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Clinical Study

Obesity and calcification of the ligaments of the spine: a comprehensive CT analysis of the entire spine in a random trauma population

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Abstract

BACKGROUND CONTEXT: Obesity, which is currently surging to epidemic levels within the United States, has been linked to hyperostotic conditions like diffuse idiopathic skeletal hyperostosis (DISH) and ossification of the posterior longitudinal ligament (OPLL). Excess adipose tissue and insulin-resistance may cause a systemic increase in serum levels of proinflammatory cytokines and these signals can affect bone metabolism. Spinal ligaments and discs may have receptors for these signaling molecules. Anecdotal observations at this institution suggested that there is a clinically important subset of younger patients with obesity and multilevel stenosis in the presence of unusual calcification of the spinal ligaments that is distinct from DISH.

PURPOSE: To determine if there is an association between truncal obesity and calcifications of the spine in nonelderly adults.

STUDY DESIGN/SETTING: This is a retrospective analysis of 214 sequential trauma patients between the ages of 29 and 50. Patients' age, sex, truncal obesity, history of hypertension, and diabetes were assessed for association with ligamentous calcification of the spine.

PATIENT SAMPLE: Sequential trauma patients were chosen from our institution's trauma database between 2006 and 2007.

METHODS: Full spine computed tomography (CT) imaging was examined for bone formation in the region of the anterior longitudinal ligament (ALL) and annulus, posterior longitudinal ligament (PLL) and annulus, and the ligamentum flavum (LF). Visceral and subcutaneous abdominal fat were also evaluated. The authors report no study funding sources or conflicts of interest.

OUTCOME MEASURES: Calcification of the ALL, PLL, and LF were assigned a score at each level and then combined for a total calcification score (TCS) for the entire spine. Obesity was estimated using a truncal body mass index (TBMI) by using a previously validated CT derived truncal total adiposity volume (TAV).

RESULTS: ALL calcification was associated with age, male gender, hypertension, and increased adiposity. PLL calcification was significantly associated with age and hypertension. LF calcification was only associated with increased obesity.

CONCLUSIONS: In our analysis of nonelderly patients, LF calcification was independently associated with truncal obesity. This implies obesity plays a greater role in calcification than could be accounted for by simply age-related degeneration or gender.

Keywords: Obesity; Calcification; Ligamentum flavum; Anterior Longitudinal Ligament; Posterior Longitudinal Ligament

FDA device/drug status: Not applicable.

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Introduction

Approximately 35% of adult Americans are obese (BMI>30) and the prevalence is climbing [1,2]. The Center for Disease Control (CDC) recently reported that "In 2009, about 2.4 million more adults were obese than in 2007. The medical care costs of obesity in the United States are staggering. In 2008 dollars, these costs totaled about $147 billion" [3].

Multiple studies have reported an association between obesity and hyperostotic conditions like Diffuse Idiopathic Skeletal Hyperostosis (DISH) and Ossification of the Posterior Longitudinal Ligament (OPLL) [4−7]. Although the mechanism by which these abnormal ossifications form is not fully understood, a strong genetic predisposition in the Japanese and Han Chinese for OPLL has been described [8−10]. DISH is much more common in older males, and both OPLL and DISH appear to be associated more commonly with insulin resistant states [4−7,11,12]. It is possible that excess adipose tissue contributes to these hyperostotic states via cytokine or hormonal factors as well as mechanical factors, and there is evidence that bone and adipose regulation is interrelated [13−19]. Metabolic syndrome (as defined by central obesity and at least two of the following: insulin resistance, hypertension, or dyslipidemia) represents a proinflammatory state which may also contribute [20].

The two senior authors (CDC and MDR) have observed a number of patients who presented with multilevel calcifications of the spinal ligaments and severe thoracic myelopathy. These patients did not fit the typical clinical picture of DISH. They were typically younger adults, often female, and, while OPLL or ossification of the anterior longitudinal ligament (ALL) might be present, calcification of the ligament flavum (LF) was more prominent (Fig. 1). However, these patients did exhibit the typical phenotype of metabolic syndrome.

