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Quantitative Assessment of Abdominal Aortic Calcification and Associations with Lumbar Intervertebral Disk Height Loss: The Framingham Study

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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[9-11].

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 [12-14]. Vascular disease is thought to cause disk degeneration by compromising the nutritional supply to the avascular intervertebral disk[15, 16]. This suggests that impaired vascular flow may be a factor associated with disk degeneration that is modifiable through lifestyle changes, physical activity, and medical treatment—quite unlike the risk factors of heredity and age. Vascular disease may therefore be a potential target for preventive and rehabilitative spine care.

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However, there are limitations to the literature supporting the association between vascular disease and disc degeneration[12-14, 17]. 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 osteophytosis and endplate sclerosis[6, 8, 18]. 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[12, 19], and lumbar arterial flow by aortography[20]. Third, no prior study has examined a large community-based population using quantitative markers of vascular disease and standardized assessment of disk degeneration with 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 a 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 potential risk factors for spinal degeneration.

METHODS

Study Sample

This ancillary investigation to the Framingham Heart Study was approved by the Institutional Review Board of New England Baptist Hospital. Methods of recruitment for the Framingham Offspring and Third Generation cohorts have been described elsewhere.[21, 22] 3529 individuals from these cohorts underwent assessment of AAC using computed tomography (CT). The recruitment, conduct, and specifications CT scanning have been previously reported[23, 24]. Subjects for the current study were randomly sampled using a random number generator, irrespective of clinical information, from amongst those individuals within each cohort who received CT scans; the Offspring cohort was oversampled to ensure that older adults were adequately represented.

Quantitative Assessment of AAC

CT scans were assessed for the presence and quantity of AAC by experienced readers on a dedicated workstation as part of the multidetector CT studies of aortic vascular calcification conducted as part of the Framingham Heart Study. Three of the readers were trained physicians, one was a trained technician, and all were unaware of the research questions and clinical information relevant to this ancillary study. Briefly, thirty contiguous 5-mm thick slices of the abdomen were evaluated sequentially, calcific lesions were identified, and quantity of calcific lesions were measured and summed over all slices, using a modified Agatston score[25]. This score defines each calcific lesion as an area of at least 3 connected pixels with CT attenuation >130 Hounsfield units, with higher lesion scores for progressively more densely calcified lesions. Scores are summed over all areas and slices to create a continuous summary score with a lower limit of '0' (no calcification), which accounts for both the amount of calcification and the density of calcification over the entire abdominal aorta. Methods of scoring are described in greater detail elsewhere and these

modified Agaston scores for AAC been demonstrated to have excellent reliability (ICC $r > 0.96$) [23-25].

Assessment of Disk Height Loss

DHL assessment was performed using eFilm Workstation (Version 2.0.0) software. CT scans were interpreted with blinding to clinical data and results of the quantitative AAC assessments. DHL was graded at spinal levels L2-L3, L3-L4, L4-L5, and L5-S1, using a system that was developed for research purposes by Videman et al., and has been used extensively in prior studies of spinal degeneration on MRI [10, 26, 27]. 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). It should be noted that the grading system of Videman as applied utilized some important aspects that are qualitative. First, accuracy limitations of the caliper measurements (to the nearest millimeter) necessitated some qualitative judgments. For instance, in situations where contiguous interspace heights had the same quantitative measurement in millimeters, but one interspace appeared clearly higher or lower than the other to the reader, the qualitative assessment of interspace height differences trumped the quantitative measurement. Second, since this system compares each level to the level superior (at L4-L5 and above), in instances where the reference level had DHL, subjective judgment by the reader was necessary. Third, due to the fact that the ratio for normal L5-S1 disk height as compared to L4-L5 may be more variable [18, 27], the L5-S1 interspace was graded using a 0-3 grade scale based on reader experience, with '0' signifying normal height, '1' signifying mild narrowing, '2' signifying moderate narrowing, and '3' having endplates almost in contact. Ascertainment of L5-S1 DHL is based on a range of anatomic considerations including relationships to the L4-L5 and/or L3-L4 spinal levels, but L5-S1 height was generally considered normal if equal, or slightly narrowed as compared to L4-L5.

