University of Alberta

THE ROLES OF VERTEBRA AND VERTEBRAL ENDPLATE IN LUMBAR DISC DEGENERATION

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ABSTRACT

Background

The adjacent vertebrae and endplates are important to maintaining the integrity and functions of the intervertebral disc. Yet, they have received relatively little attention and their roles in disc degeneration (DD) and back pain remain unclear.

Purpose

The purpose of this doctoral research was to describe the morphometrics of the lumbar vertebral endplate, characterise endplate lesions, and explore the roles of morphological and pathological findings of the adjacent vertebrae and vertebral endplates in the pathogenesis of DD.

Materials and Methods

Studies were extended from a cadaveric lumbar spine archive of 157 Caucasian men (mean age 51.2 years). Using discography, DD was rated as absent, slight, moderate or severe. A sample of 150 vertebrae was scanned with micro-CT to explore the relationship between vertebral bone mineral density (BMD) and DD, BMD and thickness of the vertebral endplate and DD. Using a laser digitizer, morphological measurements of 591 vertebral endplates were quantified to determine their associations with DD. In addition, a total of 1148 vertebral endplates were visually examined to determine the prevalence rate, pathological classification, and distribution patterns of lumbar endplate lesions, as well as their associations with age, DD and back pain history.

Results and Conclusions

Higher BMD of the vertebral body, but not that of the whole vertebra, was associated with more severe adjacent DD. Among the endplate morphological measurements measured, including size, thickness, circularity, concavity and BMD, only greater endplate thickness and size were found to associate with more DD. Yet, the associations observed were relatively weak, suggesting a modest role of endplate morphometrics in DD. In contrast, endplate lesions were common findings in the lumbar spine of mid-aged men and were strongly associated with DD. Furthermore, four types of endplate lesions were identified, including Schmorl's nodes, fracture, erosion and calcification. These lesions had distinct morphological features, different distribution patterns and varying degrees of association with adjacent DD. Lumbar endplate lesions tended to affect both adjacent endplates of a disc together and appear to play an important role in DD. Findings also suggest endplate lesions may be a source of back pain.

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CHAPTER 1

Introduction

1.1. Background

Low back pain is one of the most prevalent disorders in human beings. Over 2/3 of adults suffer from it at some time in their life[1] and it is one of the most common reasons for visits to a physician in North America.[2,3] The cost for back pain related health care, disability and work loss, workers' compensation and other social consequences, is enormous. Yet, the understanding of this common symptom continues to pose a challenge. Even with the best diagnostic techniques currently available, only approximately 15% of patients with back pain can be given a precise pathoanatomical diagnosis.[4]

It is the back pain puzzle that led to the focus on the intervertebral disc in spine research. As early as the 1930's, it was realized that a diseased disc might cause back pain symptom.[5,6] Disc degeneration (DD), a common finding of the intervertebral disc which could either be a sign of physiological aging or a pathological manifestation, has long been suspected as a main cause of back pain. Yet, the casual association between DD and back pain is generally weak and remains controversial today.[7-10]

Great efforts have been made to better understand DD and its clinical relevance in the past three decades. The etiology and pathogenesis of DD have been intensively studied with techniques and approaches from a variety of disciplines, such as biomechanics, molecular biology, epidemiology and genetics,[11-14] substantially advancing the knowledge of DD. Among these advancements, the most profound perhaps is the shift in the concept of DD as a result of aging and mechanical "wear and tear" to a condition that

is mainly genetically determined.[15] Yet, a lot remains unexplained about the pathomechanisms of DD.[16]

A growing number of individual genes have been identified to associate with DD, supporting the paradigm that heredity dominates the pathogenesis of DD.[17] Yet, within the chain from associated etiologic factors (including age, genes and other determinants) to the final outcome of DD there is a series of complex pathological cascades which are far from explicit. Such pathological processes may be further complicated by modifications and interactions between different etiological factors. In other words, hereditary factors could affect the disc through a combination of multiple mechanisms. For example, genetic factors could determine the size and shape of spinal structures,[18] which influence mechanical properties of the spine and thus its vulnerability of mechanical forces and nutrient insufficiency, and finally result in an overall susceptibility to DD. The vertebra, particularly its endplate, is among the structures of such considerations.

The vertebrae anchor and support the intervertebral discs, supply metabolic substances to the discs, and interact directly with the discs.[19] Given the multiple physiological functions of vertebra to the disc, it is possible that the vertebra and endplate are important mediators through which etiological determinants cause DD. The vertebra and disc have long been studied together as a vertebra-disc complex or a segmental function unit in biomechanics.[20] Surprisingly, the vertebra and vertebral endplate have not yet been substantially taken into account in the pathogenesis of DD. To date, scientific literature on the direct interactions between the vertebra, vertebral endplate and disc is sparse. The morphometrics of the vertebral endplate, such as thickness, circularity,

area, concavity and bone mineral density (BMD), have yet to be systematically investigated, nor have their associations with adjacent DD. As both the cartilaginous endplate and osseous endplate are thin,[21,22] measuring the endplate is challenging, particularly in vivo.

Another under-studied area is pathology of the endplate. Despite Schmorl's nodes as the most common endplate pathology were reported even before the modern medicine started,[23] the current understanding of Schmorl's nodes is limited and somewhat conflicting. The reported prevalence of Schmorl's nodes ranges widely. Their origin, such as congenital or traumatic, remains controversial. So do their associations with age, DD and back pain. More importantly, in addition to Schmorl's nodes, there are other lesions affecting the endplate. Yet, knowledge of different types of endplate pathologies is currently lacking. Their pathological characteristics, distribution patterns as well as influence on the adjacent disc remain largely unknown.

Different from traditional approaches in DD research, this thesis attempts to expand the understanding of DD by studying the adjacent bony vertebra and vertebral endplate from both physiological and pathological perspectives. In chapter 6, the association between endplate lesions and back pain history will also be briefly discussed. All studies were approved by the Health Research Ethics Board at the University of Alberta.

1.2. Objectives

Based on a cadaver spine archive, the overall purpose of this doctoral thesis is mainly to determine the morphometrics and pathologies of the vertebral endplate and explore the roles of the vertebra and its endplate in the pathogenesis of DD. Using micro-CT (μCT), laser scanner and visual assessments, a series of studies were conducted to characterize

endplate morphometrics, classify endplate lesions and determine their relationships with DD and back pain. Specifically, the objectives of this doctoral research include:

1) To examine the association between vertebral BMD and DD, with and without posterior elements, osteophytes and endplate sclerosis in the vertebral BMD measurements;
2) To determine the thickness and BMD of the lumbar vertebral endplates in men and explore their associations with age and adjacent DD;
3) To characterize the endplate morphometrics and investigate endplate lesions in relation to DD;
4) To determine the prevalence of endplate lesions in the lumbosacral spine, classify endplate lesions and depict their pathological characteristics, and to further clarify their associations with age;
5) To examine the associations of various types of endplate lesions with DD, occupational history and back pain history.

1.3. An introduction to relevant lumbar spine anatomy

The lumbar spine is comprised of five lumbar vertebrae, five intervertebral discs and other associated soft tissues. The lumbar ***vertebrae*** are separated by ***intervertebral discs*** anteriorly and they articulate posteriorly through ***facet joints***, both of which facilitate and control the flexibility of the lumbar spine. Two adjacent vertebrae and the intervertebral disc between constitute a functional spinal unit or spinal motion segment.[20,24]

1.3.1 Vertebra

A lumbar vertebra consists of a vertebral body, a vertebral arch and seven processes (**Figure 1-1**).[25] The ***vertebral body*** is the anterior, more massive part of the bone. The

vertebral body mainly consists of trabecular bone, which is enclosed by a thin external layer of cortical bone. The superior and inferior surfaces of the vertebral body are the vertebral endplates, and will be specifically introduced later. The vertebral components behind the vertebral body together are called ***posterior elements***, which are largely cortical bone.[26]

1.3.2. Intervertebral disc

The lumbar vertebrae are connected by intervertebral discs and ligaments. The discs provide strong attachments between two adjacent vertebral bodies, uniting them into a continuous semi-rigid column (**Figure 1-2A**).[25] Each intervertebral disc consists of an ***annulus fibrosus***, an outer fibrous part, and a highly gelatinous hydrated central mass, called the ***nucleus pulposus***. The annulus fibrosus is a fibrous ring consisting of concentric lamellae of fibrocartilage (**Figure 1-2B**). Its annuli insert into the smooth, solid epiphysial rims and form the circumference of the disc. The nucleus pulposus is the inner core of the disc. At birth these pulpy nuclei are about 88% water and are initially more cartilaginous than fibrous.[25] Their semi-fluid nature is responsible for much of the flexibility and resilience of the intervertebral disc. In a degenerated disc, the amount of water and nucleus matrix decrease, and thus the elasticity of the disc.[11]

The intervertebral disc is the largest avascular organ in the human body. It depends, to a large extent, on diffusion of nutrients through the cartilaginous endplate **(Figure 1-3)**.[14,21] Another route for intradiscal nutrition is the outer 1/3 of the annulus fibrosus, which contains clearly defined blood vessels. The vascular channels in the endplate are particularly important for the nutrition of the nucleus pulposus because of the relative distance of the nucleus from the annular blood supply.[14,27]

1.3.3. Endplate

At the cranial and caudal ends of each disc are the endplates. Thus, the endplate is an interface tissue between the vertebral body and the intervertebral disc (**Figure 1-2 A & B**). It is necessary to emphasize that the endplate comprises two components: the ***cartilaginous endplate*** and ***osseous endplate***.[28] In some studies the endplate is considered to be the endplate cartilage while in others the endplate is specifically referred to the osseous endplate.

The ***cartilaginous endplate*** consists of a thin layer of hyaline cartilage between the disc and the vertebral bodies. Its average thickness is 0.6 mm and it is generally thinnest in the region of the nucleus.[21] The cartilaginous endplate is comprised of a gel of hydrated proteoglycan molecules reinforced by a network of collagen fibrils. A network of microscopic blood vessels penetrates the endplates during development of the spine, principally to provide nutrition for the disc, before disappearing around the time of skeletal maturity.[28] During aging, the cartilaginous endplate undergoes progressive mineralization and eventually could be resorbed and completely replaced by bone tissue.[29,30]

The ***osseous endplate*** virtually is the cranial or caudal shell of the vertebral body, thus, is also called the ***vertebral endplate***. A vertebral endplate consists of two components: the ***epiphysial rim***[25] *(or* ***epiphysial ring***[31]) and the ***central endplate*** (**Figure 1-4**). The epiphysial rim is a ring of raised smooth bone at the peripheral margin of the endplate. Derived from an annular epiphysis, the epiphysial rim is the place where the annulus fibrosis anchors. Surrounded by the epiphysial rim, the remaining central portion of the endplate is called central endplate, which is a layer of spongy bone. Derived from

the primary vertebral body ossification center, the central endplate in a fresh sample is covered by the cartilaginous endplate, which is in direct contact with the nucleus pulposus. The center of the endplate, or ***endplate center***, is the place where the notochord regresses and, thus, is a developmental weak spot of the endplate.[23] Between the endplate center and the epiphysial rim is an oval region rich with marrow contact channels or blood vessel openings,[32,33] through which capillary buds emerge. These capillary buds connect the trabecular spaces to the cartilaginous endplate and are the most important nutrition resource for the avascular discs. In aging, calcification plaques accumulate on the surface of the osseous endplate (**Figure 1-4**). The epiphysial rim is relatively solid, strong and impermeable compared to the thin and porous central endplate and it is well established that the central endplate is more important than the epiphysial rim in terms of nutrient supply.[14,32]

The endplate is essential to maintain the integrity and physiological function of the intervertebral disc. First of all, the endplates as a physical shield separate discs from the vertebral bone and prevent the highly hydrated nucleus from bulging or penetrating into the adjacent vertebral bodies.[34] Second, the endplate, particularly the cartilaginous endplate, is a mechanical interface between stiff bone and resilient disc. It not only absorbs the considerable hydrostatic pressure that results from mechanical loading of the spine,[35] but also together with the disc helps to distribute the compressive load evenly across the vertebral body.[36,37] Most importantly, the endplate is the gateway of nutrient transport between the vertebral marrow and intervertebral disc. While diffusion through the annulus supplies nutrients for the outer portion of the annulus,[38] diffusion through the

marrow contact channels in the vertebral endplate is the main nutrition pathway for the avascular intervertebral disc in adults.[14,32,33]

1.3.4. The innervation of the vertebra-disc complex

Similar to its blood supply, the healthy adult disc is an organ with poor nerve distribution. Typically, only the outer layers of the annulus fibrosus are innerved sporadically to a depth of a few millimeters.[39-41] The nerve fibres can either be perivascular or run independently. Other components of the intervertebral disc, such as the inner portion of the annulus fibrosus, the nucleus pulposus, as well as the cartilaginous endplate usually are avascular and aneural in a healthy adult disc. Under certain circumstances, especially severe DD,[42] there can be ingrowth of nerve fibres in the inner portion of the annulus fibrosus, or even in the nucleus pulposus.[43]

As in other long bones, the periosteum around the vertebral body is rich in innervation. Nerves enter the vertebral body via the posterior vascular foramen (accompanying the basivertebral vessels),[44] and by penetrating the anterior cortex into the vertebral marrow.[40,44] Accompanying the vertebral vascular distribution, branches from these nerves extend from central to peripheral regions of the vertebral body, including the vertebral endplates. Recent quantitative analysis identified that the central endplate, which is adjacent to the nucleus pulposus, is the region where nerve endings concentrate.[40] In a degenerative disc, an increase in number and density of sensory nerves in the vertebral endplate region has also been observed.[45]

In brief, the nerve supply for a healthy disc is meager as only the outmost layer of the annulus fibrosus has nerve endings distribution. Although not part of the disc, the central vertebral endplate, which is immediately adjacent to the disc, is relatively well-

innervated. Therefore, the annulus and endplate may be two locations where disc-related back pain is generated, if the adjacent sufficiently innervated vertebral periosteum[44] and periannular connective tissues[40] have not been involved yet.

1.4. The Cadaveric Spine Archive

This thesis is based on a precious cadaveric spine archive which consists of 157 cadaveric spines of Caucasian men.[46] This archive was collected by Dr. Tapio Videman in Helsinki, during the 1980's. The inclusion criteria for subjects were men below the age of 64 years, who had been employed immediately before the illness for which they were hospitalized, and who died in the hospital following a short history of illness. Most of the subjects died from cardiovascular complications. Exclusion criteria were chronic illness and death from cancer or infectious diseases. The mean age of the subjects in the archive is 51.2 years, ranging from 21 to 64 years.

Age, weight, height and body mass index (BMI, kg/m^2) were obtained at the time of death. For each lumbar spine, routine autopsy examination, radiography and then discography were performed sequentially. After discography the soft tissues around the vertebra, including the discs and endplate cartilage, were removed. Vertebrae were dried and then archived under room temperature and humidity, together with radiography and discography films. To acquire other needed medical history information, such as history of back pain, back injury and occupation, a telephone interview of the subject's immediate family member (usually the spouse) was conducted, using a structured questionnaire. These data were obtained for 86 subjects (55%).

Some of the vertebrae were lost in the long-time preservation and some were made into histological slices for other research projects. The available vertebrae and

discography data for the lumbosacral spine (L1-S1) were used to test corresponding hypotheses, as will be further mentioned in individual chapters.

1.5. Measurement of disc degeneration: discography

We used discography to rank the general degeneration condition of the lumbar intervertebral discs. The cadaveric spines allowed the use of Barium Sulfate (BaSO4) to improve the enhancement of discogram.

Discography was performed after a routine autopsy examination of the lumbar spines. Using a 20-gauge needle and maximal finger pressure, 2-5ml BaSO4 was injected anteriorly into the center of the intervertebral disc. Usually all the five lumbar intervertebral discs, from L1/2 to L5/S1, were examined for each lumbar spine. Anterior-posterior and lateral X-ray radiographs were taken after the injection of contrast.

According to the spread or distribution of the BaSO4 in the discogram, a 4-grade ordinal scale was used to rate the degree of DD pathology. DD was given a rating of **none** if the dye remained in the center of the disc; **slight** if the dye spread into the inner annulus; **moderate** if the dye spread from the inner to the middle region of the annulus; and **severe** if the dye spread to the outer part of the annulus (**Figure 1-5**). Intra-observer agreement for measurements using this scale yielded a weighted kappa of 0.81.[46]

The first discography using barium sulfate (BaSO4) was performed in cadaveric spine by Schmorl in the 1920s to demonstrate various types of annular tears.[23] Discography was first used in clinical patients by Lindblom in 1948.[47] Discography is a validated disc-specific measure designed to assess the integrity of the inner annulus fibrosus.[48] The distribution patterns of injected dye seen on discogram reflect different stages of morphologic changes of DD.[49] Before magnetic resonance (MR) imaging was generally

used in clinical practice, traditionally discography was considered as the best approach to evaluate DD. MR imaging of the disc depends on the changes of water content,[50] which probably is the first step in the process of DD. Therefore, MRI is able to detect DD in very early stages, even before morphological degenerative changes appear. However, MR cannot differentiate successive morphological changes inside the disc,[51] as with discography.[49] Although discography may not be able to detect all annular lesions (e.g. those that do not connect to the nucleus cavity), it was reported to be more sensitive in detecting annular tears than using MRI.[52] Yet, due to the invasive nature and the possibility of accelerating the progression of DD,[53] the application of discography in clinical practice is decreasing and may even fade out in spine practice.

The following chapters present a series of five studies using the archived data from the cadaveric spine archive and additional recent measurements to address my doctoral research objectives.

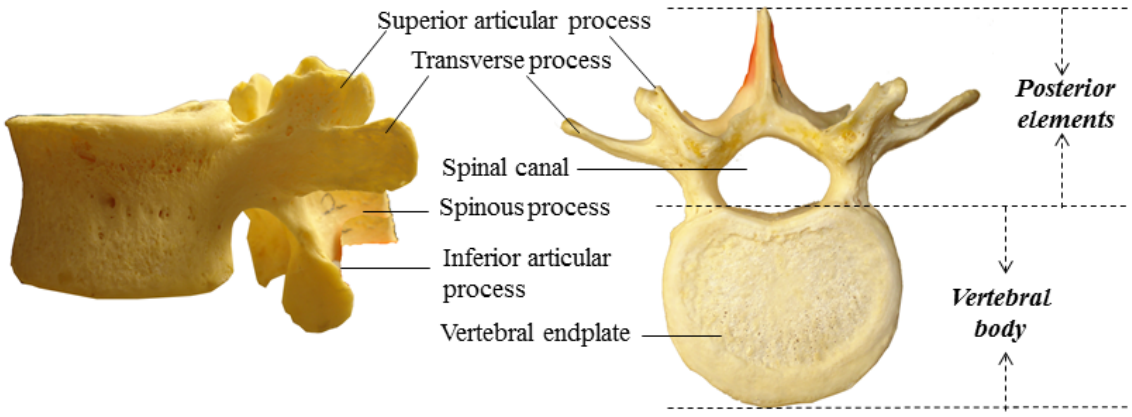


Figure 1-1: Lumbar vertebra and its components

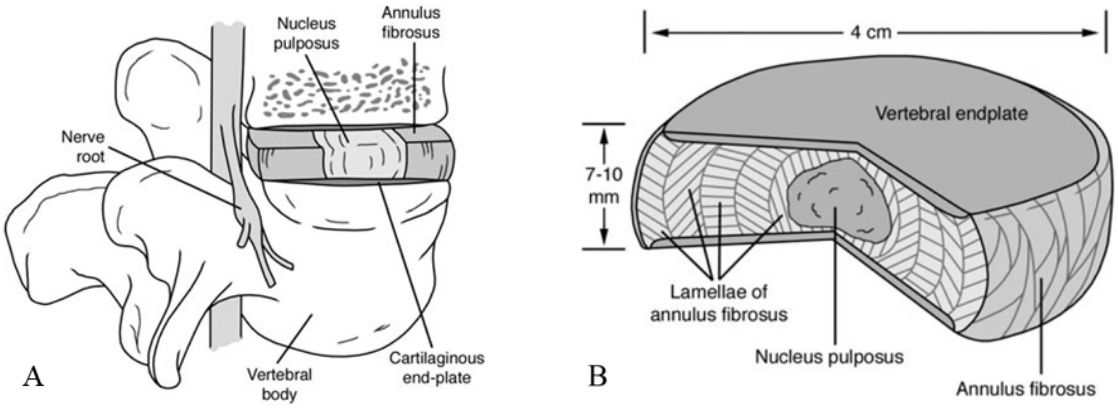


Figure 1-2: Vertebral body and intervertebral disc. Reprinted from Raj PP et al,[54] with permission from John Wiley and Sons.