It was hypothesized that obesity could be associated with unusual calcifications of the spinal ligaments in younger populations than typically described with OPLL or DISH. The purpose of this study is to determine if increased obesity is associated with calcifications of the ALL, posterior longitudinal ligament (PLL) and LF in a nonelderly patient group. Increasing age, the amount of visceral versus subcutaneous abdominal fat (SAF), and the presence of diabetes and hypertension were also examined for any association with increased calcification.

Materials and methods

Patient selection

Two hundred and fourteen sequential trauma patients were chosen from our institution's trauma database between 2006 and 2007. All patients were polytrauma patients in a Level 1 trauma center, in whom full body computed tomography (CT) scans are standard. Inclusion criteria were: (1) subjects were trauma activation patients; (2) 29−50 years of age; (3) helical CT imaging was obtained from the cranium to coccyx; (4) access to trauma/medical history to ascertain the diagnosis of hypertension and diabetes. Exclusion criteria included: (1) trauma to the spine; (2) inadequate imaging.

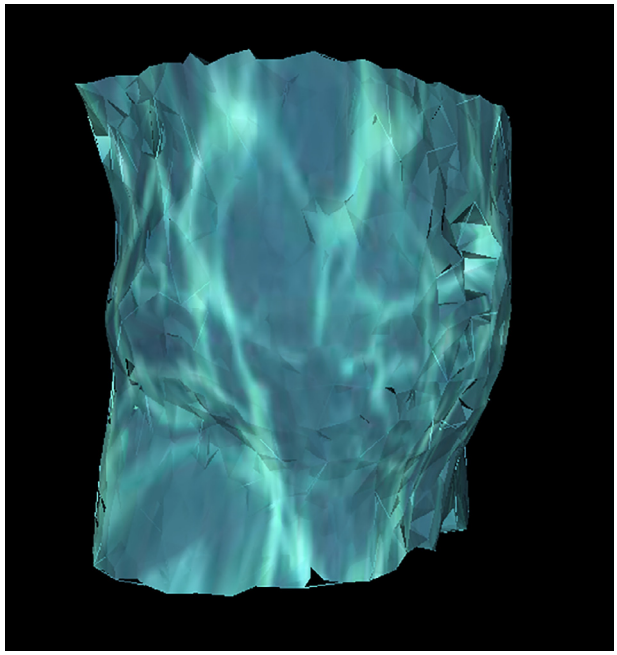


Fig. 1. Truncal three-dimensional reconstruction of adiposity in a nonobese patient obtained from the thoracoabdominal trauma CT scans and three-dimensional reconstruction software, which is then used to determine a truncal three-dimensional reconstruction BMI estimate. Reprinted from "The use of routine thoracoabdominal CT scans in the polytrauma patient to estimate obesity," by Ferguson DF, Busenlehner BJ, Rahm MD, Mehta SM, Song J, Davis ML, Sampson HW, Chaput CD. Obesity (Silver Spring), 2013 May;21(5):997−1003.

Multidetector CT acquisition and reconstruction technique

All multidetector computerized tomographic images from 2006 to 2007 were performed on a model Siemens 64 Sensation (Erlangen, Germany). Patients were scanned in the supine position in a cranial to caudal direction from the level of the occiput to the femoral shaft with a zero point reference of the external auditory meatus (Fig. 2). A kVp/Ma of 120/CAREDOSE or 120/400 was used to optimize penetration with a slice/detector rows setting of 3 mm 64 × 0.6 mm at a pitch of 0.9 and rotation time of 1 second.

