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SCIENTIFIC ARTICLE

Five-year development of lumbar disc degeneration—a prospective study

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Abstract

Objective To examine the impact of demographic, clinical, and genetic factors as well as herniated discs on 5-year development of disc degeneration in the lumbar spine, and to investigate associations between changes in lumbar degenerative findings and pain.

Materials and methods In 144 patients with lumbar radicular pain or low back pain, we scored disc degeneration, herniated discs, and high-intensity zones in the posterior annulus fibrosus on lumbar magnetic resonance imaging (MRI) at baseline and 5-year follow-up. Genotyping (TaqMan assay) was performed for genes encoding vitamin D receptor (VDR), collagen XIα (COL11A), matrix metalloproteinase 1/9 (MMP1/MMP9), and interleukin 1α/1RN (IL-1α/IL-1RN). Associations were analyzed using multivariate linear regression adjusted for age, sex, smoking, body mass index, and baseline scores for degenerated discs and herniated discs (when analyzing impact of baseline factors) or for pain (when analyzing associations with pain).

Results Progression of disc degeneration over 5 years was significantly ($p < 0.001$) related to higher age and less disc degeneration at baseline, but not to sex, smoking, body mass index, herniated discs, or variants in the studied genes. No associations were identified between changes in disc degeneration or high-intensity zones and pain at 5-year follow-up. However, increased number of herniated discs over 5 years was associated with pain at rest ($p = 0.019$).

Conclusions Age and disc degeneration at baseline, rather than genetic factors, influenced the 5-year development of disc degeneration in patients with lumbar radicular pain or low back pain. Development of herniated discs was related to pain at rest.

Keywords Lumbar spine · Disc degeneration · Herniated disc · High-intensity zone · Magnetic resonance imaging · Candidate gene polymorphisms

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Introduction

Despite the increasing incidence and substantial socioeconomic burden of chronic low back pain (LBP), the pathophysiology of back pain due to degenerative changes in the spine remains unclear [1, 2]. Magnetic resonance imaging (MRI) is commonly used to examine degeneration of the spine [3]. MRI findings such as disc degeneration (DD), herniated discs, disc bulges, high-intensity zones (HIZ), and Modic changes have been suggested to promote pain. Especially, there is evidence for an association between LBP conditions and DD [4, 5].

Progression of DD may be influenced by genetic factors, i.e., genetic variability, environmental factors such as high repetitive mechanical loading, twisting of the trunk, postural stresses, as well as life style factors like smoking and obesity [6–8]. Twin studies suggest that heredity may play a more

important role in DD than environmental factors [9]. Since DD involves dehydration, fragmentation of collagens and development of annular tears, all genes involved in the breakdown of the extracellular matrix (such as genes encoding collagen and matrix metalloproteinases) are relevant to study for an effect on DD [10]. Vitamin D receptor (VDR) gene polymorphism contributes to suboptimal disc structure that is prone to early DD [11]. Inflammatory genes, including genes encoding interleukins (ILs), may be associated with predisposition for DD, herniated disc, and lumbar radicular pain [12]. Demographic factors such as gender and age, and anatomical factors such as the degree of lumbar lordosis [13] can also be involved in degeneration of the spine. Lumbar DD increases with age, however, and the physiological process of aging should be distinguished from pathological degeneration [14].

The pathogenesis of DD represents a multifaceted chronic process that alters the structure and function of intervertebral discs [11, 14]. However, the development of degenerative lumbar MRI findings over time, and its relevance for pain, is poorly understood. Therefore, the aim of the present study was (a) to examine the impact of demographic, clinical, and genetic factors as well as herniated discs on 5-year development of DD in the lumbar spine, and (b) to investigate associations between changes in lumbar degenerative findings and pain.

