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Osteophyte Formation in the Lumbar Spine and Relevance to Low Back Pain

Yoshihito Sakai

*Department of Orthopaedic Surgery
National Center for Geriatrics and Gerontology
Japan*

1. Introduction

Vertebral osteophyte formation is a well-documented phenomenon that is associated with degeneration and altered mechanics of the spine, both of which have been considered to be the result of aging, a purely physiologic response to load bearing, or intrinsic spinal disease as etiologic factors. (Lane et al., 1993, O'Neill et al., 1999) They are recognized radiologically as hyperostosis at the region of the attachment of the annular fibers to the vertebral body and localized increases in bone mineral density. (Nathan et al., 1994) As the etiologic factors, the compressive forces on the vertebral endplates (Nathan et al., 1962), bone mineral density (Kinoshita et al., 1998), obesity (O'Neill et al., 1999) and genetic factors (Sambrook et al., 1999) have been reported as causes, although the absence of a single definitive factor causing spinal degeneration has led to a suggestion that several factors including both genetic and nongenetic ones contribute to the development of osteophyte formation. (Harada et al., 1998, Liu et al., 1997)

On the other hand, low back pain (LBP) is one of the most common musculoskeletal disorders of the elderly, of which risk factor seems to be related to lumbar disc degeneration. (van Tulder et al., 1997) While data from many studies suggest an association with lumbar disc degeneration and LBP (Lawrence, 1969, Simmons et al., 1991, Jayson, 1994), asymptomatic lumbar disc degeneration is common (Powell et al., 1986, Borenstein et al., 2001), and the correlation between LBP and disc degeneration observed in radiographs is only moderate or poor (Witt et al., 1984). Osteophyte formation in the lumbar spine is a characteristic feature of intervertebral disc degeneration, however, the relationship between osteophytes and LBP is less clear (van Tulder et al., 1997). Simmons et al. reported that osteophytes were no more common among women with recurrent back pain compared to those without (Simmons et al., 1991), while O'Neill et al. concluded that osteophytes affecting the lumbar spine are associated with LBP in men (O'Neill et al., 1999). Meanwhile, we often encounter prominent osteophytes in the absence of intervertebral disc degeneration as supporting a lack of association between the two factors reported by Oishi *et al* (Oishi et al, 2003). They concluded intervertebral disc degeneration and osteophyte formation of the vertebral bodies seemed to represent different factors affecting the lumbar spine. Thus, there are some doubts as to the relationship between osteophyte formation and disc degeneration. We investigated the factors influencing osteophyte formation of the

lumbar spine without disc degeneration and estimate the implications of osteophytes from the viewpoint of LBP and gene polymorphism.

2. Methods

2.1 Study subjects

The subjects consisted of Japanese volunteers who attended “a basic health checkup” supported by a local government. A total of 387 elderly persons from 60 to 81 years (average 68.0 ± 6.4 years, 153 males, 234 females), most of whom were engaged in farming and fishing, were invited to participate in the study with a written informed consent form as well as a sheet describing the study outline. Patients with rheumatoid arthritis, vertebral fracture, or disorders known to affect bone metabolism, including diabetes mellitus and other endocrinologic diseases were excluded from this study.

2.2 Evaluation of chronic LBP

Two spine surgeons performed a brief interview including visual analogue scale (VAS) for low back pain (0-100) and physical examination regarding LBP after taking blood samples and radiograms of the lumbar spine. LBP was defined as more than 20 in VAS and lasting for recent 3 months. Body weight, height, body mass index (BMI), body fat ratio, bone stiffness (QUS), back muscle strength, smoking status and alcohol intake were evaluated. Bone stiffness was measured with a quantitative ultrasound (QUS) densitometry device (A-1000PlusII; LUNAR, WI, USA) to calculate the Stiffness Index on the calcaneus recognized by the American Food and Drug Administration (FDA) and which has become the world standard. Back muscle strength was determined as the maximal isometric strength of the trunk muscles in standing posture with 30° lumbar flexion using a digital back muscle strength meter (T.K.K.5402, TAKEI Co., Japan).

2.3 Radiographic evaluation

The participants were instructed to stand on both feet shoulder-width apart while maintaining a level gaze. Film-focus distance was unified at 150 cm, and a film was correctly put along a gravity plum line. According to Miyakoshi (Miyakoshi et al., 2003), the degree of disc height narrowing was scored as 0 (0-20% reduction in disc height, as compared with the L1/2 disc), 1 (20-50% reduction), or 2 (more than a 50% reduction), and the total score from the L2/3 to the L5/S1 disc was defined as the disc score. The disc score of 0 was defined as “no disc degeneration”. Osteophyte formation was assessed according to Nathan’s classification (0-4) (Nathan et al., 1962), and a total number from L1/2 to L5/S1 (Osteophyte score) of more than 6 was defined as osteophyte (+).