Three dimensional reconstructions of truncal body fat were made using the volume of interest Cutter tool included with OsiriX software (version 3.1 32-bit, OsiriX Foundation, Geneva, Switzerland). This tool allows one to define a cubic area of interest and exclude certain tissues of disinterest (in this case, nonfat tissue). Images were cropped by focusing between an axial view of the T10 vertebral body at the pedicles inferiorly to the inferior-most portion of the coccyx. If transitional levels were encountered, the films were

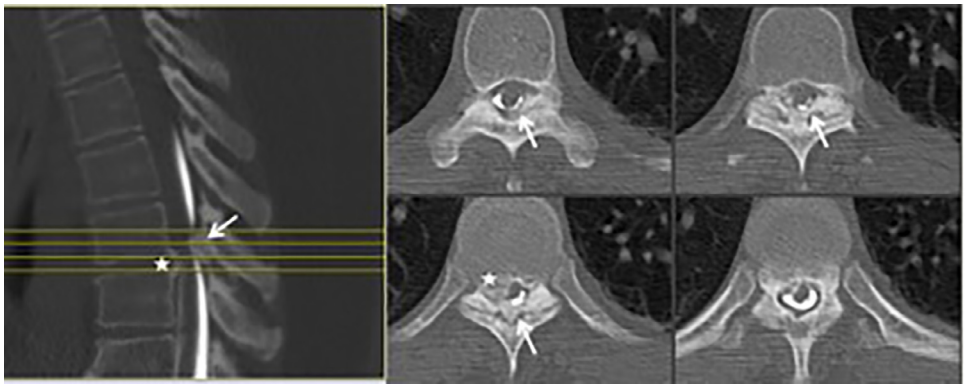


Fig. 2. CT Myelogram of 33-year-old female (formerly 500 lb patient) now 337 lbs. (BMI 54) with thoracic myelopathy, inability to stand and neurogenic bowel and bladder. Arrow indicating ossification of the ligamentum flavum. Star indicating calcification of herniated disc.

reviewed and S1 identified, then eight vertebrae were counted superiorly until T10 was visualized. The total number of images and thickness were then recorded from the cropped image and their product determined the total image length. An image was then brought into the plane where the superior most portion of the Superior Iliac Crest could be seen. A 1 cm measurement was made perpendicularly and the adipose tissue at this measurement was highlighted. Using the "Segmentation Parameters" function, truncal adiposity was constructed within ±110 Hounsfield units of the highlighted tissue. This resulted in a 3DR model of adiposity, thus yielding truncal adiposity volume (TAV), which was measured in cubic centimeters and rounded to the nearest whole number [21]. TAV (cm^3) was then utilized to calculate the truncal body mass index (TBMI). TBMI is calculated with the following equation: $0.00004X^3-0.0041X^2+0.4071X+19$, where X is TAV/total image length (mm) [21]. TAV is made up of both SAF and visceral abdominal fat (VAF), which were also analyzed separately.

Statistical analysis

All variables were summarized for the entire study group using descriptive statistics: mean (SD) for continuous variables and frequency (percent) for categorical variables. The cumulative calcification score of each of 3 ligaments (ALL, PLL, and LF) and total calcification score (TCS) were outcome variables of interest. Inter- and intraobserver agreements of each calcification score measured by two evaluators at two time points were assessed by intraclass correlation coefficient. Correlation analyses were performed to assess the associations of VAF, SAF, and VAF/SAF with calcification scores.

To study risk factors for significant calcification, univariate and multivariable logistic regression models by stepwise selection were utilized. Cutoff points of significant calcification for three ligaments and TCS were determined based on the distribution of each score for patients 40 years and younger, and calcification scores of 95 percentiles and higher were considered as significant calcification. Age, gender, insulin resistance state, hypertension, and obesity determined by TBMI were included in the model as predictor variables. The presence/absence of significant calcification based on each score was considered as a response variable. A p value of less than 0.05 indicated a statistical significance. SAS 9.2 (SAS Institute INC, Cary, NC, USA) was used for data analysis.