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 representative DHL grades 0-3 was created by the investigative team and used throughout the reading process to maintain a standard throughout the reading process, as is often done in high-quality imaging studies [28]. Calibration of the primary reader to the musculoskeletal radiologist was performed using a training set prior to the start of formal reads, 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, and inter-rater reliability was periodically reassessed by inserting one repeated scan for every 10 new scans. Inter-observer reliability assessed with the κ 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 substantial to excellent reproducibility.

Covariates

Information on covariates was collected at the contemporaneous Framingham examinations. Body mass index (BMI) was calculated as weight (kg) by height (meters²), and divided into categories according to the classification by National Heart Lung and Blood Institute: Underweight/Normal (BMI <25.0 kg/m²), (BMI 25.0-29.9 kg/m²), and Obesity Classes I-III (BMI 30.0+ kg/m²)[29]. Diabetes was defined as a fasting plasma glucose ≥126 mg/dl, current treatment with either insulin or a hypoglycemic agent, or a prior diagnosis of diabetes. Participants who smoked regularly within the past year were defined as current smokers. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg, or a diastolic blood pressure of ≥90 mm Hg, or the use of antihypertensive therapy. Hypercholesterolemia was defined as a fasting total cholesterol ≥240 mg/dL.

Statistical analysis

The study sample (n=435) was characterized using means and standard deviations for continuous variables, and frequencies and proportions for categorical variables. Variables were examined using descriptive statistics and graphic plots. The AAC variable was highly skewed to the right, with approximately 1/3 of the sample having no AAC. Hence, we created three categories of quantitative AAC scores: 'no AAC', 'low AAC' (Agatston score <949.39), and 'high AAC' (Agatston score ≥949.39), roughly distributing the sample into tertiles; this method has been used previously in studies of AAC[30]. 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, with '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=428). 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 individual variables using odds ratios (ORs) and 95% confidence intervals (CIs), and calculated the c statistic as a general measure of model fit appropriate to the binary outcome used for DHL. The c statistic is equivalent to the probability that the model's risk is higher for a case (with DHL) than for a non-case (without DHL) and therefore ranges from 0.50 (no fit) to 1.00 (perfect fit). As a secondary analysis to examine whether AAC may be associated with the extent of DHL

(that is, where multiple spinal levels may be affected by moderate or severe DHL), we repeated the above process treating DHL not as a binary outcome, but as an ordinal (count) outcome of the number of spinal levels with moderate/severe DHL (possible range: 0-4), using negative binomial regression for count outcomes. The exponential of the parameter estimates from negative binomial regression modeling in this context yield a relative risk for the number of spinal levels with moderate/severe DHL (as a multiplicative effect). 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 45.5% female, with a mean age of 58.2 ± 13.1 years. 41.4% of individuals were overweight, and 29.1% were obese. 37.3% of individuals had hypertension, 24.8% had hypercholesterolemia, 12.0% were current smokers, and 6.4% 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 2. 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 2.05[1.27-3.30]; $p=0.003$) and high AAC (OR 2.24[1.38-3.62]; $p=0.001$) 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 0.59 to 0.61, as compared to a model not containing cardiovascular risk factors.

Having shown a strong bivariate relationship between AAC tertile and DHL, further regression models were used to examine the relationship between the factors of age, female sex, and BMI classification, and the outcome of DHL. These results are presented in Table 3. Age (per year) was highly significantly associated with DHL (OR 1.04 [1.02-1.06]; $p<0.0001$), and the c statistic for this model (Model 4) was substantially larger than that for AAC tertile (0.64 vs. 0.59, respectively). Female sex and BMI classification (Models 5 and 6, respectively) were not significantly associated with DHL, and produced only minimal increases in the c statistic from the null value of 0.50. 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 (0.65 vs. 0.64, respectively). In the final model including all demographic features (Model 8), only age was independently and significantly associated with DHL.