2.4 Classification of osteophyte formation

The cases with osteophyte formation were classified by the presence of disc height narrowing into two groups: Group A; osteophyte (+) with disc height narrowing, Group B; osteophyte (+) without disc height narrowing. Group C was defined as the cases without osteophyte formation.

2.5 Selected polymorphisms

The gene polymorphism examinations were conducted in accordance with "Ethical Guidelines for Human Genome and Gene Research" (approved: March 29, 2001, implemented: April 1, 2001), with adequate explanation provided to the subjects. The genotypes of the alcohol sensitivity related polymorphisms (alcohol dehydrogenase 2 (ADH2 Arg47His), aldehyde dehydrogenase 2 (ALDH2 Glu487Lys)), tobacco sensitivity related polymorphisms (NADH quinone oxidoreductase 1 (NQO1 C609T), glutathione S transferase M1 (GSTM1), glutathione S transferase T1 (GSTT1)), inflammation related polymorphisms (interleukin 1 β (IL-1B), tumor necrosis factor α (TNF-A)), longevity-associated polymorphism of mitochondrial DNA (mt5179), allergy-associated polymorphism of interleukin-4 (IL-4), immunity-associated polymorphism of CD14, vitamin D receptor (VDR) and transforming growth factor β (TGFB1) were characterized by a polymerase chain reaction with the confronting two-pair primers (PCR-CTPP) method (Hamajima et al., 2000). This is a new genotyping method invented independently, recently found to be based on the same logic as bi-directional PCR amplification of specific alleles. Twenty-eight subjects were excluded because of inadequate blood samples. A total of 197 subjects in group A, 93 in group B and 65 in group C were recruited for the polymorphism study. To characterize the features of osteophyte formation without disc degeneration, group B was compared with combined groups A and C (n=262).

3. Results

Disc height narrowing and presence of osteophytes were observed in 245 cases (63.3%) and 316 cases (81.6%), respectively. Vacuum phenomenon and degenerative spondylolithesis were seen in 107 cases (27.6%) and 73 cases (18.9%), respectively. Osteophyte formation and vacuum phenomenon were significantly seen in elderly person. ($p < 0.01$) (Fig.1) Whereas disc height narrowing was almost seen in L4/5 and L5/s1, osteophyte formation was extensively presented from L1/2 to L5/s1.