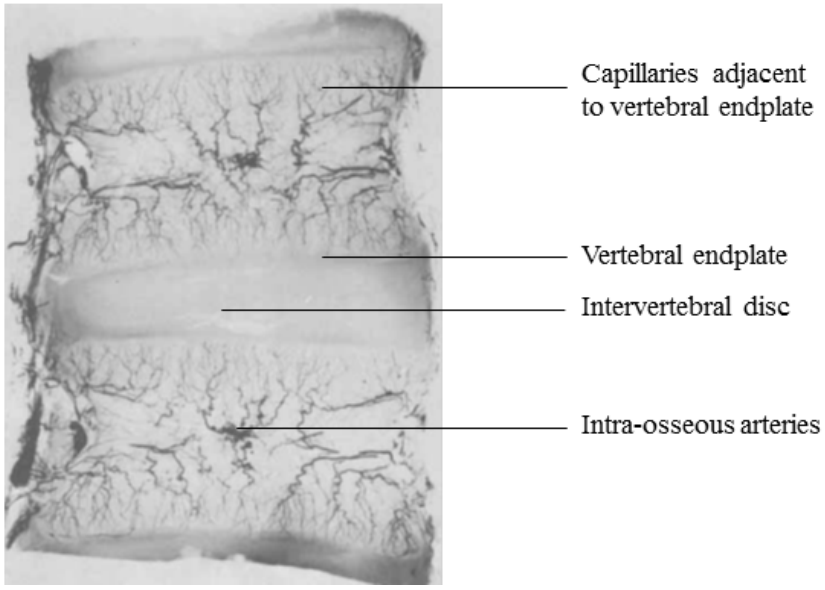


Figure 1-3: The arterial distribution pattern within the vertebral body. In adults, the capillary buds terminated in the vertebral endplate. The nutrient supply for the avascular intervertebral disc largely relies on the diffusion from vertebral body through the endplate. Adapted from Crock et al.[55]

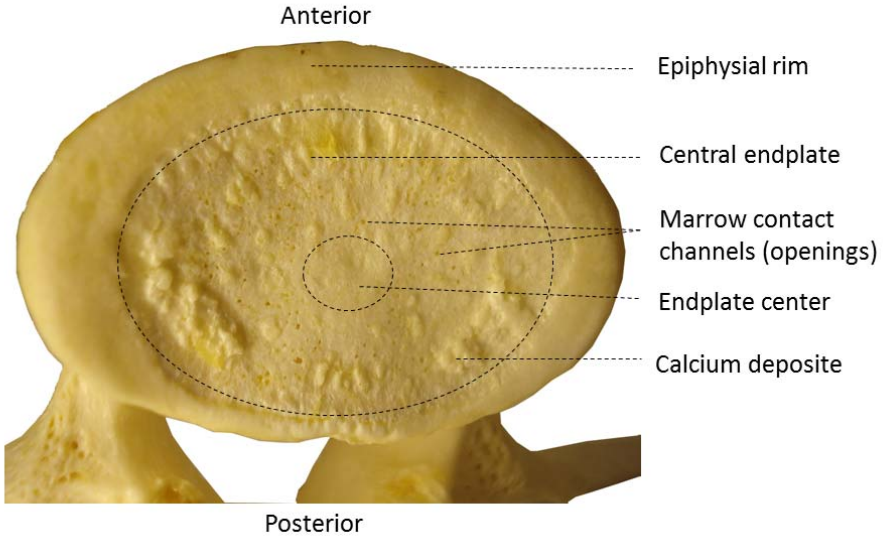
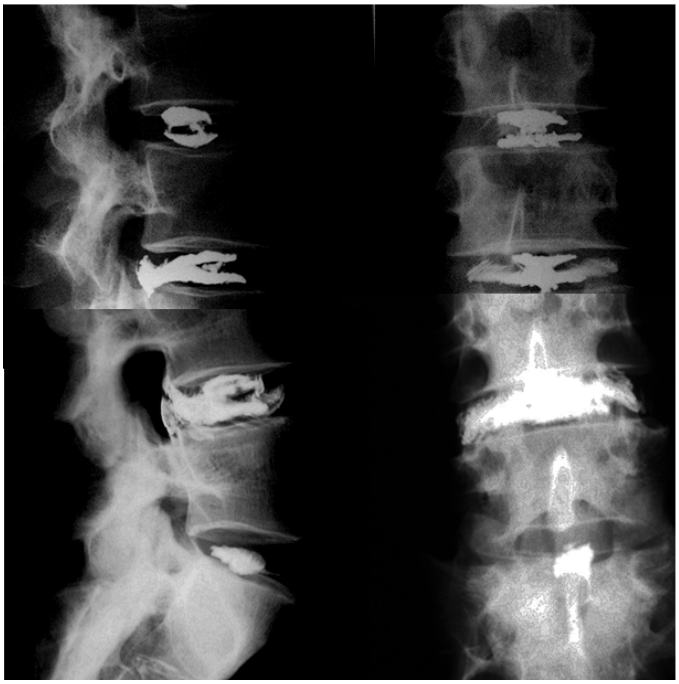


Figure 1-4: The osseous endplate and its components



From the top down, disc degeneration pathology was evaluated as:

"Slight", dye spread into the inner anulus;

"Moderate", dye spread to the middle region of anulus;

"Severe", dye spread to the outer layer of anulus;

"None", the dye remain in the center of the disc.

Figure 1-5: Disc degeneration evaluation in discography. Adapted from Videman T et al[56], reprint permitted.

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CHAPTER 2

Greater Bone Mineral Density of Lumbar Vertebral Body Is Associated with More Severe Disc Degeneration*[1]

2.1. Introduction

It has been well documented that there is an inverse relationship between osteoarthritis and osteoporosis in peripheral extremities.[1-5] In other words, good bones are associated with bad joints. When this concept was introduced to the lumbar spine and the relationship between vertebral BMD and intervertebral disc degeneration (DD) was examined, however, findings were inconsistent and remain controversial. Although most of the studies reported greater vertebral BMD associated with more DD,[6-10] some studies failed to find such an association,[11,12] and others found that more DD was associated with greater spine BMD but not with greater hip BMD.[13,14]

The problems underlying the inconsistent findings may lie in the limitations of the BMD and DD measures used. In previous studies, the BMD measurement was obtained using dual-energy X-ray absorptiometry (DXA), which only provides an areal BMD (aBMD, g/cm^2) instead of a true volumetric BMD (g/cm^3). Moreover, in measuring vertebral BMD the main concern is the trabecula-rich vertebral body. Yet, as a two dimensional technique, DXA is unable to distinguish the vertebral body from other vertebral components. Many vertebral degenerative changes, such as facet joint proliferation,[15,16] osteophyte formation[9,17-19] and endplate sclerosis,[13,14,18] have been reported to falsely inflate DXA aBMD measurements and thus, could possibly confound the association between vertebral BMD and DD. On the other hand, measurements of DD

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using radiographic disc height[9,14] or disc bulging acquired from magnetic resonance images[7] have limitations, as well. These visual evaluations of DD are also prone to bias by hypertrophic bony degenerative features, such as osteophytes and endplate sclerosis,[20] resulting in an erroneous association between vertebral BMD and DD. In addition, previous study results were based on measurements of BMD and DD for the entire lumbar spine. Little attention has been given to the association between vertebral BMD and adjacent DD at a spinal segment.

As osteoporotic vertebral fracture and lumbar DD are common conditions in the spines of older adults, clarifying the relation between the vertebral BMD and DD will contribute to a better understanding of the local interaction between bone and disc and corresponding pathologies in the lumbar spine. In order to clarify if there is a true association between vertebral BMD and DD, we used micro-CT (μCT) to measure the volumetric BMD for each vertebra with and without posterior elements, osteophytes, and endplates, and used discography to assess DD in cadaveric lumbar spines. We hypothesized that the apparent association between vertebral BMD and DD is an artifact from the posterior elements, osteophytes and sclerotic endplates. After controlling these confounders by excluding them from the vertebral BMD measurements and using an intrinsic DD measure that is not influenced by proliferative vertebral changes, this association would be weakened or disappear. In this study, we specify the volumetric BMD measured from μCT as BMD and areal BMD acquired from DXA as aBMD.

2.2. Materials and Methods

Subjects

We had access to a cadaveric spine archive which consists of 157 cadavers of Caucasian men.[21] The inclusion criteria for subjects were men below the age of 64 years, who died in the hospital and the history of illness was short. Most of the subjects died from cardiovascular complications. Exclusion criteria were chronic illness and death from cancer or infectious diseases. Age, weight, height and body mass index (BMI) were obtained from the time of death. For each lumbar spine, routine autopsy examination, radiography and then discography were performed by one of the authors (T.V). After discography, the soft tissues around the vertebra (including the discs) were removed and the vertebrae were dried under a well-ventilated fume hood at room temperature. The dried vertebrae were then archived until later μCT scanning, together with radiography and discography films.

Because some of the vertebrae and archived DD data in the spine archive were missing, only the intact vertebrae with available adjacent DD data were included. In the current study, the sample comprised 137 cadaveric lumbar vertebrae (L2-L5) from 48 male human spines, with a mean age of 50 years (range 21-64). The study was approved by the Health Research Ethics Board of the University of Alberta.

Measurement of Intervertebral Disc Degeneration

DD was evaluated using discography after a routine autopsy examination of the lumbar spines.[21] Using a 20-gauge needle and finger pressure, 2-5ml Barium Sulfate (BaSO4) was injected anteriorly into the center of the intervertebral disc. The five intervertebral discs (L1/2-L5/S1) were examined for each lumbar spine. X-ray radiographs were taken after the injection of contrast. According to the distribution of the BaSO4 in the

discogram, the DD was rated as none, slight, moderate, or severe, as reported previously.[21]

Measurements of Vertebral BMD

All BMD measurements were obtained on a μCT system (XtremeCT, Scanco Medical, Switzerland) using standard scanning parameters (60kVp, 1000μA, 200ms integration time). First, the dried vertebrae were scanned using μCT at a nominal isotropic resolution of 82 μm (field of view 125 mm, 1536×1536 pixels). A total number of 500 to 800 axial images was acquired for each vertebra. Scans were performed in air.

Regions of interest (ROI) were contoured using a semi-automated contouring method. ROI were filtered using a Laplace-Hamming filter and segmented using a global threshold. In order to individually mask the posterior elements, osteophytes and endplates from the BMD measurements, four sets of ROI were contoured such that the vertebral bone mineral content (BMC) and BMD measurements could be determined for each vertebra for each case as follows: 1) the whole vertebra: ROI included all bony tissue; 2) the vertebral body: ROI included the vertebral body, but excluded the posterior elements; 3) the vertebral body without osteophytes: ROI included the vertebral body, but excluded the posterior elements and all osteophytes, if present; 4) the vertebral body without osteophytes and endplates: upon excluding osteophytes, the two endplates were also excluded (**Figure 2-1**). The technique details of extracting the cortical endplates have been reported previously.[22]

Finally, structure analyses were performed (Image Processing Language, v4.29d, Scanco Medical AG, Switzerland) to obtain the volume (cm^3), BMC (mg HA) and BMD (mg HA/cm^3) measurements for the posterior elements, osteophytes (if present),

endplates and the vertebral body without osteophytes and endplates. The reliability, validity and precision of μCT for the measurement of BMC and BMD are well established.[23,24]

In brief, using μCT and 3D reconstruction techniques, each vertebra was radiologically dissected into posterior elements, osteophytes (if present), two endplates and the vertebral body without osteophytes and endplates (**Figure 2-1**), and the volume, BMC and BMD were quantified, respectively.

Statistical Analysis

Pearson correlation coefficient was used to explore the correlations between the different definitions of vertebral BMD. Because a lumbar spine consists of 5 vertebrae and 5 intervertebral discs, BMD and DD data obtained from the same spine are likely to be more similar to each other than to those from other spines. A traditional statistical approach is to examine the association between vertebral BMD and DD by spinal level. Statistically inefficient, the obtained multiple results may be difficult to interpret. Because of the positive correlation between measurements of the same spine, it is not appropriate to pool and analyze the data together without adjustment for the dependency of the data. Another approach is to aggregate the measurements for each spine by summing and averaging the measurements, or to use the maximal measurement. In addition to the reduced statistical power, this approach is problematic when missing data are present. In order to account for the within-spine correlation and analyze data efficiently, a 2-level random effect model[25] was used in the regression analyses. In this model, the vertebra and disc were the first level and the lumbar spine was the second level. We assumed that the effects of independent variables on BMD outcome variables

were common across the 5 segments in the lumbar spine. Because the association of adjacent vertebrae and discs are of particular interest, we matched vertebral BMD to degeneration scores of two adjacent discs in the model. For example, the BMD of the L5 vertebra was matched with degeneration scores from L4/5 and L5/S1 intervertebral discs. Age, BMI and lumbar level were controlled as potential confounders in assessing the BMD-DD relationship. Statistical analyses were performed using STATA (Release 9.2, StataCorp, Texas, USA).

2.3. Results

Disc degeneration and its association with age

Among the 209 intervertebral discs evaluated using discography, DD was absent in 33 (16%) discs, 69 (33%) were rated as having slight DD, 42 (20%) had moderate DD and 65 (31%) had severe DD. Greater age was associated with more DD (Odds ratio=1.08 for each additional year, $p<0.001$).

Different definitions of vertebral BMD and their correlations

The overall mean BMD was 170.1 mg HA/cm^3 for the whole vertebra, 87.8 mg HA/cm^3 for the vertebral body, 82.9 mg HA/cm^3 for the vertebral body without osteophytes and 65.6 mg HA/cm^3 for the vertebral body without osteophytes and endplates. After excluding posterior elements in the BMD measurement, the vertebral body BMD moderately correlated with the whole vertebral BMD (r=0.74, $p<0.001$). This correlation did not change substantially after excluding osteophytes (r=0.79, $p<0.001$) and endplates (r=0.73, $p<0.001$) in the vertebral body BMD measurement. The BMDs of the vertebral body, with or without osteophytes and endplates, strongly correlated with each other (r=0.96~0.98, $p<0.001$).

There were 90 (65.7%) vertebrae with osteophytes around the vertebral body. After controlling for age and BMI, the size (volume) of osteophytes was statistically significantly associated with moderate (p=0.01) and severe DD (p=0.003), but not slight DD. There was no statistical association between endplate BMD and DD, as has been reported previously.[22]

The variance components model

With a 2-level random effect model of whole vertebral BMD without any explanatory variable, it was estimated that 82% of the variance in the BMD measurements was from between spines and the remaining 18% from different spinal levels within the lumbar spine. The percentage of variance explained by inter-spine variation dramatically dropped to 26% after excluding the posterior elements in the BMD measurement, but did not change substantially after excluding the osteophytes (31%) and endplates (28%) from the BMD measurement.

The associations between vertebral BMDs and DD

While the BMDs of the L5 vertebrae were significantly greater than those of other vertebrae, no statistically significant difference in BMDs was found between the L2 through L4 vertebrae. Thus, we grouped the vertebrae into upper (L2-4) and lower (L5) lumbar levels. No statistically significant association was found between whole vertebra BMD and DD at the adjacent discs after controlling for age, BMI and lumbar level. However, when the posterior elements were excluded and the BMD of the vertebral body was measured, there was an association between greater BMD and severe DD in the disc cranial to the vertebra (p=0.008). This association remained after excluding osteophytes (p=0.03), and endplates (p=0.017) from the vertebral body BMD measurements (**Table**

2-1). However, the associations between different vertebral body BMD measurements and DD in the caudal disc were not statistically significant (**Table 2-1**). Age, BMI and lumbar level all explained statistically significant portions of the variance of the BMD measurements.

Trend analyses of BMD and DD

When age, BMI and lumbar level were controlled and the trend between BMDs and DD in the adjacent discs was tested, there was a clear trend of greater vertebral body BMDs associated with more severe DD in the adjacent cranial discs ($p<0.05$, **Figure 2-2**). This trend was present regardless of whether or not osteophytes and endplates were included in the vertebral body BMD measurement, but was not statistically significant in the caudal disc. No trend between the BMD of the whole vertebra and DD was detected.

2.4. Discussion

The availability of a large sample of cadaveric spines on which discography and later μCT could be performed allowed a more detailed examination of the relation between vertebral BMD and DD than had previously been conducted. The results clarified the relation and provide an explanation for the conflicting findings of previous reports. An association between greater vertebral body BMD and more severe degeneration in the adjacent intervertebral disc became clear only after posterior elements were excluded from the BMD measurement. Although masked by posterior elements, the relationship between increased vertebral body BMD and more severe DD was not confounded by either osteophytes or endplates.

The current study findings are concordant with two other studies, both of which used lateral DXA to exclude posterior elements and measure aBMD specifically for the

vertebral body, observing a positive association between higher vertebral body aBMD and more DD.[9,19] Most previous studies, however, measured vertebral aBMD with anterior-posterior DXA and visually evaluated DD with radiography. The posterior elements[26,27] and vertebral degeneration changes, such as osteophytes[9,17-19] and endplate sclerosis,[13,18] may falsely inflate measurements of both DXA BMD and radiologically evaluated DD,[20] introducing errors and bias. We speculated that the previously detected association between higher vertebral BMD and more DD may be attributable, at least in part, to the artificial effects of the vertebral degenerative changes. Contrary to our hypothesis, however, no significant association between the BMD of the whole vertebra and DD was observed. Furthermore, when the posterior elements were excluded and the BMD of the vertebral body was measured, a significant association between higher BMD and more DD was evident, which remained following the exclusion of the osteophytes and vertebral osseous endplates. This indicated that neither osteophytes nor endplate sclerosis was responsible for the association between the vertebral body BMD and DD.

The finding of an association between greater global BMD of the vertebral body and more adjacent DD echoes previous histological observations that regional vertebral BMD and trabecular morphology are related to DD. An increased proportion of bone volume to total volume (BV/TV)[28,29] and increased trabecular number and thickness[28] were observed in the vertebral body adjacent to degenerated discs. As DD shifts the load from the vertebral body center toward the periphery,[30,31] such regional architecture changes of the trabecular bone were thought to be an adaption to load redistribution.[28,29] Although similar adaption responses are also expected in the endplates adjacent to a degenerated

disc, our previous work suggests that DD is associated with greater thickness but not greater BMD of the adjacent vertebral endplate.[22]

For BMD measurement, μCT has a number of advantages over commonly used DXA. First, the excellent spatial resolution provides a precise and accurate assessment of BMD. Second, μCT is able to quantify bone volume and thus obtain true volumetric BMD of the vertebra, rather than an areal measurement as provided by DXA. A limitation with DXA is that it measures all bone mass in the path of X-ray projection and therefore the areal measurements can be substantially influenced by including untargeted bone.[32] A third advantage, corresponding to the 3D nature of μCT, is that bone components can be measured selectively. As bone loss or gain first occurs at the trabecula-rich skeletal sites with high bone turnover rates, it is the vertebral body, rather than the whole vertebra, that is the main concern in measuring vertebral BMD.[33] Unlike DXA, the ability of μCT to measure the vertebral components separately allows for the control of possible confounding factors, such as osteophytes and endplate sclerosis, and less relevant bony structures, such as the posterior elements.

While there is no universally accepted definition of DD,[34,35] the use of discography has advantages over intervertebral space narrowing and disc bulging, which are nonspecific degenerative findings, insensitive to detect DD in the early stages, and may not always be the result of DD.[20] Moreover, these visual measures may be prone to bias from the presence of proliferative degeneration features of the vertebrae, such as osteophytes. Discography is a validated disc-specific measure designed to assess the integrity of the inner annulus fibrosus[36] and the cadaveric spines allowed the use of BaSO4, a sharp contrast to improve the enhancement of discogram. However, the routine

plain discography used in the present study does not provide an axial view of annulus disruption which may better demonstrate DD pathology. Nevertheless, the use of μCT and discography resulted in an association between vertebral body BMD and DD that was unbiased by degenerative bony changes.

In previous studies, results were based on the maximal measurements of BMD and DD for each spine or summed BMD and DD scores, which ignore the variations of BMD and DD within a spine and, thus, fail to detect the effect of local vertebra-disc interaction, if present. The random effect model we used adjusted the positive correlation of measuring multiple lumbar levels of each spine and allowed us to look at associations between adjacent vertebrae and discs. As a result, we detected a stronger association of DD in the cranial disc than was observed in the caudal disc. Moreover, the association between vertebral BMD and DD appeared to be stronger in the lower lumbar than in the upper lumbar region.

The association between higher vertebral body BMD and more DD may be a collaborative effect of general factors and local interaction. Genetic and environmental factors may affect all vertebrae and discs simultaneously, resulting in a systematic effect in the whole lumbar spine. It is well recognized that genes predominate both bone mass[37,38] and DD.[39] In a recent twin study, the genetic contribution to the association between spine BMD and DD was estimated to be 23%.[10] There is evidence suggesting some common genes, for example polymorphisms of the Vitamin D receptor gene,[40] have double-edged effects that contribute to better BMD in the vertebra,[41,42] but also more degeneration in the intervertebral disc.[43] Anthropometric features such as weight[44] and other undetermined environmental factors may also have opposite effects on vertebrae

and discs.[10] On the other hand, the local interaction between the stiff bone and resilient disc could also play a role in the pathogenesis of DD related to higher vertebral BMD. In the current study, a stronger association was observed at the lower lumbar region. Segment-specific effects, such as more compressive mechanical loading and a different strain distribution model[45] may contribute to this enhanced association of BMD and DD. It has been suggested that stiffened vertebrae could result in increased mechanical stress on the adjacent disc, while an osteoporotic vertebra may cushion or protect the disc from degeneration.[7] Furthermore, the compressive loading pathways through the vertebra-disc complex could be altered by either osteoporotic bone[46] or degenerated discs.[47] Thus, while it is possible that DD is influenced by altered mechanical loading due to BMD changes, it is also possible that the elevated BMD is an adaptation of vertebral bone to the changing mechanical environment related to DD.[12]

There are limitations in our study that need to be noted. First, the subjects are all Caucasian men, which may not fully represent the general population. Also, although no sex difference was previously observed in terms of the association between vertebral BMD and DD,[8,14] the inclusion of female subjects would have enhanced the generalizability of the findings. Second, the age of our subjects was relatively young and a mean age of 50 is probably too young to determine the full extent of the association studied. As both the vertebrae and the discs degenerate in aging, a stronger association between the vertebral BMD and DD would be expected in older adults.

In summary, our study clarified the association between vertebral BMD and DD, and specifically identified that it is higher BMD of the vertebral body, not the entire vertebra, that is associated with more severe adjacent disc degeneration. This association may be

obscured by the posterior elements, which dominate vertebral BMD measurements, but was not distorted by osteophytes and endplate sclerosis in this sample of middle-aged men. An understanding of the association between vertebral BMD and DD may lead to novel insights into the interaction between vertebra and disc, and the etiology of lumbar DD.

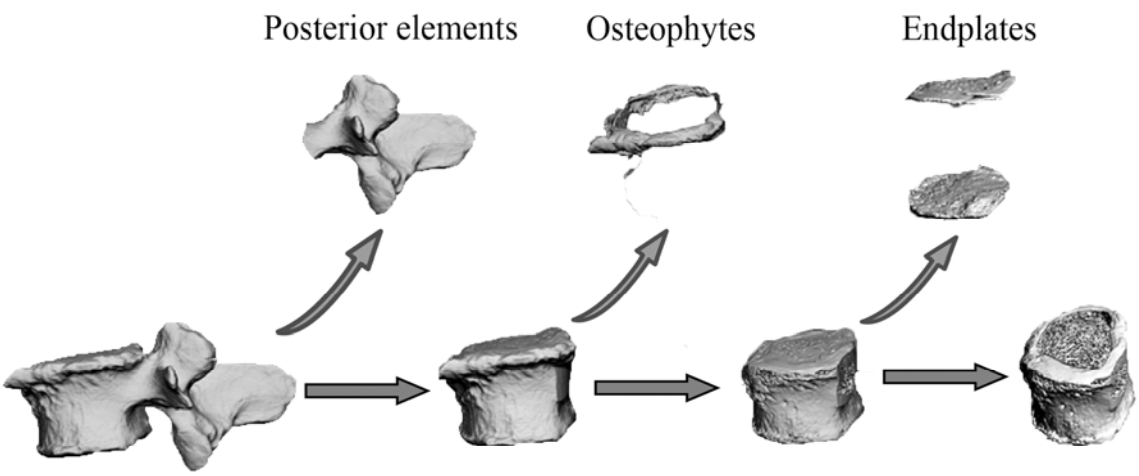

Figure 2-1: The μCT data were post-processed to isolate the posterior elements, osteophytes and endplates for each vertebra such that independent BMD measurements could be acquired.

