Quantitative Assessment of Abdominal Aortic Calcification and Disk Height Loss: The Framingham Study

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ABSTRACT

Introduction- Prior epidemiologic studies have demonstrated associations between vascular disease and spinal degeneration. We sought to characterize the relationship between a quantitative measure of abdominal aortic calcifications (AAC) and disk height loss (DHL) in a community-based population.

Design- 436 participants from the Framingham Heart Study Multi-Detector Computed Tomography (CT) Study were included in this ancillary study. We used a quantitative summary measure of AAC from the parent study as a marker for vascular disease. AAC was categorized into tertiles of ‘no’ (reference), ‘low’, and ‘high’ calcification. DHL was evaluated on CT scans using a 4-grade scale. For analytic purposes, DHL was dichotomized as moderate DHL of at least one level at L2-S1 vs. less than moderate or no DHL. We examined the association of AAC and DHL using logistic regression before and after adjusting for cardiovascular risk factors, and before and after adjusting for age, sex and body mass index (BMI).

Results- In crude analyses, low AAC (OR 2.20[1.37-3.55]; p=0.0012) and high AAC (OR 2.33[1.44-3.77]; p=0.0006) were strongly associated with DHL, when compared with the reference group of no AAC. Diabetes, hypercholesterolemia, hypertension, and smoking were not associated with DHL, and did not attenuate the observed relationship between AAC and DHL. Adjustment for age, sex, and BMI markedly attenuated the associations between DHL and low AAC (OR 1.34[0.78-2.31]; p=0.29) and high AAC (OR 0.74[0.36-1.51]; p=0.40).
Conclusions- AAC was associated with DHL in this community-based population. This relationship was independent of cardiovascular risk factors. However, the association of AAC with DHL was explained by the effects of age, sex, and BMI.

KEYWORDS

Intervertebral disk; degeneration; vascular diseases; aortic calcification; lumbar; spine
INTRODUCTION

Low back pain (LBP) results in substantial disability which places an enormous burden on the health care systems and economies of developed countries[1-5]. Lumbar intervertebral disk height loss (DHL) is a feature of intervertebral disk degeneration often associated with LBP [6-8]. The etiology of DHL and disk degeneration more generally, remain poorly understood. Although age and genetic factors appear to play an important role, few other risk factors have demonstrated consistent associations with DHL in epidemiologic studies.

Postmortem and clinical studies have demonstrated associations between vascular disease and composite measures of disk degeneration, including the degenerative features of DHL, vertebral osteophytosis, and/or endplate sclerosis [9-11]. This prior work draws attention to the importance of nutrition to the avascular intervertebral disk, and suggests that impaired vascular flow may be an important modifiable factor associated with disk degeneration. However, there are limitations to the existing literature. First, the use of composite outcome measures in earlier studies does not allow us to identify which specific parameters of degeneration are most strongly associated with vascular disease. This is important, because certain imaging parameters of disk degeneration, such as DHL, have demonstrated more consistent associations with LBP than other parameters, such as vertebral osteophytosis and endplate sclerosis[6, 7]. Second, prior studies have used markers for vascular disease which are infeasible to measure in clinical practice, such as direct visualization of lumbar artery stenosis at autopsy[9, 12], and lumbar arterial flow by aortography[13]. Third, no prior study has examined a large community-
based population using a standardized assessment of disk degeneration by cross-sectional imaging techniques. Therefore, it is unknown whether the association between vascular disease and disk degeneration can be demonstrated in a typical, unselected population using accurate imaging methods.

We conducted a study to further examine the relationship between vascular disease and disk degeneration, using the predictor of abdominal aortic calcification (AAC), and the outcome of DHL as measured by computed tomography (CT) of the lumbar spine. The aims of this study were 1) to determine whether abdominal aortic calcification, as a marker of vascular disease, is associated with DHL in the community based population; 2) to examine the effect of controlling for known cardiovascular risk factors on the association between AAC and DHL; and 3) to determine whether the association between AAC and DHL persists after adjusting for other putative risk factors for spinal degeneration.

