit 15 patients for each group to compensate for dropouts.

4.5 Randomisation

Independent clinicians (AP, NG, OD) who did not participate in the clinical and analytical parts of the study was responsible for dispensing either the active vibration device or the placebo vibration device to patients according to a computer-generated randomisation list. The randomisation sequence was generated using the Excel program developed by Kim *et al.*[10] (http://cafe.naver.com/easy2know/6427) and was stratified by centre, with a 1:1 allocation using a random block size of 4.

4.6 Blinding

Both the patients and the clinical operator who was responsible for providing functional appliance therapy and data analysis were blinded in this study. All patients received an intraoral mechanical vibration device. The patients in the placebo control groups were given non-operable devices, while the patients in the experimental groups were given full instructions and operable devices. The clinical operator responsible for treatment and data analysis was the chief investigator (LC), who did not participate in the randomisation and group allocation processes.

4.7 Intervention

All patients were treated with a Hanks Telescoping Herbst appliance (American Orthodontics Corporation, Sheboygan, WI, USA) incorporated with a hyrax expander (Dentaurum GmbH & Co. KG, Ispringen, Germany) as Class II fixed functional appliance therapy. (Figure 2) This minimised the compliance issue of functional appliance therapy as the appliance was cemented onto the teeth during treatment. The Hanks Telescoping Herbst (American Orthodontics Corporation, Sheboygan, WI, USA) system used in this study composed of two maxillary Rollo® bands (American Orthodontics Corporation, Sheboygan, WI, USA) and two mandibular Rollo® bands with cantilever (American Orthodontics Corporation, Sheboygan, WI, USA) that extended approximately to the first premolar as anchors for the telescopic arms and were cemented on all first molar teeth. The maxillary component of the appliance is integrated with a hyrax expander (Dentaurum GmbH & Co. KG, Ispringen, Germany) and occlusal rests on the upper first premolars. Transbond™ Plus Light Cure Band Adhesive (3M Unitek, Minneapolis, MN, USA) was used to secure the occlusal rests onto the upper first premolars. The mandibular component of the appliance had a lingual arch connecting the lower left and right first molars with occlusal rests on all lower premolars. Similarly, Transbond Plus Light Cure Band Adhesive (3M Unitek, Minneapolis, MN, USA) was used to secure the occlusal rests on the lower premolars. The lower lingual arch was positioned such that it rested on the cingulum of the lower incisors. (Figure 2)

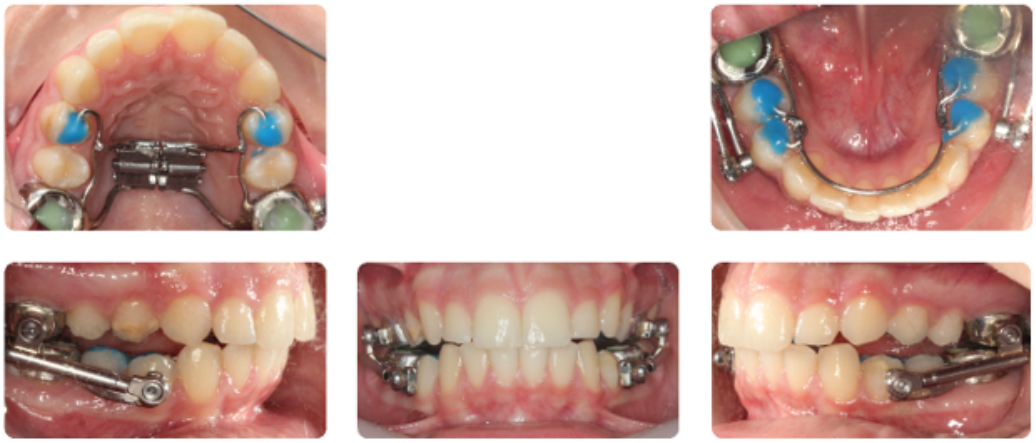

Figure 13 - Intraoral photos with Hanks Telescoping Herbst

The bite registration for the functional appliance was taken with the mandible positioned forward to a straight profile and super Class I molar and canine relationship. Hanks Telescoping Herbst (American Orthodontics Corporation, Sheboygan, WI, USA) mechanism were carefully chosen to induce the amount of mandibular advancement from the bite registration and screwed onto the attachment on the Rollo® bands (American Orthodontics Corporation, Sheboygan, WI, USA) with a dedicated hex wrench (American Orthodontics Corporation, Sheboygan, WI, USA). No other fixed orthodontic appliance, such as braces and wires, was used during the functional appliance therapy. All clinical procedures were carried out by the chief investigator (LC).

At the same appointment, all subjects received a VPro5 C-shaped vibration device (Propel Orthodontics, Milpitas, USA), which could exert a frequency of 120 Hz and a magnitude of 50 g, to be worn for 5 minutes a day. (Figure 3) The subjects randomised in the placebo control group were given a dummy device with a flat battery, and the charging cable was not provided to them. On the other hand, the subjects who were randomised in the experimental group were shown the full working instructions. The issuing of the vibration device was carried out by clinicians (AP, NG, OD) who were not involved in the treatment or data analysis.

Figure 14 - VPro5 intraoral vibration device (courtesy of Propel Orthodontics website: https://www.propelortho.com/products/)

All subjects commenced maxillary expansion at the subsequent visit, which was six weeks following the cementation of the Herbst appliance. Subjects and their parents or guardians were instructed to turn the expander once daily until the desired amount of expansion was achieved. The amount of expansion required was calculated to accommodate the space needed to improve crowding and crossbite, with an additional 30% allowance to account for potential relapse.

All subjects were reviewed every six weeks to assess the need for adjustment, which could involve activating the telescoping system or repairing appliance breakages. The treatment time was at least nine months. At the review appointment just before the nine months, telescoping mechanisms were removed to check if the mandibular position was not postural. It was then decided on the timing of appliance removal. Unfortunately, due to the COVID-19 pandemic, some subjects had the appliance therapy extended to 13 months. The average treatment time was 10.36 ± 1.04 months.

4.8 Records and Outcome Measured

Clinical photographs, study models, and cone-beam computed tomography (CBCT) images were taken before treatment (T1) and immediately after functional appliance therapy (T2). Low dose CBCT images were taken with a NewTom 5G CBCT machine (QR, Verona, Italy) at 110 kV and 3.21 mA. The imaging parameters were as follows: 18 cm by 16 cm field of view (FOV), 0.3 mm voxel size, and an exposure time of 3.6 s. CBCT scans were taken by a specialised dental radiographer or dental radiography auxiliary who had specialised training with CBCT. Patients were in a supine position and instructed to occlude in centric occlusion, hold their tongue lightly touching the roof of the mouth, and remain still during the scan. Low dose CBCT images were used in place of conventional lateral cephalograms as three-dimensional airway analysis was included as part of the investigation. This is reported in Chapter 3.

Lateral cephalograms were extracted from the CBCT images. All radiographs were digitised and traced using the Dolphin Imaging (Version 11.5, Dolphin Imaging, Chatsworth, California) by the chief investigator (LC). Classic linear and angular measurements from the analyses of Steiner,[11] Ricketts,[12] and McNamara[13] were measured using a customised digitisation regimen within the Dolphin Imaging software program. The magnification factor of all lateral cephalograms was 0%. The lateral cephalograms were also analysed manually by using the method described by Pancherz[14] and later modified by Franchi.[15]

4.9 Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL). An exploratory Shapiro-Wilks test showed normal distribution of some

parameters but not for all; therefore, both parametric and non-parametric tests were used to analyse the data.

The "p" values quoted in the analyses were two-tailed. A statistically significant level for any individual test was chosen as five per cent. A statistically significant level of less than one per cent was deemed highly statistically significant.

4.9.1 T1 Comparison

An independent samples t-test was used to analyse data that conformed to normality. For data that did not meet the normality assumption, the Mann-Whitney U test was utilised.

4.9.2 Intragroup Comparison

A paired t-test was used to analyse data that were normally distributed. On the contrary, when data did not conform to normality, the Wilcoxon signed-rank test was applied.

4.9.3 Intergroup Comparison

For data that met the normality assumption, a one-way Analysis of Variance (ANOVA) F-test was used to determine the significance of differences in the parameters of subjects from the four groups under study. Post-hoc multiple comparisons were performed using the Bonferroni test. In contrast, a non-parametric test, the independent-samples Kruskal-Wallis test, was used to analyse and compare changes with those variables that did not meet the normality assumption. A Post-hoc pairwise comparison was used to detect differences between the groups with parameters that were not normally distributed.

4.9.4 Reliability Test

To determine the errors associated with radiographic measurements, pre- and post-treatment radiographs of ten randomly selected patients, chosen using a random number generator (https://www.random.org/), totalling twenty radiographs, were traced and measured repeatedly at least one month after the initial measurements. Intraclass correlation coefficients for all cephalometric measurements ranged from 0.878 to 0.994, indicating excellent agreement.

5.0 Results

5.1 Demographics

The average age, gender distribution and CVS distribution of each group of subjects were recorded in Table 1. The differences in age between the young groups (Groups FA-Y and Vib-FA-Y) were statistically insignificant. Similarly, the difference in age between the mature groups (Groups FA-M and Vib-FA-M) was statistically insignificant. Moreover, the gender and CVS distributions between Groups FA-Y and Vib-FA-Y, and between Groups FA-M and Vib-FA-M, were not statistically significant.

Groups	No. of Subjects	Gender		Mean Age (years)	Standard Deviation	Number of subjects in each CVS stage			
		Male	Female			CVS2	CVS3	CVS4	CVS5
FA-Y	12	7	5	12.89	1.02	3	5	4	0
Vib-FA-Y	12	8	4	13.51	1.27	0	7	5	0
FA-M	14	8	6	14.78	1.30	0	0	0	14
Vib-FA-M	12	7	5	15.38	0.71	0	0	0	12

Table 3 - Subject's age, gender and growth status distribution at T1

5.2 Baseline Data Comparison

Table 2 displays the mean and standard deviation for all parameters at T1 for Groups FA-Y and Vib-FA-Y. There was no statistically significant difference between the FA-Y and Vib-FA-Y groups except for overbite (p=0.03). Vib-FA-Y had a greater mean overbite (4.92±1.67 mm) than the FA-Y group (3.43±1.49 mm).

Cephalometric Measurements	FA-Y		Vib-FA-Y		Mean Difference		Significance
	Mean	SD	Mean	SD	Mean	SE	
SNA (º)	83.55	6.83	80.97	4.34	2.58	2.34	NS
SNB (º)	77.01	6.57	74.77	2.43	2.24	2.02	NS
ANB (º)	6.53	1.99	6.19	2.54	0.34	0.93	NS
Wits (mm)	6.85	2.49	7.83	2.19	-0.98	0.96	NS
A-Nperp (mm)	2.65	3.45	1.63	3.22	1.02	1.36	NS
Pog-Nperp (mm)	-5.03	6.00	-5.88	6.52	0.85	2.56	NS
Co-Gn (mm)	104.92	6.82	103.62	4.19	1.30	2.31	NS
SN-GoMe (º)	33.05	6.54	33.25	6.22	-0.20	2.60	NS
Y-axis (º)	69.29	5.66	69.41	4.19	-0.12	2.03	NS
U1-SN (º)	115.20	7.95	114.86	6.55	0.34	2.97	NS
L1-GoMe (º)	97.88	5.82	95.98	6.35	1.90	2.49	NS
OJ (mm)	9.48	1.93	9.81	2.20	-0.33	0.85	NS
OB (mm)	3.43	1.49	4.92	1.67	-1.49	0.65	0.03*
Nasolabial Angle (º)	115.65	8.42	117.95	7.45	-2.30	3.25	NS
UL-E (mm)	0.85	2.19	-0.14	1.82	0.99	0.82	NS
LL-E (mm)	1.47	2.78	-0.07	3.17	1.53	1.22	NS

*Table 4 - Results from cephalometric analysis: descriptive data, mean differences and associated significances between Groups FA-Y and Vib-FA-Y at T1 (NS = not statistically significant, *= p<0.05, **= p<0.01)*

Table 3 displays the mean and standard deviation for all parameters at T1 for Groups FA-M and Vib-FA-M. There was no statistically significant difference between the FA-M and Vib-FA-M groups.

Cephalometric Measurements	FA-M		Vib-FA-M		Mean Difference		Significance
	Mean	SD	Mean	SD	Mean	SE	
SNA (º)	81.86	3.38	81.23	3.73	0.63	1.41	NS
SNB (º)	76.23	3.47	76.34	4.32	-0.11	1.53	NS
ANB (º)	5.64	0.83	4.86	1.69	0.14	0.51	NS
Wits (mm)	5.76	2.10	6.37	3.15	-0.60	1.04	NS
A-Nperp (mm)	2.75	3.27	1.83	2.84	0.92	1.21	NS
Pog-Nperp (mm)	-2.43	5.78	-2.12	6.88	-0.31	2.48	NS
Co-Gn (mm)	108.34	6.83	110.47	8.49	-2.13	3.00	NS
SN-GoMe (º)	33.61	4.29	31.13	7.41	2.47	2.33	NS
Y-axis (º)	69.03	3.16	67.5	5.13	1.53	1.64	NS
U1-SN (º)	111.01	7.24	112.93	10.80	-1.92	3.56	NS
L1-GoMe (º)	95.01	5.05	93.90	6.27	1.11	2.22	NS
OJ (mm)	8.66	2.19	8.82	2.24	-0.15	0.87	NS
OB (mm)	4.25	2.53	4.78	2.43	-0.53	0.98	NS
Nasolabial Angle (º)	115.17	13.25	119.48	11.83	-4.30	4.92	NS
UL-E (mm)	-0.91	2.55	-2.67	2.15	1.76	0.93	NS
LL-E (mm)	0.26	1.66	-1.21	2.58	1.47	0.84	NS

*Table 5 - Results from cephalometric analysis: descriptive data, mean differences and associated significances between Groups FA-M and Vib-FA-M at T1 (NS = not statistically significant, *= p<0.05, **= p<0.01)*

5.3 Intra-group T1-T2 Comparison

5.3.1 Group FA-Y

Table 4 displays the mean and standard deviation for all parameters at T1 and T2 for Group FA-Y. There were highly statistically significant differences between the two time points for the parameters ANB, Wits appraisal, Pog-Nperp, Co-Gn, U1-SN, L1-GoMe, overjet, overbite, and UL-E.

Cephalometric Measurements	T1		T2		Mean Difference		95% Confidence Interval of the Difference		Significance	
	Mean	SD	Mean	SD	Mean	SE	Lower	Upper	p-value	Significant levels
SNA (º)	83.55	6.83	82.93	5.06	-0.62	0.66	-2.07	0.84	0.37	NS
SNB (º)	77.01	6.57	78.15	4.72	1.14	0.81	-0.64	2.93	0.19	NS
ANB (º)	6.53	1.99	4.78	2.59	-1.75	0.34	-2.51	-0.99	0.00	**
Wits (mm)	6.85	2.49	3.25	2.98	-3.60	0.31	-4.29	-2.91	0.00	**
A-Nperp (mm)	2.65	3.45	3.32	4.07	0.67	0.36	-0.12	1.45	0.09	NS
Pog-Nperp (mm)	-5.03	6.00	-1.03	6.59	4.00	0.59	2.69	5.31	0.00	**
Co-Gn (mm)	104.92	6.82	110.19	7.02	5.28	0.69	3.77	6.78	0.00	**
SN-GoMe (º)	33.05	6.54	32.63	4.68	-0.43	0.88	-2.36	1.51	0.64	NS
Y-axis (º)	69.29	5.66	68.87	4.64	-0.43	0.51	-1.54	0.69	0.42	NS
U1-SN (º)	115.20	7.95	109.33	7.86	-5.87	0.95	-7.97	-3.77	0.00	**
L1-GoMe (º)	97.88	5.82	103.30	6.73	5.43	1.28	2.60	8.25	0.00	**
OJ (mm)	9.48	1.93	4.38	1.74	-5.10	0.36	-5.90	-4.30	0.00	**
OB (mm)	3.43	1.49	1.83	2.11	-1.60	0.41	-2.50	-0.70	0.00	**
Nasolabial Angle (º)	115.65	8.42	116.57	10.62	0.92	1.75	-2.93	4.77	0.61	NS
UL-E (mm)	0.85	2.19	-1.13	1.90	-1.98	0.29	-2.63	-1.34	0.00	**
LL-E (mm)	1.47	2.78	0.88	2.32	-0.59	0.67	-2.07	0.88	0.40	NS

*Table 6 - Results from cephalometric analysis: descriptive data, mean differences and associated significances between T1 and T2 for Group FA-Y (NS = not statistically significant, *= p<0.05, **= p<0.01)*

5.3.2 Group Vib-FA-Y

Table 5 displays the mean and standard deviation for all parameters at T1 and T2 for Group Vib-FA-Y. There were statistically significant differences between the two time points for the parameters ANB, Pog-Nperp, and Y-axis. The mean deduction of 0.54º in the Y-axis would not be deemed clinically significant. There were highly statistically significant differences

between the two time points for the parameters SNB, Wits appraisal, Co-Gn, U1-SN, L1-GoMe, overjet, overbite, and UL-E.

Cephalometric Measurements	T1		T2		Mean Difference		95% Confidence Interval of the Difference		Significance	
	Mean	SD	Mean	SD	Mean	SE	Lower	Upper	p-value	Significant levels
SNA (º)	80.97	4.34	80.88	3.57	-0.09	0.37	-0.91	0.72	0.81	NS
SNB (º)	74.77	2.43	76.07	2.64	1.30	0.31	0.63	1.97	0.00	**
ANB (º)	6.19	2.54	4.83	1.98	-1.36	0.43	-2.31	-0.41	0.01	*
Wits (mm)	7.83	2.19	3.92	2.39	-3.92	0.53	-5.09	-2.74	0.00	**
A-Nperp (mm)	1.63	3.22	1.93	3.34	0.30	0.34	-0.45	1.05	0.40	NS
Pog-Nperp (mm)	-5.88	6.52	-3.44	6.99	2.43	0.92	0.42	4.45	0.02	*
Co-Gn (mm)	103.62	4.19	107.28	4.99	3.66	0.53	2.50	4.82	0.00	**
SN-GoMe (º)	33.25	6.22	32.85	6.69	-0.40	0.42	-1.33	0.53	0.37	NS
Y-axis (º)	69.41	4.19	68.87	4.72	-0.54	0.24	-1.08	0.00	0.04	*
U1-SN (º)	114.86	6.55	108.48	7.50	-6.38	0.92	-8.40	-4.35	0.00	**
L1-GoMe (º)	95.98	6.35	102.03	7.87	6.05	1.30	3.18	8.92	0.00	**
OJ (mm)	9.81	2.20	4.84	1.78	-4.97	0.41	-5.88	-4.05	0.00	**
OB (mm)	4.92	1.67	2.88	1.81	-2.04	0.30	-2.70	-1.38	0.00	**
Nasolabial Angle (º)	117.95	7.45	116.77	5.66	-1.18	1.43	-4.32	1.96	0.43	NS
UL-E (mm)	-0.14	1.81	-2.62	1.89	-2.48	0.32	-3.19	-1.77	0.00	**
LL-E (mm)	-0.06	3.17	-0.58	2.84	-0.52	0.35	-1.30	0.26	0.17	NS

*Table 7 - Results from cephalometric analysis: descriptive data, mean differences and associated significances between T1 and T2 for Group Vib-FA-Y (NS = not statistically significant, *= p<0.05, **= p<0.01)*

5.3.3 Group FA-M

Table 6 displays the mean and standard deviation for all parameters at T1 and T2 for Group FA-M. There was a statistically significant difference between the two timepoints for parameter SNA; however, the mean deduction of 0.66º would not be considered clinically significant. There were highly statistically significant differences between the two time points for the parameters SNB, ANB, Wits appraisal, Co-Gn, U1-SN, L1-GoMe, overjet, overbite, and UL-E.

Cephalometric Measurements	T1		T2		Mean Difference		95% Confidence Interval of the Difference		Significance	
	Mean	SD	Mean	SD	Mean	SE	Lower	Upper	p-value	Significant levels
SNA (º)	81.86	3.38	81.19	3.62	-0.66	0.26	-1.23	-0.10	0.02	*
SNB (º)	76.23	3.47	76.96	3.51	0.73	0.18	0.34	1.11	0.00	**
ANB (º)	5.64	0.83	4.24	1.28	-1.39	0.23	-1.89	-0.89	0.00	**
Wits (mm)	5.76	2.10	1.94	2.18	-3.82	0.43	-4.74	-2.90	0.00	**
A-Nperp (mm)	2.75	3.27	2.06	2.84	-0.69	0.50	-1.78	0.40	0.19	NS
Pog-Nperp (mm)	-2.43	5.78	-1.24	5.71	1.19	0.96	-0.89	3.26	0.24	NS
Co-Gn (mm)	108.34	6.83	112.07	8.04	3.74	0.60	2.44	5.03	0.00	**
SN-GoMe (º)	33.61	4.29	33.42	4.43	-0.19	0.29	-0.81	0.44	0.53	NS
Y-axis (º)	69.03	3.16	68.84	3.04	-0.19	0.23	-0.69	0.30	0.41	NS
U1-SN (º)	111.01	7.24	104.98	5.58	-6.04	1.09	-8.40	-3.67	0.00	**
L1-GoMe (º)	95.01	5.05	101.64	7.73	6.63	1.19	4.06	9.19	0.00	**
OJ (mm)	8.66	2.19	4.14	1.83	-4.53	0.45	-5.50	-3.56	0.00	**

OB (mm)	4.25	2.53	2.49	1.77	-1.76	0.45	-2.72	-0.79	0.00	**
Nasolabial Angle (º)	115.17	13.25	115.95	11.29	0.78	1.95	-3.44	5.00	0.70	NS
UL-E (mm)	-0.91	2.55	-2.77	2.61	-1.86	0.21	-2.33	-1.40	0.00	**
LL-E (mm)	0.26	1.66	-0.44	2.33	-0.70	0.35	-1.45	0.04	0.06	NS

*Table 8 - Results from cephalometric analysis: descriptive data, mean differences and associated significances between T1 and T2 for Group FA-M (NS = not statistically significant, *= p<0.05, **= p<0.01)*

5.3.4 Group Vib-FA-M

Table 7 displays the mean and standard deviation for all parameters at T1 and T2 for Group FA-M. There was a statistically significant difference between the two time points for the parameters SNA, SNB, A-Nperp, Pog-Nperp, and U1-SN. However, the mean increase for SNA, SNB and A-Nperp was less than 1 mm or 1 °, which would not be considered clinically significant. There were highly statistically significant differences between the two time points for the parameters Wits appraisal, Co-Gn, L1-GoMe, overjet, overbite, and UL-E.

