

Mari Kuisma

MAGNETIC RESONANCE
IMAGING OF LUMBAR
DEGENERATIVE BONE
MARROW (MODIC) CHANGES

*DETERMINANTS, NATURAL COURSE AND
ASSOCIATION WITH LOW BACK PAIN*

FACULTY OF MEDICINE,
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UNIVERSITY OF OULU

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MEDICA



ACTA UNIVERSITATIS OULUENSIS
D Medica 1008

MARI KUISMA

**MAGNETIC RESONANCE IMAGING
OF LUMBAR DEGENERATIVE BONE
MARROW (MODIC) CHANGES**

Determinants, natural course and association with
low back pain

Academic dissertation to be presented, with the assent of
the Faculty of Medicine of the University of Oulu, for
public defence in Auditorium 7 of Oulu University
Hospital, on April 24th, 2009, at 12 noon

OULUN YLIOPISTO, OULU 2009

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Acta Univ. Oul. D 1008, 2009

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ISBN 978-951-42-9060-2 (Paperback)
ISBN 978-951-42-9061-9 (PDF)
<http://herkules.oulu.fi/isbn9789514290619/>
ISSN 0355-3221 (Printed)
ISSN 1796-2234 (Online)
<http://herkules.oulu.fi/issn03553221/>

Cover design
Raimo Ahonen

OULU UNIVERSITY PRESS
OULU 2009

Kuisma, Mari, Magnetic resonance imaging of lumbar degenerative bone marrow (Modic) changes. Determinants, natural course and association with low back pain

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Acta Univ. Oul. D 1008, 2009

Oulu, Finland

Abstract

Modic changes are vertebral bone marrow signal intensity changes adjacent to the endplates of the degenerated intervertebral discs in magnetic resonance imaging (MRI).

This study evaluated the prevalence and the determinants of Modic changes and their association with low back pain symptoms in an occupational cohort of middle-aged Finnish men. The prevalence and the natural course of Modic changes were assessed over a 3-year follow-up period among sciatica patients. Finally, in a patient population, the characteristics of bone marrow changes in MRI were compared to the imaging findings in CT.

The prevalence of Modic changes was 56% in an occupational cohort of middle-aged males. Besides age, the determinants of Modic changes and disc degeneration were different. Weight-related factors, which add to the load of the lumbar spine, were associated with Modic changes, whereas whole-body vibration was associated with severe disc degeneration.

The prevalence of Modic changes among sciatica patients was 65%, type II change being the most frequent. During the 3-year follow-up, 14% of changes converted to another type, while the incidence of new Modic changes was 6%.

Among middle-aged working males, Modic changes located at L5–S1 and type I Modic changes were more likely to be associated with pain symptoms than other types of Modic changes or changes located at other lumbar levels.

Thirty-eight percent of the endplates with Modic changes had sclerosis in CT. Of specific Modic types, mixed I/II and II/III associated significantly with endplate sclerosis. Endplate sclerosis was not detected in MRI.

In conclusion, Modic changes are a common MRI finding both among patients and middle-aged working males. In addition to age, weight-related factors seem to be important in the pathogenesis of Modic changes. Modic changes can convert from one type to another and type II changes may be less stable than previously assumed. A considerable proportion of Modic changes are sclerotic as observed in CT. Modic changes were always found in combination with a degenerative intervertebral disc and thus they are assumed to be a specific phenotype of degenerative disc disease. Finally, Modic changes may be painful – especially when located at L5–S1 and type I changes.

Keywords: disc degeneration, low back pain, lumbar spine, magnetic resonance imaging, Modic changes

To Jani, Laura and Mikko

Acknowledgements

This study was carried out at the Department of Diagnostic Radiology, Oulu University Hospital in collaboration with the Department of Physical Medicine and Rehabilitation, Oulu University Hospital during the years 2004–2009.

I wish to express my deepest gratitude to my supervisors Professor Osmo Tervonen, M.D., Head of the Department of Diagnostic Radiology, and Professor Jaro Karppinen, M.D., Department of Physical Medicine and Rehabilitation, for providing me with excellent research facilities, and for their enthusiastic and endless support during the whole study period. I owe my sincere thanks to Professor Tervonen for giving me the opportunity to carry out this study in an encouraging and inspiring atmosphere as a member of his research group. His valuable advice and guidance have been essential for completing this study. Professor Karppinen deserves my warm thanks for his never-ending optimism and enthusiastic attitude to this work. His knowledge in the field of low back pain research has been of great importance.

I wish to thank Professor (emeritus) Ilkka Suramo, M.D., and Professor (emeritus) Juhani Pyhtinen, M.D., for their support during these years.

I am grateful to Docent Mats Grönblad, M.D., and Docent Antti Lamminen, M.D., the reviewers of this thesis. Their constructive criticism and encouraging comments are appreciated.

All the collaborators deserve my sincere thanks. I had the great honor of working with a group of specialists and inspiring people, including Professor Heikki Vanharanta, M.D., Docent Markku Heliövaara, M.D., Docent Raija Korpelainen, Ph.D., Docent Antero Natri, M.D., and Docent Simo Taimela, M.D., whose clinical expertise have been essential for this work. I am deeply grateful to Kaisu Kaikkonen, M.Sc., Mauno Kurunlahti, M.D., Ph.D., Eveliina Lammentausta, Ph.D., and Risto Ojala, M.D., Ph.D., for their collaboration and friendly assistance during these years. Special thanks are due to Jaakko Niinimäki, M.D., for fruitful conversations and help in numerous things concerning this work. I wish to thank Marianne Haapea, M.Sc., for her friendly help with statistical analysis, and for the long coffee breaks.

I am grateful to Anna Vuolteenaho, M.A., for the careful revision of the language of this thesis. Mrs. Seija Leskelä is warmly acknowledged for preparing posters related to this work and Mrs. Helena Saari for helping me with the final layout of this thesis. I want to thank Docent Miika Nieminen, Ph.D., for technical help with references. I owe my warm thanks to Mr. Kari Kylmäniemi and the staff

of the MRI unit for help in collecting data for the study. I thank Mrs. Kaisa Punakivi, Mrs. Marja-Liisa Raipola, Mrs. Leila Salo and Ms. Arja Väisänen for their friendly assistance in practical issues.

