ELSEVIER

The Spine Journal 9 (2009) 47–59

THE SPINE JOURNAL

Review Articles

The Twin Spine Study: Contributions to a changing view of disc degeneration†

Michele C. Battié, PhD[a,b,*], Tapio Videman, MD, PhD[a,b], Jaakko Kaprio, MD, PhD[b], Laura E. Gibbons, PhD[c], Kevin Gill, MD[d], Hannu Manninen, MD, PhD[e], Janna Saarela, MD, PhD[f], Leena Peltonen, MD, PhD[g,h,i]

[a]*Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, Canada*
[b]*Department of Public Health, The Finnish Twin Cohort Study, University of Helsinki, Finland*
[c]*University of Washington, Seattle, WA, USA*
[d]*Southwestern Medical Center, University of Texas, Dallas, TX, USA*
[e]*Department of Radiology, Kuopio University Hospital, Kuopio, Finland*
[f]*Department of Molecular Medicine, Biotechnology Unit, National Public Health Institute, Helsinki, Finland*
[g]*National Public Health Institute, Helsinki, Finland*
[h]*Department of Medical Genetics, University of Helsinki, Helsinki, Finland*
[i]*The Broad Institute, MIT, Harvard, Boston, MA, USA*

Received 22 September 2008; accepted 18 November 2008

Abstract

BACKGROUND CONTEXT: Disc degeneration was commonly viewed over much of the last century as a result of aging and "wear and tear" from mechanical insults and injuries. Thus, prevention strategies and research in lumbar degenerative changes and associated clinical conditions focused largely on mechanical factors as primary causes using an "injury model." The Twin Spine Study, a research program on the etiology and pathogenesis of disc degeneration, has contributed to a substantial revision of this view of determinants of lumbar disc degeneration.

PURPOSE: To provide a review of the methods and findings of the Twin Spine Study project.

STUDY DESIGN/SETTING: Narrative review of the Twin Spine Study.

METHODS: The Twin Spine Study, which started in 1991, is a multidisciplinary, multinational research project with collaborators primarily in Canada, Finland, and the United States. The most significant investigations related to determinants of disc degeneration included occupational exposures, driving and whole-body vibration exposure, smoking exposure, anthropomorphic factors, heritability, and the identification of genotypes associated with disc degeneration.

RESULTS: Among the most significant findings were a substantial influence of heredity on lumbar disc degeneration and the identification of the first gené forms associated with disc degeneration. Conversely, despite extraordinary discordance between twin siblings in occupational and leisure-time physical loading conditions throughout adulthood, surprisingly little effect on disc degeneration was observed. Studies on the effects of smoking on twins with large discordance in smoking exposure demonstrated an increase in disc degeneration associated with smoking, but this effect was small. No evidence was found to suggest that exposure to whole-body vibration through motorized vehicles leads to accelerated disc degeneration in these well-controlled studies. More recent results indicate that the effect of anthropometric factors, such as body weight and muscle strength on disc degeneration, although modest, appear in this work to be greater than those of occupational physical demands. In fact, some indications were found that routine loading may actually have some benefits to the disc.

† This review article was awarded the Kappa Delta Foundation's 2008 Elizabeth Winston Lanier Award in March during the 75th Annual Meeting of the American Academy of Orthopaedic Surgeons in San Francisco. This award is presented to authors who have exemplified outstanding research in orthopedics.

FDA device/drug status: Not applicable.

Nothing of value received from a commercial party.

* Corresponding author. Faculty of Rehabilitation Medicine, University of Alberta, Corbett Hall 2-50, Edmonton, AB, T6 G 2G4 Canada. Tel.: (780) 492-5968; fax: (780) 492-1626.

E-mail address: mc.battie@ualberta.ca (M.C. Battié)

doi:10.1016/j.spinee.2008.11.011

CONCLUSIONS: The once commonly held view that disc degeneration is primarily a result of aging and "wear and tear" from mechanical insults and injuries was not supported by this series of studies. Instead, disc degeneration appears to be determined in great part by genetic influences. Although environmental factors also play a role, it is not primarily through routine physical loading exposures (eg, heavy vs. light physical demands) as once suspected.

Keywords: Disc; Degeneration; Heredity; Spine; Genetics

Background

A precise pathoanatomical diagnosis is not available in the vast majority of people with back pain problems [1]. Yet, theories and models of underlying pathology and its etiology have been adopted over the past half century that have had profound effects on how the problem is viewed and approached by those afflicted, their health-care providers and health and insurance policy-makers [2].

Although the specific underlying pathology is unknown in most cases of back pain, lumbar disc degeneration is a primary suspect and is commonly believed to be responsible for back symptoms, as well as being a major culprit in sciatica and lumbar spinal stenosis [3–6]. Consequently, the disc is a primary target for diagnostic and therapeutic interventions. Nachemson suggested that painful conditions may result from premature aging changes that render the disc mechanically incompetent, creating abnormal motion patterns that subject various spinal structures to undue stress [7]. Neuropathic changes, including abnormal firing in neurons innervating back tissues and nerve ingrowth into degenerated discs have been added to the list of suspected causal factors, as well [8–10]. In the case of symptomatic disc herniations, the findings of Olmarker et al. indicate that irritation of nerve roots may not only be caused by compression but also by biochemical effects of exposure to the nucleus pulposus [11]. There is also evidence that cytokines, such as tumor necrosis factor-α, may be factors in nucleus pulposus-induced neuropathy [12,13]. In addition, a possible role for bacterial infections in discs with patients with severe sciatica has been suggested [14]. Although the pain mechanisms are unclear and likely to be complex, evidence suggests that the disc plays a role in back symptoms, sciatica, and spinal stenosis [15–17], but the extent of the role remains unknown.

Before the past decade, the traditional injury or repetitive loading model of disc degeneration had dominated related prevention strategies and research for nearly half a century [18]. Such a model of disc degeneration implied that overloading from exposure to a single excessive force or repetitive loading results in structural damage (eg, accelerated disc degeneration or herniation), which in turn leads to symptomatic conditions. Among the factors most commonly suspected of accelerating degenerative changes in the discs were various occupational physical loading conditions [19]. In particular, attention has been given to heavy materials handling, postural loading, and vehicular vibration [20]. Numerous studies of the relationship between heavy materials handling and postural loading resulted in mixed findings related to the presence and degree of association with disc degeneration [21–30].

Vehicular driving had been associated with a higher incidence of back symptoms and degenerative changes, which were attributed to the effects of whole-body vibration on the intervertebral disc [31]. Yet, in an extensive review of the scientific literature, Kjellberg and others from the Swedish National Institute for Working Life [32] cautioned that although most of the studies revealed significantly higher frequencies of back symptoms and degenerative changes in the vertebrae and intervertebral discs of drivers compared with referents, "uncontrolled confounding factors may have affected the results in all studies, and the conclusions about the causal role of whole-body vibration for the observed injuries and/or disorders, therefore, becomes uncertain." Buckwalter cited several mechanisms of age-related deterioration of intervertebral discs, but acknowledged that activities and agents that accelerate degeneration remain speculative [33].

Based on the studies available at the time, Frymoyer summarized the state of knowledge on determinants of "degenerative disc disease" 15 years ago. He wrote "*Among the factors associated with its occurrence are age, gender, occupation, cigarette smoking, and exposure to vehicular vibration. The contribution of other factors such as height, weight, and genetics is less certain*" [34]. A decade later Ala-Kokko conducted a literature review on the same topic, "degenerative disc disease," and concluded "*Even though several environmental and constitutional risk factors have been implicated in this disease, their effects are relatively minor, and recent family and twin studies have suggested that sciatica, disc herniation and disc degeneration may be explained to a large degree by genetic factors*" [35]. A dramatic change in views of determinants of disc degeneration was underway.

Disc degeneration which was once viewed as a result of aging and "wear and tear" from mechanical insults and injuries is now viewed as being determined in great part by genetic influences [36–38], suggesting new models through which to conceptualize and study disc degeneration and associated pathology. We will summarize briefly some of our

group's research, through the Twin Spine Study, that has contributed to this substantial change in views on the etiology of disc degeneration.

The Twin Spine Study

The Twin Spine Study, which started in 1991, is a multidisciplinary and multinational research project with collaborators primarily in Canada, Finland, and the United States. Among the most significant findings related to determinants of disc degeneration were a substantial influence of heredity on lumbar disc degeneration and the identification of the first gene forms associated with disc degeneration [36,38,39]. Also, the studies on the effects of smoking and driving exposures using exposure-discordant identical twins have provided perhaps the most well-controlled studies on the effects of these exposures on human disc degeneration to date [40,41]. Among recent results are findings indicating that the effect of individual physical factors, such as body weight and muscle strength, on disc degeneration, although modest, may be greater than that of occupational physical demands [42]. Following is a brief description of the subjects and data on which the studies summarized in this article are based.

Subjects of the Twin Spine Study were recruited from the population-based Finnish Twin Cohort (with 13,888 male pairs of known zygosity) based on relevant prior information available from surveys conducted in 1975 and 1981, which had elicited response rates of 89% and 84%, respectively. The cohort has been found to be representative of the general Finnish population [43]. The Twin Spine Study subjects drawn from the Finnish Twin Cohort include 147 monozygotic (MZ) and 153 dizygotic (DZ) male twin pairs (as determined through original zygosity questionnaire data). The initial selection of 117 pairs of MZ twins was based solely on discordance between twin siblings for a specific common behavioral or environmental factor (eg, sedentary or heavy occupational physical demands, routine exercise participation, or occupational driving). The factors were selected because of their suspected importance in the etiology of spinal degeneration, back symptom complaints, and the availability of relevant information from the Finnish Twin Cohort database. In addition, a random sample of 30 MZ pairs, stratified by age, were added, as were 153 pairs of DZ twins selected using analogous criteria, yielding a total sample of 600 subjects. The volunteer rate was approximately 82%.

Study subjects were found to be quite representative of the Finnish Twin Cohort, which is representative of the Finnish population. No statistically significant differences were observed when comparing MZ twin subjects to the entire Finnish Twin Cohort for level of education, social class, smoking, level of leisure-time physical activity, or history of work-incapacitating neck, shoulder, or back pain, or sciatica. The MZ study pairs did differ from the entire Finnish Twin Cohort for work status, they were somewhat more likely to be working, and physical loading at work (slightly higher among study subjects), due to the inclusion of related factors in the selection criteria [44]. DZ pairs were selected in an analogous fashion. The validity of zygosity was studied previously in a subsample of 104 twin pairs. The agreement in classification between the questionnaire data and 11 blood markers yielded an estimated probability of misclassification of less than 1.7% [45].

Data acquisition involved transporting twins from all parts of Finland to a central location where a team of project investigators, technicians, and other staff ensured that interviews, physical examinations, and clinical testing were completed over a two-day period for each twin pair.

A structured interview was conducted by trained interviewers to obtain data on lifetime exposures of interest from adolescence through the present. Interviewers were blind with respect to the specific discordance or selection criteria for the twins, and project investigators avoided discussions with the interviewers regarding the study hypotheses. Demographic information and health history; occupational history; history of regularly performed leisure-time activities and exercise; specific recalled incidents or trauma resulting in acute "back injury"; general dietary history, particularly related to calcium intake; and smoking and driving history were obtained from the interview. For example, for each job held during a subject's lifetime, the subject was asked to describe the job activities, including his most common lifting activity and estimate the weight lifted, the frequency of lifting, and the number of hours spent sitting during an average work day. This information along with the job title was used to appropriately categorize the job in terms of its general demands related to materials handling and postural stress. Exposure to cigarette smoking was calculated in pack-years. Optimal means of acquiring adequate estimates of lifetime exposure data is an unresolved issue in research requiring such data. However, using standardized in-depth interviews noting common life "milestones" to assist with recall are expected to assist in providing valid estimates of exposures of interest. Coded data were checked for congruence, outliers were identified, and in some cases phone calls were used to verify unclear or unusual recorded responses.

One year after the initial data collection, all subjects were asked to complete an additional questionnaire, which was provided by approximately 98% of subjects. The follow-up questionnaire afforded the opportunity to determine response reliability for several exposure history variables. Responses were compared with those at the time of the initial interview among those who said that there had been no change in their jobs. The intraclass correlation coefficient was 0.75 for estimates of time spent sitting, 0.77 for driving and 0.60 for total lifting per day. Also, a five-year follow-up interview and examination was conducted on a subgroup of 150 MZ subjects that allowed for reliability estimates for lifetime exercise history data.

Test-retest reliability of lifetime exercise history (using a five-year interval) yielded an intraclass correlation coefficient of 0.69 for lifetime years of exercise type and 0.73 for associated mean exercise hours per week [46].

Clinical examinations included anthropometric measurements (weight, height, % body fat using acoustic impedance) and evaluation of spinal range of motion, isokinetic lifting strength, back muscle static endurance, psychomotor reaction time, and blood and urine samples (for inflammatory mediators, connective tissue markers, and DNA analysis). The Twin Spine Study was provided extraordinary access to the 1.5-Tesla MRI scanner at Kuopio University Hospital and magnetic resonance images (MRIs) of the lumbar spine were obtained for all subjects using a set protocol. Collected blood samples were appropriately stored and transported to the Department of Human Molecular Genetics at the Finnish National Public Health Institute, where DNA was extracted.

Defining disc degeneration—The accuracy of phenotype measurement is critical in genetic epidemiology when trying to identify genes for conditions with multifactorial etiologies and in studies of gene-environment interactions. The strengths of the Twin Spine Study have been the acquisition of data on a broad spectrum of possible determinants and confounding factors, which can be controlled in analyses when appropriate, and the precision of the outcome measures, particularly with respect to degenerative and structural variations.

From the beginning of the Twin Spine Study, the research team has invested much time in methodological developments, such as in spine MRI protocols and image analysis programming. The gross qualitative ratings of spine degeneration in common use [47] were replaced or augmented when possible with quantitative measures with higher reliability and precision.

Then there is the deceptively simple issue of defining disc degeneration. The term disc degeneration is commonly used for an overall subjective impression of imaging findings, including signal loss, bulging, herniation, end plate irregularities, osteophytes, and narrowing of the disc space, but no universally accepted standard definition exists. One might expect degenerative findings to correlate with age, but such correlations have been modest within the 35-year period spanning 35–70 years of age using qualitative MRI findings (Fig. 1) [48]. The MRI finding most highly associated with age to date has been CSF-adjusted disc signal based on T2 sequence, a measure of tissue hydration. Still age explains only a minor portion of the variance in disc signal.

The various MRI findings associated with disc degeneration represent both atrophic (ie, annular tears) and proliferative (ie, osteophytes) changes and may appear at different times in the overall sequence of events collectively termed disc degeneration. Findings may also differ with respect to effects on the occurrence or severity of symptoms. Furthermore, the influence of various risk

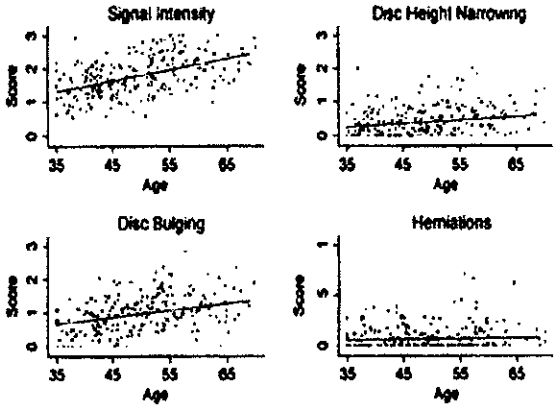


Fig. 1. Associations between age 35 and 70 years and four common findings of disc degeneration based on spine magnetic resonance imaging. The overall associations are weak (From *Spine*, Battié et al., 2004 [48]).

factors may vary in different stages of the degenerative process. Thus, a decision was made early in the Twin Spine Study to examine the distinct findings associated with disc degeneration separately, as opposed to using summary scores that aggregate different findings, which proved particularly useful for studies of genetic influences [38,49].

In an effort to refine MRI assessments of disc degeneration and explore the development of quantitative measurements using the digital data, a UNIX-based image analysis program was developed in 1994 [36], with a later version programmed to run on Windows NT to provide outcome files simultaneously for all spine levels and regions of interest. It also allowed new measures to be easily programmed, as such needs routinely arose as new questions were posed [49–52]. To obtain quantitative measurements using the program, the contours of the anatomical boundaries of lumbar discs, vertebrae, and the spinal canal are manually segmented on sagittal proton density (PD) images (Fig. 2). The evaluator follows the contour of the vertebrae, including the anterior and posterior longitudinal ligaments, and posterior wall of the spinal canal. To segment the disc from the vertebrae, the evaluator follows the boundary between the vertebral end plates and disc. Segmented areas are then adjusted using T2- and T1-weighted images, if necessary, taking advantage of different contrasts. The areas created by the intersections of those segmentation lines form the regions of interest corresponding to the disc and vertebra from which measures are derived by the software. Manual segmentation is also used in axial slices, for example, to evaluate mid-axial disc area and the central spinal canal.

Perhaps the most useful quantitative measure developed was of disc signal, adjusted for the intrabody reference of adjacent CSF. This measure has been more highly correlated with age than any of the other degenerative signs in the disc. It was also found to be the measure of disc

Fig. 2. The left picture shows how the manual segmentation was performed using PD-weighted images: the first and second vertical lines follow the anterior and posterior longitudinal ligaments, the fifth vertical line follows ligamentum flavum, and the third and fourth lines provide cerebrospinal fluid (CSF) samples adjacent to the disc (this is confirmed in T2-weighted images). The horizontal lines follow the disc-vertebra interface. The picture on the right shows the areas of interest created: in the upper disc level, the mean disc signal and mean signal of adjacent CSF (black lines) are obtained. The lower disc level demonstrates the "bulging" areas and the remaining disc area (minus bulging) is divided by its diameter (the horizontal "mid-disc" line) to compute mean disc height [52].

degeneration exhibiting the greatest change over a five-year follow-up period, as compared with little mean progression in disc narrowing, bulging, and other measures [52]. The importance of quantitative measures of greater reliability and precision was demonstrated in the earlier study of associations with Vitamin D receptor polymorphisms, which were identified when using the quantitative measure of signal intensity, but would have been missed using the gross ordinal scales of qualitative measurements [49].

Quantitative degenerative measures are of particular interest for longitudinal studies where more precise measurements of change are needed than available through ordinal rating scales. Quantitative measures included disc signal intensity adjusted by the signal intensity of adjacent CSF, disc volume, disc height, anthropometrics, and adjusted signal intensity of vertebrae, disc bulging, and osteophytes. Intrarater reliability coefficients for lumbar spine measurements are generally above 0.90.

Although quantitative measurements have many benefits in terms of reliability and precision, there are many findings that remain best evaluated by qualitative means. Thus, a combination of qualitative and quantitative image analysis measures have been used to depict various findings associated with degeneration. Each of the 600 subjects' films was assessed by one experienced spine specialist following a set protocol. The assessor was blinded to subject exposures and twinship. Among the specific findings assessed, either quantitatively or qualitatively, were:

From sagittal sections	From transverse sections
Disc signal (desiccation)	Disc signal (desiccation)
Disc height	Dural sac compression
Annular tears	Annular tears
Disc bulging and herniation	Disc bulging and herniation
End plate irregularities and sclerosis	Spinal canal size diameter/area
Vertebral osteophytes	

Exposure-discordant twin studies of suspected environmental and behavioral risk factors

The research program on the etiology and pathogenesis of disc degeneration began under the paradigm that disc degeneration was primarily the cumulative result of tissue injuries and degradation from trauma and repetitive loading. Yet, findings of studies of suspected physical loading risk factors were often contradictory or equivocal, possible confounding was a major concern, and dose-response relations were unclear. Also, at the time the Twin Spine Study began, MRI was just becoming available and most prior epidemiological or clinical studies had been limited to evaluating disc degeneration through radiographs. Thus, in an effort to clarify the effects of a variety of suspected risk factors, MRI and a unique study design that had been used successfully in the examination of exposure effects on cardiovascular disease were used [53]. An exposure-discordant twin model was used. Studying MZ twin siblings grossly discordant for a suspected environmental exposure of interest, controlled not only for age and gender, but also genetic influences and many other known and unknown confounding factors because of the high degree of similarity in identical twins' home and social environments and exposures. Fortunately, the onset of the study in 1992 coincided with the installation of the first 1.5-Tesla scanner in Finland, which was used to acquire study images.

As mentioned earlier, the primary suspected environmental risk factors for disc degeneration were various physical loading conditions, driving and associated whole-body vibration, and smoking. Thus, a series of investigations were conducted with identical twins discordant for a common environmental factor suspected of influencing disc degeneration or risk of back symptoms. The first "pilot" study using the exposure-discordant twin design was of 20 pairs of smoking discordant twins (mean cigarette smoking discordance, 31.6 pack-years), which revealed a lumbar disc degeneration score 18% higher, in mean, for heavy smokers as compared with their "nonsmoking" siblings (Fig. 3, top). The total amount of variance in disc degeneration scores among all subjects explained by smoking, however, was less than 2%. The statistical power to detect this small effect size attested to the efficiency of the MZ twin study design [40]. Based on this experience, recruitment and data collection protocols were established for the Twin Spine Study and the effects of various physical loading conditions at work and leisure were investigated

Fig. 2. The left picture shows how the manual segmentation was performed using PD-weighted images: the first and second vertical lines follow the anterior and posterior longitudinal ligaments, the fifth vertical line follows ligamentum flavum, and the third and fourth lines provide cerebrospinal fluid (CSF) samples adjacent to the disc (this is confirmed in T2-weighted images). The horizontal lines follow the disc-vertebra interface. The picture on the right shows the areas of interest created: in the upper disc level, the mean disc signal and mean signal of adjacent CSF (black lines) are obtained. The lower disc level demonstrates the "bulging" areas and the remaining disc area (minus bulging) is divided by its diameter (the horizontal "mid-disc" line) to compute mean disc height [52].

degeneration exhibiting the greatest change over a five-year follow-up period, as compared with little mean progression in disc narrowing, bulging, and other measures [52]. The importance of quantitative measures of greater reliability and precision was demonstrated in the earlier study of associations with Vitamin D receptor polymorphisms, which were identified when using the quantitative measure of signal intensity, but would have been missed using the gross ordinal scales of qualitative measurements [49].

Quantitative degenerative measures are of particular interest for longitudinal studies where more precise measurements of change are needed than available through ordinal rating scales. Quantitative measures included disc signal intensity adjusted by the signal intensity of adjacent CSF, disc volume, disc height, anthropometrics, and adjusted signal intensity of vertebrae, disc bulging, and osteophytes. Intrarater reliability coefficients for lumbar spine measurements are generally above 0.90.

Although quantitative measurements have many benefits in terms of reliability and precision, there are many findings that remain best evaluated by qualitative means. Thus, a combination of qualitative and quantitative image analysis measures have been used to depict various findings associated with degeneration. Each of the 600 subjects' films was assessed by one experienced spine specialist following a set protocol. The assessor was blinded to subject exposures and twinship. Among the specific findings assessed, either quantitatively or qualitatively, were:

From sagittal sections	From transverse sections
Disc signal (desiccation)	Disc signal (desiccation)
Disc height	Dural sac compression
Annular tears	Annular tears
Disc bulging and herniation	Disc bulging and herniation
End plate irregularities and sclerosis	Spinal canal size diameter/area
Vertebral osteophytes	

Exposure-discordant twin studies of suspected environmental and behavioral risk factors

The research program on the etiology and pathogenesis of disc degeneration began under the paradigm that disc degeneration was primarily the cumulative result of tissue injuries and degradation from trauma and repetitive loading. Yet, findings of studies of suspected physical loading risk factors were often contradictory or equivocal, possible confounding was a major concern, and dose-response relations were unclear. Also, at the time the Twin Spine Study began, MRI was just becoming available and most prior epidemiological or clinical studies had been limited to evaluating disc degeneration through radiographs. Thus, in an effort to clarify the effects of a variety of suspected risk factors, MRI and a unique study design that had been used successfully in the examination of exposure effects on cardiovascular disease were used [53]. An exposure-discordant twin model was used. Studying MZ twin siblings grossly discordant for a suspected environmental exposure of interest, controlled not only for age and gender, but also genetic influences and many other known and unknown confounding factors because of the high degree of similarity in identical twins' home and social environments and exposures. Fortunately, the onset of the study in 1992 coincided with the installation of the first 1.5-Tesla scanner in Finland, which was used to acquire study images.

As mentioned earlier, the primary suspected environmental risk factors for disc degeneration were various physical loading conditions, driving and associated whole-body vibration, and smoking. Thus, a series of investigations were conducted with identical twins discordant for a common environmental factor suspected of influencing disc degeneration or risk of back symptoms. The first "pilot" study using the exposure-discordant twin design was of 20 pairs of smoking discordant twins (mean cigarette smoking discordance, 31.6 pack-years), which revealed a lumbar disc degeneration score 18% higher, in mean, for heavy smokers as compared with their "nonsmoking" siblings (Fig. 3, top). The total amount of variance in disc degeneration scores among all subjects explained by smoking, however, was less than 2%. The statistical power to detect this small effect size attested to the efficiency of the MZ twin study design [40]. Based on this experience, recruitment and data collection protocols were established for the Twin Spine Study and the effects of various physical loading conditions at work and leisure were investigated

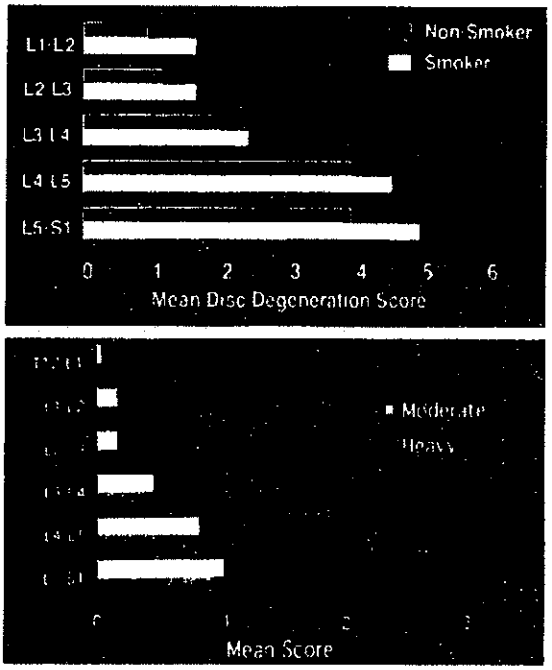


Fig. 3. (Top) The visual degeneration score for smoker and nonsmoker monozygotic siblings by disc level. Smoking had a small harmful statistically significant effect across spinal levels. (Modified from Spine, Battié et al., 1991 [40]). (Bottom) Disc height narrowing score by disc level for monozygotic siblings with physically heavy versus moderate lifetime work history. There was no consistent, statistically significant effect.

[36], including regular participation in various forms of exercise and occupational loading [54], as well as driving and associated whole-body vibration (Fig. 3, bottom) [41].

As mentioned earlier, a higher incidence of back symptom reports in driving occupations had been attributed to the effects of whole-body vibration on the intervertebral disc [31]. The investigation of 45 pairs of MZ twin siblings highly discordant for occupational driving is arguably the most well-controlled study of the effects of driving and associated whole-body vibration on human discs to date, and did not demonstrate significant differences between siblings in MRI findings of the lumbar discs. Besides qualitative measures of disc degeneration, quantitative measurements of CSF-adjusted disc signal intensity were included, which should be highly sensitive for disc degeneration [55,56]. Yet, no tendency for greater disc degeneration was seen among drivers (Fig. 4).

Despite extraordinary discordance between MZ twin siblings in occupational and leisure-time physical loading conditions throughout adulthood, surprisingly little effect on disc degeneration was observed. The findings indicated that although physical loading, that is handling heavy loads, bending, twisting, and static work in awkward postures, appears to influence disc degeneration, the effect size is very modest, which would help explain the inconsistent results of previous studies on the effects of occupational physical loading [42,52]. When the subjects from all the exposure-discordant twin studies were aggregated for analysis, occupational and leisure-time activities explained no more than 7% of the variance in disc degeneration [36]. Perhaps not surprisingly, smoking effects were not detected in this larger, independent group of twins with substantially less smoking discordance. As mentioned earlier, no evidence was found to suggest that exposure to whole-body vibration through motorized vehicles leads to accelerated disc degeneration, which was one of the primary hypotheses of possible mechanisms behind the association between driving occupations and back pain problems [57].

The findings of modest or negligible effects of the primary suspected environmental risk factors despite high exposures and gross discordance would explain the failure to demonstrate uniform, clear effects in earlier studies. It was concluded that the particular extrinsic factors studied, which had been among those most widely suspected of influencing disc degeneration, had modest effects, if any. In fact, some indications were found that routine loading may actually have some benefits to the disc. In a recent study, associations of anthropometric variables, including lifting strength and routine occupational and leisure-time physical loading with disc signal intensity and narrowing were examined in multiple regression modeling [42]. Lower disc signal (representing more disc desiccation) was associated with older age, as could be expected, but also various measures of less routine physical loading of the spine. In addition to older age, lower body mass and lifting strength, and larger disc area were associated with lower signal in multivariable analyses. Although associations were more modest, greater age and occupational loading exposures entered the multivariable model explaining disc height narrowing. The conclusion was that, "body weight, lifting strength, and axial disc area were more highly associated with disc degeneration than occupational and leisure physical activity histories, although all had modest influences. Furthermore, higher body mass, greater lifting strength, and heavier work were all associated with more disc height narrowing, but less disc desiccation contrary to current views" [42]. This observation may represent an important finding in better understanding the relation between various loading conditions and disc degeneration and suggests that responses of the disc may be more in keeping with other musculoskeletal structures that benefit from adaptation to routine physical loading (Fig. 5). The findings also suggest that determinants of disc degeneration and their effect sizes differ between specific degenerative findings. Thus, aggregating findings associated with disc degeneration into summary scores may mask relations.

In summary, the findings of the exposure-discordant twin studies raised questions about the adequacy of an injury model or "wear and tear" view of disc degeneration. Moreover, more recent findings suggest that greater routine physical loading may actually have some beneficial effects

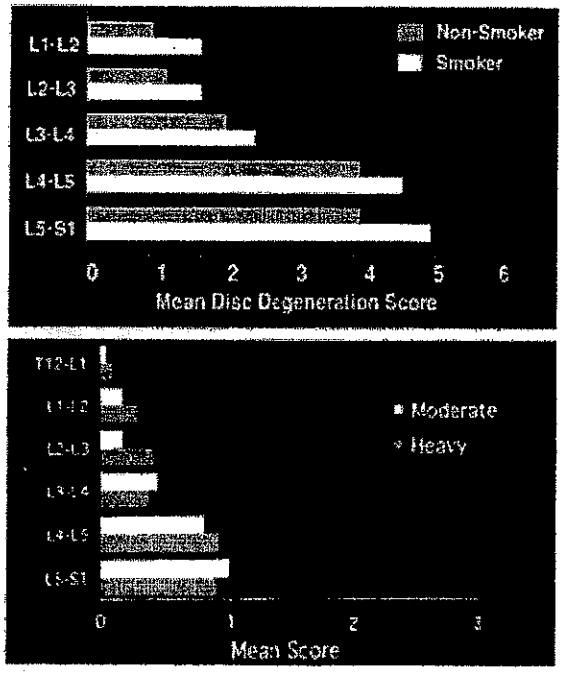


Fig. 3. (Top) The visual degeneration score for smoker and nonsmoker monozygotic siblings by disc level. Smoking had a small harmful statistically significant effect across spinal levels. (Modified from Spine, Battié et al., 1991 [40]). (Bottom) Disc height narrowing score by disc level for monozygotic siblings with physically heavy versus moderate lifetime work history. There was no consistent, statistically significant effect.