Cephalometric Measurements	**T1**		**T2**		**Mean Difference**		**95% Confidence Interval of the Difference**		**Significance**	
	Mean	SD	Mean	SD	Mean	SE	Lower	Upper	p-value	Significant levels
SNA (º)	81.23	3.73	81.68	3.88	0.46	0.18	0.05	0.86	0.03	*
SNB (º)	76.34	4.32	77.12	4.51	0.78	0.25	0.23	1.32	0.01	*
ANB (º)	4.86	1.69	4.57	1.97	-0.29	0.25	-0.85	0.26	0.27	NS
Wits (mm)	6.37	3.15	3.80	2.49	-2.57	0.55	-3.77	-1.37	0.00	**
A-Nperp (mm)	1.83	2.84	2.42	3.29	0.58	0.23	0.07	1.10	0.03	*
Pog-Nperp (mm)	-2.12	6.88	-0.55	7.49	1.57	0.61	0.22	2.91	0.03	*
Co-Gn (mm)	110.47	8.49	112.28	8.24	1.81	0.37	0.99	2.62	0.00	**

SN-GoMe (º)	31.13	7.41	30.63	8.13	-0.51	0.48	-1.57	0.56	0.32	NS
Y-axis (º)	67.50	5.13	67.17	5.25	-0.33	0.30	-1.02	0.35	0.31	NS
U1-SN (º)	112.93	10.80	106.97	9.34	-5.97	1.96	-10.28	-1.66	0.01	*
L1-GoMe (º)	93.90	6.27	102.11	8.79	8.21	1.38	5.17	11.25	0.00	**
OJ (mm)	8.82	2.24	4.93	1.53	-3.88	0.67	-5.35	-2.42	0.00	**
OB (mm)	4.78	2.43	2.52	1.79	-2.26	0.54	-3.44	-1.08	0.00	**
Nasolabial Angle (º)	119.48	11.83	116.09	9.32	-3.38	1.86	-7.48	0.72	0.10	NS
UL-E (mm)	-2.66	2.15	-3.83	1.84	-1.17	0.27	-1.76	-0.57	0.00	**
LL-E (mm)	-1.21	2.58	-1.70	2.22	-0.49	0.28	-1.12	0.13	0.11	NS

*Table 9 - Results from cephalometric analysis: descriptive data, mean differences and associated significances between T1 and T2 for Group Vib-FA-M (NS = not statistically significant, *= p<0.05, **= p<0.01)*

5.4 Inter-group T1-T2 Comparison

Table 8 presents the mean changes, standard deviations, and standard errors for all parameters in each group. There were statistically significant differences in mean changes for SNA, ANB, Pog-Nperp, and UL-E among the four groups. Post-hoc analysis revealed that the differences for SNA were detected between Groups FA-M and Vib-FA-M ($p<0.01$), with Group FA-M showing SNA retrusion of -0.66±0.97º and Group Vib-FA-M exhibiting protrusion of 0.46±0.64º. As for ANB, Group FA-Y, with the most remarkable mean change of -1.75±1.19º, showed statistically significantly greater reduction ($p<0.05$) than Group Vib-FA-M, which had the least mean change of -0.29±0.87º. In terms of parameter Pog-Nperp, there were statistically significant differences between Group FA-Y and the two other groups (Groups FA-M ($p< 0.01$) and Vib-FA-M ($p<0.05$)). Group FA-M showed the least improvement (1.19±3.59mm), and Group FA-Y presented the most improvement (5.28±2.06 mm). As for UL-E, there was a statistically significant difference between both experiment groups ($p<0.05$), with Group Vib-FA-Y showing the most mean upper lip retrusion of (-2.48±1.12 mm) and Group Vib-FA-M recording the least mean retrusion of (-1.17±0.94 mm). Additionally, there were highly

statistically significant differences in the mean changes in Co-Gn. Post-hoc analysis revealed that the mean changes in Co-Gn were greatest in Group FA-Y (5.28±2.37 mm), which was significantly different ($p < 0.01$) from the least changed Group Vib-FA-M (1.81±1.28 mm).

Groups	FA-Y			Vib-FA-Y			FA-M			Vib-FA-M			Significance	
Cephalometric Measurements	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE	p-value	Significant level
SNA (°)	-0.62	2.29	0.66	-0.09	1.28	0.37	-0.66	0.97	0.26	0.46	0.64	0.18	0.04	*
SNB (°)	1.14	2.81	0.81	1.30	1.06	0.31	0.73	0.67	0.18	0.78	0.86	0.25	0.17	NS
ANB (°)	-1.75	1.19	0.34	-1.36	1.50	0.43	-1.39	0.87	0.23	-0.29	0.87	0.25	0.02	*
Wits (mm)	-3.60	1.08	0.31	-3.92	1.85	0.53	-3.82	1.60	0.43	-2.57	1.89	0.55	0.17	NS
A-Nperp (mm)	0.67	1.24	0.37	0.30	1.19	0.34	-0.69	1.89	0.05	0.58	0.81	0.23	0.08	NS
Pog-Nperp (mm)	4.00	2.06	0.59	2.43	3.18	0.92	1.19	3.59	0.96	1.57	2.12	0.61	0.02	*
Co-Gn (mm)	5.28	2.37	0.69	3.66	1.83	0.53	3.74	2.24	0.60	1.81	1.28	0.37	0.00	**
SN-GoMe (°)	-0.43	3.04	0.88	-0.40	1.47	0.42	-0.19	1.09	0.29	-0.51	1.67	0.48	0.50	NS
Y-axis (°)	-0.43	1.76	0.51	-0.54	0.84	0.24	-0.19	0.85	0.23	-0.33	1.08	0.31	0.60	NS
U1-SN (°)	-5.87	3.31	0.94	-6.38	3.18	0.92	-6.04	4.09	1.09	-5.97	6.78	1.98	0.48	NS
L1-GoMe (°)	5.43	4.44	1.28	6.05	4.52	1.30	6.63	4.44	1.19	8.21	4.78	1.38	0.60	NS
OJ (mm)	-5.10	1.25	0.36	-4.97	1.44	0.41	-4.53	1.68	0.45	-3.88	2.31	0.67	0.31	NS
OB (mm)	-1.60	1.42	0.41	-2.04	1.04	0.30	-1.76	1.67	0.45	-2.26	1.86	0.54	0.72	NS
Nasolabial Angle (°)	0.92	6.06	1.75	-1.18	4.94	1.43	0.78	7.31	1.95	-3.38	6.45	1.86	0.30	NS
UL-E (mm)	-1.98	1.01	0.29	-2.48	1.12	0.32	-1.86	0.80	0.21	-1.17	0.94	0.27	0.02	*
LL-E (mm)	-0.59	2.32	0.67	-0.52	1.23	0.35	-0.71	1.29	0.35	-0.49	0.98	0.28	0.98	NS

*Table 10 - Results from cephalometric analysis: mean differences, standard deviation (SD) and standard error (SE) for each group between T1 and T2 and the differences among all groups and the associated significances (NS = not statistically significant, *= p<0.05, **= p<0.01)*

5.5 Pancherz Analysis

Table 9 recorded the mean measurements, standard deviation and standard error for measurements in the Pancherz analysis for each group. There was a highly statistically significant difference detected in the maxillary molar parameter ($p<0.01$). Post-hoc Pairwise

comparison found significant differences ($p<0.05$) between Group Vib-FA-Y and FA-M, with Group Vib-FA-Y recording the greatest mean molar movement of -2.33±0.78 mm and Group FA-M displaying the least mean molar movement of -1.11±1.15 mm.

Groups	FA-Y			Vib-FA-Y			FA-M			Vib-FA-M			Significance	
Measurements (mm)	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE	p-value	Significant level
Overjet (is/OLp minus ii/OLp)	-5.13	1.38	0.40	-4.83	1.89	0.54	-5.18	2.72	0.73	-4.04	2.57	0.74	0.30	NS
Molar relation (ms/OLp minus mi/OLp)	-5.25	1.36	0.39	-5.33	1.61	0.47	-4.71	1.55	0.42	-4.29	1.37	0.4	0.28	NS
Maxillary base (A point/OLp)	0.33	0.81	0.23	0.42	0.82	0.24	0.00	0.20	0.05	0.13	0.57	0.16	0.61	NS
Mandibular base (pg/OLp)	2.42	1.56	0.45	2.67	1.63	0.47	2.25	1.50	0.40	1.42	1.22	0.35	0.35	NS
Condylar head (Co/OLp)	0.96	0.92	0.26	0.63	0.64	0.19	0.54	0.77	0.21	0.54	0.69	0.20	0.63	NS
Composite mandibular length (pg/Olp+Co/OLp)	3.38	1.79	0.52	3.29	1.67	0.48	2.79	1.71	0.46	1.96	1.57	0.45	0.21	NS
Maxillary incisor (is/Olp minus A point OLp)	-1.75	0.66	0.19	-1.38	1.52	0.44	-1.21	1.25	0.33	-1.54	1.32	0.38	0.67	NS
Mandibular incisor (ii/Olp minus pg/OLp)	1.29	1.56	0.45	1.21	1.01	0.29	1.71	2.18	0.58	1.21	1.81	0.52	0.98	NS
Maxillary molar (ms/Olp minus A point/OLp)	-1.88	0.93	0.27	-2.33	0.78	0.22	-1.11	1.15	0.31	-1.96	0.94	0.27	0.04	*
Mandibular molar (mi/OLp minus pg/OLp)	1.29	1.23	0.36	0.75	0.81	0.23	1.36	1.79	0.48	1.04	0.84	0.24	0.74	NS

*Table 11 - Results of Pancherz Analysis: mean differences, standard deviation (SD) and standard error (SE) for each group between T1 and T2 and the differences among all groups and the associated significances (NS = not statistically significant, *= p<0.05, **=p<0.01)*

Pancherz's analysis is used to describe the contribution of skeletal and dental components to overjet and molar correction. Figures 4 to 7 display the maxillary and mandibular skeletal and dentalveolar changes contributing to sagittal overjet and molar correction for each group. Figure 8 is a graphical representation of the skeletal proportion of overjet and molar correction for all groups. For overjet correction, Group Vib-FA-Y showed the highest skeletal component of correction (47%), and Group Vib-FA-M showed the least (32%). On the other hand, for molar correction, Group FA-M showed the greatest skeletal correction of 48%, and Group Vib-FA-M showed the least (30%).

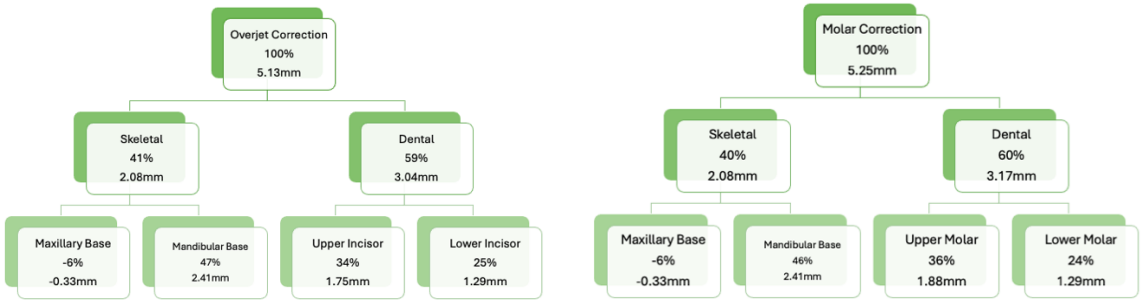

Figure 15 - The skeletal and dental components of overjet and molar correction for Group FA-Y

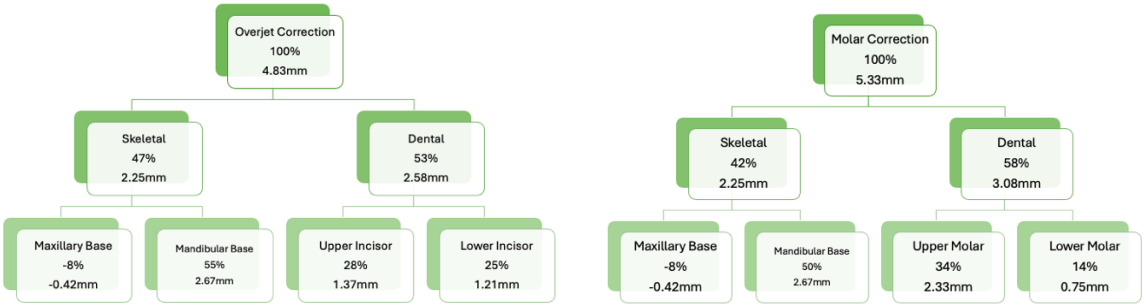

Figure 16 - The skeletal and dental components of overjet and molar correction for Group Vib-FA-Y

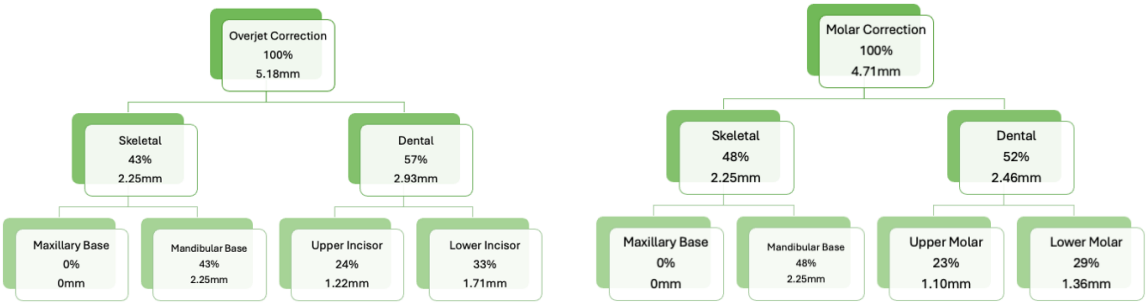

Figure 17 - The skeletal and dental components of overjet and molar correction for Group FA-M

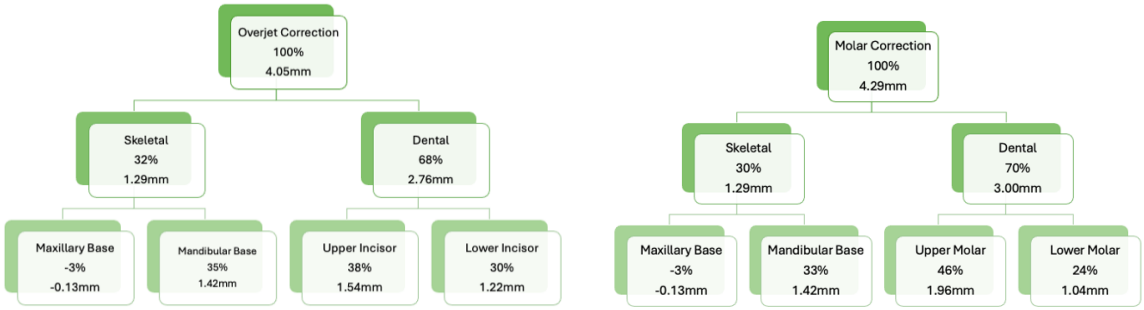

Figure 18 - The skeletal and dental components of overjet and molar correction for Group Vib-FA-M

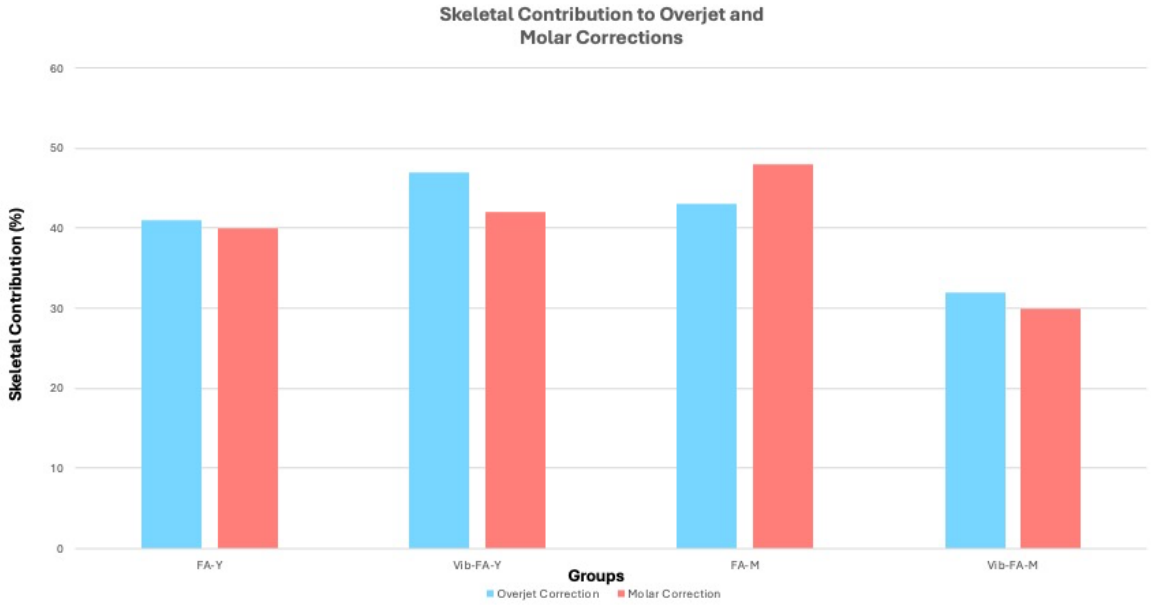

Figure 19 - Graphical representation of the skeletal contribution to overjet and molar corrections for all groups

6.0 Discussion

This study is the first to investigate the impact of mechanical vibration on the dental, skeletal and facial soft tissue effects of Class II functional appliance therapy at different skeletal maturities. The discussion will be divided into three parts: baseline comparison, intra-group T2-T1 comparison, and intergroup comparison of mean changes.

6.1 Baseline Data Comparison

The age, gender, CVS, dental, skeletal and soft tissue parameters at the beginning of treatment were similar for Groups FA-M and Vib-FA-M, making both groups comparable. As for the FA-Y and Vib-FA-Y groups, overbite was the only parameter that showed a statistically significant difference between the groups at T1, with group Vib-FA-Y displaying a deeper overbite. However, this did not affect the interpretation of the result because the intergroup comparison examined the mean changes between the two timepoints, rather than the value of overbite at the end of T2. The most important fact was that both group pairs were comparable skeletally, as the primary objective of this research was to see if the mechanical vibration device could be used to enhance the skeletal change induced by the functional appliance.

6.2 Intra-group T2-T1 Comparison

The overall skeletal and dental changes for all groups aligned with previously reported effects of the Herbst appliance.[14,16,17] All groups showed statistically significant changes between T1 and T2 for Wits appraisal, Co-Gn, U1-SN, L1-GoMe, overjet, and overbite, indicating both skeletal and dental corrections of the Class II malocclusion. There was no significant change in the maxillary parameter, except for Group FA-M, which displayed a mean decrease of 0.66^{o} in SNA. With such a small extent of deduction, it would not be deemed clinically significant, especially when measurement error is considered. This meant that skeletal correction was attributed to changes in the mandible, which was indicated by a statistically significant increase in mandibular length (Co-Gn). This finding was in agreement with most Herbst appliance literature and systematic reviews, which showed minimal maxillary restraint and moderate mandibular lengthening.[17-20] The mean changes in Co-Gn were 5.28±0.69mm, 3.66±0.53mm,

3.74±0.6mm and 1.81±0.37mm for Groups FA-Y, Vib-FA-Y, FA-M, Vib-FA-M, respectively. These were similar to the mean Co-Gn changes recorded in previous studies,[21-24] which ranged from 3.4±2.3mm[24] to 5.65±2.24mm.[16] Group FA-Y seemed to have the greatest mean increase in mandibular length (5.28±0.69mm), which was similar to the increase found in Baysal and Uysal[16] (5.65±2.24mm).

The significant mean dental changes found across all groups were upper incisor retroclination (U1-SN) and lower incisor proclination (L1-GoMe), which also coincided with previous review literature.[18,25] The mean changes in upper incisor retroclination were -5.87±0.95°, -6.38±0.92°, -6.04±1.09° and -5.97±1.96° for Groups FA-Y, Vib-FA-Y, FA-M and Vib-FA-M, respectively. The results suggested slightly more upper incisor retroclination than what was reported by Jakobsone *et al.*,[22] of -2.9±4.9°. The reason for this was the use of a dissimilar reference line to measure the incisor angulation. In the study by Jakobsone *et al.*,[22] T-FMN was used as the reference line, whereas SN was used in the current study. Although both depicted the cranial base, the landmarks used were dissimilar, which likely contributed to the difference in the results. Other studies that examined upper incisor angulations used disparate reference planes of NA, which makes the comparison with the present research difficult. Nevertheless, these literatures recorded retroclination of upper incisors.[21,25] The mean changes in lower incisor proclination for Groups FA-Y, Vib-FA-Y, FA-M, and Vib-FA-M were 5.43±1.28°, 6.05±1.30°, 6.63±1.19° and 8.21±1.38°, respectively. These reported results appeared to be higher than those reported by Baysal and Uysal[16] (0.50±1.60°) and similar to those of de Almeida *et al.*[21] (5.00±6.10°). This is mainly due to the differences in the time point when measurements were made. In the Baysal and Uysal[16] study, treatment completion records were taken when the occlusion had settled into Class I or super Class I molar relationship after the active treatment phase. Therefore, there was sufficient time for the lower

incisors to relapse, resulting in less proclination. Differences in results can also be attributed to variations in appliance design, typically resulting from the spatial relationship between the lower lingual bar and the dentition, as well as the degree of mandibular advancement activated. Unfortunately, the appliance designs were not detailed in the literature, so a comparison could not be made. However, in terms of the degree of mandibular advancement, Baysal and Uysal[16] recorded the bite when the mandible is in an edge-to-edge incisor position, and de Almeida *et al.*[21] utilised a standard one-step 5 mm advancement for all researched cases. On the contrary, in the current study, the amount of advancement patients needed to achieve a pleasing profile was used as a gauge for the bite registration.

Both overjet and overbite recorded statistically significant improvement during treatment for all groups. The overjet reduced by -5.10±0.36 mm, -4.97±0.41 mm, -4.53±0.45 mm, and-3.88±0.67 mm for Groups FA-Y, Vib-FA-Y, FA-M, Vib-FA-M respectively. The overbite was also decreased -1.6±0.41 mm, -2.04±0.3 mm, -1.76±0.45 mm and -2.26±0.54 mm for Groups FA-Y, Vib-FA-Y, FA-M, and Vib-FA-M, respectively. Changes in both of these parameters in all groups were similar to what has been reported by Yang *et al.*[17] In their systematic review the mean difference and 95% confidence (95%CI) interval for overjet and overbite was -4.82 mm (95%CI: -5.83 mm, -3.80 mm) and -2.40 mm (95%CI: -4.33 mm, -0.47 mm) respectively.

In addition, there were favourable changes in the upper lip in reference to the E line. The retraction of the upper lip and the changes were statistically significant between the two time points. The mean changes in UL-E were -1.98±1.01 mm, -2.48±1.12 mm, -1.86±0.80 mm, -1.17±0.94 mm for Groups FA-Y, Vib-FA-Y, FA-M, Vib-FA-M respectively. These results differed from those reported by Baysal and Uysal[26] in which they recorded a mean lip

protrusion of 0.1±2.7 mm. As discussed earlier, the differences in the reported results could be due to the settling period included in Baysal and Uysal's[26] study. When comparing these soft tissue changes with those in a previous study by Pancherz and Anehus-Pancherz[27] (-1.8±0.3 mm) and Booij *et al.*[28] (-1.7±2.43 mm), the results were comparable. Some literature has also reported improvement in lower lip position;[29] however, this was not evident in the current study.

