ELSEVIER

The Spine Journal 20 (2020) 94−100

THE SPINE JOURNAL

Clinical Study

Lifestyle and lifetime occupational exposures may not play a role in the pathogenesis of Modic changes on the lumbar spine MR images

Jialong Wu, MD[a], Jiawei Huang, MD[a], Michele C. Battié, PhD[b], Yue Wang, MD, PhD[a,*]

[a] *Department of Orthopedic Surgery, Spine Lab, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, People's Republic of China*

[b] *Department of Physical Therapy, Faculty of Health Sciences, University of Western Ontario, London, Ontario, Canada*

Received 2 May 2019; revised 14 August 2019; accepted 15 August 2019

Abstract

BACKGROUND CONTEXT: Modic changes (MCs) have long been suspected as a pathologic cause of back pain. Although much attention has been focused on clinical perspectives, the etiology of MCs remains unclear. Although some studies have reported that sex, body mass index (BMI), cigarette smoking, and physical loading may associate with MCs, the observed associations are inconsistent among studies.

PURPOSE: To investigate associations between MCs and lifestyle and lifetime occupational exposures using a general population sample.

STUDY DESIGN: Cross-sectional study.

PATIENT SAMPLE: The study was an extension of the Hangzhou Lumbar Spine Study, a population-based study of mainland Chinese focusing on lumbar degenerative changes. A total of 644 randomly selected subjects from a typical community in Hangzhou, Eastern China participated.

OUTCOME MEASURES: The presence and type of MCs in the lumbosacral spine were evaluated on sagittal magnetic resonance images. Demographics, lifestyle factors, and occupational exposures were measured using a structured interview.

METHODS: Univariate and multivariate logistic regressions were used to examine the associations of MCs with various environmental exposures.

RESULTS: Among the 644 subjects (52.6±13.9 years; range 20−88 years) included in this study, 44.7% had MCs. In univariate regression analyses, the presence of MCs was associated with greater age, higher BMI, greater cigarette smoking, regular exercise, and absence of daily vehicle vibration. Modic changes were not univariately associated with sex or alcohol consumption. In addition, all occupational loading measurements were associated with the occurrence of MCs in univariate analyses, except work time spent in vehicles and work-related back injuries. However, in multivariate regression analyses, no statistically significant associations between the occurrence of MCs and lifestyle or lifetime occupational exposures were observed after adjusting for age, sex, and BMI.

CONCLUSIONS: Age is an important determinant of MCs, with BMI and sex also playing a role. Lifestyle and occupational factors appear to have minor effects, if any, on the pathogenesis of MCs in the lumbar spine.

Keywords: Etiology; Lumbar spine; Magnetic resonance; Modic changes; Occupational exposure; Population study

FDA device/drug status: Not applicable.

Author disclosures: ***JW:*** Nothing to disclose. ***JH:*** Nothing to disclose. ***MCB:*** Nothing to disclose. ***YW:*** Nothing to disclose.

* Corresponding author. Department of Orthopedic Surgery, Spine Lab, The First Affiliated Hospital, School of Medicine, Zhejiang University, 79# Qingchun Road, Hangzhou 310003, People's Republic of China. Tel.: +86 571 87236128; fax: +86 571 87236166.

E-mail address: wangyuespine@zju.edu.cn (Y. Wang).

https://doi.org/10.1016/j.spinee.2019.08.009

1529-9430/

Introduction

Modic changes (MCs), signal variations of the end plate and adjacent vertebral marrow, are common findings on lumbar spine magnetic resonance (MR) images [1,2]. Modic changes are classified as type I (hypointense on T1W images and hyperintense on T2W images), type II (hyperintense on both T1W and T2W images), type III (hypointense on both T1W and T2W images), and mixed types, such as I/II and II/III. Although different types of MCs were thought to represent different pathologies of the vertebral marrow, under certain circumstances MCs may transfer from one type to another [3,4]. Modic changes have long been suspected as a pathologic cause of back pain, yet findings on the relationship between MCs and back pain are inconsistent and controversial [5−12].