[36], including regular participation in various forms of exercise and occupational loading [54], as well as driving and associated whole-body vibration (Fig. 3, bottom) [41].

As mentioned earlier, a higher incidence of back symptom reports in driving occupations had been attributed to the effects of whole-body vibration on the intervertebral disc [31]. The investigation of 45 pairs of MZ twin siblings highly discordant for occupational driving is arguably the most well-controlled study of the effects of driving and associated whole-body vibration on human discs to date, and did not demonstrate significant differences between siblings in MRI findings of the lumbar discs. Besides qualitative measures of disc degeneration, quantitative measurements of CSF-adjusted disc signal intensity were included, which should be highly sensitive for disc degeneration [55,56]. Yet, no tendency for greater disc degeneration was seen among drivers (Fig. 4).

Despite extraordinary discordance between MZ twin siblings in occupational and leisure-time physical loading conditions throughout adulthood, surprisingly little effect on disc degeneration was observed. The findings indicated that although physical loading, that is handling heavy loads, bending, twisting, and static work in awkward postures, appears to influence disc degeneration, the effect size is very modest, which would help explain the inconsistent results of previous studies on the effects of occupational physical loading [42,52]. When the subjects from all the exposure-discordant twin studies were aggregated for analysis, occupational and leisure-time activities explained no more than 7% of the variance in disc degeneration [36]. Perhaps not surprisingly, smoking effects were not detected in this larger, independent group of twins with substantially less smoking discordance. As mentioned earlier, no evidence was found to suggest that exposure to whole-body vibration through motorized vehicles leads to accelerated disc degeneration, which was one of the primary hypotheses of possible mechanisms behind the association between driving occupations and back pain problems [57].

The findings of modest or negligible effects of the primary suspected environmental risk factors despite high exposures and gross discordance would explain the failure to demonstrate uniform, clear effects in earlier studies. It was concluded that the particular extrinsic factors studied, which had been among those most widely suspected of influencing disc degeneration, had modest effects, if any. In fact, some indications were found that routine loading may actually have some benefits to the disc. In a recent study, associations of anthropometric variables, including lifting strength and routine occupational and leisure-time physical loading with disc signal intensity and narrowing were examined in multiple regression modeling [42]. Lower disc signal (representing more disc desiccation) was associated with older age, as could be expected, but also various measures of less routine physical loading of the spine. In addition to older age, lower body mass and lifting strength, and larger disc area were associated with lower signal in multivariable analyses. Although associations were more modest, greater age and occupational loading exposures entered the multivariable model explaining disc height narrowing. The conclusion was that, "body weight, lifting strength, and axial disc area were more highly associated with disc degeneration than occupational and leisure physical activity histories, although all had modest influences. Furthermore, higher body mass, greater lifting strength, and heavier work were all associated with more disc height narrowing, but less disc desiccation contrary to current views" [42]. This observation may represent an important finding in better understanding the relation between various loading conditions and disc degeneration and suggests that responses of the disc may be more in keeping with other musculoskeletal structures that benefit from adaptation to routine physical loading (Fig. 5). The findings also suggest that determinants of disc degeneration and their effect sizes differ between specific degenerative findings. Thus, aggregating findings associated with disc degeneration into summary scores may mask relations.

In summary, the findings of the exposure-discordant twin studies raised questions about the adequacy of an injury model or "wear and tear" view of disc degeneration. Moreover, more recent findings suggest that greater routine physical loading may actually have some beneficial effects

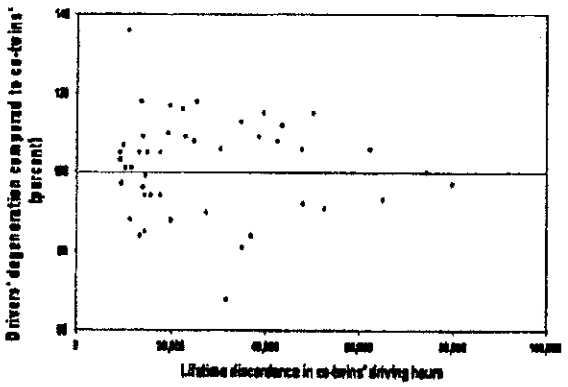


Fig. 4. The points represent the percentage difference in degeneration scores of drivers relative to their "nondriving" monozygotic twin siblings (scores standardized to 100). There was no indication of a dose-response relationship or threshold effect. (From the Lancet, Battié et al., 2002 [41]).

on the disc. During the course of the exposure-discordant twin studies, the striking observation of anyone who had the opportunity to view twin sibling images side-by-side was the strong resemblance in disc degeneration, not just in the degree of degeneration, but also in the types of findings and spinal levels involved. These observations led to subsequent studies of genetic influences.

Heredity as a major determinant of disc degeneration

The observations of co-twin similarities led to two studies of independent samples of MZ twins to systematically evaluate familial aggregation of disc degeneration. Familial aggregation in MZ twins can be viewed as representing the upper limit of genetic influences, as similarities can reflect both shared genes and shared early environments. Because there are very few traits that exhibit shared environmental (ie, nongenetic familial) effects in adulthood, familial aggregation is generally viewed as a proxy of total genetic effects. The resulting two articles were published in 1995 and supported a major shift in the way disc degeneration and its determinants are viewed.

Although occupational physical loading and other environmental exposures had received much attention as possible risk factors [20], detailed studies focusing on hereditary aspects of disc degeneration were lacking [58]. Before our work, there were only case series reports of similarities between twin siblings and relatives in the extent and location of degenerative changes in the spine and other joints [59,60]. We first conducted a systematic evaluation of lumbar degenerative changes blinded to twinship using the 20 twin pairs of MZ twins enrolled in the "pilot" study of twins discordant for smoking. We found a striking degree of similarities (matching by type of finding and spinal level) within identical twin pairs, well beyond that expected by chance or because of similarities in age (Fig. 6) [39]. This was followed by a larger, more comprehensive investigation of the role of familial aggregation and environmental influences in disc degeneration, which has been among the most important contributions to date from the research program [36]. Spine MRIs from 115 pairs of MZ twins were used to estimate the effects of commonly suspected risk factors on disc degeneration relative to the effects of age and familial aggregation, representing both genetic and early shared environmental influences. In the multivariable analysis of the T12–L4 region, 61% of the variance in disc degeneration was explained by familial aggregation, beyond that of age and occupational physical loading that together explained 16%. In the L4–S1 discs, 11% of disc degeneration was explained by physical loading and age, which rose to 43% once familial aggregation was added to the model (Fig. 7). In contrast to the upper lumbar levels, 57% remained unexplained in the lower lumbar region. These study findings led to the conclusion that lumbar disc degeneration may be explained primarily by genetic influences, early environmental exposures and yet unidentified factors, which may include complex interactions, such as between environmental factors and individual spinal anthropometrics [36].

Later, in a sample composed primarily of women from the UK and Australia, Sambrook et al. (1999) reported on heritability estimates for lumbar disc degeneration of 73%, supporting a substantial genetic influence [37]. Heritability estimates refer to the proportion of population variance in a trait attributable to genetic variation. Interestingly, although heritability estimates were high for disc bulging and narrowing (65% and 79%, respectively), a genetic influence on disc signal intensity was not apparent. Preliminary analyses from a classic twin study of 300 pairs of MZ and DZ male twins from the Twin Spine Study indicate substantial but somewhat lower heritability estimates closer to 50%, more in line with expectations from the earlier study of MZ twins [36]. Contrary to Sambrook et al.'s finding of no genetic influence on disc signal intensity using a qualitative four-point rating system, similar heritability estimates for signal intensity as for disc height narrowing were found in the Twin Spine Study when using the more reliable, precise measure of CSF-adjusted disc signal intensity. This provides an example of the importance of phenotype measurements.

The high heritability estimates for different degenerative findings in spine MRI provide motivation for identifying associated genes. Yet, disc degeneration and associated pathology likely represent complex conditions with multifactorial inheritance, presenting challenges to mapping out the genetic architecture of disc degeneration.

The search for susceptibility genes

Common diseases generally have a genetic contribution from multiple gene loci. We are interested in knowing how many alleles exist in each gene locus and their frequencies.

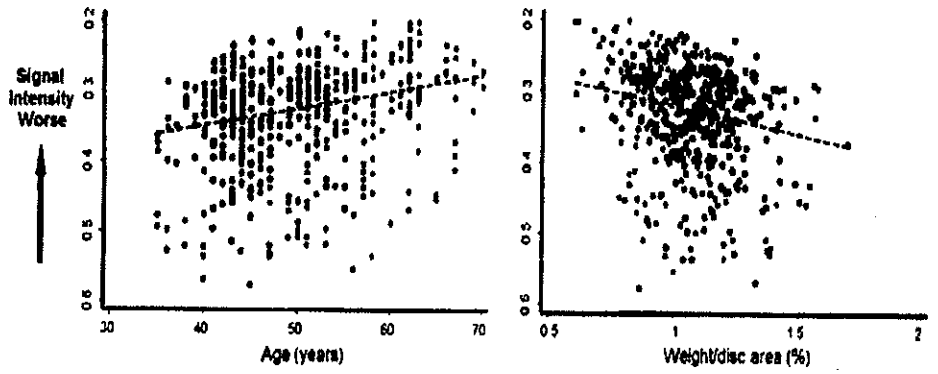


Fig. 5. Scatter plots of quantitative CSF-adjusted disc signal versus age and body weight/axial disc area. Higher body weight per disc area (and other indicators of greater routine loading on the spine) was associated with better (higher) disc signal. (From *Spine*, Videman et al. 2007 [42]).

Allele frequencies and average effects associated with the alleles determine the contribution of allelic variation to the trait of interest, which can then be partitioned into additive genetic variance (gene "dosage") and variance due to gene dominance [61]. Candidate genes may be used as targets, with potential genetic variation leading to differences in the proteins encoded by these genes. These proteins are part of the physiological system that, when disturbed, may give rise to the condition. Thus, the identification of associated genes, given their basic role in determining cell structure and function and hence tissue structure and function, can provide insights into mechanisms underlying disease. The candidate gene approach is promising for the analysis of common diseases, which are complex in their etiology and development, and has been used in most "gene hunting" studies of disc degeneration and associated pathology to date. However, undoubtedly gene-gene and gene-environment interactions are present in common polygenic conditions, such that simple linear models are unlikely to grasp the complexity. Thus, unraveling the contribution of genes and environment to etiology will be a difficult task.

After the discovery of a substantial genetic influence on disc degeneration, there has been considerable effort focused on identifying associated genes. The first gene polymorphisms associated with disc degeneration were identified through the Twin Spine Study in 1998 [38]. They were two polymorphisms of the Vitamin D receptor gene, *TaqI* and *FokI* identified in 170 MZ male twins. The associations were revealed with the phenotype of CSF-adjusted disc signal intensity. Signal intensities were 12.9% lower (more desiccation) in men with the *TaqI* tt genotype and 4.5% lower with the Tt genotype, as compared with signal intensities in men with the TT genotype. A similar pattern was seen between disc signal and *FokI* genotypes. Associations with degenerative scores using qualitative, gross ordinal scales did not reach statistical significance, emphasizing the value of more precise phenotype definition and measurement. As was written in the BackLetter [62] after the presentation of the findings at the annual International Society of the Study of the Lumbar Spine meeting in 1998, the study "*confirmed for the first time the existence of genetic susceptibility to this progressive, age related degenerative process...This is the first step in a long process. However, this research opens the door to more accurate assessment of susceptibility to degenerative problems, and perhaps even prevention of these problems.*"

Since that time, there have been more than 30 studies of genes associated with disc degeneration and related pathology (Table 1). Among 23 studied genes, including aggrecan (AGC), collagen (COL), vitamin D receptor (VDR), inflammatory (IL), degradative (MMP), and some other genes, 17 have been associated with disc degeneration or related pathology in at least one study. However, many observed associations were based on small sample sizes and have not been replicated in other studies. Phenotypes also vary; in one quarter of studies the phenotype was based on X-ray images, which can provide only indirect evidence of disc degeneration through disc space assessment. In the studies based on spine MRI, the specific findings of disc degeneration have been assessed visually (in most studies using a four-point qualitative scale). Despite the challenges with sample sizes and phenotype definitions and associated misclassification, there is reasonable evidence suggesting associations of disc degeneration with the VDR gene (7/8 studies), with COL9A2 (8/10), and with COL9A3 (4/8). Yet, the available findings indicate that each gene has only modest effects.

DNA data for single nucleotide polymorphisms and haplotypes in 25 candidate genes, including 15 structural (aggrecan, 12 collagen, 8 interleukin, and 4 matrix metalloproteinase genes), selected for lumbar degenerative phenotypes were recently analyzed within the Twin Spine Study [63]. For genotype-phenotype associations, we used the FBAT (Family-Based Association Tests) in genetic analyses program package [64]. These tests are based on the classic transmission/disequilibrium test (TDT) [65], and permit testing of the hypotheses of no linkage and no association

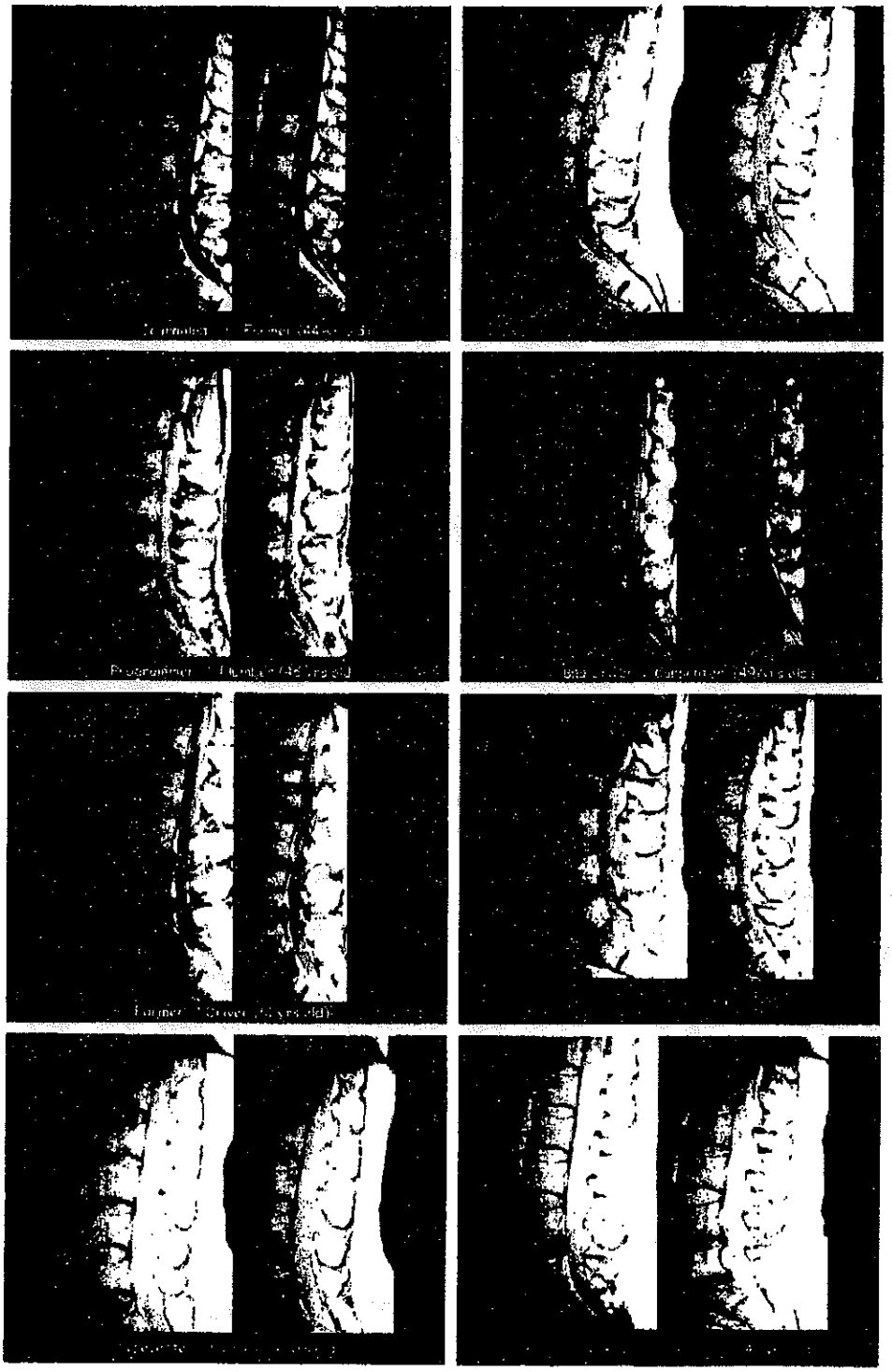


Fig. 6. High degrees of similarities in disc degeneration were noted between twin siblings, often despite high discordance in lifetime physical loading exposures. (In part from *Spine*, Battié et al., 2004 [48]).

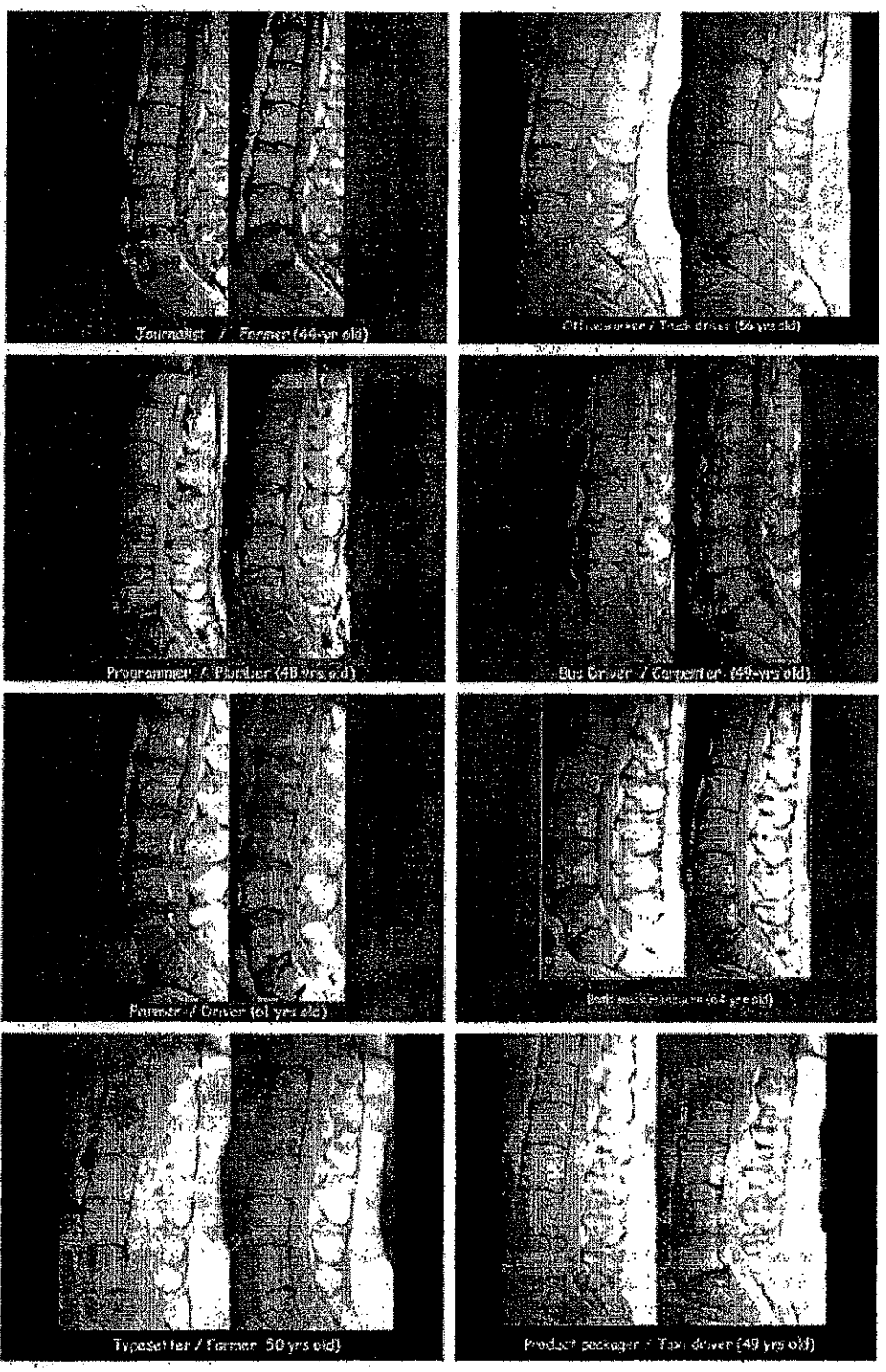


Fig. 6. High degrees of similarities in disc degeneration were noted between twin siblings, often despite high discordance in lifetime physical loading exposures. (In part from *Spine*, Battié et al., 2004 [48]).

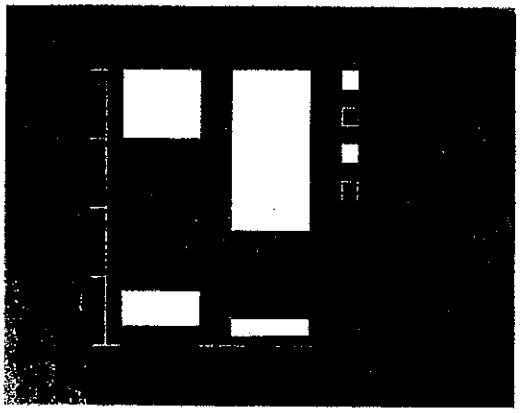


Fig. 7. The variability (adj. R^2) in qualitative disc degeneration summary scores explained by physical loading, age, and familial aggregation (proxy of heredity) demonstrated that significantly more variability remained unexplained in the L4–S1 disc levels. (Modified from *Spine*, Battié et al. 1995 [36]).

and linkage but no association. We used a strict statistical method (including 1,000 permutations) to accept an "overall gene association." The main phenotype was quantitative CSF-adjusted disc signal, in addition to the typical qualitative ordinal scores of disc height narrowing and bulging in 579 MZ and DZ twin subjects. Analyses yielded associations of lumbar disc signal, bulging, and disc height narrowing with the *AGC1* gene. Disc signal was also associated with *COL9A1* and *COL1A1* genes, and interleukin genes, *IL1RL2* and *IL18R1* [63]. Some of these findings support those of earlier analyses, whereas others await replication.

The specific interests in this study were variations in "durability" of structural proteins (disc matrix synthesis and degradation) and in inflammatory and degradative reactions. However, other mechanisms of disc degeneration may exist, such as those related to spinal morphology, muscularity, and lifting strength, which all have genetic correlations and are also included in the genetic component of disc degeneration [42].

Is the disc a pathway through which genes influence back pain problems?

Disc degeneration and back pain are clearly not synonymous and the association between the two is routinely debated. Yet, if disc degeneration does influence back pain problems, and both have a substantial genetic component, disc degeneration may be one pathway through which genes influence back pain. To examine the hypothesis that genetic influences on back pain are mediated through genetic influences on disc degeneration, a classic twin study was conducted on 300 MZ and DZ twin pairs of the Twin Spine Study using multivariate quantitative genetic models to estimate the degree to which genetic effects on back pain are correlated with genetic effects on disc degeneration [95]. Disc height narrowing was used to index disc degeneration as it was the finding most associated with back pain in earlier analyses of MZ twins [51]. In support of the hypothesis, statistically significant genetic correlations were found for various definitions of back pain and disc height narrowing. A substantial minority (up to one-fourth) of the genetic influences on pain was due to the same genetic influences affecting disc height narrowing. Yet, the substantial portion of genetic influences on pain left unexplained suggests an important role for other genetic influences that may affect pain processing, reporting, or other underlying pathological conditions.

In contrast, less than 5% of the variance in back pain outcomes explained by environmental factors was due to the same environmental factors influencing disc height narrowing. This is concordant with the earlier exposure-discordant twin studies revealing negligible or modest effects on disc degeneration of occupational activities associated with back pain complaints. This raises the question, do some of the particular environmental physical loading exposures serve primarily to exacerbate symptoms rather than cause the underlying pathology? It is also important to note that although little overlap was found between environmental factors influencing pain reporting and disc narrowing, environmental factors do appear to have a substantial role in disc height narrowing as do genes. The challenge is to refine or reconceptualize influential environmental exposures, such as biomechanical forces, which may include hypotheses on interactions with other systems, and the pathways through which they may affect lumbar disc degeneration and associated pathology.

Summary

Knowledge gained through the Twin Spine Study has added to others' efforts over more than a decade to enhance our understanding and revise views of disc degeneration. Disc degeneration is now considered a condition that is genetically determined in large part, with environmental factors, although elusive, also playing an important role. Most of the specific environmental factors once thought to be the primary risk factors for disc degeneration appear to have very modest effects, if any [34]. This advance in the understanding of disc degeneration provides a foundation from which to develop new hypotheses and more fruitful research to further elucidate the etiology of disc degeneration.

Earlier work on disc degeneration in MZ twins [36,39] established a substantial role of heredity in disc degeneration through the identification of high degrees of familial aggregation, suggesting a substantial genetic influence. This has been further substantiated by classic twin studies of MZ and DZ twins [37,95]. The initial discovery of two gene forms associated with disc degeneration [38] ushered in the

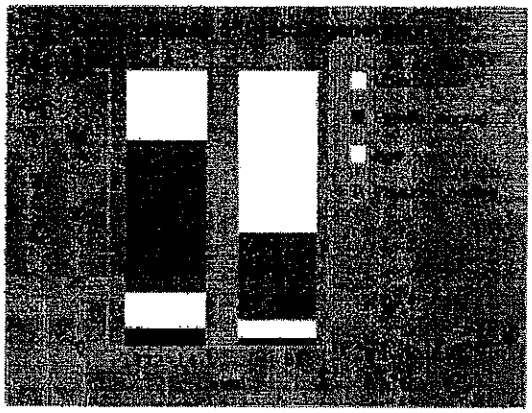


Fig. 7. The variability (adj. R^2) in qualitative disc degeneration summary scores explained by physical loading, age, and familial aggregation (proxy of heredity) demonstrated that significantly more variability remained unexplained in the L4–S1 disc levels. (Modified from *Spine*, Battié et al, 1995 [36]).

and linkage but no association. We used a strict statistical method (including 1,000 permutations) to accept an "overall gene association." The main phenotype was quantitative CSF-adjusted disc signal, in addition to the typical qualitative ordinal scores of disc height narrowing and bulging in 579 MZ and DZ twin subjects. Analyses yielded associations of lumbar disc signal, bulging, and disc height narrowing with the *AGC1* gene. Disc signal was also associated with *COL9A1* and *COL1A1* genes, and interleukin genes, *IL1RL2* and *IL18R1* [63]. Some of these findings support those of earlier analyses, whereas others await replication.

The specific interests in this study were variations in "durability" of structural proteins (disc matrix synthesis and degradation) and in inflammatory and degradative reactions. However, other mechanisms of disc degeneration may exist, such as those related to spinal morphology, muscularity, and lifting strength, which all have genetic correlations and are also included in the genetic component of disc degeneration [42].

Is the disc a pathway through which genes influence back pain problems?

Disc degeneration and back pain are clearly not synonymous and the association between the two is routinely debated. Yet, if disc degeneration does influence back pain problems, and both have a substantial genetic component, disc degeneration may be one pathway through which genes influence back pain. To examine the hypothesis that genetic influences on back pain are mediated through genetic influences on disc degeneration, a classic twin study was conducted on 300 MZ and DZ twin pairs of the Twin Spine Study using multivariate quantitative genetic models to estimate the degree to which genetic effects on back pain are correlated with genetic effects on disc degeneration [95]. Disc height narrowing was used to index disc degeneration as it was the finding most associated with back pain in earlier analyses of MZ twins [51]. In support of the hypothesis, statistically significant genetic correlations were found for various definitions of back pain and disc height narrowing. A substantial minority (up to one-fourth) of the genetic influences on pain was due to the same genetic influences affecting disc height narrowing. Yet, the substantial portion of genetic influences on pain left unexplained suggests an important role for other genetic influences that may affect pain processing, reporting, or other underlying pathological conditions.

In contrast, less than 5% of the variance in back pain outcomes explained by environmental factors was due to the same environmental factors influencing disc height narrowing. This is concordant with the earlier exposure-discordant twin studies revealing negligible or modest effects on disc degeneration of occupational activities associated with back pain complaints. This raises the question, do some of the particular environmental physical loading exposures serve primarily to exacerbate symptoms rather than cause the underlying pathology? It is also important to note that although little overlap was found between environmental factors influencing pain reporting and disc narrowing, environmental factors do appear to have a substantial role in disc height narrowing as do genes. The challenge is to refine or reconceptualize influential environmental exposures, such as biomechanical forces, which may include hypotheses on interactions with other systems, and the pathways through which they may affect lumbar disc degeneration and associated pathology.

Summary

Knowledge gained through the Twin Spine Study has added to others' efforts over more than a decade to enhance our understanding and revise views of disc degeneration. Disc degeneration is now considered a condition that is genetically determined in large part, with environmental factors, although elusive, also playing an important role. Most of the specific environmental factors once thought to be the primary risk factors for disc degeneration appear to have very modest effects, if any [34]. This advance in the understanding of disc degeneration provides a foundation from which to develop new hypotheses and more fruitful research to further elucidate the etiology of disc degeneration.