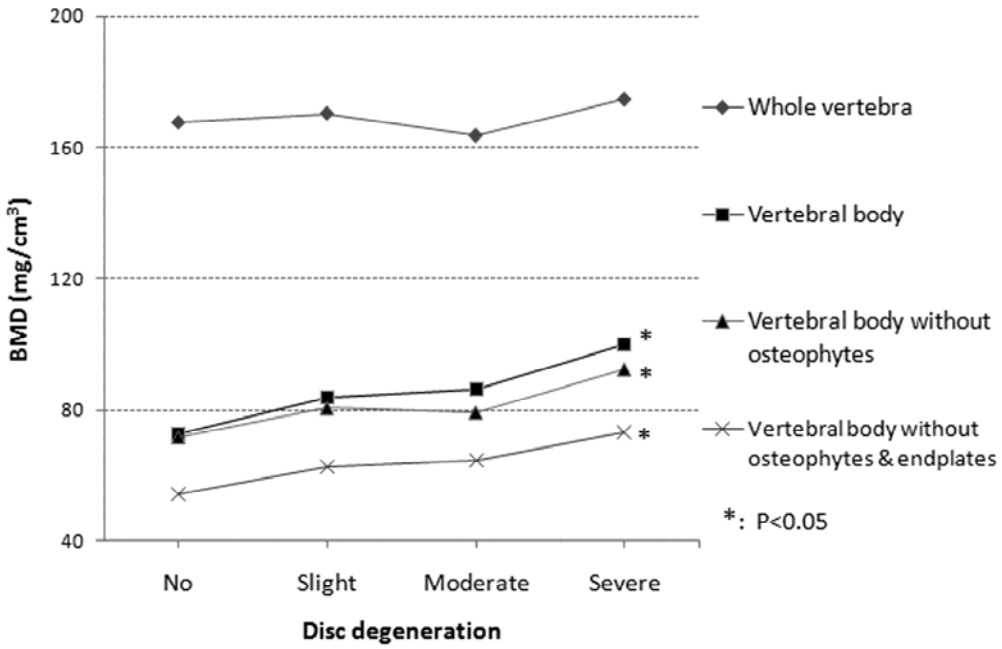

Figure 2-2: Trend analyses between BMDs and DD in the adjacent cranial intervertebral disc, adjusting for age, BMI and spinal level. No trend between the whole vertebra BMD and DD was found. However, a trend of greater vertebral body BMD (with or without osteophytes and endplates) associated with more severe DD was clear.

Table 2-1. Results from the 2-level random effect model: Associations between different definitions of lumbar vertebral BMD (mg HA/cm^3) and adjacent intervertebral disc degeneration

BMD of	***Whole Vertebra***		***Vertebral Body***		***Vertebral Body (without osteophytes)***		***Vertebral Body (without osteophytes & endplates)***	
	Coef	***p***	**Coef**	***p***	**Coef**	***p***	**Coef**	***p***
Level 1: Vertebra*								
Upper lumbar level	0.0		0.0		0.0		0.0	
Lower lumbar level	12.9	<0.001	17.7	<0.001	17.0	<0.001	18.3	<0.001
Degeneration in cranial disc								
No**	0.0		0.0		0.0		0.0	
Slight	2.9	0.60	10.8	0.15	8.6	0.21	8.7	0.16
Moderate	2.5	0.74	10.5	0.29	4.7	0.60	7.8	0.34
Severe	9.2	0.21	25.7	0.008	19.3	0.03	18.9	0.017
Degeneration in caudal disc								
No**	0.0		0.0		0.0		0.0	
Slight	5.8	0.42	15.0	0.11	12.7	0.13	11.9	0.12
Moderate	4.6	0.47	5.2	0.56	3.8	0.64	4.6	0.60
Severe	1.3	0.84	15.6	0.08	13.5	0.09	12.1	0.10
Level 2: Individual								
Age	-1.2	0.04	-0.8	0.05	-0.9	0.02	-0.9	0.014
BMI	2.4	0.06	1.8	0.02	1.6	0.03	1.4	0.033

In this 2-level random effect model, the vertebra and disc were at level 1 and the individual (lumbar spine) was level 2. Within a lumbar spine, vertebrae have different adjacent cranial and caudal disc degeneration conditions as well as different spinal levels. However, all the vertebrae within the same lumbar spine share the same variables in level 2, such as age and BMI.

BMD: volumetric bone mineral density; Coef: regression coefficient; BMI: body mass index.

*: While the BMDs of L5 vertebrae were greater than those of L2~4 vertebrae, there was no statistical difference between the BMDs of L2 through L4 vertebrae. Thus, we grouped the lumbar vertebrae into upper (L2~4) and lower (L5) lumbar levels. The upper lumbar level was the reference.

**: No disc degeneration was the reference.

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CHAPTER 3

Lumbar Vertebral Endplates: Thickness, Bone Mineral Density and Associations with Age and Disc Degeneration*[2]

3.1. Introduction

Consisting of cartilaginous and osseous components, the endplate is a thin layer of tissue located at the cranial and caudal ends of the intervertebral disc. During aging, the cartilaginous endplate undergoes progressive mineralization and eventually is resorbed and replaced by bone, leaving only the osseous endplate.[1,2] Virtually, the osseous endplate is the superior or inferior shell of the vertebral body, and thus, is also called the vertebral endplate.

Lying between the vertebral body and intervertebral disc, the endplate is essential to maintain the integrity and function of the intervertebral disc. Most importantly, the endplate is the gateway of nutrient transport between the vertebral marrow and intervertebral disc. While diffusion through the annulus supplies nutrients for the outer portion of the annulus,[3] diffusion through the marrow contact channels in the vertebral endplate is the main nutrition pathway for the avascular intervertebral disc in adults.[4-6] On the other hand, the vertebral endplate also is a shield between stiff bone and resilient disc and serves as a mechanical interface. It not only prevents the highly hydrated nucleus pulposus from penetrating into the adjacent vertebral body,[7] but together with the disc, it helps to distribute the compressive load evenly across the vertebral body.[8]

Yet, the endplate is far less understood than the disc.[9] Scientific literature on structural features of the endplate, which might be important in maintaining the wellness of the

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intervertebral disc, such as thickness and bone mineral density (BMD), are sparse. Endplate thickness has been examined in a limited number of subjects and spinal levels, primarily by sampling several points in selected sagittal sections of the endplate and measuring local point-to-point thickness, with the reported mean thickness ranging from 0.35 to 0.95mm.[10-14] Probably due to technical challenges, the overall mean thickness, which measures the entire endplate as a whole, has not been reported. Nor have studies been reported examining variations in endplate thickness across lumbar spinal levels. Also, despite a well-established link between endplate calcification and disc degeneration from histological studies,[4-7] with age-related endplate calcification thought to thicken the endplate,[15] findings on the associations between endplate thickness and age and disc degeneration are conflicting.[12,14,16] In addition, although endplate sclerosis shown on radiographs, reflecting increased BMD resulting from endplate ossification, has long been regarded as a risk factor of disc degeneration, it was only quantified recently in a rodent model using dual energy X-ray absorptiometry (DXA).[17,18] Despite a strong association reported between elevated endplate areal BMD and disc degeneration, supporting a role for endplate calcification in disc degeneration, the results are somewhat ambiguous due to the 2-dimensional basis of the DXA measurements. Moreover, the association between endplate BMD and disc degeneration remains unexplored in humans.

A better knowledge of the vertebral endplate structure and function would enhance understanding of the interaction between vertebra and disc and therefore, shed light on the pathogenesis of disc degeneration. The purposes of this study were to use micro-CT (μCT) to determine the thickness and BMD of lumbar vertebral endplates in men and explore their associations with age and disc degeneration. We hypothesized that greater thickness

and BMD of the endplate, if resulting from an accumulation of calcification deposition during aging, would be associated with greater age. Further, we hypothesized that greater thickness and higher BMD of the endplate would impede the nutrient supply to the disc and thus, would be associated with more severe degeneration in the adjacent intervertebral disc.

3.2. Materials and Methods

Subjects

We had access to a lumbar spine archive from 149 Caucasian male cadavers.[19] Subjects in the database passed away in the hospital wards or clinics. The inclusion criteria for this archive were men below the age of 64 years, who had been employed before death and whose history of illness or disease was short. Most of the subjects died from cardiovascular complications. Exclusion criteria were chronic illness or hospitalization and death from cancer or infectious diseases. Age, body weight and height were obtained at the time of death. Body mass index (BMI) (kg/cm^2) was calculated as weight divided by height squared.

Because some of the vertebrae and archived disc degeneration data in this spine archive were missing, only the vertebrae with available adjacent disc degeneration data were selected. Thus, 150 cadaveric lumbar vertebrae (L1~L5) and 209 adjacent intervertebral discs (L1/2 ~ L5/S1) from 48 male human spines were included in the current study. The mean age for the sample is 50 years (range 21-64). The study was approved by the Health Research Ethics Board of University of Alberta.

Measurement of Intervertebral Disc Degeneration

Disc degeneration was evaluated using discography after a routine autopsy examination of the lumbar spines.[19] Using a 20-gauge needle and finger pressure, 2~5ml Barium Sulfate (BaSO4) was injected anteriorly into the center of the intervertebral disc. All five intervertebral discs (L1/2 to L5/S1) were examined for each lumbar spine. Anterior-posterior and lateral x-ray radiographs were taken immediately after the injection of contrast. According to the spread or distribution of the BaSO4 in the discogram, a 4-grade ordinal scale was used to rate the degree of disc degeneration pathology. Disc degeneration was given a rating of none if the dye remained in the center of the disc; slight if the dye spread into the inner annulus; moderate if the dye spread from the inner to the middle region of the annulus; and severe if dye spread to the outer part of the annulus. Intraobserver agreement for measurements using this scale yielded a weighted kappa of 0.81.[19] After discography, the soft tissues around the vertebrae were removed. Vertebrae were dried and then archived under room temperature and humidity.

μCT scanning and image processing

All thickness and BMD measurements were obtained on a μCT system (XtremeCT, Scanco Medical, Brüttisellen, Switzerland) using the standard manufacturer's in vivo parameters (60kVp, 1000μA, 200ms integration time).[20]

The vertebra was axially scanned using μCT with a nominal isotropic resolution of 82 μm (field of view 125 mm, 1536×1536 pixels, integration time 200 ms). A total number of 500 to 800 slices of axial vertebra μCT images was acquired for each vertebra. Scans were performed in air.

The superior and inferior ends of the vertebral body were identified in the axial images, referring to the articular processes. At each end of the vertebral body, 20 to 40 axial slices (corresponding to 1.64 to 3.28 mm in thickness) were used to capture the osseous endplate tissues. Regions of interest (ROI) were identified and contours were drawn adjacent to the endosteal surface of the vertebral cortex shell on these selected images using a semi-automated contouring approach. ROI were filtered using a Laplace-Hamming filter and segmented using a global threshold.

An endplate consists of an epiphysial rim, which is the peripheral margin of the endplate near the vertebral body ring, and central endplate, which is the central portion of the endplate. The epiphysial rim is the place where the annulus fibrosus attaches and is relatively solid and impermeable compared with the thin and porous central endplate. It is well established that the central endplate is more important than the epiphysial rim in terms of nutrient supply.[5,6] With the aim of measuring the central endplate and avoiding the noise from osteophytes, all the endplate contours were shrunk 3mm inward. Hence, the outer portion of the epiphysial rim (in the width of 3 mm) was not extracted for endplate 3-dimensional (3-D) image reconstruction (**Figure 3-1**) and, therefore, was excluded from the thickness and BMD measurements.

As the ROIs contoured in the axial image of the vertebral body include cortical endplate and trabecular bone, a fully-automatic image analysis algorithm based on a dual threshold was applied to the ROIs to extract the cortical endplate and exclude trabecular bone. For all samples, the input thresholds of 3000 and 4000 were employed to ensure maximal consistency in segmenting the bone compartments. This technique is robust for segmenting cortical bone from trabecular bone and has been reported as highly reliable in

extracting and measuring cortical bone.[21] The extracted endplate tissues were then 3-D reconstructed (**Figure 3-1**) and all the 3-D endplate images were visually assessed to verify the quality of endplate extraction. If needed, ROI contours were adjusted to optimize the quality of segmentation.

Measurements of endplate thickness and BMD

A volume-based thickness analysis technique was employed to assess the overall mean thickness of the endplate, using the true 3-D images. This measure defines local thickness at a given point in the structure as the diameter of the largest sphere which includes the point and which can be fitted completely inside the structure.[22] As the thickness within an endplate varies at different sites, this method assesses the distribution of thickness and provides parameters such as the mean and the standard deviation. Only the mean thickness measure was used in this study.

Analyses were performed (Image Processing Language, v4.29d, Scanco Medical AG, Brütisellen, Switzerland) to obtain the volume (cm^3), BMC (mg) and volumetric BMD (mg/cm^3) measurements for the vertebral endplates. The reliability, validity and precision of μCT for the measurement of BMD and BMC are well established.[23,24]

In summary, using μCT techniques, each vertebra was scanned axially and the endplates were extracted from the μCT images to reconstruct 3-D images. Structure and density parameters such as mean thickness, volume and volumetric BMD were thus measured, respectively. In the current study, the osseous vertebral endplates are labelled as cranial or caudal relative to the disc (not the vertebra).

Statistical Analysis

Descriptive statistics were used to document the thickness and BMD of the endplates. When comparing endplates cranial and caudal to discs, paired t-tests were used. ANOVA (analysis of variance) was performed to examine differences of thickness and BMD at different lumbar spinal levels. If a significant difference was observed in ANOVA, a trend analysis[25] was further used to examine the overall association with spinal level. Univariable and multivariable regressions were performed to examine the associations between the thickness and BMD of the endplate with age, BMI and disc degeneration. If not specified, the cranial endplate and caudal endplate were analyzed separately. Statistical analysis was performed using STATA (Version 9.2, StataCorp LP, USA). As data acquired for endplates were clustered in a lumbar spine, the command 'cluster' in STATA was used to account for the dependency in the regression analyses. A *p* value less than 0.05 was considered statistically significant.

3.3. Results

Endplate thickness and BMD

Overall, the mean thickness was 1.03mm (SD=0.24, range 0.58-2.0mm, N=150) for the cranial endplates and 0.78mm (SD=0.16, range 0.44-1.28mm, N=137) for the caudal endplates. The mean BMD was 413mg/cm^3 (SD=79, range 234-625mg/cm^3) for the cranial endplates and 332mg/cm^3 (SD=65, range 221-579mg/cm^3) for the caudal endplates. Thirteen cranial endplates of L1 belong to T12/L1 disc and thus, were excluded in data analysis. For endplates from different levels, the mean thickness and BMD are presented in **Table 3-1**.

For lumbar intervertebral discs from L1/2 to L4/5, the cranial endplate was significantly thicker than the caudal endplate (paired t-tests, p=0.03 for L1/2 disc, p=0.003 for L2/3 disc and p<0.001 for L3/4 and L4/5 discs, **Figure 3-2A**). Similarly, the endplate cranial to the disc was denser than the endplate caudal (paired t-tests, p=0.009 for L2/3 disc and p<0.001 for other discs, **Figure 3-2B**). [26]

There was a statistically significant difference in the thickness of the cranial endplates of the upper four lumbar intervertebral discs (ANOVA, p<0.05). Furthermore, a trend analysis revealed that the thickness of the cranial endplates increased from the L1/2 disc down to L4/5 disc (P<0.001). As is apparent in **Figure 3-2A,** this trend did not extend to the L5/S1 cranial endplate. For the caudal endplates, a significant difference in thickness was not observed between the upper four lumbar intervertebral discs (ANOVA, p=0.07). For both cranial and caudal endplates, no statistically significant BMD difference was detected between discs at the upper four lumbar intervertebral discs (ANOVA, p=0.07 for cranial endplates and p=0.11 for caudal endplates, **Figure 3-2B**).

Associations between endplate thickness and BMD with age and BMI: results from univariable regression models

The endplate thickness was moderately correlated to the endplate BMD (r=0.46, p<0.001 for both cranial and caudal endplates). For both cranial and caudal endplates, no significant association between thickness and age was found at any spinal level in an univariable regression model or when data from all spinal levels were merged and analyzed together (p>0.05). Similarly, BMD of both cranial and caudal endplates was also independent of age (p=0.18-0.90).

Greater BMI was associated with greater thickness (p=0.005) and elevated BMD (p=0.02) of the caudal endplate, but the associations were statistically insignificant in the cranial endplate (p=0.07, 0.31, respectively).

Associations of endplate thickness and BMD with disc degeneration: results from the multivariate model

Based on discography, disc degeneration was absent in 33 (15.8%) discs, 69 (33%) were rated as having slight disc degeneration, 42 (20%) had moderate disc degeneration and 65 (31.1%) had severe disc degeneration. In a multiple regression model, a trend of more severe disc degeneration associated with greater thickness in both the cranial and caudal endplates was observed after controlling for age and BMI. This trend was most marked for severely degenerated discs, for which cranial and caudal endplates were on average 0.15mm and 0.12mm thicker than for non-degenerated discs (p=0.04 for both endplates). However, no evidence was detected for a link between disc degeneration and BMD of cranial or caudal endplates (**Table 3-2**). The association between disc degeneration and endplate BMD remained insignificant when cranial and caudal endplate BMD were either averaged or added into a model together to explain disc degeneration (p>0.05).

3.4. Discussion

Using μCT, the thickness and BMD of the osseous vertebral endplates were measured for 150 vertebrae from 48 lumbar spines. Both the thickness and BMD of endplates were independent of age, which ranged from 21 to 64 years. The endplates cranial to intervertebral discs were thicker and had higher BMD than the corresponding caudal endplates. Judged from discography, more degeneration in the adjacent intervertebral disc was associated with greater endplate thickness, but not higher endplate BMD. Thus,

endplate sclerosis, reflecting elevated endplate BMD, may not be a risk factor for disc pathology in men.

Different from previous histological studies, which measured the endplate from the sagittal vertebral slices, in this study we used μCT techniques to segment the endplate and acquire specific measurements. μCT is a powerful imaging method for assessing and quantifying bone architecture.[23,24,27] Moreover, the dual threshold based image analysis algorithm allows efficient and reliable extraction even for highly thinned bone cortices.[21] The separation of the osseous endplate from the vertebral body and exclusion of the outer portion of peripheral ring substantially avoided artificial effects from trabecular bone and osteophytes, resulting in specific endplate measurements which are beyond the DXA and traditional histological approach.

This is the first time, to our knowledge, that a volume-based local thickness definition was introduced to measure the endplate and a clear description of endplate thickness was provided for the lumbar spine. The conventional surface-based thickness measure is not appropriate to measure an object such as the endplate, which is porous and rough in surface, and the thickness varies considerably at different sub-regions.[10,12-14,16] Moreover, earlier observations were restricted to sagittal sections of histological or radiological images, and the endplate thickness was measured from sampled points. Although variations in thickness of the endplate were detected, this method may miss substantial information by sampling only a few points and sections. Using 3-D μCT images, the volume-based thickness technique used in the current study measured the entire defined endplate and thus, prevented sampling bias. Probably because a different thickness definition was applied and the whole specified endplate was measured, the average

thickness of endplate acquired in this study, is larger in magnitude than those reported previously.[10,12-14]

In accordance with most[12-14] though not all[10] studies, the endplate cranial to the intervertebral disc was thicker than the corresponding caudal endplate. Noted by a few researchers, the greater thickness in the cranial endplate was suggested to contribute to less vertebral fracture there.[14] To a large extent, the exchange of metabolites between the vertebral marrow and disc relies on the thinness and porosity of the endplate.[6] Thus, the asymmetry in thickness of cranial and caudal endplates suggests that endplates may play a different role in the nutrition supply to the avascular intervertebral disc. However, the porosity, may also differ in cranial and caudal endplates and needs to be further investigated.

In the few published studies there are conflicting findings about the association between endplate thickness and age. The vertebral endplate has been reported as either thickening[14] or thinning[12] in aging. In line with Silva[13] and Edwards's studies,[10] however, no significant association between endplate thickness and age was observed in our study. The inconsistent findings in previous studies may be due to the small sample sizes, different age ranges and gender of the subjects studied and different measures of endplate thickness used, as well as different endplate sub-regions measured. Age-related endplate calcification and osteopenia bone loss are two distinct pathologies which often coexist in the endplate. The accumulative endplate calcification tends to thicken the endplate while osteopenia bone absorption offsets the thickening. Thus, the mean thickness of the endplate may remain unchanged, if a balance is reached to some extent. The observed positive association of more BMI with more endplate thickness and more BMD only in the

caudal endplate may suggest an effect of mechanical loading on endplate remodelling differs between the cranial and caudal endplates.

The current study provides further evidence to support an association between greater endplate thickness and more severe disc degeneration. Cartilaginous endplate remodelling, resulting in calcium deposited upon the endplate and thickening of the endplate, is thought to block the marrow contact channels, impede the diffusion and restrict the nutrition supply to disc and, therefore, trigger or accelerate disc degeneration.[28] Despite evidence from histological studies that endplate calcification is associated with more disc degeneration,[7,9] when the proteoglycan content in the nucleus pulposus was measured to indicate disc degeneration, greater thickness of endplate was associated with more proteoglycan ('good' disc) in one study[16] and less ('bad' disc) in another.[12] It is likely that some endplate features other than thickness, such as porosity, may influence the permeability of the endplate and disc nutrient supply. However, as we failed to find an association between endplate thickness and age, it is not clear whether this 'greater' thickness is congenital or a result of endplate calcification.

To our knowledge, volumetric BMD of the human lumbar vertebral endplates has not been previously quantified. Similar to thickness, the endplate BMD was independent of age within our adult sample. Moreover, in contrast to our hypothesis, the endplate BMD was not associated with disc degeneration. Endplate sclerosis, reflecting accumulative calcium deposition and increased BMD, has long been thought to be an important risk factor of disc degeneration, and even has been used as an indicator of disc degeneration. Yet, most studies of endplate BMD have been based on animal models, rather than human spines. Our data disagree with the findings of Gruber and colleagues, who consistently

reported a strong association between more endplate BMD and more severe disc degeneration in the rat.[17,18,29] However, the endplate BMD reported was measured using DXA in vivo and the disc degeneration was evaluated using a dichotomous measure of intervertebral space narrowing. DXA is a projection technique which cannot quantify bone volume and is unable to distinguish the endplate from the adjacent trabecular bone and vertebral cortical shell. The DXA BMD acquired for the endplate may have been substantially inflated by the inclusion of other vertebral components,[30] confounding the association between endplate BMD and disc degeneration. Moreover, some lumbar spine degeneration features, such as osteophytes, may not only inflate DXA BMD measurement,[31] but also inflate the visually assessed disc degeneration measurement.[32]

Endplate BMD was independent of age and disc degeneration as assessed from discography in the current study. The highly specified endplate BMD measurement, which was volume adjusted, was expected to be more sensitive to detect an association between endplate BMD and age and disc degeneration, if present. But despite the improved measurement, evidence to support a link between endplate BMD and age and disc degeneration was not observed. It is possible that a balance of bone gain (endplate ossification) and bone loss (osteopenia) in the endplate may result in unchanged endplate BMD in aging, as discussed previously. On the other hand, as the endplate BMD was adjusted for volume, it could remain unvaried if the deposited mineralized tissue has the same BMD as the original endplate.

There are some limitations in this study that should be addressed. First, all the subjects were men and findings may not be generalizable to women. Second, bone was scanned in air and the BMD measurement may have been biased due to beam hardening effects.

Third, the thickness measured for the vertebral endplate was averaged over the entire analysis region, and the regional thickness variation within the endplate was not studied. Theoretically, it is possible that more specific measurements of the thickness and BMD acquired from sub-regions of the central endplate may have demonstrated stronger associations with disc degeneration. Also with respect to study limitations, while the sample was relatively large, a greater number of subjects, particularly of older age, may have enhanced power to detect the associations studied, if present.

In summary, a large sample of human lumbar vertebrae was measured with μCT to determine the thickness and BMD of lumbar vertebral endplates and their relations to age and discographic disc degeneration. The cranial endplate of the intervertebral disc was found to be thicker and denser than the corresponding caudal endplate. Both the endplate thickness and BMD were independent of age. While more severe disc degeneration tended to associate with greater thickness of the endplate, no significant association was detected between disc degeneration and endplate BMD. The findings suggest that endplate sclerosis, reflecting increased endplate BMD, may not be a risk factor for disc degeneration.