Although most studies on MCs have focused on clinical perspectives, relatively little attention has been paid to the etiopathogenesis of MCs, which remains largely unknown. A variety of theories, such as mechanical alteration [8], low-virulence infections [8,13], autoimmune inflammation [14], and genetic determination [15], have been proposed to explain the pathogenesis of MCs. In epidemiologic studies, the occurrence of MCs has generally been found to associate with greater age [16−18], greater weight, and male sex [19,20]. Among various environmental factors, an association has been observed between MCs and cigarette smoking [7,10], and heavy physical loading, particularly related to occupation in some selected samples [21,22], but not in population-based samples [10,12].

As disc degeneration is closely associated with MCs, some suggest that the development of MCs mainly depends on the status of the adjacent intervertebral disc [23−25]. If lumbar MCs have a degenerative origin that parallels disc degeneration, as suggested by a recent study [26], specific lifestyle and lifetime loading exposures may play a minor role in MCs, as is the case for disc degeneration [27]. However, population-based studies of associations of MCs with various lifetime environmental and behavioral exposures are needed to clarify the presence or absence of such relationships.

Using a general population sample of Chinese adults, the purpose of the current study was to determine the presence and magnitude of associations of various lifetime exposures with the occurrence of MCs.

Materials and methods

Subjects

The current study was an extension of the Hangzhou Lumbar Spine Study of a population-based sample of Chinese adults [28]. Subjects of the study were randomly selected from the residency registry of a typical Chinese community. To be eligible for inclusion, subjects had to be a Han Chinese resident of the community, older than 18 years of age, had no known history of spinal surgery, spinal tumors, infections, or inflammatory diseases of the spine. Exclusion criteria were contraindications for MR imaging and X-ray. The study was approved by the Ethical Committee of the First Affiliated Hospital of Zhejiang University, and written informed consent was obtained from each participant.

Assessment of demographics and lifetime exposures

The study research nurse met with each subject approximately 1 hour before MR imaging to conduct an extensive, structured interview to collect demographic and lifetime exposure data. Body weight and height were also measured, and body mass index (BMI, kg/m^2) was calculated.

Smoking history, alcohol consumption, exposure to vehicular vibration, exercise history, and occupational physical demands were evaluated, in part, using methodologies adapted from the Twin Spine Study [29]. Nonsmokers were defined as those who had never used nicotine products. Lifetime exposure to smoking was defined as the total amount of cigarettes smoked (packs), calculated from cigarette smoking frequency and duration. Alcohol consumption was evaluated by asking the subject whether he or she drank regularly and, if yes, the frequency of drinking alcoholic beverages. Exposure to motorized vehicles was evaluated by asking "How many hours per day do you spend, on average, driving or as a passenger in motorized vehicles?". Vehicle use was analyzed as a dichotomous variable dependent on whether the subject spent time daily in motorized vehicles.

Exercise history was reviewed and regular exercise was noted if the subject ever exercised more than twice a week after 18 years of age. Further, ballgames, running, and aerobics were grouped as high-impact exercise and Yoga, walking, and dancing as low-impact exercise [30].

To assess specific lifetime occupational exposures, subjects were asked to recall their work history over their lifetime. For each job from the beginning of the subject's work history, he or she was asked the age span during which the job was held and to describe the job activities. Specifically, for each job, subjects were asked to estimate the most common weights lifted, the frequency of lifting, the time per day spent working in twisted or bent postures, and the time spent sitting and driving at work. The most common weight lifted multiplied by the frequency formed a summary measure of lifting for each job, which was then summed across jobs as a lifetime occupational lifting measurement. Lifetime occupational lifting was a continuous variable, but data were skewed and were, therefore, categorized as: 1=almost no lifting, 2=light or moderate lifting, or 3=heavy lifting. The lifetime hours spent in on-the-job driving were calculated as the time per day multiplied by the number of working days. Lifetime occupational sitting time was calculated using a similar method. Any recalled back injuries associated with work activities or accidents during each job were also noted.