I want to express my warmest thanks to my colleagues in Southern Central Radiology and MRI for their help and support during these years. I thank especially Docent Eija Pääkkö, M.D. and Airi Jartti, M.D., Ph.D., for their favorable attitude towards scientific work and for the excellent way of teaching body radiology. Heli Reinikainen, M.D., Ph.D., Michaela Bode, M.D., Ph.D., Johanna Ronkainen, M.D., Ph.D., and Maria Suo-Palosaari, M.D., Ph.D., deserve my warm thanks for their important advice at the final stage of preparing this thesis. All my colleagues and friends in the field of radiology and CC-Oulu are gratefully acknowledged for the collaboration and the joyful moments we have shared.

I am deeply grateful to my parents Mirja and Reino for their love and support throughout my life. I thank you for always believing in me. I want to warmly thank my sister Erja, my brother Arto and my friends Teija, Arja and Katri for all the great times spent together and for brightening my days.

I owe my most loving thanks to my daughter Laura and my son Mikko. Your smiles and laughter keep me going. Thank you for reminding me of the most important aim in my life.

Finally, I express my deepest feelings of gratitude and love to my husband Jani for patience and encouragement during these years. He and the children fill my heart with joy.

This study was financially supported by the Finnish Cultural Foundation, the Finnish Medical Foundation, the Orion-Farmos Research Foundation, the Foundation for Medical Research in Oulu and the Radiological Society of Finland, all of which are gratefully acknowledged.

Oulu, February 2009

Mari Kuisma

Abbreviations

AF	Annulus fibrosus
BMI	Body Mass Index
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
DD	Disc degeneration
EP	Endplate
ETL	Echo train length
FLAIR	Fluid-attenuated inversion recovery
FOV	Field of view
FSE	Fast spin echo
hsCRP	High-sensitivity C-reactive protein
HU	Hounsfield unit
IL-6	Interleukin-6
IVD	Intervertebral disc
L	Lumbar disc level
LBP	Low back pain
M	Modic
MRI	Magnetic resonance imaging
N	Number of patients
NEX	Number of excitations
NP	Nucleus pulposus
OR	Odds ratio
PG	Proteoglycan
PGP	Protein gene product
ROI	Region of interest
S	Sacrum
SD	Standard deviation
SE	Spin echo
SI	Signal intensity
STIR	Short tau inversion recovery
T	Tesla
T1	Longitudinal relaxation time
T2	Transverse relaxation time
TE	Echo time
TI	Inversion time
TR	Repetition time
TNF- α	Tumor necrosis factor-alpha
US	Ultrasound
W	Weighted
VAS	Visual analog scale
VS.	Versus

List of original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:

- I Kuisma M, Karppinen J, Haapea M, Niinimäki J, Ojala R, Heliövaara M, Korpelainen R, Kaikkonen K, Taimela S, Natri A & Tervonen O (2008) 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* 9:51.
- II Kuisma M, Karppinen J, Niinimäki J, Kurunlahti M, Haapea M, Vanharanta H & Tervonen O (2006) A three-year follow-up of lumbar spine endplate (Modic) changes. *Spine* 31:1714–1718.
- III Kuisma M, Karppinen J, Niinimäki J, Ojala R, Haapea M, Heliövaara M, Korpelainen R, Taimela S, Natri A & Tervonen O (2007) Modic changes in endplates of lumbar vertebral bodies: prevalence and association with low back and sciatic pain among middle-aged male workers. *Spine* 32:1116–1122.
- IV Kuisma M, Karppinen J, Haapea M, Lammentausta E, Niinimäki J & Tervonen O (2009) Modic changes in vertebral endplates: a comparison of MR imaging and multislice CT. *Skeletal Radiol* 38:141–147.

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1 Introduction

Low back pain (LBP) is a common clinical problem and of major socioeconomic importance in Western countries (Andersson 1998, Walker 2000). In the past 25 years, interest in LBP has increased, presumably because of its cost to industry and society. Lifetime prevalence of low back pain has been reported to range between 60% and 80% (Nachemson 2004). Finland does not differ from other Western countries, as over one million people suffer from low back pain every year (Heistaro *et al.* 1998). The results of the Health 2000 health examination survey in Finland reported the prevalence of chronic low back syndrome as being 10% in men and 11% in women (Aromaa & Koskinen 2004). Although low back pain episodes are usually of short duration, recurrences are common, and 17% of Finnish adults are disabled for long periods because of LBP (Heliövaara *et al.* 1989, Pohjolainen *et al.* 2007).

Imaging studies are recommended in recurrent or prolonged back pain, or before spinal surgery is considered (Simmons *et al.* 1995). Magnetic resonance imaging (MRI) provides a non-invasive precise morphologic appraisal of the lumbar spine and permits direct relation of morphologic findings to LBP (Haughton 2006). However, the clinical significance of abnormal findings is debatable, because in the majority of cases, the origin of the pain remains obscure. Several studies (Boden *et al.* 1990, Jensen *et al.* 1994, Boos *et al.* 1995, Stadnik *et al.* 1998) have shown the occurrence of a wide spectrum of disc abnormalities, including disc degeneration, disc bulging, disc protrusion, and annular tears, in a substantial percentage of healthy volunteers. In contrast, disc extrusions and nerve root compression are rare in asymptomatic volunteers (Jensen *et al.* 1994, Boos *et al.* 1995, Weishaupt *et al.* 1998).

In recent years, vertebral degenerative bone marrow (Modic) changes have come into focus in the search for the source of back pain symptoms. Modic changes are vertebral subchondral bone marrow signal intensity changes visible in magnetic resonance imaging. They were first described in the 1980s with a prevalence of 20–50% in patients with degenerative intervertebral disc disease. (de Roos *et al.* 1987, Modic *et al.* 1988b.) Three different types have been described. Type I lesions [low signal intensity (SI) in T1-weighted (W) and high signal intensity in T2-weighted images] are assumed to indicate an ongoing active degenerative process. Type II lesions (high SI in T1W and T2W images) are thought to manifest a more stable and chronic degeneration. Type III lesions (low

SI in T1W and T2W images) are associated with subchondral bone sclerosis. (Modic *et al.* 1988a, Modic *et al.* 1988b.)