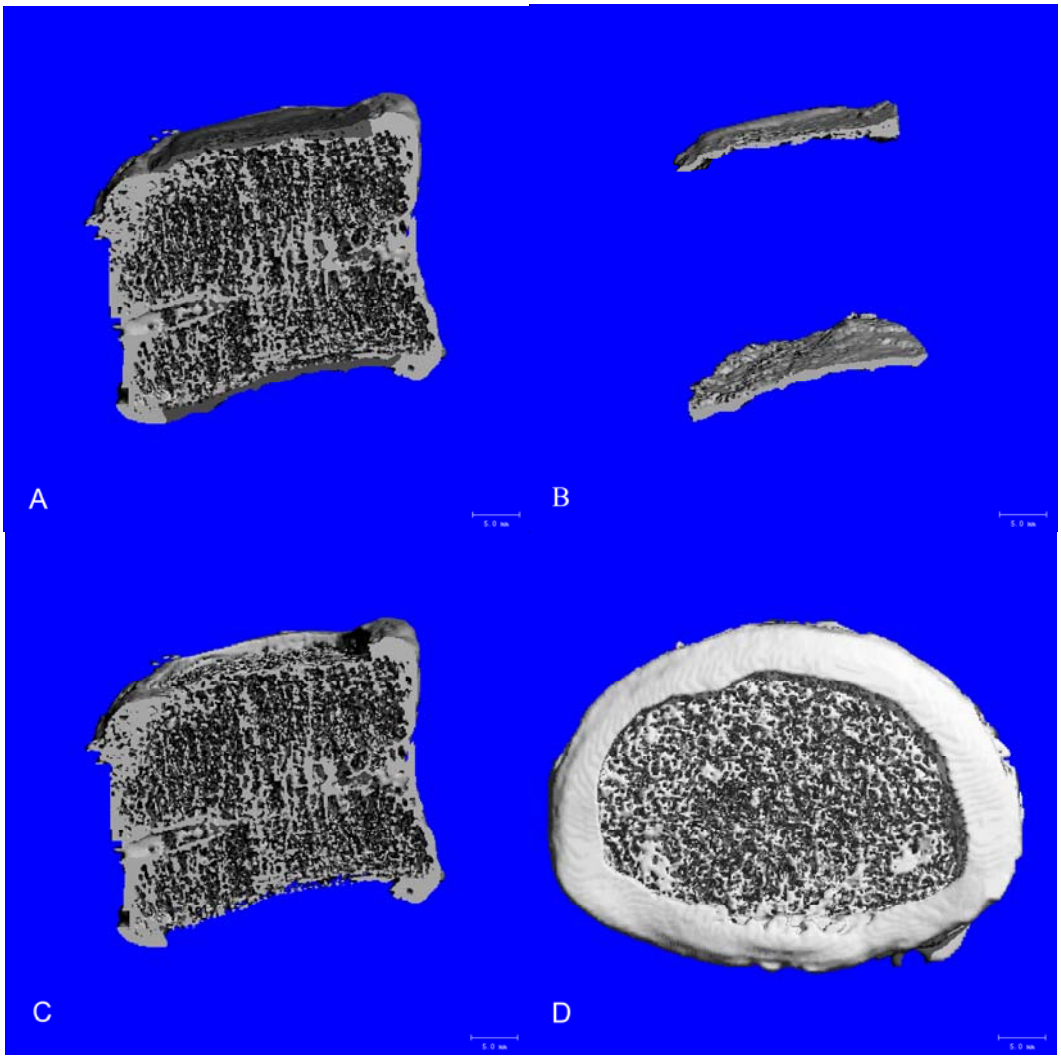

Figure 3-1: The endplates were extracted from the vertebral body and reconstructed into 3-D images before structure analysis. **A**: Mid-sagittal section of a vertebral body. The gray regions are the defined osseous endplates. **B**: The mid-sagittal section of the extracted cranial and caudal endplates. A 3mm epiphysial rim of the endplate was left on the vertebral body: **C**: mid-sagittal view; **D**: superior view.

Table 3-1: Thickness and BMD of lumbar osseous endplates by discal level (95% CI)*

Disc level	*Cranial endplate*			*Caudal endplate*		
	N	***Thickness (mm)***	***BMD (mg/cm^3)***	***N***	***Thickness (mm)***	***BMD (mg/cm^3)***
L1/2	13	0.82 (0.75, 0.89)	383 (345, 421)	24	0.70 (0.64, 0.76)	348 (292, 403)
L2/3	24	0.97 (0.89, 1.06)	424 (388,459)	19	0.79 (0.70, 0.87)	372 (343, 401)
L3/4	19	1.04 (0.94, 1.14)	457 (422, 492)	47	0.78 (0.74, 0.82)	350 (325, 375)
L4/5	47	1.11 (1.04, 1.17)	422 (400, 445)	47	0.81 (0.75, 0.86)	342 (321, 362)
L5/S1	47	1.04 (0.96, 1.12)	391 (368, 414)		NA	

* Thirteen cranial endplates of L1 belong to T12/L1 disc and thus, were excluded in the present study. The caudal endplate of L5/S1 intervertebral discs were not examined.

Table 3-2: Associations of the thickness and BMD of the endplates with age, BMI and disc degeneration: results from a multiple regression model*

	Cranial Endplate				*Caudal Endplate*			
	Thickness		***BMD***		***Thickness***		***BMD***	
	Coef	***P***	***Coef***	***P***	***Coef***	***P***	***Coef***	***P***
Age	-.0004	0.86	0.87	0.43	-0.002	0.47	0.88	0.31
BMI	0.008	0.19	2.57	0.28	0.011	0.003	3.61	0.08
Disc degeneration**								
No	0.0		0.0		0.0		0.0	
Slight	0.11	0.07	13.8	0.52	0.05	0.31	27.2	0.11
Moderate	0.04	0.50	-19.2	0.38	0.04	0.47	-6.4	0.77
Severe	0.15	0.04	-39.4	0.06	0.12	0.04	10.60	0.61

BMD: bone mineral density; BMI: body mass index; Coef: regression coefficient.

* The 'cluster' command in STATA was used to account for the dependency in the data.

** No disc degeneration was the reference.

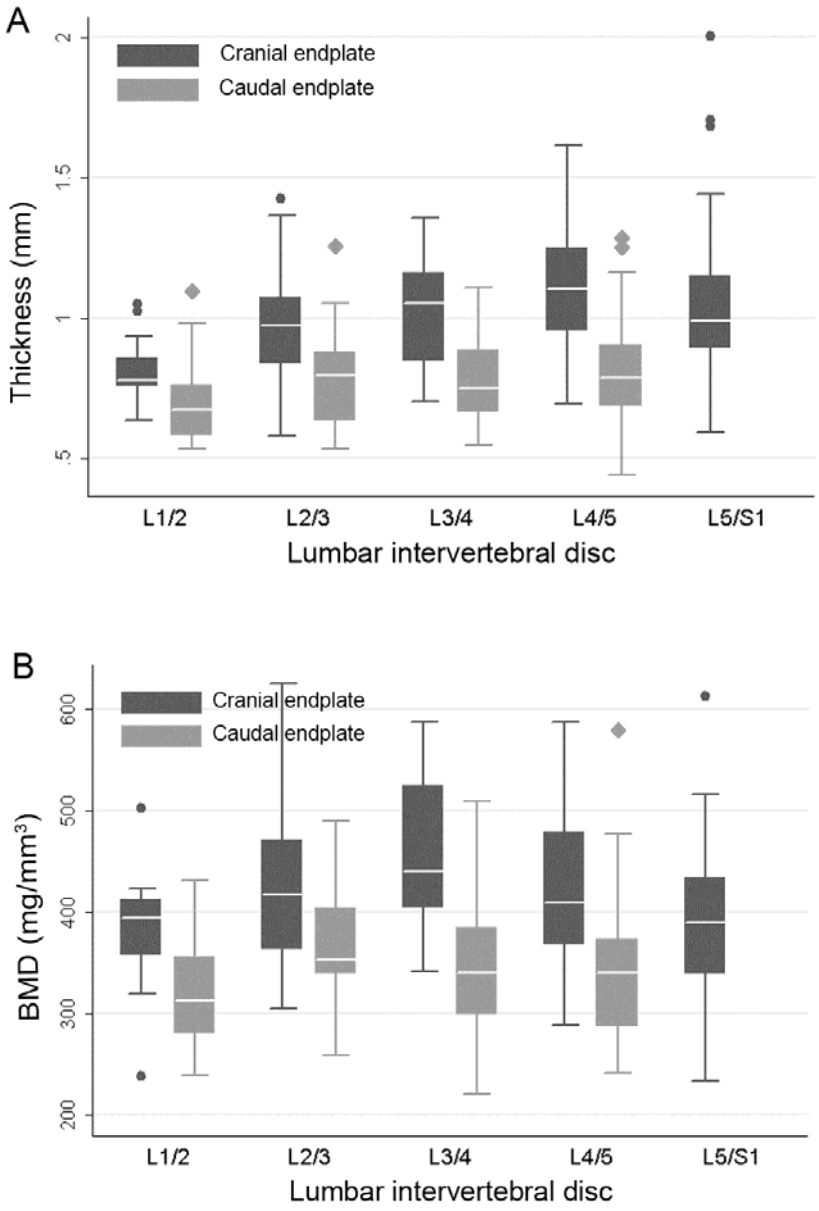

Figure 3-2: Box plots of the thickness (**A**) and BMD (**B**) of lumbar vertebral endplates. The measurements of cranial and caudal endplates of intervertebral discs were graphed side by side at different spinal levels. The plots clearly showed that both the thickness and BMD of cranial endplates were always greater than that of corresponding caudal endplates. The caudal endplates of L5/S1 discs were not examined in the current study and therefore, data were absent. (The box describes the middle 50% of the distribution, with a white line inside indicating the median of the data. The two whiskers represent the minimal and maximal measurements while the dots or diamonds represent the outliers in the data.)

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CHAPTER 4

Morphometrics and Lesions of Lumbar Vertebral Endplates Are Associated with Lumbar Disc Degeneration* [3]

4.1. Introduction

Despite decades of interdisciplinary research on disc degeneration (DD), from epidemiology to molecular biology,[1,2] much remains unknown about its etiology and pathogenesis. Traditionally, research into the pathogenesis of DD has mainly focused on the disc itself and global determinants. The endplate, a thin structure located at the cranial and caudal ends of the intervertebral disc, has long been neglected,[3] despite that it interacts directly with the intervertebral disc and may be in the pathogenic pathway of DD.

Consisting of osseous and cartilaginous components, the endplate is essential to maintain the health and function of the intervertebral disc. The endplate is a physical shield to prevent the nucleus pulposus from penetrating into the adjacent vertebral body,[4] while also acting as the gateway of nutrient transport between the vertebral marrow and intervertebral disc.[5,6] In addition, it serves as a mechanical interface between stiff bone and resilient disc and contributes to an even distribution of physical load in the vertebra-disc complex.[7]

Despite its importance, surprisingly little is known about the endplate. For example, literature on the morphometrics of the vertebral endplate, which might be important to understanding the physiological interactions between the vertebral body and intervertebral disc, is scarce. The shape, size and concavity of the vertebral endplate have been measured in vivo, suggesting a role of endplate morphometrics in DD[8,9] and disc herniation.[10]

* Some data presented in this chapter have been submitted to ***European Spine Journal*** for publication.

However, such studies sampled only one or several sections of the vertebral body with routine CT or MR. As the morphology of the vertebral endplate varies considerably in sub regions,[11] such measures are likely inadequate to fully characterize the endplate and its relation to disc pathology.

Most previous research of the endplate actually focused on abnormalities or lesions, such as Schmorl's nodes. As the most common form of endplate lesion,[12] Schmorl's nodes were often studied in the thoracic region where they are more prevalent, with the main interest being their etiology. Schmorl's nodes in the lumbar region are less commonly studied and their role in disc pathology remains controversial. For example, earlier cadaveric studies suggested that Schmorl's nodes were related to DD in the thoracic region but not in the lumbar region,[13] or associated with moderate but not advanced DD, with the size of the nodes being irrelevant to the severity of DD.[14] However, more recent epidemiological studies using large samples and lumbar magnetic resonance (MR) images suggest that Schmorl's nodes are associated with lumbar DD,[15] with a dose-dependent linear relationship.[16]

The inconsistency between earlier and more recent study results may be due, in part, to the definitions of DD used, which vary from study to study. It may also be attributable, in greater part, to measurement acquisition of Schmorl's nodes. There is striking variation in the reported prevalence of Schmorl's nodes, ranging from 9% to 75%,[13,15,17,18] with the prevalence measured from cadaveric spines being much higher than that from MRI. In other words, it appears that a substantial percent of Schmorl's nodes seen in cadaveric vertebrae are not detected on MR images. Therefore, firsthand data from cadaveric spines may be critical to accurately identifying endplate lesions and determining their relations to

DD. Yet, to date, such data are rare and fundamental evidence from cadaveric spines to substantiate a link between endplate lesions and lumbar DD is absent.

The primary aims of the current study were to determine the prevalence of endplate lesions, characterize endplate morphology and explore their associations with lumbar DD using cadaveric spines. Based on previous reports, we tested the hypotheses that smaller size and more concavity of vertebral endplates are beneficial to the adjacent disc, while lesions on the vertebral endplates are detrimental, with larger lesions associated with more severe DD. As the main foci of this study are the associations between the endplate and the disc, we specified the endplates as cranial or caudal with respect to the intervertebral disc.

4.2. Materials and Methods

Subjects

We had access to a lumbar spine archive of 149 Caucasian male cadavers.[19] Men included in the archive were below the age of 64 years, had passed away in hospital wards, had a short history of illness and had been employed before death. Most of the subjects died from cardiovascular accidents or complications. Exclusion criteria were long hospitalization and death from cancer or infectious diseases. Age, body weight and height were obtained at the time of death. For 86 subjects, their families provided detailed information about occupation, back injury and back pain history.[19] As one of the planned aims was to explore the association between endplate lesions and back pain, we included all available lumbosacral vertebrae and corresponding discography data for this subgroup. While all radiographs of the lumbar spines were available, some of the vertebrae were made into histological slices for other projects or lost in preservation. The study was approved by the Health Research Ethics Board at the University of Alberta.

Measurement of Intervertebral Disc Degeneration

DD was evaluated using discography, which was performed after a routine autopsy examination of the lumbar spines.[19] Using a 20-gauge needle and finger pressure, 2~5ml of Barium Sulfate (BaSO4) was injected anteriorly into the center of the intervertebral disc. For most spines, all five lumbar intervertebral discs (L1/2 to L5/S1) were examined. Anterior-posterior and lateral radiographs were taken after the injection of contrast. According to the spread or distribution of the BaSO4 in the discograms, a 4-grade ordinal scale was used to rate the degree of DD as judged through annular disruption. DD was given a rating of none if the dye remained in the center of the disc; slight if the dye spread into the inner annulus; moderate if the dye spread from the inner to the middle region of the annulus; and severe if dye spread to the outer part of the annulus. Intraobserver agreement for measurements using this scale yielded a weighted kappa of 0.81.[19] In evaluating DD, discography is based on morphological changes within the disc while MR depends on the changes of water content of the disc. Despite less commonly used now, as a traditional approach discography is able to differentiate successive stages of DD,[20] and is comparable to MRI in DD evaluation.[21]

After discography, the soft tissues around the vertebrae, including the endplate cartilage and the intervertebral discs, were removed. Vertebrae were dried and then archived under room temperature and humidity. In the current study, the bony vertebral endplate was studied.

Visual assessments

An adult vertebral endplate consists of an epiphysial rim, which is a ring of smooth bone at the peripheral margin of the endplate, and central endplate, which is the central portion of the endplate.[22] The epiphysial rim is where the annulus fibrosus anchors and is relatively smooth and solid, compared with the thin and porous central endplate which is covered by cartilaginous endplate and adjacent to the nucleus pulposus.[12] Therefore, while the epiphysial rim approximately reflects the size of the annulus fibrosus, the central endplate largely mirrors the size of the nucleus pulposus.

Endplate shape. The visual assessments of endplate shape were performed by one of the authors (Y.W). According to the relationship of the central endplate and the epiphysial rim, the endplates were classified into concave, flat or irregular. The apex of the concavity was further classified as none (absent), single or double.

Endplate lesions. In preparation for developing methodology for categorization of endplate lesions, a sample of vertebrae was examined. Schmorl's nodes, characterized by localized indentation in the central endplate with a smooth margin and osseous casing,[12] commonly appear in our sample. Yet, it was evident that Schmorl's nodes were not the only lesions affecting the vertebral endplates. We also identified other forms of endplate pathology, such as what appeared to be trauma-related fissures and compressions, intensive calcium deposition and some diffusive, shallow endplate 'erosions'. It was difficult at times to differentiate Schmorl's nodes from other lesions by visual examination and it was not rare for two or more forms of lesions to present on an endplate. As there is no currently available classification system to separate different endplate pathologies, in the present study we grouped them together as 'endplate lesions'.

According to the maximal diameter, the size of endplate lesions was rated as **none** if the endplate had no lesion; **small to moderate** if the lesion was less than half of the anterior-posterior diameter of the vertebral endplate and **large** if larger than half. The size measurement was mainly acquired using visual inspection. If necessary, a Vernier caliper was used.

As two vertebral endplates border an intervertebral disc, measurements of endplate lesions from the paired cranial and caudal endplates were further combined when studied in relation to DD. The combined endplate lesions for the disc were classified as none if both endplates were intact; small to moderate if one of them had small to moderate lesions and another had no lesion; or large if one of them had large lesions or both endplates had small to moderate lesions.

To evaluate the reliability of these visual assessments, a sample of 200 vertebral endplates were randomly selected and re-evaluated one week later. The intra-rater reliability was good or excellent. The κ was 0.78 for the endplate shape and 0.82 for concavity apex measurement. The weighted κ for the size of endplate lesions was 0.89.

Digital measurements of endplate morphometrics

Each vertebral endplate was scanned using a Konica Minolta non-contact 3D digitizer (VIVID 910, Konica Minolta Sensing Americas, USA) to measure the surface geometry. The 3D virtual images of endplates were processed and measured using the affiliated program Polygon Editing Tool (PET, version 2.21).

The acquisition of endplate morphometrics from 3D image is illustrated in **Figure 4-1**. First, the sagittal and transverse diameters (mm) of the endplate were measured. The circularity, which was defined as the ratio of the sagittal diameter to the transverse

diameter, was calculated to indicate the axial shape of the endplate. Then, the central endplate and the peripheral rim were separated in the endplate 3D images. Corresponding, surface area measurements (cm^2) were acquired for the whole endplate, the central endplate and the peripheral rim using the PET program. In addition, we further measured the axial area (cm^2) of the endplates, which was defined as the planar area within the outermost rim of the endplate. As almost all endplates are concave to some extent, the axial area measurement is usually less than the corresponding surface area measurement. Finally, the endplate 3D images were imported into a 3D graph software Dplot (version 2.2.6.3, HydeSoft Computing LLC., USA) to measure the mean depth (mm) and volume (mm^3) of the endplate concavity.

In brief, each vertebral endplate was digitized to acquire geometric measurements, including diameters, surface and axial area, mean depth and volume of concavity, and areas of endplate components. A random sample of 30 endplates were measured twice to calculate the intra-class correlation coefficient (ICC) for these digital measurements resulting in excellent intra-rater reliability (ICC=0.93-0.97 for different definitions of area measurements and endplate circularity measurement. ICC=0.85 for the concavity mean depth and 0.94 for the volume measurements).

Statistical Analysis

Descriptive statistics were used to explore endplate shape and lesions. As the prevalence of DD is substantially different in the upper and lower lumbar spine,[23] lumbar discs were grouped into upper (L1/2, L2/3 and L3/4 discs) and lower lumbar (L4/5, L5/S1 discs) regions. Ordinal logistic regressions were used to examine the associations between the endplate morphometrics, lesions and adjacent DD. First, univariable regressions were

performed and the cranial and caudal endplates were analyzed separately, with age and spinal level controlled. Then, data from the cranial and caudal endplates were merged together. A purposeful procedure was used to build a multivariable regression model. For selected quantitative measurements, data from cranial and caudal endplates were averaged. For endplate lesions, the combined endplate lesions measurement (as described previously) was used. If data were missing for one endplate, data from the other available endplate were used for the adjacent DD. Age, lumbar region (upper vs. lower lumbar) and body mass index (BMI) were controlled. Statistical analyses were performed using STATA (Version 9.2, StataCorp, USA). As data acquired for endplates were clustered in a lumbar spine, the command 'cluster' in STATA was used to account for the dependency in all regression analyses.

4.3. Results

The current study included 266 cadaveric lumbar vertebrae (L1-L5), 69 sacral vertebrae (S1) and 313 adjacent intervertebral discs (L1/2 -L5/S1) from 76 male human spines. In the radiographic and visual endplate assessments, there were 600 endplates (264 cranial endplates and 336 caudal endplates) studied, including that of S1. In digital measurements, 9 endplates were excluded because of poor digital images, leaving a total number of 591 vertebral endplates. The mean age of the sample was 51.3 years (range 21-64 years).

Prevalence of findings

Endplate lesions were found in 55 (72.4%) lumbar spines and 197 (32.8%) endplates. Among these lesions, 122 (62%) were evaluated as small to moderate and 75 (38%) were rated as large. The prevalence of lesions was not statistically different between the cranial and caudal endplates (χ^2 test, p=0.87). While small or moderate lesions were more

common in the upper lumbar region (69.7%), large endplate lesions were more common (70.7%) in the lower lumbar region (χ^2 test, p<0.001).

Overall, with respect to ***endplate shape,*** 58.2% of endplates were visually evaluated as concave, 33.3% were flat and 8.5% were irregular. Among the concave endplates, 238 (39.8%) had a single apex, 111 (18.5%) had two apexes and the remaining 41.8% of endplates had no apparent apex.

Based on discography, DD was absent in 40 (12.8%) discs, 101 (32.3%) were rated as having slight DD, 71 (22.7%) had moderate DD and 101 (32.3%) had severe DD.

The distribution of DD by endplate lesion size is presented in **Figure 4-2**.

Morphometrics of endplate and its components

The diameters, area and mean concavity depth of endplate, as well as the area of central endplate and epiphysial rim, are reported by spinal level in **Table 4-1**. For both cranial and caudal endplates, the AP diameters were relatively constant from L1/2 disc to L5/S1 disc (ANOVA, p>0.05). However, the transverse diameter increased gradually from L1/2 down to L5/S1 disc (**Figure 4-3A**). Therefore, the circularity of the endplate decreased gradually from the upper to the lower lumbar disc, such that the endplates became more elliptical (**Figure 4-3B**).

Associations of endplate morphometrics and lesions with DD:

Results from univariable regressions (Table 4-2)

Age (OR=1.08, p<0.001) and lumbar region (lower vs. upper, OR=1.76, p<0.001), but not BMI (p=0.33), explained a portion of the variance in the DD.