Some measurements showed statistically significant changes in most groups, but not in all groups. These included Pog-Nperp and SNB. Both positive changes in these parameters supported the mandibular protrusion effect of the Herbst appliance. The mean changes of Pog-Nperp were measured as 4.00±0.59mm, 2.43±0.92mm and 1.57±0.61mm for Groups FA-Y, Vib-FA-Y, and Vib-FA-M, respectively. As for SNB, the statistically significant mean increase was 1.30±0.31°, 0.73±0.18° and 0.78±0.25° for Groups Vib-FA-Y, FA-M and Vib-FA-M, respectively. This fell within the 95% CI for mean SNB changes of 0.53 mm to 1.60 mm, which was reported in the meta-analysis on the skeletal effect of the Herbst appliance by Yang *et al.*[17]

6.3 Intergroup Comparison

From the analysis of the cephalometric outcomes of this study, intraoral mechanical vibration did not appear to enhance the skeletal effects of a functional appliance during the peak pubertal period, as there was no statistically significant difference in all parameters measured between Groups FA-Y and Vib-FA-Y. However, according to the result from Pancherz analysis, there appeared to be slightly more skeletal components in the overjet and molar corrections in Group Vib-FA-Y (47% and 42% respectively) in comparison to Group FA-Y (41% and 40% respectively). The discrepancies between the results from cephalometric analysis and Pancherz

analysis prompted the need for further investigation with a larger sample size to draw more definitive conclusions.

In contrast, intraoral mechanical vibration used in conjunction with a functional appliance in late adolescents (CVS 5) resulted in less favourable maxillary changes than those without mechanical vibration at a similar growth stage. This was evident in significantly lesser restraint found in the maxilla as reflected in a difference of slightly more than 1^{o} with SNA (-0.66±0.97^{o} and 0.46±0.64^{o} for Groups FA-M and Vib-FA-M, respectively). In fact, there was a mean maximum advancement of the maxilla when mechanical vibration was used. When examining other cephalometric skeletal parameters, such as ANB, Wits, and Co-Gn, it appeared that there were fewer skeletal improvements when mechanical vibration was used during functional appliance therapy in late adolescents; however, these differences were not statistically significant. In addition, the results from Pancherz analysis confirmed the negative influence of intraoral mechanical vibration during functional appliance therapy in late adolescence. The skeletal component for overjet and molar corrections was 32% and 30%, respectively, for Group Vib-FA-M, which was lower than the 43% and 48%, respectively, for Group FA-M. Therefore, it could be concluded that intraoral mechanical vibration had the potential to reduce the skeletal effects of Herbst therapy at the late adolescent stage.

The question is, “Why did the animal studies show such promising results, and did this not translate to human clinical studies?” This could be explained by the location where the mechanical vibration was initiated. Whole-body vibration platforms were used in animal studies that transmitted vibration through the bones, resulting in the proliferation of osteoblasts and chondrocytes. In contrast, in the current study, mechanical vibration was exerted on the teeth, and it was hoped that this vibration would be transmitted through the teeth to the

mandibular body and condyles. The lack of a significant skeletal response from the current examination has led to the belief that the intraoral mechanical vibration device did not induce adequate stimulation that could be transmitted to the mandibular body and condyles and absorbed mainly by the dentoalveolar complex. Perhaps, mechanical vibration that is localised to the mandibular body or condyle should be considered for future investigations.

Evidence has shown that LMHF mechanical vibration accelerated tooth movement during orthodontic treatment.[30,31] Together with the lack of skeletal response, would it be possible that application of intraoral mechanical vibration during functional appliance therapy in late adolescent patients resulted in a predilection for tooth movement? Based on the result from Pancherz's analysis, there was more dental correction than skeletal improvement in Group Vib-FA-M than in all other groups. Moreover, by examining the mean changes in ANB and Co-Gn among the groups, Group FA-Y showed significantly better improvement in ANB and greater lengthening of Co-Gn when compared with Group Vib-FA-M. This was logical, as literature has confirmed that there was less mandibular skeletal improvement when a functional appliance was used in late adolescents compared to the peak pubertal growth stage.[4,32] However, the current results showed that the other placebo control adolescent (Group FA-M) did not display a significant difference in ANB and Co-Gn when compared with Group FA-Y or Group Vib-FA-M. Therefore, together with the numerical data, it can be inferred that the mandibular skeletal effect from Group FA-M falls in between the mandibular skeletal effects of Group FA-Y and Group Vib-FA-M, i.e. less than that of Group FA-Y but not quite as deficient as Group Vib-FA-M. Therefore, the difference in mandibular skeletal effect between Group FA-M and Group Vib-FA-M could be due to preferential mechanical vibration-induced tooth movement in Group Vib-FA-M, which compensated for the skeletal discrepancy before mandibular growth and condylar remodelling initiated.

Furthermore, maxillary molar distalisation appeared to be more effective under the influence of mechanical vibration, which could be a favourable change in dental Class II malocclusion. This was illustrated in the maxillary molar measurement of the Pancherz analysis, which showed significantly greater maxillary molar distalisation in Group Vib-FA-Y (-2.33±0.78 mm) than in Group FA-M (-1.11±1.15 mm). In fact, there was a general trend of greater maxillary molar distalisation in the vibration groups when compared with the non-vibration groups. In contrast, mechanical vibration did not have additive effects on incisors or mandibular molars. An explanation for the lack of additive incisor movement could be attributed to the design of the VPro5 device's biting wafer. The biting wafer had a flat surface, and during the initial period of Herbst treatment, the occlusal contact was frequently located in the molar region only; therefore, mechanical vibration stimulation was confined in the posterior part of the dentition until the occlusion eventually adapted to the new protrusive position. Moreover, the effect was more pronounced in the maxillary molar than in the mandibular molar, which could likely be attributed to differences in bone density.[33]

Although Group Vib-FA-Y showed marked maxillary molar distalisation, the skeletal component of overjet and molar correction was not compromised, unlike Group Vib-FA-M. The following reasons could explain this. As mentioned earlier, when examining the results from the younger CVS groups, there were no statistically significant differences in all skeletal, dental and soft tissue cephalometric parameters between Groups FA-Y and Vib-FA-Y. Under the assumption that the mechanical stimulation was not adequately transmitted to the condyle or body of the mandible, the growth of the mandible and condyle for both groups would be similar whether mechanical vibration was used or not. In addition, there was greater growth capacity in the mandible and condyle during peak pubertal growth than during the late

adolescence period, such that dental compensation was not required as much to obtain overjet and molar correction. Therefore, even though intraoral mechanical stimulation enhanced tooth movement, the growth of the mandible and condyle was adequate and fast enough during the peak pubertal period, negating the extent of dental compensation required in the late adolescence group and resulting in similar skeletal correction in both peak pubertal growth groups.

Interestingly, there were statistically significant differences in soft tissue changes, specifically upper lip retraction, between the two mechanical vibration groups, with younger patients exhibiting more upper lip retraction than the more mature patients. This was quite interesting as the degree of upper incisor retraction was quite similar for both groups, and upper lip position usually followed the upper incisor position. Firstly, this could be due to the anterior movement of the pogonion. Measurement UL-E used the E-line as the reference plane, and the E-line is primarily affected by the position of the pogonion. Generally, the increase in UL-E value can be produced by upper lip retraction and/or anterior movement of the pogonion. Group Vib-FA-Y seemed to have a greater, although not statistically significant, mean Pog-Nperp change than the Group Vib-FA-M group, thereby partly contributing to the significant differences in mean change of UL-E. Secondly, this significant mean change difference could be due to the normal growth process of the soft tissue of the upper lip during the pubertal stage. According to Bishara *et al.,*[34] the incremental values of UL-S increased and peaked at 14 years old; therefore, the most remarkable growth-related change in the upper lip could coincide with the treatment period of Group Vib-FA-Y, contributing to the significant differences.

Ruf and Pancherz[4] compared the dentoskeletal effects of the Herbst appliance between early adolescence and young adulthood. The results showed that the skeletal contribution to overjet

and molar corrections was 22% and 25% in young adults, respectively, and 39% and 41% in early adolescents, respectively. Additionally, Konik *et al.*[3] reported slightly higher skeletal contribution to overjet and molar corrections (37% and 27%, respectively) in young adults. These results from the young adult groups differed from those of the current study, which revealed 43% and 48% skeletal influences on overjet and molar corrections, respectively. The difference in the reported results could be due to the dissimilar gender distribution. There were more females enrolled in the Ruf and Pancherz[4] and Konik *et al.*[3] studies, whereas the present study recruited more males. This potentially has a significant impact, as males have a greater mandibular incremental and duration growth than females.[35] Secondly, the discrepancies in results may lie in the method of maturity staging. Unlike the present study, which determined growth status by a combination of chronological age, secondary sexual characteristics, and CVS staging, hand-wrist x-rays were used to assess maturity status. Although hand-wrist x-rays have long been the gold standard for maturity staging, this could not be carried out in the present study, as additional radiographs were deemed unjustifiable in recent years due to current ALARA concepts.

7.0 Limitations

The current investigation was affected by the COVID-19 pandemic. This has impacted several aspects of the study. Some subjects had prolonged treatment periods due to the "lockdown" and restricted practice in the Sydney Dental Hospital for urgent care. The recruitment process was also impaired as new treatment could not be carried out for an extended period. Therefore, the number of subjects intended to be recruited has been reduced, and the clinical research period has been prolonged.

Due to the randomisation and selection criteria of this study, a gender balance could not be achieved, as the eligible patients obtained from the waiting list at Sydney Dental Hospital were predominantly male subjects.

As mentioned in the discussion, there was a possibility that the stimulation from the intraoral mechanical vibration device did not transmit to the mandibular body and or condyle; therefore, it may not be effective in inducing skeletal changes. This was not foreseen at the outset, as the intention was to use a commercially available mechanical vibration device. Further study that involves the use of mechanical stimulation more locally to the mandible should be considered.

8.0 Conclusion

1. Intraoral mechanical vibration with a frequency of 120 Hz and a magnitude of 50g, when used in conjunction with a functional appliance, increased dental compensation and reduced skeletal efficacy of functional appliance therapy during the post-pubertal growth stage.
2. Intraoral mechanical vibration with a frequency of 120 Hz and a magnitude of 50 g provoked greater maxillary molar distalisation during functional appliance therapy, which was favourable in correcting dental Class II malocclusion.
3. Mechanical vibration therapy may enhance the skeletal effects of Class II functional appliance therapy during peak pubertal growth; however, further study with a larger sample size is required to draw a definitive conclusion.

9.0 Other Information

This prospective clinical trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12625000194460). The trial was funded by the Australian Society of Orthodontists Foundation for Research and Education (ASOFRE).

10.0 List of Figures

11.0 List of Tables

Table 9 - Results of Pancherz Analysis: mean differences, standard deviation (SD) and standard error (SE) for each group between T1 and T2 and the differences among all groups and the associated significances (NS = not statistically significant, *= $p<0.05$, **=$p<0.01$)

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Chapter 3: Effects of Mechanical Vibration on Class II Orthopaedic Appliance Therapy at Different Stages of Skeletal Maturity – Airway Analysis

1.0 Introduction

Narrowing of pharyngeal airway space and collapse of the airway during respiration due to reduced muscle tone while sleeping is a central pathogenesis of Obstructive Sleep Apnoea Syndrome (OSAS).[1] A recent systematic review by Finke *et al.*[2] indicated mandibular retrusion and vertical growth directions were risk factors for OSAS. The benefits of functional appliance therapy on OSAS, especially in paediatric patients, have been widely documented.[3-5] The most recent systematic review by Gorikapudi *et al.*[6] reported promising improvements in OSAS symptoms, such as AHI, nasal resistance, sleep parameters, and upper airway dimensions in paediatric populations treated orthodontically and orthopaedically. The concept behind airway changes with Class II orthopaedic appliance therapy is based on the anterior movement of the mandible, which brings the posterior soft tissue away from the airway and, as a result, increases the volume or anteroposterior dimension of the airway.

CBCT provides a three-dimensional (3D) assessment of the upper airway with high spatial resolution, clearly defining the soft tissues and airway space.[7,8] This has become a more widely used imaging technique because the radiation exposure is significantly lower and less costly than that of conventional computed tomography. In addition, unlike cephalometric radiography, which provides linear and angular measurements, CBCT eliminates the overlap of structure in two-dimensional (2D) radiography and provides 3D imagery that allows volumetric calculation of the airway space. Currently, several computer software programs are available for analysing airway volumes. The process of software analysis involves 3D reconstruction of volumetric data obtained from CBCT, followed by segmentation of the airway, which can be accomplished either manually or semi-automatically. Dolphin Imaging software utilises a semi-automatic airway segmentation function that allows for fast airway

volume and minimal airway cross-sectional area (MCA) computations. Most of the research studies have shown that this software program is highly reproducible and reliable.[9-12]

As discussed in Chapter 2, whole-body mechanical vibration in a mouse model resulted in a significant decrease in condylar cartilage volume and a significant increase in bone histomorphometric parameters, suggesting an enhancement of adaptive remodelling of the condylar cartilage.[13] Unfortunately, when intraoral mechanical vibration stimulation was used during Class II functional appliance therapy in humans, no significant enhancement of skeletal effects was observed. Nevertheless, the patency of the posterior airway is not solely dependent on the position or the length of the mandible. In fact, Finke *et al.*[2] discovered nine craniofacial measurements that may have a possible influence on patients with OSAS when compared to control groups. These findings included a decreased NSBa angle in males only, an increased ANB angle, an increased ML-NSL angle, an obtuse Me-Go-Ar angle, a shorter SN distance, a longer N-ANS distance, a higher MP-H distance, a longer uvula length in adults, and increased uvula thickness. Some of these measurements may be affected by mandibular protrusion induced by functional appliances. Additionally, the upper airway is a pliable muscular organ that possesses mechanoreceptors, which help maintain the patency of the airway. Therefore, due to the myriad factors that could affect the patency of the upper airway, it remained essential to assess the dimensional and volumetric changes of the posterior airway during functional appliance therapy under the influence of mechanical vibration stimulation despite the lack of significant skeletal findings in the previous chapter.

2.0 Aims

This pilot study aimed to quantitatively measure and compare airway dimensional changes during Class II functional appliance therapy with or without simultaneous mechanical stimulation, and to determine whether these changes were similar during two different stages: the peak-pubertal and post-pubertal phases of growth.

2.1 Significance of the Aims

This study investigated the impact of mechanical vibration on the airway measurements in patients undergoing Class II functional appliance therapy at different skeletal maturities. Previous literature has suggested improvement in airway dimensions following functional appliance therapy. However, most of these studies were 2D analyses and not well-designed, high-quality randomised clinical trials.[3] In addition, the medical use of mechanical vibration has been shown not only to enhance bone density but also to improve muscle and soft tissue architectures and functions.[14-17] Therefore, the results of this study may enhance the understanding of the effect of mechanical vibration on airway structure during functional appliance therapy at different stages of maturity.

3.0 Null Hypothesis

1. There were no statistically significant differences in nasopharyngeal volume, oropharyngeal volume and MCA of oropharynx between Class II functional appliance therapy with and without concomitant use of mechanical vibration during peak pubertal growth.
2. There were no statistically significant differences in nasopharyngeal volume, oropharyngeal volume and MCA of oropharynx between Class II functional appliance

therapy with and without concomitant use of mechanical vibration during post-pubertal growth.

3. There were no statistically significant differences in nasopharyngeal volume, oropharyngeal volume and MCA of oropharynx from Class II functional appliance therapy between the two different skeletal maturity statuses.
4. There were no statistically significant differences in nasopharyngeal volume, oropharyngeal volume and MCA of oropharynx from Class II functional appliance therapy with concomitant use of mechanical vibration between the two different skeletal maturity statuses.

4.0 Method and Materials

This is a pilot study that utilised the Cone beam computed tomography (CBCT) records originating from the experiment carried out in Chapter 2. CBCT images were taken before treatment (T1) and immediately after functional appliance therapy (T2). CBCT images were acquired using the NewTom 5G CBCT machine (QR, Verona, Italy) at 110 kV and 3.21 mA. The imaging parameters were: 18 cm by 16 cm field of view (FOV), 0.3 mm voxel size, and 3.6 s of exposure time. CBCT scans were taken by a specialised dental radiographer or dental radiography auxiliary who had specialised training with CBCT. Patients were in a supine position and instructed to occlude in centric occlusion, hold their tongue lightly touching the roof of the mouth, and remain still during the scan.

Digital Imaging and Communications in Medicine (DICOM) files from the reconstructed CBCT datasets were imported into Dolphin Imaging (Version 11.5, Dolphin Imaging, Chatsworth, California) computer software for airway analysis. Firstly, the 3D images were oriented with the mid-sagittal plane aligned with the skeletal midline of the face, the axial plane

matched with the Frankfort horizontal plane, and the coronal plane adjusted to be perpendicular to both the mid-sagittal plane and the axial plane that pass through the deepest part of the lateral aspect of the zygomatic bone. (Figure 1)

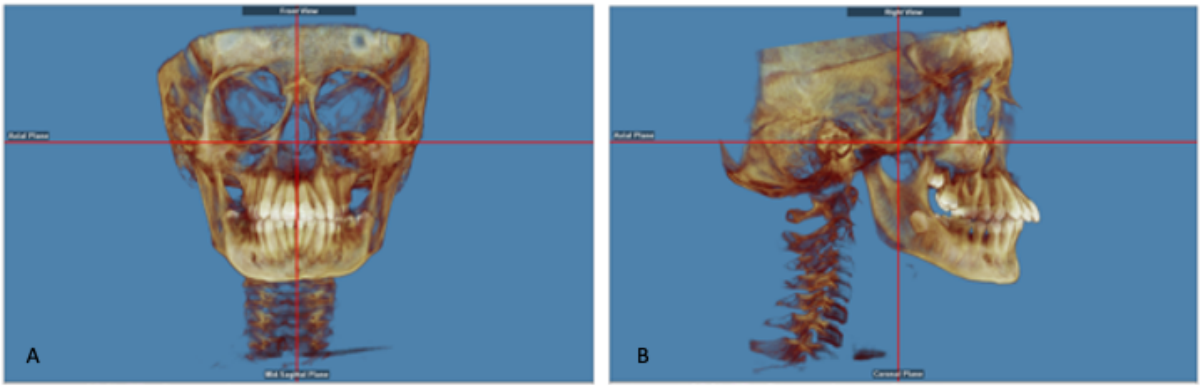

Figure 1 - Orientation of CBCT reconstructed 3D image (A) The mid-sagittal plane and axial plane (B) Coronal and axial plane

The landmarks used for the boundaries of the nasopharynx and oropharynx were obtained from previous literature.[18,19] (Table 1, Figure 2)

	Anterior Boundary	Posterior Boundary	Superior Boundary	Inferior Boundary
Nasopharynx	Line from Sella (S) to Posterior Nasal Spine (PNS)	Line from S to the tip of the odontoid process	Intersection of anterior and posterior boundaries	Line from PNS to the tip of the odontoid process
Oropharynx	Line from PNS to the posterior superior point of the hyoid bone (H)	Line from the tip of the odontoid process to the superior posterior border of the 4th cervical vertebrae (C4)	Line from PNS to the tip of the odontoid process	Line from H to the superior posterior border of C4

Table 1 - Landmarks used to delineate the boundaries of the nasopharynx and oropharynx

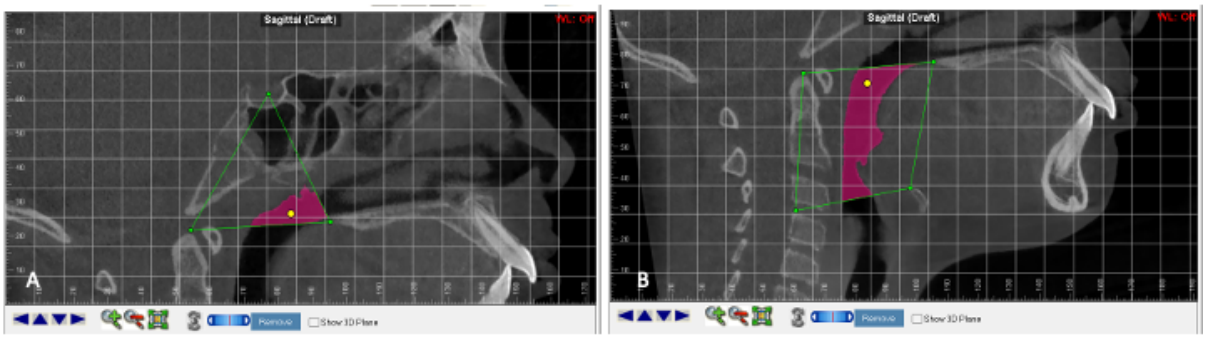

Figure 2 - Constructed boundary lines for (A) nasopharynx (B) oropharynx (in green). Yellow points denote seed points.