It has been suggested that Modic changes can convert from one type to another and that they all represent different stages of the same pathological process (Modic *et al.* 1988b, Braithwaite *et al.* 1998). It has been shown that a multitude of factors determine the risk of disc degeneration (Adams & Roughley 2006), but there is only limited information about the determinants of Modic changes. Attempts have been made to correlate Modic changes with clinical symptoms (Toyone *et al.* 1994, Braithwaite *et al.* 1998, Sandhu *et al.* 2000, Weishaupt *et al.* 2001, Kokkonen *et al.* 2002, Mitra *et al.* 2004, Kjaer *et al.* 2006, Albert & Manniche 2007), but the results have been controversial.

The goal of this thesis was to increase our knowledge about Modic changes visible in magnetic resonance imaging and thus gain a better understanding of their role in degenerative disc disease. The determinants of Modic changes were evaluated in an occupational cohort, and a comparison of the determinants to those in severe disc degeneration was performed in the same cohort. The prevalence and incidence of Modic changes were assessed over a three-year follow-up period among sciatica patients. The association between Modic changes and back pain symptoms were assessed among middle-aged male workers. Finally, the presence of endplate sclerosis in different Modic types was scrutinized with the aid of computed tomography (CT).

2 Review of the literature

2.1 Spine

The vertebral column extends from the base of the skull to the pelvis. The adult vertebral column usually consists of 33 vertebrae, but only 24 of them are movable: 7 cervical, 12 thoracic and 5 lumbar. The five sacral vertebrae are fused to form the sacrum and the four coccygeal vertebrae are fused to form the coccyx. The structure of the vertebrae differs between the different segments, but the basic structure remains the same throughout the whole vertebral column. Each vertebra consists of the anterior vertebral body and the posterior neural arch. (Moore 1999.) The intervertebral disc (IVD) is the structural link between adjacent vertebrae, providing strong attachment between the bodies of the vertebrae. A cartilaginous endplate (EP), which joins the vertebral body and intervertebral disc, provides a nutritional pathway to the avascular intervertebral disc (Holm & Holm 2004). The vertebrae are also connected to each other by paired facet joints between the articular processes and by strong anterior and posterior longitudinal ligaments. These ligaments extend the length of the whole vertebral column and are attached to the intervertebral discs and vertebral bodies. (Moore 1999.) The neural arch, covered by a thick layer of compact bone, includes the pedicles, laminae, superior and inferior facets, transverse processes, and spinous process (Grossman & Yousem 2003). The body and the neural arch enclose the vertebral canal, which contains the spinal cord and its protective membranes, blood vessels and nerve roots (Moore 1999).

2.1.1 Vertebral body

The vertebral body is the main portion of the vertebra. The vertebral bodies increase in size from the head to the sacrum, being the weight-bearing structures of the spinal column. (Moore 1999.) The vertebral body contains trabecular bone with marrow and fat, covered by a thin layer of compact bone (Grossman & Yousem 2003). The cortex is very thin throughout, on average only 0.6 millimeters (mm) (Edwards *et al.* 2001). The trabecular network is constructed to sustain vertical compressive forces consisting of 0.20–0.22 mm thick vertical columns connected by slightly thinner horizontal struts. The strength of the vertebral body is dependent on the bone mass, the trabecular bone architecture, the thickness of

the cortex and the size of the vertebral body. (McBroom *et al.* 1985, Mosekilde 1993, Hulme *et al.* 2007.)

The vertebral bone marrow is found in the space bounded by the trabecular bone. The main function of the bone marrow is hematopoietic, providing the optimal supply of circulating platelets, white and red blood cells to meet the body's requirements for coagulation, immunity and oxygenation. The vertebral bone marrow consists of two main types: red and yellow bone marrow. (Schiller 1988, Tall *et al.* 2007.) Hematopoietically active red (cellular) marrow contains approximately 40% water, 40% fat, and 20% protein. Hematopoietically inactive yellow (fatty) marrow contains approximately 15% water, 80% fat, and 5% protein. These differences in chemical composition account for the appearance of red and yellow marrow on various MRI pulse sequences. (Vogler & Murphy 1988, Vanel *et al.* 2000.) The normal distribution of bone marrow varies with age. As maturation occurs, a normal physiologic conversion of active red marrow to inactive yellow marrow occurs in an orderly fashion, eventually establishing an adult distribution by the age of 25. In adults, the hematopoietic marrow is concentrated in a central distribution within the axial skeleton. In the spine, the presence of fatty marrow increases with advancing age. (Ricci *et al.* 1990, Tall *et al.* 2007.)

2.1.2 Intervertebral disc

The intervertebral discs lie between the vertebral bodies, linking them together. Their major role is mechanical, as they constantly transmit loads arising from body weight and muscle activity through the vertebral column. They provide flexibility, allowing bending, flexion and torsion, and maintain the stability of the spine. (Urban & Roberts 2003.) The intervertebral discs are complex structures composed of a gelatinous core known as the nucleus pulposus (NP), which is surrounded by a lamellar outer annulus fibrosus (AF) (Holm & Holm 2004). The three major constituents of the intervertebral disc are water, collagen and proteoglycans (PG). Their proportions vary within the disc, as well as with ageing and degeneration. (Eyre 1979.)

The intervertebral disc of an adult is avascular (Holm & Holm 2004). There are two main routes of nutrition. Outer annular cells obtain nutrients from blood vessels in the soft tissues around the periphery of the AF. However, in the case of the nucleus, the distance may be up to 8 mm from the nearest blood vessels. (Urban *et al.* 2004.) The nutritional supply of the NP takes place mainly by passive

diffusion through the subchondral bone and endplate (Urban *et al.* 1978, Eyre 1979, Holm *et al.* 1981).

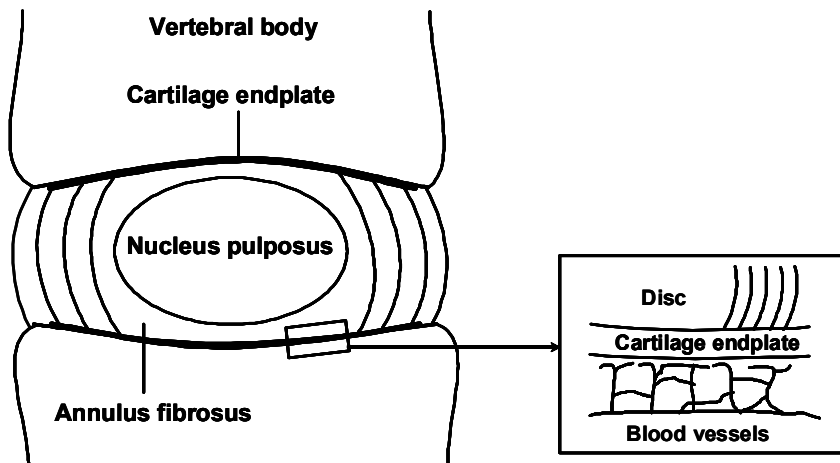


Fig. 1. Schematic coronal illustration of the structure of the intervertebral disc and the blood vessels under the cartilage endplate.