In addition to the specific occupational exposure estimates, two variables representing overall occupational physical demands were created. First, the physical demands of each job the participant held were reviewed and the job was classified as sedentary work if it involved spending nearly all day sitting, with little lifting; light, if the job involved a mix of sitting and standing or walking activities with light lifting (generally <5 kg); medium, if lifting and handling of weights were generally <20 kg; heavy, if the job involved frequent lifting of materials of 20 to 40 kg; or very heavy, if the job required frequent lifting of materials over 40 kg. Using these categories, an overall measure of lifetime occupational demands was based on the physical demands of the jobs the subject held for the majority of his or her working years. An overall measure of occupational bending or twisting demands was formulated by asking “During the majority of your working years, which of the following best describes how much of the work was done in awkward twisted or bent postures?”, which was classified as none, occasionally, over an hour per day, or the majority of the day. Forty subjects were re-evaluated 1 month later using the structured interview and the reliabilities for these measures were found to be fair or good (Kappa=0.56−1.00), as reported previously [28].

Magnetic resonance imaging

The lumbar spine was imaged using a 3.0T MR scanner (Philips, Best, the Netherlands). Magnetic resonance images included T1W and T2W sagittal images of the lumbar spine, with TE/TR of 8/442 and 100/3500 milliseconds, respectively. The matrix sizes of T1W and T2W images were 268 × 191 and 300 × 229, respectively, and the field views were both 24 × 24 cm. The slice thickness was 3 mm and the intersection gap was 0.3 mm for both T1W and T2W images. In general, 15 sagittal T1W and T2W sagittal images were obtained for each lumbar spine, which were all evaluated in the present study.

Evaluation of Modic changes

Evaluation of MCs was performed by a senior spine surgeon (YW, 18 years of experience with MRIs) in a PC station. Only the signal changes of vertebral bone marrow, which were extended from the end plate and involved three or more adjacent sagittal MRIs, were regarded as MCs [31]. Modic changes were further classified as types I, II, III, or mixed. The intrarater kappa was 0.85 for occurrence of MCs and 0.81 for MCs classification [26].

Data analysis

When investigating associations, MC types were analyzed together and then separately for subgroup analysis. As type I MCs were assumed to be a more active pathology than type II [32], type I/II MCs were merged with type I MCs for analysis. A forward stepwise multiple regression technique was used to determine associations of the occurrence of MCs with various factors. Univariate logistic regressions were first used to examine the associations of MCs with age, BMI, sex, lifestyle, and various lifetime exposures. A variable was entered into the final multiple regression models if the p value was less than .20 in univariate regression. Statistical analyses were performed using STATA (Version 13.1, StataCorp LP, College Station, TX, USA).

Results

There were 644 subjects (male: 284, female: 360) in the Hangzhou Lumbar Spine Study at the time of the current study, who were all included. The mean age was 52.6± 13.9 years (range 20−88 years) and the mean BMI was 23.9±2.8 kg/m^2 for males and 22.5±2.8 kg/m^2 for females.

Lifestyle and occupational exposure measurements

In this sample, 75.2% of subjects were nonsmokers and 56.8% never or rarely drank alcohol (Table 1). For smokers, the mean lifetime cigarette intake was 7720 packs. There were 488 (75.8%) subjects who had used motorized vehicles routinely, and 350 (54.4%) had regularly exercised, with 20.5% having high-impact exercise.

For overall occupational physical demands, 242 (37.6%) were classified as having sedentary work and 259 (40.2%)

Table 1
Measurements of lifetime lifestyle and occupational exposures (N=644)

Variable	Number (%)
Smokers	160 (24.8%)
Cigarette intake, mean (SD), ×10^3 packs	1.92 (4.35)
Regular alcohol use	278 (43.2%)
Daily vehicle use	488 (75.8%)
Regular exercise	
None	275 (42.7%)
Low impact	237 (36.8%)
High impact	132 (20.5%)
Overall occupational physical demands	
Sedentary work	242 (37.6%)
Light physical demands	259 (40.2%)
Medium physical demands	85 (13.2%)
Heavy physical demands	35 (5.4%)
Very heavy physical demands	23 (3.6%)
Overall occupational bending/twisting demands	
None	183 (28.4%)
Occasionally	190 (29.5%)
Over an hour per day	162 (25.2%)
Majority of the day	109 (16.9%)
Specific lifetime occupational exposures (summed for each job the subject had)	
Occupational lifting, mean (SD), ×10^5 kg·h	1.49 (6.12)
Specific occupational lifting category, n (%)	
Almost no lifting	359 (55.8%)
Light or medium lifting	149 (23.1%)
Heavy lifting	136 (21.1%)
Work time spent in vehicles, mean (SD), ×10^3 h	2.59 (8.47)
Occupational sitting time, mean (SD), ×10^4 h	3.13 (2.03)
Recalled occupational back injury (%)	73 (11.3%)