The increase in DHL prevalence with increasing level of AAC is depicted graphically in Figure 1. The prevalence of DHL is higher in individuals with AAC than in those without, but is generally similar in low and high AAC groups. The primary importance of age as a predictor of DHL, however, 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 analyses, we repeated the above process for model building, using instead the alternate outcome of the number of spinal levels with moderate/severe DHL. These results were similar to the primary analysis: the bivariate association between the number of spinal levels with moderate/severe DHL and low AAC (relative risk [RR] for number of affected levels as a multiplicative effect: 1.66; 95% confidence interval [CI] 1.29-2.13) or high AAC (RR 2.09; 95% CI 1.65-2.65) was no longer significant once age, sex, and BMI was accounted for low AAC (RR 1.19 [95% CI 0.91-1.56]) or (high AAC: RR 1.11 [95% CI 0.80-1.54]), or even when age alone was accounted for (data not shown).

We conducted sensitivity analyses to examine the effect of using different measures for the outcome of DHL (while adjusting for AAC tertile and all independent variables from Model 8), as well as to examine the effect of treating AAC as a continuous variable (rather than AAC tertile). When using the outcome of grade 3 (severe) DHL at any level, AAC tertile was not independently associated with DHL. When using the outcome of continuous disk height in millimeters at the individual spinal levels L2-S1, AAC tertile was not independently associated with DHL at any lumbar spinal level. When using the outcome of a summary index of DHL scores at all lumbar spinal levels (the sum of 0-3 grades at the four spinal levels L2-S1, with 0 indicating no DHL at any level, and 12 indicating severe DHL at all four levels), AAC tertile was not independently associated with DHL. In all models, any observed bivariate association between AAC tertile and DHL outcome was no longer significant after adjustment for age, gender, and BMI (data not shown). In a final sensitivity analysis, we repeated the primary analysis leaving AAC as a continuous variable and using DHL as a dichotomous outcome. Again, the bivariate association between continuous AAC and DHL outcome was non-significant when other covariates were accounted for, even after considering both linear and non-linear trends for AAC.

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. 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 predominant influence of age on DHL is best demonstrated graphically by a comparison of Figures 1 and 2 above. While in crude analysis (Figure 1) the prevalence of DHL appears to be clearly higher in low AAC and high AAC patients as compared to patients without AAC, Figure 2 demonstrates that the high prevalence of DHL in low and high AAC categories simply reflects the fact that individuals in these categories are substantially older than individuals with no AAC and- as noted above-AAC is itself highly positively associated with age ($p < 0.0001$). This is a classic example of confounding, whereby the apparent relationship between AAC and DHL is explained by the effect of age. This is demonstrated numerically in Table 3, where we see that the odds ratios for the crude association between low/high AAC and DHL (point estimates of 2.05 and 2.24,

respectively) approach 1.0 when age is accounted for (point estimates of 1.30 and 0.91, respectively).