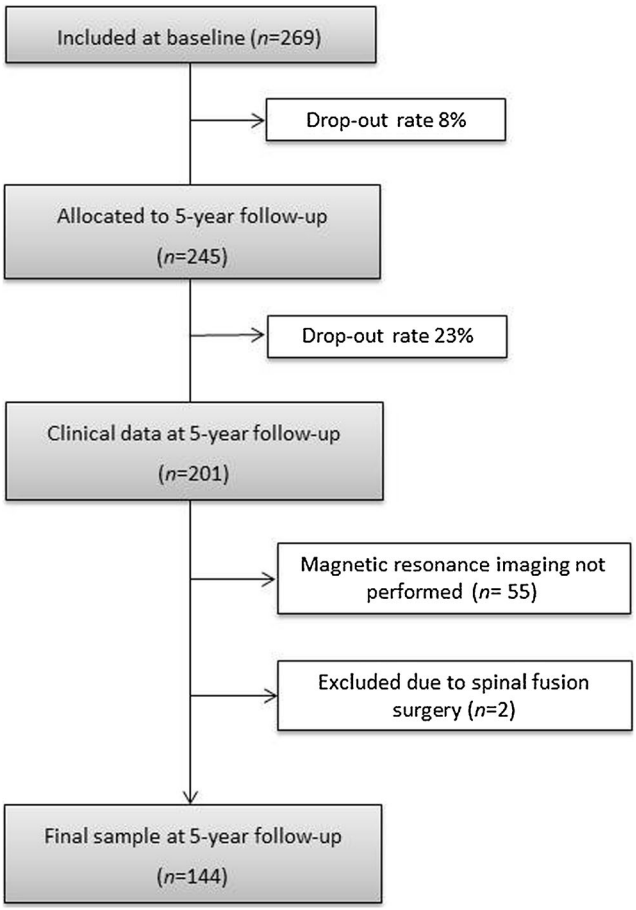

Fig. 1 Flow diagram of study population

Materials and methods

The study was conducted in accordance with the Helsinki Declaration and approved by the Regional Committee for Medical Research Ethics (reference number 2014/1754). All participants provided their written informed consent at baseline and at 5-year follow-up.

Study population

A total of 269 patients with lumbar radicular pain ($n = 121$) or LBP ($n = 148$) were recruited at the outpatient clinic at Oslo University Hospital (OUH) Ulleval in a prospective study. The patients with lumbar radicular pain caused by herniated discs were originally recruited from 2007 to 2009, whereas patients with LBP were recruited to another original prospective study between 2009 and 2011. The drop-out rate was 8%, and 245 patients were allocated to the follow-up assessment, of whom 201 patients attended to a 5-year follow-up. However, because of MRI drop-outs ($n = 55$) and exclusions due to spinal fusion surgery ($n = 2$), the present analyses included 144 patients (75 had radicular pain, 69 had LBP) (Fig. 1). More than half of the 144 patients (76; 53%) were men. The mean age of the study participants was 47 (range, 24–64) years for men and 46 (range, 28–64) years for women. Baseline data from the original studies on these patients have been published before [15, 16].

The inclusion criteria for patients with radicular pain were age between 18 and 60 years, herniated disc on lumbar MRI corresponding to the pain, and a positive straight leg raising test. The specific exclusion criteria for this cohort were symptomatic lumbar spinal stenosis, previous spinal surgery for a herniated disc at the same level or lumbar fusion at any level, recent surgery (within 1 month), and non-European-Caucasian ethnicity. MRI was performed on all of the 121 radicular pain patients at baseline and 77 of the patients at 5 years, of whom two patients were excluded due to spinal fusion surgery and 75 were included in this study.

The inclusion criteria for patients with LBP were age between 18 and 60 years, persisting LBP (> 3 months), as well as patients had to be employed and have a sick leave duration between 4 weeks and 12 months. The specific exclusion criteria for the LBP cohort were lumbar radiculopathy requiring surgical treatment; cardiac, pulmonary, or metabolic disease with functional restrictions; and legal labor disputes. The exclusion criteria common for both cohorts were cauda equine syndrome, symptomatic spinal deformities, osteoporosis with fractures, diabetic polyneuropathy, cancer, cardiovascular

disease (NYHA class III and IV), inflammatory rheumatic disease, generalized musculoskeletal pain, psychiatric disease, drug misuse or alcoholism, pregnancy, and insufficient Norwegian language skills. In total, 148 LBP patients were included. Among the LBP patients allocated to 5-year follow-up, 97 (71%) had baseline MRI and 69 had both baseline and 5-year MRI and were included in this study.

Clinical procedures and outcome measures

All patients underwent a standardized clinical examination with assessment of straight leg raising test, reflexes, sensory and motor function in the lower limbs, at baseline and 5-year follow-up. Furthermore, age, sex, weight, height, education level, and smoking habits were registered. Body mass index was calculated using the formula weight/height^2 (kg/m^2). Pain-related functional disability was reported using the validated Norwegian version of the Oswestry Disability Index (scale, 0–100%; 0% = no disability, 100% = very severe disability) [17].