To analyse the volume of the nasopharynx and oropharynx, these landmarks were first identified on the mid-sagittal plane in the sagittal view. Once the points were identified, the

boundary was outlined in green. Then, multiple seed points were placed in all air cavities within the boundary. Seed points were used to select the densities that represent the airway. The images were cross-checked in all three plane views, and additional seed points were placed to include all cavities. After that, the sensitivity threshold was adjusted for each sample by manually increasing the threshold setting to a maximum level without including space outside the anatomical limits of the airway. The range of sensitivity threshold was -201 to -314HU. Once the airway of interest was defined, the Dolphin 3D sinus/airway analysis feature calculated the volume. (Figures 3 and 4)

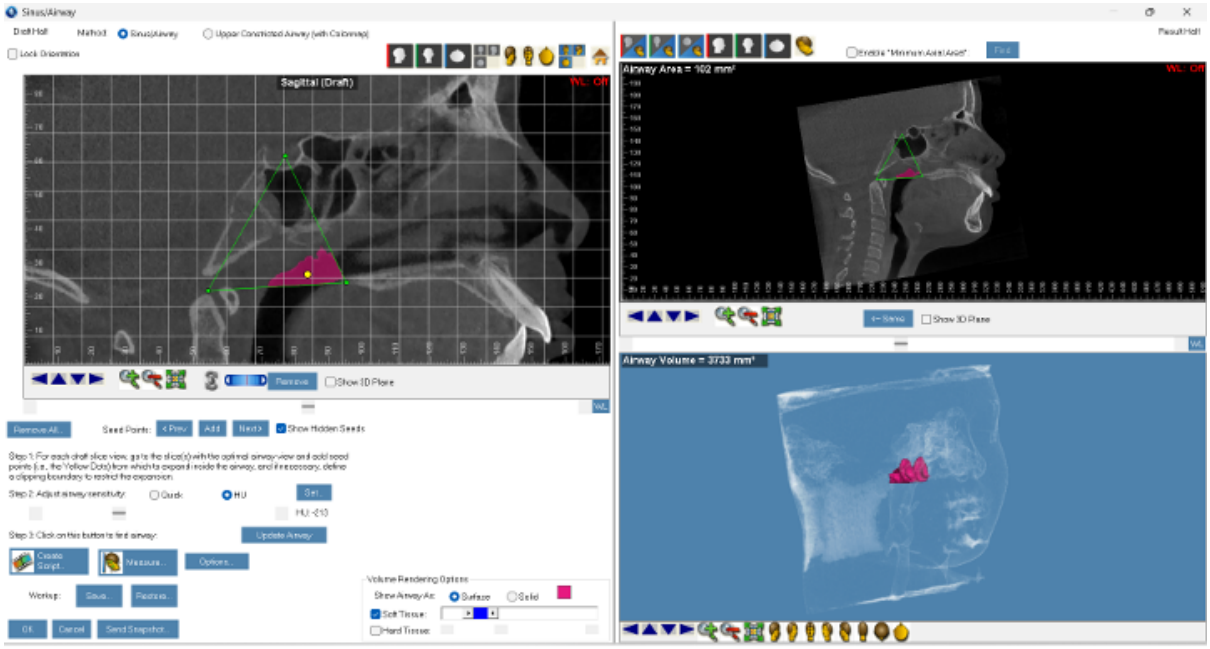

Figure 3 - Dolphin imaging software showing nasopharynx in 3D with volume measurement output

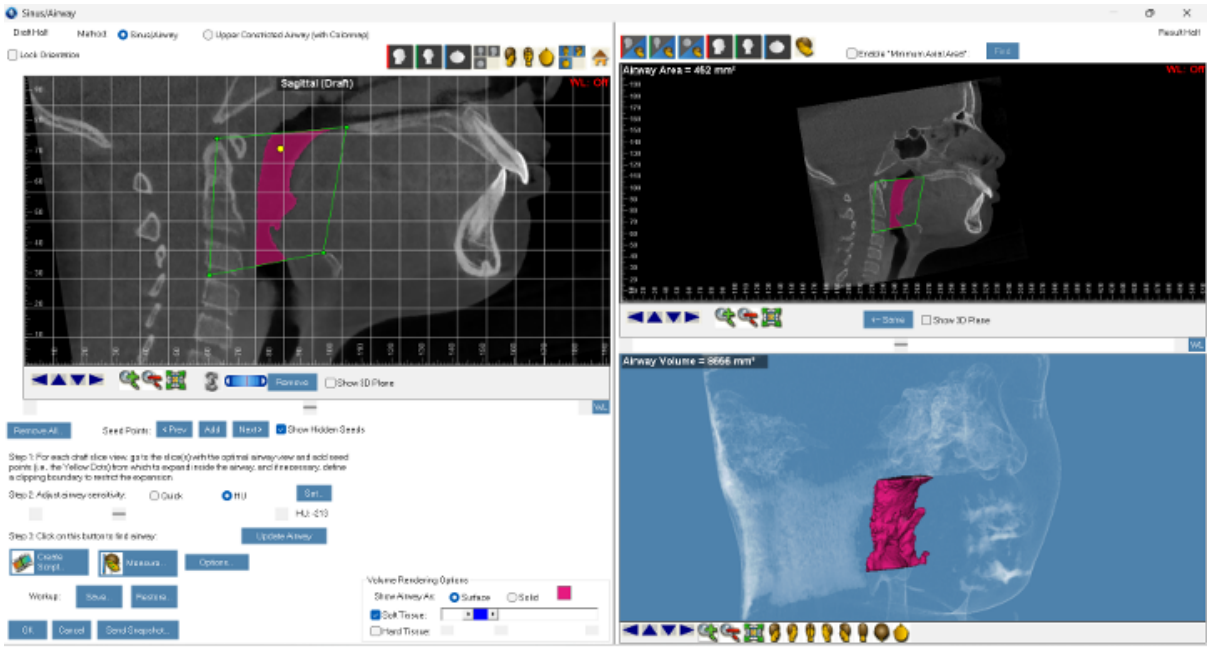

Figure 4 - Dolphin imaging software showing oropharynx in 3D with volume measurement output

Similarly, the cross-sectional area of the most constricted part of the airway was identified and measured under the upper constricted airway feature. (Figure 5)

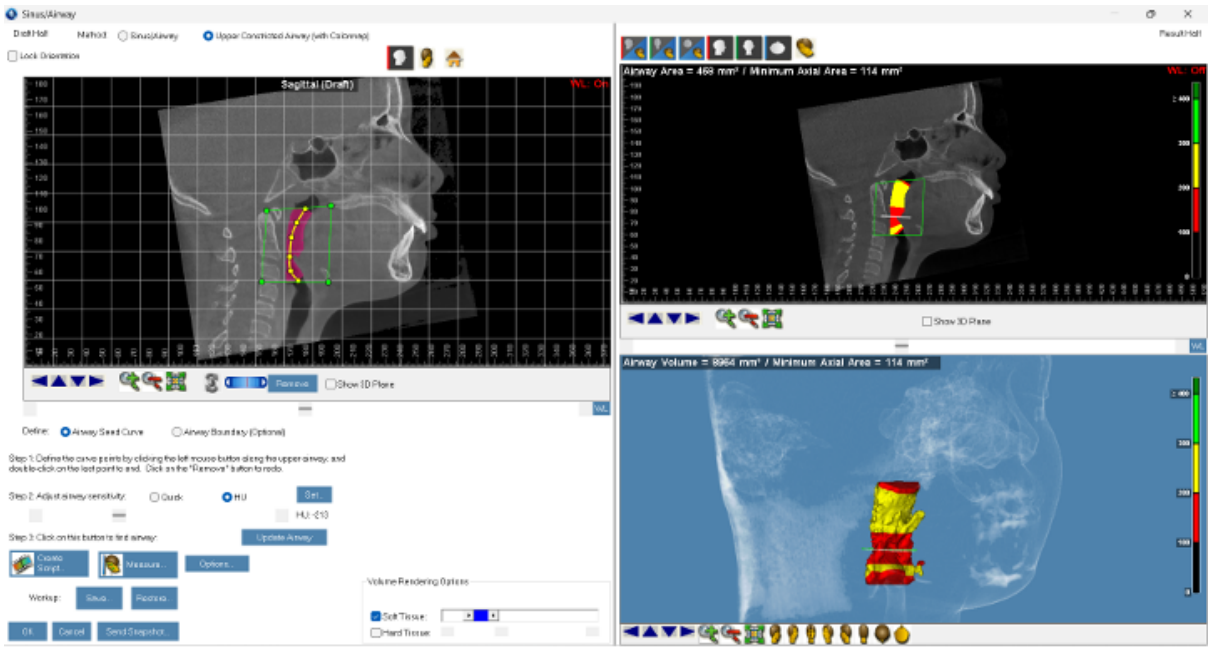

Figure 5 - Dolphin imaging software showing constricted airway tool with minimum cross-sectional area output

4.1 Statistical analysis

The power of the study was calculated based on the sample size from Chapter 2. Harvard University's ARDS Network tool was used to carry out a power analysis (https://hedwig.mgh.harvard.edu/sample_size/js/js_parallel_quant.html) based on a sample size of 12 and a significance level of 0.05 to detect a clinically meaningful difference between treatments of 1.8 times the standard deviation. The power of the study was 0.80, which is equivalent to 80%.

All statistical analyses were performed using IBM SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL). An exploratory Shapiro-Wilk test revealed a normal distribution of some parameters but not for all; therefore, both parametric and non-parametric tests were used to analyse the data.

The "p" values quoted in the analyses were two-tailed. A statistically significant level for any individual test was chosen as five percent.

4.1.1 Baseline Data Comparison

An independent samples t-test was used to analyse data that conformed to normality. For data that did not meet the normality assumption, the Mann-Whitney U test was utilised.

4.1.2 Intragroup Comparison

A paired t-test was used to analyse data that were normally distributed. On the contrary, data that did not conform to normality, the Wilcoxon signed-rank test was applied.

4.1.3 Intergroup Comparison

Since the data violated the normality assumption, an independent-samples Kruskal-Wallis test was used to analyse and compare changes.

4.1.4 Reliability Test

To determine the errors associated with CBCT volumetric analysis, pre- and post-treatment CBCTs of randomly selected ten patients, chosen by a random number generator (https://www.random.org/), totalling twenty CBCTs, were reconstructed, segmented, and analysed repeatedly at least one month after the first measurements. Intraclass correlation coefficients for all airway measurements ranged from 0.933 to 0.996, indicating excellent agreement.

5.0 Results

5.1 Baseline Data Comparison

Table 2 displays the mean and standard deviation for all parameters at T1 for Groups FA-Y and Vib-FA-Y. There was no statistically significant difference between the FA-Y and Vib-FA-Y groups.

Groups	FA-Y			Vib-FA-Y			Mean Difference	SE	p-value	Significance
	Mean	SD	SE	Mean	SD	SE				
Nasopharyngeal Volume (mm^3)	4142.56	1608.37	464.3	3924.72	758.15	218.86	217.83	513.29	0.68	NS
Oropharyngeal Volume (mm^3)	10145.36	3494.09	1008.66	11083.53	2411.18	696.05	-938.17	1225.51	0.45	NS
Minimal Cross Section Area (mm^2)	123.89	54.23	15.65	117.72	35.18	10.16	6.17	18.66	0.75	NS

*Table 2 - Results from airway analysis: descriptive data, mean differences and associated significances between Groups FA-Y and Vib-FA-Y at T1 (NS = not statistically significant, *= p<0.05, **= p<0.01)*

Table 3 displays the mean and standard deviation for all parameters at T1 for Groups FA-M and Vib-FA-M. There was no statistically significant difference between the FA-M and Vib-FA-M groups.

Groups	FA-M			Vib-FA-M			Mean Difference	SE	p-value	Significance
	Mean	SD	SE	Mean	SD	SE				
Nasopharyngeal Volume (mm^3)	5064.33	1629.08	435.39	4860.56	1754.55	506.5	203.78	663.96	0.68	NS
Oropharyngeal Volume (mm^3)	14565.12	4255.56	1137.35	12970.06	6052.57	1747.23	1595.06	2028.95	0.20	NS
Minimal Cross Section Area (mm^2)	166.9	67.96	18.16	159.94	105.9	30.57	6.40	34.39	0.41	NS

*Table 3 - Results from airway analysis: descriptive data, mean differences and associated significances between Groups FA-M and Vib-FA-M at T1 (NS = not statistically significant, *= p<0.05, **= p<0.01)*

5.2 Intra-group T1-T2 Comparison

5.2.1 Group FA-Y

Table 4 displays the mean and standard deviation for all parameters at T1 and T2 for Group FA-Y. There were no significant differences between the two timepoints for nasopharyngeal volume, oropharyngeal volume and MCA.

Timepoints	T1			T2			Mean Difference	SD	SE	% of Change	p-value	Significance
	Mean	SD	SE	Mean	SD	SE						
Nasopharyngeal Volume (mm^3)	4142.56	1608.37	464.30	4286.97	1601.30	462.26	144.42	1181.89	341.18	3%	0.68	NS
Oropharyngeal Volume (mm^3)	10145.36	3494.09	1008.66	5925.67	3326.26	960.21	1530.31	2743.83	792.07	15%	0.06	NS
Minimal Cross Section Area (mm^2)	123.89	54.23	15.65	133.58	80.33	23.19	9.69	65.96	19.04	8%	0.53	NS

*Table 4 - Results from airway analysis: descriptive data, mean differences and associated significances between T1 and T2 for Group FA-Y (NS = not statistically significant, *= p<0.05, **= p<0.01)*

5.2.2 Group Vib-FA-Y

Table 5 displays the mean and standard deviation for all parameters at T1 and T2 for Group Vib-FA-Y. There were statistically significant differences between the two time points for oropharyngeal volume ($p < 0.01$), with a mean increase of 2428.14 ± 2003.94 mm^3 (equivalent to 22% increase).

Timepoints	T1			T2			Mean Difference	SD	SE	% of Change	p-value	Significance
	Mean	SD	SE	Mean	SD	SE						
Nasopharyngeal Volume (mm^3)	3924.72	758.15	218.86	4100.53	1088.36	314.18	175.81	1133.27	327.15	4%	0.60	NS
Oropharyngeal Volume (mm^3)	11083.53	2411.18	696.05	13511.67	3358.45	969.50	2428.14	2003.94	578.49	22%	0.00	**
Minimal Cross Section Area (mm^2)	117.72	35.18	10.16	138.78	40.07	11.57	21.06	39.55	11.42	18%	0.12	NS

*Table 5 - Results from airway analysis: descriptive data, mean differences and associated significances between T1 and T2 for Group Vib-FA-Y (NS= not statistically significant, *= p<0.05, **= p<0.01)*

5.2.3 Group FA-M

Table 6 displays the mean and standard deviation for all parameters at T1 and T2 for Group FA-M. There were no significant differences between the two timepoints for nasopharyngeal volume, oropharyngeal volume and MCA.

Timepoints	T1			T2			Mean Difference	SD	SE	% of Change	p-value	Significance
	Mean	SD	SE	Mean	SD	SE						
Nasopharyngeal Volume (mm^3)	5064.33	1629.08	435.39	5630.38	1740.67	732.47	566.05	1703.01	455.15	11%	0.24	NS
Oropharyngeal Volume (mm^3)	14565.12	4255.56	1137.35	14160.52	6186.37	1653.38	404.60	3503.35	936.31	3%	0.67	NS
Minimal Cross Section Area (mm^2)	166.90	67.96	18.16	164.76	112.06	29.95	-2.14	84.83	22.67	-1%	0.93	NS

*Table 6 - Results from airway analysis: descriptive data, mean differences and associated significances between T1 and T2 for Group FA-M (NS= not statistically significant, *= p<0.05, **= p<0.01)*

5.2.4 Group Vib-FA-M

Table 7 displays the mean and standard deviation for all parameters at T1 and T2 for Group Vib-FA-M. There was a statistically significant difference between the two timepoints for nasopharyngeal volume ($p<0.05$), oropharyngeal volume ($p<0.05$) and MCA ($p<0.05$). The

significant increases were 18%, 29%, and 26% for nasopharyngeal volume, oropharyngeal volume, and MCA, respectively.

Timepoints	T1			T2			Mean Difference	SD	SE	% of Change	p-value	Significance
	Mean	SD	SE	Mean	SD	SE						
Nasopharyngeal Volume (mm^3)	4860.56	1754.55	506.5	5715.42	1691.55	488.31	854.86	1234.81	356.46	18%	0.04	*
Oropharyngeal Volume (mm^3)	12970.06	6052.57	1747.23	16686.00	5846.32	1687.69	3715.94	5104.45	1473.53	29%	0.02	*
Minimal Cross Section Area (mm^2)	159.94	105.9	30.57	201.61	82.11	23.7	41.67	71.29	20.58	26%	0.04	*

*Table 7 - Results from airway analysis: descriptive data, mean differences and associated significances between T1 and T2 for Group Vib-FA-M (NS= not statistically significant, *= p<0.05, **= p<0.01)*

5.3 Inter-group T1-T2 Comparison

Table 8 presents the mean changes, standard deviations, and standard errors for all parameters in each group. There were no statistically significant differences for mean changes in nasopharyngeal volume, oropharyngeal volume and MCA among all four groups.

Groups	FA-Y			Vib-FA-Y			FA-M			Vib-FA-M			p-value	Significance
	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE		
Nasopharyngeal Volume (mm^3)	144.42	1181.89	341.18	175.81	1133.27	327.15	566.05	1703.01	455.15	854.86	1234.81	356.46	0.58	NS
Oropharyngeal Volume (mm^3)	1530.31	2743.83	792.07	2428.14	2003.94	578.49	-404.6	3503.35	936.31	3715.94	5104.45	1473.53	0.09	NS
Minimal Cross-Sectional Area (mm^2)	9.69	65.96	19.04	21.06	39.55	11.42	-2.14	84.83	22.67	41.67	71.29	20.58	0.23	NS

Table 8 - Descriptive analysis of airway changes during treatment (T2-T1) for all groups

6.0 Discussion

The airway parameters at T1 for both placebo control groups (Groups FA-Y and FA-M) were similar to those of the respective experimental groups (Groups Vib-FA-Y and Vib-FA-M), making the groups comparable at the start of treatment. In fact, there was no statistically significant difference in all airway parameters among the four groups, suggesting that both nasopharyngeal and oropharyngeal volumes were similar during the peak and late pubertal growth stages. A previous longitudinal study has shown that the peak growth of the sagittal dimension of the nasopharynx occurs between the ages of 12 and 13 years.[20] In the present study, there were only four subjects who were under 12 years old. Therefore, most of the subjects were either at the peak growth or past peak growth stage of the nasopharynx; hence, the similarity in nasopharyngeal volume among groups of different maturity. In addition, the effect of pharyngeal lymphoid tissue on restricting the airway occurred to some degree up to the age of eight.[21] Therefore, the pharyngeal lymphoid tissues likely had a minimal influence on the results of the current study.

An inspirational finding from this pilot study was that mechanical vibration had a positive effect on the upper airway as shown in significant mean increase in oropharyngeal volume (MD 2428.14±2003.94 mm^3, equivalent to 22% increase) in Group Vib-FA-Y and significant mean increases in nasopharyngeal volume (MD 854.86±1234.81 mm^3, equivalent to 18% increase), oropharyngeal volume (MD 3715.94±5104.45 mm^3, equivalent to 29% increase) and minimal airway cross-sectional area (41.67±71.29 mm^2, equivalent to 26% increase) in Group Vib-FA-M. The lack of significant differences detected in the placebo control groups (Groups FA-Y and FA-M) could very well mean that the favourable effects were solely due to mechanical vibration. In Chapter 2, it was established that mechanical vibration has no statistically significant mandibular effect in the vibration groups when compared with the

corresponding placebo control groups. Therefore, the positive airway changes observed in this study may be attributed to the impact of mechanical vibration on the muscles or surrounding soft tissues. Upper airway muscles, such as extrinsic tongue muscles, are activated to ensure a patent airway passage against collapsing forces.[22] It has been demonstrated through both human and animal studies that the upper airway contains mechanoreceptors that are responsive to oscillations and sudden changes in pressure.[23-25] Erdogan and Sahin[22] have shown that mechanical vibration applied to the mandible and submandibular muscles enhances genioglossus activity, possibly improving airway patency. This elevated genioglossus activity persisted even after mechanical stimulations were ceased. It was also suggested that the heightened genioglossus activity was generated by some complex neuronal networks with integration properties. Therefore, intraoral mechanical vibration may be therapeutic in maintaining an open airway. Further investigation is warranted to clarify these findings.

In Group Vib-FA-Y, statistically significant improvement was observed only in oropharyngeal volume, whereas in the other experimental group (Group Vib-FA-M), considerable improvement was noted in all airway parameters. The boundary for nasopharyngeal volume measurement was from Sella to the Posterior Nasal Spine and the tip of the odontoid process. This means that any growth or therapeutic-related changes in these landmark points would impact the volumetric measurements. In Chapter 2, Group Vib-FA-M recorded a statistically significant greater increase in SNA, i.e. anterior movement of maxilla, than all other groups. In fact, all other groups displayed maxillary restraint. Hence, the posterior nasal spine in Group Vib-FA-M may have also moved anteriorly, justifying a greater increase in nasopharyngeal volume. On the contrary, SNA was not significantly altered during treatment in Group Vib-FA-Y; hence, a statistically significant change in the nasopharyngeal volume was not detected.

Class II functional appliance therapy has been shown by numerous studies to significantly improve airway dimensions.[3,5,26] The concept behind airway changes is based on the anterior movement of the mandible, which pulls the posterior soft tissue away from the airway, thereby increasing the volume or sagittal dimension of the pharynx. In addition, mandibular protrusion resulted in an increased functional space for the tongue, minimising the blockage to the posterior airway space.[27] However, the intra-group comparison for Groups FA-Y and FA-M did not support this phenomenon. There were no significant differences between the two timepoints for nasopharyngeal volume, oropharyngeal volume and MCA. The inconsistency in the findings among the literature could be attributed to variations in methodologies in image acquisition, image analysis, and the type of functional appliance.

Firstly, some of the studies that found significant airway volumetric changes recorded the CBCT images while patients were upright using the iCAT Cone Beam 3D Imaging System. In contrast, the NewTom 5G, used in this study, acquired CBCT images while the patient was in a supine position. It was understood from previous investigations that posture affects the patency of the airway because the gravitational effect of soft tissues in the airway, such as the soft palate, epiglottis, and oesophagus, differs between the supine and sitting positions.[28] In addition, the head position was difficult to standardise with NewTom 5G because the head cushion allowed patients to over- or under-extend or rotate their head easily. Muto *et al.*[29] have shown that head posture (cranio-cervical inclination) could influence the pharyngeal airway space. A change of 10^{o} in cranio-cervical inclination resulted in a 4 mm change in the posterior airway space. Apart from head posture, respiration and tongue position could also produce image distortion.[30] Therefore, meticulous instructions were always given during supine CBCT. To obtain optimal CBCT quality, Scarfe and Farman[31] suggested asking the patient to remain

still, avoid swallowing, and hold their breath during the scan. Unfortunately, this was deemed difficult to control, especially when the subjects were children.

Secondly, there are many different approaches available in image analysis and volumetric calculations. Currently, several computer software programs are available to analyse airway dimensions. Dolphin imaging was used for airway volumetric calculation in the present investigation, and it is a highly reproducible and reliable method.[9-12] However, not all imaging programs have been tested by independent studies, and some have exhibited more than 5% error.[10] Even when similar computer software programs are used, the landmarks to delineate the nasopharynx and oropharynx can vary vastly. When different landmarks are used, it can make the measured net volume between studies incomparable. In addition, most programs are currently semi-automated and utilise grey values to determine empty airway space. This signifies that human determines the sensitivity threshold. Unfortunately, human vision can be affected by lighting, fatigue, grayscale ability, and visual acuity, which subsequently affect the accuracy and reliability of the results.[32]

Thirdly, the discrepancy in the findings could be explained by the type of functional appliance used in the investigation. According to the systematic review carried out by AlQahtani *et al*.,[5] a better oropharyngeal outcome was recorded in growing patients who received removable functional appliance treatment compared to those treated with fixed functional appliance treatment. The highest amount of oropharyngeal volume increase was observed with the Mandibular Anterior Repositioning Appliance, followed by the Twin Block and Herbst. There was only one CBCT study that utilised the Herbst appliance as the functional appliance therapy which showed a significant increase in airway dimension.[33] However, the timing of the end of the treatment record could contribute significantly to the conflicting results. In the present

investigation, CBCT was taken on the day of appliance removal. However, according to Iwasaki *et al.,*[33] the end of treatment record was taken after fixed appliance therapy that followed the Herbst appliance. Therefore, the effect of airway volumetric changes was not solely obtained from functional appliance therapy. In addition, the average Herbst treatment time in the study by Iwasaki *et al.*[33] was longer (12.3±4.2 months) than in the present study (10.36±1.04 months), making these studies incomparable.

Additionally, there are individual anatomical factors that may make a functional appliance less effective in improving airway patency. Sakamoto *et al.*[34] investigated cephalometric factors associated with OSAS severity and the outcome of oral appliance therapy. Oral appliances used for OSAS are similar to functional appliances, in which the mandible is protruded forward with the aid of the appliances. It was found that patients who had a high position of the hyoid bone had a poor response to oral appliance therapy. Therefore, it would be beneficial to analyse the current data further to differentiate whether functional appliance therapy has no impact on the airway or whether the position of the hyoid bone results in a poor airway response.

Furthermore, CBCT has gained popularity only in recent years. Many previous studies on airway analysis were based on cephalometric measurements derived from 2D images. Although Martins *et al.*[35] found positive correlation in nasopharynx and oropharynx sagittal areas with their respective volumes and the most constricted area in the oropharynx with the oropharyngeal volume, Lenza *et al.*[7] showed weak correlation between most of the 2D and 3D measurements. In fact, it was concluded that single linear measurements did not depict the morphology of the airway. This means a positive change in sagittal airway measurement does not necessarily imply an improvement in transverse dimension or the 3D volume.

These incongruities in methodologies reinforced the findings from a Cochrane review that assessed the effect of oral appliances and functional appliances in children with OSAS. In this review, only one trial met the inclusion criteria. The inconsistency across outcome measures and time points provided insufficient evidence to support or refute the effectiveness of oral appliances and functional orthopaedic appliances for the treatment of OSA in children.[36]

Although promising results were shown in the mean changes in airway parameters for both experimental groups (Groups Vib-FA-Y and Vib-FA-Y), no statistically significant differences were detected when the four groups were compared, which meant that the mean changes were not significant within the sample size utilised in this pilot study, future studies with a larger sample size would be beneficial in delineating the efficacy of intraoral mechanical vibration in upper airway patency.