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[12]. In a cross-sectional analysis of the cohort at baseline, Kauppila found 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[12]. 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[17]. The discordance between our findings and these prior studies are likely explained by various methodologic strengths of our study. First, 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). The use of composite outcomes in the studies by Kauppila and Turgut combined effects for different disk degeneration measures that may each have very different relationships to AAC. Combining different disk degeneration measures obscures knowledge of which factors may have significant relationships with AAC, and which do not. Second, our study used a quantitative and highly reliable measure of AAC, rather than subjective gradings used in the prior studies. Third, our study ensured blinding of the quantitative AAC assessment to the results of the DHL assessments, and vice versa, by using separate blinded readers for each parameter, who were unaware of the results from the other readers for the other parameter. This is in contrast to the studies by Turgut and Kauppila, where both AAC and disk degeneration measurements were performed by the same readers, who may potentially have been influenced by the a priori hypothesis of an association between the dependent and independent variables. Last, our study used a well-described index for DHL with CT imaging. Although the study by Turgut also utilized CT, 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[10, 26, 27]. Furthermore, Turgut and colleagues did not adjust for other factors, and as shown above, this was necessary to account for the strong confounding by age. Our overall study findings, moreover, are supported by the results of work by Kurunlahti and colleagues, which found no correlation between the quantity of aortic calcifications and the amount of degeneration found on CT discography[31]. Taken together, the existing literature on the association between AAC and disk degeneration suggests 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, anterior thoracolumbar osteophytosis was linked to AAC in a recent study by Karasik and colleagues in the Framingham Original cohort [32]. To test this supposition, we conducted *post-hoc* analyses repeating our analytic methods above but using instead the alternate outcome of anterior lumbar osteophytes, applying the 0-3 ordinal grading system by Jarosz [33]. When using the outcome of any moderate/severe osteophytosis at any level L2-S1, low AAC (OR 1.87 [1.08-3.25]; $p=0.03$) and high AAC (OR 2.11 [1.07-4.17]; $p=0.03$) were associated with osteophytosis, independent of age, although this effect was diminished when sex and BMI were accounted for (data not shown). When using the outcome of number of levels with moderate/severe lumbar osteophytes, low AAC (relative risk [RR] for number of affected levels as a multiplicative effect: 1.49 [1.03-2.14]; $p=0.03$) and high AAC (RR 1.48

[0.97-2.25]; $p=0.06$) were associated with osteophytosis independent of all other factors including age, sex, and BMI. This *post-hoc* analysis supports the idea that different disk degeneration parameters may have different associations with AAC, and argues against the use of combination disk degeneration scales for this research question. Indeed, different basic mechanisms may link AAC to individual disk degeneration parameters. Although nutrition has been proposed as a major pathway connecting AAC to DHL and disk dessication, AAC may be associated with osteophytosis by other mechanisms, such as an underlying tendency to ectopic mineralization common to both AAC and osteophytosis[32], or through local inflammation [32] (for example, via cyclooxygenase-2 [COX-2], which is expressed both in osteophyte fibrocartilage and atherosclerotic plaques[34]).

This study has other distinguishing features from prior works investigating vascular disease and spinal disorders. First, it should be noted that the quantitatively measured 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 or LBP[12, 19, 20, 31]. Second, the outcome used in this study was DHL. DHL is a pathoanatomic finding distinct from the symptom of LBP. Some studies have suggested an association between vascular disease and LBP[13, 31]. 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. The findings of the current study suggest that the potential link between vascular disease and LBP may be mediated by factors other than DHL; other possible intermediates include the pathoanatomical changes of disc desiccation[35], vertebral osteophytosis[32], endplate sclerosis, or facet joint osteoarthritis[36].

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[37]. Nevertheless, no better markers exist for vascular disease in vessels proximal to the lumbar spine which can be feasibly measured with objective and commonly available non-invasive methods.

CONCLUSIONS

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 preventive 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 use individual disk degeneration parameters rather than combination indexes, 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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REFERENCES