Earlier work on disc degeneration in MZ twins [36,39] established a substantial role of heredity in disc degeneration through the identification of high degrees of familial aggregation, suggesting a substantial genetic influence. This has been further substantiated by classic twin studies of MZ and DZ twins [37,95]. The initial discovery of two gene forms associated with disc degeneration [38] ushered in the

Table 1
Candidate gene studies to date seeking associations with disc degeneration, sciatica, "lumbar disc disease" or spinal stenosis in general population sample and patients

Authors	Genes	Sample size	Phenotype	Ethnicity
Videman et al., 1998 [38]	*VDR*	170 Population	MRI	Finnish
Jones et al., 1998 [66]	*VDR*	282 Elderly subject	Radiograph (K/L)	Australian
Jordan et al., 2005 [67]	*VDR*	291 Subjects UK	Radiograph (K/L)	
Videman et al., 2001 [49]	*VDR*	142 Population	MRI	Finnish
Kawaguchi et al., 2002 [68]	*VDR*	205 Subjects	MRI	Japanese
Cheung et al., 2006 [69]	*VDR*	804 Population	MRI	Chinese
Kawaguchi 1999 [70]	*AGC*	64 Mix	MRI	Japanese
Roughley 2006 [71]	*AGC*	44 Patients	MRI/radiograph	Canadian
Annunen et al., 1999 [72]	*COL9A2*	157 Patients +101 controls	MRI	Finnish
Paassilta et al., 2001 [73]	*COL9A1–3*	171 Patients	MRI/CT	Finnish
Solovieva et al., 2002 [74]	*COL9A3*	135 Subjects	MRI	Finnish
Karppinen et al., 2002 [75]	*COL9A2*	159 Patients +22 families	MRI	Finnish
Matsui et al., 2004 [76]	*COL9A 2–3*	107 Spondylolisthesis patients	Radiograph/MRI?	United States
Kales et al., 2004 [77]	***COL9A2–3***	105 Patients; 102 controls	Radiograph (K/L)	European
Jim et al., 2005 [78]	*COL9A2*	804 Population	MRI	Chinese
Seki et al., 2006 [79]	***COL9A2***	470 LDD Patients, 658 controls	MRI	Japanese
Higasheno 2006 [80]	*COL9A2*; *COL9A3*	84 Herniation patients	MRI	Japanese
Solovieva et al. 2006 [81]	*COL9A2–3*; *COL2A1*; *COL11A2 IL-1β*	135 Subjects	MRI	Finnish
Noponen-H. et al., 2003 [82]	*COL9A1–2–3*; *COL11A1*; *AGC1*; *VDR*; *MMP-3*	29 Stenosis; 56 controls	MRI/CT	Finnish
Pluijm et al., 2004 [83]	*COL1A1*	966 Subjects	Radiograph (K/L) Dutch	
Tilkeridis et al., 2005 [84]	*COL1A1*	36 Subjects	Radiograph (K/L)	European
Takahashi et al., 2001 [85]	*MMP-3*	103 Subjects	MRI	Japanese
Valdes et al., 2005 [86]	*MMP-3*; *TIMP1*; *COX2*; *VDR*; *THSD2*	720 Subjects	Radiograph (K/L)	UK
Solovieva et al., 2006 [81]	*IL-1β*; *COL9A2*; *COL9A3*; *COL11A2*; *COL2A1*	135 Subjects	MRI	Finnish
Solovieva et al., 2004 [87]	*IL-1α*; *IL-1β*	133 Subjects	MRI	Finnish
Le Maitre et al., 2005 [88]	*IL-1α*; *IL-1β*; *IL1Ra–RI*	30 Tissue samples or	MRI	UK
Noponen-H. et al., 2005 [89]	*IL6*; *IL1A*; *IL1B*; *TNFA*	155 Patients; 179 controls	MRI	Finnish
Min et al., 2006 [90]	*MATN3*	809 Subjects + 382 OA patients	Radiograph (K/L)	Dutch, Icelandic
Seki et al., 2005 [91]	*CILP*	467 Patients 664 controls	MRI Surg. patients	Japanese
Virtanen et al., 2007 [92]	*CIL*	602 LDD patients/602 controls	MRI	Finnish, Chinese
Koshizuka et al., 2007 [93]	*ER*; *PTH*; *IL1b*; *VDR*	381 Spondylosis population	Radiograph (K/L)	Japanese

K/L, Kellgren/Lawrence osteophyte—disc height classification [94].

We found 31 studies on the association of genes and spine degeneration. No association was found with genes in bold-italics. There were 12 studies with sample sizes of more than 200 subjects or cases. Half of the studies were based on population samples and half on patients with spinal disorders. The phenotypes were based on visual grading of MRI in 14 studies, on radiograph in 8–10 studies, and on back pain histories in 8 studies. Quantitative MRI measures were used in 2 studies.

current wave of studies to identify genes associated with disc degeneration, with the hope of better understanding important pathways leading to pathology. Yet, the investigation of genetic influences on disc degeneration is still in its infancy. Future research will aim to clarify the genetics of disc degeneration, identify influential environmental factors, and explore the interplay between the two.

References

[1] Deyo RA, Weinstein JN. Low back pain. N Engl J Med 2001;344: 363–70.

[2] Hadler NM. Workers' Compensation schemes and regional back or leg pain, . Occupational Musculoskeletal Disorders. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 1999. p. 249–78.

[3] Mooney V, Brown M, Modic M. Clinical perspectives. In: Frymoyer JW, Gordon ST, editors. New Perspectives on Low Back Pain. Illinois: AAOS, 1989.

[4] Andersson GB, An HS, Oegema TR Jr, Setton LA. Intervertebral disc degeneration. Summary of an AAOS/NIH/ORS workshop, September 2005. J Bone Joint Surg Am 2006;88:895–9.

[5] Brisby H. Pathology and possible mechanisms of nervous system response to disc degeneration. J Bone Joint Surg Am 2006;88(Suppl 2): 68–71.

[6] Buckwalter JA, Martin J. Intervertebral disc degeneration and back pain. In: Weinstein JN, Gordon SL, editors. Low Back Pain. A Scientific and Clinical Overview. Rosemont, IL: AAOS, 1995:602–23.

[7] Nachemson AL. The future of low back pain research. In: Frymoyer JW, Gordon ST, editors. New Perspectives on Low Back Pain. Illinois: AAOS, 1989.

[8] Devor M. Pain arising from the nerve root and the dorsal root ganglion. In: Weinstein JN, Gordon SL, editors. Low Back Pain. A Scientific and Clinical Overview. Rosemont, IL: AAOS, 1996.

[9] Freemont AJ, Peacock TE, Goupille P, Hoyland JA, O'Brien J, Jayson MI. Nerve ingrowth into diseased intervertebral disc in chronic back pain. Lancet 1997;350:178–81.

[10] Friberg S, Hirsch C. Anatomical and clinical studies on lumbar disc degeneration. Acta Orthop Scand 1949;19:222–42.

[11] Olmarker K, Rydevik B, Nordborg C. Autologous nucleus pulposus induces neurophysiologic and histologic changes in porcine cauda equina nerve roots. Spine 1993;18:1425–32.
[12] Igarashi T, Kikuchi S, Shubayev V, Myers RR. 2000 Volvo Award winner in basic science studies: Exogenous tumor necrosis factor-alpha mimics nucleus pulposus-induced neuropathology. Molecular, histologic, and behavioral comparisons in rats. Spine 2000;25: 2975–80.
[13] Olmarker K, Rydevik B. Selective inhibition of tumor necrosis factor-alpha prevents nucleus pulposus-induced thrombus formation, intraneural edema, and reduction of nerve conduction velocity: possible implications for future pharmacologic treatment strategies of sciatica. Spine 2001;26:863–9.
[14] Stirling A, Worthington T, Rafiq M, Lambert PA, Elliott TS. Association between sciatica and Propionibacterium acnes. Lancet 2001 June 23;357:2024–5.
[15] Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am 1990;72: 403–8.
[16] Buirski G, Silberstein M. The symptomatic lumbar disc in patients with low-back pain. Magnetic resonance imaging appearances in both a symptomatic and control population. Spine 1993;18:1808–11.
[17] Frymoyer JW, Newberg A, Pope MH, Wilder DG, Clements J, MacPherson B. Spine radiographs in patients with low-back pain. An epidemiological study in men. J Bone Joint Surg Am 1984;66: 1048–55.
[18] Hadler NM, Carey TS, Garrett J. The influence of indemnification by workers' compensation insurance on recovery from acute backache. North Carolina Back Pain Project. Spine 1995;20:2710–5.
[19] Riihimäki H. Low-back pain, its origin and risk indicators. Scand J Work Environ Health 1991;17:81–90.
[20] Andersson GBJ. The epidemiology of spinal disorders. In: Frymoyer W, editor. The Adult Spine: Principles and Practice. 2nd ed. Philadelphia: Lippincott-Raven, 1997:107–46.
[21] Caplan PS, Freedman LM, Connelly TP. Degenerative joint disease of the lumbar spine in coal miners—a clinical and x-ray study. Arthritis Rheum 1966;9:693–702.
[22] Hardcastle P, Annear P, Foster DH, et al. Spinal abnormalities in young fast bowlers. J Bone Joint Surg Br 1992;74:421–5.
[23] Hult L. Cervical dorsal and lumbar spinal syndromes. Acta Orthop Scand 1954;17(Suppl):1–102.
[24] Kellgren JH, Lawrence JS. Rheumatism in miners. Part II: X-ray study. Brit J Industr Med 1952;9:197–207.
[25] Lawrence JS. Rheumatism in miners. Part III: occupational factors. Brit J Industr Med 1955;12:249–61.
[26] Lawrence JS, Molyneux MK, Dingwall-Fordyce I. Rheumatism in foundry workers. Brit J Industr Med 1966;23:42–52.
[27] Riihimäki H, Wickström G, Hänninen K, Mattsson T, Waris P, Zitting A. Radiographically detectable lumbar degenerative changes as risk indicators of back pain. A cross-sectional epidemiologic study of concrete reinforcement workers and house painters. Scand J Work Environ Health 1989;15:280–5.
[28] Sairanen E, Brushaber L, Kaskinen M. Felling work, low-back pain and osteoarthritis. Scand J Work Environ Health 1981;7:18–30.
[29] Troup JD. Relation of lumbar spine disorders to heavy manual work and lifting. Lancet 1965;1:857–61.
[30] Videman T, Nurminen M, Troup JD. 1990 Volvo Award in clinical sciences. Lumbar spinal pathology in cadaveric material in relation to history of back pain, occupation, and physical loading. Spine 1990;15:728–40.
[31] Kelsey JL, Hardy RJ. Driving of motor vehicles as a risk factor for acute herniated lumbar intervertebral disc. Am J Epidemiol 1975;102:63–73.
[32] Kjellberg A, Wikström B-O, Landström U. Injuries and other adverse effects of occupational exposure to whole-body vibration: a review for criteria documentation. Arbete och Hälsa—vetenskaplig skriftserie 1994;41:1–74.
[33] Buckwalter JA. Aging and degeneration of the human intervertebral disc. Spine 1995;20:1307–14.
[34] Frymoyer JW. Lumbar disk disease: epidemiology. Instr Course Lect 1992;41:217–23.
[35] Ala-Kokko L. Genetic risk factors for lumbar disc disease. Ann Med 2002;34:42–7.
[36] Battié MC, Videman T, Gibbons LE, Fisher LD, Manninen H, Gill K. 1995 Volvo Award in clinical sciences. Determinants of lumbar disc degeneration. A study relating lifetime exposures and magnetic resonance imaging findings in identical twins. Spine 1995;20:2601–12.
[37] Sambrook PN, MacGregor AJ, Spector TD. Genetic influences on cervical and lumbar disc degeneration: a magnetic resonance imaging study in twins. Arthritis Rheum 1999;42:366–72.
[38] Videman T, Leppävuori J, Kaprio J, et al. Intragenic polymorphisms of the vitamin D receptor gene associated with intervertebral disc degeneration. Spine 1998;23:2477–85.
[39] Battié MC, Haynor DR, Fisher LD, Gill K, Gibbons LE, Videman T. Similarities in degenerative findings on magnetic resonance images of the lumbar spines of identical twins. J Bone Joint Surg Am 1995;77:1662–70.
[40] Battié MC, Videman T, Gill K, et al. 1991 Volvo Award in clinical sciences. Smoking and lumbar intervertebral disc degeneration: an MRI study of identical twins. Spine 1991;16:1015–21.
[41] Battié MC, Videman T, Gibbons LE, et al. Occupational driving and lumbar disc degeneration: a case-control study. Lancet 2002;360: 1369–74.
[42] Videman T, Levälahti E, Battié MC. The effects of anthropometrics, lifting strength, and physical activities in disc degeneration. Spine 2007;32:1406–13.
[43] Kaprio J, Koskenvuo M, Langinvainio H, Romanov K, Sarna S, Rose RJ. Genetic influences on use and abuse of alcohol: a study of 5638 adult Finnish twin brothers. Alcohol Clin Exp Res 1987 August;11:349–56.
[44] Simonen RL, Videman T, Kaprio J, Levalähti E, Battié MC. Factors associated with exercise lifestyle—a study of monozygotic twins. Int J Sports Med 2003 October;24:499–505.
[45] Sarna S, Kaprio J, Sistonen P, Koskenvuo M. Diagnosis of twin zygosity by mailed questionnaire. Hum Hered 1978;28:241–54.
[46] Ropponen A, Levälahti E, Simonen R, Videman T, Battié MC. Repeatability of lifetime exercise reporting. Scand J Med Sci Sports 2001;11:185–92.
[47] Raininko R, Manninen H, Battié MC, Gibbons LE, Gill K, Fisher LD. Observer variability in the assessment of disc degeneration on magnetic resonance images of the lumbar and thoracic spine. Spine 1995;20:1029–35.
[48] Battié MC, Videman T, Parent E. Lumbar disc degeneration: epidemiology and genetic influences. Spine 2004;29:2679–90.
[49] Videman T, Gibbons LE, Battié MC, et al. The relative roles of intragenic polymorphisms of the vitamin D receptor gene in lumbar spine degeneration and bone density. Spine 2001;26:E7–E12.
[50] Parent EC. Development of Quantitative Measures of Lumbar Disc Contour Abnormalities for MRI: Reliability and Validity. University of Alberta, 2005.
[51] Videman T, Battié MC, Gibbons LE, Maravilla K, Manninen H, Kaprio J. Associations between back pain history and lumbar MRI findings. Spine 2003;28:582–8.
[52] Videman T, Battié MC, Parent E, Gibbons LE, Vainio P, Kaprio J. Progression and determinants of quantitative magnetic resonance imaging measures of lumbar disc degeneration: a five-year follow-up of adult male monozygotic twins. Spine 2008;33:1484–90.
[53] Haapanen A, Koskenvuo M, Kaprio J, Kesäniemi YA, Heikkilä K. Carotid arteriosclerosis in identical twins discordant for cigarette smoking. Circulation 1989 July;80:10–6.

[54] Videman T, Battié MC, Gibbons LE, et al. Lifetime exercise and disk degeneration: an MRI study of monozygotic twins. Med Sci Sports Exerc 1997;29:1350–6.
[55] Videman T, Nummi P, Battié MC, Gill K. Digital assessment of MRI for lumbar disc desiccation. A comparison of digital versus subjective assessments and digital intensity profiles versus discogram and macroanatomic findings. Spine 1994;19:192–8.
[56] Weidenbaum M, Foster RJ, Best BA, et al. Correlating magnetic resonance imaging with the biochemical content of the normal human intervertebral disc. J Orthop Res 1992 July;10:552–61.
[57] Dupuis H. Medical and occupational preconditions for vibration-induced spinal disorders: occupational disease no. 2110 in Germany. Int Arch Occup Environ Health 1994;66:303–8.
[58] Heikkilä JK, Koskenvuo M, Heliovaara M, et al. Genetic and environmental factors in sciatica. Evidence from a nationwide panel of 9365 adult twin pairs. Ann Med 1989;21:393–8.
[59] Bull J, el Gammal T, Popham M. A possible genetic factor in cervical spondylosis. Br J Radiol 1969;42:9–16.
[60] King JB. A radiographic survey of nine pairs of elderly identical twins. Clin Radiol 1971 July;22:375–8.
[61] Sing CF, Moll PP. Genetics of atherosclerosis. Annu Rev Genet 1990;24:171–87.
[62] Schoene ML. Award-winning genetic advances promise new approaches to common spinal problems. Backletter 1998;13(7):73–80.
[63] Videman T, Saarela J, Kaprio J, et al. Associations of 25 structural, degradative and inflammatory candidate genes with lumbar disc desiccation, bulging and height narrowing. Arthritis Rheum 2009;60.
[64] van Steen K, Laird NM. Family based association tests and the FBAT-toolkit. Users Manual, 2005.
[65] Spielman RS, McGinnis R, Ewens WJ. Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (DDM). Am J Hum Genet 1993;65:578–80.
[66] Jones G, White C, Sambrook P, Eisman J. Allelic variation in the vitamin D receptor, lifestyle factors and lumbar spinal degenerative disease. Ann Rheum Dis 1998;57(2):94–9.
[67] Jordan KM, Syddall H, Dennison EM, et al. Birthweight, vitamin D receptor gene polymorphism, and risk of lumbar spine osteoarthritis. J Rheumatol 2005 April;32(4):678–83.
[68] Kawaguchi Y, Kanamori M, Ishihara H, et al. The association of lumbar disc disease with vitamin-D receptor gene polymorphism. J Bone Joint Surg Am 2002;84-A(11):2022–8.
[69] Cheung KM, Chan D, Karppinen J, et al. Association of the Taq I allele in vitamin D receptor with degenerative disc disease and disc bulge in a Chinese population. Spine 2006 May 1;31(10):1143–8.
[70] Kawaguchi Y, Osada R, Kanamori M, et al. Association between an aggrecan gene polymorphism and lumbar disc degeneration. Spine 1999;24(23):2456–60.
[71] Roughley P, Martens D, Rantakokko J, et al. The involvement of aggrecan polymorphism in degeneration of human intervertebral disc and articular cartilage. Eur Cell Mater 2006;11:1–7.
[72] Annunen S, Paassilta P, Lohiniva J, et al. An allele of COL9A2 associated with intervertebral disc disease. Science 1999;285(5426):409–12.
[73] Paassilta P, Lohiniva J, Goring HH, Perala M, et al. Identification of a novel common genetic risk factor for lumbar disk disease. Jama 2001;285(14):1843–9.
[74] Solovieva S, Lohiniva J, Leino-Arjas P, Raininko R, Luoma K, Ala-Kokko L, Riihimäki H. COL9A3 gene polymorphism and obesity in intervertebral disc degeneration of the lumbar spine: evidence of gene-environment interaction. Spine 2002 December 1;27(23):2691–6.
[75] Karppinen J, Pääkkö E, Raina S, et al. Magnetic resonance imaging findings in relation to the COL9A2 tryptophan allele among patients with sciatica. Spine 2002;27(1):78–83.
[76] Matsui Y, Mirza SK, Wu JJ, et al. The association of lumbar spondylolisthesis with collagen IX tryptophan alleles. J Bone Joint Surg Br 2004 September;86(7):1021–6.
[77] Kales SN, Linos A, Chatzis C, Sai Y, et al. The role of collagen IX tryptophan polymorphisms in symptomatic intervertebral disc disease in Southern European patients. Spine 2004 June 1;29(11):1266–70.
[78] Jim JJ, Noponen-Hietala N, Cheung KM, et al. The TRP2 allele of COL9A2 is an age-dependent risk factor for the development and severity of intervertebral disc degeneration. Spine 2005 December 15;30(24):2735–42.
[79] Seki S, Kawaguchi Y, Mori M, et al. Association study of COL9A2 with lumbar disc disease in the Japanese population. J Hum Genet 2006;51(12):1063–7.
[80] Higashino K, Matsui Y, Yagi S, et al. The alpha2 type IX collagen tryptophan polymorphism is associated with the severity of disc degeneration in younger patients with herniated nucleus pulposus of the lumbar spine. Int Orthop 2007 February;31(1):107–11.
[81] Solovieva S, Lohiniva J, Leino-Arjas P, et al. Intervertebral disc degeneration in relation to the COL9A3 and the IL-1ss gene polymorphisms. Eur Spine J 2006 May;15(5):613–9.
[82] Noponen-Hietala N, Kyllönen E, Mannikkö M, et al. Sequence variations in the collagen IX and XI genes are associated with degenerative lumbar spinal stenosis. Ann Rheum Dis 2003 December;62(12):1208–14.
[83] Pluijm SM, van Essen HW, Bravenboer N, et al. Collagen type I alpha1 Sp1 polymorphism, osteoporosis, and intervertebral disc degeneration in older men and women. Ann Rheum Dis 2004 January;63(1):71–7.
[84] Tilkeridis C, Bei T, Garantziotis S, Stratakis CA. Association of a COL1A1 polymorphism with lumbar disc disease in young military recruits. J Med Genet 2005 July;42(7):e44.
[85] Takahashi M, Haro H, Wakabayashi Y, et al. The association of degeneration of the intervertebral disc with 5a/6a polymorphism in the promoter of the human matrix metalloproteinase-3 gene. J Bone Joint Surg Br 2001;83(4):491–5.
[86] Valdes AM, Hassett G, Hart DJ, Spector TD. Radiographic progression of lumbar spine disc degeneration is influenced by variation at inflammatory genes: a candidate SNP association study in the Chingford cohort. Spine 2005 November 1;30(21):2445–51.
[87] Solovieva S, Kouhia S, Leino-Arjas P, et al. Interleukin 1 polymorphisms and intervertebral disc degeneration. Epidemiology 2004 September;15(5):626–33.
[88] Le Maitre CL, Freemont AJ, Hoyland JA. The role of interleukin-1 in the pathogenesis of human intervertebral disc degeneration. Arthritis Res Ther 2005;7(4):R732–45.
[89] Noponen-Hietala N, Virtanen I, Karttunen R, et al. Genetic variations in IL6 associate with intervertebral disc disease characterized by sciatica. Pain 2005 March;114(1-2):186–94.
[90] Min JL, Meulenbelt I, Riyazi N, et al. Association of matrilin-3 polymorphisms with spinal disc degeneration and osteoarthritis of the first carpometacarpal joint of the hand. Ann Rheum Dis 2006 August;65(8):1060–6.
[91] Seki S, Kawaguchi Y, Chiba K, et al. A functional SNP in CILP, encoding cartilage intermediate layer protein, is associated with susceptibility to lumbar disc disease. Nat Genet 2005 June;37(6):607–12.
[92] Virtanen IM, Karppinen J, Taimela S, et al. Occupational and genetic risk factors associated with intervertebral disc disease. Spine 2007 May 1;32(10):1129–34.
[93] Koshizuka Y, Ogata N, Shiraki M, et al. Distinct association of gene polymorphisms of estrogen receptor and vitamin D receptor with lumbar spondylosis in post-menopausal women. Eur Spine J 2006 October;15(10):1521–8.
[94] Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
[95] Battié MC, Videman T, Levälahti E, Kaprio J. Genetic and environmental effects on disc degeneration by phenotype and spinal level. A multivariate twin study. Spine 2008;33:2801–8.

ELSEVIER

The Spine Journal 8 (2008) 258–265

THE SPINE JOURNAL

A brief overview of evidence-informed management of chronic low back pain with surgery

Angus S. Don, FRACS, Eugene Carragee, MD*

Stanford University Medical Center, Stanford, CA, USA

Received 3 October 2007; accepted 13 October 2007

Abstract

EDITORS' PREFACE: The management of chronic low back pain (CLBP) has proven to be very challenging in North America, as evidenced by its mounting socioeconomic burden. Choosing among available nonsurgical therapies can be overwhelming for many stakeholders, including patients, health providers, policy makers, and third-party payers. Although all parties share a common goal and wish to use limited health-care resources to support interventions most likely to result in clinically meaningful improvements, there is often uncertainty about the most appropriate intervention for a particular patient. To help understand and evaluate the various commonly used nonsurgical approaches to CLBP, the North American Spine Society has sponsored this special focus issue of *The Spine Journal*, titled Evidence-informed management of chronic low back pain without surgery. Articles in this special focus issue were contributed by leading spine practitioners and researchers, who were invited to summarize the best available evidence for a particular intervention and encouraged to make this information accessible to nonexperts. Although this special focus issue was focused on nonoperative care, it was deemed important to provide an overview of the surgical management of CLBP. This is intended to inform stakeholders of surgical options that are available to them should nonsurgical interventions prove ineffective or contraindicated. It is hoped that articles in this special focus issue will be informative and aid in decision making for the many stakeholders evaluating nonsurgical interventions for CLBP.

Keywords: CLBP; Psychosocial; Diagnostics; Surgical versus alternatives

Introduction

Over the last few years, billions of dollars have been spent worldwide on surgery for people with chronic low back pain (CLBP), and thousands of research articles have been dedicated to the subject. Despite numerous technological advances in surgical procedures and devices, there are still no clearly defined clinical practice guidelines related to surgical intervention of CLBP in the absence of serious structural disease such as instability, infection, or neoplasm.

Low back pain (LBP) is extremely common, with point prevalence as high as 33% [1] and 6-month prevalence as high as 73% [2]. Most cases of LBP are self-limiting, with no persistent or serious sequelae. Even among those with LBP and comorbidities associated with the development of disability, less than 10% experienced loss of work longer than 1 week over a 5-year period [3]. For the small percentage of patients with incapacitating CLBP, the question remains as to why are they so severely affected when others with similar degenerative findings can be asymptomatic. This is perhaps not surprising given that the cause of CLBP in the absence of serious spinal disease is poorly understood. Therefore, any decision regarding the appropriate use of surgery for CLBP must be made not only with regard to the presumed structural cause of pain, but also by considering the psychosocial and economic context of the patient. Disabling CLBP develops more frequently in patients who, at the initial evaluation, have a high level of "fear avoidance" (an exaggerated fear of pain leading to avoidance of beneficial activities), psychological distress, disputed compensation claims, involvement in a tort-compensation system, or job dissatisfaction [3–7].

FDA device/drug status: approved for these indications (Total disc replacement and IDET); approved but not for this indication (Posterior dynamic Stabilizers/Interspinous Devices).

Nothing of value received from a commercial entity related to this manuscript.

* Corresponding author. Stanford University Medical Center, 300 Pasteur Drive, Room R171, Stanford, CA 943065, USA. Tel.: (650) 723-7797; fax: (650) 723-9805.

E-mail address: carragee@stanford.edu (E. Carragee)

1529-9430/08/$ – see front matter
doi:10.1016/j.spinee.2007.10.027

History

Despite the tenuous link between degenerative disc disease (DDD) and CLBP, the disc has been the focus of a large majority of information and research regarding the etiology of LBP since it was recognized as a distinct entity in the last century. Surgery for disc herniation was first performed by Oppenheim and Kruse in 1909, and Holdsworth and Hardy were the first to report on internal fixation of the spine in patients with fracture dislocations of the thoracolumbar spine in 1953 [8]. Boucher was the first to use transpedicular screws for spinal fusions in 1959 [9] after it had been suggested earlier by King in 1944 [10]. Harrington published his results for spinal instrumentation surgery for scoliosis in 1962 [11], and was followed by Luque 20 years later [12]. As the century moved on, the Cotrel-Dubousset system for spine surgery was introduced, followed by the Texas Scottish Rite system in 1991, the Moss Miami system in 1994, and others. Threaded cages and anterior instrumentation were later introduced for spine surgery. Although a large number of these surgical instrumentations, techniques, and devices were originally designed for scoliosis, many were later used to treat patients with DDD and CLBP.

Despite the recent attention brought to the topic, the concept of disc replacement is not new. Nachemson began implanting silicon testicular prosthesis into the disc space in the 1950, though this procedure was later abandoned when the implants disintegrated [13]. Fernstrom reported his experience with implanting a steel ball in the disc space in 1966, but this also met with poor results [13,14]. Since that time, there has been a plethora of failed artificial disc designs including silicon spacers, plastic spacers, silicon or plastic spacers with metal end plates, and various end plate designs including screws, pins, keels, cones, and suction caps [15]. Various hygroscopic agents have also been used to replace the disc, followed by elastic beads, springs, oils, and expandable gels [15]. Currently, there are four disc replacements on the US market: ProDisc, SB Charité, Maverick, and Flexicore.

Advances in understanding the pathophysiology of DDD as it relates to CLBP followed surgical developments in a parallel fashion. The basis for much research followed is from the original work by MacNab on the structural changes in the disc and its relationship to disc disease [16]. A further advance in the understanding of the morphological changes of DDD came with the advent of computed tomography scanning, myelography with computed tomography scanning, and magnetic resonance imaging (MRI). Unfortunately, these diagnostic tests are not sophisticated enough to determine whether abnormalities are related to the pathoanatomic cause of CLBP. The problem remains that the overwhelming majority of patients with CLBP have nonspecific findings on such imaging studies, rather than serious pathology at which surgery may be directed. Structural findings of disc degeneration [17], annular disruption [17–19], and end plate changes [20,21] are commonly seen in patients with CLBP in clinical studies. However, such findings are also common in cross-sectional studies of asymptomatic populations [22,23]. It is therefore impossible to draw conclusions between findings of common degenerative changes on imaging and patient complaints of CLBP. Imaging findings are also not able to identify those at risk of developing CLBP because DDD on MRI in asymptomatic subjects is not predictive of experiencing LBP in the future [24]. Similarly, subjects with new episodes of severe LBP and previous MRI scans are unlikely to detect changes in disc protrusion, annular fissures, high-intensity zones, or end plate signal changes with repeated MRI [25].

Discography was described by Lindblom in 1948 and gave the first detailed structural evaluation of the internal disc architecture in patients with back problems [26]. Although the pain response to disc injection provided a different insight into the pathology of DDD, the validity of provocative discography has not been confirmed because there is no histopathological gold standard against which a positive result could be validated. Further limiting the usefulness of disc injections as a diagnostic tool for CLBP is that they are painful in 30% to 80% of asymptomatic subjects, especially in the presence of psychological distress, previous disc surgery, local or remote concurrent pain processes, or disputed compensation [27,28]. Their anatomic basis has also been questioned because disc injections have been shown to reproduce the quality and location of pain from other sources (eg, pelvic pain, tumor, etc) [29]. Even in a best-case scenario using provocative discography in a group of patients with LBP and no comorbidities, the positive predictive value of a single level injection was—at best—50% to 60% for resolution of LBP after surgical removal of the suspected pain generator with discectomy and solid interbody fusion [30].

Indications

Because physical examination and detailed imaging techniques have failed to delineate a clear pathoanatomic cause for patients with CLBP, it is difficult to identify those individuals who would benefit from surgical intervention, and the type of intervention that is most suitable to a particular patient. Not surprisingly, this lack of consensus had lead to huge geographical variations in use of surgery for LBP across the United States [31]. In addition to uncertainty regarding the efficacy of surgery for CLBP, it should also be noted that the potential harms and costs associated with these interventions are substantial.

There are generally two schools of thought on the clinical approach to CLBP in the absence of serious structural disease: 1) pain generator approach and 2) psychosocial/economic approach. Each is briefly discussed below.

Pain generator approach

This philosophy has focused on the identification and subsequent treatment of a specific "pain generator" in patients

with CLBP. This approach assumes that a specific pathoanatomic cause can account for individuals' symptoms, independently of any psychological, social, economical, or neurophysiological factors. Based on those assumptions, treatment aimed at removing or correcting the suspected "pain generator" would therefore be expected to be highly effective in eliminating symptoms of CLBP.

Psychosocial/economic approach

The opposing view holds that the pain generator approach to CLBP is misplaced, as indicated by epidemiological trends of the worsening prognosis for CLBP and generally poor results in clinical trials of treatments directed at specific anatomical structures. Given that imaging studies often reveal similar findings in those with mild, moderate, severe, or even no CLBP, differences in clinical presentation must be because of factors other than the presence of specific pathology. According to this approach, treatment of CLBP should therefore be directed at these other factors, which may include central pain processes, psychological factors, social disincentives, poor coping strategies, etc. This approach is generally aimed at restoring function rather than attempting to rapidly eliminate symptoms, and educating patients about supporting adaptive techniques.

Combined approach

A more comprehensive method of managing CLBP could be achieved by combining the best of both approaches. Such a combined approach could direct medical and—if necessary—surgical treatments at specific structures in the lumbar spine if warranted, while promoting the use of functional restoration, fear-avoidance training, lifestyle modifications, education, and supporting adaptive techniques. Many of these interventions are reviewed elsewhere in this special focus issue. An important consideration in a combined approach is the timing of surgical intervention. Generally, surgery should not be considered for CLBP unless the patient has suffered functional disability, unremitting pain for a prolonged period (eg, longer than 6 months), and has failed a lengthy period of appropriate nonoperative treatment. Defining the latter remains challenging [32].

Before any surgical intervention is considered for nonspecific CLBP with findings of DDD, the patient and surgeon should be confident that the intervention directed at a specific structure has a high chance of obtaining a positive clinical improvement. This is challenging given the wide variation in possible imaging findings in patients with CLBP. At one extreme, there may be the severe facet fragmentation and disc changes that are associated with segmental instability, spondylolisthesis, and concomitant radicular complaints. Such pathological changes rarely seen in healthy individuals may reasonably be suspected of causing serious CLBP. At the other end of the spectrum, there may be only minimal changes consisting of disc dissecation or annular bulging with early fissuring. These types of changes are common and highly unlikely to account for the severity of illness reported, especially in a patient with serious depression, ongoing litigation, or a long history of poorly defined somatic illnesses. Surgical management aimed at annular tears in this type of patient is uncertain at best.