2.1.3 Vertebral endplate

Structure

The vertebral endplate forms a structural boundary between the vertebral body and the intervertebral disc. While the structure and function of the intervertebral disc is well known, much less is known about the endplates. In an early anatomical study the endplates were described as the transitional zone between the vertebral body and the adjacent disc because they were composed of both an osseous and a hyaline cartilage component (Harris & Macnab 1954). Other authors, however, proposed a more limited structure, and described the endplates as a thin layer of hyaline cartilage between the vertebral body and the disc (Peacock 1951, Walmsley 1953). The latter concept has survived, and they are commonly known as cartilaginous endplates or simply endplates (Moore 2004).

The endplate is typically less than 1 mm thick, being thinnest in the central region (Roberts *et al.* 1989). The structure of the EP is similar to that of articular hyaline cartilage, but unlike the articular cartilage of the synovial joints, the endplate cartilage is not connected directly to the cortical bone of the vertebral

body. However, the EP does have intimate contact with the disc through the lamellae of the inner annulus. (Moore 2004.)

The biochemical characteristics of the EP are similar compared to the IVD, water, collagen and proteoglycans being the most important molecular components. However, the collagen content of the EP is higher and the proteoglycan and water contents lower compared to the adjacent disc. (Roberts *et al.* 1989.) Of the different collagens, type X (Aigner *et al.* 1998) and II (Sahlman *et al.* 2001) are probably the most important in maintaining the integrity of the endplate.

Function

The endplate has an important role in disc nutrition (Eyre 1979). At an early stage of the development of the axial skeleton, tiny blood vessels penetrating the endplates provide nutrition for the EP itself and for the developing IVD. These blood vessels persist only until skeletal maturity, at which time the discs become, for the most part, avascular. (Moore 2000.) However, in adults, the outer parts of the annular lamellae may contain tiny collateral vessels (Moore *et al.* 1992, Kauppila 1995). Apart from a sparse blood supply in the outer layer of the AF, mature discs are almost totally reliant on diffusion of nutrients across the cartilage endplate (Urban *et al.* 1978, Eyre 1979, Moore 2000). The diffusion is a selective process based on molecular size and ionic charge of the molecules involved (Moore 2000). Additionally, degenerative changes of the subchondral bone (Roberts *et al.* 1997b) and endplate calcification (Roberts *et al.* 1993, Urban *et al.* 2001) may limit the penetration of nutrients into the disc.

The endplate is also an important structure for the mechanical function of the spine. In the course of normal physical activity, mechanical loading can alter the shape of the disc to the extent that the endplate and the subchondral bone become deformed (Brinckmann *et al.* 1983). This deformation is reversible in young healthy endplates, but high compressive loads, when applied repeatedly, may result in irreversible damage. The endplate appears to be susceptible to mechanical failure as this is a weak link in the structure of the disc. (Adams *et al.* 2000, Moore 2000.)

The endplate acts as a physical barrier preventing the disc from bulging into the adjacent vertebral body (Moore 2000). A Schmorl's node is a vertical protrusion of the contents of the nucleus into the adjacent vertebral body. They are found in more than 70% of autopsy spines with equal frequency above and below

the age of 50 years, suggesting that they appear relatively early in life and may precede disc degeneration. (Hilton *et al.* 1976.) Despite being relatively common, the etiology of these changes remains a mystery.

2.2 Disc degeneration

Disc degeneration (DD) is the deterioration and remodeling of the physical and chemical properties of the tissue with retrogressive pathologic changes in the cells or macromolecules (Holm 1993). With increasing age comes an increased incidence of degenerative changes, including cell death, cell proliferation, mucous degeneration, granular change and concentric tears (Boos *et al.* 2002). The most significant biochemical change to occur in disc degeneration is loss of proteoglycan, which results in dehydration of the disc (Lyons *et al.* 1981). Individual variation in DD is great, which makes it difficult to differentiate changes that occur solely due to aging from those that might be considered pathological (Boos *et al.* 2002, Holm & Holm 2004). Despite intensive research, the sequelae of progression of catabolic changes and especially the association of DD with pain production remain unclear.

The etiologies of disc degeneration include age, genetic inheritance, physical loading history and impaired nutrition, all of which can weaken IVDs to such an extent that structural failure occurs during the activities of daily living (Adams & Roughley 2006). Several studies suggest that familial predisposition has an important role in the pathomechanism of degenerative changes (Battie *et al.* 1995, Annunen *et al.* 1999, Sambrook *et al.* 1999). Abnormal mechanical loading is also thought to provide a pathway to disc degeneration (Adams *et al.* 2000). Traumatic events (Osti *et al.* 1990, Kerttula *et al.* 2000) and heavy physical occupational loading (Videman *et al.* 1995, Luoma *et al.* 1998) have been suspected to lead to disc degeneration. One of the primary causes of DD is thought to be failure of the nutrient supply to the disc cells (Nachemson *et al.* 1970, An *et al.* 2004). The pathway from the blood supply to the nucleus cells is precarious because these cells are supplied by capillaries that originate in the vertebral bodies, penetrate the subchondral plate and terminate just above the cartilaginous endplate (Urban *et al.* 1978). In this regard, EP is an important structure in transporting nutrients and maintaining the health of the intervertebral disc.

2.3 Degenerative changes of the vertebral endplates and subchondral bone

2.3.1 Morphologic changes

Morphologic changes to the endplates and subchondral bone occur with advancing age, but also in association with disc degeneration. It is difficult to differentiate changes that occur solely due to aging from those that are associated with degeneration. Interestingly, however, endplate changes have been observed to precede the intradiscal changes. (Boos *et al.* 2002.)