7.0 Limitations

This investigation was a pilot study utilising data available from Chapter 2; therefore, it had several limitations. There were no untreated control groups to negate the natural developmental effect of the upper airway, which means that the isolation of treatment effect could not be determined. There was a suggestion of utilising historical data from growth studies. However, these records consisted of two-dimensional lateral cephalograms or CBCT data of Class III malocclusion only. In addition, the investigated results were confined to patients who do not have OSAS. All patients completed either the Sleep Disturbance Scale for Children[37] or the Epworth Sleepiness Scale[38] questionnaires at the beginning of treatment, and approximately ten patients had results that required a sleep study to diagnose OSAS. Two out of the ten patients who underwent a sleep study were found to have an OSAS outcome. The

upper airway response to mechanical vibration in OSAS patients may be different, so further studies would be valuable to investigate the effect of mechanical vibration on airway patency in subjects with OSAS. Moreover, the sample size was fixed as it was determined according to the research parameters in Chapter 2. A proper sample size calculation would be required for future studies.

8.0 Conclusion

The results of this pilot study indicated that intraoral mechanical vibration has a favourable effect on the upper airway in patients undergoing functional appliance therapy. This positive effect was observed across the nasopharynx and oropharynx during the late adolescence growth stage, but was limited to the oropharynx during the peak pubertal growth stage. Unfortunately, this current investigation did not show statistically significant changes in airway dimension during functional appliance therapy when carried out during peak pubertal growth or late adolescence growth stages.

9.0 Other Information

This prospective clinical trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12625000194460). The trial was funded by the Australian Society of Orthodontists Foundation for Research and Education (ASOFRE).

10.0 List of Figures

11.0 List of Tables

12.0 Reference

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FUTURE DIRECTIONS

The present investigation has extended the frontiers of clinical mechanical vibration usage in orthodontics. The potential for its application in dentofacial orthopaedics and sleep medicine has been demonstrated. As outlined in previous chapters, several limitations were associated with both studies, necessitating further exploration to draw more definitive conclusions regarding the use of intraoral mechanical vibration during functional appliance therapy.

Results from Chapter 2 have identified the need for a larger cohort with a balanced gender distribution to establish the effectiveness of intraoral mechanical vibration in combination with functional appliance therapy during peak pubertal growth. In addition, one of the flaws of the current investigation was the suspicion of vibration stimulation being localised in the dentition and unable to dissipate to the mandibular body or the condyle. Further investigation could reveal that applying mechanical vibration directly to the skeletal structure may induce a more substantial biological change, leading to better and more stable skeletal improvement.

The cellular response to stimulation varies with the amplitude and frequency of the mechanical vibration. There is another commercially available intraoral mechanical vibration device, AcceleDent, that exerts a lower frequency and magnitude than VPro5, at 30 Hz and 20 grams of force. A comparison study between the two devices could identify the appropriate vibration frequency and magnitude that is conducive to positive skeletal change during functional appliance therapy.

Oscillatory mechanical stimuli have been shown to promote sutural cell proliferation in vivo when the pre-maxillary and nasofrontal sutures were subjected to small doses of oscillatory

strain.[1] Therefore, it would be clinically beneficial to extend the scope of the research experiment to evaluate the dentoskeletal effects of mechanical vibration usage in conjunction with Class III orthodontic treatment and maxillary expansion therapy.

The promising results from Chapter 3 served as a starting point for engaging in larger-scale, prospective, controlled studies to enhance airway patency with the use of mechanical vibration. This could benefit patients with sleep-disordered breathing and may provide an adjunctive or alternative treatment to oral appliances.

There are still many research projects that could utilise the current CBCT materials. With computer software such as Mimics and Anatomage, previous researchers were able to investigate the densities of the condyle bone and alveolar bone.[2] CBCT could also enable a 3D condyle analysis, evaluating the joint space and condylar head sizes.[3] Both aspects would provide further insight into the biological structural changes, if any, that occur during functional appliance therapy with and without the concomitant use of intraoral mechanical vibration. It was also noted in Chapter 3 that individual anatomical factors, such as the position of the hyoid bone, can elicit a poor response to oral appliances. Further analysis of the current material could identify whether there was a correlation between the hyoid bone position and the change in airway dimension during functional appliance therapy at different maturity stages.

In summary, there is a high potential for discovering the wider clinical applications of mechanical vibration stimulation as an adjunct to orthodontics, dentofacial orthopaedics therapy, orthognathic surgery, and sleep medicine. In addition, the current CBCT materials open avenues to a myriad of research studies that would provide a better understanding of the

skeletal structural changes associated with the use of mechanical therapy during functional appliance therapy.

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Appendix

Appendix 1 – Information for Parents and Guardians

M. Ali Darendeliler, BDS, PhD, Dip Orth., Certif. Orth.,Priv.Doc
Professor and Chair,
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University Mail Code (C12)

The Effects of Mechanical Vibration on Class II Orthopaedic Appliance Therapy at Different Stages of Skeletal Maturity

INFORMATION FOR PARENT / GUARDIAN

Introduction

Your child is invited to take part in a research study, the objective of which is to see if the use of a vibration device (C-Shaped Vibration Device, Propel Orthodontics, Milpitas, USA), can improve the efficiency and outcome of the treatment of a short lower jaw at different ages.

The study is being conducted within Sydney Dental Hospital by Dr. Lam L Cheng, a registered specialist orthodontist, and will form the basis for the degree of Doctor of Philosophy at the University of Sydney under the supervision of Professor M Ali Darendeliler and Doctors Oyku Dalci, Alexandra Pappadopoulou and Lorenzo Franchi.

Study Procedure

The treatment being investigated in this study is in addition to standard treatment offered in this institution. The current standard treatment would involve expanding the child's upper jaw, along with using a functional appliance to position the lower jaw forward. The functional appliance, composed of metal capping on the upper and lower first molars, is cemented onto the teeth. The lower jaw is postured forward by the telescopic arms that are attached to the metal cappings (Figure 1). The functional appliance will be used for 9-12 months. The effect on the teeth and the bone level will differ at different stages of maturity. For this research study, some patients will be undergoing the standard treatment and some patients will be using a vibration device (Figure 2) in conjunction with the functional appliance. Previous research suggested an enhanced effect on tooth movement and possible jaw growth when a vibration device was used together with orthodontic or functional appliance. This vibration device is to be used inside the mouth and on top of the teeth. When the vibration device is operating, your child will feel mild vibration through the teeth and possibly to the surrounding bone in the jaw. The vibration may stimulate the surrounding bone cells to enhance the rate of tooth movement and the growth of the jaw.

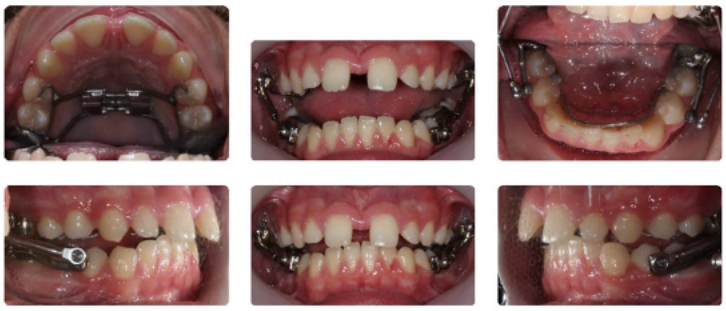

Figure 1 – Functional appliance

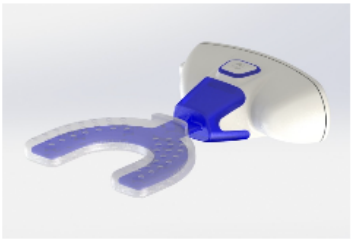

Figure 2 C-Shaped Vibration Device

The following outlines the appointment visits and clinical procedures of this research:

Visit 1. Standard orthodontic records i.e. photographs, radiographs (cone beam computer tomography) and moulds of the upper and lower teeth will be taken.

Visit 2. 4 to 8 small separating elastics will be placed between the back teeth to create spaces so to allow the metal capping be placed in the following visits.

Visit 3. One week later, the metal cappings will be trialled for the right size and moulds of the upper and lower teeth will be taken. A wax bite which records the ideal lower jaw position will be taken. The metal cappings are then removed and the separating elastics will be replaced.

Visit 4. Two weeks later, the metal cappings with the expander will be cemented to the teeth. The telescopic arms will be attached to the metal cappings using an allen key. You will be instructed to perform the expansion using an expansion key once a day for 2-3 weeks depending on the amount of expansion needed. This may vary with individual. If you are assigned to the vibration protocol, you child and yourself would be instructed on the use of the mechanical vibration device. This device needs to be used for 5 minutes a day throughout the whole treatment.

Visit 5. Three weeks later, the appliance will be checked to see if adequate expansion has achieved. Adjustment of the appliance may be done accordingly.

Visit 6-11. Review appointments 6 weekly. The appliance will be checked at each review appointment. If your child is in the vibration protocol group, the vibrating device will be checked for compliance rate.

Visit 12. The duration of the functional appliance therapy is 9 months. At the end of this phase of treatment, the standard records will be taken i.e. photographs, radiographs (cone beam computer tomography) and moulds of the upper and lower teeth. The research procedures will be finished at this point but his/her standard orthodontic care will continue as needed.

Finally, the researchers would like to have access to your child's dental records to obtain information relevant to this study.

Non-participation in this study will have no effect on your child's clinical care. The aim of this method is to produce better results while eliminating the possible need for surgery in the future.

Voluntary Participation

Paticipation in this study is entirely voluntary. Your child does not have to take part in it. If you do allow them to take part and if you change your mind, you can withdraw them at any time without having to give a reason. Whatever your decision, please be assured that it will not affect your child's treatment or relationship with the staff who are caring for them.

The study procedures will be performed by Dr. Lam L Cheng. After the study has been completed your child will continue any further necessary orthodontic treatment in our department with one of the Orthodontic Registrars.

Risks

As with all medical procedures – whether for diagnosis or treatment, routine or experimental – involve some risk of injury. In addition, there may be risks associated with the study that are presently unknown and unforeseeable. In spite of all precautions, your child might develop medical complications from participating in this study.

The risks of participating in this study are:

- The functional appliance or vibration device may break during the study period
- The functional appliance could come off the teeth. Usually the appliances remain attached to the other teeth and to the other components of the appliance; but they may come off totally and there is the risk of them being swallowed (this is similar to the risk of regular orthodontic treatment)
- Functional appliance may be slightly uncomfortable for the tongue and cheeks during the first few days (similar to that of regular orthodontic treatment). This may also affect your child's speech for the first few days
- Vibration devices may also be slightly uncomfortable for the tongue and cheeks during the first few uses just like the functional appliance
- Mild discomfort may be experienced in the teeth and jaws (similar to that of regular orthodontic treatment)

Benefits

We intend that this research study furthers dental knowledge and may improve orthodontic treatment in the future.

Cost

Participation in this study will not cost you anything.

Compensation for Injuries or Complications

If your child suffers any injuries or complication as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment for your child. If your child is eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

In addition, you may have a right to take legal action to obtain compensation or any injuries or complication resulting from the study. Compensation may be available if your child's injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). You and your child do not give up any legal rights to compensation by participating in the study.

Confidentiality

All the information collected from your child for the study will be treated confidentially in the same way as outlined by the guidelines of the Sydney Dental Hospital. Photographic records are routinely done throughout the course of any orthopaedic/orthodontic treatment. These records will be stored in a Sydney Dental Hospital computer with password protection. The study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such a presentation. The study results may also be used for future research projects as comparison.

Further Information

When you have read this information, Dr. Lam L Cheng or Dr. Oyku Dalci will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact them on (02) 9293 3388.

Dr. Lam L Cheng
Dr. Oyku Dalci

Faculty of Dentistry / Orthodontic Department
Sydney Dental Hospital
Level 2, 2 Chalmers Street
Surry Hills NSW 2010
Telephone: (02) 9293 3388
Fax: (02) 9351 8336

This information sheet is for you to keep

Ethics Approval and Complaints

This study has been approved by the Ethics Review Committee RPAH Zone of the Sydney Local Health District. Any person with the concerns or complaints about the conduct o this study should contact the Executive Officer on 02 9515 6766 and quote the protocol number X16-0473

Appendix 2 – Information for Adolescents

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University Mail Code (C12)

The Effects of Mechanical Vibration on Class II Orthopaedic Appliance Therapy at Different Stages of Skeletal Maturity

INFORMATION FOR ADOLESCENCE (14-16 YEARS OLD)

Introduction

You are invited to take part in a research study to see if the use of a vibration device (C-Shaped Vibration Device, Propel Orthodontics, Milpitas, USA), can improve the efficiency and outcome of the treatment of a short lower jaw at different ages.

The study is being conducted within Sydney Dental Hospital by Dr. Lam L Cheng, a registered specialist orthodontist, and will form the basis for the degree of Doctor of Philosophy at the University of Sydney under the supervision of Professor M Ali Darendeliler and Doctors Oyku Dalci, Alexandra Pappadopoulou and Lorenzo Franchi.

Study Procedure

The treatment being investigated in this study is in addition to standard treatment offered in this institution. The current standard treatment for you would involve expanding your upper jaw, along with using a functional appliance to position your lower jaw forward. The functional appliance, composed of metal capping on the upper and lower first molars, is cemented onto the teeth. The lower jaw is postured forward by the telescopic arms that are attached to the metal cappings (Figure 1). The functional appliance will be used for 9-12 months. The effect on the teeth and the bone level will differ at different stages of maturity. The older you are, the less effect can be achieved at the bone level. For this research study, some patients will be undergoing the standard treatment and some patients will be using a vibration device (Figure 2) in conjunction with the functional appliance. Previous research suggested the teeth may move faster and the jaw may grow better when a vibration device was used together with braces or functional appliance. This vibration device is to be used inside the mouth and on top of the teeth. When the vibration device is operating, you will feel mild vibration through the teeth and possibly to the surrounding bone in the jaw. The vibration may stimulate the surrounding bone cells to make the teeth move faster and the jaw grow better.

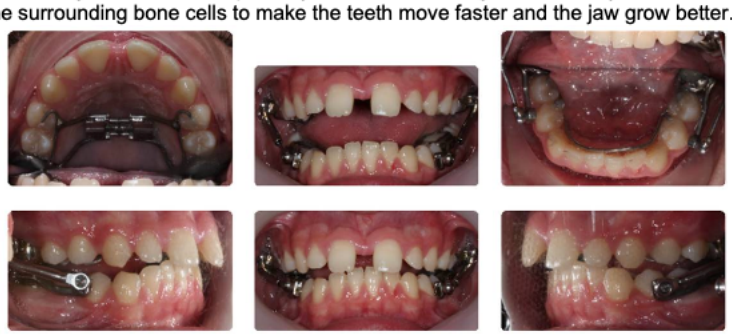
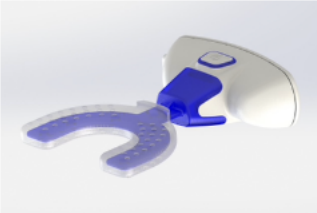


Figure 1 – Functional appliance



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Visit 4. Two weeks later, the metal cappings with the expander will be cemented to the teeth. The telescopic arms will be attached to the metal cappings using an allen key. You and/or your parent/guardian will be instructed to perform the expansion using an expansion key once a day for 2-3 weeks depending on the amount of expansion needed. This may vary with individual. If you are assigned to the vibration protocol, you and/or your parent/guardian would be instructed on the use of the mechanical vibration device. This device needs to be used for 5 minutes a day throughout the whole treatment.
Visit 5. Three weeks later, the appliance will be checked to see if adequate expansion has achieved. Adjustment of the appliance may be done accordingly.
Visit 6-11. Review appointments 6 weekly. The appliance will be checked at each review appointment. If you are in the vibration protocol group, the vibrating device will be checked for compliance rate.
Visit 12. The duration of the functional appliance therapy is 9 months. At the end of this phase of treatment, the standard records will be taken i.e. photographs, radiographs (cone beam computer tomography) and moulds of the upper and lower teeth. The research procedures will be finished at this point but your standard orthodontic care will continue as needed.

Finally, the researchers would like to have access to your dental records to obtain information relevant to this study.

If you do not wish to participate in this study, there will be no effect on your clinical care. The aim of this method is to produce better results while eliminating the possible need for surgery in the future.

Voluntary Participation

Paticipation in this study is entirely voluntary. You do not have to take part in it. If you do participate and if you change your mind, you can withdraw them at any time without having to give a reason. Whatever your decision, please be assured that it will not affect your treatment or relationship with the staff who are caring for you.

The study procedures will be performed by Dr. Lam L Cheng. After the study has been completed you will continue any further necessary orthodontic treatment in our department with one of the Orthodontic Registrars.

Risks

As with all medical procedures – whether for diagnosis or treatment, routine or experimental – involve some risk of injury. In addition, there may be risks associated with the study that are presently unknown and unforeseeable. In spite of all precautions, you might develop medical complications from participating in this study.

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- The functional appliance could come off the teeth. Usually the appliances remain attached to the other teeth and to the other components of the appliance; but they may come off totally and there is the risk of them being swallowed (this is similar to the risk of regular orthodontic treatment)
- Functional appliance may be slightly uncomfortable for the tongue and cheeks during the first few days (similar to that of regular orthodontic treatment). This may also affect your speech for the first few days
- Vibration devices may also be slightly uncomfortable for the tongue and cheeks during the first few uses just like the functional appliance
- Mild discomfort may be experienced in the teeth and jaws (similar to that of regular orthodontic treatment)

Benefits

We intend that this research study furthers dental knowledge and may improve orthodontic treatment in the future.

The added benefit is that this treatment may result in a better outcome compared with that achieved with the conventional functional appliance. For the older adolescents, this treatment may eliminate the possible need for surgery in the future for the correction of the underlying bone problem.

Cost

Participation in this study will not cost you anything.

Compensation for Injuries or Complications

If you suffer any injuries or complication as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment for you. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

In addition, you may have a right to take legal action to obtain compensation or any injuries or complication resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). You do not give up any legal rights to compensation by participating in the study.

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All the information collected from you for the study will be treated confidentially in the same way as outlined by the guidelines of the Sydney Dental Hospital. Photographic records are routinely done throughout the course of any orthopaedic/orthodontic treatment. These records will be stored in a Sydney Dental Hospital computer with password protection. The study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such a presentation. The study results may also be used for future research projects as compariso

Further Information

When you have read this information, Dr. Lam L Cheng or Dr. Oyku Dalci will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact them on (02) 9293 3388.

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Dr. Oyku Dalci
Faculty of Dentistry / Orthodontic Department
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Appendix 3 – Parent/Guardian Consent Form

M. Ali Darendeliler, BDS, PhD, Dip Orth., Certif. Orth.,Priv.Doc
Professor and Chair,
Discipline of Orthodontics
(ASO (NSW Branch) Inc)

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University Mail Code (C12)

The Effects of Mechanical Vibration on Class II Orthopaedic Appliance Therapy at Different Stages of Skeletal Maturity

PARENT / GUARDIAN CONSENT FORM

I, ... *[name of parent/guardian]*

of .....*[address]*,

parent/guardian of ..... *[name of child]*

have read and understood the Information for Parent/Guardian on the abovenamed research study and have discussed the study with Dr. Lam L Cheng or Dr Oyku Dalci.

I have been made aware of the procedures involved in the study, including any known or expected inconvenience, risk, discomfort or potential side effect and of their implications as far as they are currently known by the researchers.

I understand that participation in this study will allow the researchers to have access to my child's medical and dental records (photographs, radiographs and moulds of the teeth), and I agree to this.

I understand that the dental records (photographs, radiographs and moulds of the teeth) will be kept for this study and may be used in future research studies, and I agree to this.

I freely choose to allow my child to participate in this study and understand that I can withdraw him/her at any time.

I understand and agree that photographs will be taken of my child's face and teeth for research purposes and these may be use to present the results of the study in a scientific journal or presentation.

I also understand that the research study is strictly confidential.

I hereby agree to my child's participation this research study.

NAME OF PARENT/GUARDIAN: .....

SIGNATURE: .....

DATE: .....

NAME OF WITNESS: .....

SIGNATURE OF WITNESS: .....

Version 1, 12th August 2016 Pages: 1-1

Appendix 4 – Patient Consent Form

M. Ali Darendeliler, BDS, PhD, Dip Orth., Certif. Orth.,Priv.Doc
Professor and Chair,
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The Effects of Mechanical Vibration on Class II Orthopaedic Appliance Therapy at Different Stages of Skeletal Maturity

PARTICIPANT CONSENT FORM

I, ... *[name]*

of .....*[address]*,

have read and understood the Information for Parent/Guardian on the abovenamed research study and have discussed the study with Dr. Lam L Cheng or Dr Oyku Dalci.

I have been made aware of the procedures involved in the study, including any known or expected inconvenience, risk, discomfort or potential side effect and of their implications as far as they are currently known by the researchers.

I understand that participation in this study will allow the researchers to have access to my medical and dental records (photographs, radiographs and moulds of the teeth), and I agree to this.

I understand that the dental records (photographs, radiographs and moulds of the teeth) will be kept for this study and may be used in future research studies, and I agree to this.

I freely choose to participate in this study and understand that I can withdraw at any time.

I understand and agree that photographs will be taken of my face and teeth for research purposes and these may be use to present the results of the study in a scientific journal or presentation.

I also understand that the research study is strictly confidential.

I hereby agree to participate in this research study.

NAME : .....

SIGNATURE: .....

DATE: .....

NAME OF WITNESS: .....

SIGNATURE OF WITNESS: .....

Appendix 5 – Ethics Approval Letter

ADDRESS FOR ALL CORRESPONDENCE
RESEARCH ETHICS AND GOVERNANCE OFFICE
ROYAL PRINCE ALFRED HOSPITAL
CAMPERDOWN NSW 2050

TELEPHONE: (02) 9515 6766
EMAIL: sharon.falleiro@sswahs.nsw.gov.au
REFERENCE: X16-0473 & HREC/16/RPAH/681

NSW GOVERNMENT Health
Sydney
Local Health District

10 February 2017

Dr L Cheng
Sydney Dental Hospital
Discipline of Orthodontics
Level 2, 2 Chalmers St.
SURRY HILLS NSW 2010

Dear Dr Cheng,

Re: Protocol No X16-0473 & HREC/16/RPAH/681 - "The effects of mechanical vibration on Class II orthopaedic appliance therapy at different stages of skeletal maturity"

The Executive of the Ethics Review Committee, at its meeting of 8 February 2017 considered your correspondence of 18 January 2017 and subsequent correspondence of 10 February 2017. In accordance with the decision made by the Ethics Review Committee, at its meeting of 14 December 2016, ethical approval is granted.

The proposal meets the requirements of the *National Statement on Ethical Conduct in Human Research.*

This approval includes the following:

- NEAF (AU/1/D9A927)
- Protocol (Version 1, 12 August 2016)
- Invitation to Participate (Version 1, 1 July 2016)
- Information for Parent/Guardian (Version 2, 18 January 2017)
- Parent Guardian Consent Form (Version 1, 12 August 2016)
- Information for Adolescence (14-16 Years Old) (Version 1, 18 January 2017)
- Participant Consent Form (Version 2, 10 February 2017)

You are asked to note the following:

- **This letter constitutes ethical approval only.**

- **You must NOT commence this research project at ANY site until you have submitted a Site Specific Assessment Form to the Research Governance Officer and received separate authorisation from the Chief Executive or delegate of that site.**

  On the basis of this ethics approval, authorisation may be sought to conduct this study within any NSW/QLD/VIC/SA/ACT public health organisation and/or within any private organisation which has entered into an appropriate memorandum of understanding with the Sydney Local Health District, Sydney Local Health Network or the Sydney South West Area Health Service.