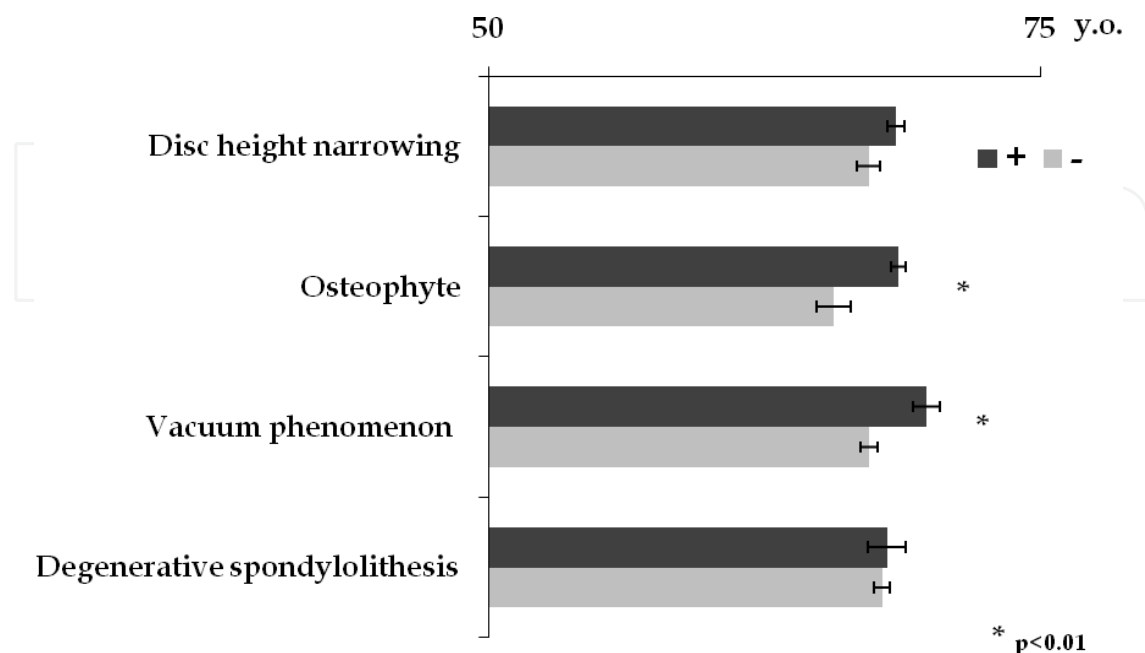


Fig. 1. X-ray findings and averaged age

3.1 Disc score and osteophyte score

Averaged disc score and osteophyte score were 1.4 ± 1.5 and 8.3 ± 3.1 , respectively. (Fig.2) There were no significant correlation between Disc score and Osteophyte score with Spearman's rank test. ($p=0.084$, $r=0.293$) Multiple regression analysis revealed that Disc score was associated with age, and Osteophyte score was associated with age, gender (male > female). (Table 1) Subjects who present vacuum phenomenon had significantly higher Disc score and Osteophyte score. ($p<0.01$) (Fig. 3)

According to the classification of osteophyte formation (2.4), Group A (osteophyte (+) with disc height narrowing) and Group B (osteophyte (+) without disc height narrowing) were seen in 217 and 99 cases, respectively. Group C (without osteophyte formation) was seen in 71 cases. Reduction of disc height was significantly associated with the presence of osteophyte. ($p<0.01$) (Table 2)

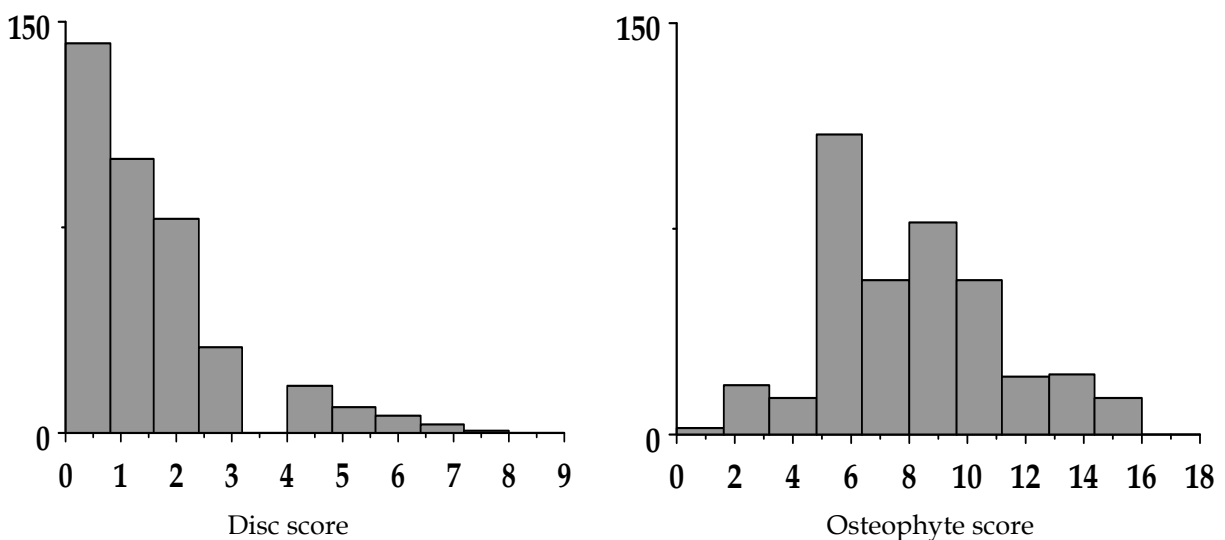


Fig. 2. Frequency distribution of disc score and osteophyte score

	Disc score		Osteophyte score	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Age	0.150	0.006	0.122	0.021
Gender	0.061	0.568	0.400	<0.001
Height	0.181	0.664	0.462	0.223
Weight	0.312	0.619	0.593	0.283
BMI	0.271	0.592	0.224	0.617
Body fat ratio	0.015	0.891	0.142	0.156
Brinkman index	0.106	0.089	0.061	0.276
Alcohol consumptio	0.044	0.461	0.002	0.970
Bone stiffness	0.046	0.392	0.046	0.340

Data are correlation coefficients (*r*) by Spearman's rank test and statistical significance (*p* value)

Table 1. Correlations between the parameters of physical factors and Disc score, Osteophyte score