Intensity of LBP and/or leg pain during activity and at rest during the past week was reported on a visual analogue scale (VAS) with anchor values from 0 (no pain) to 10 (worst possible pain). The Hopkins symptoms check list, a 10-item questionnaire, was used to screen for symptoms of anxiety and depression, and scores ≥ 1.85 indicated emotional distress symptoms [18]. Pain scores and emotional distress were registered at baseline and at 5-year follow-up.

Candidate genes selection and genotyping

Based on potential biologic relevance for DD, we studied the genes encoding vitamin D receptor (VDR), collagen XIα (COL11A), matrix metalloproteinase 1/9 (MMP1 / MMP9) and interleukin 1α/1RN (IL-1α / IL-1RN) [11, 19]. In the radicular pain cohort, genomic DNA was extracted from blood using a FlexiGene DNA isolation kit (Qiagen). However, in the LBP cohort, the genomic DNA was extracted from saliva using the more modern Oragene DNA sample collection kit (DNA Genotek Inc.) instead. Single-nucleotide polymorphism (SNP) is a variation in a single nucleotide that occurs at a specific position in the genome. SNPs result in a substitution of one base with another in the DNA, which can have important functional effects. We examined six SNPs possibly relevant for DD (Table 1). SNP genotyping was carried out using predesigned TaqMan assays (a common methodological approach to perform analysis of genetic variation). Genotypes were determined using the SDS 2.2 software (Applied Biosystems). Approximately 10% of the samples were re-genotyped and the concordance rate was 100%.

Imaging technique

Lumbar 1.5-T MRI was performed at 5-year follow-up from April 2014 to March 2016. This MRI included sagittal T2-weighted fast spin-echo (FSE) (repetition time (TR)/echo time (TE), 2376–4280 ms/88–121 ms) or (in one patient) 3-D turbo spin echo (SPACE) images (TR/TE, 1500 ms/251 ms), sagittal T1-weighted spin-echo images (TR/TE, 400–720 ms/7–14 ms) and axial T2-weighted images of the L3/L4, L4/L5, and L5/S1 levels (TR/TE, 2209–6040 ms/93–124 ms). Baseline lumbar MRI (1.0–3.0 T, 1.5 T in > 85% of the cases) included sagittal T2-weighted FSE (TR/TE, 2300–4500 ms/80–125 ms) or (in ten patients) SPACE images (TR/TE, 1100 ms/124 ms), sagittal T1-weighted spin-echo (TR/TE, 400–750 ms/9–15 ms) or (in 13 patients) fast fluid-attenuated inversion-recovery images (TR/TE, 1989–2000 ms/20 ms), and axial T2-weighted images of the L3/L4, L4/L5, and L5/S1 levels (TR/TE, 3000–7140 ms/90–131 ms). For this study, all MRIs were de-identified.

Imaging evaluation

A radiologist (> 15 years of experience in musculoskeletal radiology) and a physician specialist in physical medicine and rehabilitation (10 years of clinical experience in spinal MRI) independently graded DD and the presence of HIZ at baseline and at 5-year follow-up, by comparing initial and follow-up MRIs. The observers had both assessed spine MRIs in previous research studies, and they performed a pilot study before evaluating MRIs for the present study. Both observers were blinded to clinical data. In all cases of disagreement, they negotiated a consensus score. The physical medicine specialist evaluated the presence of herniated discs at baseline and at 5-year follow-up with the routine radiology report available, to avoid overlooking some reported herniated discs that might be difficult to diagnose.