During the first decade, vascular channels through the endplate diminish (Coventry *et al.* 1945, Boos *et al.* 2002) and the first endplate cracks are seen (Boos *et al.* 2002). Vascular channels disappear by the age of 20 (Coventry *et al.* 1945, Boos *et al.* 2002) and only the outer parts of the annular lamellae may contain tiny collateral vessels (Moore *et al.* 1992, Kauppila 1995). At this stage, cartilage cracks and microfractures of the adjacent subchondral bone with new bone formation are frequently seen. From the third decade, abnormalities of the EP are very similar to those seen in younger groups, but in increasing numbers. Starting in the fourth decade, trabeculae in the vertebral body change in size and pattern resulting in decreased vertebral body strength and density (Mazess 1982). In the fourth and fifth decades, advanced degeneration with structural disorganization of the EP is observed. During the sixth and seventh decades, tissue alterations become most severe, including microfractures and bone sclerosis. (Boos *et al.* 2002.) After this stage, scar formation, large tissue defects (Coventry *et al.* 1945, Boos *et al.* 2002) and calcification of the endplates are seen (Bernick & Cailliet 1982).

2.3.2 Biochemical changes

The biochemistry of the endplate is important in maintaining the integrity of the disc (Roberts *et al.* 1996). The composition of the endplate has been shown to change in degeneration with a loss of proteoglycan in the matrix (Roberts *et al.* 1989). Therefore, where this occurs it will effectively “open up” channels through which substances can pass into disc and vice versa. The loss of proteoglycans of the endplate has been shown to lead to loss of proteoglycans from the nucleus. (Roberts *et al.* 1996.) These authors speculated that, similarly, the flow of substances into the disc, which would normally not occur, may be possible where

proteoglycans have been lost. Such substances could include cytokines or enzymes, which might have deleterious effects on the disc. Interestingly, the loss of proteoglycans from the endplate has been shown to precede disc degeneration (Pearce *et al.* 1987). Collagen type X is probably the most important in the endplates because it is a marker of hypertrophic chondrocytes and is thought to be involved in cartilage calcification (Aigner *et al.* 1998). Additionally, inactivation of one Collagen II gene allele in young mice has been shown to lead to lower glycosaminoglycan concentration in the endplates and thicker and more irregular endplates that become prematurely calcified (Sahlman *et al.* 2001).

The bone marrow in the spine can vary in appearance according to the patient's age, and can be affected by infectious, inflammatory, metabolic, neoplastic or degenerative processes. With increasing age, the amount of fatty marrow increases. (Ricci *et al.* 1990, Tall *et al.* 2007.) Degenerative disc disease can cause changes in the bone marrow adjacent to the cartilaginous endplates. Three different types of changes have been described (Modic *et al.* 1988b). Bone marrow edema reflects an increased amount of extracellular water and fibrovascular changes in the bone marrow. Fatty bone marrow changes reflect the replacement of the normal bone marrow with fat cells. The dense bone without marrow elements has been thought to correlate with subchondral bone sclerosis. (Modic *et al.* 1988a, Modic *et al.* 1988b.)

2.4 Magnetic resonance imaging techniques of vertebral bone marrow

Magnetic resonance imaging is the modality of choice in detecting bone marrow abnormalities (Daffner *et al.* 1986, Modic *et al.* 1988b, Vogler & Murphy 1988, Ricci *et al.* 1990, Vanel *et al.* 2000, Tall *et al.* 2007). Differentiation of red and yellow marrow with other imaging modalities, such as plain film radiography, ultrasound (US), computed tomography (CT) or scintigraphy, has not been proved (Modic *et al.* 1988b, Vogler & Murphy 1988, Lusins *et al.* 1998). Additionally, the lack of ionizing radiation and multiplanar imaging capability of MRI makes it superior compared to the other imaging modalities in detecting bone marrow diseases.

Standard sequences to image vertebral bone marrow include T1- and T2-weighted fat saturation or STIR (short tau inversion recovery) sequences (Mirowitz *et al.* 1994, Tall *et al.* 2007). Normal marrow is composed of an intermixture of red hematopoietic marrow, yellow fatty marrow and trabeculae in

varying proportions, based on patient's age and other factors. Its normal appearance in MRI reflects this combination (Ricci *et al.* 1990, Tall *et al.* 2007).

There is superb differentiation between red and yellow bone marrow in T1-weighted sequences. In T1-weighted images the yellow marrow is hyperintense in signal intensity, in contrast with the relatively decreased signal of red marrow. These differences in signal intensity are a direct reflection of the differences in fat/water content within red and yellow marrow. (de Roos *et al.* 1987, Modic *et al.* 1988b, Ricci *et al.* 1990, Tall *et al.* 2007.) Both T1-weighted spin echo (SE) and fluid-attenuated inversion recovery (FLAIR) sequences are used to image the vertebral bone marrow (Melhem *et al.* 1997, Erdem *et al.* 2005).

T2-weighted fast spin echo (FSE) with fat saturation and STIR sequences have similar sensitivity to detect bone marrow pathology. The clinical advantages are based on marked fat suppression. Both sequences demonstrate high contrast and conspicuousness for the depiction of most types of bone marrow pathology. The disadvantage of T2-weighted FSE is its dependence on excellent magnetic field homogeneity for adequate fat suppression. (Mirowitz *et al.* 1994, Tall *et al.* 2007.)

Newer imaging techniques, such as diffusion-weighted (Baur *et al.* 2001, Zhou *et al.* 2002) and gradient echo (Erly *et al.* 2006) imaging, have been developed. Both techniques may be useful in differentiating acute benign compression fractures from malignant infiltration and pathologic fractures. Intravenous gadolinium administration is useful for assessing the paraspinal soft tissues and the enhancement of the disc (Van Goethem *et al.* 2000), but it is not essential for routine assessment of the vertebral bone marrow (Tall *et al.* 2007).

2.5 Vertebral degenerative bone marrow (Modic) changes

2.5.1 Definition

Vertebral degenerative bone marrow (Modic) changes are signal intensity changes visible in MRI. These changes occur adjacent to the cartilaginous endplates of the degenerative intervertebral discs. (de Roos *et al.* 1987, Modic *et al.* 1988b.) Bone marrow signal intensity changes in the vertebral bodies were first reported by de Roos *et al.* (1987). The classification of changes was provided by Modic *et al.* (1988b) based on 474 patients, most of whom had chronic low back pain (Table 1). The histological correlation was based on six operative specimens. These authors described two types of changes: Modic type I changes (low SI in T1W and high SI

in T2W images) indicated an ongoing active degenerative process and demonstrated vascularized fibrous tissue within the bone marrow. Modic type II changes (high SI in T1W and T2W images) were more stable during a three-year follow-up and reflected fatty replacement of the bone marrow. (Modic *et al.* 1988b.) Type III lesions were found later (low SI in T1W and T2W images), and they are thought to associate with endplate sclerosis in plain film radiography (Modic *et al.* 1988a). The histological nature of type III changes remains undetermined. The detection of different Modic types with other imaging modalities, such as plain film radiography, ultrasound, computed tomography or scintigraphy, has not been proved (Modic *et al.* 1988b, Lusins *et al.* 1998).