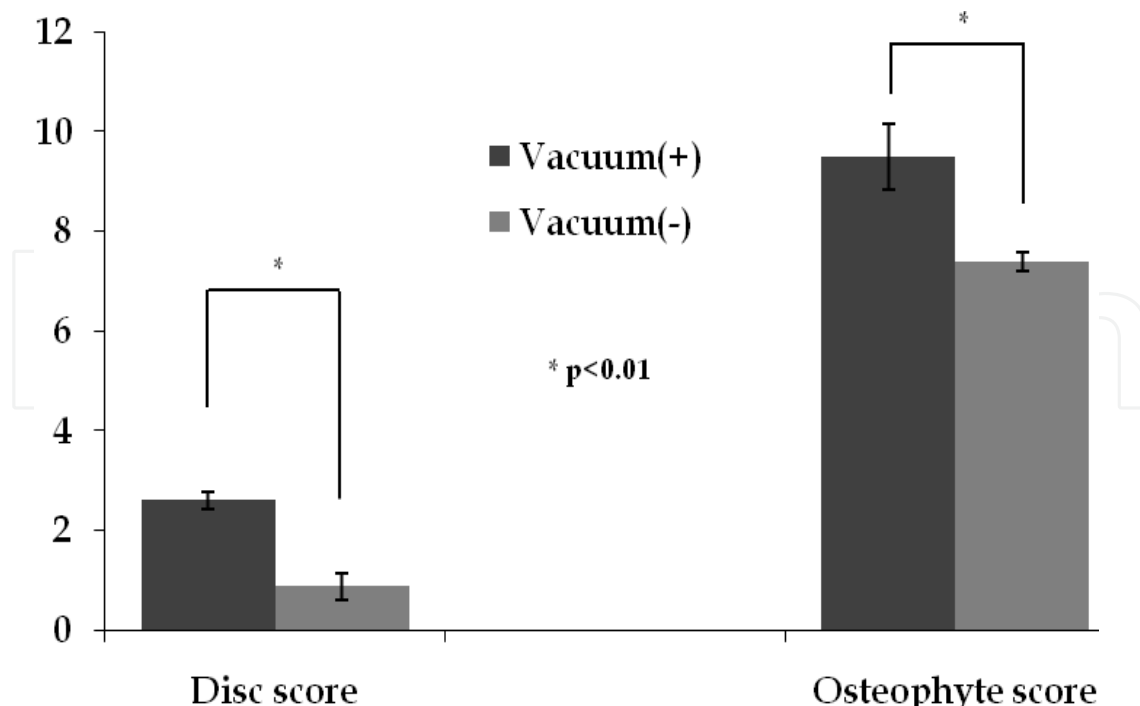


Fig. 3. Disc score and Osteophyte score according to the presence of vacuum phenomenon.

	Reduction of Disc height (+)	Reduction of Disc height (-)	Total
Osteophyte (+)	217 case * (Group A)	99 cases (Group B)	316 cases
Osteophyte (-)	28 cases	43 cases	71 cases (Group C)
Total	245 cases	142 cases	387 cases

* p<0.01

Table 2. Presence of disc height loss and osteophyte formation

3.2 Osteophyte and gene polymorphism (Sakai et al., 2007)

There were no significant differences in the disc score, osteophyte score or the ratio of group B in all polymorphisms, though Arg/Arg polymorphism in ADH2 tended to be less frequent. (p=0.051) (Table 3) Results of the logistic regression model to select gene polymorphism factors associated with the presence of osteophyte formation without disc height narrowing were shown in Table 4. In the polymorphism of alcohol dehydrogenase

	Genotypes			P value
	His/His (n=212)	Arg/His (n=124)	Arg/Arg (n=19)	
Disc score	1.33 ± 1.56	1.42 ± 1.47	1.30 ± 1.83	0.812
Osteophyte score	8.12 ± 3.12	7.91 ± 3.05	6.75 ± 2.90	0.160
No. of Group A+C/B	147/65	98/26	17/2	0.051

Group A=the cases with osteophyte formation with disc height narrowing
 Group B=the cases with osteophyte formation without disc height narrowing
 Group C=the cases with no osteophyte formation

Table 3. Disc score and Osteophyte score for ADH2 polymorphism

(ADH2; Arg47His), the prevalence of osteophyte formation without disc height narrowing (group B) was less in His/Arg (OR=0.57, 95%CI=0.33-0.97,p=0.041) and Arg/Arg (OR=0.41, 95%CI=0.1-1.5,p=0.18) than His/His. In the other polymorphisms, there were no significant differences in osteophyte formation without disc height narrowing.

	Group A+C (n=262)	Group B (n=93)	Genotypes (Arg/Arg, Arg/His, His/His)		
			Arg/Arg	Arg/His versus His/His	Arg/Arg + Arg/His
Allele Frequency (Arg, His)					
ADH2 Arg His	0.25 0.75	0.16 0.84			
<i>P</i> value			0.183	0.035	0.027
Odds ratio (95% CI)			0.41 (0.10-1.50)	0.57 (0.33-0.97)	0.55 (0.32-0.93)

Allele frequencies were estimated by the gene counting method. *P* values were adjusted for age, gender, BMI, body fat ratio, bone stiffness, smoking habit and alcohol consumption.