MATERIALS AND METHODS

Study Sample: This cross-sectional study was an ancillary project to the Framingham Heart Study. The Framingham Heart Study began in 1948 as a longitudinal population-based cohort study of the causes of heart disease. Initially, 5209 men and women between the ages of 30 and 60 years living in Framingham, Massachusetts were enrolled (the Original cohort). Biennial examinations were conducted by trained research staff at the study clinic located in Framingham. In 1971, 5,124 offspring of the original cohort and their spouses were entered into the Offspring cohort[14]. In 2002, 4095 men and women
who were children of the Offspring cohort were enrolled in the Third Generation cohort (Gen 3)[15]. 3529 participants of the Framingham study (participants in both the Offspring and Gen 3 cohorts) aged 40-80 years underwent abdominal and chest multi-detector computed tomography (MDCT) scanner to assess coronary and aortic calcification as well as lumbar spine degeneration. The recruitment and conduct of CT scanning have been previously reported [16, 17].

**CT Evaluation Parameters:** Study participants were imaged with an eight-slice MDCT scanner (Lightspeed Ultra, GE Healthcare, Milwaukee, WI, USA). Each subject underwent unenhanced abdominal CT that was performed using a sequential scan protocol with a slice collimation of 8 mm × 2.5 mm (120 KVP, 320/400 mA for 220 lbs body weight, respectively) during a single end-inspiratory breath hold (typical duration 18 s). For the abdominal scan, thirty contiguous 2.5 mm thick slices of the abdomen were acquired covering 150 mm above the level of S1.

**Quantitative AAC Evaluation:** The MDCT scans were quantified for the presence and quantity of AAC by experienced readers using a dedicated off-line workstation. A calcified lesion was defined as an area of at least 3 connected pixels with CT attenuation > 130 Hounsfield units applying 3D connectivity criteria (6 points). A modified Agatson score was computed by multiplying each lesion area by a weighted MDCT attenuation score in Hounsfield units within the lesion. This method of scoring has been described elsewhere and has demonstrated excellent reliability (ICC r>0.96)[16, 17].
**Disk Height Loss Evaluation:** Evaluation of DHL was performed using eFilm Workstation (Version 2.0.0) software. All CT studies were read blinded to clinical information and to the results of the quantitative AAC evaluation. DHL was graded at spinal levels L2-L3, L3-L4, L4-L5, and L5-S1, using a system which was developed for research purposes by Videman et al., and has been used extensively in prior studies of spinal degeneration on MRI[18-20]. Qualitative and quantitative assessment of DHL was performed in the midsagittal plane of each disk interspace. Using sagittal CT reformatting, the midsagittal plane was determined at each spinal level by precise alignment of the mid-anterior vertebral margin with the spinous process, or in situations where spinous process alignment was clearly asymmetric, by alignment with the base of the spinous process. Measurements of DHL in millimeters were made in the midsagittal view at the midpoint of the anteroposterior diameter of the disk. The continuous measurements were used in applying the grading system of Videman: DHL was graded as ‘0’ (normal; disk height greater than disk space immediately superior), ‘1’ (mild; disk height equal to disk space immediately superior), ‘2’ (moderate; disk height narrowing as compared to disk space immediately superior), and ‘3’ (severe; endplates almost in contact). The L5-S1 interspace was graded using a 0-3 grade scale based on reader experience, due to the fact that the ratio for normal L5-S1 disk height as compared to L4-L5 may be more variable[18].