DD was graded on midsagittal T2-weighted images at each of the five disc levels (L1–S1) using Schneiderman's grading system [20]: a score of 0 indicated no signal change, a score of 1 indicated a slight decrease in signal intensity in the nucleus pulposus, a score of 2 indicated a generalized hypointense nucleus, and a score of 3 indicated a hypointense nucleus with disc space narrowing (Fig. 2). Thus, the score for each disc level ranged from 0 to 3. A summary DD score (0–15) was produced by summing the DD grades for five lumbar discs at baseline and at 5-year follow-up, respectively. For graphical presentation of DD in Fig. 3, we grouped DD at baseline and at 5 years according to Jim [21] into severe (two or more grade 3 discs, three or more grade 2 discs, or one grade 3 and two grade 2 discs), moderate (one grade 3 disc or two grade 2 discs), mild (only one grade 2 disc and no grade 3 discs), or normal (total DD score of 0 or 1). HIZ was evaluated on T2-weighted images as present or not present at each disc level,

Table 1 Genetic variants tested

Candidate gene	Gene name	rs number[a]	Base substitution[b]	Amino acid substitution[c]
VDR	Vitamin D receptor	rs731236	A > G	–
COL 11A	Collagen XI α	rs1676486	T > C	Ser1535Pro
MMP1	Matrix metallo-proteinase 1	rs1792750	1G > 2G	–
MMP9	Matrix metallo-proteinase 9	rs17576	A > G	Gln279Arg
IL-1α	Interleukin 1α	rs1800587	C > T	–
IL-1RN	Interleukin 1 receptor antagonist	rs2234677	G > A	–

[a] The rs numbers (reference SNP cluster ID) refers to the specific single-nucleotide polymorphisms (SNPs) tested. The rs number nomenclature was created by the National Center for Biotechnology Information (NCBI) in 1998

[b] A base substitution refers to the replacement of one base with another in the DNA (*A* Adenine, *G* Guanine, *T* Thymine, *C* Cytosine)

[c] An amino acid substitution indicates that the base substitution lead to an amino acid substitution (*Ser* Serine, *Pro* Proline, *Gln* Glutamine, *Arg* Arginine). Two of the six SNPs caused an amino acid substitution

and was defined as a zone in the posterior annulus fibrosus that was brighter than the nucleus pulposus and was surrounded superiorly, inferiorly, and anteriorly by the low-intensity signal of the annulus fibrosus [22]. Herniated disc was assessed at each disc level and was noted as present only if there was focal protrusion, involving less than 25% of the circumference of the disc, or extrusion (with or without or sequestration) of the disc [23]. Neither symmetric bulging disc, asymmetric bulging of disc tissue greater than 25% of the disc circumference, nor Schmorl nodes were recorded as herniated disc in this study. At levels L1/L2 and L2/L3 (not routinely imaged in the axial plane), herniated disc was diagnosed based on added axial images of the relevant level or on convincing sagittal plane findings.

The radiologist assessed all MRIs on a clinical picture archiving and communication system (PACS) unit using Agfa Impax 6.5 (Agfa HealthCare, Mortsel, Belgium) software. The other observer used a dedicated personal computer at the clinic. For decision-making in all cases of disagreement, the PACS unit was used. The two observers' independent MRI evaluations were assessed for inter-observer agreement using the kappa statistic [24].

Outcome measures

The primary outcome measure in this study was DD change, defined as the total DD score at 5-year follow-up minus the total DD score at baseline. A positive value for DD change