as having light physical demands during majority of their working years. Only 9.0% of subjects had predominantly heavy or very heavy physical demands. Although 183 (28.4%) subjects almost never worked in bent/twisted postures, 109 (16.9%) subjects worked in such postures during the majority of the work day (Table 1).

Specific lifetime occupational exposures that were summed across jobs for each subject are presented in Table 1. Although 359 (55.8%) subjects were categorized as having almost no lifetime occupational lifting (eg, sedentary jobs), 136 (21.1%) subjects were rated as having heavy lifting. In addition, 73 (11.3%) subjects recalled a back injury associated with work.

Prevalence of Modic changes

Modic changes in the lumbosacral spine were identified in 288 (44.7%) of the 644 subjects studied. Among those with MCs, 15 (5.2%) had exclusively type I changes, 220 (76.4%) had exclusively type II changes, and only 1 subject had exclusively type III MCs. In addition, 52 (18.1%) had mixed type I/II MCs, and 2 had mixed type II/III changes. The mixed type I/II changes were merged to type I MCs in analyses.

Modic changes were more commonly present in the lower lumbar region (L4/5 and L5/S1), as compared with the upper lumbar region (L1−L4). The distribution of MCs in relation to lumbar spinal level is presented in the Figure.

Univariate regressions

In univariate regression analyses, age, BMI, cigarette intake, and regular exercise, but not sex, were statistically significantly associated with the occurrence of MCs (Table 2). In addition, greater age was associated with a greater number of end plates affected by MCs (coef=0.67 for each 10 years, p<.001).

All occupational measurements, with the exception of work time spent in vehicles and work-related injuries (p>.05), were associated with the occurrence of MCs in what appeared to be a dose-response relationship (Table 2). Drinking was not associated with MCs (p=.070) but was considered in the multivariate regression models.

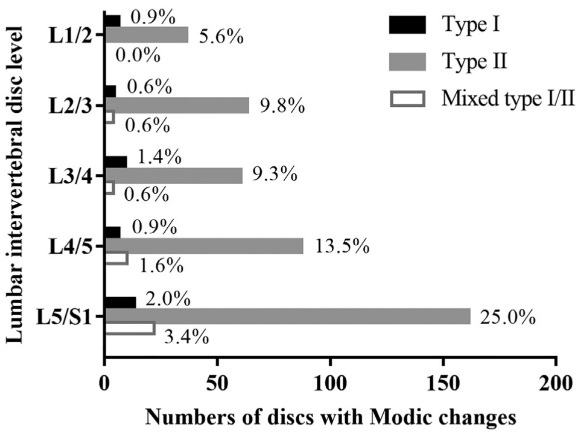

Figure. Distribution of Modic changes by lumbar disc level. Percentages represent the numbers of Modic changes relative to 644 discs at each level.

Table 2
Associations of MCs with individual characteristics and lifetime exposures: results from univariate regressions (N=644)