Mixed Modic lesions (type I/II and type II/III) have also been identified. Braithwaite *et al.* (1998) suggested that Modic changes can convert from one type to another and that they all present different stages of the same pathological process.

Table 1. The MRI signal intensity and histology of type I, II and III Modic changes.

Modic type	MRI signal intensity		Histology
	T1W	T2W	
I	↓	↑	Vascularized fibrous tissue
II	↑	↑	Fatty replacement
III	↓	↓	Unknown

2.5.2 Prevalence and distribution

The prevalence of Modic changes in patients with degenerative disc disease of the lumbar spine varies between 19 and 59% (de Roos *et al.* 1987, Modic *et al.* 1988b, Toyone *et al.* 1994, Weishaupt *et al.* 2001, Schmid *et al.* 2004, Karchevsky *et al.* 2005, Kjaer *et al.* 2005a, Albert & Manniche 2007). Conversely, Modic changes are uncommon in asymptomatic individuals without disc degeneration (Weishaupt *et al.* 1998, Kjaer *et al.* 2006). In a systematic review article, Modic changes were observed to be a common MRI-finding in patients with non-specific LBP with a median prevalence of 43%, but less common in non-clinical populations with a median prevalence of 6% (Jensen *et al.* 2008).

The most common type of Modic change in the lumbar spine is type II and it may account for up to 80% of Modic changes (de Roos *et al.* 1987, Modic *et al.* 1988b, Braithwaite *et al.* 1998, Schmid *et al.* 2004, Karchevsky *et al.* 2005). How-

ever, this has recently been questioned by two authors suggesting that Modic type I change may be a more common than type II in the lumbar spine (Weishaupt *et al.* 2001, Kjaer *et al.* 2005a). Modic changes most likely occur at L4–5 and L5–S1 and associate with degenerative disc disease (Modic *et al.* 1988b, Karchevsky *et al.* 2005, Luoma *et al.* 2008). In addition to disc degeneration, Modic changes are also observed to occur in a lumbar segment with a disc herniation (Schmid *et al.* 2004, Albert & Manniche 2007) or segmental instability (Toyone *et al.* 1994).

Most studies describe Modic changes occurring in the lumbar spine. However, these changes have also been reported in cervical (Peterson *et al.* 2007) and thoracic spine (Girard *et al.* 2004). A prevalence of 16% in the cervical spine has been observed, which is similar to previously reported values of the lumbar spine. Of specific Modic types, type I changes predominated in the cervical spine, which may be related to a greater segmental mobility as compared with the lumbar spine. (Peterson *et al.* 2007.) In the thoracic spine, a prevalence of 2.5% has been observed, which may be due to the relative lack of mobility compared with the other spinal regions (Girard *et al.* 2004).

2.5.3 Determinants

It has been shown that the risk of disc degeneration is determined by a multitude of factors including age, genetic inheritance and loading history (Sambrook *et al.* 1999, Adams & Roughley 2006). However, there is only limited information about the determinants of Modic changes.

Modic changes are positively associated with age, supporting their degenerative etiology (Modic *et al.* 1988b, Karchevsky *et al.* 2005). Conversely, Modic changes are uncommon in younger individuals. In a study of 439 thirteen-year-old children, the prevalence of changes was only 0.5% (Kjaer *et al.* 2005b). In addition, Modic changes have been shown to be associated with male gender (Karchevsky *et al.* 2005).

Obesity has been suggested as a risk factor for disc degeneration, but the results have remained controversial (Heliövaara 1987, Riihimäki *et al.* 1990, Harrington *et al.* 2001, Liuke *et al.* 2005). In a patient study, Modic changes were associated with increasing weight, but not with BMI (Karchevsky *et al.* 2005). Recently, overweight in combination with hard physical work was significantly associated with the prevalence of Modic changes (Leboeuf-Yde *et al.* 2008). In another population-based cohort, exposure to high-level physical activity at leisure time did not differ between subjects with “Modic changes and disc degeneration”

vs. those with “only disc degeneration”. However, exposure to occupational physical load was significantly higher in the subgroup of “Modic changes and disc degeneration” compared to “only disc degeneration” group. (Kjaer *et al.* 2006.)

Smoking has been suspected to carry deleterious effects on the intervertebral discs. According to a systematic review, smoking is associated with LBP (Goldberg *et al.* 2000). Smoking is a risk factor for atherosclerosis, which is assumed to cause disc degeneration through diminished nutrition (Kauppila *et al.* 1994) and diffusion (Kurunlahti *et al.* 2001). Although an association between smoking and disc degeneration was observed in an earlier study on Finnish twins (Battie *et al.* 1991), the association between smoking and disc degeneration was not confirmed in a later study (Battie *et al.* 1995). There is only one study of the effect of smoking on Modic changes. In the Danish study, self-reported hard physical work in combination with heavy smoking was strongly associated with Modic changes (Kjaer *et al.* 2006).

2.5.4 Differential diagnosis

There are many conditions that need to be considered in the differential diagnosis. Spondylodiscitis, spinal neoplasms and inflammatory spondyloarthropathias may lead to signal intensity alterations that may mimic Modic type I changes. In addition, the possibility of a signal change around Schmorl’s node must always be kept in mind.

The involvement of the disc and the bony endplate is critical when differentiating degenerative Modic changes from spinal infections. The disc signal is often reduced in Modic changes compared to increased signal intensity in T2-weighted sequences in spondylodiscitis. In Modic changes bony endplates are preserved rather than indistinct or destroyed as seen in an infective process. Contrast enhancement of the disc and adjacent bone may occur in both conditions. An important finding is the presence of paravertebral inflammatory tissue, which may considerably help in establishing the diagnosis of spondylodiscitis. (Van Goethem *et al.* 2000, Ledermann *et al.* 2003, James & Davies 2006.) In addition to these imaging study findings, clinical symptoms and laboratory tests can help to differentiate the two conditions (James & Davies 2006). Local spinal pain is the most common presenting symptom in spondylodiscitis and is seen in up to 95% of patients. In addition, C-reactive protein (CRP) is thought to be the most reliable laboratory test, being increased in up to 100% of cases at the time of diagnosis. (Wirtz *et al.* 2000.)