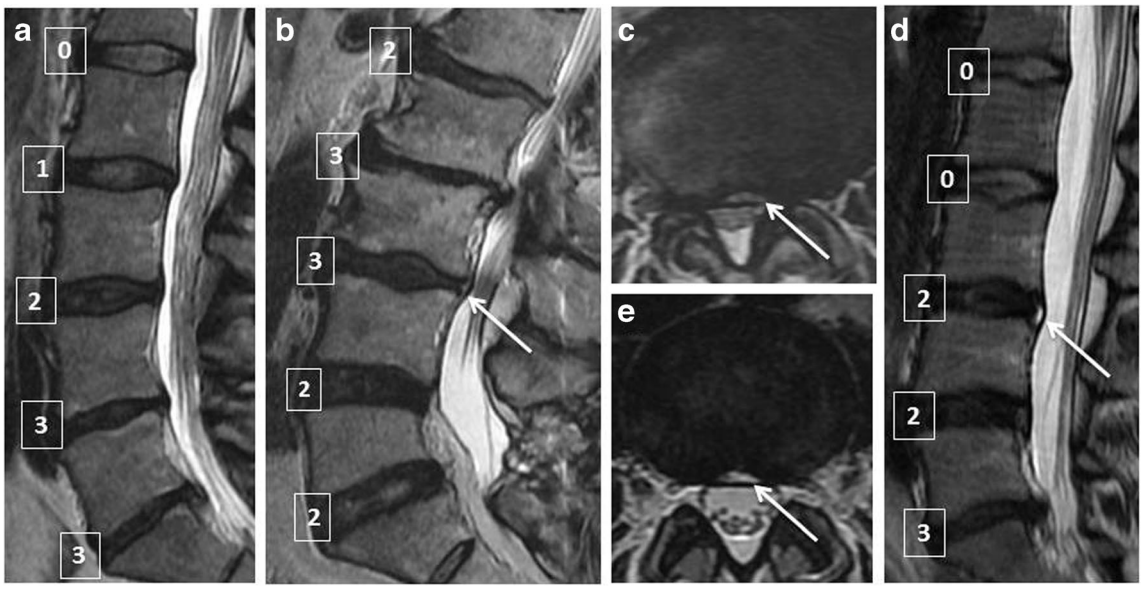

Fig. 2 Disc degeneration (DD). **a**, **b**, **d** Sagittal T2-weighted MRI images at 5-year follow-up showing DD grades according to Schneiderman's grading system (*numbers*) in **a** patient 1, a 38-year-old woman with lumbar radicular pain; **b** patient 2, a 63-year-old man with low back pain, and **d** patient 3, a 31-year-old woman with lumbar radicular pain. The high-intensity zone (HIZ) (*arrows*) is present in patients 2 and 3, and visible also on axial T2-weighted MRI (**c** and **e**, respectively)

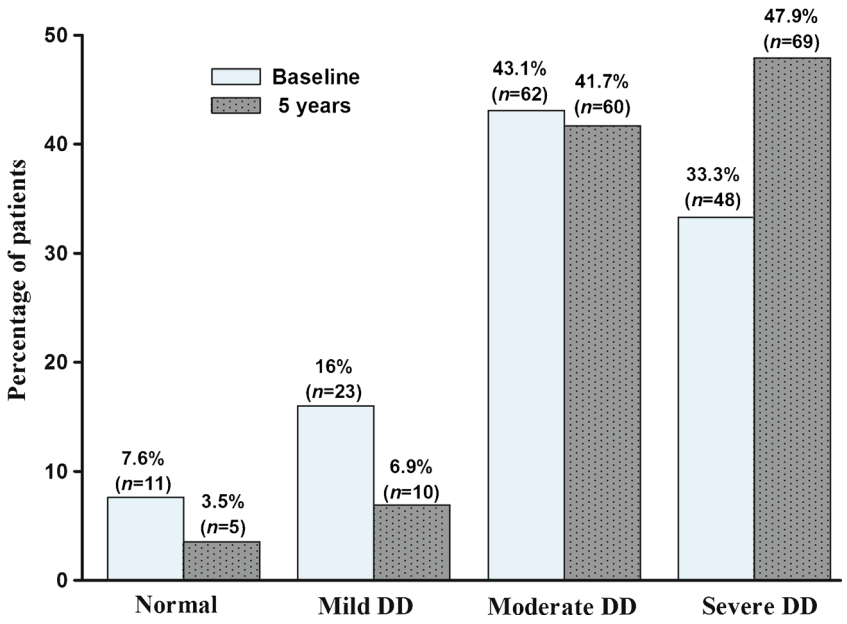

Fig. 3 Distribution of disc degeneration (DD) grades in study sample and the development of DD during 5 years

indicated DD progression during 5 years. In secondary analyses, we used VAS for pain at 5-year follow-up for evaluation of the relationship between changes in MRI findings and pain.

Statistical analysis

Continuous data are described as means and standard deviations (SD), or medians and interquartile ranges (IQR), as appropriate. Group differences were examined by parametric Student's *t* test or non-parametric Wilcoxon Mann–Whitney test, depending on data distribution. Categorical data are described as number of patients and percentages, tested with Chi-squared test for independence. Complete data at baseline and 5-year follow-up were obtained from 95.8 and 98.6% of study participants, with a few missing data coming from the Hopkins symptoms check list and self-reported smoking habits.

Univariate linear regression analysis was performed to estimate the association between six genetic variants (VDR, COL11A, MMP1, MMP9, IL-1α, and IL-1RN) and the primary outcome measure – the DD change (continuous). Due to skew distribution of minor (rare) versus major alleles, we analyzed "tri-allelic" genotypes in a dichotomized "bi-allelic" manner (homozygote rare allele and heterozygote allele vs. homozygote major allele).