Calcification score

Spinal ligament calcification was scored using a three-point system that was a simplification of a system previously described by Mata et al. (Fig. 3) [22]. At each intervertebral disc level, a calcification score was awarded: 0 for no calcification beyond the plane of the vertebral endplates, 1 for calcification extending beyond the endplates, and 2 for bridging calcification. Data collection was limited to the anatomical areas of interest. ALL data was collected at the anterior one-third of the vertebral column. Similarly, PLL scoring was limited to the posterior one-third of the vertebral column. LF was defined as the transverse interspace between the articular facets. Scoring was obtained from C2 to S1. Lateral osteophytes or calcification outside of these areas was excluded. Cumulative scores were recorded for the ALL, PLL, and LF. Additionally, a TCS was generated as the aggregate sum of each of the three locations. Both intra-observer and interobserver data were collected and analyzed for 30 random subjects.

Results

Descriptive

There were 214 patients in our study population, 175 men and 39 women. By sex, there were no statistical differences in age, TAV derived BMI, hypertension, or diabetes. Men had more calcification than women at the ALL (5.01 vs. 2.49, $p < .0206$) and aggregately (TCS 15.29 vs. 11.85, $p < .0165$). There was no significant difference in PLL or LF calcification between genders. The lowest inter- intraobserver correlation coefficient was 0.83 (Table 1).

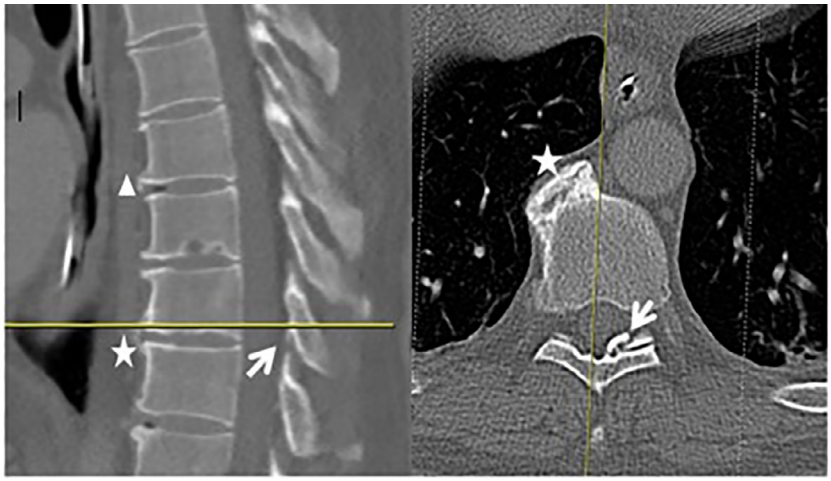


Fig. 3. Example of calcinosis scoring. Female subject with partial (triangle, score = 1) and bridging (star, score = 2) calcifications of ALL. Nonbridging calcinosis of LF (arrow, score = 1).

Table 1
Patient demographics

Characteristic	Frequency	Percentage (%)
Male	175	18.22
Female	39	81.78
Type 2 diabetes mellitus	20	9.35
Hypertension	41	19.16

Patients were divided into two age groups, ≤40 and >40. For patients 40 or less, men had significantly more calcinosis than women at the LF (9.97 vs. 7.94, $p < .0234$) and overall (TCS 13.23 vs. 9.44, $p < .0038$). This was not true at the ALL or PLL. No significant difference between men and women over 40 was seen in calcification. Calcification of the ALL and LF was found more often in the thoracic spine. Ossification occurred too infrequently to be meaningfully analyzed compared to spinal level.

Within the female population, those older than 40 had greater calcification of the LF (7.94 vs. 10, $p < .0386$) and in total (TCS 9.44 vs. 13.9, $p < .0056$) than the younger group. There was no significant difference at the ALL or PLL. Men over 40 had significantly more calcinosis than men <40 at the ALL ($p < .0001$), PLL ($p < .0012$), and in total ($p < .0056$). There was no significant increase in calcification of the LF with age (9.97 vs. 9.45, $p < .2665$).