Contraindications

Many contraindications to surgery are nonspecific and include general medical considerations of cardiac, pulmonary, and metabolic reserves, prohibitive anesthetic risk, and patients unable to comprehend the intentions and limitations of surgery. Although there is no absolute contraindication specifically related to the spine, there are certainly factors that have been shown to predict a poor outcome to surgical intervention for CLBP. Patients with high fear avoidance of pain, psychological distress, compensation claims, personal injury litigation, and job dissatisfaction generally have poorer outcomes than those without these risk factors [3–7]. Such risk factors are much more common in patients without definite pathology or destructive processes [33,34]. Additional contraindications that are specific to arthroplasty, dynamic stabilization, and other surgical procedures are summarized below.

Surgical treatment for lumbar degenerative disc disease

After the success of laminectomy and discectomy in treating patients with sciatica secondary to herniation, the same technique was applied to CLBP associated with DDD. Anecdotal reports of early success with this procedure were far outweighed by subsequent reports of failures, which were much more common. For DDD without neurological symptoms, the practice of laminectomy has largely been abandoned [35]. There are four general categories of procedures currently used for the surgical treatment of serious CLBP in the absence of significant spinal pathology: 1) lumbar fusion; 2) disc arthroplasty; 3) dynamic stabilization; and 4) percutaneous techniques. The first three categories are briefly discussed below whereas the latter category—which is also termed minimally invasive and includes Intradiscal Electrothermal Therapy and nucleoplasty—is reviewed elsewhere in this special focus issue.

Lumbar fusion

Mechanism of action

Because the elimination of motion after solid arthrodesis has been effective for pain relief in other arthritic joints

within the body (eg, ankle, wrist, hip) it is no surprise that surgical fusion to eliminate motion has been used to treat CLBP. However, the complexity of the multiple spinal articulations and uncertainty in determining whether these joints are in fact responsible for generating CLBP have brought this practice into question. Some authors have observed a lack of correlation between clinical outcomes and the presence of pseudarthrosis or solid arthrodesis after spinal fusion surgery [36–38].

Evidence of efficacy

Spinal fusion for CLBP secondary to fractures, persistent or complicated infections, progressive deformity, or demonstrable radiographic instability with spondylolisthesis has been shown to be dramatically beneficial. For example, it has been reported that 70% to 90% of patients who received spinal fusion for isthmic spondylolisthesis returned to full occupational function, had minimal impairment, and ceased all narcotic medication [30,39,40].

The evidence supporting surgical fusion for CLBP in the absence of serious pathology, instability, or neurological compression, however, is much less convincing. Most of the 30 or more randomized controlled trials (RCTs) on surgery for degenerative lumbar spondylosis have compared surgical techniques rather than addressing the more fundamental issue of whether any surgery is better than nonoperative care [41]. Four RCTs have attempted to address this question and although the first study appeared to provide some evidence in favor of fusion [42], the latter studies failed to corroborate this finding (Table 1) [43–45]. Differences in results may lie in the choice of treatment given to the nonoperative control group in those four RCTs. The three studies with negative results for spinal fusion compared it with a cognitive behavioral model or structured rehabilitation [43–45], whereas the only study with positive results for fusion compared it with continued usual care, which had likely already failed in that group [41]. In the three studies using cognitive behavioral therapy, only small differences were noted between the fusion and nonoperative groups. The nonsurgical groups had fewer complications and better coping strategies, whereas the fusion groups had a modest improvement in the Oswestry Disability Index in one study [45]. It should be noted that even the RCT that reported favorable results for fusion had excellent outcomes in only 16%, compared with 6% in the nonoperative usual care group.

Technical considerations

There are a variety of well-accepted techniques which have been used for spinal fusion, including 1) posterior-only approaches (posterolateral intertransverse fusion with or without instrumentation, posterior lumbar interbody fusion, and transforaminal interbody fusion); 2) anterior-only approaches; and 3) combined approaches. The surgical technique used for spinal fusion is largely surgeon dependent and there does not appear to be any clinical advantage between anterior, posterior, and noninstrumentation techniques according to a recent RCT [46].

The issue of instrumentation remains controversial. Although a large body of evidence suggests that pedicle screws promote fusion and decrease pseudarthrosis [47–50], there is no demonstrable improvement clinically [51]. Instrumentation, however, results in greater improvements in both back and leg pain at the 5-year follow-up compared with noninstrumented fusions when DDD is accompanied by evidence of instability (spondylolisthesis Grade 1 and 2) [52]. Studies comparing fusion with and without instrumentation have reported that use of pedicle screws increased the likelihood of reoperation, nerve injury, blood loss, longer operative time, and complication rate [46,52,53].

Disc arthroplasty

Mechanism of action

The premise for disc arthroplasty stems from the assumption that the pain in CLBP stems from an abnormal and painful spinal motion segment, and that the artificial disc would function as a painless and physiologic replacement for the degenerated disc. This premise is buoyed by the success in treating arthritic hips and knees with arthroplasty, where replacements are now expected to last 15 to 20 years in an elderly population. Proponents of disc arthroplasty often argue that this approach is superior to the often unsatisfactory results of fusion because it avoids the morbidity associated with pseudarthrosis, bone graft donor site pain, increased adjacent segment strain, and risk of accelerated DDD. Ideally, disc arthroplasty would reproduce load transmission properties of the natural disc and maintain spinal motion segment characteristics, theoretically avoiding some of the above problems related to surgical fusion.

Evidence of efficacy

For the treatment of nonspecific CLBP, the clinical results comparing disc arthroplasty with lumbar fusion have been mostly inconclusive. Results of these trials have reported minimal differences in functional outcomes, pain intensity, medication intake, or occupational disability [54–56]. Approximately 50% of the subjects who participated in clinical trials of disc arthroplasty in the UK and United States—despite rigorous study eligibility criteria intended to maximize the likelihood of success—appear to be clinical failures [54,56]. The study conducted to support the investigational device exemption of the ProDisc-L was an exception and demonstrated marginally superior results in visual analog scale, Oswestry Disability Index, and employment compared with circumferential fusion [57]. According to criteria established by the US Food and Drug

Table 1
Summary of RCTs for CLBP: fusion versus nonoperative treatment

Reference	Study design	Participants	Significant exclusion	Effect
[43]	Lumbar instrumented fusion versus "cognitive intervention" and exercise	60 patients (aged 25–60 y) with CLBP at least 1 y after surgery for disc herniation	Somatic or psychiatric disease	No difference in primary outcome (ODI) between groups after 1 y
			Widespread "myofascial pain"	Fear avoidance for physical activity and finger-tip floor distance were better in nonoperative group
			Previous fusion surgery	
			Compensation dispute not an issue (Norway)	
[45]	Fusion or Graf stabilization versus "cognitive intervention" and intensive rehabilitation	394 patients (aged 18–55 y) with CLBP and whose clinician was uncertain if fusion or nonoperative treatment would be effective	Psychiatric disease	Both groups showed clinically significant improvements (20% nonoperative versus 27% surgery decline in ODI, p = .04), difference below the ODI
			Previous fusion surgery	No significant changes in any of the other outcomes measured
			Strong clinical belief that surgery would be highly effective	
[44]	Lumbar fusion (1–2 levels) versus "cognitive intervention" and exercise	64 patients (aged 25–60 y) with CLBP (mean 10 y)	Serious psychological issues	One year after treatment begun, no differences in back pain, function, medication usage, work status, or satisfaction
			Widespread myofascial pain	Approximately 22% of fusion group returned to work, compared with 33% in the nonoperative group
			Previous fusion surgery	"Success" rated by independent observer only approximately 20%–25% in either group
			Compensation dispute not an issue (Norway) medication usage, work status or satisfaction	
[42]	Lumbar fusion (three types of fusion) versus nonstandardized physical therapy	294 patients (aged 25–65 y) with CLBP (mean of 9 y, disabled mean 3 y)	Serious psychological issues	Back pain improved 33% and function 25% in the fusion group with little change in the physical therapy group, 36% of the fusion group returned to work (versus 13% in nonoperative group), 16% of the fusion group were rated as "Excellent" results (versus 6% in nonoperative group)
			Previous fusion surgery	
			Compensation dispute not an issue (Sweden)	

RCT = randomized controlled trial; CLBP = chronic low back pain; ODI = Oswestry Disability Index.

Administration, success with disc arthroplasty was 53%, compared with 41% for fusion [57]. It should also be noted that these efficacy results are in many ways an optimistic estimate of effectiveness because study eligibility criteria excluded subjects with multiple segment disease, serious psychological distress, compensation claims, osteoporosis, metabolic diseases, and other risk factors associated with poor outcomes. Furthermore, follow-up in these trials was only short term and long-term results are required to determine the longevity of these implants given the higher physical demands that will likely be placed on them by younger patients. Possible wear changes, debris disease, implant settling, and other complications are difficult to predict without long-term data. A study with a 17-year follow-up conducted in Europe with Charite arthroplasty reported that the preservation of motion may not result in clinically beneficial improvement in pain intensity [58].

Technical considerations

To perform disc arthroplasty, a standard anterior approach to the lumbar discs is used, with the patient lying in a supine position. There are numerous contraindications to disc arthroplasty including 1) spondylolisthesis; 2) spondylolysis; 3) posterior element disease (facet joint arthritis or previous joint resection); 4) central or lateral recess

stenosis; 5) fixed deformity; 6) infection; 7) osteoporosis; and 8) herniated nucleus pulposus with radiculopathy that cannot be decompressed by way of anterior approach [15]. Strict adherence to these contraindications will severely limit the number of patients with CLBP who are potentially eligible for disc arthroplasty. In a study of 100 patients undergoing lumbar spinal surgery, it was reported that 95% had at least one contraindication to disc arthroplasty [59]. In this regard, disc arthroplasty is unlikely to replace fusion in most patients considering surgery for CLBP.

Dynamic stabilization

There are four main types of dynamic stabilization devices: 1) dynamic interspinous spacers; 2) static interspinous spacers; 3) pedicle screw-/rod-based posterior dynamic stabilizing systems (PDS); and 4) total facet replacement systems (Table 2) [60,61].

Mechanism of action

Dynamic stabilization using interspinous spacers have been proposed as an alternative to rigid instrumented fusion for the treatment of CLBP, offering the potential advantage of a more limited procedure with less morbidity that may confer less risk of adjacent segment degeneration [62]. The distraction forces exerted by the interspinous spacers are hypothesized to unload the disc, thereby reducing associated symptoms. Initial cadaveric biomechanical studies with interspinous spacers have demonstrated that they are effective at reducing the intradiscal pressure at the implanted level [63]. In neutral alignment, posterior annular pressure was reduced by 38% and nucleus pressure was decreased by 20%; pressure was reduced 63% and 41%, respectively, when measured in extension [63]. Some proponents of the interspinous spacers have also proposed their use in the treatment of CLBP associated with facet pathology, as they have been shown to reduce facet contact area and pressure in a cadaveric study [64]. It should be noted, however, that reductions in pressure observed in cadaveric discs are not sufficient to validate the use of interspinous spacers for CLBP.

Table 2
Classification of dynamic stabilization devices

Classification	Device
Dynamic interspinous spacers	CoFlex DIAM
Static interspinous spacers	XSTOP Wallis Extendsure
Pedicle screw-/rod-based posterior dynamic stabilizing	Graf ligament Dynesys AccuFlex rod Medtronic PEEK rod Scient'X Isobar
Total facet replacements systems	TFAS TOPS Stabilimax NZ

Dynamic stabilization using PDS is thought to work in a similar manner to interspinous spacers for CLBP. The PDS devices may be able to shield the disc and facet joint structures from motion that may irritate or damage surrounding structures, potentially reducing secondary local inflammatory processes or permitting self-repair mechanisms [60]. Again, this hypothesis should be considered speculative at this point.

Evidence of efficacy

Although there is evidence for the use of interspinous spacers for spinal stenosis, there is currently no acceptable clinical evidence available for dynamic stabilization in CLBP.

Technical considerations

There are several contraindications and technical considerations for each type of dynamic stabilization device, which are beyond the scope of this article.

Summary

The use of surgery for CLBP in the absence of serious structural disease is a complex issue in which decisions about the type of procedure used should be secondary to evaluating the underlying cause of pain and establishing that a particular individual is in fact an appropriate surgical candidate. Although there are multiple surgical options for the treatment of CLBP, there is currently insufficient evidence on which to draw any firm conclusions as to their effectiveness on clinical outcomes. Lumbar fusion for common degenerative changes appears to offer limited relative benefits, if any, over intensive nonoperative management. Disc arthroplasty appears to offer approximately the same outcomes as fusion in the short term, whereas long-term risks of artificial discs in young patients remain unclear. There is no convincing evidence to support the use of dynamic stabilization devices in the management of CLBP.

Emerging technologies for surgical treatment of CLBP may include biological modification of disc metabolism, alteration of disc genetic expression to change mechanical properties, synthetic nuclear augmentation devices, and combined facet and disc mechanical replacements. Before adopting these techniques, high quality RCTs comparing them with placebo, nonoperative treatment, or natural history, will be required.

Ultimately, the central question that remains unanswered and is critical to the appropriate use of surgery is establishing the precise cause of CLBP. At present, the poor correlation between apparent degenerative changes and clinical presentation of CLBP argues against the expectation that modifying the degenerative process surgically will be highly effective in modifying pain and disability.

References

[1] Skovron ML, Szpalski M, Nordin M, Melot C, Cukier D. Sociocultural factors and back pain. A population-based study in Belgian adults. Spine 1994;19.

[2] Cassidy JD. Saskatchewan health and back pain survey. Spine 1998;23.

[3] Carragee EJ, Alamin TF, Miller JL, Carragee JM. Discographic, MRI and psychosocial determinants of low back pain disability and remission: a prospective study in subjects with benign persistent back pain. Spine J 2005;5.

[4] Burton AK, Tillotson KM, Main CJ, Hollis S. Psychosocial predictors of outcome in acute and subchronic low back trouble. Spine 1995;20.

[5] Boos N, Semmer N, Elfering A, et al. Natural history of individuals with asymptomatic disc abnormalities in magnetic resonance imaging: predictors of low back pain-related medical consultation and work incapacity. Spine 2000;25.

[6] Hurwitz EL, Morgenstern H, Yu F. Cross-sectional and longitudinal associations of low-back pain and related disability with psychological distress among patients enrolled in the UCLA Low-Back Pain Study. J Clin Epidemiol 2003;56.

[7] Cassidy JD, Carroll L, Cote P, Berglund A, Nygren A. Low back pain after traffic collisions: a population-based cohort study. Spine 2003;28.

[8] Holdsworth FW, Hardy A. Early treatment of paraplegia from fractures of the thoraco-lumbar spine. J Bone Joint Surg Br 1953;35-B.

[9] Boucher HH. A method of spinal fusion. J Bone Joint Surg Br 1959;41-B.

[10] King D. Internal fixation for lumbosacral fusion. J Bone Joint Surg Am 1948;30-A.

[11] Harrington PR. Treatment of scoliosis. Correction and internal fixation by spine instrumentation. J Bone Joint Surg Am 1962;44-A.

[12] Luque ER. Segmental spinal instrumentation for correction of scoliosis. Clin Orthop Relat Res 1982.

[13] Szpalski M, Gunzburg R, Mayer M. Spine arthroplasty: a historical review. Eur Spine J 2002;11.

[14] Fernstrom U. Arthroplasty with intercorporal endoprothesis in herniated disc and in painful disc. Acta Chir Scand Suppl 1966;357.

[15] Frelinghuysen P, Huang RC, Girardi FP, Cammisa FP Jr. Lumbar total disc replacement. Part I: Rationale, biomechanics, and implant types. Orthop Clin North Am 2005;36.

[16] Macnab Ian. The classic. Disc degeneration and low back pain. Clin Orthop Relat Res 1986;208.

[17] Ito M, Incorvaia KM, Yu SF, Fredrickson BE, Yuan HA, Rosenbaum AE. Predictive signs of discogenic lumbar pain on magnetic resonance imaging with discography correlation. Spine 1998;23.

[18] Aprill C, Bogduk N. High-intensity zone: a diagnostic sign of painful lumbar disc on magnetic resonance imaging. Br J Radiol 1992;65: 361–9.

[19] Carragee EJ, Paragioudakis SJ, Khurana S. 2000 Volvo Award winner in clinical studies: lumbar high-intensity zone and discography in subjects without low back problems. Spine 2000;25.

[20] Weishaupt D, Zanetti M, Hodler J, Boos N. MR imaging of the lumbar spine: prevalence of intervertebral disk extrusion and sequestration, nerve root compression, end plate abnormalities, and osteoarthritis of the facet joints in asymptomatic volunteers. Radiology 1998;209.

[21] Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. Radiology 1988;166.

[22] Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am 1990;72: 403–8.

[23] Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. N Engl J Med 1994;331.

[24] Borenstein DG, O'Mara JW Jr, Boden SD, et al. The value of magnetic resonance imaging of the lumbar spine to predict low-back pain in asymptomatic subjects: a seven-year follow-up study. J Bone Joint Surg Am 2001;83-A.

[25] Carragee E, Alamin T, Cheng I, Franklin T, van den HE, Hurwitz E. Are first-time episodes of serious LBP associated with new MRI findings? Spine J 2006;6:624–35.

[26] Lindblom K. Technique and results of diagnostic disc puncture and injection (discography) in the lumbar region. Acta Orthop Scand 1951;20.

[27] Carragee EJ, Chen Y, Tanner CM, Truong T, Lau E, Brito JL. Provocative discography in patients after limited lumbar discectomy: a controlled, randomized study of pain response in symptomatic and asymptomatic subjects. Spine 2000;25.

[28] Carragee EJ, Tanner CM, Khurana S, et al. The rates of false-positive lumbar discography in select patients without low back symptoms. Spine 2000;25.

[29] Carragee EJ, Tanner CM, Yang B, Brito JL, Truong T. False-positive findings on lumbar discography. Reliability of subjective concordance assessment during provocative disc injection. Spine 1999;24.

[30] Carragee EJ, Lincoln T, Parmar VS, Alamin T. A gold standard evaluation of the "discogenic pain" diagnosis as determined by provocative discography. Spine 2006;31.

[31] Weinstein JN, Lurie JD, Olson PR, Bronner KK, Fisher ES. United States' trends and regional variations in lumbar spine surgery: 1992-2003. Spine 2006;31.

[32] van Tulder MW, Koes BW, Bouter LM. Conservative treatment of acute and chronic nonspecific low back pain. A systematic review of randomized controlled trials of the most common interventions. Spine 1997;22:2128–56.

[33] Cairns MC, Foster NE, Wright CC, Pennington D. Level of distress in a recurrent low back pain population referred for physical therapy. Spine 2003;28.

[34] Carragee EJ. Psychological and functional profiles in select subjects with low back pain. Spine J 2001;1.

[35] Allan DB, Waddell G. An historical perspective on low back pain and disability. Acta Orthop Scand Suppl 1989;234.

[36] Herkowitz HN, Kurz LT. Degenerative lumbar spondylolisthesis with spinal stenosis. A prospective study comparing decompression with decompression and intertransverse process arthrodesis. J Bone Joint Surg Am 1991;73.

[37] Fischgrund JS, Mackay M, Herkowitz HN, Brower R, Montgomery DM, Kurz LT. 1997 Volvo Award winner in clinical studies. Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective, randomized study comparing decompressive laminectomy and arthrodesis with and without spinal instrumentation. Spine 1997;22.

[38] Axelsson P, Johnsson R, Stromqvist B, Arvidsson M, Herrlin K. Posterolateral lumbar fusion. Outcome of 71 consecutive operations after 4 (2-7) years. Acta Orthop Scand 1994;65.

[39] Moller H, Hedlund R. Surgery versus conservative management in adult isthmic spondylolisthesis—a prospective randomized study: Part 1. Spine 2000;25.

[40] Swan J, Hurwitz E, Malek F, et al. Surgical treatment for unstable low-grade isthmic spondylolisthesis in adults: a prospective

controlled study of posterior instrumented fusion compared with combined anterior-posterior fusion. Spine J 2006;6.
[41] Gibson JN, Waddell G. Surgery for degenerative lumbar spondylosis: updated Cochrane Review. Spine 2005;30.
[42] Fritzell P, Hagg O, Wessberg P, Nordwall A. 2001 Volvo Award Winner in Clinical Studies: lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. Spine 2001;26.
[43] Brox JI, Reikeras O, Nygaard O, et al. Lumbar instrumented fusion compared with cognitive intervention and exercises in patients with chronic back pain after previous surgery for disc herniation: a prospective randomized controlled study. Pain 2006;122:145–55.
[44] Brox JI, Sorensen R, Friis A, et al. Randomized clinical trial of lumbar instrumented fusion and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration. Spine 2003;28:1913–21.
[45] Fairbank J, Frost H, Wilson-MacDonald J, Yu LM, Barker K, Collins R. Randomised controlled trial to compare surgical stabilisation of the lumbar spine with an intensive rehabilitation programme for patients with chronic low back pain: the MRC spine stabilisation trial. BMJ 2005;330:1233.
[46] Fritzell P, Hagg O, Wessberg P, Nordwall A. Chronic low back pain and fusion: a comparison of three surgical techniques: a prospective multicenter randomized study from the Swedish lumbar spine study group. Spine 2002;27.
[47] Mardjetko SM, Connolly PJ, Shott S. Degenerative lumbar spondylolisthesis. A meta-analysis of literature 1970–1993. Spine 1994;19.
[48] Yuan HA, Garfin SR, Dickman CA, Mardjetko SM. A historical cohort of pedicle screw fixation in thoracic, lumbar, and sacral spinal fusions. Spine 1994;19.
[49] Zdeblick TA. A prospective, randomized study of lumbar fusion. Preliminary results. Spine 1993;18.
[50] Wood GW 2nd, Boyd RJ, Carothers TA, et al. The effect of pedicle screw/plate fixation on lumbar/lumbosacral autogenous bone graft fusions in patients with degenerative disc disease. Spine 1995;20.
[51] France JC, Yaszemski MJ, Lauerman WC, et al. A randomized prospective study of posterolateral lumbar fusion. Outcomes with and without pedicle screw instrumentation. Spine 1999;24.
[52] Bjarke Christensen F, Stender Hansen E, Laursen M, Thomsen K, Bunger CE. Long-term functional outcome of pedicle screw instrumentation as a support for posterolateral spinal fusion: randomized clinical study with a 5-year follow-up. Spine 2002;27.
[53] Christensen FB, Hansen ES, Eiskjaer SP, et al. Circumferential lumbar spinal fusion with Brantigan cage versus posterolateral fusion with titanium Cotrel-Dubousset instrumentation: a prospective, randomized clinical study of 146 patients. Spine 2002;27.
[54] Freeman BJ, Davenport J. Total disc replacement in the lumbar spine: a systematic review of the literature. Eur Spine J 2006;15(Suppl 3).
[55] Delamarter RB, Bae HW, Pradhan BB. Clinical results of ProDisc-II lumbar total disc replacement: report from the United States clinical trial. Orthop Clin North Am 2005;36.
[56] Blumenthal S, McAfee PC, Guyer RD, et al. A prospective, randomized, multicenter Food and Drug Administration investigational device exemptions study of lumbar total disc replacement with the CHARITE artificial disc versus lumbar fusion: Part I: Evaluation of clinical outcomes. Spine 2005;30.
[57] Zigler J, Delamarter R, Spivak JM, et al. Results of the prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of the ProDisc-L total disc replacement versus circumferential fusion for the treatment of 1-level degenerative disc disease. Spine 2007;32.
[58] Putzier M, Funk JF, Schneider SV, et al. Charite total disc replacement—clinical and radiographical results after an average follow-up of 17 years. Eur Spine J 2006;15.
[59] Huang RC, Lim MR, Girardi FP, Cammisa FP Jr. The prevalence of contraindications to total disc replacement in a cohort of lumbar surgical patients. Spine 2004;29.
[60] Khoueir P, Kim KA, Wang MY. Classification of posterior dynamic stabilization devices. Neurosurg Focus 2007;22.
[61] Bono CM, Vaccaro AR. Interspinous process devices in the lumbar spine. J Spinal Disord Tech 2007;20.
[62] Minns RJ, Walsh WK. Preliminary design and experimental studies of a novel soft implant for correcting sagittal plane instability in the lumbar spine. Spine 1997;22.
[63] Swanson KE, Lindsey DP, Hsu KY, Zucherman JF, Yerby SA. The effects of an interspinous implant on intervertebral disc pressures. Spine 2003;28.
[64] Wiseman CM, Lindsey DP, Fredrick AD, Yerby SA. The effect of an interspinous process implant on facet loading during extension. Spine 2005;30.

SPINE Volume 33, Number 23, pp 2560–2565

Facet Joint Osteoarthritis and Low Back Pain in the Community-Based Population

Leonid Kalichman, PT, PhD,* Ling Li, MPH,† David H. Kim, MD,† Ali Guermazi, MD,‡ Valery Berkin, MD,* Christopher J. O'Donnell, MD, MPH,§¶ Udo Hoffmann, MD, MPH,‖ Rob Cole,* and David J. Hunter, MBBS, PhD*†

Study Design. Cross-sectional study.

Objective. To evaluate the association between lumbar spine facet joint osteoarthritis (FJ OA) identified by multidetector computed tomography (CT) and low back pain (LBP) in the community-based Framingham Heart Study.

Summary of Background Data. The association between lumbar FJ OA and LBP remains unclear.

Methods. This study was an ancillary project to the Framingham Heart Study. A sample of 3529 participants of the Framingham Heart Study aged 40 to 80 underwent multidetector CT imaging to assess aortic calcification. One hundred eighty-eight individuals were consecutively enrolled in this ancillary study to assess radiographic features associated with LBP. LBP in the preceding 12 months was evaluated using a self-report questionnaire. FJ OA was evaluated on CT scans using a 4-grade scale. The association between FJ OA and LBP was examined used multiple logistic regression models, while adjusting for gender, age, and BMI.

Results. CT imaging revealed a high prevalence of FJ OA (59.6% of males and 66.7% of females). Prevalence of FJ OA increases with age. By decade, FJ OA was present in 24.0% of <40-years-olds, 44.7% of 40- to 49-years-olds, 74.2% of 50- to 59-years-olds, 89.2% of 60- to 69-years-olds, and 69.2% of >70-years-olds. By spinal level the prevalence of FJ OA was: 15.1% at L2–L3, 30.6% at L3–L4, 45.1% at L4–L5, and 38.2% at L5–S1. In this community-based population, individuals with FJ OA at any spinal level showed no association with LBP.

Conclusion. There is a high prevalence of FJ OA in the community. Prevalence of FJ OA increases with age with the highest prevalence at the L4–L5 spinal level. At low spinal levels women have a higher prevalence of lumbar FJ OA than men. In the present study, we failed to find an association between FJ OA, identified by multidetector CT, at any spinal level and LBP in a community-based study population. **Spine 2008;33:2560–2565**

Lumbar spinal facet joints were first suggested in the medical literature as a source of low back and lower extremity pain in 1911.[1] Since then, so-called "facetogenic back pain" has become a widely accepted, though still controversial entity in the radiologic and orthopedic literature.[2–10] Perhaps, the strongest circumstantial support comes from investigations reporting successful relief of back pain following intra-articular, or periarticular joint injections.[2,8]

Estimates of the prevalence of lumbar facet joint pain based on single diagnostic blocks have been reported to range from 7.7 to 75% among patients reporting back pain.[11] On the basis of controlled, local anesthetic diagnostic blocks, the prevalence of lumbar facet joint pain in a population of injured United States workers with chronic low back pain (LBP) was shown to be 15%.[8] Similar studies have suggested the prevalence to be 40 to 45% in a pain management practice.[9,10] An Australian study reported a prevalence of 40% among patients with chronic LBP in a general rheumatology practice.[12] However, the association between pain originating from the facet joints and radiographically observed degenerative changes in those joints has not been studied and remains controversial.

The majority of published clinical investigations report no correlation between the clinical symptoms of LBP and degenerative spinal changes observed on radiologic imaging studies, including radiographs, magnetic resonance imaging (MRI), computed tomography (CT), single photon emission computed tomography (SPECT), and radionuclide bone scanning.[8–10,12–20] Specifically, the association between degenerative changes in the lumbar facet joints and symptomatic LBP remains unclear and is a subject of ongoing debate.[6–8]

In comparison with radiographs, CT improves anatomic evaluation of the facet joints due to its ability to provide cross-sectional images of the opposing joint surfaces in the axial plane.[4] Abnormalities of the facet joints that can be demonstrated and categorized by CT include osteophyte formation, hypertrophy of articular processes, articular cartilage thinning, vacuum joint phenomenon, synovial and subchondral cysts, and calcifi-

From the *Boston University School of Medicine, Boston, MA; †Division of Research, New England Baptist Hospital, Boston, MA; ‡Department of Radiology, Boston University School of Medicine, Boston, MA; §National Heart, Lung and Blood Institute and its Framingham Heart Study, Framingham, MA; ¶Cardiology Division, MA General Hospital, Harvard Medical School, Boston, MA; and ‖Cardiac MR CT PET Program, Department of Radiology, MA General Hospital, Harvard Medical School, Boston, MA.

Acknowledgment date: March 28, 2008. First revision date: June 6, 2008. Acceptance date: June 9, 2008.

The manuscript submitted does not contain information about medical device(s)/drug(s).

Federal funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

This work was supported by the National Heart, Lung, and Blood Institute's Framingham Heart Study contract (No. N01-HC-25195) for the recruitment, enrollment, and examination of the Offspring and Third Generation Cohort and the imaging by computed tomography scan. L.K. is supported by an Arthritis Foundation Postdoctoral Grant.

Address correspondence and reprint requests to David J. Hunter, Chief, Division of Research, New England Baptist Hospital, 125 Parker Hill Ave, Boston MA. 02120; E-mail: djhunter@caregroup.harvard.edu

cation of the joint capsule.[4,21] Due to its precise demonstration of osseous details[5,22] and relatively low cost, CT is the preferred method for imaging lumbar facet joint osteoarthritis (FJ OA).

The efficacy of intra-articular or periarticular injection therapy on LBP potentially associated with FJ OA has not been clearly established. Despite the observation by Lewinnek GE and Warfield CA[2] that 96% of patients with CT-documented FJ OA responded to such injections, Schwarzer *et al*[13] were not able to demonstrate a significant correlation between the degree of OA seen on CT and the pain score achieved after the intra-articular facet block.

There are very few published studies regarding the prevalence of FJ OA. Eubanks *et al*[23] in a recent study of 647 cadaveric lumbar spines found that FJ OA is a universal finding. Characteristic features of OA begin to seem early, with more than half of adults younger than 30 years demonstrating arthritic changes in the facets. The most common arthritic level seems to be L4–L5.

The aims of the present study were: 1) to evaluate the prevalence of FJ OA in different age groups and at different lumbar spinal levels in a community-based population; and 2) to evaluate the association between FJ OA, observed on CT, and the risk of experiencing LBP in the community-based Framingham Heart Study.