Multivariate linear regression analyses were performed in a block-wise manner: First, genetic factors with p values < 0.1 from univariate regression were entered as a predictor in block 1. Subsequently, demographic and lifestyle factors; age, sex, smoking (yes/no), and body mass index (continuous) were added in block 2. The final multivariate linear regression model was adjusted for the total DD score (continuous) and herniated discs (yes/no) at baseline (step 3). All variables were kept through three steps of regression model, using the enter method.

Furthermore, the relationship between changes in MRI findings and the VAS for pain at rest at 5 years was analyzed using multivariate linear regression analysis. In a stepwise manner, the MRI covariates DD change (continuous), herniated disc change (continuous), and HIZ change (continuous) were included in step 1 of the linear regression analysis, adjusted for the baseline value of the VAS at rest. Herniated disc change and HIZ change were defined as the number of disc levels with herniated disc and HIZ at 5-year follow-up minus the number of disc levels with herniated disc and HIZ at baseline. A higher value for change indicates that more disc levels show herniated disc or HIZ at 5-year follow-up compared to baseline. In step 2, age, sex, smoking (yes/no), body mass index (continuous), and Hopkins symptoms check list score (< 1.85 or ≥ 1.85) at baseline were included in the final model. Post hoc, we also analyzed the relationship between changes in MRI findings and the VAS change over 5 years using multivariate linear regression analysis, adjusted for the baseline value of the VAS at rest.

All statistical analyses were performed with advice from a statistician and using the SPSS version 24 (SPSS, Chicago, IL, USA) statistical package. A p value < 0.05 was considered statistically significant in this explorative study.

Results

Grades of disc degeneration in the study population

In total, 720 lumbar discs at five lumbar levels were analyzed at baseline and 5-year follow-up in 144 patients with lumbar

radicular pain or LBP. Figure 3 illustrates the distribution of DD grades, classified according to Jim [21]. Only 11 patients (7.6%) had no DD at baseline and were assigned as DD- (normal). All others were considered as DD+, and were divided into mild, moderate, and severe groups. A total of 110 patients (76.4%) had moderate or severe DD at baseline, compared to 129 patients (89.6%) at 5-year follow-up.

Baseline characteristics of the 144 patients in the study are shown in Table 2. Lumbar herniated disc was present in 112 patients (77.8%) at baseline. Patients with and without disc herniation had similar age, sex, smoking status, and prevalence of HIZ. There were more DD+ patients among those having herniated disc, but no clear statistical difference in DD scores between DD+ patients with or without herniated disc was observed.

Inter-observer agreement

A linearly weighted kappa (κ) coefficient was used to determine the agreement between the two observers at each disc level for DD score (0–3) and HIZ (yes/no) at 5-year follow-up. The agreement was interpreted as follows: poor, $\kappa \leq 0.20$; fair, $\kappa = 0.21$–0.40; moderate, $\kappa = 0.41$–0.60; good, $\kappa = 0.61$–0.80; and excellent, $\kappa = 0.81$–1.00 [25]. The inter-observer agreement (Table 3) was excellent for DD score at all disc levels (κ, 0.81–0.92) and for HIZ at L3/L4 (κ, 0.82), good for HIZ at L4/L5 and L5/S1, and moderate for HIZ at L2/L3 (κ, 0.48).

Impact of baseline factors on change in disc degeneration over 5 years

In total, 85 patients (59%) had increased DD at 5 years. The remaining 59 patients (41%) had unchanged DD. However, there was no significant association between DD change (increased vs. unchanged) during 5 years and the presence of herniated disc at baseline ($p = 0.07$).

Univariate linear regression analysis of six genetic variants in the genes encoding vitamin D receptor (VDR), collagen XIα (COL11A), matrix metalloproteinase 1/9 (MMP1 / MMP9), and interleukin 1α/1RN (IL-1α / IL-1RN) (Table 1) as predictors for DD change, revealed no genetic impact on development of DD during 5 years. Multivariate linear regression analysis including demographic, lifestyle-related and radiological factors, showed no significant association between DD change and genetic variability ($p > 0.197$, B range − 0.52 to 0.64). Higher age ($p < 0.001$, B range 0.03 to 0.07 for the six genes) and lower baseline DD score ($p < 0.001$, B range − 0.32 to − 0.13 for the six genes) were significantly associated with DD progression. Sex, smoking status, and body mass index had no significant impact on 5-year DD development.