- [1]. Deyo RA, Cherkin D, Conrad D, Volinn E. Cost, controversy, crisis: low back pain and the health of the public. *Annu Rev Public Health*. 1991; 12:141–56. [PubMed: 1828670]
- [2]. Deyo RA, Mirza SK, Turner JA, Martin BI. Overtreating chronic back pain: time to back off? *J Am Board Fam Med*. 2009; 22:62–8. [PubMed: 19124635]
- [3]. Katz JN. Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. *The Journal of bone and joint surgery*. 2006; 88(Suppl 2):21–4. [PubMed: 16595438]
- [4]. Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain*. 2000; 84:95–103. [PubMed: 10601677]
- [5]. van Tulder MW, Koes BW, Bouter LM. A cost-of-illness study of back pain in The Netherlands. *Pain*. 1995; 62:233–40. [PubMed: 8545149]
- [6]. Pye SR, Reid DM, Smith R, Adams JE, Nelson K, Silman AJ, et al. Radiographic features of lumbar disc degeneration and self-reported back pain. *J Rheumatol*. 2004; 31:753–8. [PubMed: 15088303]
- [7]. Kjaer P, Leboeuf-Yde C, Korsholm L, Sorensen JS, Bendix T. Magnetic resonance imaging and low back pain in adults: a diagnostic imaging study of 40-year-old men and women. *Spine*. 2005; 30:1173–80. [PubMed: 15897832]
- [8]. Videman T, Battie MC, Gibbons LE, Maravilla K, Manninen H, Kaprio J. Associations between back pain history and lumbar MRI findings. *Spine*. 2003; 28:582–8. [PubMed: 12642766]
- [9]. Battie MC, Videman T, Kaprio J, Gibbons LE, Gill K, Manninen H, et al. The Twin Spine Study: contributions to a changing view of disc degeneration. *Spine J*. 2009; 9:47–59. [PubMed: 19111259]
- [10]. Videman T, Battie MC, Ripatti S, Gill K, Manninen H, Kaprio J. Determinants of the progression in lumbar degeneration: a 5-year follow-up study of adult male monozygotic twins. *Spine*. 2006; 31:671–8. [PubMed: 16540872]
- [11]. Videman T, Gibbons LE, Kaprio J, Battie MC. Challenging the cumulative injury model: positive effects of greater body mass on disc degeneration. *Spine J*. 2009
- [12]. Kauppila LI. Prevalence of stenotic changes in arteries supplying the lumbar spine. A postmortem angiographic study on 140 subjects. *Annals of the rheumatic diseases*. 1997; 56:591–5. [PubMed: 9389219]
- [13]. Kauppila LI, McAlindon T, Evans S, Wilson PW, Kiel D, Felson DT. Disc degeneration/back pain and calcification of the abdominal aorta. A 25-year follow-up study in Framingham. *Spine*. 1997; 22:1642–7. discussion 8-9. [PubMed: 9253101]
- [14]. Kauppila LI, Tallroth K. Postmortem angiographic findings for arteries supplying the lumbar spine: their relationship to low-back symptoms. *Journal of spinal disorders*. 1993; 6:124–9. [PubMed: 8504223]
- [15]. Hadjipavlou AG, Tzermiadianos MN, Bogduk N, Zindrick MR. The pathophysiology of disc degeneration: a critical review. *J Bone Joint Surg Br*. 2008; 90:1261–70. [PubMed: 18827232]
- [16]. Urban JP, Smith S, Fairbank JC. Nutrition of the intervertebral disc. *Spine (Phila Pa 1976)*. 2004; 29:2700–9. [PubMed: 15564919]
- [17]. Turgut AT, Sonmez I, Cakit BD, Kosar P, Kosar U. Pineal gland calcification, lumbar intervertebral disc degeneration and abdominal aorta calcifying atherosclerosis correlate in low back pain subjects: A cross-sectional observational CT study. *Pathophysiology*. 2008; 15:31–9. [PubMed: 18215511]