Table 4. Multivariate logistic regression analysis of the effect of ADH2 polymorphism on the prevalence of osteophyte without disc height narrowing

3.3 LBP and osteophyte

The prevalence of LBP was 40.4% (156 cases) with average VAS scale of 34.9±28.5 (10-100). Back muscle strength was significantly lower in the LBP group than in the non-LBP group. ($p<0.05$) Disc score was significantly higher in the LBP group than in the non-LBP group ($p<0.01$), whereas there was no significant difference in the osteophyte score between the two groups. (Table 5) Characteristics of the groups A, B, and C were shown in Table 6. In group C, male subjects, Brinkman index and drinkers were significantly fewer than in group

	LBP group (n=156)	non-LBP group (n=224)
Age (years)	68.7 ± 6.8	67.7 ± 5.9
Gender (male/female)	59/97	93/131
Height (cm)	154.0 ± 8.3	155.5 ± 8.0
Body weight (kg)	58.0 ± 9.0	58.6 ± 9.5
BMI (kg/m ²)	24.3 ± 3.0	24.2 ± 3.0
Body fat ratio (%)	28.2 ± 7.2	27.4 ± 6.9
Brinkman index	277.3 ± 475.4	226.6 ± 425.3
Drinker (no. (%))	41(26.2)	53 (23.7)
VAS	34.9 ± 28.5*	3.5 ± 8.0*
Back muscle strength (kg)	63.6 ± 24.2**	72.6 ± 28.4**
Bone stiffness	97.0 ± 18.6	96.7 ± 21.0
Disc score	1.72 ± 1.71*	1.09 ± 1.33*
Osteophyte score	8.28 ± 3.10	7.71 ± 3.11

BMI = body mass index, VAS = visual analogue scale, * $p<0.01$, ** $p<0.05$

Table 5. Characteristics of the LBP group and the non-LBP group

A and the group B. Although vacuum phenomenon was more frequent in the group A ($p<0.01$), the presence of vertebral fracture and degenerative spondylolisthesis were equivalent to the group B and C. Disc score was significantly higher in the group A than in the group C. ($p<0.01$) Osteophyte score was significantly higher in the group A than in the group B. ($p<0.05$) (Fig.4) Both VAS scale and the prevalence of LBP were significantly greater in group A than group B and group C. In group B, VAS scale and numbers of LBP were equivalent to those in group B, but significantly less than those in group A. (Fig. 5)

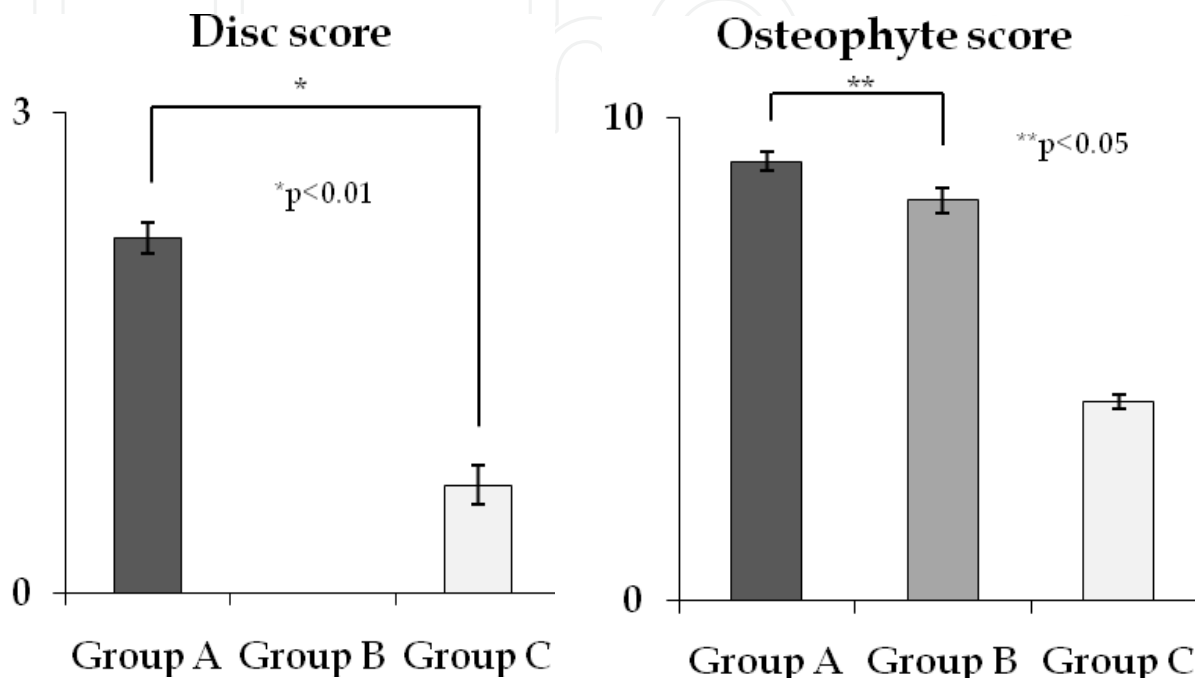


Fig. 4. Disc score and Osteophyte score in the group A, B and C.