**Reliability of CT Readings for Disk Height Loss:** CT assessment of DHL was performed by a board-certified physiatrist (PS) researcher specializing in spine care, who was trained by an experienced research musculoskeletal radiologist (AG). A reading
protocol for evaluation of DHL based on the above outlined grading scheme was developed. A standard atlas of DHL was created and used throughout the reading process. Calibration of the primary reader to the musculoskeletal radiologist was performed using a training set prior to the start of the formal reads, and intra- and inter-rater reliability was calculated for two readers at the start of the reading process. All CT scans were then analyzed in a blinded fashion. Recalibration of reader to radiologist was performed at additional time points during the reading process. To evaluate for reader-drift, intra-rater and inter-rater reliability was periodically reassessed by inserting one repeated scan for every 10 new scans. Intra-observer reliability assessed with the \( \kappa \) statistic varied between 0.65 and 0.77 for categorical grading of DHL indices, and 0.80 to 0.87 for dichotomous grading for presence or absence of moderate DHL. Inter-observer reliability assessed with the \( \kappa \) statistic varied between 0.70 and 0.84 for categorical grading of DHL indices, and 0.85 to 0.94 for dichotomous grading for presence or absence of moderate DHL. This range of kappa statistics represents moderate to excellent reproducibility.

**Covariates:** Covariates were measured at the contemporaneous seventh Offspring and first Gen 3 examinations, including information on age, sex, body mass index, and cardiovascular risk factors. Body mass index (BMI) was computed as the ratio of weight (in kg) divided by height (meters\(^2\)), and categorized based on the Classification of Overweight and Obesity by the National Heart Lung and Blood institute: Underweight/Normal (BMI <25.0 kg/m\(^2\)), Overweight (BMI 25.0-29.9 kg/m\(^2\)), Obesity I (BMI 30.0-34.9 kg/m\(^2\)), Obesity II (BMI 35.0-39.9 kg/m\(^2\)), and Obesity III (BMI 40.0+...
Fasting samples were used to measure plasma glucose and total cholesterol. Diabetes was defined as plasma glucose of 126 mg/dl or greater, current treatment with either a hypoglycemic agent or insulin, or a prior diagnosis of diabetes. Participants who reported smoking regularly within the past year were defined as current smokers. Hypertension was defined as a systolic blood pressure of $\geq 140$ mm Hg, or a diastolic blood pressure of $\geq 90$ mm Hg, or the use of antihypertensive therapy. Hypercholesterolemia was defined as a total cholesterol of 240 mg/dL.

**Statistical analysis:** We initially characterized the sample ($n=436$) using means and standard deviations for continuous variables, and frequencies and proportions for categorical variables. Each variable was examined using descriptive statistics and graphic plots. AAC measurements were highly right skewed with roughly one third of the study sample demonstrating no AAC. We therefore categorized the quantitative AAC measurements into the grades of ‘no AAC’, ‘low AAC’ (Agatson score $\leq 959.2$), and ‘high AAC’ (Agatson score $>959.2$), which roughly distributed the sample into tertiles; this method has been used previously in studies of AAC[22]. The effect of AAC tertile was considered in subsequent analyses by the inclusion of the indicator variables ‘low AAC’ and ‘high AAC’ into regression models, using ‘no AAC’ as the reference group. We defined our primary outcome as the presence of at least moderate (grade 2) DHL at any of the L2-S1 spinal levels.

We then examined relationships between independent variables and the dependent variable of moderate DHL in an iterative series of binary logistic regression models, including only participants without missing values for all variables to allow comparisons
between different models (n=429). To address the first analytic aim, we examined the crude relationship between AAC tertile and moderate DHL using bivariate logistic regression (Model 1). We then examined the relationship between the cardiovascular risk factors of diabetes, HTN, hypercholesterolemia, and current smoking, and the dependent variable of moderate DHL (Model 2). In order to address the second analytic aim (accounting for associations between cardiovascular risk factors and AAC, and possible confounding due to these factors), we included AAC tertile and cardiovascular risk factors together in the same model (Model 3). This allowed us to examine whether the effect of AAC tertile on moderate DHL would be attenuated by the addition of cardiovascular risk factors. To address the third analytic aim, we examined the effects of adding important demographic covariates to our first bivariate model (Model 1). Adjustment for confounding demographic factors such as age is essential in order to examine the association between AAC tertile and DHL that exists independent of these factors. We therefore examined the effect of adding age (Model 4), female sex (Model 5), and BMI categories (Model 6) separately as covariates to Model 1. Age and AAC tertile were highly correlated, so we examined both these independent variables in the same model (Model 7). Last, we included AAC tertile, age, female sex, and BMI categories as independent variables in the same model (Model 8). We evaluated the significance of individual variables using odds ratios (ORs) and 95% confidence intervals (CIs), and calculated the c-statistic as a general measure of model fit. All statistical analyses were performed using SAS software, (SAS Institute Inc, Cary, North Carolina, release 9.2).
RESULTS