Variable	OR (95% CI)	p Value
Age, years	1.10 (1.08, 1.12)	<.001
Male sex	0.86 (0.63, 1.17)	.338
BMI, kg/m^2	1.09 (1.03, 1.15)	.002
Cigarette intake, $\times 10^3$ packs	1.04 (1.00, 1.08)	.035
Regular alcohol use	0.75 (0.55, 1.02)	.070
Daily vehicle use	0.47 (0.32, 0.67)	<.001
Regular exercise		
None	1.00	
Low impact	2.64 (1.85, 3.78)	<.001
High impact	1.35 (0.88, 2.07)	.164
Overall occupational physical demands		
Sedentary work	1.00	
Light physical demands	1.80 (1.25, 2.58)	.001
Medium physical demands	2.13 (1.29, 3.52)	.003
Heavy physical demands	3.81 (1.80, 8.04)	<.001
Very heavy physical demands	5.63 (2.14, 14.83)	<.001
Overall occupational bending/twisting		
None	1.00	
Occasionally	1.37 (0.89, 2.09)	.148
Over an hour per day	2.44 (1.58, 3.77)	<.001
Majority of the day	2.92 (1.79, 4.76)	<.001
Specific lifetime occupational exposures		
Specific occupational lifting category		
Almost no lifting	1.00	
Light or moderate lifting	1.75 (1.19, 2.58)	.005
Heavy lifting	3.79 (2.49, 5.75)	<.001
Work time spent in vehicles, $\times 10^3$ h	1.00 (0.98, 1.02)	.910
Occupational sitting time, $\times 10^4$ h	1.23 (1.13, 1.33)	<.001
Recalled occupational back injury	1.23 (0.76, 2.01)	.402

Multivariate regressions

We performed two separate multivariate analyses to determine the associations of the lifestyle factors and occupational exposures with MCs after adjusting for age, sex, and BMI. One analysis considered lifestyle factors and overall lifetime occupational physical demands, and the other replaced consideration of overall occupational physical demands with the specific occupational exposures. Both multivariate analyses yielded similar results. After adjusting for age, sex, and BMI, none of the remaining lifestyle factors or overall occupational physical demands were statistically significantly associated with the occurrence of MCs (Table 3). Similarly, there were no significant associations between MCs and any of the specific lifetime occupational exposures (data not presented).

Factors associated with different Modic change types

Greater age was associated with both type I (odds ratio [OR]=1.04, p<.001) and type II MCs (OR=1.08, p<.001).

Table 3
Associations of MCs with individual characteristics and overall lifetime occupational exposures: results from a multivariate regression (N=644)

Variable	OR (95% CI)	p Value
Age, years	1.10 (1.08, 1.12)	<.001
Male sex	0.56 (0.35, 0.90)	.017
BMI, kg/m^2	1.10 (1.03, 1.18)	.006
Cigarette intake, $\times 10^3$ packs	1.01 (0.96, 1.06)	.771
Regular alcohol use	0.93 (0.62, 1.39)	.713
Daily vehicle use	0.96 (0.61, 1.53)	.869
Regular exercise		
None	1.00	
Low impact	1.06 (0.68, 1.66)	.801
High impact	1.33 (0.79, 2.23)	.388
Overall occupational physical demands		
Sedentary work	1.00	
Light physical demands	1.36 (0.86, 2.13)	.187
Medium physical demands	0.66 (0.34, 1.30)	.230
Heavy physical demands	1.01 (0.39, 2.58)	.991
Very heavy physical demands	1.34 (0.41, 4.36)	.629
Overall occupational bending/twisting		
None	1.00	
Occasionally	1.06 (0.63, 1.80)	.820
Over an hour per day	1.50 (0.84, 2.66)	.171
Majority of the day	1.51 (0.74, 3.08)	.252

In addition, sex and BMI were associated with type II changes, but not type I, after controlling for age, with men less likely to have type II MCs (OR=0.53, p=.005) than women (Table 4). Also, none of the overall or specific lifetime occupational factors studied were associated with either type of MCs (data not presented).

Discussion

Using a population-based sample, the current study specifically investigated the associations of lifestyle factors and occupational exposures with MCs. Greater age was closely associated with both the presence of MCs and a greater number of lumbar end plates affected, suggesting that age is an important determinant of MCs. After adjusting for age, sex, and BMI, no significant associations of MCs with lifestyle factors, overall or specific lifetime occupational physical demands, or regular participation in exercise were observed, suggested that such factors may not be determinants of MCs. Smoking, alcohol consumption, and use of motorized vehicles and associated vibration also were not associated with the occurrence of MCs in multivariate analyses.