	Group A (n=217)	Group B (n=99)	Group C (n=71)
Age (years)	68.9± 6.2	67.8± 6.2	65.6±6.6
Gender (male/female)	98/119	48/51	7/64 ^{*,**}
Height (cm)	155.0 ± 8.2	156.5± 8.8	151.9±6.1
Body weight (kg)	58.5 ± 9.4	60.2 ±9.9	55.2±7.2
BMI (kg/m ²)	24.3 ± 3.1	24.5 ± 3.0	23.9±2.8
Body fat ratio (%)	27.0 ± 7.4	27.3 ± 6.2	30.7±5.8
Brinkman index	232.2 ± 427.1	384.1 ± 532.8	95.6±276.0 ^{***}
Drinker (no. (%))	52 (30.0)	35 (35.3)	8 (11.3) ^{*,**}
Back muscle strength (kg)	70.5 ± 28.6	71.6 ± 28.5	60.5 ± 17.3
Bone stiffness	98.5 ± 19.6	95.8 ± 20.5	93.4 ± 20.1
Vertebral fracture (%)	3.26	3.06	2.85
Vacuum phenomenon (%)	45.53 ^{**}	7.37	4.35
Degenerative spondylolisthesis	21.96	18.37	28.17

Group A=the cases with osteophyte formation with disc height narrowing

Group B=the cases with osteophyte formation without disc height narrowing,

Group C=the cases with no osteophyte formation

* $p<0.01$ vs Group A; ** $p<0.01$ vs Group B; *** $p<0.05$ vs Group A

Table 6. Characteristics of the groups A, B, and C

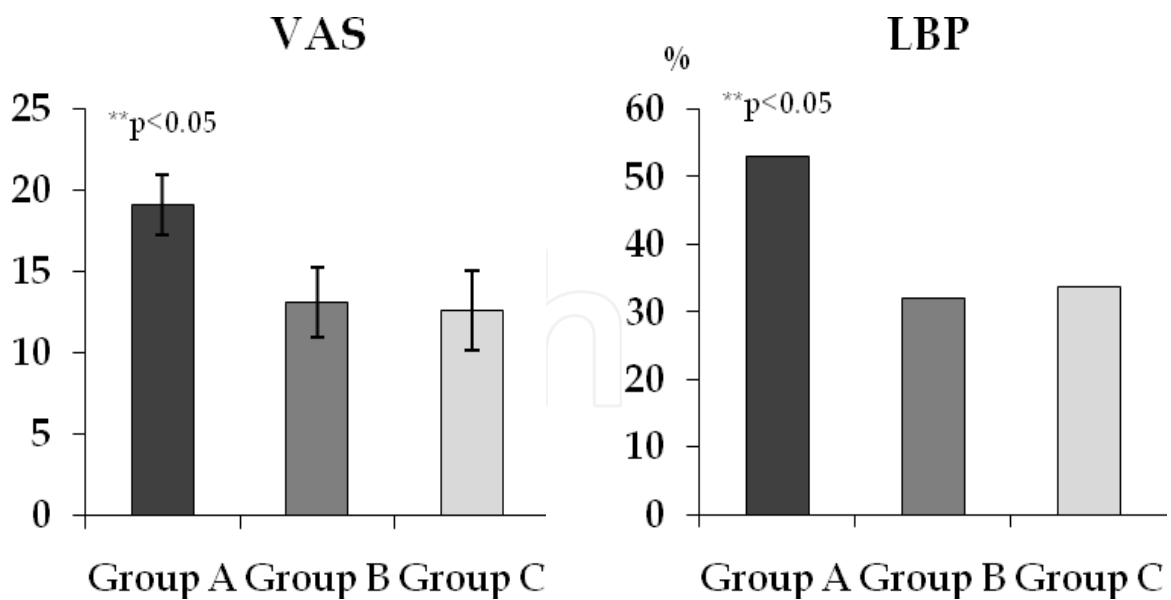


Fig. 5. Visual analogue scale and low back pain in the group A, B and C.