  The Committee noted that authorisation will be sought to conduct the study at the following sites:

  - Sydney Dental Hospital

- This approval is valid for four years, and the Committee requires that you furnish it with annual reports on the study's progress beginning in **February 2018.** If recruitment is ongoing at the conclusion of the four year approval period, a full re-submission will be required. Ethics approval will continue during the re-approval process.

- This human research ethics committee (HREC) has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review and is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

- You must immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.

- You must notify the HREC of proposed changes to the research protocol or conduct of the research in the specified format.

- You must notify the HREC and other participating sites, giving reasons, if the project is discontinued at a site before the expected date of completion.

- If you or any of your co-investigators are University of Sydney employees or have a conjoint appointment, you are responsible for informing the University's Risk Management Office of this approval, so that you can be appropriately indemnified.

- Where appropriate, the Committee recommends that you consult with your Medical Defence Union to ensure that you are adequately covered for the purposes of conducting this study.

Should you have any queries about the Committee's consideration of your project, please contact me. The Committee's Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Sydney Local Health District website.

A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The Ethics Review Committee wishes you every success in your research.

Yours sincerely,

Sharon Falleiro
Executive Officer
Ethics Review Committee (RPAH Zone)

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Appendix 6 – Statistical Output

Statistic Output for intergroup comparison at T1 (Age) – Groups FA-Y and Vib-FA-Y

Independent t-test for variables that were normally distributed

Descriptive Statistics

descriptives		N	Mean	Std. Deviation	Std. Error Mean
AGE	FA-Y	12	12.89	1.02	0.30
	Vib-FA-Y	12	13.51	1.27	0.37

Independent t-test

Independent Samples Test					
	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
				Lower	Upper
AGE	0.202	-0.6190833	0.4711529	-1.5961946	0.35802797

No statistically significant difference in age between experiment groups

Statistic Output for intergroup comparison at T1 (Age) – Groups FA-Y and Vib-FA-Y

Independent t-test for variables that were normally distributed

Descriptive Statistics

descriptives		N	Mean	Std. Deviation	Std. Error Mean
AGE	FA-M	14	14.78	1.30	0.35
	Vib-FA-M	12	15.38	0.71	0.21

Independent t-test

Independent Samples Test					
	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
				Lower	Upper
AGE	0.156	-0.5952976	0.40448484	-1.4372049	0.24660962

Statistic Output for intragroup comparison (Cephalometric Variables) – Group FA-Y

Paired t-test for variables that were normally distributed

Descriptive Statistics

	Mean	N	Std. Deviation	Std. Error Mean
T2_SNA	82.93	12	5.06	1.46
T1_SNA	83.55	12	6.83	1.97
T2_SNB	78.15	12	4.72	1.36
T1_SNB	77.01	12	6.57	1.90
T2_Wits	3.25	12	2.98	0.86
T1_Wits	6.85	12	2.49	0.72
T2_A-Nperp	3.32	12	4.07	1.18
T1_A-Nperp	2.65	12	3.45	1.00
T2_Pog-Nperp	-1.03	12	6.59	1.90
T1_Pog-Nperp	-5.03	12	6.00	1.73
T2_Co-Gn	110.19	12	7.02	2.03
T1_Co-Gn	104.92	12	6.82	1.97
T2_SN-GoMe	32.63	12	4.68	1.35
T1_SN-GoMe	33.05	12	6.54	1.89
T2_Y-Axis	68.87	12	4.64	1.34
T1_Y-Axis	69.29	12	5.66	1.63
T2_U1-SN	109.33	12	7.86	2.27
T1_U1-SN	115.20	12	7.95	2.29
T2_LI-MP	103.30	12	6.73	1.94
T1_LI-MP	97.88	12	5.82	1.68
T2_OB	1.83	12	2.11	0.61
T1_OB	3.43	12	1.49	0.43
T2_Nasolabial Angle	116.57	12	10.62	3.07
T1_Nasolabial Angle	115.65	12	8.42	2.43
T2_UL-E	-1.13	12	1.90	0.55
T1_UL-E	0.85	12	2.19	0.63
T2_LL-E	0.88	12	2.32	0.67
T1_LL-E	1.47	12	2.78	0.80

Paired t-test

	Paired Differences					Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		
				Lower	Upper	
T2_SNA - T1_SNA	-0.62	2.29	0.66	-2.07	0.84	0.37
T2_SNB - T1_SNB	1.14	2.81	0.81	-0.64	2.93	0.19
T2_Wits - T1_Wits	-3.60	1.08	0.31	-4.29	-2.91	0.00
T2_A-Nperp - T1_A-Nperp	0.67	1.24	0.36	-0.12	1.45	0.09
T2_Pog-Nperp - T1_Pog-Nperp	4.00	2.06	0.59	2.69	5.31	0.00
T2_Co-Gn - T1_Co-Gn	5.28	2.37	0.69	3.77	6.78	0.00
T2_SN-GoMe - T1_SN-GoMe	-0.43	3.04	0.88	-2.36	1.51	0.64
T2_Y-Axis - T1_Y-Axis	-0.43	1.76	0.51	-1.54	0.69	0.42
T2_U1-SN - T1_U1-SN	-5.87	3.31	0.95	-7.97	-3.77	0.00
T2_LI-MP - T1_LI-MP	5.43	4.44	1.28	2.60	8.25	0.00
T2_OB - T1_OB	-1.60	1.42	0.41	-2.50	-0.70	0.00
T2_Nasolabial Angle - T1_Nasolabial Angle	0.92	6.06	1.75	-2.93	4.77	0.61
T2_UL-E - T1_UL-E	-1.98	1.01	0.29	-2.63	-1.34	0.00
T2_LL-E - T1_LL-E	-0.59	2.32	0.67	-2.07	0.88	0.40

Wilcoxon Signed-Rank Test for variables that were not normally distributed

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
T2_ANB	12	4.78	2.59	1.60	8.00
T2_OJ	12	4.38	1.74	2.00	9.20
T1_ANB	12	6.53	1.99	3.90	9.20
T1_OJ	12	9.48	1.93	6.30	13.60

Wilcoxon Signed-Rank Test

Test Statistics		
	T1_ANB - T2_ANB	T1_OJ - T2_OJ
Z	-2.904b	-3.061b
Asymp. Sig. (2-tailed)	0.004	0.002

Statistic Output for intragroup comparison (Cephalometric Variables) – Group Vib-FA-Y

Paired t-test for variables that were normally distributed

Descriptive statistics

	Mean	N	Std. Deviation	Std. Error Mean
T2_SNA	80.88	12	3.57	1.03
T1_SNA	80.97	12	4.34	1.25
T2_SNB	76.07	12	2.64	0.76
T1_SNB	74.77	12	2.43	0.70
T2_Wits	3.92	12	2.39	0.69
T1_Wits	7.83	12	2.19	0.63
T2_A-Nperp	1.93	12	3.34	0.96
T1_A-Nperp	1.63	12	3.22	0.93
T2_Pog-Nperp	-3.44	12	6.99	2.02
T1_Pog-Nperp	-5.88	12	6.52	1.88
T2_Co-Gn	107.28	12	4.99	1.44
T1_Co-Gn	103.62	12	4.19	1.21
T2_SN-GoMe	32.85	12	6.69	1.93
T1_SN-GoMe	33.25	12	6.22	1.80
T2_Y-Axis	68.87	12	4.72	1.36
T1_Y-Axis	69.41	12	4.19	1.21
T2_U1-SN	108.48	12	7.50	2.17
T1_U1-SN	114.86	12	6.55	1.89
T2_LI-MP	102.03	12	7.87	2.27
T1_LI-MP	95.98	12	6.35	1.83
T2_OB	2.88	12	1.81	0.52
T1_OB	4.92	12	1.67	0.48
T2_Nasolabial Angle	116.77	12	5.66	1.63
T1_Nasolabial Angle	117.95	12	7.45	2.15
T2_ANB	4.83	12	1.98	0.57
T1_ANB	6.19	12	2.54	0.73
T2_OJ	4.84	12	1.78	0.51
T1_OJ	9.81	12	2.20	0.64
T2_UL-E	-2.63	12	1.89	0.54
T1_UL-E	-0.14	12	1.82	0.52
T2_LL-E	-0.58	12	2.84	0.82
T1_LL-E	-0.07	12	3.17	0.91

Paired t-test

	Paired Differences					Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		
				Lower	Upper	
T2_SNA - T1_SNA	-0.09	1.28	0.37	-0.91	0.72	0.81
T2_SNB - T1_SNB	1.30	1.06	0.31	0.63	1.97	0.00
T2_Wits - T1_Wits	-3.92	1.85	0.53	-5.09	-2.74	0.00
T2_A-Nperp - T1_A-Nperp	0.30	1.19	0.34	-0.45	1.05	0.40
T2_Pog-Nperp - T1_Pog-Nperp	2.43	3.18	0.92	0.42	4.45	0.02
T2_Co-Gn - T1_Co-Gn	3.66	1.83	0.53	2.50	4.82	0.00
T2_SN-GoMe - T1_SN-GoMe	-0.40	1.47	0.42	-1.33	0.53	0.37
T2_Y-Axis - T1_Y-Axis	-0.54	0.84	0.24	-1.08	0.00	0.04
T2_U1-SN - T1_U1-SN	-6.38	3.18	0.92	-8.40	-4.35	0.00
T2_LI-MP - T1_LI-MP	6.05	4.52	1.30	3.18	8.92	0.00
T2_OB - T1_OB	-2.04	1.04	0.30	-2.70	-1.38	0.00
T2_Nasolabial Angle - T1_Nasolabial Angle	-1.18	4.94	1.43	-4.32	1.96	0.43
T2_ANB - T1_ANB	-1.36	1.50	0.43	-2.31	-0.41	0.01
T2_OJ - T1_OJ	-4.97	1.44	0.41	-5.88	-4.05	0.00
T2_UL-E - T1_UL-E	-2.48	1.12	0.32	-3.19	-1.77	0.00
T2_LL-E - T1_LL-E	-0.52	1.23	0.35	-1.30	0.26	0.17

Statistic Output for intragroup comparison (Cephalometric Variables) – Group FA-M

Paired t-test for variables that were normally distributed

Descriptive statistics

	Mean	N	Std. Deviation	Std. Error Mean
T2_SNA	81.19	14	3.62	0.97
T1_SNA	81.86	14	3.38	0.90
T2_SNB	76.96	14	3.51	0.94
T1_SNB	76.23	14	3.47	0.93
T2_Wits	1.94	14	2.18	0.58
T1_Wits	5.76	14	2.10	0.56
T2_A-Nperp	2.06	14	2.84	0.76
T1_A-Nperp	2.75	14	3.27	0.88
T2_Pog-Nperp	-1.24	14	5.71	1.53
T1_Pog-Nperp	-2.43	14	5.78	1.55
T2_Co-Gn	112.07	14	8.04	2.15
T1_Co-Gn	108.34	14	6.83	1.83
T2_SN-GoMe	33.42	14	4.43	1.18
T1_SN-GoMe	33.61	14	4.29	1.15
T2_Y-Axis	68.84	14	3.04	0.81
T1_Y-Axis	69.03	14	3.16	0.84
T2_U1-SN	104.98	14	5.58	1.49
T1_U1-SN	111.01	14	7.24	1.93
T2_LI-MP	101.64	14	7.73	2.07
T1_LI-MP	95.01	14	5.05	1.35
T2_OB	2.49	14	1.77	0.47
T1_OB	4.25	14	2.53	0.68
T2_Nasolabial Angle	115.95	14	11.29	3.02
T1_Nasolabial Angle	115.17	14	13.25	3.54
T2_ANB	4.24	14	1.28	0.34
T1_ANB	5.64	14	0.83	0.22
T2_UL-E	-2.77	14	2.61	0.70
T1_UL-E	-0.91	14	2.55	0.68
T2_LL-E	-0.44	14	2.33	0.62
T1_LL-E	0.26	14	1.66	0.44

Paired t-test

	Paired Differences					Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		
				Lower	Upper	
T2_SNA - T1_SNA	-0.66	0.97	0.26	-1.23	-0.10	0.02
T2_SNB - T1_SNB	0.73	0.67	0.18	0.34	1.11	0.00
T2_Wits - T1_Wits	-3.82	1.60	0.43	-4.74	-2.90	0.00
T2_A-Nperp - T1_A-Nperp	-0.69	1.89	0.50	-1.78	0.40	0.19
T2_Pog-Nperp - T1_Pog-Nperp	1.19	3.59	0.96	-0.89	3.26	0.24
T2_Co-Gn - T1_Co-Gn	3.74	2.24	0.60	2.44	5.03	0.00
T2_SN-GoMe - T1_SN-GoMe	-0.19	1.09	0.29	-0.81	0.44	0.53
T2_Y-Axis - T1_Y-Axis	-0.19	0.85	0.23	-0.69	0.30	0.41
T2_U1-SN - T1_U1-SN	-6.04	4.09	1.09	-8.40	-3.67	0.00
T2_LI-MP - T1_LI-MP	6.63	4.44	1.19	4.06	9.19	0.00
T2_OB - T1_OB	-1.76	1.67	0.45	-2.72	-0.79	0.00
T2_Nasolabial Angle - T1_Nasolabial Angle	0.78	7.31	1.95	-3.44	5.00	0.70
T2_ANB - T1_ANB	-1.39	0.87	0.23	-1.89	-0.89	0.00
T2_UL-E - T1_UL-E	-1.86	0.80	0.21	-2.33	-1.40	0.00
T2_LL-E - T1_LL-E	-0.71	1.29	0.35	-1.45	0.04	0.06

Wilcoxon Signed-Rank Test for variables that were not normally distributed

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
T2_OJ	14	4.14	1.83	2.6	9.6
T1_OJ	14	8.66	2.19	6.5	14.5

Wilcoxon signed-rank test

Test Statistics	
	T1_OJ - T2_OJ
Z	-3.297b
Asymp. Sig. (2-tailed)	0.001

Statistic Output for intragroup comparison (Cephalometric Variables) – Group Vib-FA-M

Paired t-test for variable that were normally distributed

Descriptive statistics

	Mean	N	Std. Deviation	Std. Error Mean
T2_SNA	81.68	12	3.88	1.12
T1_SNA	81.23	12	3.73	1.08
T2_SNB	77.12	12	4.51	1.30
T1_SNB	76.34	12	4.32	1.25
T2_Wits	3.80	12	2.49	0.72
T1_Wits	6.37	12	3.15	0.91
T2_A-Nperp	2.42	12	3.29	0.95
T1_A-Nperp	1.83	12	2.84	0.82
T2_Pog-Nperp	-0.55	12	7.49	2.16
T1_Pog-Nperp	-2.12	12	6.88	1.99
T2_Co-Gn	112.28	12	8.24	2.38
T1_Co-Gn	110.47	12	8.49	2.45
T2_SN-GoMe	30.63	12	8.13	2.35
T1_SN-GoMe	31.13	12	7.41	2.14
T2_Y-Axis	67.17	12	5.25	1.51
T1_Y-Axis	67.50	12	5.13	1.48
T2_U1-SN	106.97	12	9.34	2.70
T1_U1-SN	112.93	12	10.80	3.12
T2_LI-MP	102.11	12	8.79	2.54
T1_LI-MP	93.90	12	6.27	1.81
T2_OB	2.52	12	1.79	0.52
T1_OB	4.78	12	2.43	0.70
T2_Nasolabial Angle	116.09	12	9.32	2.69
T1_Nasolabial Angle	119.48	12	11.83	3.41
T2_ANB	4.57	12	1.97	0.57
T1_ANB	4.86	12	1.69	0.49
T2_UL-E	-3.83	12	1.84	0.53
T1_UL-E	-2.67	12	2.15	0.62
T2_LL-E	-1.70	12	2.17	0.63
T1_LL-E	-1.21	12	2.58	0.75
T2_OJ	4.93	12	1.53	0.44
T1_OJ	8.82	12	2.24	0.65

Paired t-test

	Paired Differences					Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		
				Lower	Upper	
T2_SNA - T1_SNA	0.46	0.64	0.18	0.05	0.86	0.03
T2_SNB - T1_SNB	0.78	0.86	0.25	0.23	1.32	0.01
T2_Wits - T1_Wits	-2.57	1.89	0.55	-3.77	-1.37	0.00
T2_A-Nperp - T1_A-Nperp	0.58	0.81	0.23	0.07	1.10	0.03
T2_Pog-Nperp - T1_Pog-Nperp	1.57	2.12	0.61	0.22	2.91	0.03
T2_Co-Gn - T1_Co-Gn	1.81	1.28	0.37	0.99	2.62	0.00
T2_SN-GoMe - T1_SN-GoMe	-0.51	1.67	0.48	-1.57	0.56	0.32
T2_Y-Axis - T1_Y-Axis	-0.33	1.08	0.31	-1.02	0.35	0.31
T2_U1-SN - T1_U1-SN	-5.97	6.78	1.96	-10.28	-1.66	0.01
T2_LI-MP - T1_LI-MP	8.21	4.78	1.38	5.17	11.25	0.00
T2_OB - T1_OB	-2.26	1.86	0.54	-3.44	-1.08	0.00
T2_Nasolabial Angle - T1_Nasolabial Angle	-3.38	6.45	1.86	-7.48	0.72	0.10
T2_ANB - T1_ANB	-0.29	0.87	0.25	-0.85	0.26	0.27
T2_UL-E - T1_UL-E	-1.17	0.94	0.27	-1.76	-0.57	0.00
T2_LL-E - T1_LL-E	-0.49	0.98	0.28	-1.12	0.13	0.11
T2_OJ - T1_OJ	-3.88	2.31	0.67	-5.35	-2.42	0.00

Statistic Output for intergroup comparison (Cephalometric Variables)

ANOVA with Bonferroni post hoc test for normally distributed variable

Multiple Comparisons							
Bonferroni							
Dependent Variable	(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
T2-T1_ANB	FA-Y	Vib-FA-Y	-0.39	0.46	1.00	-1.66	0.88
		FA-M	-0.36	0.44	1.00	-1.58	0.87
		Vib-FA-M	-1.46*	0.46	0.02	-2.73	-0.19
	Vib-FA-Y	FA-Y	0.39	0.46	1.00	-0.88	1.66
		FA-M	0.03	0.44	1.00	-1.19	1.26
		Vib-FA-M	-1.07	0.46	0.15	-2.34	0.20
	FA-M	FA-Y	0.36	0.44	1.00	-0.87	1.58
		Vib-FA-Y	-0.03	0.44	1.00	-1.26	1.19
		Vib-FA-M	-1.10	0.44	0.10	-2.32	0.12
	Vib-FA-M	FA-Y	1.46*	0.46	0.02	0.19	2.73
		Vib-FA-Y	1.07	0.46	0.15	-0.20	2.34
		FA-M	1.10	0.44	0.10	-0.12	2.32
T2-T1_Wits	FA-Y	Vib-FA-Y	0.32	0.67	1.00	-1.52	2.16
		FA-M	0.22	0.64	1.00	-1.55	1.99
		Vib-FA-M	-1.03	0.67	0.77	-2.87	0.81
	Vib-FA-Y	FA-Y	-0.32	0.67	1.00	-2.16	1.52
		FA-M	-0.10	0.64	1.00	-1.87	1.68
		Vib-FA-M	-1.35	0.67	0.29	-3.19	0.49
	FA-M	FA-Y	-0.22	0.64	1.00	-1.99	1.55
		Vib-FA-Y	0.10	0.64	1.00	-1.68	1.87
		Vib-FA-M	-1.25	0.64	0.34	-3.03	0.52
	Vib-FA-M	FA-Y	1.03	0.67	0.77	-0.81	2.87
		Vib-FA-Y	1.35	0.67	0.29	-0.49	3.19
		FA-M	1.25	0.64	0.34	-0.52	3.03
T2-T1_Co-Gn	FA-Y	Vib-FA-Y	1.62	0.81	0.32	-0.62	3.86
		FA-M	1.54	0.78	0.33	-0.62	3.70
		Vib-FA-M	3.47*	0.81	0.00	1.23	5.71
	Vib-FA-Y	FA-Y	-1.62	0.81	0.32	-3.86	0.62
		FA-M	-0.08	0.78	1.00	-2.24	2.08
		Vib-FA-M	1.85	0.81	0.16	-0.39	4.09
	FA-M	FA-Y	-1.54	0.78	0.33	-3.70	0.62
		Vib-FA-Y	0.08	0.78	1.00	-2.08	2.24
		Vib-FA-M	1.93	0.78	0.11	-0.23	4.09
	Vib-FA-M	FA-Y	-3.47*	0.81	0.00	-5.71	-1.23
		Vib-FA-Y	-1.85	0.81	0.16	-4.09	0.39
		FA-M	-1.93	0.78	0.11	-4.09	0.23
T2-T1_OJ	FA-Y	Vib-FA-Y	-0.13	0.70	1.00	-2.06	1.80
		FA-M	-0.57	0.67	1.00	-2.43	1.29
		Vib-FA-M	-1.22	0.70	0.53	-3.15	0.71
	Vib-FA-Y	FA-Y	0.13	0.70	1.00	-1.80	2.06

		FA-M	-0.44	0.67	1.00	-2.30	1.42
		Vib-FA-M	-1.08	0.70	0.77	-3.01	0.85
	FA-M	FA-Y	0.57	0.67	1.00	-1.29	2.43
		Vib-FA-Y	0.44	0.67	1.00	-1.42	2.30
		Vib-FA-M	-0.65	0.67	1.00	-2.50	1.21
	Vib-FA-M	FA-Y	1.22	0.70	0.53	-0.71	3.15
		Vib-FA-Y	1.08	0.70	0.77	-0.85	3.01
		FA-M	0.65	0.67	1.00	-1.21	2.50
T2-T1_OB	FA-Y	Vib-FA-Y	0.44	0.63	1.00	-1.29	2.17
		FA-M	0.16	0.60	1.00	-1.51	1.82
		Vib-FA-M	0.66	0.63	1.00	-1.07	2.39
	Vib-FA-Y	FA-Y	-0.44	0.63	1.00	-2.17	1.29
		FA-M	-0.28	0.60	1.00	-1.95	1.38
		Vib-FA-M	0.22	0.63	1.00	-1.51	1.94
	FA-M	FA-Y	-0.16	0.60	1.00	-1.82	1.51
		Vib-FA-Y	0.28	0.60	1.00	-1.38	1.95
		Vib-FA-M	0.50	0.60	1.00	-1.16	2.17
	Vib-FA-M	FA-Y	-0.66	0.63	1.00	-2.39	1.07
		Vib-FA-Y	-0.22	0.63	1.00	-1.94	1.51
		FA-M	-0.50	0.60	1.00	-2.17	1.16
T2-T1_Nasolabial Angle	FA-Y	Vib-FA-Y	2.10	2.57	1.00	-4.99	9.19
		FA-M	0.14	2.48	1.00	-6.70	6.97
		Vib-FA-M	4.30	2.57	0.61	-2.79	11.39
	Vib-FA-Y	FA-Y	-2.10	2.57	1.00	-9.19	4.99
		FA-M	-1.96	2.48	1.00	-8.80	4.87
		Vib-FA-M	2.20	2.57	1.00	-4.89	9.29
	FA-M	FA-Y	-0.14	2.48	1.00	-6.97	6.70
		Vib-FA-Y	1.96	2.48	1.00	-4.87	8.80
		Vib-FA-M	4.16	2.48	0.60	-2.67	11.00
	Vib-FA-M	FA-Y	-4.30	2.57	0.61	-11.39	2.79
		Vib-FA-Y	-2.20	2.57	1.00	-9.29	4.89
		FA-M	-4.16	2.48	0.60	-11.00	2.67
T2-T1_UL-E	FA-Y	Vib FA-Y	0.50	0.39	1.00	-0.59	1.59
		FA-M	-0.12	0.38	1.00	-1.17	0.93
		Vib FA-M	-0.82	0.39	0.27	-1.90	0.27
	Vib FA-Y	FA-Y	-0.50	0.39	1.00	-1.59	0.59
		FA-M	-0.62	0.38	0.66	-1.67	0.43
		Vib FA-M	-1.32*	0.39	0.01	-2.40	-0.23
	FA-M	FA-Y	0.12	0.38	1.00	-0.93	1.17
		Vib FA-Y	0.62	0.38	0.66	-0.43	1.67
		Vib FA-M	-0.70	0.38	0.44	-1.75	0.35
	Vib FA-M	FA-Y	0.82	0.39	0.27	-0.27	1.90
		Vib FA-Y	1.32*	0.39	0.01	0.23	2.40
		FA-M	0.70	0.38	0.44	-0.35	1.75
T2-T1_LL-E	FA-Y	Vib FA-Y	-0.08	0.63	1.00	-1.80	1.65
		FA-M	0.12	0.60	1.00	-1.55	1.78
		Vib FA-M	-0.10	0.63	1.00	-1.83	1.63
	Vib FA-Y	FA-Y	0.08	0.63	1.00	-1.65	1.80

		FA-M	0.19	0.60	1.00	-1.47	1.85
		Vib FA-M	-0.03	0.63	1.00	-1.75	1.70
	FA-M	FA-Y	-0.12	0.60	1.00	-1.78	1.55
		Vib FA-Y	-0.19	0.60	1.00	-1.85	1.47
		Vib FA-M	-0.22	0.60	1.00	-1.88	1.45
	Vib FA-M	FA-Y	0.10	0.63	1.00	-1.63	1.83
		Vib FA-Y	0.03	0.63	1.00	-1.70	1.75
		FA-M	0.22	0.60	1.00	-1.45	1.88

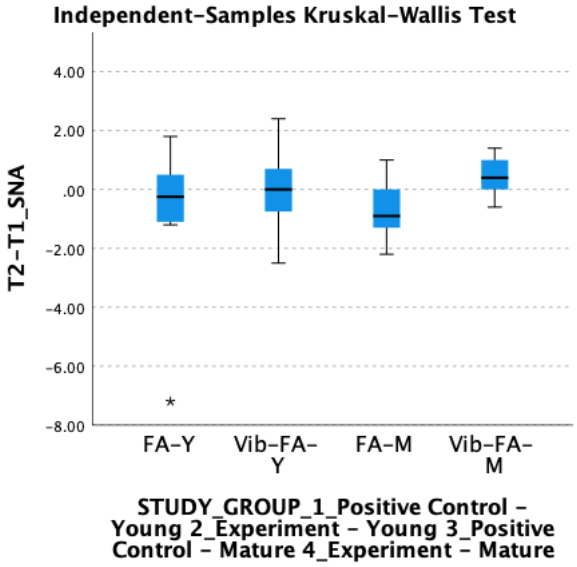
Kruskal-Wallis test for variables that were not normally distributed

SNA

Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	8.209[a]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.042

a. The test statistic is adjusted for ties.