Table 4
Associations of types I and II MCs with age, sex, and BMI: results from multivariate regressions (N=644)

	Modic type I		Modic type II	
	OR	95% CI	OR	95% CI
Age, years	1.04	(1.02, 1.06)	1.08	(1.07, 1.10)
Male sex	1.17	(0.69, 1.98)	0.54	(0.37, 0.79)
BMI, kg/m^2	0.97	(0.88, 1.06)	1.13	(1.05, 1.20)

The overall prevalence rate of MCs in our population-based sample was 44.7%, which is comparable with other population studies [11,33]. Although the current study revealed an association between MCs and the female sex, previous studies have had conflicting results with respect to an association of MCs and sex, with findings of MCs being more common in men [20] or in women [22], or similar in both sexes [10,25]. Some went so far as to attribute the greater prevalence rate of MCs observed in men to greater body weight and physical activities, and other lifestyle factors associated with the male sex [12,19].

Weight and other loading-related factors have long been suspected as risk factors for lumbar MCs. Yet, there have been inconsistencies, with some finding an association of greater weight or BMI with the occurrence of MCs [20,22] similar to the current study, and others finding no such association [21,25]. On the other hand, as reported in previous studies [19,25], we also noticed that greater BMI was associated with the presence of type II MCs, but not type I when MCs types were analyzed separately, suggesting that the pathogenesis underlying types I and II MCs may be different.

The current study also confirmed earlier findings from back pain patients and population samples that cigarette smoking, alcohol consumption, and vehicular vibration exposure do not play a significant role in MCs [20,25,32]. Previously, the prevalence of MCs was found to be similar between train engineers with intensive whole-body vibration and sedentary factory workers [12,32], providing further evidence of a lack of association between MCs and vehicular vibration exposure. Although heavy smoking combining with hard physical work [21] or with overweight [10] was reportedly associated with MCs, the rationales underlying such combinations are vague. Our findings suggesting a minimal role for the lifestyle and occupational factors studied in MCs, echo similar findings of a previous study with respect to disc degeneration [27].

It seems to be a natural assumption that various forms of physical demands and spinal loading conditions, particularly heavy materials handling [33], contribute to degenerative findings in the lumbar spine. When occupational demands were studied in relation to MCs, however, no statistically significant association was observed in most previous studies [10,20,25]. Furthermore, the prevalence rate of MCs was not found to be associated with intensive sports participation and associated physical demands [10,32]. Collectively, the evidence to date suggests that effects of occupational physical demands and exercise on MCs, if any, are negligible.

It is now widely accepted that genetics plays a predominant role in the pathogenesis of disc degeneration and that environmental factors are less important [34]. The heritability of MCs, which is defined as the proportion of phenotypic variation in a population due to underlying genetic factors, has been demonstrated in a twin study [35], motivating the search for genetic variants determining MCs. Toward this goal, studies have reported associations of MCs with gene variants implicating such genes as IL1 cluster [15], MMP3 [36], MMP20, and VDRs [33]. Given the close relation between disc degeneration and MCs [26], and little or no associations between MCs and various lifetime environmental exposures observed in the current study, we postulate that genetics may play an important role in MCs. Yet, the previously reported heritability estimate of 30% for MCs [35] suggests that environmental factors, although largely unidentified, also are important in the pathogenesis of MCs.

Among the strengths of the current study, there are the large general population-based sample, use of a 3.0T high resolution MR scanner to image the lumbar spine, and structured interviews carried out by a single research nurse to estimate lifetime occupational exposures. Yet, epidemiologic studies on mechanical loading and lumbar spine findings are challenging, as lifetime physical activities and associated loading cannot be measured accurately, which results in the dilution of true associations. Although data were collected on a variety of suspected risk factors for MCs and were considered in multivariate analyses, uncontrolled confounding may have still occurred, influencing results and interpretation.

In conclusion, other than age, sex, and BMI, the lifestyle and occupational loading exposures studied were not found to associate with the occurrence of MCs in this general population sample. Such environmental factors appear to play a minor role, if any, in the pathogenesis of MCs in the lumbar spine.