■ Materials and Methods

Study Design: Cross-Sectional Study

Sample. This project was an ancillary project to the Framingham Heart Study. The Framingham Heart Study began in 1948 as a longitudinal population-based cohort study of the causes of heart disease. Initially, 5209 men and women between the ages of 30 and 60 years living in Framingham, MA were enrolled. Biennial examinations were conducted by trained research staff at the study clinic located in Framingham. In 1971, 5124 offspring (and their spouses) of the original cohort were entered into the Offspring cohort. In 2002, 4095 men and women who were children of the Offspring cohort were enrolled in the Third Generation cohort. A description of the Offspring and Third Generation cohorts has been previously reported.[24,25] Three thousand five hundred twenty-nine participants of the Framingham study (participants in both the Offspring and Third Generation cohorts) aged 40 to 80 years underwent abdominal and chest multidetector CT scanning to assess coronary and aortic calcification. The recruitment and conduct of CT scanning have been previously reported.[26,27] During the later part of the CT study, 188 participants were consecutively enrolled in this ancillary study to assess the association between radiographic features of the lumbosacral spine and LBP.

LBP Evaluation. All study participants undergoing multidetector CT scan were asked to complete the modified Nordic Low Back Questionnaire.[28] The first question on this questionnaire was: "Have you had low back pain on most days of at least 1 month in the last 12 months?" Individuals, who answered "yes," or "no" on the above question, were categorized in the present study as the back pain outcome (dichotomous index). Similar methods are widely used in studies of work related low back pain.[29–31]

CES-D Measurement. The CES-D scale is a subjective report of depressive symptoms that has been shown to have valid and reliable psychometric properties.[32,33]

Imaging Parameters. Study participants were imaged with an 8-slice multidetector CT scanner (Lightspeed Ultra, GE, Milwaukee, WI). Each subject underwent unenhanced abdominal multidetector CT performed using a sequential scan protocol with a slice collimation of 8 mm × 2.5 mm (120 KVp, 320/400 mA for .220 lbs body weight, respectively) during a single end-inspiratory breath hold (typical duration 18 S). For the abdominal scan, 30 contiguous 2.5 mm thick slices of the abdomen were acquired covering 150 mm above the level of S1.

FJ OA Evaluation. FJ OA evaluation was performed using eFilm Workstation (Version 2.0.0) software. All CT studies were read in blinded fashion. Lumbar facet joints were graded on both the left and right side at levels L2–L3, L3–L4, L4–L5, and L5–S1. Four grades of FJ OA were defined using criteria similar to those published by Pathria *et al*[34] and Weishaupt *et al*[35]:

Grade 0–normal.

Grade 1–mild degenerative disease (narrowing of the joint space (<2 mm) and/or small osteophytes and/or mild hypertrophy of the articular process).

Grade 2–moderate degenerative disease (narrowing of the joint space (<1 mm) and/or moderate osteophytes and/or moderate hypertrophy of the articular process and/or mild subarticular bone erosions).

Grade 3–severe degenerative disease (severe narrowing of the joint space and/or large osteophytes and/or severe hypertrophy of the articular process and/or severe subarticular bone erosions and/or subchondral cysts and/or vacuum phenomenon in the joints).

Reliability of CT Readings. All readers were trained by an experienced research musculoskeletal radiologist (AG). A reading protocol for evaluation of FJ OA based on the above outlined grading scheme was developed. Using this protocol, the intra- and inter-rater reliability was calculated for 2 readers. All CT scans were then analyzed in blinded fashion. To evaluate for reader-drift, intrarater reliability was periodically reassessed by inserting 1 repeated "reliability" scan for every 10 new scans. Before analyzing each new set of CT scans, 5 previously analyzed CTs were reevaluated to "recalibrate" the readings to a standard. The intraobserver reliability for grading different FJ OA indexes varied between 0.64 and 0.91. The interobserver reliability ranged from 0.59 to 0.94. This range of kappa statistics represents fair to excellent reproducibility.

Body Mass Index (BMI). BMI was computed as the ratio of weight (in kg) divided by height (in meters squared).

Statistical Analysis. Before the analysis, the study population was dichotomized on the basis of FJ OA for the presence or absence of facet joint disease (≥Grade 2) on any side at any level. The population was then divided into 5 age strata: <40, 40–49, 50–59, 60–69, and ≥70 years. The prevalence of FJ OA between males and females was compared according to age group and according to spinal level involved using χ^2 Test. The prevalence of FJ OA was calculated by age, group, and sex and compared between individuals with and without LBP. Multiple logistic regression models were used to examine the association

Table 1. Descriptive Statistics of the Studied Sample (n = 188)

Frequencies	Males	Females
N	104	84
Age group <40	16	9
40–49	30	17
50–59	33	33
60–69	18	19
≥70	7	6
LBP	20	18
FJ OA (Grade ≥2 at L2–S1 levels)	62 (59.61%)	56 (66.66%)
Mean values		
Age (yr)	51.90	53.61
BMI (kg/m²)	27.95	27.71
Depression (CES-D) score	6.31	9.03

between FJ OA and LBP, while adjusting for gender, age, BMI, and CES-D score. We also assessed the association between FJ OA and CES-D score, while adjusting for gender, age, and BMI. All statistical analyses were performed using SAS software, (SAS Institute Inc., Cary, NC, release 9.1).

Results

Table 1 lists the demographic characteristics of the 188 study participants. The study sample included 104 males (average age 51.90) and 84 females (average age 53.61). Mean BMI was 27.95 for males and 27.71 for females. Sixty-two men and 56 women demonstrated at least 1 joint at spinal levels L2–S1 affected by FJ OA (grade ≥2). Twenty men and 18 women reported LBP.

Table 2 presents the prevalence of FJ OA by age, group, and sex. No statistically significant differences were found with respect to the prevalence of FJ OA between males and females in any age group. However, a strong statistically significant pattern emerged for an increasing prevalence of FJ OA with increasing age. This relationship was observed for males, females, and the total sample ($P = 0.0070$, $P < 0.0001$, $P < 0.0001$, respectively). Interestingly, the highest prevalence of FJ OA was found in age Group 60 to 69, where it reached 89.2.9% in total sample.

Table 3 shows the prevalence of FJ OA by spinal level in males, females, and in the combined sample. The highest prevalence of FJ OA was found at the L4–L5 spinal level (38.24%, 53.75%, and 45.05%, respectively). The second most prevalent level was L5–S1, followed by L3–L4, and L2–L3 levels. There was a trend towards more prevalent FJ OA in females at every spinal level, except L2–L3. χ^2 Test demonstrated no statistically significant difference ($P > 0.1$) between males and females at the L2–L3 and L3–L4 spinal levels. However, a significant difference was observed at spinal level L4–L5 ($\chi^2 = 7.01$, $P = 0.037$) and the difference approached significance at level L5–S1 ($\chi^2 = 4.77$, $P = 0.071$). Women demonstrated a higher prevalence of FJ OA compared to men at both the L4–L5 and L5–S1 levels.

Table 4 shows the prevalence of FJ OA among individuals with and without LBP subdivided by age group. No significant difference in the prevalence of FJ OA was identified between individuals with and without LBP for the study population as a whole or following subgroup analysis on the basis of age or sex.

Table 5 shows the results of multiple logistic regression analysis where LBP was a dependent variable and FJ OA at each spinal level, sex, age group, BMI, and CES-D score were included as independent variables. There were no statistically significant associations found between LBP and the aforementioned predicting variables ($P > 0.05$ for each association). In addition, no statistically significant associations were found while CES-D score was used as a dependent variable.

Discussion

This is the first cross-sectional study to describe the prevalence of lumbar FJ OA in a community-based population. The results show a high prevalence of FJ OA in men (59.6%) and women (66.7%).

The study also evaluates the association between FJ OA, identified by multidetector CT imaging, and LBP in the community. We found no association between FJ OA at any spinal levels and the occurrence of LBP. This study supports similar negative results of a previous CT study[13] and several facet joint injection studies.[12,15,36] Based on the results of the present study, the use of CT as a single diagnostic modality for pain originating from facet joints cannot be supported.

The observation that the L4–L5 spinal level is associated with the highest prevalence of FJ OA is not surprising. Several previous studies[23,37–40] have shown that facet joint degeneration develops much more rapidly at

Table 2. The Prevalence of Facet Joint OA by Age Group and Sex

	Males		Females		Total Sample		
Age Group	N	%	N	%	N	%	χ^2-Test (Males vs. Females by Age Group)
<40	5	31.3	1	12.5	6	24.0	$P = 0.6214$
40–49	15	50.0	6	35.3	21	44.7	$P = 0.3299$
50–59	22	66.7	27	84.4	49	74.2	$P = 0.1401$
60–69	16	88.9	17	89.5	33	89.2	$P = 1.0000$
≥70	4	57.1	5	83.3	9	69.2	$P = 0.2045$
χ^2-test (age groups)	$P = 0.0070$		$P < 0.0001$		$P < 0.0001$		

Statistically significant at level $P < 0.05$ marked bold.

Table 3. The Prevalence of FJ OA by Spinal Level in Males, Females, and in Community-Based Population

	Males		Females		Total Sample		
Spinal Level	N	%	N	%	N	%	χ^2-Test (Males vs. Females by Spinal Level)
L2–L3	17	16.50	11	13.75	28	15.05	$P = 0.6076$
L3–L4	27	26.21	29	36.25	56	30.60	$P = 0.1439$
L4–L5	39	38.24	43	53.75	82	45.05	$P = 0.0368$
L5-S1	32	32.32	36	45.57	68	38.2	$P = 0.0707$
χ^2-test (spinal levels)	$P = 0.0045$		$P < 0.0001$		$P < 0.0001$		

Statistically significant at level $P < 0.05$ marked bold.
Statistically significant at level $P < 0.10$ marked italic.

the L4–L5 motion segment than at any other level. Fujiwara *et al*[40] found that the median grade of FJ OA at L4–L5 was significantly higher than that at other lumbar spinal levels. It has been well-established that degenerative spondylolisthesis is associated with FJ OA and occurs most commonly at the L4–L5 level.[39,41] A possible reason for the high prevalence and severity of FJ OA at the L4–L5 spinal level may be the relatively greater stability of the L5–S1 spinal segment compared to L4–L5. Greater stability arises from a more coronal orientation of the L5–S1 joints as opposed to the more sagittal orientation of the L4–L5 facet joints,[42,43] an increased pedicle-facet angle at the L5–S1 level[43–45] and additional anatomic stability provided the fifth lumbar vertebra by large transverse processes supported by strong iliolumbar ligaments.[46]

This study clearly shows that the prevalence of FJ OA increases with increasing age. This is in agreement with Lewin T[37] comprehensive anatomic reviews of lumbar synovial joints, which stated that the facet joints showed only minor cartilage changes before the age of 45. After age 45, advanced cartilage changes, subchondral sclerosis, and osteophytes become common phenomena. Those findings were also confirmed in more recent studies.[38,40,47–49] However, the occurrence of FJ OA was found in this study even in individuals younger than 40. Tischer *et al*[50] in a cadaveric study found significant cartilage changes in the lumbar spinal facet joints in young (<30) individuals suffering from LBP. Gries *et al*[51] as well, in a histologic study of young individuals (<40, mean age 29.1), found instances of partial or total loss of cartilage and cartilage replacement by pannus tissue in some cases. An even higher prevalence was reported by Eubanks *et al*[23] in a recent cadaveric study in which FJ OA was present in 57% of 20- to 29-years-old, 82% of 30- to 39-years-old, 93% of 40- to 49-years-old, 97% in 50- to 59-years-old, and 100% in those >60-years-old.

In the present study, the highest prevalence of FJ OA was in the age Group 60 to 69 with a slightly lower prevalence observed in individuals older than 70. This unexpected finding is most likely explained by random error due to the relatively small group of participants within the highest age group. Another more speculative explanation is the possible indirect association between FJ OA and decreased life expectancy. Previously, the prevalence of hand osteoarthritis has been found to be inversely correlated with survival rates.[52] Published data also suggest that osteoarthritis may be associated with risks for comorbid conditions such as cardiovascular disease/death,[52–55] hypertension, chronic pulmonary disease,[56,57] peptic ulcer and renal diseases,[58] gastritis, and phlebitis.[54,55] Possibly, the slightly lower prevalence of FJ OA in the oldest age group reflects these associations.

In the present sample we did not find statistically significant differences in any age group between males and females in terms of the general prevalence of lumbar FJ OA. This finding is in agreement with the study by Alperovitch-Najenson D[49] that similarly found no sex difference in the prevalence of lumbar FJ OA. Fujiwara *et al*[40] in a MRI study of 14 patients with degenerative disc disease also found no significant sex difference in the grade of FJ OA at each lumbar spinal level. In terms of

Table 4. The Prevalence of Facet Joint OA by Age Group in Individuals With and Without LBP

	Males			Females			Total Sample		
Age Group	With LBP	Without LBP	Fisher's Exact Test (LBP vs. Non-LBP by Age Groups for Males)	With LBP	Without LBP	Fisher's Exact Test (LBP vs. Non-LBP by Age Groups for Females)	With LBP	Without LBP	Fisher's Exact Test (LBP vs. Non-LBP by Age Groups)
<40	1 (33.3)	4 (30.8)	$P = 1.0000$	0 (0.0)	1 (14.3)	$P = 1.0000$	1 (25.0)	5 (25.0)	$P = 1.0000$
40–49	2 (100.0)	13 (46.4)	$P = 0.4828$	1 (50.0)	5 (33.3)	$P = 1.0000$	3 (75.0)	18 (41.9)	$P = 0.3112$
50–59	4 (44.4)	18 (78.3)	$P = 0.0960$	7 (77.8)	20 (87.0)	$P = 0.6042$	11 (61.1)	38 (82.6)	$P = 0.1003$
60–69	2 (100.0)	14 (87.5)	$P = 1.0000$	6 (100.0)	11 (91.7)	$P = 1.0000$	8 (100.0)	25 (89.3)	$P = 1.0000$
≥70	0 (0.0)	4 (66.7)	$P = 0.4286$	1 (100.0)	4 (100.0)	*	1 (50.0)	8 (80.0)	$P = 0.4545$
All ages	9 (52.94)	53 (61.63)	$P = 0.503$†	15 (78.95)	41 (67.21)	$P = 0.3297$‡	24 (64.86)	95 (63.76)	$P = 0.9001$

*Row or column sum is zero. No statistics computed for this table.
†FJ OA by LBP for males.
‡FJ OA by LBP for females.

Table 5. Results of the Multiple Logistic Regression Analysis, Where LBP (Yes vs. No) Was Used as a Dependent Variable

Parameter	Odds Ratio Estimates		
	Point Estimate	95% Wald Confidence Limits	P
FJ OA L2L3 (Yes vs. No)	1.630	(0.547, 4.856)	0.3800
FJ OA L3L4 (Yes vs. No)	0.630	(0.221, 1.795)	0.3870
FJ OA L4L5 (Yes vs. No)	0.869	(0.336, 2.250)	0.7723
FJ OA L5S1 (Yes vs. No)	0.989	(0.413, 2.372)	0.9808
Sex (Female vs. Male)	1.465	(0.672, 3.196)	0.3368
Age group 70+ (vs. <40)	1.157	(0.162, 8.234)	0.9794
Age group 60–69 (vs. <40)	1.743	(0.372, 8.116)	0.3729
Age group 50–59 (vs. <40)	2.206	(0.605, 8.043)	0.0606
Age group 40–49 (vs. <40)	0.507	(0.112, 2.288)	0.0842
Depression (CES-D) score	0.998	(0.923, 1.079)	0.9593
BMI	1.043	(0.971, 1.121)	0.2437

specific spinal levels, however, the present study did reveal statistically significant differences in the prevalence of FJ OA between males and females of all ages at the L4–L5 spinal level with females demonstrating a significantly higher prevalence of FJ OA than males. This study supports the conclusions drawn by the meta-analysis of Srikanth *et al*[59] that there is a gender difference in the prevalence and incidence of OA affecting the hand and knees, with females generally at higher risk. The findings are in contrast to another study suggesting that men have a greater prevalence of FJ OA than women at all lumbar levels.[23]

A potential gender based difference in the prevalence of FJ OA is possible based on the fact that cartilage is a sex-hormone-sensitive tissue.[60] Ha *et al*[61] performed an immunohistochemical study of the lumbar facet joints and demonstrated estrogen receptors in the facet cartilage and found that increased expression of estrogen receptors correlated directly with the severity of FJ OA. Fujiwara *et al*[62] performed a cadaveric study in which lumbar spinal motion segments were compared between males and females with similar age, grade of disc degeneration, cartilage degeneration, and osteophytes. The female motion segments showed significantly greater motion in lateral bending, flexion, and extension. Greater motion in spinal segment can lead to excessive wear and tear, and therefore, to higher prevalence of FL OA in females.

There are some limitations of the present study that are worthy of mention. This is a cross sectional sample and inferences of increasing facet joint prevalence with age are inferred by looking at individuals in different age groups rather than following them longitudinally. At present we have not adjusted for the presence of other important covariates such as prior spine surgery and occupation which could influence the presence of LBP. This would be important in future analyses.

Conclusion

This is the first CT-based study that describes the prevalence of lumbar FJ OA at different spinal levels in community-based population. The results of this study show a high prevalence of FJ OA (59.6% of males and 66.7% of females) that increases with age. The highest prevalence was observed at the L4–L5 spinal level. At lower spinal levels women have higher prevalence of lumbar FJ OA than men. In the present study, no significant association was observed between FJ OA, identified by CT, at any spinal level and LBP.

Key Points

- There is a high prevalence of FJ OA in the community-based population (59.6% of males and 66.7% of females).
- Prevalence of FJ OA increases with age and reaches 89.2% in individuals 60- to 69- years- old.
- The highest prevalence of FJ OA is in L4–L5 spinal level.
- Individuals with FJ OA identified by CT at any spinal level showed no association with LBP.

References

1. Goldthwait JE. The lumbosacral articulation: an explanation of many cases of lumbago, sciatica, and paraplegia. *Boston Med Surg J* 1911;164:365–72.
2. Lewinnek GE, Warfield CA. Facet joint degeneration as a cause of low back pain. *Clin Orthop* 1986;213:216–22.
3. Helbig T, Lee CK. The lumbar facet syndrome. *Spine* 1988;13:61–4.
4. Carrera GF, Haughton VM, Syvertsen A, et al. Computed tomography of the facet joints. *Radiology* 1980;134:145–8.
5. Raskin SP. Degenerative changes of the lumbar spine: assessment by computed tomography. *Orthopedics* 1981;4:186–95.
6. Badgley CE. The articular facets in relation to low-back pain and sciatic radiation. *J Bone Joint Surg* 1941;23:481–96.
7. Nachemson AL. Newest knowledge of low-back pain: a critical look. *Clin Orthop* 1992;179:8–20.
8. Schwarzer AC, Aprill C, Derby R, et al. Clinical features of patients with pain stemming from the lumbar zygapophyseal joints. Is the lumbar facet syndrome a clinical entity? *Spine* 1994;10:1132–7.
9. Manchkanti L, Pampati V, Fellows B, et al. Prevalence of facet joint pain in chronic low back pain. *Pain Physician* 1999;2:59–64.
10. Manchikanti L, Pampati RR, Fellows B, et al. The diagnostic validity and therapeutic value of medial branch blocks with or without adjuvants. *Curr Rev Pain* 2000;4:337–44.
11. Dreyer SJ, Dreyfuss PH. Low back pain and the zygapophysial (facet) joints. *Arch Phys Med Rehabil* 1996;77:290–300.
12. Schwarzer AC, Wang S, Bogduk N, et al. Prevalence and clinical features of lumbar zygapophysial joint pain: a study in an Australian population with chronic low back pain. *Ann Rheum Dis* 1995;54:100–6.
13. Schwarzer AC, Wang SC, O'Driscoll D, et al. The ability of computed tomography to identify a painful zygoapophyseal joint in patients with chronic low back pain. *Spine* 1995;20:907–12.
14. Selby DK, Paris SV. Anatomy of facet joints and its correlation with low back pain. *Contemp Orthop* 1981;312:1097–103.
15. Jackson RP, Jacobs RR, Montesano PX. Facet joint injection in low back pain: a prospective study. *Spine* 1988;13:966–71.
16. Raymond J, Dumas JM. Intra-articular facet block. Diagnostic tests or therapeutic procedure? *Radiology* 1989;151:333–6.
17. North RB, Han M, Zahurak M, et al. Radiofrequency lumbar facet denervation. Analysis of prognostic factors. *Pain* 1994;57:77–83.
18. Dreyfuss PH, Dreyer SJ, Herring SA. Contemporary concepts in spine care. Lumbar zygapophysial (facet) joint injections. *Spine* 1995;20:2040–7.
19. Dreyfuss P, Dreyer S. Lumbar facet joint injections. In: Gonzalez EG, Materson RS, eds. *The Nonsurgical Management of Acute Low Back Pain*. New York, NY: Demos Vermande; 1997:123–36.
20. Bogduk N. International spinal injection society guidelines for the performance of spinal injection procedures. Part 1. Zygapophysial joint blocks. *Clin J Pain* 1997;13:285–302.
21. Resnick R, Niwayama G. Degenerative disease of the spine. In: Resnick R,

ed. *Diagnosis of Bone and Joint Disorders*. 3rd ed. Philadelphia, PA: WB Saunders; 1995:1372–462.
22. Haughton V. Imaging techniques in intraspinal diseases. In: Resnick D, ed. *Diagnosis of Bone and Joint Disorders*. Philadelphia, PA: WB Saunders; 1995:237–76.
23. Eubanks JD, Lee MJ, Cassinelli E, et al. Prevalence of lumbar facet arthrosis and its relationship to age, sex, and race: an anatomic study of cadaveric specimens. *Spine* 2007;32:2058–62.
24. Splansky GL, Corey D, Yang Q, et al. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. *Am J Epidemiol* 2007;165: 1328–35.
25. Feinleib M, Kannel WB, Garrison RJ, et al. The Framingham Offspring Study. Design and preliminary data. *Prev Med* 1975;4:518–25.
26. Hoffmann U, Siebert U, Bull-Stewart A, et al. Evidence for lower variability of coronary artery calcium mineral mass measurements by multi-detector computed tomography in a community-based cohort–consequences for progression studies. *Eur J Radiol* 2006;57:396–402.
27. Parikh NI, Hwang SJ, Larson MG, et al. Parental occurrence of premature cardiovascular disease predicts increased coronary artery and abdominal aortic calcification in the Framingham Offspring and Third Generation cohorts. *Circulation* 2007;116:1473–81.
28. Kuorinka I, Jonsson B, Kilbom A, et al. Standardised Nordic questionnaires for the analysis of musculoskeletal symptoms. *Appl Ergon* 1987;18:233–7.
29. Dovrat E, Katz-Leurer M. Cold exposure and low back pain in store workers in Israel. *Am J Ind Med* 2007;50:626–31.
30. Ghaffari M, Alipour A, Jensen I, et al. Low back pain among Iranian industrial workers. *Occup Med (Lond)* 2006;56:455–60.
31. Maul I, Laubli T, Klipstein A, et al. Course of low back pain among nurses: a longitudinal study across eight years. *Occup Environ Med* 2003;60:497–503.
32. Kessler RC, Foster CL, Saunders WB, et al. Social consequences of psychiatric disorder, I: educational attainment. *Am J Psychiatry* 1995;152:1026–32.
33. Rushton JL, Forcier M, Schectman RM. Epidemiology of depressive symptoms in the National Longitudinal Study of Adolescent Health. *J Am Acad Child Adolesc Psychiatry* 2002;41:199–205.
34. Pathria M, Sartoris DJ, Resnick D. Osteoarthritis of the facet joints: accuracy of oblique radiographic assessment. *Radiology* 1987;164:227–30.
35. Weishaupt D, Zanetti M, Boos N, et al. MR imaging and CT in osteoarthritis of the lumbar facet joints. *Skeletal Radiol* 1999;28:215–9.
36. Revel ME, Listrat VM, Chevalier XJ, et al. Facet joint block for low back pain: identifying predictors of a good response. *Arch Phys Med Rehabil* 1992;73:824–8.
37. Lewin T. Osteoarthritis in lumbar synovial joints. *Acta Orthop Scand Suppl* 1964;(suppl 73):1–112.
38. Wang ZL, Yu S, Haughton VM. Age-related changes in the lumbar facet joints. *Clin Anat* 1989;2:55–62.
39. Vogt MT, Rubin D, Valentin RS, et al. Lumbar olisthesis and lower back symptoms in elderly white women. The Study of Osteoporotic Fractures. *Spine* 1998;23:2640–7.
40. Fujiwara A, Tamai K, Yamato M, et al. The relationship between facet joint osteoarthritis and disc degeneration of the lumbar spine: an MRI study. *Eur Spine J* 1999;8:396–401.
41. Vogt MT, Rubin DA, Palermo L, et al. Lumbar spine listhesis in older African American women. *Spine J* 2003;3:255–61.
42. Grobler LJ, Robertson PA, Novomey JE, et al. Etiology of spondylolisthesis. Assessment of the role played by lumbar facet joint morphology. *Spine* 1993; 18:80–91.
43. Iguchi T, Wakami T, Kurihara A, et al. Lumbar multilevel degenerative spondylolisthesis: radiological evaluation and factors related to anterolisthesis and retrolisthesis. *J Spinal Disord Tech* 2002;15:93–9.
44. Newman PH, Stone KH. The etiology of spondylolisthesis. *J Bone Joint Surg Br* 1963;45:39–59.
45. Nagaosa Y, Kikuchi S, Hasue M, et al. Pathoanatomic mechanisms of degenerative spondylolisthesis: a radiographic study. *Spine* 1998;23:1447–51.
46. Aihara T, Takahashi K, Yamagata M, et al. Biomechanical functions of the iliolumbar ligament in L5 spondylolysis. *J Orthop Sci* 2000;5:238–42.
47. Taylor JR, Twomey LT. Age changes in lumbar zygapophyseal joints. Observations on structure and function. *Spine* 1986;11:739–45.
48. Weishaupt D, Zanetti M, Hodler J, et al. MR imaging of the lumbar spine: prevalence of intervertebral disk extrusion and sequestration, nerve root compression, end plate abnormalities, and osteoarthritis of the facet joints in asymptomatic volunteers. *Radiology* 1998;209:661–6.
49. Alperovitch-Najenson D. *A Morphological Characterization of the Lumbar Spine and Low Back Muscles in Individuals with Chronic Low Back Pain: an Imaging Study* [doctoral degree thesis]. Tel Aviv, Israel: Tel Aviv University; 2005.
50. Tischer T, Aktas T, Milz S, et al. Detailed pathological changes of human lumbar facet joints L1–L5 in elderly individuals. *Eur Spine J* 2006;15:308–15.
51. Gries NC, Berlemann U, Moore RJ, et al. Early histologic changes in lower lumbar discs and facet joints and their correlation. *Eur Spine J* 2000;9:23–9.
52. Haara MM, Manninen P, Kroger H, et al. Osteoarthritis of finger joints in Finns aged 30 or over: prevalence, determinants, and association with mortality. *Ann Rheum Dis* 2003;62:151–8.
53. Singh G, Miller JD, Lee FH, et al. Prevalence of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survey. *Am J Manage Care* 2002;8:S383–91.
54. Kadam UT, Jordan K, Croft PR. Clinical comorbidity in patients with osteoarthritis: a case-control study of general practice consulters in England and Wales. *Ann Rheum Dis* 2004;63:408–14.
55. Kalichman L, Malkin I, Livshits G, et al. Association between morbidity and radiographic hand osteoarthritis: population-based study. *Joint Bone Spine* 2006;73:406–10.
56. Schellevis FG, van der Velden J, van de Lisdonk E, et al. Comorbidity of chronic diseases in general practice. *J Clin Epidemiol* 1993;46:469–73.
57. Marks R, Allegrante JP. Comorbid disease profiles of adults with end-stage hip osteoarthritis. *Med Sci Monit* 2002;8:CR305–9.
58. Gabriel SE, Crowson CS, O'Fallon WM. Comorbidity in arthritis. *J Rheumatol* 1999;26:2475–9.
59. Srikanth VK, Fryer JL, Zhai G, et al. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage* 2005;13:769–81.
60. Rosner IA, Goldberg VM, Moskowitz RW. Estrogens and osteoarthritis. *Clin Orthop* 1986;213:77–83.
61. Ha KY, Chang CH, Kim KW, et al. Expression of estrogen receptor of the facet joints in degenerative spondylolisthesis. *Spine* 2005;30:562–6.
62. Fujiwara A, Lim TH, An HS, et al. The effect of disc degeneration and facet joint osteoarthritis on the segmental flexibility of the lumbar spine. *Spine* 2000;25:3036–44.

Lumbar Degenerative Disk Disease[1]

Michael T. Modic, MD
Jeffrey S. Ross, MD

The sequelae of disk degeneration are among the leading causes of functional incapacity in both sexes and are a common source of chronic disability in the working years. Disk degeneration involves structural disruption and cell-mediated changes in composition. Mechanical, traumatic, nutritional, and genetic factors all may play a role in the cascade of disk degeneration, albeit to variable degree in different individuals. The presence of degenerative change is by no means an indicator of symptoms, and there is a very high prevalence in asymptomatic individuals. The etiology of pain as the symptom of degenerative disease is complex and appears to be a combination of mechanical deformation and the presence of inflammatory mediators. The role of imaging is to provide accurate morphologic information and influence therapeutic decision making. A necessary component, which connects these two purposes, is accurate natural history data. Understanding the relationship of etiologic factors, the morphologic alterations, which can be characterized with imaging, and the mechanisms of pain production and their interactions in the production of symptoms will require more accurate and reproducible stratification of patient cohorts.

[1] From the Division of Radiology, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195. Received October 31, 2005; revision requested December 1; revision received February 15, 2006; accepted March 10; final version accepted June 8; final review and update by M.T.M. March 28. **Address correspondence to M.T.M.** (e-mail: *modicm1@ccf.org*).

It has been stated that the term *degeneration*, as it is commonly applied to the intervertebral disk, covers such a wide variety of clinical, radiologic, and pathologic manifestations as to be really "only a symbol of our ignorance" (1). Despite this admonition, or perhaps because of it, we will attempt in this review to summarize current thoughts about the etiology, manifestations, and symptom production in lumbar degenerative disk disease and the role imaging currently plays in its identification and management. Given the gaps in our knowledge and the complexity of the subject, which will become readily apparent, we have chosen to exclude detailed treatment options from the discussion.

The sequelae of disk degeneration remain among the leading causes of functional incapacity in both sexes and are a common source of chronic disability in the working years. In accordance with its incidence, morbidity, and socioeconomic impact, degenerative disk disease has given and continues to give rise to extensive research efforts into its epidemiology, anatomy, biomechanics, biochemistry, and neuromechanisms (2).

Etiology

Traditionally, disk degeneration has been linked to mechanical loading. The importance of mechanical factors has been emphasized by experiments on cadaver spines with both a severe single event and relentless loading (3–7). Failure of disks is more common in areas where there are the heaviest mechanical stresses, such as the lower lumbar region. It has been suggested that mechanical factors produce endplate damage, the antecedent to disk degeneration (8).

The disk is metabolically active, and the metabolism is dependent on diffusion of fluid either from the marrow of the vertebral bodies across the subchondral bone and cartilaginous endplate or through the annulus fibrosus from the surrounding blood vessels. Morphologic changes in the vertebral bone and cartilaginous endplate, which occur with advancing age or degeneration, can interfere with normal disk nutrition and further the degenerative process. This disruption of the normal endplate results in deformation when under loading. This allows nuclear material to pass through the endplate, reducing intradiscal pressure with subsequent bulging and loss of height and adding more stress to the surrounding annulus. Compressive damage to the vertebral body endplate alters the distribution of stresses in the adjacent disk. Continual cyclic loading makes these changes worse. Diminished blood flow in the endplate initiates tissue breakdown first in the endplate and then in the nucleus. These altered stress distributions adversely affect disk cell metabolism. These changes then alter the integrity of the proteoglycans and water concentration, reducing the number of viable cells with subsequent alteration in the movement of solutes into and out of the disk (9).