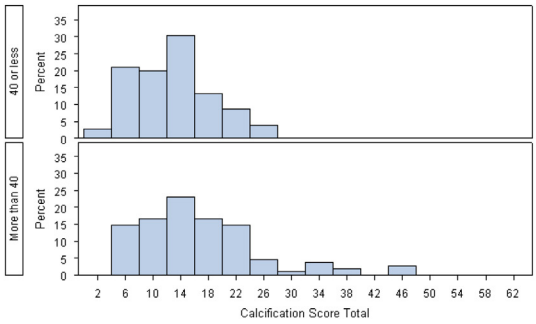
Correlation with obesity analysis

In relation to VAF, there was a significant positive correlation with calcification at all areas of interest and TCS: ALL (group $r = 0.58767$, $p < .0001$), PLL (group $r = 0.31012$, $p < .0001$), LF (group $r = 0.36414$, $p < .0001$), and TCS (group $r = 0.63398$, $p < .0001$).

The pattern of correlation was similar for SAF at the ALL (group $r = 0.19288$, $p = .0046$) and TCS (group $r = 0.30391$, $p < .0001$). No significant correlation was seen in PLL (group $r = 0.00663$, $p = .9232$), or at the LF in women (group $r = 0.36019$, $p < .0001$; men $r = 0.40432$, $p < .0001$; women $r = 0.29999$, $p = .0635$).

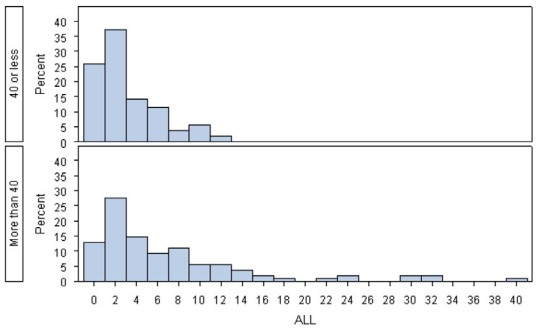
Significant positive correlation of VAF/SAF and calcification was found with male patients at the ALL ($r = 0.46638$, $p < .0001$), PLL ($r = 0.354$, $p < .0001$), and TCS ($r = 0.39072$, $p < .0001$). The VAF/SAF ratio was not associated

Table 2
Association between age and TCS (total calcification score) frequency



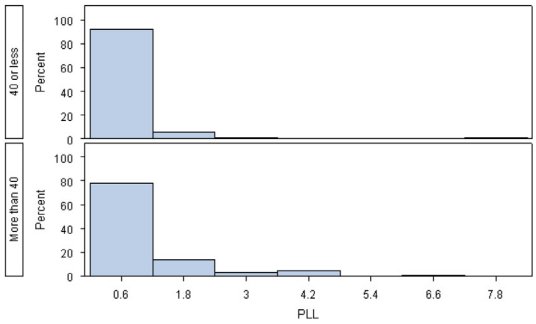
TCS	95 percentile
Entire group	31
<=40 yrs	23
>40 yrs	38

Table 3
Association between age and ALL (anterior longitudinal ligament) calcification score frequency



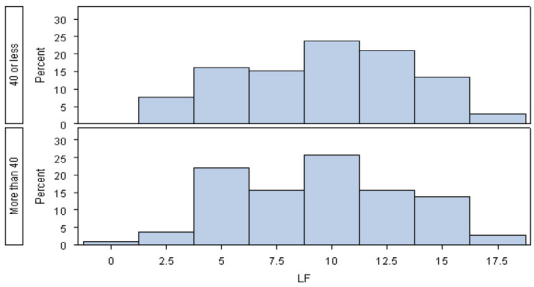
ALL	95 percentile
Entire group	15
<=40 yrs	9
>40 yrs	24