Acknowledgments

The authors thank the clinic staffs at the Department of Orthopedic Surgery, Radiology, and Clinical Laboratory Center at the First Affiliated Hospital of Zhejiang University, and staffs in Caihe community, for their continuous assistance. This work was supported by the National Natural Science Foundation of China (NSFC, no. 81371995), Key Platform Project of the Health Department of Zhejiang Province (2015ZDA014, 2018ZD005 (2018247243)).

References

[1] 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;149:531–4.
[2] 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;166:193–9.
[3] Dudli S, Fields AJ, Samartzis D, Karppinen J, Lotz JC. Pathobiology of Modic changes. Eur Spine J 2016;25:3723–34.
[4] Teichtahl AJ, Finnin MA, Wang Y, Wluka AE, Urquhart DM, O'Sullivan R, et al. The natural history of Modic changes in a community-based cohort. Joint Bone Spine 2017;84:197–202.
[5] Kjaer P, Leboeuf-Yde C, Korsholm L, Sorensen JS, Bendix T. Magnetic resonance imaging and low back pain in adults: a diagnostic imaging study of 40-year-old men and women. Spine 2005;30:1173–80.
[6] Jarvik JG, Hollingworth W, Heagerty PJ, Haynor DR, Boyko EJ, Deyo RA. Three-year incidence of low back pain in an initially asymptomatic cohort: clinical and imaging risk factors. Spine 2005;30:1541–8. discussion 9.
[7] Kjaer P, Korsholm L, Bendix T, Sorensen JS, Leboeuf-Yde C. Modic changes and their associations with clinical findings. Eur Spine J 2006;15:1312–9.
[8] Albert HB, Kjaer P, Jensen TS, Sorensen JS, Bendix T, Manniche C. Modic changes, possible causes and relation to low back pain. Med Hypotheses 2008;70:361–8.
[9] Jarvinen J, Karppinen J, Niinimaki J, Haapea M, Gronblad M, Luoma K, et al. Association between changes in lumbar Modic changes and low back symptoms over a two-year period. BMC Musculoskelet Disord 2015;16:98.
[10] Mok FP, Samartzis D, Karppinen J, Fong DY, Luk KD, Cheung KM. Modic changes of the lumbar spine: prevalence, risk factors, and association with disc degeneration and low back pain in a large-scale population-based cohort. Spine J 2016;16:32–41.
[11] Jensen TS, Karppinen J, Sorensen JS, Niinimaki J, Leboeuf-Yde C. Vertebral endplate signal changes (Modic change): a systematic literature review of prevalence and association with non-specific low back pain. Eur Spine J 2008;17:1407–22.
[12] Kuisma M, Karppinen J, Niinimaki J, Ojala R, Haapea M, Heliovaara M, et al. Modic changes in endplates of lumbar vertebral bodies: prevalence and association with low back and sciatic pain among middle-aged male workers. Spine 2007;32:1116–22.
[13] Albert HB, Manniche C, Sorensen JS, Deleuran BW. Antibiotic treatment in patients with low-back pain associated with Modic changes type 1 (bone oedema): a pilot study. Brit J Sports Med 2008;42:969–73.
[14] Ma XL, Ma JX, Wang T, Tian P, Han C. Possible role of autoimmune reaction in Modic type I changes. Med Hypotheses 2011;76:692–4.
[15] Karppinen J, Solovieva S, Luoma K, Raininko R, Leino-Arjas P, Riihimaki H. Modic changes and interleukin 1 gene locus polymorphisms in occupational cohort of middle-aged men. Eur Spine J. 2009;18:1963–70.
[16] Wang Y, Videman T, Battie MC. Modic changes: prevalence, distribution patterns, and association with age in white men. Spine J 2012;12:411–6.
[17] Hayashi T, Daubs MD, Suzuki A, Scott TP, Phan KH, Ruangchainikom M, et al. Motion characteristics and related factors of Modic changes in the lumbar spine. J Neurosurg Spine 2015;22:511–7.
[18] Martinez-Quinones JV, Aso-Escario J, Gonzalez-Garcia L, Consolini F, Arregui-Calvo R. Are Modic changes able to help us in our clinical practice? A study of the Modic changes in young adults during working age. Clin Spine Surg 2017;30:259–64.
[19] Karchevsky M, Schweitzer ME, Carrino JA, Zoga A, Montgomery D, Parker L. Reactive endplate marrow changes: a systematic morphologic and epidemiologic evaluation. Skelet Radiol 2005;34:125–9.
[20] Arana E, Kovacs FM, Royuela A, Estremera A, Asenjo B, Sarasibar H, et al. Modic changes and associated features in Southern European chronic low back pain patients. Spine J 2011;11:402–11.
[21] Leboeuf-Yde C, Kjaer P, Bendix T, Manniche C. Self-reported hard physical work combined with heavy smoking or overweight may result in so-called Modic changes. BMC Musculoskelet Disord 2008;9:5.
[22] Han C, Kuang MJ, Ma JX, Ma XL. Prevalence of Modic changes in the lumbar vertebrae and their associations with workload, smoking and weight in northern China. Sci Rep 2017;7:46341.
[23] Kuisma M, Karppinen J, Niinimaki J, Kurunlahti M, Haapea M, Vanharanta H, et al. A three-year follow-up of lumbar spine endplate (Modic) changes. Spine 2006;31:1714–8.
[24] Albert HB, Manniche C. Modic changes following lumbar disc herniation. Eur Spine J 2007;16:977–82.
[25] Jensen TS, Kjaer P, Korsholm L, Bendix T, Sorensen JS, Manniche C, et al. Predictors of new vertebral endplate signal (Modic) changes in the general population. Eur Spine J 2010;19:129–35.