The importance of normal blood flow to the homeostatic nutritional process in the intervertebral disk complex has been suggested to explain the association of atherosclerosis and aortic calcification with increased disk degeneration and subjective low back pain (10). As degeneration progresses, structures of the disk become more disarranged and greater stresses are placed on the annulus and facet joints. As increased forces are transmitted to the annulus, there may be fragmentation and fissuring. Disk degeneration involves structural disruption and cell-mediated changes in composition, but which occurs first is not clear. Biochemical factors can increase susceptibility to mechanical disruption, and this could adversely influence disk cell metabolism. Regardless of the initiating mechanism, these mechanisms would be interactive and additive, the end result being an altered functional ability of the disk to resist applied forces.

In addition to mechanical and nutritional causes, a genetic predisposition has been suggested by animal models that consistently develop degenerative disk disease at an early age, as well as by reports of familial osteoarthritis and lumbar canal stenosis in humans (11). In a study (12) of 115 male identical twin pairs, the effects of lifetime exposure to commonly suspected risk factors on disk degeneration, including job type, lifting, twisting, sitting, driving, exercise, trauma, and cigarette smoking, were investigated. The particular environmental factors studied, which have been among those most widely suspected of accelerating disk degeneration, had only modest effects. These small effects would help to explain the mixed results of previous studies. Considering the very minor effects the particular environmental factors studied had in determining disk degeneration, a strong genetic influence was suggested (12). While failing to find a strong association or clear-cut etiologic influence, the authors concluded that disk degeneration may be explained primarily by genetic influences and by unidentified

Essentials

- Mechanical, traumatic, nutritional, and genetic factors all play a role in the cascade of disk degeneration.
- Reliable and reproducible terminology is critical to meaningful description of morphologic abnormalities.
- The etiology of pain in degenerative disease is more complex than a simple mechanical explanation.
- The prognostic value of imaging is confounded by the high prevalence of morphologic changes in the asymptomatic population.
- In patients with uncomplicated low back pain or radiculopathy, MR imaging may not have an additive value over clinical assessment.

Published online
10.1148/radiol.2451051706

Radiology 2007; 245:43–61

Abbreviations:
ADC = apparent diffusion coefficient
IL = interleukin
MMP = matrix metalloproteinase
SE = spin echo
TNF = tumor necrosis factor

Authors stated no financial relationship to disclose.

factors, which may include complex unpredictable interactions.

In a cohort study (13) based on a Danish twin registry, substantial genetic influence on the susceptibility to degenerative disk disease and low back pain was shown. Shared environment was important until the age of 15 years, but as the twins grew older, the effect of a nonshared environment increased and nonadditive genetic effects became more evident. These findings suggest increasing genetic interaction (13).

Abnormalities of collagen are most often cited to support genetic influence in degenerative disk disease. Type II collagen is the most abundant collagen of cartilaginous tissues and is often referred to as the major collagen, forming heterotypic fibrils with the less abundant minor collagen types IX and XI. These fibrils provide the strength necessary to resist tensile forces. Disease that causes mutations in types II and XI collagen has been demonstrated in a number of chondrodystrophies. Multiple epiphyseal dysplasia is associated with a disease causing mutation in collagen IX, an important structural component of the annulus fibrosus, nucleus pulposus, and hyaline cartilage of the endplates. In a study looking for additional disease-producing mutations, researchers closely examined the genes coding the three chains of type IX collagen. While no changes typical of disease producing mutations were identified, two amino acid substitutions were identified that are substantially more prevalent in patients with lumbar degenerative disk disease than in normal controls. Both of these involve a tryptophan substitution (Trp2 and Trp3). In the case of the Trp3 allele, it is a genetic factor associated with a threefold increase in the risk of symptomatic degenerative disk disease (14–16). While these Trp alleles together occurred in 16% of the Finnish patients with lumbar disk disease, it has been pointed out that other loci are almost certainly involved. A prime candidate is one that encodes aggrecan, an abundant proteoglycan, in cartilage whose extensive hydration contributes to resistance to tissue deformation. Knock-out mice for aggrecan have a high prevalence of disk herniation and degeneration (15,17).

Several additional studies (18–21) suggest that not just the process of degenerative disk disease but perhaps even its sequelae, including disk herniation, low back pain, and radiculopathy, are strongly influence by genetic factors. Studies suggest that low back pain is also associated with polymorphism in the interleukin (IL) 1 locus (22). This is of interest in that cytokines such as tumor necrosis factor α (TNF-α), IL-1, and IL-6 are important inflammatory mediators, as will be discussed latter.

Clearly there are many interactive factors at play. Mechanical, traumatic, nutritional, and genetic factors all may play a role in the cascade of disk degeneration, albeit to variable degrees in different individuals. Whatever the etiology, by the age of 50 years, 85%–95% of adults show evidence of degenerative disk disease at autopsy (23).

Morphologic Alterations and Imaging

Terminology

No less a problem than understanding etiology is agreeing on terminology that is reliable and reproducible to describe the morphologic alterations produced by the degenerative process (24–27). For the purposes of this review, we have used the terminology described by Milette (28). The term *degeneration* includes any or all of the following: real or apparent desiccation, fibrosis, narrowing of the disk space, diffuse bulging of the annulus beyond the disk space, extensive fissuring (ie, numerous annular tears) and mucinous degeneration of the annulus, defects and sclerosis of the endplates, and osteophytes at the vertebral apophyses. At magnetic resonance (MR) imaging, these changes are manifested by disk space narrowing, T2-weighted signal intensity loss from the intervertebral disk, presence of fissures, fluid, vacuum changes and calcification within the intervertebral disk, ligamentous signal changes, marrow signal changes, osteophytosis, disk herniation, malalignment, and stenosis. While there is confusion in the differentiation of changes of the pathologic degenerative process in the disk from those of normal aging, we will use the term *degenerative* to include all such changes (29–31).

Conventional theory would imply that degeneration and aging are very similar processes, albeit occurring at different rates (32). Resnick and Niwayama (32) emphasized the differentiating features of two degenerative processes involving the intervertebral disk, which had been previously described by Schmorl and Junghanns (33). These include "spondylosis deformans," which affects essentially the annulus fibrosus and adjacent apophyses, and "intervertebral osteochondrosis," which affects mainly the nucleus pulposus and the vertebral body endplates but also includes extensive fissuring (numerous tears) of the annulus fibrosus. Scientific studies suggest that spondylosis deformans is the consequence of normal aging, whereas intervertebral osteochondrosis, sometimes also called deteriorated disk, results from a clearly pathologic, through not necessarily symptomatic, process (33–38). Anterior and lateral marginal vertebral body osteophytes have been found in 100% of skeletons of individuals over 40 years of age, and therefore are consequences of normal aging, whereas posterior osteophytes have been found in only a minority of skeletons of individuals over 80 years, and therefore are not inevitable consequences of aging (34). Endplate erosions with osteosclerosis and chronic reactive bone marrow changes also appear to be pathologic.

Anatomic Considerations

The intervertebral joint is a three-joint complex consisting of the endplate-disk-endplate joint of the anterior column and the two facet joints of the posterior column supported by ligaments and muscle groups. Understanding the interrelationship of these elements has become more critical as surgical intervention, much like joint surgery in the past, is transitioning from fusion to joint replacement.

The intervertebral disk and the diarthrodial joints (zygoapophyseal joint or

facet joints) interactively degenerate, causing altered stresses on the integrity and mechanical properties of the spinal ligaments, which results in degeneration of the spinal unit as a whole (39,40). The manner of degeneration of the various components of the spine is mediated and manifested by the specific structure involved. The cartilaginous, synovial, and fibrous structures each degenerate in a specific manner, which is associated with characteristic imaging and pathologic aberrations.

Degenerative Disk Changes

The major cartilaginous joint (amphiarthrosis) of the vertebral column is the intervertebral disk. Each disk consists of an inner portion, the nucleus pulposus, surrounded by a peripheral portion, the annulus fibrosus. The nucleus pulposus is eccentrically located and more closely related to the posterior surface of the intervertebral disk. With degeneration and aging, type II collagen increases outwardly in the annulus and there is a greater water loss from the nucleus pulposus than from the annulus. This results in a loss of the hydrostatic properties of the disk, with an overall reduction of hydration in both areas to about 70%. In addition to water and collagen, the other important biochemical constituents of the intervertebral disk are the proteoglycans. The individual chemical structures of the proteoglycans are not changed with degeneration, but their relative composition is. The ratio of keratin sulfate to chondroitin sulfate increases, and there is a diminished association with collagen that may reduce the tensile strength of the disk. The decrease in water-binding capacity of the nucleus pulposus is thought to be related to the decreased molecular weight of its nuclear proteoglycan complexes (aggregates). The disk becomes progressively more fibrous and disorganized, with the end stage represented by amorphous fibrocartilage and no clear distinction between nucleus and annulus (41–43). On T2-weighted images, the central disk signal intensity is usually markedly decreased and at distinct variance to that seen in unaffected disks of the same individual. Work with T2-weighed spin-echo (SE) sequences (44) suggests that MR is capable of depicting changes in the nucleus pulposus and annulus fibrosus relative to degeneration and aging based on a loss of signal intensity.

In work with cadaver spines of various ages, absolute T2 measurements correlated more closely with glycoaminoglycan concentration than absolute water content. Thus, the signal intensity may not be related to the total amount of water but rather the state of water. At present, the role that specific biochemical changes (proteoglycan ratios, aggregation of complexes) play in the altered signal intensity is not well understood. Given that the T2 signal intensity in the disk appears to track the concentration and regions of high glycoaminoglycan percentages more than absolute water content, it seems likely that the health and status of the proteoglycans are major determinates of signal intensity (45).

It has been proposed that annular disruption is the critical factor in degeneration and, when a radial tear develops in the annulus, there is shrinkage with disorganization of the fibrous cartilage of the nucleus pulposus and replacement of the disk by dense fibrous tissue with cystic spaces (31,46–49). Annular tears, also properly called annular fissures, are separations between annular fibers, avulsion of fibers from their vertebral body insertions, or breaks through fibers that extend radially, transversely, or concentrically and involve one or many layers of the annular

Figure 1

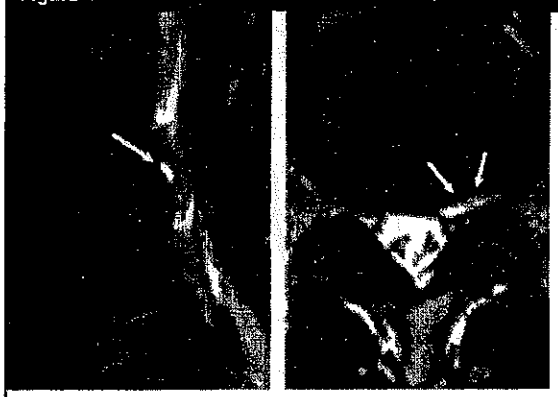


Figure 1: Annular tear. **(a)** Left parasagittal and **(b)** transverse T2-weighted fast SE (repetition time msec/echo time msec, 4000/120) MR images through L4-5 disk space. Note high signal intensity in the outer annulus and/or longitudinal ligament complex in a left parasagittal location, which represents area of anular disruption (arrows).

Figure 2

Figure 2: Histologic slide of degenerated intervertebral disk. Endplate shows areas of cracks, fissures, and pale staining (long arrow). Chondrocytes (short arrows) and granulation tissue *(G)*, characteristic of regeneration and degeneration, are noted. Adjacent marrow space shows increased lipid elements and the trabeculae appear thickened.

lamellae. The term *tear* or *fissure* describes the spectrum of such lesions and does not imply that the lesion is consequent to trauma (Fig 1). Although it has certainly been verified that annular disruption is a sequela of degeneration and certainly is often associated with it, its role as the causal agent of disk degeneration has certainly not been proved. MR is the most accurate anatomic method for assessing intervertebral disk disease. The signal intensity characteristics of the disk on T2-weighted images reflect changes caused by aging or degeneration. A classification scheme for lumbar intervertebral disk degeneration has been proposed that has reasonable intra- and interobserver agreement (50). To date, however, there has been no correlation between MR disk changes and patient's symptoms.

Figure 3

a. b. c.

Figure 3: Calcified intravertebral disk. Sagittal midline **(a)** T1-weighted (450/12), **(b)** contrast-enhanced T1-weighted (450/12), and **(c)** T2-weighted (4000/120) SE images of lumbar spine. High signal intensity (arrows) is identified within L5-S1 disk space on a and b.

With loss of water and proteoglycans, the nucleus pulposus is desiccated and friable with yellow-brown discoloration. Its onion-skin appearance begins to unravel, and cracks, clefts, or crevices appear within the nucleus and extend into the annulus fibrosus. Fissuring, chondrocyte generation, and granulation tissue formation may be noted within the endplate, annulus fibrosis, and nucleus pulposus of degenerative disks, indicating attempts at healing (49) (Fig 2). Radiolucent collections (vacuum disk phenomena) representing gas, principally nitrogen, occur at sites of negative pressure produced by the abnormal spaces (51). The vacuum phenomenon within a degenerated disk is represented on SE images as areas of signal void (52). Whereas the presence of gas within the disk is usually suggestive of degenerative disease, spinal infection may (rarely) be accompanied by intradiscal or intraosseous gas (53).

As intervertebral osteochondrosis progresses, there may be calcification of the disk. Calcification has usually been described on MR images as a region of decreased or absent signal intensity. The loss of signal is attributed to a low mobile proton density, as well as, in the case of gradient-echo imaging, to its sensitivity to the heterogeneous magnetic susceptibility found in calcified tissue. There is, however, variability in signal intensity of calcium at various sequences, and the type and concentration of calcification are important factors. Hyperintense disks on T1-weighted MR images may be secondary to calcification (Fig 3) (54). For concentrations of calcium particulate up to 30% by weight, the signal intensity on standard T1-weighted images increased but then subsequently decreased (55,56). These data likely reflect particulate calcium reducing T1 relaxation times by a surface-relaxation mechanism. Hyperintensities that are affected by fat-suppression techniques have also been noted within intervertebral disks and are thought to be related to ossification with lipid marrow formation in severely degenerated or fused disks.

Figure 4

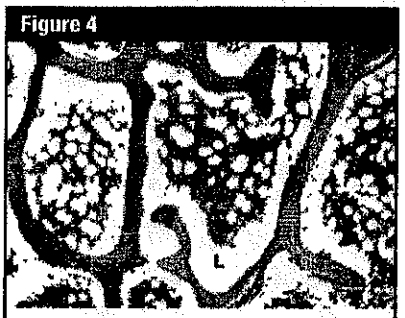


Figure 4: Normal marrow. Histologic slide of normal hematopoetic *(H)*, lipid *(L)*, and bone trabecular *(T)* elements.

Degenerative Marrow Changes

The relationship among the vertebral body, endplate, annulus, and disk has been studied (57–59) by using both degenerated and chymopapain-treated disks as models. Signal intensity changes in vertebral body marrow (Fig 4) adjacent to the endplates of degenerated disks are a common observation on MR images and appear to take three main forms.

Type 1 changes demonstrate decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images and have been identified in approximately 4% of patients scanned for lumbar disease (Fig 5), approximately 8% of patients after diskectomy (60,61), and in 40%–50% of chymopapain-treated disks, which may be viewed as a model of acute disk degeneration (58). Histopathologic sections of disks with type 1 changes show disruption and fissuring of the endplate and vascularized fibrous tissues within the adjacent marrow, prolonging T1 and T2. Enhancement of type 1 vertebral body marrow changes is seen with administration of gadopentetate dimeglumine that at times extends to involve the disk itself and is presumably related to the vascularized fibrous tissue within the adjacent marrow (Fig 6).

Type II changes are represented by increased signal intensity on T1-weighted images and isointense or slightly hyperintense signal on T2-weighted images and have been identified in approximately 16% of patients at MR imaging (Fig 7). Disks with type II changes also show evidence of endplate disruption, with yellow (lipid) marrow replacement in the adjacent vertebral body resulting in a shorter T1 (Fig 8).

Type III changes are represented by a decreased signal intensity on both T1- and T2-weighted images and correlate with extensive bony sclerosis on plain radiographs. The lack of signal in the type III change no doubt reflects the relative absence of marrow in areas of advanced sclerosis (Fig 9). Unlike type III, types I and II changes show no definite correlation with sclerosis at radiography (59). This is not surprising when one considers the histology; the sclerosis seen on plain radiographs is a reflection of dense woven bone within the vertebral body, whereas the MR changes are more a reflection of the intervening marrow elements.

Similar marrow changes have also been noted in the pedicles. While originally described as being associated with spondylolysis, they have also been noted in patients with degenerative facet disease and pedicle fractures. Again, the changes are probably a reflection of abnormal stresses, be they loading or motion (62,63).

Degenerative Facet and Ligamentous Changes

The superior articulating process of one vertebra is separated from the inferior articulating process of the vertebra above by a synovium-lined articulation, the zygoapophyseal joint. Like all diarthrodial synovium lined joints, the lumbar facet joints are predisposed to arthropathy with alterations of the articular cartilage. With disk degeneration and loss of disk space height, there are increased stresses on the facet joints with craniocaudal sub-

Figure 5

Figure 5: Degenerative type I marrow change. **(a)** Sagittal midline T1-weighted SE (450/12) image demonstrates decreased signal intensity of marrow space adjacent to L5-S1 disk (arrows). **(b)** T2-weighted SE (4000/120) image in the same region (arrows) shows increased signal intensity.

Figure 6

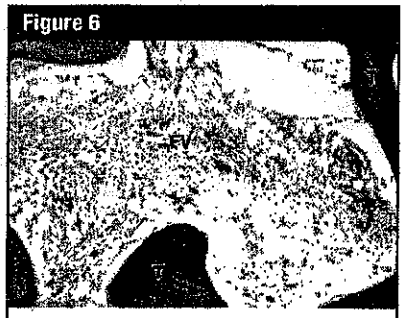


Figure 6: Histologic slide of type I degenerative marrow changes. Fibrovascular tissue *(FV)* has replaced normal marrow elements between thickened bone trabeculae *(T)*.

Figure 7

Figure 7: Degenerative type II vertebral body marrow changes. **(a)** Sagittal midline T1-weighted SE (450/12) image demonstrates degenerative changes of L5-S1 disk space and high signal intensity (arrows) in adjacent vertebral body marrow. **(b)** T2-weighted SE (4000/120) image shows that marrow signal intensity adjacent to degenerated L5-S1 disk is now only slightly hyperintense relative to more normal marrow.

Figure 8

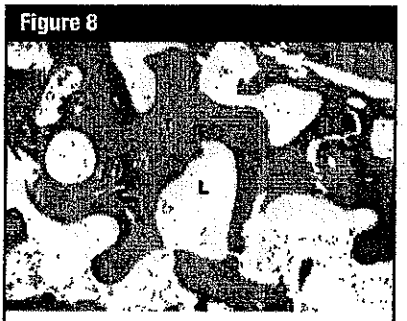


Figure 8: Histologic slide of degenerative type II marrow changes shows increased lipid content of the marrow space *(L)*. Note also thickened woven bone trabeculae *(T)*.

luxation resulting in arthrosis and osteophytosis. The superior articular facet is usually more substantially involved. Facet arthrosis can result in narrowing of the central canal, lateral recesses, and foramina and is an important component of lumbar stenosis (Fig 10). However, it has been proposed that facet arthrosis may occur independently and be a source of symptoms on its own (64,65). Synovial villi may become entrapped within the joint with resulting joint effusions. The mechanism of pain may be related to nerve root compression from degenerative changes of the facets or by direct irritation of pain fibers from the innervated synovial linings and joint capsule (65). Osteophytosis and herniation of synovium through the facet joint capsule may result in synovial cysts, although the etiology of these facet joint cysts is unclear (Fig 11). There is a more straightforward relationship of synovial cysts with osteoarthritis and the instability of the facet joints than degeneration of the intervertebral disk alone. In a review of patients with degenerative facet disease, synovial cysts occurred at anterior or intraspinal location in 2.3% of cases and posterior or extraspinal location in 7.3% (66).

The important ligaments of the spine include the anterior longitudinal ligament, the posterior longitudinal ligament, the paired sets of ligamenta flava (connecting the laminae of adjacent vertebrae), intertransverse ligaments (extending between transverse processes), and the unpaired supraspinous ligament (along the tips of the spinous processes). As these ligaments normally provide stability, any alteration in the vertebral articulations can lead to ligamentous laxity with subsequent deterioration. Loss of elastic tissue, calcification and ossification, and bone proliferation at sites of ligamentous attachment to bone are recognized manifestation of such degeneration.

Excessive lordosis or extensive disk space loss in the lumbar spine leads to close approximation and contact of spinous processes and to degeneration of

Figure 9

Figure 9: Degenerative type III vertebral body marrow changes. Sagittal midline **(a)** T1-weighted (450/12) and **(b)** fast SE T2-weighted (4000/120) images demonstrate markedly decreased signal intensity of adjacent marrow spaces at L4-5 in the presence of severe degenerative disk disease (arrows).

Figure 10

Figure 10: Spinal stenosis. Sagittal **(a)** T1-weighted SE (450/15) and **(b)** T2-weighted fast SE (4000/120) images through lower lumbar spine. There is grade I degenerative spondylolisthesis at L4-5, thickening of the ligaments posteriorly, and severe stenosis of central canal (arrows). Transverse **(c)** T1-weighted (450/15) and **(d)** T2-weighted fast SE (4000/120) images through L4-5 disk space show severe bilateral degenerative facet changes with distraction and fluid in the left joint (arrows). There is severe central canal stenosis and thickening of posterior ligaments.

intervening ligaments (67,68). Histologically, granulomatous reaction and perivascular cellular infiltration characterize the condition (Fig 12).

Morphologic and Functional Sequellae

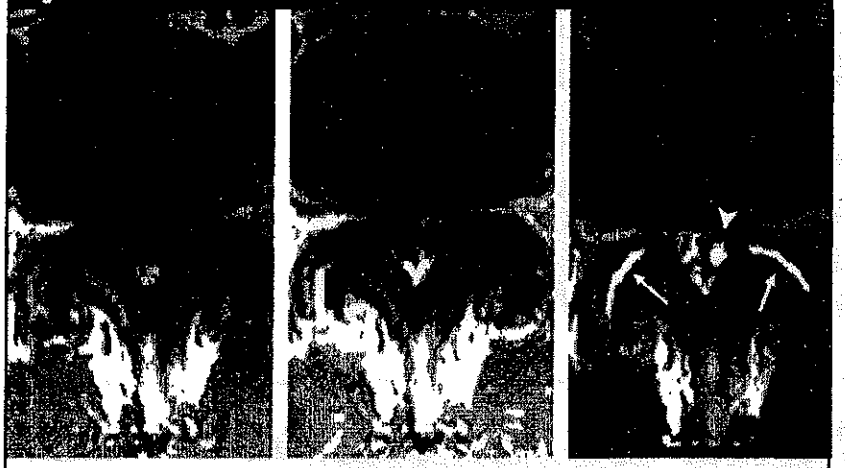
Common, potential complications of degenerative disk disease include alignment abnormalities, intervertebral disk displacement, and spinal stenosis. Various types of alignment abnormalities can exist alone or in combination, but the two most frequent are segmental instability and spondylolisthesis.

Instability

Segmental instability can result from degenerative changes involving the intervertebral disk, vertebral bodies, and facet joints that impair the usual pattern of spinal movement, producing motion that is irregular, excessive, or restricted. It can be translational or angular.

Spondylolisthesis results when one vertebral body becomes displaced relative to the next most inferior vertebral body. The most common types include degenerative, isthmic, iatrogenic, and traumatic. Degenerative spondylolisthesis is seen usually with an intact pars interarticularis, is related primarily to degenerative changes of the apophyseal joints, and is most common at the L4-5 vertebral level (Fig 10). Predilection for degenerative spondylolisthesis at that level is thought to be related to the more sagittal orientation of the facet joints, which makes them increasingly prone to anterior displacement. Degenerative disk disease may predispose to or exacerbate this condition secondary to narrowing of the disk space, which can pro-

Figure 11



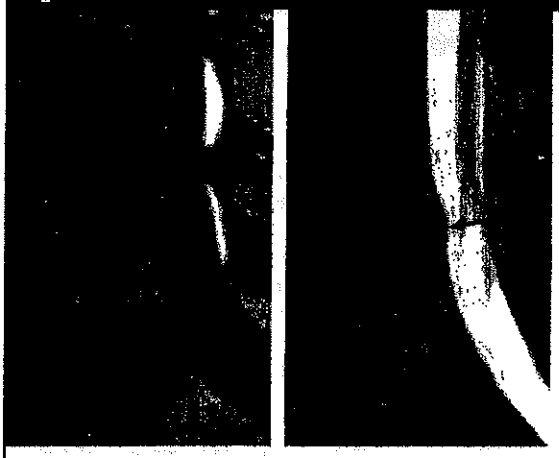
a. b. c.

Figure 11: Degenerative synovial cyst. Transverse **(a)** T1-weighted SE (450/15), **(b)** T1-weighted contrast-enhanced SE (450/15), and **(c)** T2-weighted fast SE (4000/120) images through L4-5 disk space. Note severe bilateral degenerative facet changes and degenerative synovial cyst projecting medially from the left facet, causing central canal stenosis (arrowhead). There is distraction and fluid within degenerated facet joints (arrows).

Figure 12

Figure 12: Severe degenerated posterior ligaments. Sagittal midline T2-weighted SE (4000/120) image shows mild grade I degenerative spondylolisthesis at L4-5. There is close approximation of spinous processes of L4 and L5 and high-signal-intensity degenerative changes in the region of intraspinal ligaments (arrows) (Baastrup disease).

Figure 13



a. b.

Figure 13: Degenerated L4-5 disk. Sagittal midline **(a)** T1-weighted SE (450/15) and **(b)** T2-weighted fast SE (4000/120) images show mild reduction in L4-5 disk space and loss of signal intensity on **b**. There is mild convex posterior bulging of the intervertebral disk at this level (arrow). Note normal signal intensity and morphology of L3-4 and L5-S1 disks.

duce subsequent malalignment of the articular processes and lead to rostrocaudal subluxation.

Herniation

Herniation refers to localized displacement of nucleus, cartilage, fragmented apophyseal bone, or fragmented annular tissue beyond the intervertebral disk space. The disk space is defined rostrally and caudally by the vertebral body endplates and peripherally by the outer edges of the vertebral ring apophyses, exclusive of osteophytic formations. The term *localized* contrasts with the term *generalized*, the latter being arbitrarily defined as greater than 50% (180°) of the periphery of the disk (28) (Fig 13).

Displacement, therefore, can occur only in association with disruption of the normal annulus or, as in the case of intravertebral herniation (Schmorl node) (Fig 14), a break in the vertebral body endplate. Since details of the integrity of the annulus are often unknown, the diagnosis of herniation is usually made by observation of displacement of disk material beyond the edges of the ring apophyses that is localized, meaning less than 50% (180°) of the circumference of the disk.

Localized displacement in the axial (horizontal) plane can be focal, signifying less than 25% of the disk circumference, or broad based, meaning between 25% and 50% of the disk circumference. Presence of disk tissue circumferentially (50%–100%) beyond the edges of the ring apophyses may be called bulging and is not considered a form of herniation.

A disk may have more than one herniation. The term *herniated disk* does not imply any knowledge of etiology, relation to symptoms, prognosis, or need for treatment. When data are sufficient to make the distinction, a herniated disk may be more specifically characterized as protruded or extruded. These distinctions are based on the shape of the displaced material. Protrusion is present if the greatest distance, in any plane, between the edges of the disk material beyond the disk space is less than the distance between the edges of the base in the same plane (Fig 15).

Figure 14

Figure 14: (a) Sagittal T1-weighted SE (450/15) and (b) sagittal midline T2-weighted fast SE (4000/120) images through lumbar spine. There is intrabody herniation into anterior superior aspect of L5 vertebral body and type II degenerative marrow change surrounding this herniation (arrow).

Figure 15

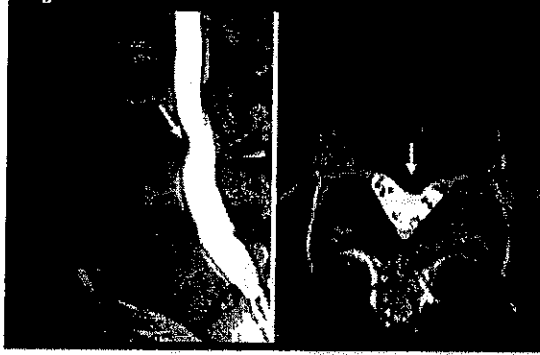


Figure 15: Protruded herniated disk. Sagittal (left) and transverse (right) T2-weighted fast SE (4000/120) images through lower lumbar spine and L4-5 disk level. Note convex posterior margin on left image (arrow). Protruded disk herniation is characterized by broader base than the extension of disk material beyond the disk space (arrow).

Extrusion is present when, in at least one plane, any one distance between the edges of the disk material beyond the disk space is greater than the distance between the edges of the base in the same plane or when no continuity exists between the disk material beyond the disk space and that within the disk space (Fig 16). Extrusion may be further specified as sequestration if the displaced disk material has lost completely any continuity with the parent disk. The term *migration* may be used to signify displacement of disk material away from the site of extrusion, regardless of whether it is sequestrated or not (Fig 17).

Herniated disks in the craniocaudal (vertical) direction through a break in the vertebral body endplate are referred to as intravertebral herniations (Fig 14). Nonacute Schmorl-node intrabody herniations are common spinal abnormalities regarded as incidental observations. They have been reported in 38%–75% of the population (69,70). While intrabody herniations may occur secondary to endplate weakness related to bone displasia, neoplasms, infec-

tions, or any process that weakens the endplate or the underlying bone, most intrabody herniations probably form after axial loading trauma, with preferential extrusion of nuclear material through the vertebral endplate rather than an intact and normal annulus fibrosis. It has been suggested that asymptomatic intrabody herniations may be traceable to a specific occurrence of acute nonradiating low back pain in the patient's history, which supports the concept that intrabody herniations (Schmorl nodes) occur through sites of endplate fracture. Type I vertebral body marrow changes have been described surrounding the acute interbody herniations (71).

Stenosis

Spinal stenosis was defined in 1975 as any type of narrowing of the spinal canal, nerve root canals, or intervertebral foramina (72). Two broad groups have been defined: acquired (usually related to degenerative changes) and congenital or developmental. Developmental stenosis can be exacerbated by superimposed acquired degenerative changes. In the acquired type, there has been no association between the severity of pain and the degree of stenosis. The most common symptoms are sensory disturbances in the legs, low back pain, neurogenic claudication, weakness, and relief of pain by bending forward. The imaging changes are in general more extensive than expected from the clinical findings (73). Patients with symptoms referable to spinal stenosis tend to have narrower spines than asymptomatic patients. While there does appear to be a correlation between cross-sectional area and midsagittal measurements in patients with symptomatic spinal stenosis, absolute values and correlation between measurements and symptoms appear to be lacking. The degree of stenosis is not static, and extension worsens the degree of central and foraminal stenosis by 11%, while flexion appears to improve it by an average of 11%. Segmental instability, which can cause static and dynamic stenosis, is considered a cause of low back pain but is poorly defined (74). Some evidence suggests that disk degeneration, narrowing of the spinal canal, and degenerative changes in the facets and spinal ligaments contribute to stenosis and that instability increases with age. Unfortunately, there do not appear to be reliable prognostic imaging findings that would correlate with surgical success or even whether patients would benefit from surgery (75).