4. Discussion

It is commonly recognized that the degenerative changes that occur in the intervertebral discs are the point of departure of osteophyte formation. During the degeneration process, the discs undergo progressive structural changes in the form of dehydration of the nucleus and disintegration of the annulus fibrosus resulting in decreased disc height (Buckwalter et al., 1995), and lead to an increase in the compression stiffness and reduction in disc fiber strain (Kim et al., 1991). Biomechanically, the nucleus has lost some of its proteoglycan and water contents and increased its collagen content (Andersson, 1998). With progressive matrix alterations of the nucleus, changes in disc morphology such as a reduction in disc height become visible in plane radiographs. Degenerative changes within may result in an alteration of its mechanical properties, increased flexibility and decreased disc height, which in turn contribute to changes in the local stress within the disc (An et al., 2004). There is a general agreement that changes induced by aging lead to alternations in the thickness of the disc, but some differences are seen in the account of the effect of aging on the thickness of the lumbar disc. Vernon-Roberts et al. stressed that reduction of the disc height with age is inevitable (Vernon-Roberts et al., 1977), however, an increase in disc height with age has been reported. (Twomery et al., 1987, Amonoo-Kuofi, 1991, Roberts et al., 1997) Shao et al. demonstrated that the vertebral endplates became more concave with age, resulting the lumbar disc height increase (Shao et al., 2002). The effect of aging on the disc height has not been well understood, and the term of disc degeneration is imprecisely defined.

On the other hands, osteophytes form as a specific tissue reaction to these stresses and strains (Bick, 1995), and are attributed to higher stress more frequently anteriorly than posteriorly. Schmorl et al. formulated a pathogenic hypothesis that as a result of tears in the attachment of the annulus fibrosus into the marginal ring of the vertebral body, the nucleus protrudes forward against the anterior longitudinal ligament. The increased strain causes the formation of spurs in the area of its attachment to the periosteum covering the cortex of the vertebral bodies (Schmorl et al., 1932). (Schmorl's rim lesion theory) Colins formulated a theory of osteophyte formation that associates degeneration of the entire

intervertebral disc (collapsed disc) and the resultant anterior protrusion with subsequent osteophyte formation. The protrusion of the disc lifts the periosteum lateral to anterior longitudinal ligament and stimulates new subperiosteal bone (Collons, 1949). (Collins' bulging disc theory) According to Macnab's theory, osteophytes form as a result of instability between adjacent vertebral bodies (Macnab, 1971)(Macnab's instability theory). Traction spur, which projects horizontally and never curve toward the disc, differentiated from claw osteophytes (Nathan et al., 1962). Nathan concluded that osteophytes form as a natural physiologic response to compressive loads, serving to stabilize the spine (Nathan et al., 1962). In any case, there is wide agreement about the close association of disc degeneration with osteophyte formation and precedence in disc degeneration over vertebral deformities (Nathan et al., 1962, Vernon-Roberts et al., 1977, Lipson et al, 1980, Milgram, 1982). Our study date results provide further evidence substantiating that osteophyte formation and disc height narrowing are not always closely correlated, as identified by the prevalence of osteophytes without disc height narrowing in about 30% and the lack of correlation between disc height reduction and osteophytes. This finding stresses that these two features of spinal "degenerative" changes represent different factors affecting lumbar spine and the potential for osteophyte formation caused by factors other than spinal degeneration. Oishi et al. showed that intervertebral disc degeneration and osteophyte formation of the vertebral bodies represented different factors affecting the lumbar spine in postmenopausal Japanese women; however, the difference of osteophytes with or without disc degeneration was not mentioned. There are no detailed studies concerning osteophytes not accompanied with disc degeneration. We considered it informative to investigate the features of such osteophytes that are often observed clinically (Oishi et al., 2003).

There are few epidemiological data about osteophyte formation on the lumbar spine compared to the number of studies about osteoarthritis of the knee and hip. Nathan reported with regard to the frequency and degree of development of anterior osteophytes that the prevalence of osteophytes was greater in whites of both sexes than in Negroes with no statistically significant differences, with the frequency being much higher in the males in both races (Nathan et al., 1962). Our results revealed a significant influence of gender, smoking and alcohol consumption on osteophyte formation irrespective of the presence of disc height narrowing, however, showed no epidemiological differences between osteophyte formation with disc height narrowing and without narrowing, namely the differences in osteophytes depending on intervertebral disc degeneration. The present study illustrated that the prevalence of LBP in group B was significantly lower than in group A, and this suggests that lumbar disc narrowing may have a propensity for LBP, indicating osteophytes may prevent the clinical manifestation of pain. While data from many studies suggest an association between LBP and osteophyte formation (Frymoyer et al., 1984, Biering-Sorensen et al., 1985, Symmons et al., 1991, Pye et al., 2004), several studies indicate that osteophyte formation do not have an independent association with LBP (van Tulder et al., 1997, O'Neill et al., 1999, Schepper et al. 2004). Whether the stabilization of osteophytes or low frequency of disc degeneration decreased the prevalence of LBP is not clear. However, when osteophyte formation occurs before disc degeneration advances as a physiologic response to stabilize the spine, LBP may be evitable. While many studies have focused on LBP in relation to lumbar disc degeneration (Parkkola et al., 1993, Paajanen et al., 1997, Luoma et al., 2000, Jarvik et al., 2001, Videman et al., 2003), there are no reports regarding the association of LBP with osteophytes without lumbar disc degeneration.