Relationship between change in degenerative findings and pain after 5 years

Increased number of herniated discs over 5 years was associated with high VAS score for pain at rest at 5-year follow-up (B = 0.44, 95% CI 0.07–0.81, $p = 0.019$). This pain score was also related to baseline scores for anxiety and depression (B = 1.03, 95% CI 0.20–1.86, $p = 0.016$) and pain at rest (B = 0.28, 95% CI 0.11–0.45, $p = 0.002$). No associations between changes in DD or HIZ during 5 years and pain scores at 5-year follow-up were identified. Results were principally unchanged in a post hoc multivariate linear regression analysis, performed with change in VAS pain score over 5 years as dependent variable in the model.

Discussion

The present study underscores the age-related development of lumbar DD. Higher age and less baseline DD, but not the studied genetic factors, were significantly related to progression of DD. Increased number of herniated discs over 5 years was associated with pain in rest at 5 years, whereas changes in DD or HIZ over 5 years were not related to pain at 5-year follow-up.

In our study sample, 85 patients (59%) had increased lumbar DD at 5 years. Similarly, 52.0% of men and 60.4% of women in a previous population-based study had progression of lumbar DD over 4 years [26]. About 20% of teenagers have mild DD. DD increases steeply with age, and about 10% of 50-year-old discs and 60% of 70-year-old discs are severely degenerated [27]. Despite increasing DD with higher age, progression in DD is less in patients with later-stage DD, where the disc height is already reduced and the hydrostatic nucleus is lost. In line with this, we found that less baseline DD predicted increased DD over 5 years. In a population-based study, aging was a risk factor for the incidence, but not for the progression, of lumbar DD [26]; however, our results were that higher age was related to progression of DD in the selected symptomatic cohort.

The current study revealed no significant association between DD change and genes assumed to be involved in degenerative processes (VDR, COL11A, MMP1, MMP9, IL-1α, and IL-1RN). Genetic influence on the persistence of LBP with or without radicular symptoms is represented by structural genes for matrix (COL11A), catabolic genes (MMPs), bone mineralization and remodeling gene (VDR), and inflammatory genes (ILs). A systematic review highlighted that several genetic variants including MMP1, IL1α, and IL1RN may predict slow recovery of lumbar radicular pain [19]. In a previous study, we found that the rare allele of MMP9 rs17576 was associated with poor pain recovery [28]. Hence, the relationship between recovery of pain and

Table 2 Baseline characteristics of total study population grouped by the presence of herniated discs

	Herniated disc ($n = 112$)	No herniated disc ($n = 32$)	p value
Age (years), median (IQR)	43.0 (15)	42.5 (13)	$p = 0.870$[a]
Sex (men), *n* (%)	54 (48.2)	22 (68.8)	$p = 0.064$[b]
Smoking status (smokers), *n (%)*	30 (27.0)	11 (35.5)	$p = 0.487$[b]
Emotional distress, *n (%)*			
Hopkins symptom check list-10 ≥ 1.85	48 (44.4)	20 (64.5)	$p = 0.077$[b]
Pain intensity (VAS), mean (SD)			
at rest	4.0 (2.5)	5.1 (2.2)	**$p = 0.025$**[c]
during activity	5.6 (2.7)	6.8 (1.9)	**$p = 0.034$**[c]
Function, *mean (SD)*			
Oswestry Disability Index (0–100)	34.5 (15.7)	38.0 (11.1)	$p = 0.157$[a]
DD grouped by Jim [21], *n (%)*			
normal	3 (2.7)	8 (25.0)	**$p < 0.001$**[b]
mild	21 (18.8)	2 (6.3)	$p = 0.153$[b]
moderate	49 (43.8)	13 (40.6)	$p = 0.910$[b]
severe	39 (34.8)	9 (28.1)	$p = 0.620$[b]
HIZ, *n (%)*	43 (38.4)	11 (34.4)	$p = 0.836$[b]

IQR interquartile range, *n* number, *VAS* visual analogue scale 0–10, *SD* standard deviation, *DD* disc degeneration, *HIZ* high-intensity zone

Bold type indicates statistical significance ($p < 0.05$)

[a] Student's *t* test

[b] Chi-squared test for independence

[c] Mann–Whitney *U* test

[21] J. J. Jim et al. Spine (2005)

MMP9 might be independent of DD. To the best of our knowledge, candidate gene studies have detected only a small number of convincing associations of genetic variants with lumbar DD. A previous review investigated cumulative genetic association evidence, and showed weak evidence level for most of the associations between genetic markers and lumbar DD and moderate level of evidence for COL11A1 and MMP9 (rs17576) [29]. Clear definition of DD phenotypes and large population-based cohorts of persons with and without back pain and of different ethnicity are needed for advances in understanding of the role of genetic factors in the development of DD.