Figure 16

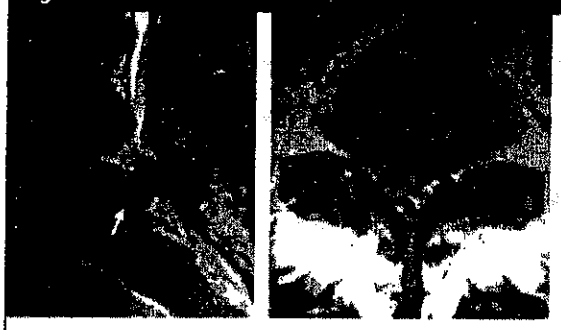


Figure 16: Extruded disk herniation. **(a)** Right parasagittal and **(b)** transverse T2-weighted fast SE images (4000/120) through lumbar spine and L5-S1 disk space. Extruded disk herniations are characterized by a base that is narrower than the distance of disk material extension beyond the disk space (arrow).

Figure 17

Figure 17: Extruded disk and free fragment. Sagittal T1-weighted SE (450/17) before (left) and after (right) contrast enhancement through lower lumbar spine. Note large extruded L4-5 disk fragment that has migrated superiorly behind the body of L4 (arrow). After administration of paramagnetic contrast media, there is peripheral enhancement of this mass, which represents granulation tissue within the epidural fibrosis surrounding nonenhancing central core of disk material.

Technical Considerations for MR Imaging

Traditional clinical imaging has emphasized orthogonal T1- and T2-weighted imaging for morphologic assessment of the discovertebral complex. These sequences also provide an evaluation of the signal intensity changes associated with degenerative disk disease. Fast SE T2-weighted images have replaced conventional T2-weighted images because of their shorter acquisition times, but they provide no increased diagnostic advantage. Short inversion time inversion-recovery or fat-suppressed T2-weighted images have been added by many groups, ours included, because it is believed they are more sensitive to marrow and soft-tissue changes.

While these standard sequences remain the mainstay of diagnostic imaging of the spine, new techniques continue to

be evaluated in hopes of providing stronger correlation between imaging findings and patient symptoms. The utility of many of these techniques for the routine evaluation of degenerative disk disease remains unknown, and the number of subjects in which they have been evaluated remains small. Nevertheless, these approaches may be important for redefining the direction of spinal imaging away from strictly anatomic one to one that combines more physiologic and functional information (76). Techniques that have been evaluated to greater or lesser degrees of success include assessment of spinal motion (dynamic imaging, kinetic assessment, or axial loading), diffusion imaging (water or contrast agents), MR neurography, spectroscopy, functional MR of the spinal cord, and ultrashort echo-time imaging. Of the variety of techniques available, only MR neurography and dynamic imaging have expanded beyond the experimental phase and have demonstrated specific clinical utility (albeit in niche or select populations).

Dynamic Imaging

The utility of dynamic spine MR remains unclear, in part due to the varied methods used. Methods to date include axial loading in the supine position by means of a harness that is attached to a nonmagnetic compression footplate with nylon straps that can be tightened or use of an upright open MR system that allows flexion and extension imaging (77,78). Dynamic MR has been used to evaluate the occurrence of occult herniations, which may not be visible or be less visible when the patient is supine, to measure motion between spinal segments, and to measure the canal or foraminal diameter when subjected to axial loading (76,78–81). Hiwatashi et al (80) evaluated 200 patients with clinical symptoms of spinal stenosis and found 20 patients with detectable differences in caliber of the dural sac on routine and axial loaded studies. In five of these selected patients, all three neurosurgeons involved in the clinical evaluation changed their treatment decisions from conservative to decompressive surgery. While a small subset of patients may benefit from this type of evaluation, the benefit appears small for the added machine time and patient discomfort.

Neurography

A large and varied literature exists concerning the use of MR neurography for the evaluation of peripheral nerves, including brachial and lumbar plexi. Thin-section MR neurography uses a high-resolution T1 imaging for anatomic detail and fat-suppressed T2-weighted or short inversion time inversion-recovery imaging to show abnormal nerve hyperintensity. Several reviews exist on this subject (82–84). The technique is capable of depicting a wide variety of pathologic conditions involving the sciatic nerve, such as compression, trauma, hypertrophy, neuroma, and tumor infiltration (85,86). MR neurography demonstrating piriformis syndrome (piriformis muscle asymmetry and sciatic nerve hyperintensity) has 93% specificity and 64% sensitivity (87).

Ultrashort Echo-time Imaging

Typical clinical MR imaging does not allow evaluation of tissues with very short relaxation times, since echo times are on the order of 8–15 msec. Ultrashort echo-time sequences have been preliminarily evaluated for a number of tissues, including the spine. These sequences have echo times as short as 0.08 msec. The images show normal contrast enhancement, with high signal intensity from longitudinal ligaments, endplate, and interspinous ligaments (88–90).

Diffusion

Several authors have evaluated the apparent diffusion coefficient (ADC) in normal and degenerated intervertebral disks. Antoniou et al (91) evaluated the ADC of cadaveric human disks related to matrix composition and matrix integrity by using a stimulated echo sequence. They found the ADCs in healthy subjects were significantly greater in the nucleus pulposus than in the annulus fibrosis. The ADCs were noted to generally decrease with degeneration grade and age in the nucleus. A similar correlation of ADC measurements and annular degeneration was not found. The most notable correlations were observed between the ADCs of nucleus pulposus and the water and glycoaminoglycan contents. Kealey et al (92) evaluated 39 patients with multishot SE echo-planar technique. They found a significant decrease in ADC of degenerated disks compared with that of normal disks. Kurunlahti et al (93) evaluated the ADC of disk and lumbar magnetic resonance angiograms in 37 asymptomatic volunteers. The lumbar artery status correlated with the diffusion values within the disks, suggesting that impaired blood flow may play an important role in disk degeneration. Kerttula et al (94) compared disk ADC values in normal controls with those in patients with prior compression fractures (at least 1 year previously) and found ADC values in x and y directions decreased in degenerated disks and in disks of normal signal intensity in the trauma area.

Diffusion-tensor imaging has been evaluated for imaging of the annulus fibrosus (95) and potentially for imaging defects or disruptions within the annulus (76). Differences in diffusion have been demonstrated for the intervertebral disk in compressed versus uncompressed states (96).

Intravenous contrast enhancement may also be used to assess diffusion into the intervertebral disk. Normal disks slowly enhance after contrast material injection, which may be as much as 36% in animal models. This enhancement is modified by the type of contrast agent (ionic vs nonionic) and molecular weight (97,98). Ionic material diffuses less rapidly into the disk than does nonionic media. Degenerated disks with decreased glycoaminoglycan have more intense and rapid enhancement (99). Disk enhancement has been documented in normal and degenerated human lumbar disks (100).

Symptoms

The etiology of symptoms in patients with degenerative disk disease is diverse, and there is often ambiguity in the diagnosis (101). The symptom com-

plexes are more often characterized by variability and change rather than predictability and stability (102).

The most common symptom is pain. Anatomic areas of the spine can serve as sites of pain generation through intrinsic innervation or acquired innervation as a product of soft-tissue reparation. Mechanisms, which often act in combination, include *(a)* instability with associated disk degeneration, facet hypertrophy, or arthopathy; *(b)* mechanical compression of nerves by bone, ligament, or disk material; and *(c)* biochemical mediators of inflammation and/or pain.

It is important to reemphasize that disk degeneration per se is not painful, and in fact has a very high prevalence in the asymptomatic population. In addition, imaging findings of degenerative disk disease do not help predict a subsequent symptom development over time (103).

Mechanical compression or deformity of nerve roots as a cause of pain or nerve dysfunction is the classic concept related to displacement and effacement of neural tissue by disk herniation and dates to the observation of Mixter and Barr (104). Similar mechanical compression or traction mechanisms may be involved with instability or stenosis. A variety of morphologic changes occur in the nerve root with compression, including venous stasis, edema, and ultimately intraneural and perineural fibroses. Compression-induced impairment of both arterial and venous supply is one mechanism for nerve root dysfunction. Intraneural edema can occur even at low compression pressure levels (105). Mechanical compression itself may also be capable of producing changes in nerve impulses, which could be interpreted by the central nervous system as pain (106). However, the concept of neural compression by itself is inadequate to explain part or all of many symptom complexes.

The perplexing clinical scenario of patients who complain of incapacitating back pain, but may have no overt morphologic abnormality, has given rise to the concept of the disk as a pain generator. This was classically described by Crock (107) as "chronic internal disc disruption syndrome" (108,109). Many different names have been given to this idea, which becomes more confusing when combined with the various diagnostic tests that are used in an attempt to diagnose this protean syndrome. Additional terms in the literature include internal annular tear, internal disk disruption, black disk disease, and discogenic pain. In a normal human lumbar disk, nerve endings can be found only in the periphery of the annulus, and the pain fibers are part of the sympathetic chain via the sinuvertebral nerve (110–112). This innervates the outer layer of the annulus fibrosis. However, in very degenerated disks, nerves may even penetrate into the nucleus pulposus (113). Potentially, stimulation of these fibers can occur not only from direct disruption and mechanical pressure on the annulus but also from various breakdown products of the nucleus pulposus or secondarily upregulated inflammatory mediators. Discography has been cited as the reference standard for the diagnosis of discogenic pain, but what it means in terms of patient care has never been prospectively tested.

The concept of disk tissue producing an inflammatory response is not new, but has become more sophisticated and targeted with the application of monoclonal antibody technology, and other assay techniques (114) demonstrated chemical radiculitis, which was thought related to nuclear material and its glycoproteins, as being highly irritant to nerve tissue. McCarron et al (115), using a dog model, demonstrated in 1987 that autogenous placement of nucleus pulposus into the epidural space caused acute and chronic inflammatory reaction, with influx of histocytes and fibroblasts. Kayama et al (116) and Olmarker et al (117) demonstrated that nucleus pulposus applied to spinal nerves induces a wide variety of functional, vascular, and morphologic abnormalities, often followed by intraradicular fibrosis and neural atrophy. Nucleus pulposus can cause an inflammatory reaction with leukotaxis and increased vascular permeability (118). Direct placement of nuclear material is not necessary in animal models to induce an inflammatory response, but simply an incision of the annulus fibrosus can produce morphologic and functional changes in the adjacent nerves, such as increased capillaries and reduced nerve conduction velocities (116), with the presumed mechanism of disk material leakage into the epidural space. Monoclonal antibody staining of disk material has shown that the cells demonstrate an immunophenotype of inflammatory response, that is, macrophages (119). As a manifestation of this inflammatory response, higher systemic plasma levels of C-reactive protein have been found in patients with sciatica versus healthy controls (120).

Multiple studies have demonstrated vascularized granulation tissue surrounding the cartilage component of disk herniations (121,122), which correspond to the common enhanced MR findings of peripheral enhancement surrounding nonenhancing lumbar disk extrusions in unoperated patients. Blood vessels have been demonstrated in up to 91% of herniations, being most prevalent with disk sequestrations (123). Gronblad et al (124), using monoclonal antibodies, evaluated the types of inflammatory cells found with disk herniations and found them to be dominated by macrophages. There was also evidence of IL-1β expression, an important proinflammatory cytokine.

Disk cells are also capable of expressing other proinflammatory substances, such as TNF-α, which can produce radicular morphologic abnormalities similar to those seen with nucleus pulposus application (125). TNF-α is overexpressed in degenerated disks and is a proinflammatory cytokine affecting matrix metalloproteinases (MMP) expression and increasing prostaglandin E2. Weiler et al (126) demonstrated TNF-α in cross-sections of human disks and found synthesis of TNF-α in annular and disk regions, increased TNF-α with symptomatic disk disease, and TNF-α expression associated with increasing disk degeneration. Olmarker and Rydevik (127) showed that inhibition of TNF-α prevented thrombus formation and intraneural edema and reduced

nerve conduction velocity. This set the stage for an open label trial of anti-TNF therapy in patients with sciatica (128–130). Infliximab (Remicade; Centocor, Malvern, Pa), a chimeric monoclonal human and mouse antibody, inhibits TNF-α–induced infiltration of leukocytes to the site of injury. A single infusion of infliximab produced a rapid beneficial effect on pain, which persisted over 1 year, at the 3 mg/kg dose level. Sustained improvement was also demonstrated with the subcutaneous injection of another anti-TNF agent, etanercept (Enbrel; Immunex-Amgen, Thousand Oaks, Calif) (128). While intriguing, the off-label use of these TNF inhibitors is not recommended, since little data are currently available and only a very small number of patients have been treated. This trial does point out the direction of research for treatment of disk disease, with specific targeting of inflammatory pathways.

A wide variety of inflammatory agents are capable of expression from both migratory macrophages into the site of herniation and directly from stimulated chondrocytes (131). Burke et al (132) found increased levels of IL-6, IL-8, prostaglandin E2, and monocyte chemoattractant protein-1 in disk extracts of patients undergoing fusion for discogenic pain. Monocyte chemoattractant protein-1 is a CC chemokine that contributes to the activation and recruitment of macrophages and is expressed by chrondrocytes that are stimulated by other cytokines and some MMPs. Disk tissue is biologically active and can respond to a proinflammatory stimulus by secreting IL-6, IL-8, and prostaglandin E2, but not TNF-α. In a rabbit disk herniation model, however, Yoshida et al (133) demonstrated infiltrating macrophages at day 3 postoperatively, with intervertebral disk cells producing TNF-α and IL-1β on day 1 and monocyte chemoattractant protein-1 on day 3. In a mouse-derived coculture system of disk material and macrophages, Kato et al (134) also demonstrated upregulation of TNF-α messenger RNA and protein expression as the first point of the inflammatory cascade. The TNF-α–dependent glycoprotein, TNF-α–stimulated gene-6 (TSG-6), which is found in inflammatory diseases of related connective tissues, has been demonstrated in 98% of disk herniations in one series (135).

Another component of the inflammatory response involves the matrix-degrading enzymes called MMPs. There are approximately 25 MMPs in five classes based on the specificity of their substrate. These enzymes degrade the extracellular matrix at physiologic pH levels. They are released by resident cells such as fibroblasts, macrophages in herniated disks, and chondrocytes from protrusions and nonherniated disk (136). MMPs can play a direct role in disk degeneration by causing matrix proteolysis and disk resorption and have an indirect role in angiogenesis. MMPs involved in disk degeneration include MMP-1 (collagenase); MMP-3 (stromelysin-1); MMP-9 (gelatinase B); and MMPs-2, -7, -8, and -13 (137). Cells within granulation tissue in disk herniations express MMP-1 and MMP-3 (138,139). MMP-3, but not MMP-7 (matrilysin), appears necessary for disk resorption, although the mechanism may be indirect and correlates with macrophage infiltration (140). The angiogenic properties are more indirect, with endothelial cell migration occurring only after a proteolytic reaction produced by MMP-3 (141). Cytokines leading to MMP production within the disk herniation may then result in angiogenesis and disk resorption. Given the wide variety of MMPs present, it is likely that there is a cascade of interacting proteases for different components of the disk matrix involved in disk resorption and degeneration.

Many other molecules have also shown to be present in degenerated or herniated disks that may play additional roles in the inflammatory cascade, such as intercellular adhesion molecule-1, fibroblast growth factor, and vascular endothelial growth factor (142,143). These two latter agents contribute to neoangiogenesis. Vascular endothelial growth factor appears to require TNF-α for induction. Additionally, it is a potent inducer of plasmin and results in activation of a variety of MMPs. Interaction between the vascular endothelial growth factor and MMPs could promote disk matrix degeneration, as well as neovascularization of herniations.

Nerve fibers have been identified in the outer third of the annulus in the normal state, but may extend into the inner annulus and nucleus pulposus, accompanied by blood vessels, in chronic back pain patients (113). These nerves also stain for substance P, a putative nociceptive neurotransmitter, along with calcitonin gene-related peptide and vasoactive intestinal peptide. These small nonmyelinated nerve fibers grow into the disk in areas with local production of nerve growth factor, which is produced by the neoangiogenesis of the disk material (113). Coupled with nerve ingrowth and angiogenesis is the production of inflammation by liberation of the potent inflammatory agent phospholipase A2, which catalyzes the hydrolysis of phosphoglyceride, an important membrane constituent (144,145). This production of phospholipase A2 is induced by, among other signals, the presence of IL-1 and TNF-α, with the subsequent upregulation of the arachadonic acid cascade, which produces prostaglandin E2 and leukotrienes (146,147). Prostaglandin E2 production has the critical rate-limiting enzyme cyclooxygenase-2, which appears to be primarily upregulated during inflammation (148). The other branch of the arachadonic acid cascade is the production of leukotrienes by means of the enzyme lipoxygenase. A bell-shaped pain behavior dose response curve has been demonstrated for intraneural injection of TNF-α and IL-1β in a rat model, peaking at doses equivalent to those of endogenous cytokines released locally after nerve injury. An increase in perineural macrophages was also observed, particularly for IL-1β (149).

Sensory and motor deficits would appear to be the result of both a combination of mechanical deformation and the presence of inflammation. A variety of mechanisms and mediators are involved in the inflammatory side of the equation, and a brief general overview is attempted in Figure 18. Clearly, the etiology of pain in degenerative disease

is much more complex than a simple mechanical explanation, and work on these other factors will hopefully bring us a greater understanding of the relationship between morphologic alteration and clinical symptoms.

Importance of Imaging Findings

The role of an imaging test is to provide accurate morphologic information and influence therapeutic decision making (150). A necessary component, which connects these two purposes, is accurate natural history data.

Modern imaging has made important strides in supporting the first goal, accurate morphologic information. Not only are morphologic changes depicted in ever-increasing anatomic detail, but additional information from the imaging study has been made available that is helping us to understand cellular and biochemical alterations. The ability to better characterize these alterations should provide a means of more accurately stratifying patient changes that may allow a more accurate understanding of etiology.

Figure 18

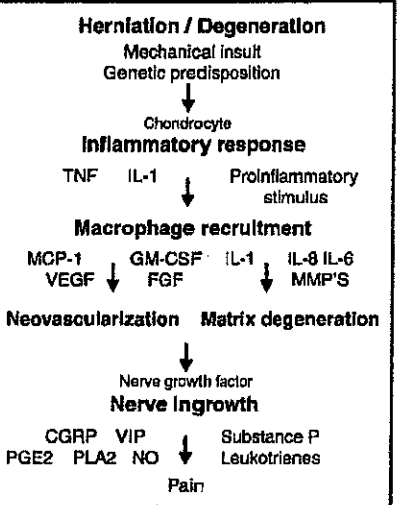


Figure 18: Flowchart of hypothetical inflammatory cascade for degenerative disk disease. *CGRP* = calcitonin gene-related peptide, *FGF* = fibroblast growth factor, *GM-CSF* = granulocyte-macrophage colony-stimulating factor, *MCP* = monocyte chemoattractant protein-1, *NO* = nitric oxide, *PGE2* = prostaglandin E2, *PLA2* = phospholipase A2, *VEGF* = vascular endothelial growth factor, *VIP* = vasoactive intestinal peptide.

Any study looking at the natural history of degenerative disk disease, prognostic value of imaging, or its effect on therapeutic decision making will be confounded by the high prevalence of morphologic change in the asymptomatic population (151–153). A 20%–28% of asymptomatic patients demonstrate disk herniations, and the majority have evidence of additional degenerative disk disease (151–153). These findings are not only nonpredictive at the moment, but prospectively as well. In a 7-year follow-up of the Borenstein et al (103) original patient group, the original MR findings were not predictive of the development or duration of low back pain.

As to natural history, some information is available. Degenerative disk space narrowing, facet disease, and stenosis tend to slowly progress over time. Eventual stabilization of the three-joint discovertebral complex is thought to be part of the natural history of degenerative disease, and it is assumed to be accompanied by a decrease in pain. These impressions, however, are anecdotal and have not been tested by a formal natural history study. Some findings, such as disk herniation and degenerative marrow changes, are known to change. Multiple studies in which computed tomography or MR imaging has been used have shown that the size of disk herniations, especially larger ones, can reduce dramatically in patients undergoing conservative treatment (154,155).

In a study of symptomatic patients, the prevalence of disk herniation in patients with low back pain and those with radiculopathy at presentation was similar (156). There was a higher prevalence of herniation, 57% in patients with low back pain and 65% in patients with radiculopathy, than the 20%–28% prevalence reported in asymptomatic series (152,153). Disks characterized as extruded showed more marked regression in patients with both low back pain and radiculopathy. In general, one-third of patients with disk herniation at presentation had significant resolution or disappearance by 6 weeks and two-thirds by 6 months (155,156). The type, size, and location of herniation at presentation and changes in herniation size and type over time did not correlate with outcome. In fact, the presence of a herniation at a MR was a positive prognostic finding (156).

Interestingly, not only do disk herniations have a tendency to regress, but also new or larger ones may appear after the onset of symptoms. In this study, 13% of patients in this symptomatic series developed new or larger disk herniations over a 6-week period. In looking at patients with low back pain or radiculopathy, MR did not have additive value over clinical assessment. No prognostic sign that might alter treatment versus clinical assessment alone was identified. The size and type of disk herniation and location and presence of nerve root compression, significant in terms of morphologic alteration, were not related to patient outcome. Likewise, the presence or absence of stenosis, facet disease, or degenerative marrow changes did not correlate with patient outcome (156).

This lack of prognostic value also appears to apply to the conservative management of spinal stenosis. There do not appear to be reliable prognostic imaging findings that would correlate with surgical success or even whether patients would benefit from surgery and spinal stenosis (75,157). A study of the qualitative morphologic features of the spinal canal dimensions and herniated disks has not proved helpful in predicting outcomes in patients with back pain and sciatica. Demographic and clinical features appear to predict outcome of nonsurgical treatment, whereas morphometric features of disk herniation and spinal canal are more powerful predictors of surgical outcome (158).

Degenerative marrow changes may also change over time. In all three types, there is always evidence of associated degenerative disk disease at the level of involvement. Type I changes may revert to normal or convert to type II changes, with time suggesting some stabilization of the degenerative process. Type II changes tend to be more stable but may

convert to type I or a mixed combination of types I and II. When changes do occur in type II marrow, they are usually associated with evidence of additional or accelerated degeneration or a superimposed process such as infection or trauma.

The clinical importance of marrow changes associated with degenerative disk disease remains unclear. Type I changes seem to be associated with a higher prevalence of active low back pain symptoms. The exact etiologic mechanism or mechanisms, while unknown, have been thought related to some type of unusual stresses, micro- or macroinstabilility or microtrauma. Some studies of discography in patients with degenerative marrow changes have suggested that type I marrow changes are invariably associated with painful disks (159–162). Surgical studies have suggested that patients with type I marrow changes who undergo fusion for low back pain do better than those without endplate changes or type II patterns (159). The hypothesis is that type I degenerative marrow changes are related to or are indicators of some degree of instability. Authors of a surgical study looking at the prognostic value of type I marrow changes related to surgical outcome demonstrated that persistence of type I marrow changes after fusion was associated with significantly worse outcome (163). The authors speculate that type I changes may not only be an important criterion for surgery, but type I change disappearance may be an indicator of successful fusion and stabilization. Additional evidence to support that these changes are a reflection of a more active process related to microtrauma and instability is a surgical study that found that in the overwhelming majority of patients with type I marrow changes who undergo fixation and fusion, the marrow changes will convert to a normal marrow signal intensity or type II changes, with good clinical results (159).

Surgery

Degeneration of the intervertebral disk complex is a process that begins early in life and is a consequence of a variety of genetic, physiologic, and environmental factors, as well as normal aging. Given the ubiquitous nature of the process and its high prevalence in both symptomatic and asymptomatic individuals, the jump from identifying an anatomic derangement to proposing a symptom complex must be made with caution (2). There is an opportunity for imaging to further our understanding of the process.

What separates individuals with dramatic morphologic findings who have no symptoms from individuals with identical alterations who do? Understanding the relationship of etiologic factors, the morphologic alterations, which can be characterized at imaging, and the mechanisms of pain production and their interactions in the production of symptoms will require more accurate and reproducible stratification of patient cohorts. This may be a strong suit of imaging, the phenotyping of morphologic alterations to compare with the emerging genotyping work relative to etiology and clinical manifestations. The ultimate translational goal is the integration of this newfound understanding into the therapeutic decision-making process.

References

1. Pritzker KP. Aging and degeneration in the lumbar intervertebral disc. Orthop Clin North Am 1977;8:66–77.
2. White AA 3rd, Gordon SL. Synopsis: workshop on idiopathic low-back pain. Spine 1982;7:141–149.
3. Adams MA, Hutton WC. Gradual disc prolapse. Spine 1985;10:524–531.
4. Adams MA, Hutton WC. Prolapsed intervertebral disc: a hyperflexion injury 1981 Volvo Award in Basic Science. Spine 1982; 7:184–191.
5. Gordon SJ, Yang KH, Mayer PJ, Mace AH Jr, Kish VL, Radin EL. Mechanism of disc rupture: a preliminary report. Spine 1991; 16:450–456.
6. McNally DS, Adams MA, Goodship AE. Can intervertebral disc prolapse be predicted by disc mechanics? Spine 1993;18: 1525–1530.
7. Shirazi-Adl A. Strain in fibers of a lumbar disc: analysis of the role of lifting in producing disc prolapse. Spine 1989;14:96–103.
8. Adams MA, Freeman BJ, Morrison HP, Nelson IW, Dolan P. Mechanical initiation of intervertebral disc degeneration. Spine 2000;25:1625–1636.
9. Hurri H, Karppinen J. Discogenic pain. Pain 2004;112:225–228.
10. Kauppila LI, McAlindon T, Evans S, Wilson PW, Kiel D, Felson DT. Disc degeneration/back pain and calcification of the abdominal aorta: a 25-year follow-up study in Framingham. Spine 1997;22:1642–1647.
11. Kresina TF, Malemud CJ, Moskowitz RW. Analysis of osteoarthritic cartilage using monoclonal antibodies reactive with rabbit proteoglycan. Arthritis Rheum 1986;29: 863–871.
12. Battie MC, Videman T, Gibbons LE, Fisher LD, Manninen H, Gill K. 1995 Volvo Award in clinical sciences: determinants of lumbar disc degeneration—a study relating lifetime exposures and magnetic resonance imaging findings in identical twins. Spine 1995;20: 2601–2612.
13. Hestbaek L, Iachine IA, Leboeuf-Yde C, Kyvik KO, Manniche C. Heredity of low back pain in a young population: a classical twin study. Twin Res 2004;7:16–26.
14. Annunen S, Paassilta P, Lohiniva J, et al. An allele of COL9A2 associated with intervertebral disc disease. Science 1999;285: 409–412.
15. Marini JC. Genetic risk factors for lumbar disk disease. JAMA 2001;285:1886–1888.
16. Paassilta P, Lohiniva J, Goring HH, et al. Identification of a novel common genetic risk factor for lumbar disk disease. JAMA 2001;285:1843–1849.
17. Watanabe H, Nakata K, Kimata K, Nakanishi I, Yamada Y. Dwarfism and age-associated spinal degeneration of heterozygote cmd mice defective in aggrecan. Proc Natl Acad Sci U S A 1997;94:6943–6947.
18. Nelson CL, Janecki CJ, Gildenberg PL, Sava G. Disk protrusions in the young. Clin Orthop Relat Res 1972;88:142–150.
19. Varlotta GP, Brown MD, Kelsey JL, Golden AL. Familial predisposition for herniation of a lumbar disc in patients who are less than 21 years old. J Bone Joint Surg Am 1991;73:124–128.
20. Matsui H, Terahata N, Tsuji H, Hirano N, Naruse Y. Familial predisposition and clustering for juvenile lumbar disc herniation. Spine 1992;17:1323–1328.
21. Scapinelli R. Lumbar disc herniation in eight siblings with a positive family history

for disc disease. Acta Orthop Belg 1993;59: 371–376.

22. Solovieva S, Leino-Arjas P, Saarela J, Luoma K, Raininko R, Riihimaki H. Possible association of interleukin 1 gene locus polymorphisms with low back pain. Pain 2004;109:8–19.

23. Quinet RJ, Hadler NM. Diagnosis and treatment of backache. Semin Arthritis Rheum 1979;8:261–287.

24. Bonneville JF, Dietemann JL. Imaging in sciatica [in French]. Rev Prat 1992;42: 554–566.

25. Brant-Zawadzki MN, Jensen MC, Obuchowski N, Ross JS, Modic MT. Interobserver and intraobserver variability in interpretation of lumbar disc abnormalities: a comparison of two nomenclatures. Spine 1995;20:1257–1263.

26. Breton G. Is that a bulging disk, a small herniation or a moderate protrusion? Can Assoc Radiol J 1991;42:318.

27. Fardon DF, Balderston RA, Garfin SR, Nasca RJ, Pinkerton S, Salib RM. Disorders of the spine: a coding system for diagnoses. Philadelphia, Pa: Hanley & Belfus, 1991; 20–22.

28. Milette PC. Reporting lumbar disk abnormalities: at last, consensus! AJNR Am J Neuroradiol 2001;22:428–429.

29. Czervionke LF. Lumbar intervertebral disc disease. Neuroimaging Clin N Am 1993;3: 465–485.

30. Modic MT, Herfkens RJ. Intervertebral disk: normal age-related changes in MR signal intensity. Radiology 1990;177:332–333.

31. Sether LA, Yu S, Haughton VM, Fischer ME. Intervertebral disk: normal age-related changes in MR signal intensity. Radiology 1990;177:385–388.

32. Resnick D, Niwayama G. Degenerative disease of the spine. Philadelphia, Pa: Saunders, 1995; 1372–1462.

33. Schmorl G, Junghanns H. The human spine in health and disease. 2nd American ed. New York, NY: Grune & Stratton, 1971; 141–148.

34. Nathan H. Osteophytes of the vertebral column: an anatomical study of their development according to age, race, and sex with consideration as to their etiology and significance. J Bone Joint Surg 1962;44: 243–268.

35. Sauser DD, Goldman AB, Kaye JJ. Discogenic vertebral sclerosis. J Can Assoc Radiol 1978;29:44–50.

36. Twomey L, Taylor J. Age changes in lumbar intervertebral disc. Acta Orthop Scand 1985;56:496–499.

37. Twomey LT, Taylor JR. Age changes in lumbar vertebrae and intervertebral discs. Clin Orthop Relat Res 1987;224:97–104.

38. Thalgott JS, Albert TJ, Vaccaro AR, et al. A new classification system for degenerative disc disease of the lumbar spine based on magnetic resonance imaging, provocative discography, plain radiographs and anatomic considerations. Spine J 2004;4(6 suppl):167S–172S.

39. Iida T, Abumi K, Kotani Y, Kaneda K. Effects of aging and spinal degeneration on mechanical properties of lumbar supraspinous and interspinous ligaments. Spine J 2002;2:95–100.

40. Kirkaldy-Willis WH, Wedge JH, Yong-Hing K, Reilly J. Pathology and pathogenesis of lumbar spondylosis and stenosis. Spine 1978;3:319–328.

41. Adams P, Eyre DR, Muir H. Biochemical aspects of development and ageing of human lumbar intervertebral discs. Rheumatol Rehabil 1977;16:22–29.

42. Brown MD. The pathophysiology of disc disease. Orthop Clin North Am 1971;2: 359–370.

43. Lipson SJ, Muir H. Experimental intervertebral disc degeneration: morphologic and proteoglycan changes over time. Arthritis Rheum 1981;24:12–21.