Controlling for age and lumbar region, irregular shape (OR=2.6~2.7, p<0.05), lesions (OR=2.2~4.9, p=0.00~0.01) and greater area (OR=1.18~1.23, p=0.003~0.05) of both

cranial and caudal endplates were associated with more adjacent DD. More adjacent DD was also associated with less mean depth of concavity (OR=0.7, p=0.02) and more circularity (OR=1.07, p=0.004) in the endplates cranial to the disc, but not in the caudal endplates. Further, adjacent DD was associated with greater central endplate area both cranially and caudally (OR=1.23~1.32, p<0.05), but not with that of the epiphysial rim (p=0.23~0.41).

Results from multivariable regression

The visual assessments of endplate shape and apex more or less indicated the degree of concavity, which was further measured digitally. Therefore, only the digital measurements were considered in the multivariable model. While the measurements of mean depth and volume of endplate concavity were highly correlated (r=0.92), the volume measurement was not associated with DD in the univariable model. Thus, only the mean depth measurement was selected. Similarly, between the highly correlated endplate surface area and axial area measurements (r=0.95), the endplate axial area measurement, which was independent of the concavity, was selected to indicate endplate size. Therefore, the final model included endplate lesions and three endplate morphological measurements: mean depth of concavity, axial area and circularity.

After controlling for age, BMI and lumbar region, endplate lesions were statistically significantly associated with DD, with greater size of lesions associated with more severe adjacent DD (OR=2.3 for small to moderate lesions and 3.54 for large lesions, p<0.001, **Table 4-3**).

Among the three measurements of endplate morphometrics, only the axial size was significantly associated with adjacent DD (OR=1.2, p=0.027), with larger endplate size

associated with more DD. There was a tendency for more circularity and less concavity of the endplate to associate with more adjacent DD, but neither reached statistical significance (**Table 4-3**). When lesioned endplates were excluded and the associations between morphometrics and adjacent DD were analyzed for only the intact endplates, similar results were obtained: only endplate axial area was associated with adjacent DD (OR=1.21, $p<0.05$).

Further, when the area of the central endplate was used to replace the total endplate axial area, an association between the greater axial size of the central endplate and more DD was observed (OR=1.22, $p=0.018$). However, when the epiphysial rim area was used in the model, no statistically significant association was found (OR=1.06, p=0.40).

4.4. Discussion:

The morphometrics and lesions of a large sample of vertebral endplates were studied in relation to lumbar disc degeneration. The current cadaveric data from men revealed that the integrity of the vertebral endplate and intervertebral disc were interdependent. Endplate lesions were common in the lumbar spine, appearing in approximately 1/3 of endplates, and were associated with adjacent discographic DD, with greater lesion size associated with more severe adjacent DD. Findings also supported an association between larger endplates and more adjacent DD. Specifically, it was a larger central endplate, reflecting a larger nucleus pulposus, that was associated with more adjacent DD. Greater endplate concavity and lesser circularity may play a marginal role in the pathogenesis of DD.

Using a broad definition, the prevalence of endplate lesions observed in this study was high with respect to MR imaging findings,[15-17] but was in line with previous cadaver studies using Caucasian adults of similar age where Schmorl's nodes were present in

48~75% of spines.[13,14,18,24] Evidence from the current study of cadaveric spines provides strong support for an association between endplate lesions and lumbar DD, as well as a dosage effect of larger size lesions associated with more severe DD.

Endplate lesions may initiate a pathological cascade which ultimately results in the degenerative changes in the adjacent disc. The loss of nucleus matrix contents through the endplate breach[25] and the subsequent inflammatory and autoimmune reactions could destroy the homostasis within the disc and impair the metabolism of disc cells.[26,27] The activated reparatory reactions may further block the marrow contact channels and impede nutrient supply to the disc.[28] In addition, endplate lesions alter the distribution of matrix compressive stress in the adjacent disc, inhibiting disc cell metabolism [29] and instigating internal disc disruption, which eventually may lead to progressive structural failure of the disc.[30]

There are several strengths of the current study over previous studies. First, the visual inspection of the vertebral endplates examined the entire endplate and measured the lesion size directly and, thus, was inherently superior to radiological evaluation. MR is unlikely to detect all Schmorl's nodes and endplate lesions as only a few sections of the vertebra are typically sampled, with added limitations of resolution, inter-slice space and partial volume effects. This is supported by the substantial difference in prevalence of Schmorl's nodes observed on images and measured directly from cadaveric vertebrae, as mentioned previously. Second, discography provides a reliable and valid DD measurement.[19,31] Designed to measure the integrity of the inner annulus fibrosus of the disc, discography assessments are not influenced by bony degenerative features, which could bias associations between endplate lesions and DD. Third, appropriate statistical models were

used to examine the local interactions between endplates and adjacent discs. Conversely, earlier studies typically measured Schmorl's nodes and DD by spinal level and then summed the scores for the entire spine region studied.[16,32] The use of global DD scores based on the whole lumbar spine may have diluted the associations studied as an association between endplate lesions and DD, if present, is more likely a consequence of local interactions. This later point was supported by our observation of a clear dosage effect of greater lesion size and more severe adjacent DD.

Echoing a clinical CT study which suggested that larger endplate size was associated with disc herniation in men,[10] findings of the current study support an association between greater endplate size and more adjacent DD. The mechanism underlying this association remains unexplained. Based on our earlier MRI findings that greater axial disc size is a risk factor for DD,[9] we speculated that it is larger size of the disc, rather than the endplate, that explains the association studied. The axial area of the endplate measured reflects the 'original' size of the corresponding intervertebral disc. Furthermore, we identified that the size of the central endplate, but not the epiphysial rim, was associated with the adjacent DD. As the nucleus pulposus lies between the central endplates,[12] we postulate that larger discs, especially discs with large nucleus pulposus, are more susceptible to degeneration than smaller discs. Although a larger central endplate tends to have more marrow channels supplying nutrients to the disc,[33] a larger nucleus also has more cells demanding nutrients and nutrient transport within the nucleus matrix may be impeded by a larger size. Thus, the association between larger endplates and more adjacent DD may be due to an overall decreased efficiency of nutrient supply to a large disc.

Endplate shape, as judged from sagittal MR images, has been correlated to adjacent DD in surgically treated patients[8], with flat and irregular endplates associated with more severe DD when compared with concave endplates. While our findings support an association of irregular endplates with adjacent DD, whether the irregular endplate shape is a cause or consequence of DD remains unknown. Endplate concavity was thought to be an adaptation of age[34] or axial compression loading.[35] By sinking into the vertebral body, the disc was believed to be protected,[34] and more endplate concavity was associated with less DD.[8] Using accurate digital measurements, however, the current study supports the observation with respect to the cranial endplate, but not for the caudal endplate. This difference in associations between cranial and caudal endplates, which was also present with respect to the association of greater endplate circularity and DD[10], is puzzling, but may be due to the structural asymmetries between the endplates. For example, the cranial endplate is more concave, thicker and has greater BMD than the corresponding caudal endplate.[11,36] In contrast to endplate fracture, which has been reported to be more common in the caudal side (to a disc) than in cranial,[37] yet the distribution of lesions between cranial and caudal endplates was not different in the current study. This may be due to the definition of endplate lesions we used, which included endplate pathologies other than fracture.

There are some limitations in this study that need to be noted. All subjects were men and most of them were employed labour workers. Thus, findings on the prevalence of endplate lesions may not be generalizable to women and non-labour employees. Second, some vertebrae were missing in the spine archive. It is possible that the prevalence rate of endplate lesions may have been underestimated due to missing. Third, endplate lesions as

defined in the present study included a variety of endplate pathologies. Thus, it is not appropriate to compare the related findings specifically to those of Schmorl's nodes. Although there is no currently available protocol to distinguish different endplate lesions from one another, it is possible that different endplate lesions may play distinct roles in the pathogenesis of DD.

In summary, endplate lesions were common and were associated with adjacent DD, with greater size associated with more severe adjacent DD. Findings strongly suggested that the integrity of the vertebral endplate is essential to maintain the health of the adjacent intervertebral disc. The morphometrics of the endplate, particularly area reflecting axial disc size, may play a modest role in the pathogenesis of DD.

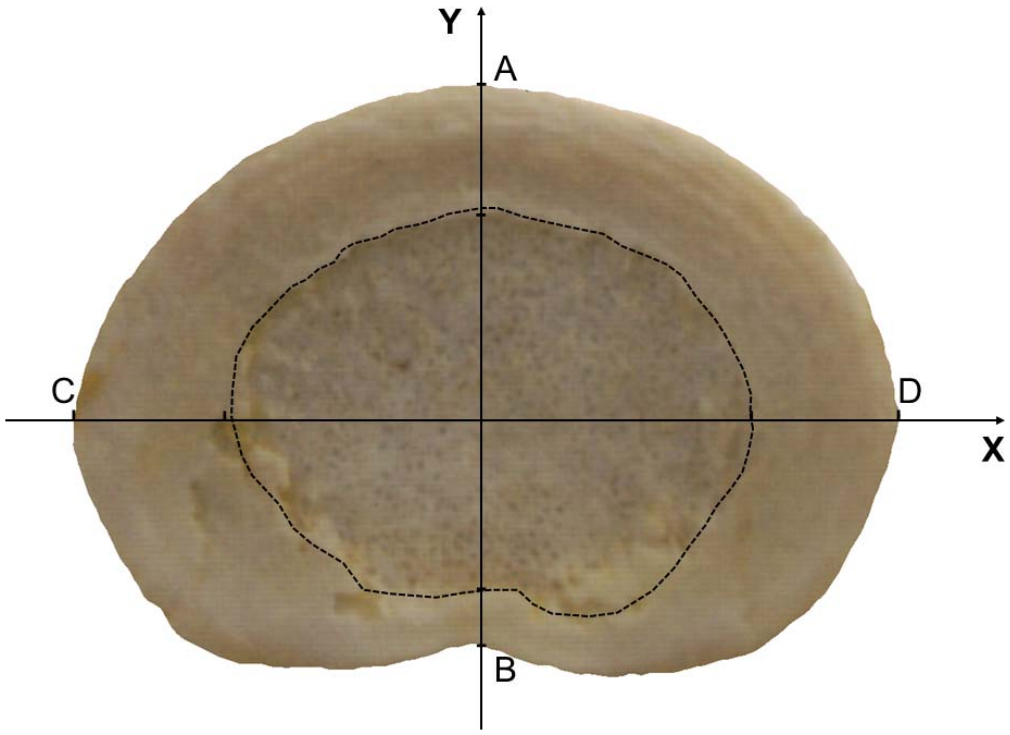

Figure 4-1: A typical scanned 3D image of vertebral endplate (cranial endplate of L3/4 disc). The vertebral endplate consists of a ring of solid epiphysial rim outside and a porous central endplate inside. Diameter measurements were acquired from X axis (the mid-coronal plane) and Y axis (the mid-sagittal plane). Line AB and CD were measured as AP and transverse diameters of the endplate, respectively. Three points at the axis (A, B and C) were used to define an axial reference plane for measuring the concavity of the endplate. The central endplate and the epiphysial rim were later radiologically separated along their boundary (dash line in the figure) to measure their surface areas.

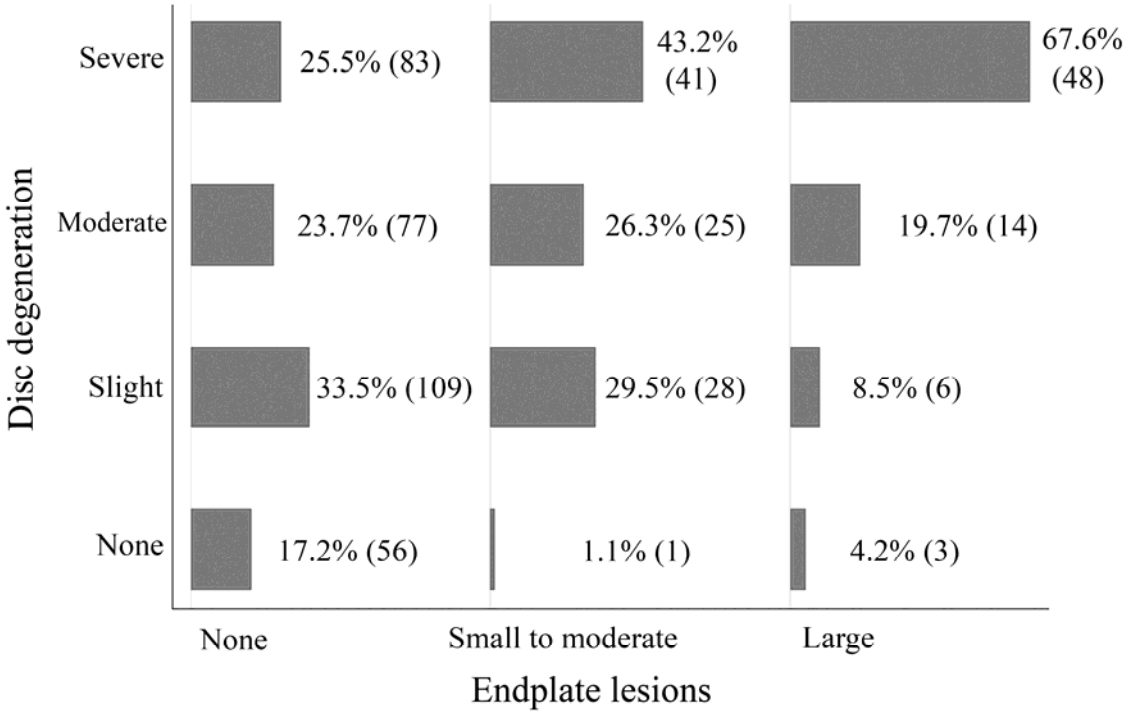

Figure 4-2: The distribution of disc degeneration by the size of endplate lesion.

* Data from cranial and caudal endplates were presented together (N=491). If lesion data were available for both adjacent endplates of a disc, the degeneration score of the disc were then repeatedly used.

** The percentages referred to the total number of lesioned endplates in that size.

Table 4-1: Digital geometric measurements of lumbar vertebral endplates*

Disc	*Endplate*	N	*Endplates*				*Central Endplate*	*Epiphysial rim*
			APD	TD	Depth	Area	Area	Area
T12/L1	Cranial		NA				NA	NA
	Caudal	36	34.8±3.2	45.3±3.7	0.3±0.7	12.5±2.1	7.3±1.3	5.9±1.5
L1/2	Cranial	39	35.5±2.9	47.6±4.0	1.0±0.7	14.1±2.2	7.4±1.0	6.7±1.7
	Caudal	61	35.7±2.3	47.0±3.5	0.5±0.9	14.4±2.1	7.9±1.3	6.5±1.5
L2/3	Cranial	61	36.2±2.8	50.3±3.6	1.2±0.6	15.4±2.3	7.5±1.4	8.0±1.9
	Caudal	19	35.7±3.1	48.0±3.1	0.8±0.9	14.9±2.4	7.8±1.7	7.1±1.3
L3/4	Cranial	19	35.6±2.8	51.5±3.4	1.5±0.7	15.6±2.1	6.7±1.5	9.0±2.2
	Caudal	73	35.8±2.8	51.3±3.7	0.7±0.9	15.8±2.4	8.2±1.4	7.7±2.1
L4/5	Cranial	73	36.1±2.8	53.6±3.7	1.9±0.8	16.7±2.4	7.9±1.9	8.8±2.2
	Caudal	69	35.5±2.9	53.0±4.1	0.5±0.7	16.1±2.5	8.2±1.8	7.8±2.4
L5/S1	Cranial	72	34.7±3.2	52.3±4.7	1.5±0.9	15.8±3.0	8.3±2.2	7.4±2.2
	Caudal	69	33.8±3.5	51.2±5.3	1.0±1.1	15.1±2.8	8.2±1.8	7.8±2.4
Overall	Cranial	264	35.6±3.0	51.4±4.5	1.5±0.8	15.7±2.6	7.8±1.8	7.9±2.2
	Caudal	327	35.2±3.1	50.0±4.9	0.7±0.9	15.3±2.5	8.0±1.7	7.1±2.1
Range	Cranial	264	26-44.2	38-69.7	0-3.7	9.7-27.7	3.7-17	3.3-15.7
	Caudal	327	23-44.9	36-69.3	0-3.9	10.2-23.9	3.8-17.3	3.2-16.0

***:** Data were mean ± standard deviation.

APD: anterior-posterior diameter (mm); TD: transverse diameter (mm); Depth: mean depth of concavity (mm); area: surface area (cm^2).

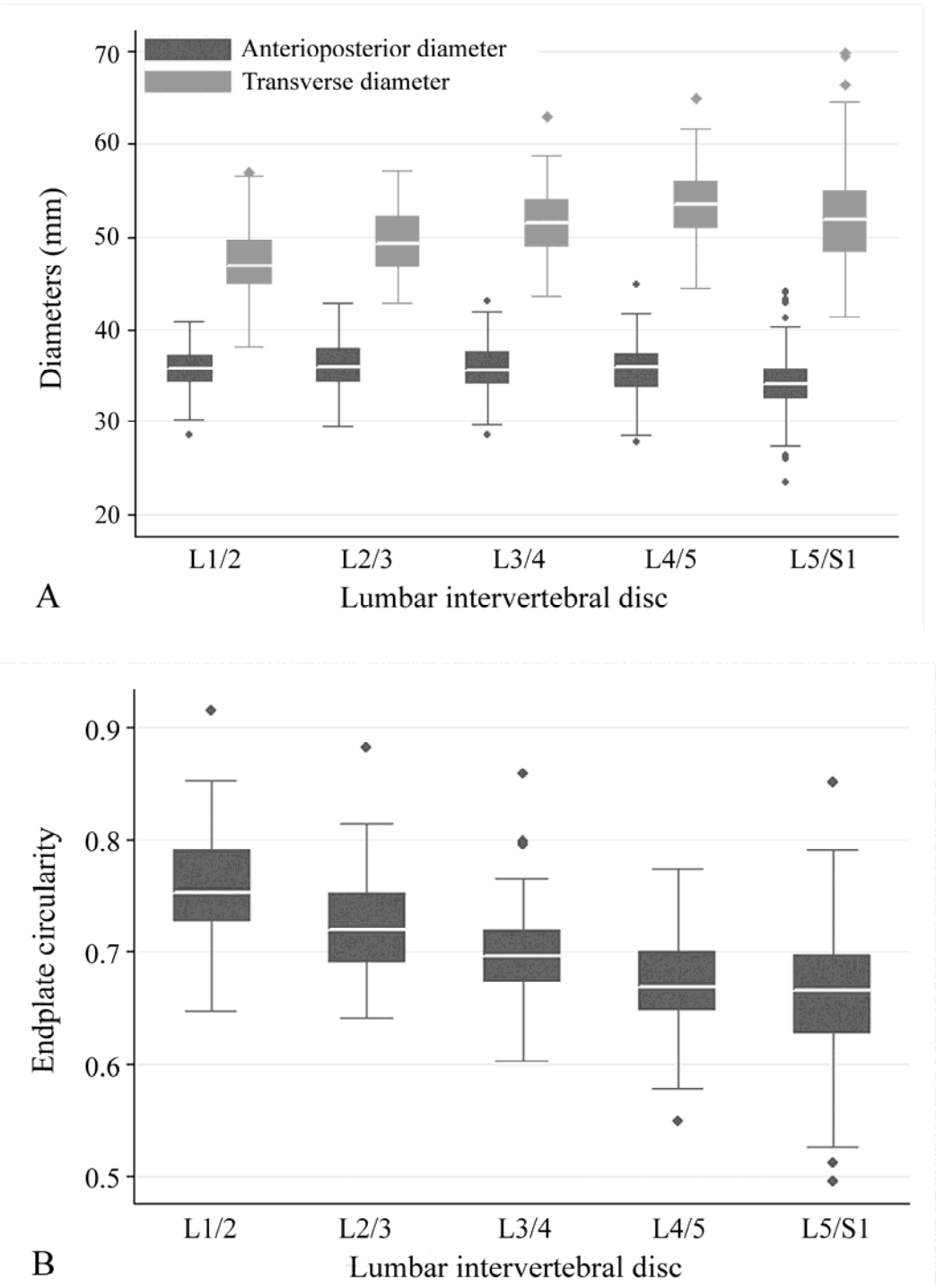

Figure 4-3: The geometry of the cranial endplate in different spinal levels. **A**: diameters; **B**: circularity.

Table 4-2: Associations between endplate morphometrics and lesions and DD: Results from univariable regressions*

Independent Variables	*Cranial endplate (N=235)*		*Caudal endplate (N=256)*	
	OR	**P**	**OR**	**P**
Endplate Shape				
Concave	1.00		1.00	
Flat	1.71	0.272	0.88	0.641
Irregular	2.71	0.052	2.62	0.019
Concavity Apex				
Single apex	1.00		1.00	
Double Apex	0.89	0.689	0.36	0.012
No Apex	2.03	0.043	0.81	0.464
Endplate Lesions				
None	1.00		1.00	
Small to moderate	2.24	0.010	4.28	0.000
Large	4.94	0.000	4.84	0.000
Digital measurements				
Depth of concavity	0.71	0.020	0.92	0.541
Volume of concavity	1.00	0.173	0.99	0.864
Circularity	1.07	0.004	1.04	0.145
Area measurements				
Axial area	1.19	0.047	1.23	0.003
Surface area	1.18	0.025	1.18	0.005
Central endplate area	1.23	0.020	1.32	0.002
Epiphysial Rim area	1.05	0.408	1.07	0.229

*: Disc degeneration was the dependent variable. Age and lumbar region (upper vs. lower) were controlled.

Table 4-3: Associations between endplate morphometrics and lesions and DD: Results from multivariable regression*

Independent Variables	Disc degeneration (N=300)		
	OR	**95%CI**	***p***
Age	1.06	(1.03, 1.10)	0.000
BMI	0.99	(0.93, 1.04)	0.649
Lumbar region			
Upper lumbar	1.00		
Lower lumbar	6.04	(3.65, 10.0)	0.000
Endplate lesions			
None	1.00		
Small to moderate	2.31	(1.14, 3.79)	0.001
Large	3.54	(1.93, 6.48)	0.000
Endplate morphometrics**			
Circularity	1.03	(0.98, 1.08)	0.208
Concavity	0.78	(0.51, 1.20)	0.258
Axial Area***	1.20	(1.02, 1.41)	0.027

*:Data from the paired cranial and caudal endplates were merged together in this final model.

** When endplates with lesions were excluded, results were similar for endplate morphometrics.

*** If the axial area of the endplate was replaced with the area of the central endplate, OR=1.22, p=0.018. If the axial area of the endplate was replaced with the area of the epiphysial rim, OR=1.06, p=0.40.

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CHAPTER 5

Lumbar Vertebral Endplate Lesions: Part I

Prevalence, Pathological Classification and Association with Age *[4]

5.1. Introduction

In searching for the causes of back pain, much emphasis has been focused on the largely avascular[1] and aneural[2,3] intervertebral disc. With sporadic blood and nerve supply limited to the outmost layer of the annulus, the disc as a source of back pain remains controversial. Meanwhile, the endplate, a thin structure adjacent to the disc that is rich in both vessels[4] and nerve endings[3,5] in its osseous component, has received little attention. Probably due to increased difficulties in acquiring spine specimens and limited visualization of the endplate using standard radiological approaches, the role the endplate may play in disc degeneration and back pain is not clear.