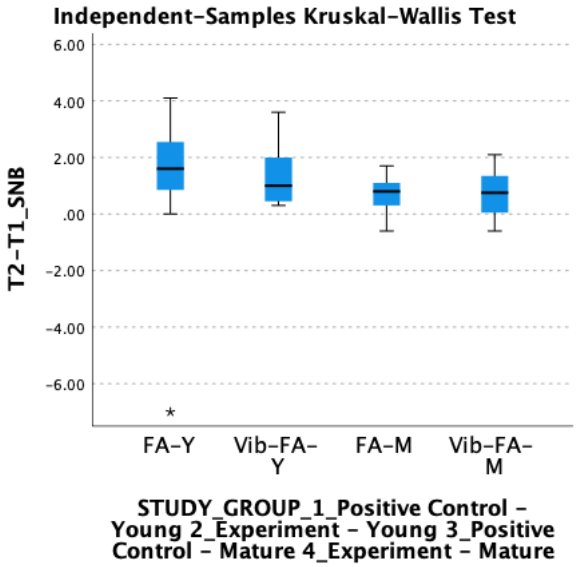
SNB

Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	4.996[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.172

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.



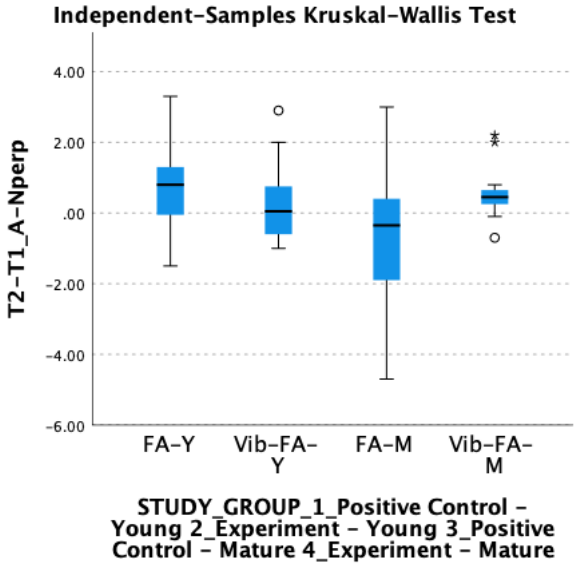
A-Nperp

Independent-Samples Kruskal-Wallis Test Summary

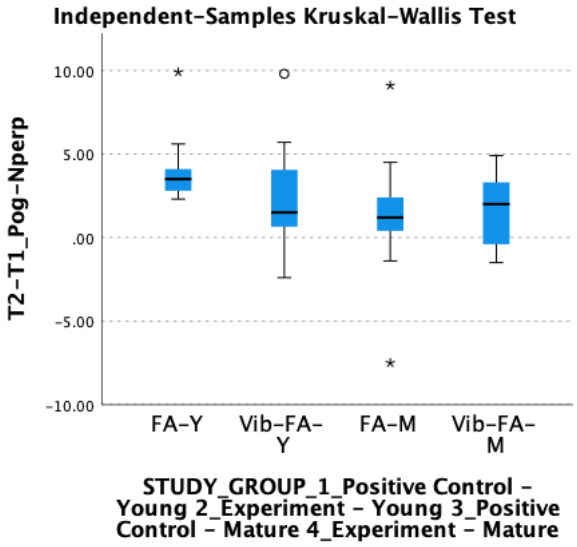
Total N	50
Test Statistic	6.790[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.079

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.



Pog-Nperp

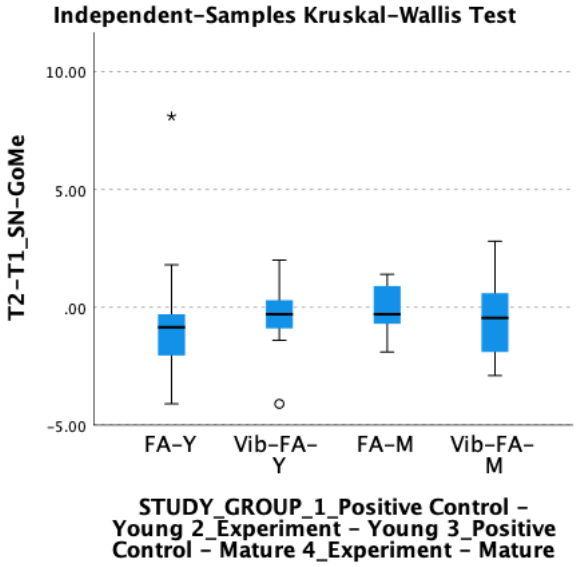


Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	9.674[a]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.022

a. The test statistic is adjusted for ties.

SN-GoMe



Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	2.356[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.502

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.

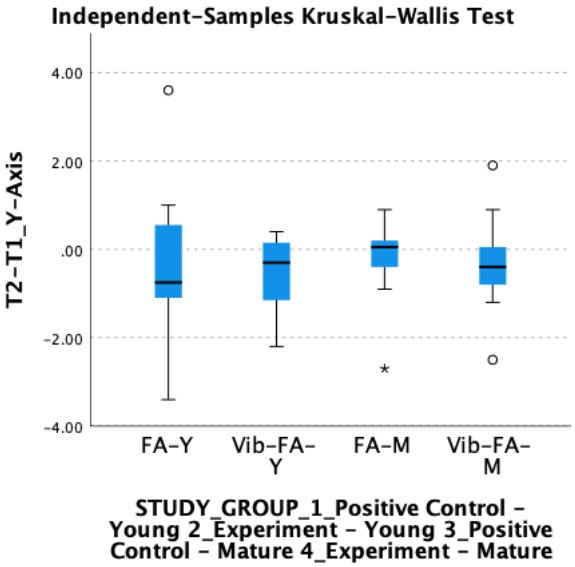
Y-axis

Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	1.859[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.602

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.



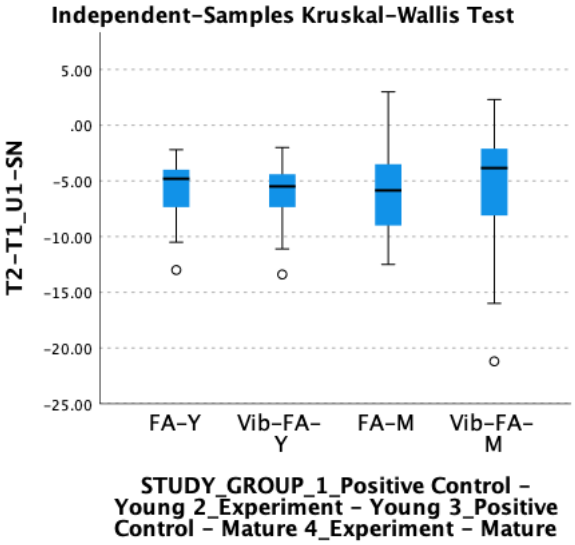
U1-SN

Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	2.481[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.479

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.



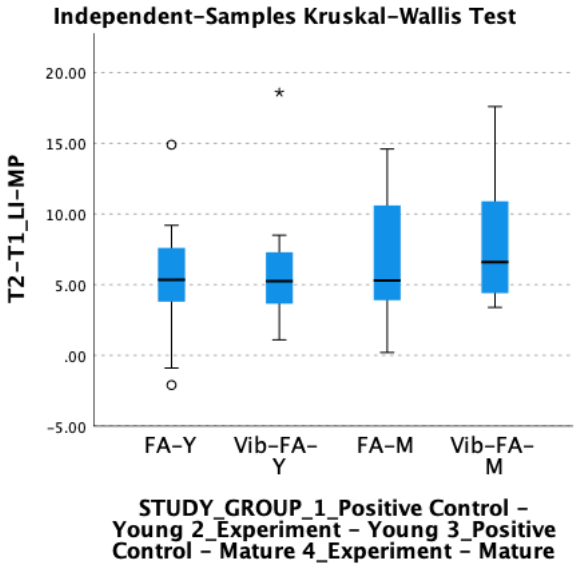
LI-MP

Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	1.875[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.599

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.



Statistic Output for intergroup comparison (Pancherz Analysis Variables)

Independent-Samples Kruskal-Wallis Test for variables that were not normally distributed

Descriptive statistics

Descriptives									
		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
Overjet	FA-Y	12	-5.13	1.38	0.40	-6.00	-4.25	-6.50	-2.00
	Vib-FA-Y	12	-4.83	1.89	0.54	-6.03	-3.63	-7.50	-1.50
	FA-M	14	-5.18	2.72	0.73	-6.75	-3.61	-13.00	-2.50
	Vib-FA-M	12	-4.04	2.57	0.74	-5.68	-2.41	-10.50	-0.50
	Total	50	-4.81	2.21	0.31	-5.44	-4.18	-13.00	-0.50
Molar Relation	FA-Y	12	-5.25	1.36	0.39	-6.11	-4.39	-7.00	-3.00
	Vib-FA-Y	12	-5.33	1.61	0.47	-6.36	-4.31	-9.00	-3.50
	FA-M	14	-4.71	1.55	0.42	-5.61	-3.82	-8.50	-2.50
	Vib-FA-M	12	-4.29	1.37	0.40	-5.16	-3.42	-7.00	-1.50
	Total	50	-4.89	1.50	0.21	-5.32	-4.46	-9.00	-1.50
Maxillary base	FA-Y	12	0.33	0.81	0.23	-0.18	0.85	-0.50	2.50
	Vib-FA-Y	12	0.42	0.82	0.24	-0.11	0.94	-0.50	2.00
	FA-M	14	0.00	0.20	0.05	-0.11	0.11	-0.50	0.50
	Vib-FA-M	12	0.13	0.57	0.16	-0.24	0.49	-1.00	1.00
	Total	50	0.21	0.64	0.09	0.03	0.39	-1.00	2.50
Mandibular base	FA-Y	12	2.42	1.56	0.45	1.42	3.41	0.00	5.00
	Vib-FA-Y	12	2.67	1.63	0.47	1.63	3.70	0.50	6.00
	FA-M	14	2.25	1.50	0.40	1.38	3.12	0.00	5.00
	Vib-FA-M	12	1.42	1.22	0.35	0.64	2.19	-1.50	2.50
	Total	50	2.19	1.51	0.21	1.76	2.62	-1.50	6.00
Condylar head	FA-Y	12	0.96	0.92	0.26	0.38	1.54	0.00	2.50
	Vib-FA-Y	12	0.63	0.64	0.19	0.22	1.03	0.00	2.00
	FA-M	14	0.54	0.77	0.21	0.09	0.98	-1.00	2.00
	Vib-FA-M	12	0.54	0.69	0.20	0.10	0.98	0.00	2.00
	Total	50	0.66	0.76	0.11	0.44	0.88	-1.00	2.50
Composite mandibular length	FA-Y	12	3.38	1.79	0.52	2.24	4.51	0.00	6.00
	Vib-FA-Y	12	3.29	1.67	0.48	2.23	4.35	1.50	6.50
	FA-M	14	2.79	1.71	0.46	1.80	3.77	0.50	5.00
	Vib-FA-M	12	1.96	1.57	0.45	0.96	2.96	-1.50	4.00
	Total	50	2.85	1.73	0.24	2.36	3.34	-1.50	6.50
Maxillary Incisor	FA-Y	12	-1.75	0.66	0.19	-2.17	-1.33	-3.00	-1.00

	Vib-FA-Y	12	-1.38	1.52	0.44	-2.34	-0.41	-3.00	2.50
	FA-M	14	-1.21	1.25	0.33	-1.94	-0.49	-3.00	1.50
	Vib-FA-M	12	-1.54	1.32	0.38	-2.38	-0.70	-4.00	0.00
	Total	50	-1.46	1.21	0.17	-1.80	-1.12	-4.00	2.50
Mandibular Incisor	FA-Y	12	1.29	1.56	0.45	0.30	2.28	-1.00	4.00
	Vib-FA-Y	12	1.21	1.01	0.29	0.57	1.85	-0.50	2.50
	FA-M	14	1.71	2.18	0.58	0.45	2.97	-0.50	8.00
	Vib-FA-M	12	1.21	1.81	0.52	0.06	2.36	-3.00	4.50
	Total	50	1.37	1.68	0.24	0.89	1.85	-3.00	8.00
Maxillary molar	FA-Y	12	-1.88	0.93	0.27	-2.47	-1.28	-2.50	0.00
	Vib-FA-Y	12	-2.33	0.78	0.22	-2.83	-1.84	-3.50	-1.00
	FA-M	14	-1.11	1.15	0.31	-1.77	-0.45	-3.00	1.00
	Vib-FA-M	12	-1.96	0.94	0.27	-2.56	-1.36	-3.00	0.50
	Total	50	-1.79	1.05	0.15	-2.09	-1.49	-3.50	1.00
Mandibular Molar	FA-Y	12	1.29	1.23	0.36	0.51	2.08	-0.50	3.50
	Vib-FA-Y	12	0.75	0.81	0.23	0.23	1.27	-0.50	2.00
	FA-M	14	1.36	1.79	0.48	0.32	2.39	-0.50	5.50
	Vib-FA-M	12	1.04	0.84	0.24	0.51	1.57	-0.50	2.50
	Total	50	1.12	1.25	0.18	0.77	1.47	-0.50	5.50

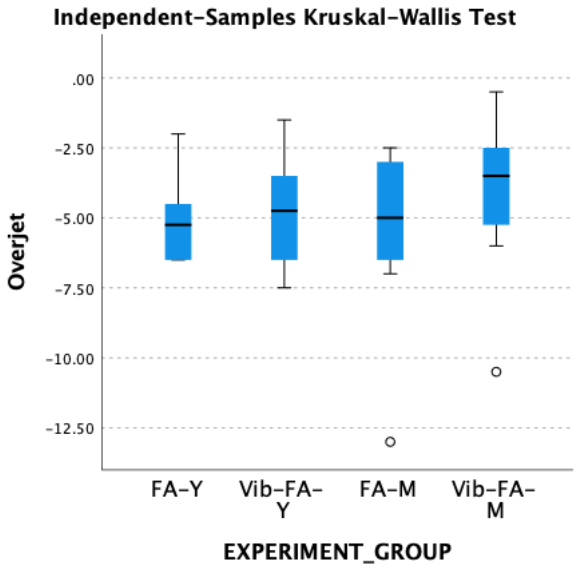
Overjet

Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	3.694[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.296

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.



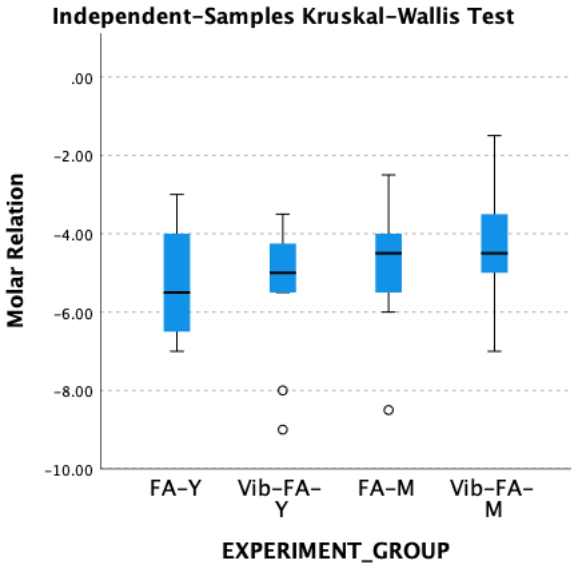
Molar Relation

Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	3.848[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.278

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.



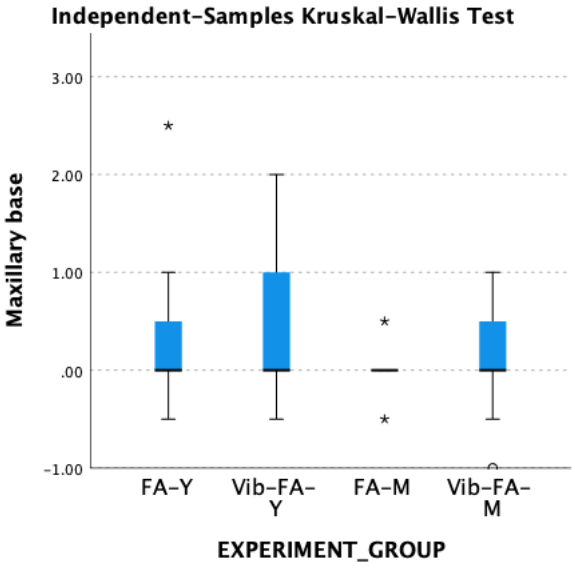
Maxillary Base

Independent-Samples Kruskal-Wallis Test Summary

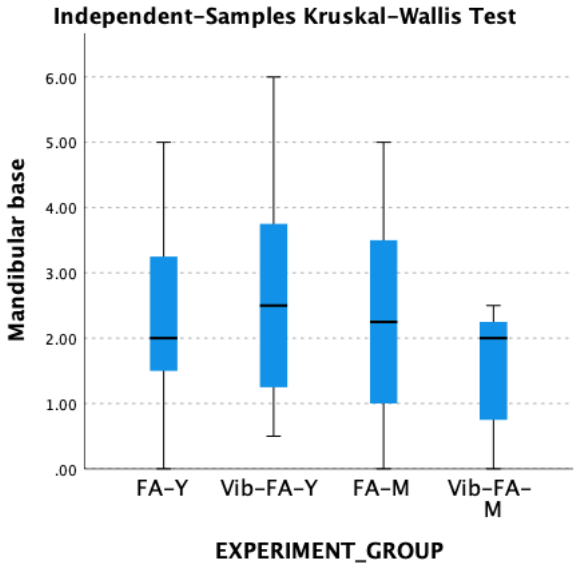
Total N	50
Test Statistic	1.819[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.611

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.



Mandibular Base



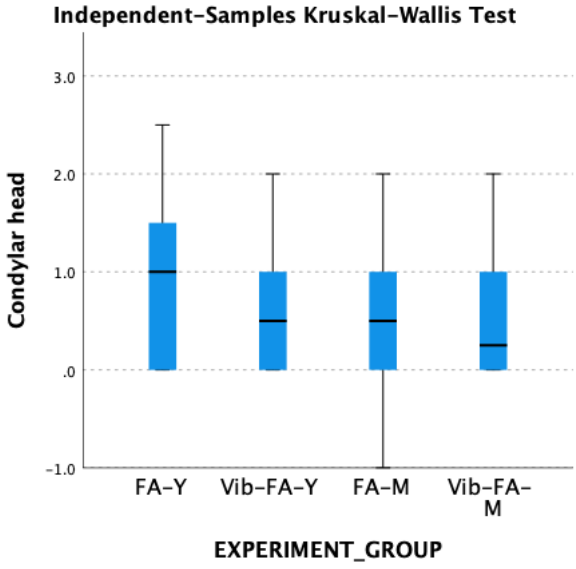
Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	3.310[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.346

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.

Condylar Head



Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	1.729[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.630

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.

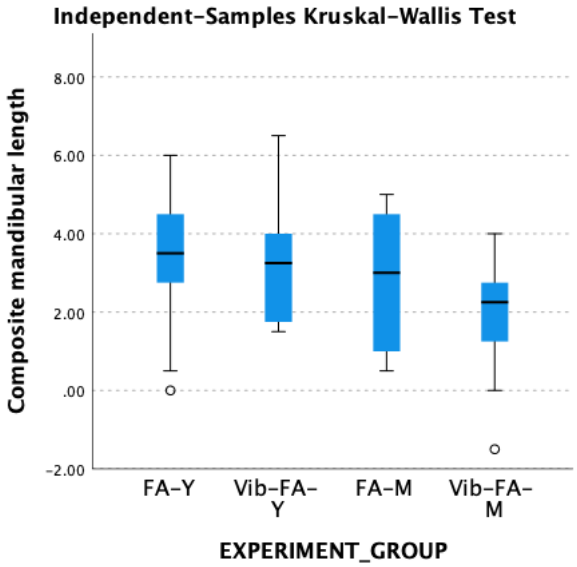
Composite Mandibular Length

Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	4.503[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.212

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.