44. Modic MT, Pavlicek W, Weinstein MA, et al. Magnetic resonance imaging of intervertebral disk disease: clinical and pulse sequence considerations. Radiology 1984; 152:103–111.

45. Majors AW, McDevitt CA, Silgalis I, Modic MT. A correlative analysis of T2, ADC and MT radio with water, hydroxyproline and GAG content in excised human intervertebral disk. New Orleans, La; Orthopedic Research Society, 1994; 116–120.

46. Yu S, Haughton VM, Sether LA, Ho KC, Wagner M. Criteria for classifying normal and degenerated lumbar intervertebral disks. Radiology 1989;170:523–526.

47. Friberg S, Hirsch C. Anatomical and clinical studies on lumbar disc degeneration. Acta Orthop Scand 1949;19:222–242.

48. Hirsch C. Studies on the pathology of low back pain. J Bone Joint Surg Br 1959;41-B: 237–243.

49. Coventry MB. Anatomy of the intervertebral disk. Clin Orthop Relat Res 1969;67: 9–15.

50. Pfirrmann CW, Metzdorf A, Zanetti M, Hodler J, Boos N. Magnetic resonance classification of lumbar intervertebral disc degeneration. Spine 2001;26:1873–1878.

51. Knutsson F. The vacuum phenomenon in the intervertebral discs. Acta Radiol 1942; 23:173–179.

52. Grenier N, Grossman RI, Schiebler ML, Yeager BA, Goldberg HI, Kressel HY. Degenerative lumbar disk disease: pitfalls and usefulness of MR imaging in detection of vacuum phenomenon. Radiology 1987;164: 861–865.

53. Bielecki DK, Sartoris D, Resnick D, Van Lom K, Fierer J, Haghighi P. Intraosseous and intradiscal gas in association with spinal infection: report of three cases. AJR Am J Roentgenol 1986;147:83–86.

54. Bangert BA, Modic MT, Ross JS, et al. Hyperintense disks on T1-weighted MR images: correlation with calcification. Radiology 1995;195:437–443.

55. Boyko OB, Burger PC, Shelburne JD, Ingram P. Non-heme mechanisms for T1 shortening: pathologic CT, and MR elucidation. AJNR Am J Neuroradiol 1992;13: 1439–1445.

56. Henkelman RM, Watts JF, Kucharczyk W. High signal intensity in MR images of calcified brain tissue. Radiology 1991;179:199–206.

57. de Roos A, Kressel H, Spritzer C, Dalinka M. MR imaging of marrow changes adjacent to end plates in degenerative lumbar disk disease. AJR Am J Roentgenol 1987; 149:531–534.

58. Masaryk TJ, Boumphrey F, Modic MT, Tamborrello C, Ross JS, Brown MD. Effects of chemonucleolysis demonstrated by MR imaging. J Comput Assist Tomogr 1986;10:917–923.

59. Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. Radiology 1988;166:193–199.

60. Ross JS, Robertson JT, Frederickson RC, et al. Association between peridural scar and recurrent radicular pain after lumbar discectomy: magnetic resonance evaluation. ADCON-L European Study Group. Neurosurgery 1996;38:855–861.

61. Ross JS, Obuchowski N, Zepp R. The postoperative lumbar spine: evaluation of epidural scar over a 1-year period. AJNR Am J Neuroradiol 1998;19:183–186.

62. Morrison JL, Kaplan PA, Dussault RG, Anderson MW. Pedicle marrow signal intensity changes in the lumbar spine: a manifestation of facet degenerative joint disease. Skeletal Radiol 2000;29:703–707.

63. Ulmer JL, Elster AD, Mathews VP, Allen AM. Lumbar spondylolysis: reactive marrow changes seen in adjacent pedicles on MR images. AJR Am J Roentgenol 1995; 164:429–433.

64. Harris RI, MacNab I. Structural changes in the lumbar intervertebral discs: their relationship to low back pain and sciatica. J Bone Joint Surg Br 1954;36-B:304–322.

65. Schellinger D, Wener L, Ragsdale BD, Patronas NJ. Facet joint disorders and their role in the production of back pain and sciatica. RadioGraphics 1987;7:923–944.

66. Doyle AJ, Merrilees M. Synovial cysts of the lumbar facet joints in a symptomatic population: prevalence on magnetic resonance imaging. Spine 2004;29(8):874–878.

67. Baastrup CI. On the spinous processes of the lumbar vertebrae and the soft tissue between them and on pathological changes in that region. Acta Radiol Scan 1933;14: 52–54.

68. Jacobson HG, Tausend ME, Shapiro JH, Poppel MH. The swayback syndrome. Am J Roentgenol Radium Ther Nucl Med 1958; 79:677–683.

69. Hilton RC, Ball J, Benn RT. Vertebral endplate lesions (Schmorl's nodes) in the dorsolumbar spine. Ann Rheum Dis 1976;35: 127–132.

70. Resnick D, Niwayama G. Intravertebral disk herniations: cartilaginous (Schmorl's) nodes. Radiology 1978;126:57–65.

71. Wagner AL, Murtagh FR, Arrington JA, Stallworth D. Relationship of Schmorl's nodes to vertebral body endplate fractures and acute endplate disk extrusions. AJNR Am J Neuroradiol 2000;21:276–281.

72. Arnoldi CC, Brodsky AE, Cauchoix J, et al. Lumbar spinal stenosis and nerve root entrapment syndromes: definition and classification. Clin Orthop Relat Res 1976; 115:4–5.

73. Amundsen T, Weber H, Lilleas F, Nordal HJ, Abdelnoor M, Magnaes B. Lumbar spinal stenosis: clinical and radiologic features. Spine 1995;20:1178–1186.

74. Inufusa A, An HS, Lim TH, Hasegawa T, Haughton VM, Nowicki BH. Anatomic changes of the spinal canal and intervertebral foramen associated with flexion-extension movement. Spine 1996;21:2412–2420.

75. ECRI. Treatment of degenerative lumbar spinal stenosis. I. Evidence report. Agency for Healthcare Research and Quality publication no. 01-E048 #32. Plymouth Meeting, Pa: ECRI, 2001.

76. Haughton V. Medical imaging of intervertebral disc degeneration: current status of imaging. Spine 2004;29:2751–2756.

77. Jinkins JR, Dworkin JS, Damadian RV. Upright, weight-bearing, dynamic-kinetic MRI of the spine: initial results. Eur Radiol 2005; 15(9):1815–1825.

78. Danielson B, Willen J. Axially loaded magnetic resonance image of the lumbar spine in asymptomatic individuals. Spine 2001; 26:2601–2606.

79. Kimura S, Steinbach GC, Watenpaugh DE, Hargens AR. Lumbar spine disc height and curvature responses to an axial load generated by a compression device compatible with magnetic resonance imaging. Spine 2001;26:2596–2600.

80. Hiwatashi A, Danielson B, Moritani T, et al. Axial loading during MR imaging can influence tratment decision for symptomatic spinal stenosis. AJNR Am J Neuroradiol 2004;25:170–174.

81. Tanaka N, An HS, Lim TH, Fujiwara A, Jeon CH, Haughton VM. The relationship between disc degeneration and flexibility of the lumbar spine. Spine J 2001;1:47–56.

82. Aagaard BD, Maravilla KR, Kliot M. Magnetic resonance neurography: magnetic resonance imaging of peripheral nerves. Neuroimaging Clin N Am 2001;11:viii, 131–146.

83. Filler AG, Maravilla KR, Tsuruda JS. MR neurography and muscle MR imaging for image diagnosis of disorders affecting the peripheral nerves and musculature. Neurol Clin 2004;22:643–682, vi–vii.

84. Maravilla KR, Bowen BC. Imaging of the peripheral nervous system: evaluation of peripheral neuropathy and plexopathy. AJNR Am J Neuroradiol 1998;19:1011–1023.

85. Moore KR, Tsuruda JS, Dailey AT. The value of MR neurography for evaluating extraspinal neuropathic leg pain: a pictorial essay. AJNR Am J Neuroradiol 2001;22: 786–794.

86. Ellegala DB, Monteith SJ, Haynor D, Bird TD, Goodkin R, Kliot M. Characterization of genetically defined types of Charcot-Marie-Tooth neuropathies by using magnetic resonance neurography. J Neurosurg 2005;102:242–245.

87. Filler AG, Haynes J, Jordan SE, et al. Sciatica of nondisc origin and piriformis syndrome: diagnosis by magnetic resonance neurography and interventional magnetic resonance imaging with outcome study of resulting treatment. J Neurosurg Spine 2005;2:99–115.

88. Gatehouse PD, He T, Hughes SP, Bydder GM. MR imaging of degenerative disc disease in the lumbar spine with ultrashort TE pulse sequences. MAGMA 2004;16:160–166.

89. Hall-Craggs MA, Porter J, Gatehouse PD, Bydder GM. Ultrashort echo time (UTE) MRI of the spine in thalassaemia. Br J Radiol 2004;77:104–110.

90. Robson MD, Gatehouse PD, So PW, Bell JD, Bydder GM. Contrast enhancement of short T2 tissues using ultrashort TE (UTE) pulse sequences. Clin Radiol 2004;59:720–726.

91. Antoniou J, Demers CN, Beaudoin G, et al. Apparent diffusion coefficient of intervertebral discs related to matrix composition and integrity. Magn Reson Imaging 2004; 22:963–972.

92. Kealey SM, Aho T, Delong D, Barboriak DP, Provenzale JM, Eastwood JD. Assessment of apparent diffusion coefficient in normal and degenerated intervertebral lumbar disks: initial experience. Radiology 2005;235:569–574.

93. Kurunlahti M, Kerttula L, Jauhiainen J, Karppinen J, Tervonen O. Correlation of diffusion in lumbar intervertebral disks with occlusion of lumbar arteries: a study in adult volunteers. Radiology 2001;221:779–786.

94. Kerttula L, Kurunlahti M, Jauhiainen J, Koivula A, Oikarinen J, Tervonen O. Apparent diffusion coefficients and T2 relaxation time measurements to evaluate disc degeneration: a quantitative MR study of young patients with previous vertebral fracture. Acta Radiol 2001;42:585–591.

95. Hsu EW, Setton LA. Diffusion tensor microscopy of the intervertebral disc anulus fibrosus. Magn Reson Med 1999;41:992–999.

96. Chiu EJ, Newitt DC, Segal MR, Hu SS, Lotz JC, Majumdar S. Magnetic resonance imaging measurement of relaxation and water diffusion in the human lumbar intervertebral disc under compression in vitro. Spine 2001;26:E437–E444.

97. Perlewitz TJ, Haughton VM, Riley LHI, Nguyen-minh C, George V. Effect of molecular weight on the diffusion of contrast media into cartilage. Spine 1997;22:2707–2710.

98. Akansel G, Haughton VM, Papke RA, Censky S. Diffusion into human intervertebral disks studied with MR and gadoteridol. AJNR Am J Neuroradiol 1997;18:443–445.

99. Ibrahim MA, Haughton VM, Hyde JS. Effect of disk maturation on diffusion of low-molecular-weight gadolinium complexes:

an experimental study in rabbits. AJNR Am J Neuroradiol 1995;16:1307–1311.

100. Nguyen-minh C, Haughton VM, Papke RA, An H, Censky SC. Measuring diffusion of solutes into intervertebral disks with MR imaging and paramagnetic contrast medium. AJNR Am J Neuroradiol 1998;19:1781–1784.

101. Deyo RA. Practice variations, treatment fads, rising disability: do we need a new clinical research paradigm? Spine 1993;18:2153–2162.

102. Von Korff M, Saunders K. The course of back pain in primary care. Spine 1996;21:2833–2837.

103. Borenstein DG, O'Mara JW Jr, Boden SD, et al. The value of magnetic resonance imaging of the lumbar spine to predict low-back pain in asymptomatic subjects: a 7-year follow-up study. J Bone Joint Surg Am 2001;83-A:1306–1311.

104. Mixter W, Barr JS. Rupture of the intervertebral disc with involvement of the spinal canal. N Engl J Med 1934;211.

105. Olmarker K, Rydevik B, Holm S. Edema formation in spinal nerve roots induced by experimental, graded compression: an experimental study on the pig cauda equina with special reference to differences in effects between rapid and slow onset of compression. Spine 1989;14:569–573.

106. Howe JF, Loeser JD, Calvin WH. Mechanosensitivity of dorsal root ganglia and chronically injured axons: a physiological basis for the radicular pain of nerve root compression. Pain 1977;3:25–41.

107. Crock HV. Internal disc disruption: a challenge to disc prolapse fifty years on. Spine 1986;11:650–653.

108. Thompson KJ. Diagnostic lumbar disc injection. 3rd ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2004; 87–90.

109. Yonemura KS, Yuan H. The black disc. In: Benzel E, ed. Spine surgery: techniques, complication avoidance and management. 2nd ed. Philadelphia: Pa: Elsevier, 2004; 626–631.

110. Edgar MA, Ghadially JA. Innervation of the lumbar spine. Clin Orthop Relat Res 1976; 115:35–41.

111. Ashton IK, Roberts S, Jaffray DC, Polak JM, Eisenstein SM. Neuropeptides in the human intervertebral disc. J Orthop Res 1994;12:186–192.

112. Fagan A, Moore R, Vernon Roberts B, Blumbergs P, Fraser R. ISSLS prize winner: the innervation of the intervertebral disc—a quantitative analysis. Spine 2003; 28:2570–2576.

113. Freemont AJ, Peacock TE, Goupille P, Hoyland JA, O'Brien J, Jayson MI. Nerve ingrowth into diseased intervertebral disc in chronic back pain. Lancet 1997;350:178–181.

114. Marshall LL, Trethewie ER, Curtain CC. Chemical radiculitis: a clinical, physiological and immunological study. Clin Orthop Relat Res 1977;129:61–67.

115. McCarron RF, Wimpee MW, Hudkins PG, Laros GS. The inflammatory effect of nucleus pulposus: a possible element in the pathogenesis of low-back pain. Spine 1987; 12:760–764.

116. Kayama S, Konno S, Olmarker K, Yabuki S, Kikuchi S. Incision of the anulus fibrosus induces nerve root morphologic, vascular, and functional changes: an experimental study. Spine 1996;21:2539–2543.

117. Olmarker K, Nordborg C, Larsson K, Rydevik B. Ultrastructural changes in spinal nerve roots induced by autologous nucleus pulposus. Spine 1996;21:411–414.

118. Olmarker K, Blomquist J, Stromberg J, Nannmark U, Thomsen P, Rydevik B. Inflammatogenic properties of nucleus pulposus. Spine 1995;20:665–669.

119. Kawaguchi S, Yamashita T, Yokogushi K, Murakami T, Ohwada O, Sato N. Immunophenotypic analysis of the inflammatory infiltrates in herniated intervertebral discs. Spine 2001;26:1209–1214.

120. Le Gars L, Borderie D, Kaplan G, Berenbaum F. Systemic inflammatory response with plasma C-reactive protein elevation in disk-related lumbosciatic syndrome. Joint Bone Spine 2000;67(5):452–455.

121. Doita M, Kanatani T, Harada T, Mizuno K. Immunohistologic study of the ruptured intervertebral disc of the lumbar spine. Spine 1996;21:235–241.

122. Ito T, Yamada M, Ikuta F, et al. Histologic evidence of absorption of sequestration-type herniated disc. Spine 1996;21:230–234.

123. Virri J, Gronblad M, Savikko J, et al. Prevalence, morphology, and topography of blood vessels in herniated disc tissue: a comparative immunocytochemical study. Spine 1996;21:1856–1863.

124. Gronblad M, Virri J, Tolonen J, et al. A controlled immunohistochemical study of inflammatory cells in disc herniation tissue. Spine 1994;19:2744–2751.

125. Igarashi T, Kikuchi S, Shubayev V, Myers RR. 2000 Volvo Award winner in basic science studies: exogenous tumor necrosis factor-alpha mimics nucleus pulposus-induced neuropathology—molecular, histologic, and behavioral comparisons in rats. Spine 2000;25:2975–2980.

126. Weiler C, Nerlich AG, Bachmeier BE, Boos N. Expression and distribution of tumor necrosis factor alpha in human lumbar intervertebral discs: a study in surgical specimen and autopsy controls. Spine 2005;30:44–53.

127. Olmarker K, Rydevik B. Selective inhibition of tumor necrosis factor-alpha prevents nucleus pulposus-induced thrombus formation, intraneural edema, and reduction of nerve conduction velocity: possible implications for future pharmacologic treatment strategies of sciatica. Spine 2001;26:863–869.

128. Genevay S, Stingelin S, Gabay C. Efficacy of etanercept in the treatment of acute, severe sciatica: a pilot study. Ann Rheum Dis 2004;63:1120–1123.

129. Karppinen J, Korhonen T, Malmivaara A, et al. Tumor necrosis factor-alpha monoclonal antibody, infliximab, used to manage severe sciatica. Spine 2003;28:750–753.

130. Korhonen T, Karppinen J, Malmivaara A, et al. Efficacy of infliximab for disc herniation-induced sciatica: 1-year follow-up. Spine 2004;29:2115–2119.

131. Takahashi H, Suguro T, Okazima Y, Motegi M, Okada Y, Kakiuchi T. Inflammatory cytokines in the herniated disc of the lumbar spine. Spine 1996;21:218–224.

132. Burke JG, Watson RW, McCormack D, Dowling FE, Walsh MG, Fitzpatrick JM. Spontaneous production of monocyte chemoattractant protein-1 and interleukin-8 by the human lumbar intervertebral disc. Spine 2002;27:1402–1407.

133. Yoshida M, Nakamura T, Sei A, Kikuchi T, Takagi K, Matsukawa A. Intervertebral disc cells produce tumor necrosis factor alpha, interleukin-1beta, and monocyte chemoattractant protein-1 immediately after herniation: an experimental study using a new hernia model. Spine 2005;30:55–61.

134. Kato T, Haro H, Komori H, Shinomiya K. Sequential dynamics of inflammatory cytokine, angiogenesis inducing factor and matrix degrading enzymes during spontaneous resorption of the herniated disc. J Orthop Res 2004;22:895–900.

135. Roberts S, Evans H, Menage J, et al. TNFalpha-stimulated gene product (TSG-6) and its binding protein, Ialphal, in the human intervertebral disc: new molecules for the disc. Eur Spine J 2005;14:36–42.

136. Grang L, Gaudin P, Trocme C, Phelip X, Morel F, Juvin R. Intervertebral disk degeneration and herniation: the role of metalloproteinases and cytokines. Joint Bone Spine 2001;68:547–553.

137. Liu J, Roughley PJ, Mort JS. Identification of human intervertebral disc stromelysin and its involvement in matrix degradation. J Orthop Res 1991;9:568–575.

138. Matsui Y, Maeda M, Nakagami W, Iwata H. The involvement of matrix metalloproteinases and inflammation in lumbar disc herniation. Spine 1998;23:863–868.

139. Kanemoto M, Hukuda S, Komiya Y, Katsuura A, Nishioka J. Immunohistochemical study of matrix metalloproteinase-3 and tissue inhibitor of metalloproteinase-1 human intervertebral discs. Spine 1996;21:1–8.

140. Haro H, Crawford HC, Fingleton B, et al. Matrix metalloproteinase-3-dependent generation of a macrophage chemoattractant in a model of herniated disc resorption. J Clin Invest 2000;105:133–141.

141. Karelina TV, Goldberg GI, Eisen AZ. Matrix metalloproteinases in blood vessel development in human fetal skin and in cutaneous tumors. J Invest Dermatol 1995;105:411–417.

142. Minamide A, Hashizume H, Yoshida M, Kawakami M, Hayashi N, Tamaki T. Effects of basic fibroblast growth factor on spontaneous resorption of herniated intervertebral discs: an experimental study in the rabbit. Spine 1999;24:940–945.

143. Haro H, Kato T, Komori H, Osada M, Shinomiya K. Vascular endothelial growth factor (VEGF)-induced angiogenesis in herniated disc resorption. J Orthop Res 2002;20:409–415.

144. Franson RC, Saal JS, Saal JA. Human disc phospholipase A2 is inflammatory. Spine 1992;17(6 suppl):S129–S132.

145. Saal JS, Franson RC, Dobrow R, Saal JA, White AH, Goldthwaite N. High levels of inflammatory phospholipase A2 activity in lumbar disc herniations. Spine 1990;15:674–678.

146. Saal JS. The role of inflammation in lumbar pain. Spine 1995;20:1821–1827.

147. Pruzanski W, Vadas P. Phospholipase A2—a mediator between proximal and distal effectors of inflammation. Immunol Today 1991;12:143–146.

148. Miyamoto H, Saura R, Doita M, Kurosaka M, Mizuno K. The role of cyclooxygenase-2 in lumbar disc herniation. Spine 2002;27:2477–2483.

149. Zelenka M, Schafers M, Sommer C. Intraneural injection of interleukin-1beta and tumor necrosis factor-alpha into rat sciatic nerve at physiological doses induces signs of neuropathic pain. Pain 2005;116:257–263.

150. Sox H, Stern S, Owens D, Abrams HL. Assessment of diagnostic technology in health care: rationale, methods, problems and directions. Washington, DC: National Academy Press, 1989.

151. Wiesel SW, Tsourmas N, Feffer HL, Citrin CM, Patronas N. A study of computer-assisted tomography. I. The incidence of positive CAT scans in an asymptomatic group of patients. Spine 1984;9:549–551.

152. Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects: a prospective investigation. J Bone Joint Surg Am 1990;72:403–408.

153. Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. N Engl J Med 1994;331:69–73.

154. Saal JA, Saal JS, Herzog RJ. The natural history of lumbar intervertebral disc extrusions treated nonoperatively. Spine 1990;15:683–686.

155. Modic MT, Ross JS, Obuchowski NA, Browning KH, Cianflocco AJ, Mazanec DJ. Contrast-enhanced MR imaging in acute lumbar radiculopathy: a pilot study of the natural history. Radiology 1995;195:429–435.

156. Modic MT, Obuchowski NA, Ross JS, et al. Acute low back pain and radiculopathy. Radiology 2005;237:597–604.

157. Benoist M. The natural history of lumbar degenerative spinal stenosis. Joint Bone Spine 2002;69:450–457.

158. Carragee EJ, Kim DH. A prospective analysis of magnetic resonance imaging findings in patients with sciatica and lumbar disc herniation: correlation of outcomes with disc fragment and canal morphology. Spine 1997;22:1650–1660.

159. Vital JM, Gille O, Pointillart V, et al. Course of Modic 1 6 months after lumbar posterior osteosynthesis. Spine 2003;28:715–720.

160. Weishaupt D, Zanetti M, Hodler J, et al. Painful lumbar disk derangement: relevance of endplate abnormalities at MR imaging. Radiology 2001;218:420–427.

161. Braithwaite I, White J, Saifuddin A, Renton P, Taylor BA. Vertebral end-plate (Modic) changes on lumbar spine MRI: correlation with pain reproduction at lumbar discography. Eur Spine J 1998;7:363–368.

162. Sandhu HS, Sanchez-Caso LP, Parvataneni HK, Cammisa FP Jr, Girardi FP, Ghelman B. Association between findings of provocative discography and vertebral endplate signal changes as seen on MRI. J Spinal Disord 2000;13:438–443.

163. Buttermann GR, Heithoff KB, Ogilvie JW, Transfeldt EE, Cohen M. Vertebral body MRI related to lumbar fusion results. Eur Spine J 1997;6:115–120.

N Engl J Med. 1994 Jul 14;331(2):69-73.

Magnetic resonance imaging of the lumbar spine in people without back pain.

Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS.

Hoag Memorial Hospital, Newport Beach, Calif. 92663.

Comment in:

N Engl J Med. 1994 Jul 14;331(2):115-6.
N Engl J Med. 1994 Dec 1;331(22):1526.
N Engl J Med. 1994 Dec 1;331(22):1525-6.
N Engl J Med. 1994 Dec 1;331(22):1525; author reply 1526.
N Engl J Med. 1994 Dec 1;331(22):1525.

BACKGROUND. The relation between abnormalities in the lumbar spine and low back pain is controversial. We examined the prevalence of abnormal findings on magnetic resonance imaging (MRI) scans of the lumbar spine in people without back pain. METHODS. We performed MRI examinations on 98 asymptomatic people. The scans were read independently by two neuroradiologists who did not know the clinical status of the subjects. To reduce the possibility of bias in interpreting the studies, abnormal MRI scans from 27 people with back pain were mixed randomly with the scans from the asymptomatic people. We used the following standardized terms to classify the five intervertebral disks in the lumbosacral spine: normal, bulge (circumferential symmetric extension of the disk beyond the interspace), protrusion (focal or asymmetric extension of the disk beyond the interspace), and extrusion (more extreme extension of the disk beyond the interspace). Nonintervertebral disk abnormalities, such as facet arthropathy, were also documented. RESULTS. Thirty-six percent of the 98 asymptomatic subjects had normal disks at all levels. With the results of the two readings averaged, 52 percent of the subjects had a bulge at at least one level, 27 percent had a protrusion, and 1 percent had an extrusion. Thirty-eight percent had an abnormality of more than one intervertebral disk. The prevalence of bulges, but not of protrusions, increased with age. The most common nonintervertebral disk abnormalities were Schmorl's nodes (herniation of the disk into the vertebral-body end plate), found in 19 percent of the subjects; annular defects (disruption of the outer fibrous ring of the disk), in 14 percent; and facet arthropathy (degenerative disease of the posterior articular processes of the vertebrae), in 8 percent. The findings were similar in men and women. CONCLUSIONS. On MRI examination of the lumbar spine, many people without back pain have disk bulges or protrusions but not extrusions. Given the high prevalence of these findings and of back pain, the discovery by MRI of bulges or protrusions in people with low back pain may frequently be coincidental.

PMID: 8208267 [PubMed - indexed for MEDLINE]

J Bone Joint Surg Am. 1995 Nov;77(11):1631-8.

Magnetic resonance imaging of the thoracic spine. Evaluation of asymptomatic individuals.

Wood KB, Garvey TA, Gundry C, Heithoff KB.

Department of Orthopaedic Surgery, University of Minnesota, Minneapolis 55407, USA.

We reviewed magnetic resonance imaging studies of the thoracic spines of ninety asymptomatic individuals to determine the prevalence of abnormal anatomical findings. This group included sixty individuals who had no history of any thoracic or lumbar pain and thirty individuals who had a history of low-back pain only. In addition, we reviewed imaging studies of eighteen patients who had an operatively proved herniation of a thoracic disc and studies of thirty-one patients who had been seen with thoracic pain. Sagittal T1-weighted spin-echo and axial multiplanar gradient refocused images at each disc level were interpreted by us (two neuroradiologists and two orthopaedic spine surgeons); we had no clinical information about the patients. Sixty-six (73 percent) of the ninety asymptomatic individuals had positive anatomical findings at one level or more. These findings included herniation of a disc in thirty-three subjects (37 percent), bulging of a disc in forty-eight (53 percent), an annular tear in fifty-two (58 percent), deformation of the spinal cord in twenty-six (29 percent), and Scheuermann end-plate irregularities or kyphosis in thirty-four (38 percent). This study documents the high prevalence of anatomical irregularities, including herniation of a disc and deformation of the spinal cord, on the magnetic resonance images of the thoracic spine in asymptomatic individuals. We emphasize that these findings represent roentgenographic abnormalities only, and any clinical decisions concerning the treatment of pain in the thoracic spine usually require additional studies.

PMID: 7593072 [PubMed - indexed for MEDLINE]

Eur Spine J. 1997;6(2):106-14.

The relationship between the magnetic resonance imaging appearance of the lumbar spine and low back pain, age and occupation in males.

Savage RA, Whitehouse GH, Roberts N.

Magnetic Resonance and Image Analysis Research Centre, University of Liverpool, UK.

The purpose of this study was to undertake a critical review of the potential role of magnetic resonance imaging (MRI) in the evaluation of low back pain (LBP) and to determine if there were differences in the MRI appearances between various occupational groups. The study group, 149 working men (78 aged 20-30 years and 71 aged 31-58 years) from five different occupations (car production workers, ambulance men, office staff, hospital porters and brewery draymen), underwent MRI of the lumbar spine. Thirty-four percent of the subjects had never experienced LBP. Twelve months later, the examination was repeated on 89 men. Age-related differences were seen in the MRI appearances of the lumbar spine. Disc degeneration was most common at L5/S1 and was significantly more prevalent ($P < 0.01$) in the older age group (52%) than in the younger age group (27%). Although LBP was more prevalent in the older subjects there was no relationship between LBP and disc degeneration. No differences in the MRI appearance of the lumbar spine were observed between the five occupational groups. Overall, 45% had 'abnormal' lumbar spines (evidence of disc degeneration, disc bulging or protrusion, facet hypertrophy, or nerve root compression). There was not a clear relationship between the MRI appearance of the lumbar spine and LBP. Thirty-two percent of asymptomatic subjects had 'abnormal' lumbar spines and 47% of all the subjects who had experienced LBP had 'normal' lumbar spines. During the 12-month follow-up period, 13 subjects experienced LBP for the first time. However, there was no change in the MRI appearances of their lumbar spines that could account for the onset of LBP. Although MRI is an excellent technique for evaluating the lumbar spine, this study shows that it does not provide a suitable pre-employment screening technique capable of identifying those at risk of LBP.

PMID: 9209878 [PubMed - indexed for MEDLINE]

J Bone Joint Surg Am. 2001 Sep;83-A(9):1306-11.

The value of magnetic resonance imaging of the lumbar spine to predict low-back pain in asymptomatic subjects : a seven-year follow-up study.

Borenstein DG, O'Mara JW Jr, Boden SD, Lauerman WC, Jacobson A, Platenberg C, Schellinger D, Wiesel SW.

Division of Rheumatology, George Washington University Medical Center, Washington, DC 20037, USA.

BACKGROUND: In 1989, a group of sixty-seven asymptomatic individuals with no history of back pain underwent magnetic resonance imaging of the lumbar spine. Twenty-one subjects (31%) had an identifiable abnormality of a disc or of the spinal canal. In the current study, we investigated whether the findings on the scans of the lumbar spine that had been made in 1989 predicted the development of low-back pain in these asymptomatic subjects. METHODS: A questionnaire concerning the development and duration of low-back pain over a seven-year period was sent to the sixty-seven asymptomatic individuals from the 1989 study. A total of fifty subjects completed and returned the questionnaire. A repeat magnetic resonance scan was made for thirty-one of these subjects. Two neuroradiologists and one orthopaedic spine surgeon interpreted the original and repeat scans in a blinded fashion, independent of clinical information. At each disc level, any radiographic abnormality, including bulging or degeneration of the disc, was identified. Radiographic progression was defined as increasing severity of an abnormality at a specific disc level or the involvement of additional levels. RESULTS: Of the fifty subjects who returned the questionnaire, twenty-nine (58%) had no back pain. Low-back pain developed in twenty-one subjects during the seven-year study period. The 1989 scans of these subjects demonstrated normal findings in twelve, a herniated disc in five, stenosis in three, and moderate disc degeneration in one. Eight individuals had radiating leg pain; four of them had had normal findings on the original scans, two had had spinal stenosis, one had had a disc protrusion, and one had had a disc extrusion. In general, repeat magnetic resonance imaging scans revealed a greater frequency of disc herniation, bulging, degeneration, and spinal stenosis than did the original scans. CONCLUSIONS: The findings on magnetic resonance scans were not predictive of the development or duration of low-back pain. Individuals with the longest duration of low-back pain did not have the greatest degree of anatomical abnormality on the original, 1989 scans. Clinical correlation is essential to determine the importance of abnormalities on magnetic resonance images.

PMID: 11568190 [PubMed - indexed for MEDLINE]