Lying between the vertebral body and the intervertebral disc, the endplate is essential to maintain the morphological integrity and physiological function of the intervertebral disc. It is the physical shield separating the disc from the vertebra[6] and the main gateway of nutrient supply to the disc.[1,7] As a mechanical interface between the stiff bone and resilient disc, the endplate is the weakest portion of the vertebra-disc complex[8] and is predisposed to mechanical failure.[9] Taking into account the special location, structural fragility, and multiple physiological functions to which it contributes, the endplate may be vulnerable to a number of common factors affecting the spine, resulting in clinical consequences. Yet, research on endplate pathology is rare.

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In fact, most endplate pathologies or lesions have been generally regarded as Schmorl's nodes. First recognized by Luschka about 150 years ago and further described in detail by Schmorl in 1927,[10] Schmorl's nodes are the protrusion of disc tissue through the endplate into the vertebral marrow.[11] Although common, to date the understanding of Schmorl's nodes is limited and somewhat obscure. The pathogenic origin of Schmorl's nodes, such as congenital[11-13] or traumatic,[14-16] remains controversial, as do associations between Schmorl's nodes and disc degeneration[12,17,18] and back pain.[15,19,20] Even the association between Schmorl's nodes and age is not clear: Schmorl's nodes were either found to form at an early age,[13] to be present more commonly in older adults[10] or at equivalent frequencies in subjects above and below 50 years of age.[12]

Among the factors underlying these inconsistencies are variations of study materials and definitions of Schmorl's nodes, which may have influenced the prevalence and distribution patterns of endplate lesions, as well as biased or diluted associations. The prevalence rate of Schmorl's nodes reported varies dramatically from 9% to 75%,[12,20-22] with that evaluated from cadaver spines being much higher than that acquired from magnetic resonance (MR) images. On the other hand, Schmorl's nodes usually were simply defined as local 'indentations' or 'defects' on the endplate, especially in radiological studies, which may fail to differentiate Schmorl's nodes from other endplate morphological abnormalities, such as endplate fractures.

It is clear that Schmorl's nodes are not the sole pathology affecting the vertebral endplate. A few other endplate lesions, such as fracture[9,23] or micro-trauma,[24] vertebral rim lesions,[25] endplate destructive lesions,[26,27] as well as endplate calcification,[28] have been observed. Yet, a systematic study of lumbar vertebral endplate lesions is currently absent.

While the clinical significance of vertebral endplate signal changes (Modic changes)[29] remains controversial, their underlying pathologies largely remain unknown.[30] Comprehensive studies of endplate lesions using large cadaveric samples are needed to deepen knowledge of endplate lesions, as such studies may not only contribute to the understanding of local pathological interactions between the vertebral body and the intervertebral disc, but also may provide important clues and novel insights into the pathogenesis of disc degeneration and back pain.

Based on our previous observations, we proposed a classification system to assist in identifying the etiologies of different types of endplate lesions and their effects on disc degeneration and back pain. Using a large sample of lumbar spines, the purpose of this series of studies was to: 1) determine the prevalence of endplate lesions; 2) classify these lesions according to their morphological characteristics; and 3) explore the associations of these findings with age, body mass index (BMI), occupation, disc degeneration, back pain and back injury history. In this Part I, we introduce the classification system and report the prevalence and distribution of endplate lesion types and their associations with Age and BMI. As a primary focus of the study is the association between endplate lesions and disc degeneration, we specify the endplates as cranial or caudal relative to the intervertebral disc.

5.2. Materials and Methods

Samples

The study was approved by the Health Research Ethics Board of the University of Alberta. We had access to a lumbar spine archive of 157 Caucasian cadavers of men who had passed away in hospital wards.[31,32] The inclusion criteria for the archive were men below

the age of 64 years, a history of employment immediately before hospitalization and a short history of illness or disease. Most of the subjects died from cardiovascular accidents. Exclusion criteria were chronic illness, a long hospitalization and death from cancer or infectious diseases. Age, body weight, height and body mass index (BMI, kg/cm^2) were obtained at the time of death.

After a routine autopsy examination of the lumbar spines, discography was performed to evaluate disc degeneration.[31] The soft tissues around the vertebra were then removed and the vertebrae were dried in a fume hood at room temperature. The bones were archived in a cabinet under room temperature and humidity. Some of the vertebrae in this archive were lost in preservation and some others were sectioned to make histological slices. All the available vertebrae from the lumbosacral region (from L1 to S1 vertebra) were included. There were 649 vertebrae (74 L1, 112 L2, 64 L3, 132 L4, 135 L5 and 132 S1) and archived discography data for 443 corresponding adjacent intervertebral discs (L1/2~L5/S1) from 136 male human lumbosacral spines included in the current study. Eighteen vertebral endplates were partly damaged and thus were excluded, leaving a total number of 1148 vertebral endplates (510 vertebral endplates cranial to the discs and 638 caudal to the discs) in this study. The mean age of the subjects was 52.2 years (range 21-64 years).

Evaluation of endplate lesions

An adult vertebral endplate consists of an **epiphysial rim**[33] (or **epiphysial ring**[34]), which is a closed ring of cortical bone at the peripheral margin of the endplate, and a **central endplate**, which is the inner portion of the endplate (**Figure 5-1**).[33] Derived from the annular epiphysis, the epiphysial rim is the place where the annulus fibrosus anchors and is

relatively smooth and solid, compared with the thin and porous central endplate which is covered by cartilaginous endplate.[11] In the development of the embryonic vertebral column, the notochord vertically transverses the center of the sclerotomes, the precursors of the vertebrae.[35] Thus, the **center** of a vertebral endplate is the place where the notochord regresses and is relatively solid and has less pores, as compared with the remaining portion of the central endplate (**Figure 5-1**).[11] This characteristic **endplate center** could be clearly identified in most of our samples.

Classification of endplate lesions

The examination of endplate lesions was performed by an orthopaedic surgeon (Y.W), by visually inspecting the entire vertebral endplate. In order to distinguish some tiny lesions from normal pores of the endplate, only those larger than 1mm in diameter were counted as endplate lesions. First, the endplate lesions were evaluated as present or absent. If present, the lesions were further classified into one of following four types based on their morphological features:

1) **Schmorl's nodes (Figure 5-2 A&F)** were defined according to the classical description[11] as local indentations on the vertebral endplates with an osseous casing. Thought to be the result of a chronic pathological process, Schmorl's nodes usually had a smooth and regular margin and an even bottom. They could have either a round or long appearance.

2) **Fracture** lesion **(Figure 5-2 B&C)** included small fissures, clefts, fractures and compression. Suspected to be a result of acute trauma, fracture lesions usually were long or irregular in shape, with a rough margin (with the exception of compression). There was no obvious bony casing; cortification at the bottom of the lesions was not formed or only

partly formed. Therefore, trabecular bone was exposed. In some cases, osseous callus was noticed. Vertebral compression was identified as severe indentation of the endplate.[36] The endplate usually was intact and trabecular bone was not exposed. In some cases, wedging of the vertebra and signs of reparative reactions were apparent.

3) **Erosion (Figure 5-2 D, E&F)** was defined as the break-down of the endplate in a diffusive manner. These irregular and shallow lytic lesions were without apparent bony casing and occasionally spread over the whole endplate, involving both the central endplate and epiphysial rim. The osseous endplate was somewhat eroded while reactive bone formation was not provoked and thus, underlying trabecular bone was widely exposed. The lesioned endplate had a worm-eaten appearance. The prominent features which differentiated erosion from Schmorl's nodes were the outward growth (frequently wide-spread), lack of bony cortification and an irregular shape.

4) **Calcification (Figure 5-2 G&H)** was defined as intensive calcium deposition upon the endplate. The accumulated calcium deposits substantially solidified the endplate and roughened its surface. Usually there was no apparent defect on the endplate. In some cases the calcified tissue covering the vertebral endplate was so intensive that the boundary between the central endplate and the epiphysial rim was obliterated. Commonly observed small, isolated calcium deposits[28] were not included in the study.

If two or more types of lesions were observed on an endplate, the predominant lesion was recorded.

Number of endplates with lesions

In addition to recording the specific type and the location of lesions, the number of endplates with lesions, regardless of lesion type, was counted for each intervertebral disc.

Correspondingly, intervertebral discs were grouped as having no endplate lesions, a single endplate with lesions, or both endplates affected.

Distribution of lesions within the endplate

The involved endplate component, such as the central endplate, the epiphysial rim or both, was recorded. Whether or not the endplate center was involved was examined separately. The endplate was divided into 5 zones as shown in **Figure 5-1.** The location of the lesion was recorded as anterior, central, posterior or lateral, according to the predominantly involved region. If the entire endplate was affected, the location of the lesion was recorded as 'whole'.

Size of endplate lesions

According to the involved area, a four-grade ordinal scale was used to rate the size of the lesions. The lesion size was given a rating of **none** if absent; **small** if it involved less than 1/4 of the area of the central endplate; **moderate** if it affected 1/4 to 1/2 of the area of the central endplate and **large** if the lesion was larger than half of the central endplate area. If nearly the entire endplate was affected, this was specifically noted.

A random sample of 174 vertebral endplates was re-evaluated one week later to examine the intra-rater reliability of endplate lesion measurements.

Statistical Analysis

Kappa statistics were used to examine the intra-rater reliability of the measurements of endplate lesions. Descriptive statistics were used to depict the prevalence and distribution patterns of endplate lesions. χ^2 tests were used to compare the prevalence of different types of endplate lesions and their distributions. Logistic regressions were used to explore the associations of endplate lesion findings with age and BMI. First, the dummy measurement

of endplate lesions was analyzed. Then the individual endplate lesion type was analyzed separately using nominal logistic regressions. Statistical analyses were performed using STATA (Version 9.2, StataCorp LP, USA). As data acquired for endplates were clustered in a lumbar spine, the command 'cluster' in STATA was used to account for the dependency in all regression analyses.

5.3. Results

Prevalence of endplate lesions

The intra-rater reliability of the endplate lesion measurements using the classification system was found to be "excellent" (kappa=0.80-0.89, **Table 5-1**), according to Landis and Koch.[37]

Overall, 45.6% (524) of the 1148 endplates studied had some sort of lesions. Schmorl's nodes (22%) were the most common lesions in our sample, followed by erosion (14.1%) and fracture (6.3%). The intensive calcification was the least common lesion, only observed in 3.3% of endplates (**Table 5-2**).

Size of lesions

Of the 524 endplate lesions, 69.1% (362) were evaluated as small, 16.2% (85) were rated as moderate and the remaining 14.7% (77) were rated as large, with 37 of them (7.1% of all lesions) involving almost the entire endplate.

While most Schmorl's nodes (94.4%) were small, most calcification lesions were rated as large (64.9%). About half of the fracture (48.6%) and erosion (50.0%) lesions were rated as small and the remaining were moderate or large.

Distribution of lesions within the endplate

Both the central endplate and the epiphyseal rim were often affected (**Table 5-2**). While most Schmorl's nodes involved only the central endplate, calcification lesions were more likely to involve the central endplate and the epiphysial rim together. The patterns of involved endplate components were most similar between the fracture and erosion lesions.

While most Schmorl's nodes were located in the central portion of the endplate, both fracture and erosion lesions tended to affect the anterior and lateral regions of the vertebral endplate. Of the calcification lesions, 47.4% affected the whole endplate and another 34.2% involved the posterior portion of the endplate **(Table 5-3)**.

The center of the endplate, where the notochord regresses, was involved in 82.5% (208) of Schmorl's nodes, but only 27.8% (20) of fractures and 24.1% (39) of erosion lesions.

Distribution of lesions between the cranial and caudal endplates

Of the 524 endplate lesions identified, 44.7% (234) were on the endplates cranial to intervertebral disc and 55.3% (290) were on the caudal endplates. The lesion types, sizes and involved endplate components were not statistical different between the cranial and caudal endplates (χ^2 test, $p>0.05$ for all).

Among the 433 intervertebral discs that had measurements for both adjacent endplates, 33.3% (144) of discs had lesions on both adjacent endplates, 24.7% (107) had lesions on only one endplate and the remaining 42% (182) of discs had no lesions on either endplate. The presence of lesions on one endplate was statistically associated with the presence of lesions on the opposing endplate (OR=8.0, $p<0.001$, 95%CI (5.3, 12.3)). Specifically, 67.3% (113) of endplates with Schmorl's nodes, 59.3% (32) of endplates with fracture,

78.1% (107) of endplates with erosion lesions and 94.3% (33) of endplates with calcification lesions had lesions on opposing endplate.

Distribution of lesions by disc level and lumbar region (Figure 5-3)

When all types of endplate lesions were aggregated, there was no statistical difference in prevalence rates between the upper (L1/2, L2/3 and L3/4 discs) and lower lumbar regions (L4/5 and L5/S1 discs) (χ^2 test, p=0.64). However, Schmorl's nodes (79%) were more common in the upper lumbar spine, and erosion (72.8%) and calcification lesions (92.1%) were more common in the lower lumbar region. For endplate fracture lesions, the prevalence rate was similar between the upper (55.6%) and lower (44.4%) lumbar regions.

Associations of endplate lesions with age

The presence of any type of endplate lesion was statistically significantly associated with age (OR=1.06 for each additional year, p<0.001) but not with BMI (OR=0.99, p=0.78). When the associations between specific types of endplate lesions and age were examined separately, similar results were obtained (OR=1.04, 1.05, 1.07 and 1.19 for Schmorl's nodes, fracture, erosion and calcification, respectively, p=0.000 to 0.003). Greater age was also associated with the presence of lesions on both adjacent endplates of a disc (OR=1.09, p<0.001), as compared with discs without endplate lesions. In addition, larger size of any type of endplate lesion was associated with greater age (OR=1.06, p<0.001). Similar associations between larger lesion size and greater age were observed for individual endplate lesion types (OR=1.04~1.18, p=0.000 to 0.003).

5.4. Discussion:

A morphological classification system was developed to identify four types of lumbar vertebral endplate lesions: Schmorl's nodes, fracture, erosion and calcification. Using this protocol, a large sample of cadaveric lumbar vertebral endplates were studied to determine the prevalence and distribution patterns of endplate lesions, and their associations with age and BMI. Endplate lesions were common findings in the lumbar spines of middle-aged men and tended to affect both adjacent endplates of a disc simultaneously. Schmorl's nodes were the most common type of endplate lesion. The distribution patterns of the various types of endplate lesions differed across the lumbar spine and within the endplate, suggesting they may have different pathogenic origins. Yet, despite the distinct pathological features and distribution patterns of the different types of endplate lesions, the presence and size of all lesions were associated with greater age, suggesting age or associated factors may play an important role in their pathogenesis. Previous reports of "Schmorl's nodes", which were usually judged broadly as endplate defects, may consist of different endplate pathologies.

Using cadaveric samples, the current study revealed that nearly half of the vertebral endplates studied had some sort of lesion. This is a strikingly high prevalence rate. Due to the lack of standard evaluation criteria and other variations of methods and materials, the prevalence rates of endplate lesions reported in the scientific literature vary dramatically. Taking Schmorl's nodes as an example, the prevalence evaluated from radiological images (9.4%~30% of spines)[20,21] is much lower than that from cadaveric samples (48%~75% of spines).[12,17,22,38] In another histological study, Schmorl's nodes were observed in over 80% of samples from subjects older than 60 years.[10] Vertebral rim lesions, another endplate pathology different from Schmorl's nodes, was found in 34% of endplates of selected

spinal segments, as evaluated from histological slices.[25] The prevalence of any forms of endplate lesions, however, has not been reported previously.

There are some factors that may contribute to a high prevalence rate of endplate lesions in the current study. Schmorl's nodes have been found to be very common in men and in Caucasian.[12,22] Further, a broad definition was used to encompass multiple endplate lesions, including even small endplate discontinuities. In addition, the entire endplate was thoroughly inspected, which avoided the limitations of sampling only a few sections of the endplates, as has been the case with slab radiography[12,17,25] and MRI.[20] The failure of radiological techniques to detect all endplate lesions[20] highlights the importance of the current findings, which were derived from cadaveric samples.

The different types of endplate lesions based on morphological characteristics had different distribution patterns. In accordance with traditional descriptions,[11,12] Schmorl's nodes identified in our samples typically were small endplate indentations with osseous walls, and were more common in the upper lumbar region. They also preferentially affected the endplate center where the notochord regresses, which may be a developmental weak spot. The predisposed location, regular shape and well-formed bony walls indicate these nodes likely resulted from a chronic, mild process of nucleus protrusion which may not be related to acute trauma. Concordant with predominately anterior and lateral flexion motions of the lumbar spine,[33] the anterior and lateral portions of the endplate were typically involved in both fracture and erosion lesions. Moreover, the solid epiphysial rim was also frequently involved in both lesions, suggesting they may be two different pathological forms resulting from a common etiology, such as acute endplate trauma. Mainly observed in the lower lumbar region, the calcification lesions may relate to some

segment-specific causes, or may be the end stage of some aggressive endplate pathologies. Complementary to Schmorl's conclusion that Schmorl's nodes "may appear anywhere along the surface of the vertebral body which is not covered by the rim",[11] we also observed the vast majority of Schmorl's nodes appeared in the central endplate; however, 6.8% of Schmorl's nodes localized within the epiphysial rim and some other nodes (4.8%) extended from the central endplate into the epiphysial rim.

No difference in the distribution of endplate lesions between cranial and caudal sides was observed in the current study. This somewhat contradicts previous observations that endplate fracture is more common in the endplate caudal than cranial to a disc[39] and findings that the cranial endplate is thicker[39,40] and stronger[41] than the corresponding caudal endplate. This may be due to the inclusion of multiple endplate pathologies in this study. It is likely that etiologies other than purely mechanical were involved in the pathogenesis of these endplate lesions, which was further supported by the finding that endplate lesions tended to affect both adjacent endplates of a disc together. This pattern is similar to that of Modic changes,[42] highlighting a close relationship between the disc and endplates.

Different pathogenic origins and clinical significance of Schmorl's nodes have long been reported. Schmorl's nodes have been distinguished as 'idiopathic' and 'traumatic',[11] 'central' and 'marginal',[43] 'symptomatic' and asymptomatic',[44] 'developed' and 'developing',[45] 'type A and B',[23] and 'edematous' and 'non edematous'.[46] Evidence from the current study supports that Schmorl's nodes, particularly those evaluated from radiological images, may consist of different types of endplate lesions. Traditional Schmorl's nodes are usually located in the center of the endplate where bone is the

thinnest.[39] Small and less aggressive, as evident in the present study, they may derive from congenital causes. However, if the definition of Schmorl's nodes was the presence of any endplate defect, the fracture and erosion lesions identified in our study, which were typically large and extensive, also could have largely been regarded as Schmorl's nodes.

Identifying and differentiating endplate lesions may substantially contribute to the understanding of Modic changes, which are common MR findings in the lumbar spine.[42] With limited cases of pathology reports,[29,47] currently the pathologies underlying these endplate signal changes are not clear.[30] Although the exact MR manifestations of endplate lesions identified in our study remain unknown, endplate defects and accompanying inflammatory edema in the vertebral marrow may be two main signs. The endplate erosion we identified usually was shallow but extensive, with no effective cortification. Thus, it is possible that the morphological defect on the endplate may not be visible on MR images in some cases, particularly when filled by granulation tissues. Edema resulting from the extensive erosion of the endplate, however, could spread or penetrate aggressively into the vertebral bone marrow, demonstrating prominent signal changes on MR images depicted as Modic changes. In addition, the distribution patterns of endplate erosion, particularly the higher prevalence in the lower lumbar region and tendency to affect both adjacent endplates of a disc together, are similar to that of Modic changes.[42] Our data suggest that endplate erosion may be one of the pathologies underlying Modic changes. However, further studies are needed to bridge these endplate lesions to clinical radiological findings.

Among the study limitations is that all the subjects are men and the prevalence of endplate lesions may differ in women. Another concern is that some of the vertebrae were missed in the archive. As the endplate lesions were assessed from dried vertebral

endplates, the pathological changes in corresponding cartilaginous endplates remain unknown.

To summarize, four types of endplate lesions were identified based on their morphological characteristics. Endplate lesions are common findings in the lumbar spine and were closely related to age. The classification of endplate lesions may help to explain the inconsistencies of previous reports on Schmorl's nodes, and will further enhance the understanding of Modic changes and lumbar degeneration. With different distribution patterns, the pathogenic origins of individual endplate lesions may be different, as well as their pathological roles in disc degeneration and back pain, as will be further investigated in the second part of this study.

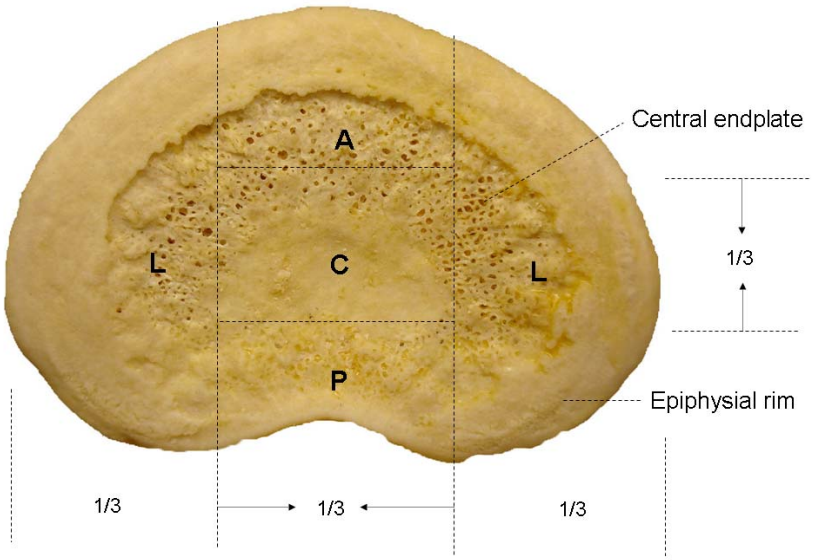

Figure 5-1: A vertebral endplate consists of an epiphysial rim and central endplate. Note that the endplate center is relatively solid while the remaining portion of the central endplate is porous. In the present study, the vertebral endplate was divided into 5 sub regions as indicated. The location of endplate lesion was recorded as anterior (A), central (C), posterior (P) and lateral (L) according to the predominantly involved sub region.

Figure 5-2 A: A typical Schmorl's nodes at the cranial endplate of a L2/3 intervertebral disc.

Figure 5-2 B: Fracture lesion, a typical transverse cleft across the central endplate. The trabecular bone is exposed.

Figure 5-2 C: Fracture lesion, a lateral compression at the caudal endplate of a L1/2 disc. At the base of the lesion the endplate is broken.