Descriptive statistics of the studied sample are shown in Table 1. The sample was 46.1% female, with a mean age of 54.5±11.6 years. 41.5% of individuals were overweight, and 28.6% were obese. 37.0% of individuals had hypertension, 8.5% had hypercholesterolemia, 12.0% were current smokers, and 6.2% had diabetes.

The results of iterative logistic regression models to examine the effect of AAC and cardiovascular risk factors on the relationship between AAC and DHL are presented in Table 3. In bivariate logistic regression analysis using the dependent variable of moderate DHL at any level, and the independent variable of categorical AAC grade, low AAC (OR 2.20[1.37-3.55]; p=0.0012) and high AAC (OR 2.33[1.44-3.77]; p=0.0006) were both associated with DHL, compared with the reference group of individuals with no AAC (Model 1). When only cardiovascular risk factors were modeled, neither diabetes, nor hypercholesterolemia, nor hypertension, nor smoking was significantly associated with DHL (Model 2). Finally, when both AAC tertile and cardiovascular risk factors were included in the same model (Model 3), addition of cardiovascular risk factors did not substantially change the parameter estimates for AAC tertile (data not shown), and did not attenuate the relationship between AAC and DHL. Inclusion of the four cardiovascular risk factors in Model 3 produced only a small increase in the c statistic from .60 to .62.

Having shown a strong bivariate relationship between AAC tertile and DHL, further regression models were used to examine the relationship between the demographic features of age, female sex, and BMI classification, and the outcome of
DHL. These results are presented in Table 4. Age (per year) was highly significantly associated with DHL (OR 1.05 [1.03-1.07]; p<0.0001), and the c statistic for this model (Model 4) was substantially larger than that for AAC tertile (0.65 vs. 0.60, respectively). Female sex and BMI classification (Models 5 and 6, respectively) were not significantly associated with DHL, and produced only small increases in the c statistic. It was noted that age was significantly associated with increasing AAC tertile (p <0.0001), suggesting that the observed bivariate associations between AAC and DHL may have been affected by confounding due to age. When age and AAC tertile were included in the same model (Model 7), age remained significantly associated with DHL, but AAC was no longer significant. Furthermore, the addition of AAC to the model produced only a small change in the c statistic as compared to the model including age alone (0.66 vs. 0.65, respectively). In the final model including all demographic features (Model 8), age and female sex were significantly associated with DHL, but no category of AAC tertile or BMI classification was.

The increase in DHL prevalence with increasing level of AAC is demonstrated in the first row of Table 4, and is depicted graphically in Figure 1. The prevalence of DHL is higher in individuals with AAC than in those without, but is roughly similar in low and high AAC groups. The primary importance of age as a predictor of DHL is illustrated graphically in Figure 2, which shows that when age is taken into account, systematic differences in DHL prevalence by AAC tertile are not seen.

In secondary multivariate analyses, we examined the effect of using different thresholds for the outcome of DHL, while adjusting for AAC tertile and all independent variables from Model 8.
AAC tertile was not independently associated with DHL. When using the outcome of continuous disk height in millimeters at individual spinal levels, AAC tertile was not independently associated with DHL at any lumbar spinal level. In all models, any observed bivariate association between AAC tertile and DHL outcome was not seen when the effects of age, gender, and BMI were adjusted for.

**DISCUSSION**

In this community-based population, AAC tertile was strongly associated with DHL in simple bivariate analyses. The cardiovascular risk factors of diabetes, hypercholesterolemia, hypertension, and smoking, however, were not associated with DHL. Furthermore, cardiovascular risk factors did not appear to attenuate the observed relationship between AAC and DHL, nor did they appear to contribute in a substantial way to overall model fit. This suggests that the association between AAC and DHL may be driven by processes independent of the traditional cardiovascular risk factors. **Age was associated with both AAC tertile and DHL.** In the final step of the analysis, the crude association between AAC tertile and DHL did not persist when age was included as a covariate. This indicates that much of the observed bivariate relationship between AAC and DHL is explained by age.