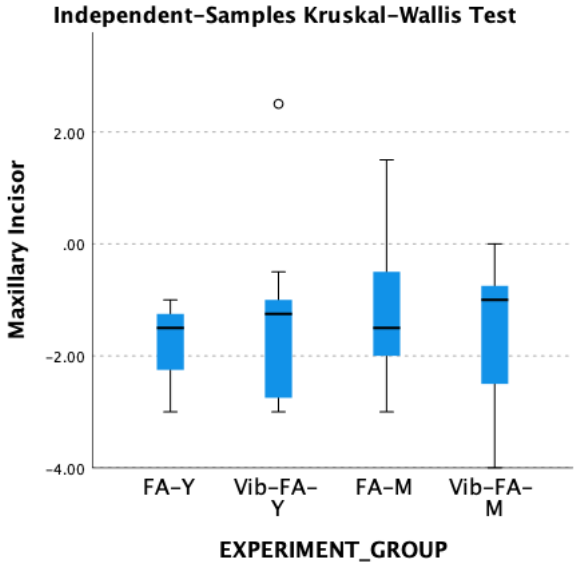
Maxillary Incisor

Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	1.557[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.669

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.



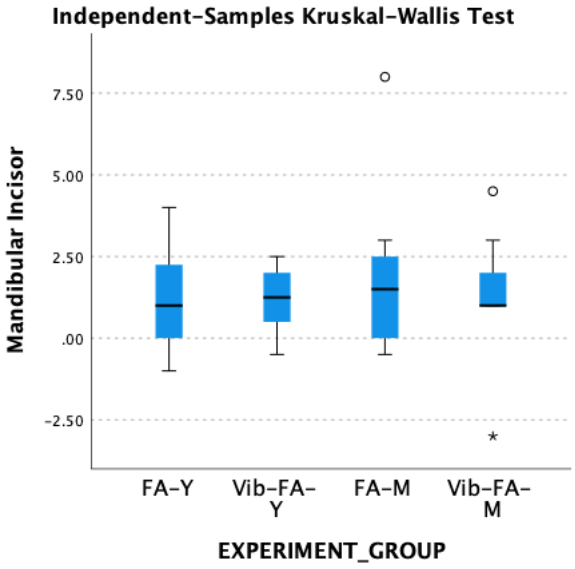
Mandibular Incisor

Independent-Samples Kruskal-Wallis Test Summary

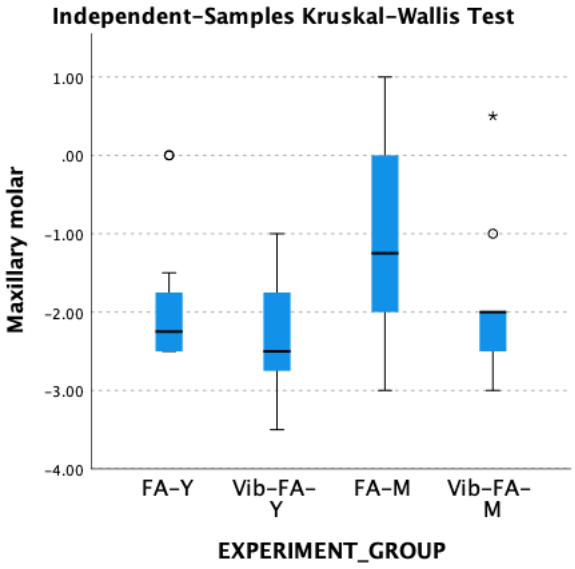
Total N	50
Test Statistic	.179[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.981

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.



Maxillary Molar



Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	8.590[a]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.035

a. The test statistic is adjusted for ties.

Pairwise Comparisons of EXPERIMENT_GROUP					
	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.a
Vib-FA-Y-Vib-FA-M	-4.88	5.83	-0.84	0.40	1.00
Vib-FA-Y-FA-Y	5.08	5.83	0.87	0.38	1.00
Vib-FA-Y-FA-M	-15.72	5.61	-2.80	0.01	0.03
Vib-FA-M-FA-Y	0.21	5.83	0.04	0.97	1.00
Vib-FA-M-FA-M	10.85	5.61	1.93	0.05	0.32
FA-Y-FA-M	-10.64	5.61	-1.90	0.06	0.35

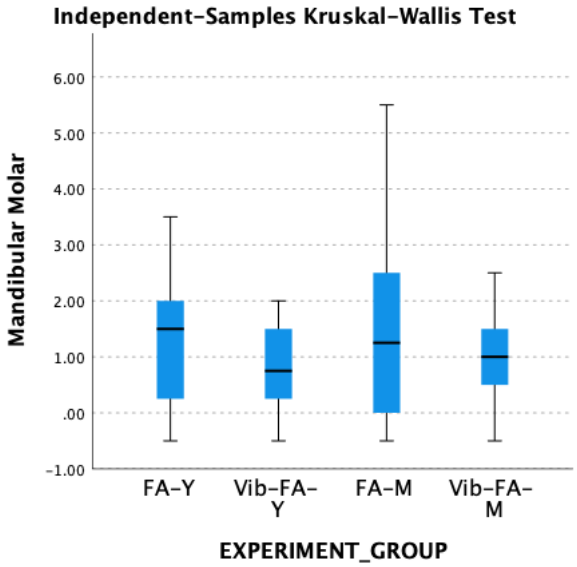
Mandibular Molar

Independent-Samples Kruskal-Wallis Test Summary

Total N	50
Test Statistic	1.242[a,b]
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	.743

a. The test statistic is adjusted for ties.

b. Multiple comparisons are not performed because the overall test does not show significant differences across samples.



Statistic Output for intergroup comparison at T1 (Airway Variables) – Groups FA-Y and Vib-FA-Y

Independent t-test for variable that were normally distributed

Descriptive Statistics

Descriptives		N	Mean	Std. Deviation	Std. Error Mean
T1_Volume of Nasal Pharynx	FA-Y	12	4142.56	1608.37	464.30
	Vib-FA-Y	12	3924.72	758.15	218.86
T1_Volume of Oropharynx	FA-Y	12	10145.36	3494.09	1008.66
	Vib-FA-Y	12	11083.53	2411.18	696.05
T1_Minimal Axial Area	FA-Y	12	123.89	54.23	15.65
	Vib-FA-Y	12	117.72	35.18	10.16

Independent t-test

	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
				Lower	Upper
T1_Volume of Nasal Pharynx	0.68	217.83	513.29	-846.67	1282.34
T1_Volume of Oropharynx	0.45	-938.17	1225.51	-3479.71	1603.38
T1_Minimal Axial Area	0.75	6.17	18.66	-32.91	45.24

Statistic Output for intergroup comparison at T1 (Airway Variables) – Groups FA-M and Vib-FA-M

Mann-Whitney U test was used for variables that were not normally distributed

Descriptive Statistics

Descriptive Statistics					
	N	Mean	Std. Deviation	Minimum	Maximum
T1_Volume of Nasal Pharynx	26	4970.28	1656.89	1829.67	8097.67
T1_Volume of Oropharynx	26	13828.94	5117.96	7049.00	28498.33
T1_Minimal Axial Area	26	163.69	85.72	64.00	432.33

Test Statistics			
	T1_Volume of Nasal Pharynx	**T1_Volume of Oropharynx**	**T1_Minimal Axial Area**
Mann-Whitney U	76	59	68
Asymp. Sig. (2-tailed)	0.681	0.198	0.41
Exact Sig. [2*(1-tailed Sig.)]	.705	.212	.432

Statistic Output for intragroup comparison (Airway Variables) – Group FA-Y

Paired t-test for variable that were normally distributed

Paired t test	**Mean**	**Std. Deviation**	**Std. Error Mean**	**95% Confidence Interval of the Difference**			
				Lower	Upper	df	p
T2_Volume of Nasal Pharynx - T1_Volume of Nasal Pharynx	144.42	1181.89	341.18	-606.52	895.35	11.00	0.68

Wilcoxon signed-rank test for variables that were not normally distributed

	T1_Volume of Oropharynx - T2_Volume of Oropharynx	**T1_Minimal Axial Area - T2_Minimal Axial Area**
Z	-1.883	-.549
Asymp. Sig. (2-tailed)	0.06	0.583

Statistic Output for intragroup comparison (Airway Variables) – Group Vib-FA-Y

Paired t-test for variable that were normally distributed

Paired t test	**Mean**	**Std. Deviation**	**Std. Error Mean**	**95% Confidence Interval of the Difference**		**df**	**Sig. (2-tailed)**
				Lower	**Upper**		
T2_Volume of Nasal Pharynx - T1_Volume of Nasal Pharynx	175.81	1133.27	327.15	-544.24	895.85	11.00	0.60
T2_Volume of Oropharynx - T1_Volume of Oropharynx	2428.14	2003.94	578.49	1154.90	3701.38	11.00	0.00

Wilcoxon signed-rank test for variables that were not normally distributed

	T2_Minimal Axial Area – T1_Minimal Axial Area
Z	-1.569
Asymp. Sig. (2-tailed)	0.117

Statistic Output for intragroup comparison (Airway Variables) – Group FA-M

Paired t-test for variable that were normally distributed:

	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		df	Sig. (2-tailed)
				Lower	Upper		
T2_Volume of Nasal Pharynx - T1_Volume of Nasal Pharynx	566.05	1703.01	455.15	-417.24	1549.34	13.00	0.24
T2_Volume of Oropharynx - T1_Volume of Oropharynx	-404.60	3503.35	936.31	-2427.37	1618.18	13.00	0.67
T2_Minimal Axial Area - T1_Minimal Axial Area	-2.14	84.83	22.67	-51.12	46.83	13.00	0.93

Statistic Output for intragroup comparison (Airway Variables) – Group Vib-FA-M

Paired t-test for variable that were normally distributed

	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		df	Sig. (2-tailed)
				Lower	Upper		
T2_Volume of Nasal Pharynx - T1_Volume of Nasal Pharynx	854.86	1234.81	356.46	70.30	1639.42	11.00	0.04

Wilcoxon signed-rank test for variables that were not normally distributed

	T2_Volume of Oropharynx - T1_Volume of Oropharynx	T2_Minimal Axial Area - T1_Minimal Axial Area
Z	-2.35	-2.04
Asymp. Sig. (2-tailed)	0.02	0.04

Statistic Output for intergroup comparison (Airway Variables)

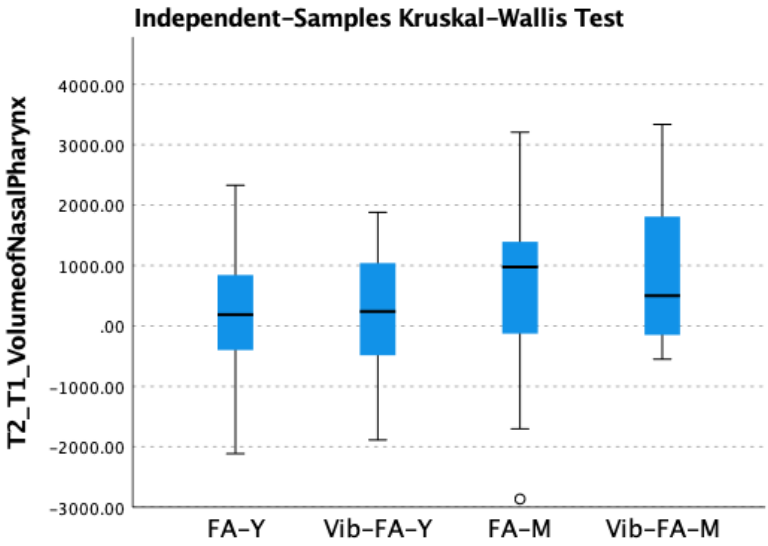
Descriptives									
		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
T2_T1_Volumeof NasalPharynx	FA-Y	12.00	144.42	1181.89	341.18	-606.52	895.35	-2114.67	2329.67
	Vib-FA-Y	12.00	175.81	1133.27	327.15	-544.24	895.85	-1887.33	1880.00
	FA-M	14.00	566.05	1703.01	455.15	-417.24	1549.34	-2865.67	3207.67
	Vib-FA-M	12.00	854.86	1234.81	356.46	70.30	1639.42	-550.67	3335.33
	Total	50.00	440.51	1341.20	189.67	59.35	821.68	-2865.67	3335.33
T2_T1_Volumeof Oropharynx	FA-Y	12.00	1530.31	2743.83	792.07	-213.04	3273.65	-2370.33	6299.67
	Vib-FA-Y	12.00	2428.14	2003.94	578.49	1154.90	3701.38	-1368.00	5460.33
	FA-M	14.00	-404.60	3503.35	936.31	-2427.37	1618.18	-5395.67	4732.33
	Vib-FA-M	12.00	3715.94	5104.45	1473.53	472.73	6959.16	-6191.67	15288.67
	Total	50.00	1728.57	3754.18	530.92	661.64	2795.49	-6191.67	15288.67
T2_T1Minimal AxialArea	FA-Y	12.00	9.69	65.96	19.04	-32.22	51.61	-117.33	134.33
	Vib-FA-Y	12.00	21.06	39.55	11.42	-4.08	46.19	-44.67	77.67
	FA-M	14.00	-2.14	84.83	22.67	-51.12	46.83	-115.33	169.33
	Vib-FA-M	12.00	41.67	71.29	20.58	-3.63	86.96	-110.00	145.00
	Total	50.00	16.78	68.18	9.64	-2.60	36.16	-117.33	169.33

Statistic Output for intergroup comparison (Nasopharyngeal Volume)

Independent-Samples Kruskal-Wallis Test for variables that were not normally distributed

A Kruskal-Wallis H test showed that there was no statistically significant difference in nasal pharynx volumes among the different experiment groups, $\chi^2(3) = 1.978$, $p = 0.577$.

Independent-Samples Kruskal-Wallis Test Summary	
Total N	50
Test Statistic	1.978
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	0.577

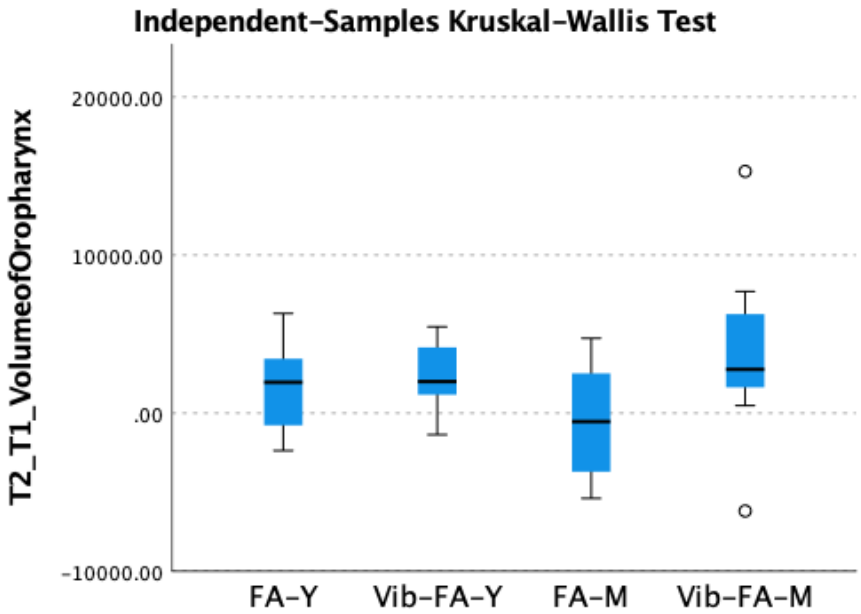


Statistic Output for intergroup comparison (Oropharyngeal Volume)

Independent-Samples Kruskal-Wallis Test for variables that were not normally distributed

A Kruskal-Wallis H test showed that there was no statistically significant difference in oropharynx volumes among the different experiment groups, $\chi^2(3) = 6.433$, $p = 0.092$.

Independent-Samples Kruskal-Wallis Test Summary	
Total N	50
Test Statistic	6.433
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	0.092

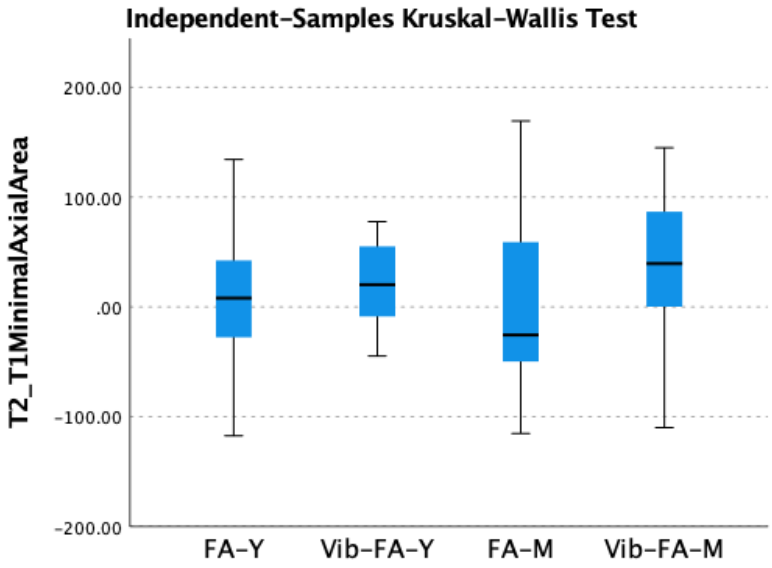


Statistic Output for intergroup comparison (Minimum cross-sectional area))

Independent-Samples Kruskal-Wallis Test for variables that were not normally distributed

A Kruskal-Wallis H test showed that there was no statistically significant difference in minimal axial area among different experiment groups, $\chi^2(3) = 4.328$, $p = 0.228$.

Independent-Samples Kruskal-Wallis Test Summary	
Total N	50
Test Statistic	4.328
Degree Of Freedom	3
Asymptotic Sig.(2-sided test)	0.228



Statistic Output for reliability test (Cephalometric Variables))

SNA

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.929[a]	.754	.982	26.716	9	9	<.001
Average Measures	.963[c]	.860	.991	26.716	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

SNB

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.879[a]	.609	.968	15.536	9	9	<.001
Average Measures	.936[c]	.757	.984	15.536	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

ANB

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.791[a]	.344	.944	7.826	9	9	.003
Average Measures	.884[c]	.512	.971	7.826	9	9	.003

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Wits Appraisal

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.909[a]	.676	.977	19.111	9	9	<.001
Average Measures	.952[c]	.807	.988	19.111	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

A-Nperp

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.820[a]	.458	.951	10.277	9	9	<.001
Average Measures	.901[c]	.629	.975	10.277	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Pog-Nperp

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.929[a]	.726	.982	33.271	9	9	<.001
Average Measures	.963[c]	.841	.991	33.271	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Co-Gn

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.969[a]	.875	.992	74.150	9	9	<.001
Average Measures	.984[c]	.933	.996	74.150	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

SN-Go-Me

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.908[a]	.685	.976	22.838	9	9	<.001
Average Measures	.952[c]	.813	.988	22.838	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Y-axis

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.898[a]	.631	.974	22.568	9	9	<.001
Average Measures	.946[c]	.774	.987	22.568	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

U1-SN

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.978[a]	.919	.995	99.388	9	9	<.001
Average Measures	.989[c]	.958	.997	99.388	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

L1-MP

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.783[a]	.313	.942	10.609	9	9	<.001
Average Measures	.878[c]	.477	.970	10.609	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Overjet

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.988[a]	.889	.998	296.081	9	9	<.001
Average Measures	.994[c]	.941	.999	296.081	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Overbite

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.882[a]	.600	.969	14.776	9	9	<.001
Average Measures	.937[c]	.750	.984	14.776	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Nasolabial Angle

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.920[a]	.726	.979	23.413	9	9	<.001
Average Measures	.958[c]	.841	.989	23.413	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T2_Original_SNA T2_REPEAT_SNA

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.973[a]	.894	.993	65.113	9	9	<.001
Average Measures	.986[c]	.944	.997	65.113	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T2_Original_SNB T2_REPEAT_SNB

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.986[a]	.946	.996	131.737	9	9	<.001
Average Measures	.993[c]	.972	.998	131.737	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T2_Original_ANB T2_REPEAT_ANB

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.979[a]	.923	.995	90.905	9	9	<.001
Average Measures	.990[c]	.960	.997	90.905	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T2_Original_Wits T2_REPEAT_Wits

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.933[a]	.765	.983	31.369	9	9	<.001
Average Measures	.965[c]	.867	.991	31.369	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T2_Original_ANperp T2_REPEAT_ANperp

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.959[a]	.851	.990	45.232	9	9	<.001
Average Measures	.979[c]	.919	.995	45.232	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T2_Original_PogNperp T2_REPEAT_PogNperp

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.975[a]	.901	.994	70.331	9	9	<.001
Average Measures	.987[c]	.948	.997	70.331	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T2_Original_CoGn T2_REPEAT_CoGn

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.979[a]	.922	.995	90.658	9	9	<.001
Average Measures	.989[c]	.959	.997	90.658	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T2_Original_SNGoMe T2_REPEAT_SNGoMe

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.985[a]	.942	.996	120.554	9	9	<.001
Average Measures	.992[c]	.970	.998	120.554	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T2_Original_YAxis T2_REPEAT_YAxis

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.985[a]	.941	.996	119.116	9	9	<.001
Average Measures	.992[c]	.970	.998	119.116	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T2_Original_U1SN T2_REPEAT_U1SN

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.935[a]	.773	.983	30.691	9	9	<.001
Average Measures	.966[c]	.872	.991	30.691	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T2_Original_LIMP T2_REPEAT_LIMP

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.951[a]	.827	.987	39.864	9	9	<.001
Average Measures	.975[c]	.905	.994	39.864	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T2_Original_OJ T2_REPEAT_OJ

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.897[a]	.660	.973	18.410	9	9	<.001
Average Measures	.946[c]	.795	.986	18.410	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T2_Original_OB T2_REPEAT_OB

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.927[a]	.748	.981	25.769	9	9	<.001
Average Measures	.962[c]	.856	.990	25.769	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T2_Original_NasolabialAngle T2_REPEAT_NasolabialAngle

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.876[a]	.594	.967	16.630	9	9	<.001
Average Measures	.934[c]	.745	.983	16.630	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

T1_UL-E	**0.94**
T2_UL-E	0.97
T1_LL-E	0.98
T2_LL-E	0.98

Reliability Analysis – Airway

Original_T1_VolumeofNasalPharynx_Average Repeat_T1_VolumeofNasalPharynx_Average

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.982[a]	.933	.996	104.357	9	9	<.001
Average Measures	.991[c]	.965	.998	104.357	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Average measures value is 0.991 which means excellent agreement.

Original_T1_VolumeofOropharynx_Average Repeat_T1_VolumeofOropharynx_Average

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.875[a]	.588	.967	16.770	9	9	<.001
Average Measures	.933[c]	.741	.983	16.770	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Original_T1_MinimalAxialArea_Average Repeat_T1_MinimalAxialArea_Average

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.984[a]	.941	.996	119.490	9	9	<.001
Average Measures	.992[c]	.970	.998	119.490	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Original_T2_VolumeofNasalPharynx_Average Repeat_T2_VolumeofNasalPharynx_Average

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.991[a]	.966	.998	212.233	9	9	<.001
Average Measures	.996[c]	.983	.999	212.233	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Original_T2_VolumeofOropharynx_Average Repeat_T2_VolumeofOropharynx_Average

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.958[a]	.798	.990	63.869	9	9	<.001
Average Measures	.979[c]	.888	.995	63.869	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Original_T2_MinimalAxialArea_Average Repeat_T2_MinimalAxialArea_Average

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.983[a]	.935	.996	108.324	9	9	<.001
Average Measures	.992[c]	.967	.998	108.324	9	9	<.001

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.