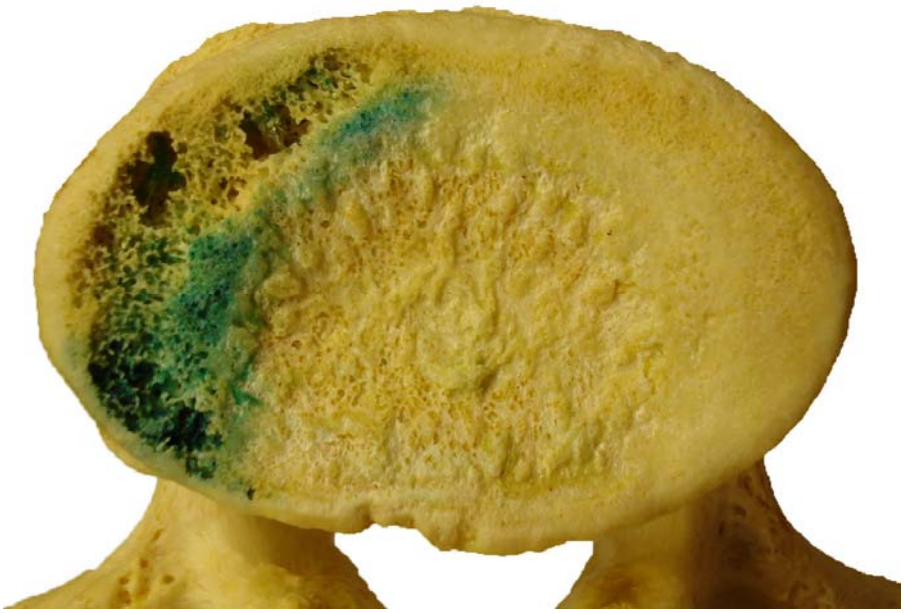

Figure 5-2 D: An erosion lesion on the lateral portion of an endplate cranial to a L4/5 disc. The shape is irregular and there is no obvious cortification. The green color is due to the use of methylene blue in discography in some cases.

Figure 5-2 E: Erosion lesions involve the epiphysial rim on both lateral sides of the caudal endplate of a L4/5 disc. The lesion has a worm-eaten appearance.

Figure 5-2 F: Diffusive erosion lesions (lateral) and an oval Schmorl's node (in the center) co-exist in a cranial endplate of a L4/5 disc. With the bony walls around well formed, the trabecular bones under the Schmorl's node are covered. With no apparent cortification, the trabecular bones under the erosion are exposed.

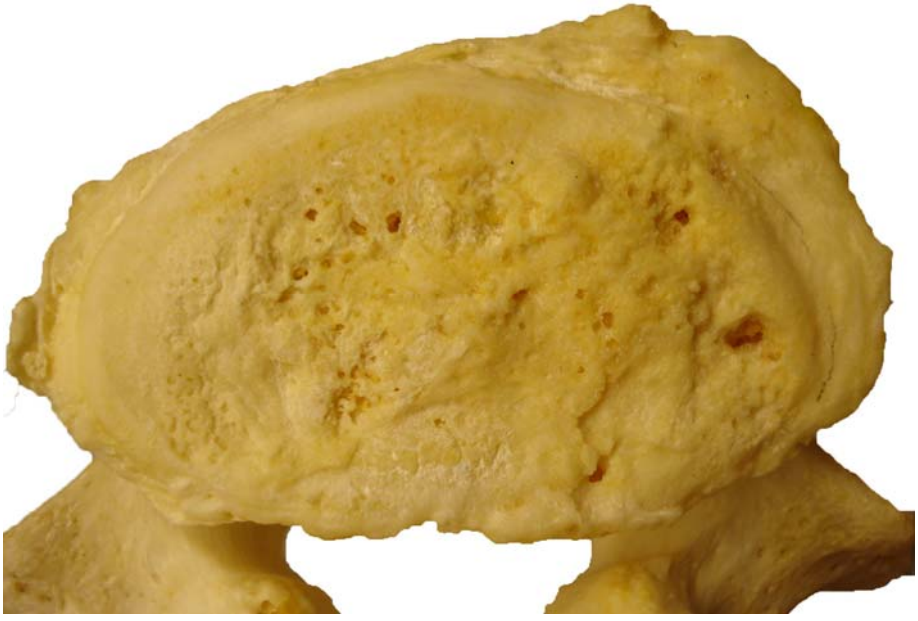

Figure 5-2 G: Calcification. The intense calcification roughened the endplate and covers the boundary of the central endplate and the epiphysial rim. Significant osteophytes formed around the vertebral rim.

Figure 5-2 H: Calcification lesions. The endplate surface was roughened and jagged, with the border of central endplate and rim disappearing.

Table 5-1: Inter-rater reliability of endplate lesion measurements

Measurement	*Kappa*	*95% CI*
Endplate lesion type	0.80	(0.72, 0.88)
Involved endplate components	0.83	(0.76, 0.91)
Involving endplate center	0.89	(0.82, 0.97)
Lesion location	0.83	(0.76, 0.90)
Lesion size*	0.86	(0.77, 0.94)
Number of endplates with lesions	0.85	(0.76, 0.94)

* Measurement is ordinal and thus, weighted Kappa is reported.

Table 5-2: The prevalence and involved endplate components for different types of endplate lesions

Endplate lesions	*Prevalence**	*Involved endplate components***		
		Central endplate	*Epiphysial Rim*	*Both*
Schmorl's Nodes	22%(252)	88.5%(223)	6.8%(17)	4.8%(12)
Fracture	6.3%(72)	20.8%(15)	29.2%(21)	50.0%(36)
Erosion	14.1% (162)	14.8%(24)	39.5%(64)	45.7%(74)
Calcification	3.3%(38)	15.8%(6)	10.5%(4)	73.7%(28)
Any lesion	45.6% (524)	51.2%(268)	20.2%(106)	28.6 %(150)

* The prevalence rate refers to a total of 1148 endplates studied.

** The percentage refers to the number of identified specific endplate lesions.

Table 5-3: The distributions of lesions within the endplate*

Endplate lesions	*Anterior*	*Central*	*Posterior*	*Lateral*	*Entire endplate*
Schmorl's Nodes	1.6%(4)	80.6% (203)	8.3% (21)	9.5% (24)	0
Fracture	45.8% (33)	2.8% (2)	11.1% (8)	37.5% (27)	2.8% (2)
Erosion	14.8% (24)	1.9% (3)	7.4% (12)	59.9% (97)	16.1% (26)
Calcification	2.6% (1)	13.2% (5)	34.2% (13)	2.6% (1)	47.4% (18)
Any lesion	11.8% (62)	40.7% (213)	10.3% (54)	28.4% (149)	8.8% (46)

* Predominant site is noted. The percentage refers to the number of identified specific endplate lesions.

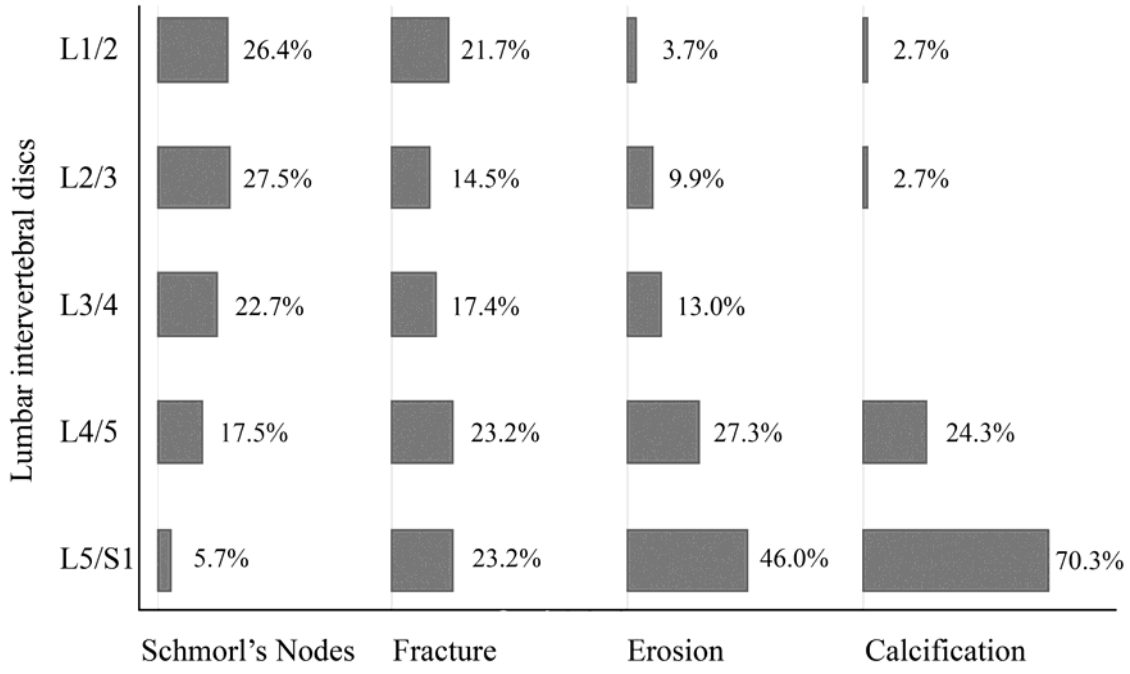

Figure 5-3: The distribution of endplate lesions by disc level. The numbers are percentages of each specific lesion identified at that disc level. Data from cranial and caudal endplates were presented together.

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CHAPTER 6

Lumbar Vertebral Endplate Lesions: Part II

Associations with Disc Degeneration and Back Pain History[5]*

6.1. Introduction

Back pain is one of the most common disorders in general practice.[1,2] Unfortunately, a pathoanatomical cause cannot be identified in most patients, even using the best diagnostic modalities available.[3] Disc degeneration (DD) has long been suspected of playing an essential role in the pathogenesis of back pain and correspondingly the disc is often targeted in medical intervention and scientific research. Yet, evidence yielded from decades of research reveals that the association between DD findings and back pain is generally weak,[4-7] challenging the traditional view that the disc is the primary back pain generator.

Unlike the intervertebral disc, which is a poorly innervated tissue, the adjacent bony endplate and vertebral body are supplied by intraosseous nerves,[8] and may be another source of back pain.[9] The innervation of the vertebral endplate usually accompanies the vertebral vascular distribution and may increase in number and density, if the adjacent disc degenerated.[9] Given the importance of the endplate to the disc[10] and the nerve supply of the vertebral endplate, pathologies affecting the vertebral endplate may alter the local vascularity, induce inflammation, irritate the surrounding nerve endings, and eventually result in both DD and back pain. Yet, endplate lesions and their association with DD and back pain have received relatively little attention. Measuring the thin endplate[11,12] and its pathologies using standard radiological approaches is challenging.

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* A version of this chapter has been submitted to ***Spine*** for publication.

Our previous work using a subgroup from the same spine archive revealed that vertebral endplate lesions are common findings in the lumbar spine and are associated with DD.[13] Previously, we identified four types of endplate lesions, including Schmorl's nodes, fracture, erosion and calcification lesions. The different morphological features and distribution patterns of these endplate lesions suggested their origins and pathological processes differ from each other, which may result in different pathological consequences on the adjacent disc and back symptoms. This paper extends previous work using the classification system and investigates whether different types of endplate lesions are likely to have different effects on DD, as well as back pain. We test the hypotheses: 1) the presence of endplate lesions is associated with back pain history; 2) different types of endplate lesions are associated with different magnitudes of DD; 3) the presence of fracture and erosion lesions, but not traditional Schmorl's nodes, is associated with heavy occupational physical loading and back injury history.

6.2. Materials and Methods

Subjects

The lumbar spine archive was described in Part I (Chapter 5). In brief, 1148 vertebral endplates (from L1 to S1 vertebra) and 443 corresponding lumbar intervertebral discs (L1/2 ~ L5/S1) that had discography data from 136 spines of men who died after a short stay in hospital were included in this study. The mean age of the subjects at the time of death was 52.2 years (range 21-64 years). Anthropometric data were also available, including weight, height and body mass index (BMI). The study was approved by the Health Research Ethics Board of the University of Alberta.

Occupation, back pain and back injury history

Occupation was obtained initially from the information recorded on the death certificate, and further occupational history information was collected by telephone interview of an immediate family member (usually the spouse) using a structured questionnaire.[14] If the subject had held more than one job, the physically heaviest occupation held for at least five years was recorded. Then two occupational health physicians independently classified the occupation according to physical demands as a **sedentary**, **mixed, driving** or **heavy** occupation. Occupational history data were available for 72 subjects. The occupations of 17 (23.6%) subjects were classified as sedentary, 17 (23.6%) as mixed, 28 (38.9%) as heavy, and 10 (13.9%) had driving occupations.

In the telephone interview, the family member was asked about the subject's history of back pain using the following questions: "Did he have back pain? If so, how often was the pain?"[14] According to the replies, back pain history was categorized as **no back pain**, **occasional back pain** if pain was present less than once a year and **frequent back pain** if the pain was more than once a year. The family member was also asked about a history of back injury, which included back pain accidents in daily life or work, such as falls associated with the onset of back pain. In the current sample, back pain history data were available for 69 subjects: 25 (36.2%) subjects reportedly had no back pain, 19 (27.5%) subjects had occasional back pain and the remaining 25 (36.2%) had frequent back pain. For those with back pain data, a back injury was recalled in 17 (25%), 47 (68%) did not have a back injury and back injury data were missing for the remaining 5 subjects.

Measurement of Disc Degeneration

After a routine autopsy examination of the lumbar spines, discography was performed to evaluate DD.[14] Using a 20-gauge needle and finger pressure, 2~5ml Barium Sulphate (BaSO4) was injected anteriorly into the center of the intervertebral disc with maximal figure pressure. All five intervertebral discs (L1/2 to L5/S1) were examined for each lumbar spine. Anterior-posterior and lateral x-ray radiographs were taken immediately after the injection of contrast agent. According to the spread or distribution of the BaSO4 in the discogram, a 4-grade ordinal scale was used to rate the degree of DD pathology. DD was given a rating of **none** if the dye remained in the center of the disc; **slight** if the dye spread into the inner annulus; **moderate** if the dye spread from the inner to the middle region of the annulus; and **severe** if dye spread to the outer part of the annulus. Intraobserver agreement for measurements using this scale yielded a weighted kappa of 0.81.[14]

Discography data were available for 443 intervertebral discs in 109 subjects. Based on discography, DD was absent in 50 (11.3%) discs, slight in 147 (33.18%), moderate in 112 (25.3%), and 134 (30.3%) had severe DD.

Endplate lesion assessment and classification

The examination of endplate lesions was performed by visually inspecting the whole vertebral endplate. First, the endplate lesions were evaluated as present or absent. If present, endplate lesions were further classified into **Schmorl's nodes, fracture, erosion** or **calcification**. If two or more types of lesions were present on an endplate, the predominant lesion (based on the size) was used. The size of the endplate lesion was rated as **none**,

small, **moderate** and **large**. Details of this classification protocol and measurement reliability were reported in Part I (Chapter 5).

Endplate lesions relative to the disc

Each intervertebral disc has two adjacent vertebral endplates. Thus, the number of lesioned endplates was recorded as 0, 1 or 2 for each disc. Further, data of endplate lesion type and size from the cranial and caudal endplates of the same disc were merged together. For the size measurements, data from the cranial and caudal endplates were summed together for the disc. If data were available only for one endplate, the disc was excluded.

Statistical Analysis

As the prevalence of DD is different in the upper and lower lumbar spine, we routinely grouped DD into upper (L1/2, L2/3 and L3/4 discs) and lower (L4/5 and L5/S1 discs) lumbar regions for analysis. Nominal logistic regressions were used to examine the associations between endplate lesions, back pain and back injury history. Ordinal logistic regressions were used to examine the associations between DD and endplate lesions, taking DD as the outcome variable. First, the dummy measurement of endplate lesions was used. Then, the associations between individual endplate lesion types and DD were examined. Further, the effects of the different types of endplate lesions on adjacent DD were compared to that of Schmorl's nodes. If not specified, we used lesion measurements from a single endplate to match the adjacent DD measurement. In addition, lesion data of the cranial and caudal endplates were merged together to match the adjacent DD. Age, BMI and lumbar region (upper vs. lower) were controlled. Statistical analyses were performed using STATA (Version 9.2, StataCorp LP, USA). As data acquired for

endplates were clustered in a lumbar spine, the command 'cluster' in STATA was used to account for the dependency in all regression analyses.

6.3. Results

Associations of endplate lesions with back pain history

The presence of ***any type of endplate lesion*** was associated with frequent back pain (OR=2.57, p=0.004) but not with occasional back pain (OR=1.47, p=0.240), after controlling for age and BMI. Large endplate lesions, but not moderate and small endplate lesions, were associated with both occasional (OR=8.68. p=0.038) and frequent (OR=17.88, p=0.004) back pain. When DD was added to the model, the associations between large endplate lesions of any type and occasional and frequent back pain remained significant (OR=8.87, p=0.035; OR=13.08, p=0.015, respectively), while moderate (OR=2.99, p=0.039) and severe DD (OR=3.13, p=0.037) were also associated with frequent back pain, but not with occasional back pain.

When the associations between the presence of individual endplate lesion type and back pain history were examined, Schmorl's nodes (OR=2.67, p=0.005), erosion (OR=2.72, p=0.040) and calcification (OR=5.50, p=0.032) were associated with frequent back pain but not occasional back pain, after controlling for age and BMI. An association between endplate fracture and back pain history was not observed (**Table 6-1**). When lesion size was added to the model, overall larger size was statistically associated with both occasional (OR=2.43, p=0.020) and frequent back pain (OR=3.18, p=0.001), and none of the associations between specific endplate lesion type and back pain history remained significant.

Associations between endplate lesions and DD

The presence of ***any type of endplate lesion*** was associated with adjacent DD (OR=3.98, p<0.001), after adjusting for age, BMI and lumbar region. Larger lesion size was significantly associated with more severe DD (OR=2.12, *P*<0.001).

When examining ***each type of endplate lesion*** separately, the presence of each type of lesion was associated with more adjacent DD, with larger size associated with more severe adjacent DD. The adjusted odds ratios are reported in **Table 6-2**, as compared with intact endplates (OR=2.40~9.71, *p*=0.000~0.040). When measurements of endplate lesions from the cranial and caudal endplates of the same disc were merged together to examine the relation with adjacent DD, similar results were obtained (data not reported).

A greater ***number of lesioned endplates*** also was associated with more adjacent DD, after controlling for age, BMI and lumbar region (OR=2.12, *p*=0.012 for discs with a single lesioned endplate and OR=6.13, *p*<0.001 for discs with two lesioned endplates, as compared to discs without endplate lesions).

We further compared the strengths of the associations between individual endplate lesion types and DD, taking Schmorl's nodes as the reference. After controlling lesion size, the associations between endplate fracture, erosion and calcification and adjacent DD were stronger than that between Schmorl's nodes and adjacent DD, but only reached statistical significance for erosion lesions (OR=2.85, *p*=0.001, **Table 6-3**). When lesion data from two endplates were combined in relation to the adjacent DD, similar results were observed: endplate erosion was statistically significantly more strongly associated with adjacent DD than were Schmorl's nodes (**Table 6-3**).

Associations of endplate lesions with back injury history and occupation history

The presence of any type of endplate lesion was associated with back injury history, controlling for age, BMI and lumbar region (OR=2.07, p=0.014). With respect to endplate lesion type, back injury history was associated with endplate fracture (OR=3.78, p=0.028) and endplate erosion (OR=2.35, p=0.043), but not with Schmorl's nodes and calcification lesions.

Overall, heavy occupation was associated with the presence of endplate lesions (OR=2.51, p=0.007), as compared to sedentary occupation. Specifically, heavy occupation was associated with the presence of Schmorl's nodes (OR=3.24, p=0.010), but not with fracture lesions (OR=3.06, p=0.10), erosion (OR=1.75, p=0.21) and calcification (OR=1.20, p=0.87). The driving and mixed occupations were not associated with the presence of any individual type of endplate lesions.

6.4. Discussion:

Findings from the current study suggest that endplate lesions are associated with back pain and that lesion size, reflecting severity of the endplate pathology, may be more important than specific lesion type. Data further confirmed our previous observation that endplate lesions are closely associated with adjacent DD, with greater number and greater size of lesions associated with more severe adjacent DD. In addition, evidence supports that different endplate lesions have different pathogenic origins, distinct pathological characteristics and thus, varied magnitudes of pathological influences on the adjacent disc.

The identified associations between endplate lesions and history of frequent back pain support our hypothesis that endplate lesion may be a source of back pain. Unlike annular fissures, endplate lesions as a possible cause of back pain have been somehow neglected.

Schmorl's nodes, the most common endplate lesions, were thought to be painful.[15] Several clinical observations of small samples have supported this belief,[9,16-18] but the association between Schmorl's nodes and back pain was not confirmed in a large population-based epidemiological study.[19] In addition to variations in definitions of back pain used, the inability of radiological approaches to detect all lesions on the endplate,[13,19] such as the small nodes and marginal diffusive lesions identified in our study, may have diluted associations with back pain.

It is not surprising that endplate lesions are associated with back pain. In contrast to the intervertebral disc, which is typically innervated only in the outmost layer of the annulus fibrosus,[20,21] the vertebral endplate has a stronger neurological basis to mediate pain. The bony vertebral endplate, particularly the central endplate, is well innervated,[22] as is the adjacent vertebral marrow.[8,9] Therefore, lesions affecting the thin[12] vertebral endplate could ignite the sensory nociceptors in both the vertebral endplate and marrow, producing pain. This is supported by clinical observations that endplate lesions, such as "traumatic Schmorl's nodes"[23,24] and "destructive lesions",[25] are painful. Moreover, nerve endings may proliferate in the area of the endplate defect,[9] or they may ingrowth through the lesioned endplate into the disc, as through annular fissures,[26] facilitating pain generation. In addition, alterations of the stress distribution within the disc[27] and inflammation of the vertebra-disc interface resulting from endplate lesions could provoke nerve endings in the bony endplate and marrow,[23,28] contributing to back pain.

Due to the variations of study materials and limitations of measures in previous studies, findings of the association between endplate lesions and DD are inconsistent and the role of endplate lesions in the pathogenesis of DD has remained controversial.[19,29-31] Using

clearer definitions and more accurate measurements acquired from cadaveric endplates, as compared with radiological studies, the current study clarified the important role of endplate integrity in maintaining disc health: endplate lesions of any type were associated with DD, with an apparent dosage effect. In addition, a greater number of endplate lesions and larger size were associated with more severe adjacent DD. Such dosage effect, which has been observed previously,[13,30] is biologically plausible, given that the relationship between endplate lesions and DD may largely be the consequence of local pathological interactions between the bone and the disc.

The disruption of endplate integrity may trigger a series of pathological cascades which eventually result in adjacent DD. First of all, the protrusion of nucleus pulposus into the vertebral body causes a direct loss of nucleus matrix contents, such as water and proteoglycan, which would lead to DD.[32] Associated inflammatory and autoimmune reactions could further destroy the homostasis within the disc and impair the metabolism of the cells.[33,34] Second, endplate lesions and the accompanying reparatory reactions may damage and block the marrow contact channels and impede nutrient supply to the disc.[35] In addition, endplate lesions alter the distribution of matrix compressive stress in the adjacent disc, which may further inhibit disc cell metabolism[36] and lead to progressive structural failure of the disc.[37]

Moreover, we observed that different lesions, in particular endplate erosion lesions, tended to have different degrees of association with DD. This may relate to their specific pathogenic origins and pathological features. The traditional Schmorl's nodes identified in this study usually are located in the endplate center where bone is thinner than that of other regions.[38] In addition, they were associated with heavy occupation but not back injury

history in our sample. These findings support the origin theory that Schmorl's nodes are the protrusion of the nucleus through the developmental weak spot of the endplate due to axial loading.[39] It appears that such nucleus protrusion may develop over time and involve a mild pathological process, with reparation adequately activated such that the lesion is well-corticated, resulting in a regular shape and relatively less detrimental influence on the adjacent disc. On the other hand, the similarities of distribution patterns and a common association with back injury history suggest that fracture and erosion lesions may share a common origin, such as trauma. In the case of endplate trauma, in addition to traumatic inflammation the trauma itself could directly induce disc cell apoptosis and promote DD,[40] resulting in more severe degenerative changes in the adjacent disc than seen with Schmorl's nodes.