The results of this study conflict with the findings of some- but not all- clinical studies which have examined the possible relationship between aortic calcifications and disk degeneration. Kauppila et al. conducted a study of the Original cohort of the Framingham Heart Study population, using plain radiographs and a semi-quantitative
grading of aortic calcifications [10]. In a cross-sectional analysis of the cohort at baseline, Kauppila reported a significant association between aortic calcification and general disk degeneration after adjusting for age and sex, using a composite measure of either endplate sclerosis or disk space narrowing [10]. Longitudinal analyses demonstrated level-specific associations between aortic calcifications and subsequent general disk degeneration at the same spinal level where calcification had occurred at baseline. These results are contrary to our finding that the bivariate relationship between AAC and DHL was explained primarily by age. A recent cross-sectional study by Turgut et al. using CT scans also found an association between aortic wall calcification and a composite measure of disk degeneration combining DHL, osteophytosis, and intradiscal calcification, though covariates such as age were not accounted for[23]. Our study differs from both these prior studies in that we examined the single outcome of DHL (rather than a composite measure of disk degeneration) and we used a reliable and quantitative measure of AAC. Although the Turgut study also utilized CT imaging, our study had the methodologic advantage of using outcome measures for DHL that were designed for research, and have been used extensively for this purpose[18-20]. In addition, our assessments of AAC and DHL were performed by different readers who were unaware of the quantitative results from the other readers. Our findings, moreover, are consistent with a prior study by Kurunlahti et al., which found no correlation between the quantity of aortic calcifications and the amount of degeneration found on CT discography [24]. Taken together, the existing literature on the association between AAC and disk degeneration suggest that either osteophytosis or endplate sclerosis-components of other studies which used a composite disk degeneration outcome- may be
the degenerative structures more closely linked with AAC than DHL. Indeed the relationship between AAC and anterior lumbar osteophytes has been recently demonstrated in the Framingham population [25].

This study has other distinguishing features from prior works investigating vascular disease and spinal disorders. First, it should be noted that the independent variable of interest in this study- AAC- is distinct from that used in prior studies examining the association between lumbar segmental arterial flow and general disk degeneration [9, 12, 13, 26]. Second, the outcome used in this study was DHL. DHL is a pathoanatomic finding distinct from the symptom of LBP. Although the relationship between vascular disease and LBP has the potential for major healthcare impact if it exists, the question of pain production involves a multitude of interrelated factors, including spinal degeneration, pain neurobiology, and psychosocial factors; vascular disease may or may not represent one component of many contributing to this complex interplay.

This study has limitations. First, this study is an analysis of cross-sectional data, and firm conclusions on longitudinal cause-and-effect cannot be made. Second, as described above, this study used aortic calcifications as a marker for vascular disease. Although AAC has been used in this manner previously, AAC may also be associated with other factors, including calcium metabolism, and may be an imperfect marker for vascular disease[27]. Nevertheless, no better markers exist for vascular disease in vessels proximal to the lumbar spine which can be feasibly measured with commonly available non-invasive methods.
The relationship of vascular disease to LBP is potentially important, as in theory such a relationship could allow primary prevention of musculoskeletal disease while treating other conditions (i.e., cardiovascular disease) for which preventative care is already an accepted standard. The current study demonstrates that the association between AAC and DHL is independent of cardiovascular risk factors, and is largely explained by the influence of age. If a relationship between vascular disease and low back pain exists, it is unlikely that this relationship is mediated by the pathoanatomic finding of DHL. Future studies of vascular disease and spinal disorders should examine the association of degenerative parameters other than DHL with the production of LBP, examine the effects of adjustment for cardiovascular risk factors, and incorporate a longitudinal design.
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