In spinal neoplasms bone marrow is typically replaced with edema. However, tumor spread rarely affects the disc, endplate and subchondral bone marrow. Thus, a well-defined endplate with normal signal within the disc favors a neoplastic process. Tumors can also cause bony destruction via osteolysis, which is not typically seen in degenerative disease. (Modic *et al.* 1988b, James & Davies 2006.)

An inflammatory spondyloarthropathy such as ankylosing spondylitis may also present diagnostic difficulties. However, the anatomical distribution of changes is different and the distinction is not usually difficult to make. The most prominent feature of ankylosing spondylitis consists of an enthesitis at the insertion of the annulus fibrosus-longitudinal ligament complex. Inflammatory tissue leads to the destruction of the attachment of ligament to bone (anterior vertebral corners) resulting in a superficial erosion and edema. (Jevtic *et al.* 2000, James & Davies 2006.) Conversely, Modic changes usually affect the whole antero-posterior length of the vertebral subchondral bone (Modic *et al.* 1988b).

Schmorl's nodes have a typical morphology compared to degenerative Modic changes. They are usually characterized by localized defects (low T1W and high T2W signals) in bony endplates (Williams *et al.* 2007), whereas Modic changes tend to be linear bone marrow changes and parallel to the cartilaginous endplates (Modic *et al.* 1988b).

2.5.5 Pathogenesis

The etiology of Modic changes is unknown. However, there are three possible hypotheses for the pathogenesis of Modic changes: a biomechanical, biochemical (these two may be interrelated) and infective hypothesis.

The endplate is a weak link of the spine in compression, and always fails before the intervertebral disc, even if the latter is injured before loading commences (Brinckmann 1986). This can result in morphologic changes in the bone marrow including microfractures and structural disorganization (Boos *et al.* 2002). Histologically, type I Modic changes demonstrated disruption and fissures of the endplates (Modic *et al.* 1988b). In a review article, Modic and Ross (2007) concluded that the altered signal intensity in MRI is not the causal pathologic process, but rather a reflection of the causal process, which is some type of biomechanical stress or instability. Further evidence in favor of the biomechanical theory comes from recent animal studies, where injuries to the disc induced changes in the adjacent vertebrae with subsequent bone marrow depletion and

regeneration (Malinin & Brown 2007, Ulrich *et al.* 2007). In the study of Toyone *et al.* (1994), 70% of patients with Modic type I change and only 16% of those with type II were found to have segmental hypermobility in the dynamic flexion-extension MR images. They suggested that Modic changes may be a marker of segmental instability. This theory has been supported by indirect evidence from lumbar fusion studies, in which nonunion was predominantly associated with the persistence of type I Modic changes (Lang *et al.* 1990, Buttermann *et al.* 1997).

Crock (Crock 1970, Crock 1986) proposed the concept of “internal disc disruption”, suggesting that repeated trauma to the intervertebral disc results in the production of chemical substances in the nucleus pulposus. Diffusion of such toxic chemicals through the vertebral endplate could then result in a local inflammatory reaction (Crock 1970). Ohtori *et al.* (2006) found that the endplates of patients with Modic type I or type II changes had more protein-gene-product (PGP) 9.5 immunoreactive nerve fibers and tumor necrosis factor-alpha (TNF- α) immunoreactive cells than those with normal endplates in MRI. Furthermore, the number of TNF immunoreactive cells in the endplates with Modic type I changes was higher than those with type II (Ohtori *et al.* 2006). In addition, Rannou *et al.* (2007) found high-sensitivity C-reactive protein (hsCRP) to be increased in patients with chronic low back pain and Modic type I change. The biochemical mechanism is also supported by the fact that the patients with chronic LBP and predominantly Modic type I changes tended to have better short-term efficacy following intradiscal steroid injections than those with predominantly type II changes (Fayad *et al.* 2007).

Recent experimental findings suggest that biomechanical and biochemical pathways may be interrelated. Ulrich *et al.* (2007) showed that repeated injury to the disc causes persistent inflammation. In addition to elevated cytokine production [interleukin-1 (IL-1), IL-8 and TNF- α] in the disc, they observed evidence of vertebral remodeling. Bone marrow spaces adjacent to the degenerated intervertebral discs were filled with granulation tissue consisting of new vessels, fibroblasts and osteoblasts that lined thickened trabecular elements. These features were analogous to those reported by Modic *et al.* (1988b) and were similar to Modic type I bone marrow changes.

The infective hypothesis has been suggested by Albert *et al.* (2008b), who speculated that low virulent bacterial infection may play a role in the pathogenesis of Modic changes. They observed in an uncontrolled study that the clinical effect of antibiotic treatment was large in a group of patients with Modic changes

suffering from persistent LBP following a disc herniation. Previously, Stirling *et al.* (2001) have found a significant positive culture rate (19 of 36; 53%), especially of *Propionibacterium acnes* and *Corynebacterium propinquum* in surgical lumbar disc herniation specimens. These bacteria are found on the skin and in oral cavities in all individuals. They frequently invade the circulatory system (for example during tooth brushing), where they do not present any health risks due to the aerobic environment in the bloodstream. (Roberts *et al.* 1997a, Olsen 2008.) However, Albert *et al.* (2008a, 2008b) hypothesized that anaerobic bacteria enter the disc through the radial tears of the annulus fibrosus causing a low virulent and slowly developing infection of the disc. As intervertebral discs are avascular, they constitute an ideal environment for the growth of anaerobic bacteria, and local inflammation in the adjacent bone may be due to the production of cytokines. However, a recent study by Wedderkopp *et al.* (2009) found no evidence of bacteria in vertebrae with Modic type I changes. The affected vertebra was biopsied from 24 consecutive patients by a strict aseptic procedure. None of the biopsies yielded growth of anaerobic bacteria. No randomized study of the effect of antibiotic treatment on Modic changes has been performed so far.