It seems necessary to differentiate Schmorl's nodes from other endplate defects. Schmorl's nodes usually are viewed as synonymous with endplate defects, especially in radiological studies. Using this definition, erosion lesions as observed in this study may have been largely regarded as Schmorl's nodes. Although Schmorl suggested long ago that these nodes may originate from different etiologies,[39] and different pathological characteristics have been reported,[41] their distribution patterns and associations with adjacent DD have not been clearly described before. Traditional Schmorl's nodes are typically small and conservative, involving the endplate center and having mild pathological effects on the disc. More commonly affecting the anterior and lateral portions of the endplate, fractures and erosions, which could have been labelled as "traumatic Schmorl's nodes", are relatively large and extensive, tend to have a more detrimental influence on the adjacent discs. In addition, variations in pathological effects on the disc

explain, at least in part, the inconsistencies of the association between Schmorl's nodes and DD.[30,31]

In addition to previously discussed limitations, the sample used to examine the associations studied is a subgroup of the entire spine archive. Data on back pain and back injury history were acquired from an immediate family member and are likely inadequate to fully capture lifetime exposure or outcome. However, such measurement error would tend to mask or dilute rather than exaggerate the associations. As such, the associations of lesion type and size with back pain observed are remarkable. Using cadaveric materials and a relatively large sample size, data derived from the current study provide strong evidence of the importance of endplate lesions in the pathogenesis of lumbar DD and LBP.

To summarize, endplate lesions are associated with frequent low back pain. Endplate lesions are closely associated with adjacent DD, with a dosage effect, suggesting the integrity of the vertebral endplate is important to maintain disc wellness. In addition, different types of endplate lesions may vary in their pathological influence on adjacent discs. Schmorl's nodes evaluated simply as any endplate defects need to be interpreted carefully as they may consist of a variety of endplate pathologies.

Table 6-1: Associations between endplate lesions and back pain history.*

Covariates	*Occasional back pain*		*Frequent back pain*	
	OR	***P***	***OR***	***P***
Schmorl's Nodes	1.04	0.933	2.67	0.005
Fracture	1.54	0.477	1.48	0.516
Erosion	2.36	0.070	2.72	0.040
Calcification	0.53	0.599	5.50	0.032

*: Sample in the statistical model included 521 endplates from 69 subjects with back pain history data. Age and BMI were adjusted.

Table 6-2: Estimated ORs for endplate lesion types of different sizes to have adjacent DD.*

Lesion Size / *Endplate Lesions*	*Small*		*Moderate*		*Large*	
	OR	***P***	***OR***	***P***	***OR***	***P***
Schmorl's Nodes	2.40	0.000	2.86	0.001	----	----
Fractures	4.09	0.000	4.88	0.000	5.81	0.000
Erosion	6.84	0.000	8.15	0.000	9.71	0.000
Calcification	5.31	0.040	6.33	0.030	7.54	0.033

* Data were estimated from a nominal regression model. Endplate lesion N=723. Age, BMI and lumbar region were adjusted. No endplate lesion was the reference group.

Table 6-3: Associations of endplate lesions with DD, compared to Schmorl's nodes.*

Endplate lesions	***Disc degeneration (N=723)****		***Disc degeneration (N=297)*****	
	OR	***P***	***OR***	***P***
Schmorl's Nodes	1.00	1.000	1.00	1.000
Fracture	1.71	0.121	1.74	0.183
Erosion	2.85	0.001	2.70	0.021
Calcification	2.21	0.312	1.88	0.545

* Age, BMI, lumbar region and lesion size were adjusted;

** Odds Ratios (ORs) were estimated from lesion measurements of a single endplate;

*** ORs were estimated from lesion measurements of both adjacent endplates of a disc. Only discs with available lesion data of both adjacent endplates were included.

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CHAPTER 7

General Discussion and Conclusions

7.1. Overview

Although research on disc degeneration (DD) has expanded into the molecular and genetic level and substantial progress has been made in better understanding its pathogenesis,[1] the pathological mechanisms or pathways leading to DD are far from explicit. The roles of the adjacent vertebrae and endplates in DD, for example, are among such unknown gray zones. The vertebral body, and specifically the vertebral endplate, are not only the structures to which the intervertebral disc anchors, but also the nutrient supplier and the mechanic load facilitator.[2] Despite their importance to the disc, the vertebra and endplate have been largely overlooked. Based on a cadaveric archive consisting of over 150 lumbar spines,[3,4] this doctoral work explored the roles of the vertebra, particularly its endplate, in the pathogenesis of DD. Specifically, this series of studies investigated the physiological (morphometrics) and pathological (lesions) conditions of the vertebral endplate in relation to age, DD, and back pain, using a variety of improved in vitro measures.

7.2. The relationship between lumbar vertebral BMD and DD

As early as 1972, Foss first reported that hip osteoarthritis is uncommon in hip fracture patients.[5] Since then, numerous studies have been conducted to examine the relationship between osteoporosis and osteoarthritis and now it is clear that high bone mineral density (BMD) is associated with more severe osteoarthritis in peripheral joints. Yet, the relationship between vertebral BMD and DD has remained controversial in the lumbar spine.[6-9]

Underlying the inconsistencies are variations in definitions of DD and challenges in measuring vertebral BMD. Typically, both DD and DXA measurements of vertebral BMD

are influenced by bony lumbar degenerative changes, such as endplate sclerosis and osteophytes. Using μCT and discography to exclude the influence of these proliferative bony changes, the study clarified that it was higher volumetric BMD of the vertebral body (not the whole vertebra) that was associated with more severe adjacent DD. In contrast to our hypothesis, osteophytes and endplate sclerosis did not influence the association between vertebral BMD and DD. Instead, the posterior elements substantially inflated the vertebral BMD measurements and therefore, confounded the association between BMD and DD.

Both global influences and local interactions may contribute to the association between higher vertebral body BMD and more DD. Global infuences, such as the effects of common genes and environmental factors, may similarly affect different skeletal sites, such as different spinal levels. Evidence from a twin study suggests that the association of higher vertebral BMD and more DD is in part genetically determined. Yet, the contribution attributable to genes was relatively small, estimated as up to 25%.[10] Anthropometric features, such as weight[11] and other undetermined environmental factors, may also have opposite effects on vertebrae and discs. On the other hand, the local mechanical interactions between stiff bone and resilient disc may play a substantial role. For example, the intervertebral disc may protect itself from mechanical failure by sinking into osteoporotic vertebral body.[12,13] The finding that the relationship between higher vertebral body BMD and more DD is stronger in lower lumbar region, as compared to that of upper lumbar spine, also supports an effect of local interactions in this association. As the local mechanical environment in the vertebra-disc complex could be altered either by

osteoporotic bone[14] or by degenerated discs,[15] it is not clear whether increased vertebral BMD causes adjacent DD or DD triggers adjacent bone adaptation.[7,16]

Overall, our data lend support to the hypothesis that higher vertebral BMD may play a role in the adjacent DD. Yet, the association between global vertebral BMD and DD identified is relatively weak, indicating the influence of vertebral body BMD on the adjacent disc might not be critical. More specific measurements of vertebral trabecular bone, such as trabeculae number and thickness, need to be further investigated in relation to adjacent DD to better understand the interaction between vertebral bone and intervertebral disc.

7.3. The role of vertebral endplate morphometrics in DD

Due to its special anatomical location, the endplate is essential to maintain the structural integrity and physiological function of the intervertebral disc.[2] It is the physical shield to prevent the nucleus pulposus from escaping[17] and the mechanical interface to facilitate load distribution in the vertebra-disc complex.[18-20] In addition, it is the gateway of metabolism substance transport between the vertebral marrow and intervertebral disc.[21-23] Given the multiple functions of the endplate, its morphometrics are generally thought to influence its functional performance and thus, play a role in the pathogenesis of DD.

Among such considerations are the thickness,[12,24,25] concavity,[12,13,27] size,[28] shape and circularity,[13,29] as well as the BMD[26] of the endplate. There is evidence from histological studies, radiological studies and animal studies to support that endplate morphometrics (particularly thickness and concavity) are related to DD. Yet, due to variations in study materials and limitations of inadequate measurements, the associations between endplate morphometrics and DD largely are unclear and remain controversial.

The morphometrics of the lumbar vertebral endplate were intensively measured in vitro to clarify their associations with DD. When endplate morphology was qualitatively classified into concave, flat or irregular, only irregular endplate shape was found to associate with more severe DD. Among a number of endplate morphometrics quantified using μCT and 3D scanning, only endplate thickness[30] and size (OR=1.2) were found to positively associate with DD. Although a tendency of greater endplate thickness associated with more severe adjacent DD was observed, this relationship was evident only in severely degenerated discs. Less concavity and greater circularity of the cranial endplate (but not the caudal endplate) appeared to associate with more adjacent DD. With μCT techniques, the vertebral endplate was extracted to acquire specific endplate BMD, excluding the influence of adjacent trabecular bone and osteophytes (if any) in the BMD measurements. Yet, we did not detect an association between greater endplate BMD and more severe DD, as was observed in a rat model.[26]

With more accurate quantitative measurements, as compared to previous studies, the identified associations between greater endplate thickness and size and more DD were relatively weak, suggesting their contribution to DD may be small. The mechanism underlying the association studied may be related to an impaired nutrient supply to the adjacent disc or inefficient nutrient transport within the disc, as discussed in previous chapters. Other endplate morphometrics such as concavity may only play a marginal role in the pathogenesis of DD, if any.

7.4. The role of endplate lesions in DD and back pain

7.4.1. Endplate Lesions: a neglected area in spine research

From 1920 to 1980 was the golden age of disc and endplate research. During this period, scientific literature on the endplate usually involved autopsy studies, with relatively large sample sizes and wide age ranges. Although many of these studies are merely descriptions of visual or histological examinations of the endplate and disc, with or without radiographic data, such studies together constitute the foundation of endplate knowledge. After 1990, histological studies using human spine materials declined dramatically. Instead, magnetic resonance (MR) has been increasingly used in both scientific research and clinical practice. As a result, most endplate studies are based on MR images. To date MR is the best approach to image the spine, however, it cannot detect all the lesions on the thin endplate.[31,32] In addition to MRI, there are a number of endplate studies using radiography. However, due to poor visualization of endplate pathologies, such as Schmorl's nodes,[33,34] the scientific value of endplate studies using radiography is limited.

Most previous studies on endplate pathology focused on Schmorl's nodes. Yet, the reported prevalence of Schmorl's nodes ranges from 9% to 75%,[32,35-37] with the prevalence measured from cadaveric spines being much higher than that from MR images. Furthermore, it is clear that Schmorl's nodes are not the only pathology affecting the vertebral endplate. Other endplate pathologies, such as 'vertebral rim lesions'[34] and 'destructive lesions of vertebral endplate'[38] have been reported. Although different morphological features and distribution patterns of Schmorl's nodes[39] or endplate lesions[38] have been observed, a comprehensive understanding of different types of endplate lesions, such as their pathogenesis and pathological features, is currently lacking. In addition, the

associations between endplate lesions and age and DD remain controversial. A systematic study is needed to depict pathological characteristics of different types of endplate lesions and to clarify their roles in DD, as was conducted and described in this thesis.

7.4.2. Prevalence, classification, characteristics and origins of endplate lesions

With the whole endplate visually examined, our study revealed that nearly half of the lumbar endplates studied had some sort of lesions in this sample of middle-aged men. It is surprising that such common findings have long been underestimated using modern radiological techniques and overlooked. One of the reasons is that identifying endplate pathologies is challenging, especially in vivo. As both the cartilaginous and osseous endplates are thin,[30,40] even MR is not able to detect all endplate pathologies, particularly lesions of small size or without substantial morphological defects.[32]

Based on visual observations of morphological characteristics, four types of endplate lesions were further identified, including **Schmorl's nodes, fracture, erosion** and **calcification**. In the lumbar region, Schmorl's nodes were the most common type of endplate lesions while calcification lesions were the least common. Schmorl's nodes usually were found in the upper lumbar region while erosion and calcification lesions were mainly located in the lower lumbar region. The pathological characteristics of different types of endplate lesions are summarized in **Table 7-1**.

Greater age was found to associate with not only the presence of endplate lesions, but also greater number and greater size of lesions, suggesting age and other associated factors may play a critical role in the pathogenesis of endplate lesions. The morphological features and preferential location of Schmorl's nodes, as well as their association with heavy occupational loading, but not back injury history, strongly support the traditional view that

Schmorl's nodes are protrusions of the nucleus pulposus in the developmental weak spot of the endplate, which may be induced by heavy physical loading.[33] The associations identified between fracture and erosion lesions and back injury history suggest they may originate from spine trauma.

Other than proliferative vertebral degenerative changes, such as osteophyte formation and endplate sclerosis, the break-down of the endplate seen in erosion lesions may also be a lytic form of vertebral degeneration. Although different types of endplate lesions have been observed to present in the same endplate, it is unclear whether or not one type of endplate lesion will transform into another. Taking into account the clear associations between age and DD and endplate lesions, we postulate that endplate lesions and DD may be two parallel signs of degeneration in the vertebra-disc complex.

7.4.3. The role of endplate lesions in DD

Some important physiological functions of the endplate with respect to the disc include physical protection, load dissipation and nutrient supply.[2,20,23] Disruption of the endplate impairs these functions and, therefore, may lead to degenerative changes in the adjacent disc. Yet, endplate lesions and their effects on the adjacent disc are poorly understood. Although an association between Schmorl's nodes and DD was proposed as early as the 1920's, this relationship remains controversial, as well as whether or not there is a dosage effect of larger size Schmorl's nodes associated with more severe DD.[31,32,36,41]

When endplate lesions were evaluated as present or absent, as judged by visual examination, we observed a marked association between the presence of any endplate lesions and adjacent DD, with a clear dosage effect of larger size associated with more severe DD. Further, when four types of endplate lesions were separated, the presence of

each type of lesion was associated with more adjacent DD. In addition, erosion lesions seem to have more detrimental effects on the adjacent disc, as compared to Schmorl's nodes. Lesion size appears to be a critical factor of the pathological influence of endplate lesions on the disc.

The breakdown of the endplate interface exposes nucleus tissue to trabecular bone and capillary circulation, which inevitably will provoke inflammatory reactions in the adjacent marrow. Such reactions include edema, ingrowth of vascular fibrous tissue into the breach and subsequent new bone formation. Due to whatever etiologic factors, these pathological reactions in the vertebra-disc interface are largely identical. What differs perhaps is the degree of the inflammation. Our findings support that traditional Schmorl's nodes typically start at the weakest spot of the endplate (the endplate center) and the pathological process is mild and slow, which allows bony reparation to take place over time, resulting in a relatively small, round shape and characteristic osseous casing.[33,36] Due to some other aggressive etiological factors, such as endplate trauma, the inflammation instigated is invasive and corresponding reparatory reactions could not be provoked on time, resulting in diffuse erosion of the endplate. One could speculate that if the inflammation cascade persists over a longer period of time, with the lack of an effective osseous wall to separate the disc and marrow and stop the pathological interaction between them, the overall influence of erosion on the adjacent disc would be more severe, as compared with that resulting from Schmorl's nodes. The pathogenesis of calcification lesions is unknown. It appeared to represent the end stage of some intensive inflammations which were introduced by severe endplate pathology.

The study revealed that various types of endplate lesions may have different pathological origins and varied degrees of pathological effects on the adjacent disc. Findings explain the inconsistencies between Schmorl's nodes and age and DD and highlight the importance of differentiating Schmorl's nodes from other endplate lesions. Previously Schmorl's nodes simply were evaluated as the presence or absence of endplate defects, particularly in radiological studies. On MR images, both fracture and erosion lesions may manifest as morphological defects, and therefore would largely be regarded as Schmorl's nodes. The controversy of the origins of Schmorl's nodes, idiopathic or traumatic, has lasted for decades.[33,34] Evidence derived from this series of studies lends support to both of these two theories: Schmorl's nodes judged as endplate defects may include different types of endplate pathologies, some of which could be idiopathic and others traumatic. The inability of radiological approaches to differentiate Schmorl's nodes from other endplate lesions may have also resulted in biased or diluted associations with DD.

7.4.4. Endplate lesions may be an overlooked source of back pain

The intervertebral disc has long been suspected as the primary back pain generator. Yet, the intervertebral disc itself is a poorly innervated tissue, with limited nerve distribution at the periphery of its annulus.[42] If back pain originates from the disc (so-called discogenic back pain), there are two possible pathways to mediate the pain. The annulus as a source of pain is well-established as disc pathologies involving the annular fibrosis, such as disc prolapse and annular fissure, are associated with back pain.[4,43,44] Another source of discogenic pain may be the adjacent endplate and vertebral marrow,[45] which are well-supplied by intraosseous nerves.[45-47] The finding that endplate lesions, particularly lesions

of large size, were associated with a history of frequent back pain supports endplate lesions as a possible cause of back pain. This is concordant with some other clinical observations, which reported that endplate lesions, such as endplate fracture[48,49] and endplate 'destructive lesions',[38] are painful. However, more clinical evidence is needed to substantiate the link between endplate pathology and back pain, ideally using a longitudinal design.

7.5. Study limitations

As mentioned in previous chapters, there are some limitations that need to be addressed. 1) All the subjects are middle-aged men (age range 21~64 years). The endplate morphometrics and lesions in women and in populations of other ages remain unexplored; 2) The BMDs of the vertebra and endplate were measured in vitro. The removal of fat tissue from the vertebral body and the absence of soft tissue around the vertebrae may have influenced the BMD measurements. However, such influence may have minimally biased findings of the relation between BMD and DD; 3) The cartilaginous endplate was not studied. Examining pathological changes on the osseous and cartilaginous endplates together may lead to a better understanding of pathological interactions between the vertebra body and the disc; 4) Studies were based on a spine archive collected over 20 years ago. It is possible that the dried bones may have become distorted to some extent and, thus, influenced the morphometrics measured; 5) Some archived bones were missing. Despite full lumbosacral spines of all subjects may lead to better dataset to depict endplate morphometrics and endplate pathologies, missing may not have biased research findings in the current studies as bones in the archive were likely missed at random; 6) Another limitation is that the developed endplate lesion classification protocol did not take into

account the possible presence of other pathologies, such as rheumatic diseases and spondylitis. Distinguishing endplate lesions specifically related to such disorders is challenging. Finally, the conducted association studies were all cross-sectional, which limits conclusions about possible cause and effect.

7.6. Conclusions

In summary, a large sample of cadaveric lumbar vertebrae was investigated to explore the relationship between the vertebra, endplate and disc. Higher vertebral body BMD, greater vertebral endplate thickness and size were associated with more severe adjacent DD, suggesting a physiological role for the vertebra and its endplate in DD. Yet, the associations identified are relatively weak and thus, the influence of vertebral morphometrics on DD may be modest. On the other hand, endplate lesions are common findings in spines of middle-aged men. These pathological lesions are closely associated with adjacent DD, with a clear dosage effect, suggesting an important role for endplate lesions in the pathogenesis of DD. In addition to Schmorl's nodes, there are various types of endplate lesions, such as diverse fracture, diffusive erosion and intensive calcification. As these endplate lesions may have different degrees of pathological influences on the adjacent disc, it is necessary to differentiate them from Schmorl's nodes in future research. In addition, endplate lesions may be a source of back pain.

7.7. Significance

This was a systematic study to determine morphometrics and pathologies of the lumbar vertebral endplate. The cadaveric specimens used allowed a number of direct and accurate measurements of the vertebral endplate. The resulting structural parameters of endplate, such as thickness, concavity, size and BMD, provided fundamental reference data for

future endplate research. More importantly, the study revealed that endplate lesions are very common findings in the lumbar spine, highlighting a research topic that has long been overlooked. Findings advance the knowledge of physiological and pathological interactions between the vertebra and intervertebral disc, and substantiate the critical roles that adjacent bony tissues play in the pathogenesis of DD. Understanding the pathogenesis of DD through studying the adjacent bony tissues provided novel insights into the etiology of DD. In addition, this doctoral work also identified a clue, endplate lesions, for understanding back pain. Together, findings contribute to a better understanding of the intriguing spine and its pathological changes.

7.8. Future research

This series of studies is based on a spine archive which consists of only middle-aged men. Therefore, studies using samples of women, or samples of a fuller range of age would substantially supplement our findings. Although a variety of endplate morphometrics have been extensively measured in vitro, there are other structural features of the vertebral endplate that need to be further investigated, such as endplate porosity. The marrow contact channels in the vertebral endplate, as well as the capillary buds accommodated inside, are the structural basis of nutrients supply from the marrow to the avascular disc. Yet, to date the size and distribution of these openings remain unknown and their associations with age and DD remain unclear. Using high resolution μCT, for example 12 μm or higher, it is feasible to depict a full spectrum of these channels and their distributions in the endplate.

The relationship between regional trabecular bone architecture of the vertebral body and adjacent DD deserves further investigation. Mechanical tests suggested that DD may

lead to stress shielding of the anterior portion of vertebral body and predispose it to fracture.[50,51] However, findings need to be confirmed using better measures on a larger sample. Using μCT to quantify trabecular bone measurements, such as trabecular bone thickness and number, would substantially enhance the understanding of mechanical remodelling in the trabecular bone adjacent to a degenerative disc.

The endplate lesions identified in the current studies are based on direct visual examination. Their radiological manifestations on MR images remain unknown. On the other hand, the pathologies underlying Modic changes on MR images largely remain unclear. Comprehensive studies correlating endplate pathologies to MR manifestations are urgently needed to bridge research findings of endplate lesions and their clinical relevance.

Table 7-1: Pathological characteristics of different types of lumbar endplate lesions

Characteristics	*Endplate lesions*			
	Schmorl's Nodes	***Fracture***	***Erosion***	***Calcification***
Preferential lumbar region	Upper	Similarly common	Lower	Lower
Involved endplate component	Central endplate	Central endplate and/or Epiphysial rim	Central endplate and/or Epiphysial rim	Usually both central endplate and rim
Susceptible location	Central	Anterior, lateral	Anterior, lateral	Entire endplate
Shape	Usually long or circular	Long fissure or cleft	Usually irregular	No defect, rough surface
Bony Casing	Yes	No, some callus	No	No
Bottom	Yes	No, with the exception of compression	No, or partly formed	No
Margin	Smooth and regular	Sharp	Rough or irregular	No
Pathological behaviour	Conservative	Aggressive	Aggressive	Aggressive
Associated with greater age?	Yes	Yes	Yes	Yes
Associated with back injury history?	No	Yes	Yes	No
Association with disc degeneration?	Yes, but relatively weak	Yes	Yes Strong	Yes

7.9. References

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