- [18]. de Schepper EI, Damen J, van Meurs JB, Ginai AZ, Popham M, Hofman A, et al. The association between lumbar disc degeneration and low back pain: the influence of age, gender, and individual radiographic features. *Spine (Phila Pa 1976)*. 2010; 35:531–6. [PubMed: 20147869]
- [19]. Kauppila LI, Mikkonen R, Mankinen P, Peltö-Vasenius K, Maenpää I. MR aortography and serum cholesterol levels in patients with long-term nonspecific lower back pain. *Spine*. 2004; 29:2147–52. [PubMed: 15454707]
- [20]. Tokuda O, Okada M, Fujita T, Matsunaga N. Correlation between diffusion in lumbar intervertebral disks and lumbar artery status: evaluation with fresh blood imaging technique. *J Magn Reson Imaging*. 2007; 25:185–91. [PubMed: 17152057]
- [21]. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. *Prev Med*. 1975; 4:518–25. [PubMed: 1208363]
- [22]. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, et al. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. *Am J Epidemiol*. 2007; 165:1328–35. [PubMed: 17372189]
- [23]. Hoffmann U, Siebert U, Bull-Stewart A, Achenbach S, Ferencik M, Moselewski F, et al. Evidence for lower variability of coronary artery calcium mineral mass measurements by multi-detector computed tomography in a community-based cohort--consequences for progression studies. *European journal of radiology*. 2006; 57:396–402. [PubMed: 16434160]
- [24]. Parikh NI, Hwang SJ, Larson MG, Cupples LA, Fox CS, Manders ES, et al. Parental occurrence of premature cardiovascular disease predicts increased coronary artery and abdominal aortic calcification in the Framingham Offspring and Third Generation cohorts. *Circulation*. 2007; 116:1473–81. [PubMed: 17785619]
- [25]. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990; 15:827–32. [PubMed: 2407762]
- [26]. Raininko R, Manninen H, Battie MC, Gibbons LE, Gill K, Fisher LD. Observer variability in the assessment of disc degeneration on magnetic resonance images of the lumbar and thoracic spine. *Spine (Phila Pa 1976)*. 1995; 20:1029–35. [PubMed: 7631232]
- [27]. Videman T, Battie MC, Gill K, Manninen H, Gibbons LE, Fisher LD. Magnetic resonance imaging findings and their relationships in the thoracic and lumbar spine. Insights into the etiopathogenesis of spinal degeneration. *Spine*. 1995; 20:928–35. [PubMed: 7644958]
- [28]. Lurie JD, Tosteson AN, Tosteson TD, Carragee E, Carrino JA, Kaiser J, et al. Reliability of readings of magnetic resonance imaging features of lumbar spinal stenosis. *Spine (Phila Pa 1976)*. 2008; 33:1605–10. [PubMed: 18552677]
- [29]. NHLBI. Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risks. National Heart Lung and Blood Institute; 2009. [cited 2009 10/20/2009]; Available from: http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/bmi_dis.htm
- [30]. Wilson PW, Kauppila LI, O'Donnell CJ, Kiel DP, Hannan M, Polak JM, et al. Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality. *Circulation*. 2001; 103:1529–34. [PubMed: 11257080]
- [31]. Kurunlahti M, Tervonen O, Vanharanta H, Ilkko E, Suramo I. Association of atherosclerosis with low back pain and the degree of disc degeneration. *Spine*. 1999; 24:2080–4. [PubMed: 10543002]
- [32]. Karasik D, Kiel DP, Kiely DK, Cupples LA, Wilson PW, O'Donnell CJ, et al. Abdominal aortic calcification and exostoses at the hand and lumbar spine: the Framingham Study. *Calcif Tissue Int*. 2006; 78:1–8. [PubMed: 16397734]
- [33]. Jarosz, J.; Bingham, JB.; Pemberton, J.; Sambrook, PN.; Spector, TD. At atlas for scoring cervical and lumbar disc degeneration. Springer Verlag; London: 1997.
- [34]. Koki A, Khan NK, Woerner BM, Dannenberg AJ, Olson L, Seibert K, et al. Cyclooxygenase-2 in human pathological disease. *Adv Exp Med Biol*. 2002; 507:177–84. [PubMed: 12664583]
- [35]. Hangai M, Kaneoka K, Kuno S, Hinotsu S, Sakane M, Mamizuka N, et al. Factors associated with lumbar intervertebral disc degeneration in the elderly. *Spine J*. 2008; 8:732–40. [PubMed: 18037353]

- [36]. Suri P, Katz JN, Rainville J, Kalichman L, Guermazi A, Hunter DJ. Vascular disease is associated with facet joint osteoarthritis. *Osteoarthritis Cartilage*. 2010; 18:1127–32. [PubMed: 20633684]
- [37]. Iribarren C, Sidney S, Sternfeld B, Browner WS. Calcification of the aortic arch: risk factors and association with coronary heart disease, stroke, and peripheral vascular disease. *Jama*. 2000; 283:2810–5. [PubMed: 10838649]

Figure 1.