Discal degeneration is generally considered as the primary source of LBP. In addition to nociceptive nerve fibers in the annulus and nucleus that can be sensitized by the cytokines and neuropeptides present in the degenerated disc, other sources of nociception can be found in the spinal unit including muscles, ligaments and facet joints (Freemont et al., 1997, Benoist, 2003). Nociception coming from these various tissues makes it difficult to distinguish from osteophytes in spinal pain. Thus, the cause of the decreased LBP should not be determined to be osteophyte formation before disc degeneration, although, it would be intriguing to investigate the genetic predisposition in cases with osteophytes without disc degeneration.

Several studies on factors associated with genetic susceptibility to spinal osteophyte formation, such as VDR (Videman et al., 2001, Jordan et al., 2005) and TGFB1 (Yamada et al., 2000) referred to osteophytes with spinal degeneration. Our results did not show any relationship between these polymorphisms and osteophyte formation without disc degeneration. Alcohol dehydrogenase β subunit is an enzyme that converts ethanol to acetaldehyde, whose gene, ADH2 located in 4q22, has a functional polymorphism Arg47His (Matsuo et al., 1989). Both ADH2 and ALDH2 (aldehyde dehydrogenase 2) are polymorphic, and genetic polymorphisms have been shown to functionally affect alcohol detoxification. The enzyme activity is higher in the 47His allele (ADH2*2) than in the 47Arg allele (ADH2*1) (Yin et al., 1984), and the former leads to a higher rate of oxidation of ethanol, resulting in an arginine/histidine exchange in the protein. In particular, an association of the 47His allele with flushing has been reported (Takeshita et al., 1996), and results of a number of studies seem to indicate that the 47His allele protects against alcohol abuse and alcoholism in Asians (Muramatsu et al., 1995, Shen et al., 1997) and Caucasians (Whitfield et al., 1998, Borrás et al., 2000). In Japanese, the incidence of 47Arg allele is low, different from Caucasians (Sherman et al., 1993, Higuchi et al., 1994). On the other hand, most alcoholics exhibit radiographic evidence of osteopenia (Bilke et al., 1985), leading to a hypothesis that reduced osteoblast activity resulting in underfilling of resorptive lacunae is primary responsible for alcohol-induced bone loss (Turner et al., 2001). Ethanol has been shown to increase bone resorption (Callaci et al., 2004) and to decrease trabecular bone volume (Rico et al., 1987). Additionally, administration of ethanol to healthy volunteers results in an acute decrease in serum osteocalcin levels (Rico et al., 1987, Nielsen et al., 1990). The present study demonstrated that carriers of 47Arg allele might suppress osteophyte formation unaffected by intervertebral disc degeneration, and this could be supported by these studies showing that ethanol contributes to decreased bone formation. Further research will be required to investigate the osteophyte development and molecular characterization, however, our study would encourage further studies on the mechanisms underlying osteophyte formation.

5. Conclusion

Osteophyte formation of the lumbar spine without disc degeneration was investigated, and estimated the implications of osteophytes from the viewpoint of LBP and gene polymorphism. The 47His polymorphism in the ADH2 may act to suppress osteophyte formation unaffected by disc degeneration. The subjects with osteophyte development preceding intervertebral disc degeneration had a lower risk of LBP compared with those without osteophytes.

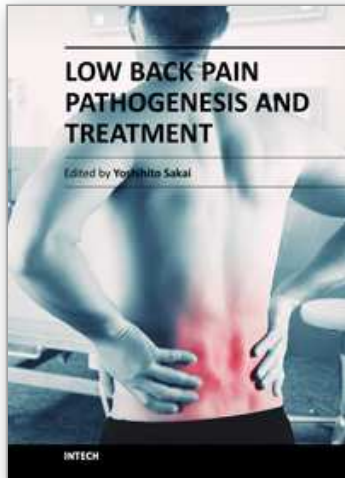
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Low Back Pain Pathogenesis and Treatment

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Low back pain is a common disorder which affects the lumbar spine, and is associated with substantial morbidity for about 80% of the general population at some stages during their lives. Although low back pain usually is a self-limiting disorder that improves spontaneously over time, the etiology of low back pain is generally unknown and the diagnostic label, "non-specific low back pain", is frequently given. This book contains reviews and original articles with emphasis on pathogenesis and treatment of low back pain except for the rehabilitative aspect. Consisting of three sections, the first section of the book has a focus on pathogenesis of low back pain, while the second and third sections are on the treatment including conservative and surgical procedure, respectively.

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University Campus STeP Ri
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51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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