Table 4
Association between age and PLL (posterior longitudinal ligament) calcification score frequency



PLL	95 percentile
Entire group	3
<=40 yrs	2
>40 yrs	4

Table 5
Association between age and LF (ligamentum flavum) calcification score frequency



LF	95 percentile
Entire group	16
<=40 yrs	15
>40 yrs	16

with calcification in the female population. Calcification of the LF was not correlated with VAF/SAF in males (r = −0.00562, p = .9412) or females (r = 0.10136, p = .5392) (Tables 2–5).

Logistic regression analysis

In descending order of odds ratio (OR), male gender (OR 12.181, p < .0098), Hypertension (HTN) (OR 2.97, p = .0214), TBMI (OR 1.263, p < .0005), and increasing age (OR 1.187, p < .0001) were all significant factors to associate with developing calcification of the ALL in the 95th or above percentile (score >9). Age (OR 1.088 p < .012) and hypertension (OR 3.885, p < .0013) were factors associated with odds of having significant calcification of the PLL (score>2). Gender, obesity, and (diabetes mellitus 2)DM2 were not found to be significant at the PLL. Only TBMI (OR 1.274, p < .0002) had a significant positive

association with the odds of having significant calcifications (score>15) in the LF. Age (OR 1.12, $p < .0071$) and TBMI (OR 1.258, $p < .0003$) were positively associated with the odds of having significant total calcification (TCS>23). Sex, Type 2 DM and, HTN lacked significant association in TCS.

Discussion

Recently, the role of adipokines and adipose derived hormones in a variety of inflammatory mediated conditions such as those associated with metabolic syndrome (insulin resistance, dyslipidemia, increased risk of cancer, type 2 DM, cardiovascular disease, and autoimmune disorders) [14,23–27]. Multiple studies have also suggested that the metabolic activity of visceral fat is significantly different than subcutaneous fat [28–31]. Research in this area is complicated by the fact that crude but common measurements of obesity like body mass index (BMI) may have limited ability to define relationships between excess adiposity, particularly visceral adiposity, and musculoskeletal disorders when the association is mediated through a metabolic mechanism as opposed to a biomechanical one [32,33]. A limitation of our study was that we could not correlate TBMI to conventional BMI measurement. BMI requires accurate measurements of height and weight, which is difficult to obtain in the setting of polytrauma, particularly during initial presentation due to injury severity and limited mobility. If these measurements are obtained later, fluid resuscitation during hospital stay precludes accurate measurement of a patient's usual weight. Our group previously validated the methodology used in the current study. In the previous study, the correlation coefficient between truncal adiposity on CT scan and BMI was 0.77 [21,49].

CT scans can be utilized to differentiate between visceral and subcutaneous fat through volumetric analysis. Our results showed a stronger correlation between calcification and VAF than SAF in both men and women. This confirmed our expectation of relatively heightened pathology with excess VAF. A correlation with the VAF/SAF ratio, theoretically, would have further illustrated the effects of "bad fat,"[34] and correlated strongly with calcification of all spinal ligaments. Interestingly, significant correlation was only determined in men at the ALL, PLL, and TCS. In women there were no significant correlations of spinal calcification and the VAF/SAF ratio. These findings may reflect a lack of power in our study (39 female subjects) or highlight the morphologic differences in fat distribution between sexes [35,36]. Additionally, no significant correlation was determined between VAF/SAF and LF calcification.

This study demonstrates an association between spinal ligament calcification and obesity as defined by TBMI. The independent association of obesity and LF calcification implies that obesity has a separate effect from other associated factors such as age and male sex. Thus, normal age-related degenerative changes may not be as important in the calcification of ligamentum flavum as are other factors related to obesity. While VAF was found to be correlated to LF calcifications in the spine, we cannot predict rate of change in LF calcification with respect to duration of obesity due to truncal CT scans were obtained for polytrauma patients at only a single point in time in our study. It would be difficult to measure rate of change of LF calcifications with TBMI because this would require serial CTs, which would lead to increased exposure to radiation; however, this would be a valuable topic for future study.