Prevalence of DHL by AAC tertile[†]. The prevalence of DHL is substantially higher in the 'Low AAC' and 'High AAC' tertiles, as compared to the 'No AAC' tertile, when age is not accounted for.

[†]AAC=Aortic abdominal calcification (by tertile), DHL=Disk height loss

Figure 2.

Prevalence of DHL by AAC tertile within age strata[†]. Within each age strata, the prevalence of DHL is not consistently higher in the 'low AAC' and 'high AAC' tertiles, as compared to the 'no AAC' tertile.

[†]AAC=Aortic abdominal calcification (by tertile), DHL=Disk height loss

Table 1
Descriptive characteristics of the Study Sample (n=435)

Characteristic	N(%) or Mean (SD)
Age (years)	58.2±13.1
Female sex	198 (45.5%)
BMI (kg/m ²)	
Normal/Underweight (BMI <25.0 kg/m ²)	127 (29.5%)
Overweight (BMI 25.0-29.9 kg/m ²)	178 (41.4%)
Obesity I-III (BMI 30.0+ kg/m ²)	125 (29.1%)
Cardiovascular Risk Factors	
Hypertension	162 (37.3%)
Hypercholesterolemia	108 (24.8%)
Smoking (regular use in past year)	52 (12.0%)
Diabetes	28 (6.4%)
Abdominal Aortic Calcification (AAC)	
No AAC	151 (34.9%)
Low AAC	141 (32.6%)
High AAC	141 (32.6%)
Moderate Disk Height Loss [†]	269 (61.8%)

[†] Moderate or severe disk height loss at L2-S1

Table 2
Associations between AAC and cardiovascular factors, and moderate DHL*

	AAC		Cardiovascular Risk Factors				c statistic
	Low	High	Diabetes	High Cholesterol	HTN	Smoking	
	Odds Ratios and 95% Confidence Intervals [†]						
Model 1- AAC	2.05 (1.27-3.30)	2.24 (1.38-3.62)	-	-	-	-	0.59
Model 2- CV risk factors	-	-	1.27 (0.55-2.93)	0.79 (0.50-1.25)	1.39 (0.91-2.13)	1.24 (0.68-2.29)	0.56
Model 3- AAC + CV risk factors	2.08 (1.28-3.40)	2.28 (1.32-3.92)	1.08 (0.46-2.52)	0.72 (0.45-1.16)	1.08 (0.68-1.72)	1.11 (0.60-2.07)	0.61

* AAC=Aortic abdominal calcification (by tertile), DHL=Disk height loss;

[†] Odds ratios for the dependent variable of DHL

Table 3
Associations between AAC and demographic features, and moderate DHL*

	AAC		Age	Female Sex	BMI categories		<i>c</i> statistic
	Low	High			Overweight	Obesity	
Odds Ratios and 95% Confidence Intervals [†]							
Model 1- AAC	2.05 (1.27-3.30)	2.24 (1.38-3.62)	-	-	-	-	0.59
Model 4- Age	-	-	1.04 (1.02-1.06)	-	-	-	0.64
Model 5- Female sex	-	-	-	0.85 (0.57-1.25)	-	-	0.52
Model 6- BMI categories	-	-	-	-	1.03 (0.64-1.63)	1.37 (0.82-2.29)	0.53
Model 7- AAC + age	1.30 (0.76-2.23)	0.91 (0.45-1.81)	1.04 (1.02-1.07)	-	-	-	0.65
Model 8- AAC + age + female sex + BMI categories	1.20 (0.69-2.09)	0.74 (0.36-1.53)	1.05 (1.02-1.07)	0.71 (0.47-1.09)	0.92 (0.56-1.50)	1.25 (0.72-2.14)	0.66

* AAC=Aortic abdominal calcification (by tertile), DHL=Disk height loss;

[†] Odds ratios for the dependent variable of DHL