In our study, increased DD was not related to pain at 5-year follow-up. As known, many asymptomatic individuals have DD. Moreover, older people can have severe DD without pain. Notably, the age-related changes that occur in DD are similar to those observed in articular cartilage and are not necessarily related to pain [30]. Weak associations between MRI findings and symptom outcomes at 3-year follow-up have been previously reported in patients with LBP or radicular symptoms [31]. The association of DD with back pain has been believed to be clinically important. However, identification of the direct sources of pain in LBP patients has been difficult. Not least, psychosocial factors may influence the severity and chronicity of LBP [32]. In line with this, the present data showed that emotional distress at baseline had significant influence on pain in rest at 5-year follow-up.

Strengths of our study include strict inclusion criteria and long (5-year) follow-up. The inter-observer kappa values were high, indicating reliable MRI findings. Changes in MRI findings were rated by direct comparison of images, which improves reliability [33] and may reduce errors in rating of changes due to ambiguous findings or slight differences in MRI technique.

The current study also has some weaknesses. First, we lacked a matched group of back pain-free individuals with spinal MRI and could not compare DD change between patients and healthy subjects. Second, the study was limited to European Caucasians. The findings may not apply to other ethnicities. Third, a high number of patients had DD and herniated disc at baseline. Hence, we cannot exclude that herniated disc may predict DD change in a healthy cohort. Fourth, Schneiderman's system for grading DD does not distinguish between different degrees of disc height reduction, so we did not note further reductions of already low discs as increased DD. Fifth, only one non-radiologist evaluated herniated discs. We did not assess the interobserver reliability of this evaluation, and the routine radiology report may have biased the

Table 3 Inter-observer agreement on magnetic resonance imaging (MRI) findings

MRI finding	Inter-observer agreement	
	Kappa[a]	95% CI
Disc degeneration (DD) (four ordered categories 0–3)		
L5/S1	0.83	0.75–0.90
L4/L5	0.92	0.87–0.97
L3/L4	0.84	0.78–0.90
L2/L3	0.83	0.76–0.90
L1/L2	0.81	0.72–0.90
High-intensity zone (HIZ) (two categories 0–1)		
L5/S1	0.73	0.59–0.88
L4/L5	0.72	0.59–0.85
L3/L4	0.82	0.70–0.95
L2/L3	0.48	0.12–0.83

[a] Linearly weighted kappa; kappa values concern agreement between two observers evaluating disc degeneration (DD) and high-intensity zone (HIZ) on MRI of 144 patients; to ensure interpretable kappa values, kappa is not given for HIZ at L1/L2, as < 10% of patients had HIZ at this level [24]. Agreement beyond chance was interpreted according to the guidelines of Landis and Koch as follows: poor, $\kappa \leq 0.20$; fair, $\kappa = 0.21–0.40$; moderate, $\kappa = 0.41–0.60$; good, $\kappa = 0.61–0.80$; and excellent, $\kappa = 0.81–1.00$

[24] Sim J et al. Phys Ther. 2005

evaluation to some degree. Furthermore, we examined variants of only six genes. The development of a genetic risk score, which might predict DD progression, should be considered in future research. Finally, participants enrolled in the LBP study were required to be on employment sick leave, so there may be an inherent bias toward malingerers.

In conclusion, this study indicated that age and DD at baseline, rather than the studied genetic factors, are associated with DD progression over 5 years in patients with lumbar radicular pain or LBP. Increased number of herniated discs over 5 years, but not changes in DD or HIZ, was related to pain at 5-year follow-up. The study also re-demonstrated that ~ 60% of people have DD progression over 5 years and that pain levels are related to anxiety and depression.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Disclosures The authors declare that there are no competing interests regarding the publication of this paper.

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