A possible contributor to the pathogenesis of the spinal calcifications seen in this study may be the chronic inflammatory state of obesity [37–40]. Signaling by inflammatory mediators (IL-6, TNF alpha, TGF-beta, VEGF) has been demonstrated in association with hypertrophy and ossification of LF previously [15,18,41,42]. In addition to the proinflammatory role obesity may play, recent studies suggest that, "the central perception of energy status, and with it body weight, may have an important impact on peripheral activity of osteoblasts and osteocytes through" centrally mediated processes [19]. Adipokines like leptin can have cytokine and hormonal properties that include both central and peripheral roles in bone metabolism, cartilage homeostasis and immune modulation [23,26,43–45]. Leptin is a proinflammatory cytokine that stimulates chondrocytes to secrete higher levels of chondrocyte degradation mediators, which can induce cytoskeletal reorganization. In addition, leptin stimulates proliferation of intervertebral disc cells, and it decrease apoptosis rate of nucleus cells, an important process in intervertebral tissue homeostasis. Leptin levels have been shown to be increased in the posterior annulus and the ligamentum flavum in the degenerated intervertebral disks [46]. Sun et al. found that leptin promotes inflammatory response by increasing IL-6 which elevates collagen expression in ligamentum flavum cells, resulting in ligamentum flavum hypertrophy and fibrosis. Leptin levels and IL-6 expression has been shown to be significantly increased ligamentum flavum tissue, which could explain why ligamentum flavum calcification was affected more by obesity than ALL and PLL [46]. This paper proposed leptin expression in ligamentum flavum and adjacent epidural fat promotes ligamentum flavum fibrosis. In contrast, adiponectin is an anti-inflammatory adipokine that has been shown to downregulate TNF alpha production by degenerated nucleus cells. Levels of adiponectin in degenerated intervertebral disks have shown to be decreased [47]. Similar to leptin, central control of fat in bone regulation has shown calorie dependent responses in central Neuropeptide Y. During high calorie states NPY precipitously decreases, which enhances osteoblast activity.

Diet in obese patients could also be an important factor in vertebral calcifications. Svenja et al. found that chronic exposure to dietary advanced glycation end products in mice was correlated with ectopic calcification of vertebral

end plates and accelerated intervertebral disk degeneration. Calcified end plates of these mice were shown to have decreased cell density and fewer chondrocytes compared to mice with low advanced glycation end products diet, contributing to disrupted bone mineral homeostasis. In addition, pathological calcification in the nucleus pulposus was associated with decreased glycosaminoglycans, representing loss of extracellular matrix [48].

A weakness of our study is the male predominance. The reliance on documentation generated during trauma scenarios for pre-existing medical conditions suggests that conclusions about HTN and DM should be interpreted with caution. Race was not analyzed secondary to difficulty in confirming this in the trauma situation. Another potential weakness was the inability to control for any increased biomechanical forces on the spine associated with obesity. In an elegant study, Nakatani et al. proved that LF cells produce collagen when mechanically stressed, a likely contributor of the pathogenesis of LF hypertrophy [15,41]. It is possible that increased tensile forces in the potentially seen in heavier individuals may play a role in LF thickening or calcification.

Ligamentous calcifications have the potential to lead to early development of spinal stenosis and premature stiffening of the spine. The growing recognition of the tremendous economic impact of obesity on musculoskeletal disease underscores the need for further investigation into hormonal and biomechanical factors that are likely involved in this process. The results of the current study support the evolving evidence that adipose tissue is intimately involved in the control of bone metabolism in general and hyperostotic conditions of the spine in particular.

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