[26] Chen L, Hu X, Zhang J, Battie MC, Lin X, Wang Y. Modic changes in the lumbar spine are common aging-related degenerative findings that parallel with disk degeneration. Clin Spine Surg 2018;31:312–7.
[27] Battie MC, Videman T, Kaprio J, Gibbons LE, Gill K, Manninen H, et al. The twin spine study: contributions to a changing view of disc degeneration. Spine J 2009;9:47–59.
[28] Hu XJ, Chen LH, Battie MC, Wang Y. Methodology and cohort profile for the Hangzhou Lumbar Spine Study: a study focusing on back health in a Chinese population. J Zhejiang Univ Sci B 2018;19:547–58.
[29] Battie MC, Videman T, Levalahti E, Gill K, Kaprio J. Heritability of low back pain and the role of disc degeneration. Pain 2007;131:272–80.
[30] Dolan SH, Williams DP, Ainsworth BE, Shaw JM. Development and reproducibility of the bone loading history questionnaire. Med Sci Sports Exerc 2006;38:1121–31.
[31] Wang Y, Videman T, Niemelainen R, Battie MC. Quantitative measures of Modic changes in lumbar spine magnetic resonance imaging: intra- and inter-rater reliability. Spine 2011;36:1236–43.
[32] Kuisma M, Karppinen J, Haapea M, Niinimaki J, Ojala R, Heliovaara M, et al. Are the determinants of vertebral endplate changes and severe disc degeneration in the lumbar spine the same? A magnetic resonance imaging study in middle-aged male workers. BMC Musculoskelet Disord 2008;9:51.
[33] Kanna RM, Shanmuganathan R, Rajagopalan VR, Natesan S, Muthuraja R, Cheung KMC, et al. Prevalence, patterns, and genetic association analysis of Modic vertebral endplate changes. Asian Spine J 2017;11:594–600.
[34] Battie MC, Videman T, Parent E. Lumbar disc degeneration: epidemiology and genetic influences. Spine 2004;29:2679–90.
[35] Maatta JH, Kraatari M, Wolber L, Niinimaki J, Wadge S, Karppinen J, et al. Vertebral endplate change as a feature of intervertebral disc degeneration: a heritability study. Eur Spine J 2014;23:1856–62.
[36] Karppinen J, Daavittila I, Solovieva S, Kuisma M, Taimela S, Natri A, et al. Genetic factors are associated with Modic changes in endplates of lumbar vertebral bodies. Spine 2008;33:1236–41.