2.5.6 Natural course

In the original study, Modic *et al.* (1988b) observed that all six patients with a type I change converted to a type II or normal bone marrow over a 14- to 36-month interval, whereas type II changes did not alter with time.

The dynamic process of Modic type I changes was recently confirmed as it was observed that only 11% of type I changes remained stable during an 18- to 72-month follow-up period (Luoma *et al.* 2008). In another study, 52% of type I changes converted into type II and 40% increased in size, while only 8% of type I changes remained stable during a 12- to 72-month follow-up period (Mitra *et al.* 2004).

Mixed Modic types (I/II and II/III) were found later and it was suggested that all Modic changes present different stages of the same degenerative process (Braithwaite *et al.* 1998). Mixed changes are assumed to develop before conversion to one of the true Modic types (Vital *et al.* 2003).

2.5.7 Association with low back pain

Several studies have shown the occurrence of a wide spectrum of disc abnormalities, including disc degeneration, disc bulging, disc protrusion, and annular tears, in a substantial percentage of healthy volunteers (Boden *et al.* 1990, Jensen *et al.* 1994, Boos *et al.* 1995, Stadnik *et al.* 1998). In contrast, disc extrusions, nerve root compression and Modic changes are rare in asymptomatic volunteers (Jensen *et al.* 1994, Boos *et al.* 1995, Weishaupt *et al.* 1998, Kjaer *et al.* 2006). In recent years, Modic changes have come into focus in the search for the source of back pain symptoms. The association of Modic changes with LBP has been studied in relation to both symptom history and discography of the affected levels.

Based on clinical symptoms, there is evidence that Modic type I changes may be associated with LBP. Toyone *et al.* (1994) stated that 73% of patients with type I change, but only 11% of patients with type II had LBP. In a longitudinal follow-up of LBP patients, a positive trend was found between the conversion of type I to type II change and symptom improvement (Mitra *et al.* 2004). In the Danish study of general population, Modic changes associated strongly with LBP during the past year. When they analyzed type I changes separately, the strength of the association increased. (Kjaer *et al.* 2006.) Recently, Albert and Manniche (2007) reported a strong association between Modic changes and LBP, as 60% of patients with Modic changes but only 20% of those without changes had LBP. They also showed that type I changes were more strongly associated with LBP than type II changes. The association between Modic changes and LBP has not only been found among patients with LBP, but also in the general (Kjaer *et al.* 2005a) and working (Schenk *et al.* 2006) populations.

The correlation of Modic changes with discogenic pain, i.e. pain provoked by discography, is controversial. Braithwaite *et al.* (1998) found high specificity and positive predictive value for all Modic types as an indicator of a painful disc at discography. Weishaupt *et al.* (2001) showed that when only moderate and severe endplate abnormalities of both type I and II were considered abnormal, all injected discs at discography caused concordant pain. However, also negative associations between Modic changes and pain provocation during discography of the affected levels have been reported (Sandhu *et al.* 2000, Kokkonen *et al.* 2002).

The reasons why Modic changes may be painful are not known. Brown *et al.* (1997) studied specimens of vertebral endplates, intervertebral discs and adjacent cancellous bone obtained during anterior discectomy and fusion from patients with

degenerative disc disease and low back pain. They observed cracks and defects in the EPs with increased vascular density and number of sensory nerve fibers. They concluded that such changes could be a source of LBP in patients with degenerative disc disease. (Brown *et al.* 1997.) Increased levels of IL-6, a proinflammatory cytokine, have been detected in the intervertebral discs in patients with LBP. In addition, the same authors reported a significant increase in the number of tumor necrosis factor immunoreactive cells in the endplates with Modic changes, especially in type I changes. They suggested that the pain may originate from the endplates in patients with Modic changes. (Ohtori *et al.* 2006.) In a randomized controlled trial, infliximab (a monoclonal antibody against TNF- α), was of similar efficacy as placebo in the treatment of disc herniation-induced sciatica (Korhonen *et al.* 2006). However, infliximab tended to be more efficacious when a Modic change co-localized at the symptomatic herniation level.

Another source of pain may be the intervertebral disc. Immunoreactive nerves have also been shown to be present in degenerated discs (Bogduk *et al.* 1981, Freemont *et al.* 1997). A positive correlation between disc degeneration and back pain has been reported (Erkintalo *et al.* 1995, Luoma *et al.* 2000, Waris *et al.* 2007), but the results are controversial. Additionally, disc degeneration has a very high prevalence in the asymptomatic population (Boden *et al.* 1990, Modic & Ross 2007). Interestingly, it has been observed that LBP symptoms were more pronounced in subjects with Modic changes and disc degeneration compared to the subjects with only disc degeneration (Kjaer *et al.* 2006).

3 Purpose of the study

The purpose of the present study was:

1. To investigate the determinants of Modic changes, and whether Modic changes and disc degeneration share common etiological factors.
2. To analyze the prevalence, extent, and natural course of Modic changes over a three-year follow-up period.
3. To study the association of Modic changes with low back and sciatic pain in a sample of middle-aged male workers.
4. To evaluate the presence of endplate sclerosis in different types of Modic changes and to assess the capability of MRI in detecting endplate sclerosis within these changes.

4 Materials and methods

The materials and methods are described in more detail in the original articles (I–IV).

4.1 Study population

4.1.1 Occupational sample of male train engineers and sedentary paper mill workers (I and III)

The study population consisted of 228 males with a mean age of 47 years (range 36–56 years) at the time of enrolment. The occupational sample, train engineers (N=159), worked for the Finnish state railways, and had a mean of 21 years (range 5–31 years) of exposure to whole-body vibration. They were all full-time train drivers with approximately five hours of daily exposure to whole-body vibration composed of both vertical and horizontal components. They were all from Northern Finland, ensuring that they had been operating the same kinds of locomotives and had similar exposure to vibration. The occupational control group consisted of 69 paper mill workers from the same geographical region with sedentary jobs and no occupational exposure to vibration.

The study design was developed by Drs. Jaro Karppinen, Antero Natri, Leena Alakokko, Osmo Tervonen and Simo Taimela. Dr. Antero Natri was responsible for the arrangements with the Finnish state railways. The study questionnaires were delivered to all the train engineers working in Northern Finland. Participation was on a voluntary basis, but 73% of the train engineers participated in the study. The occupational controls were recruited from workers of a paper mill and a chemical factory. They had to be of similar age-range and educational level as the train engineers, with sedentary work and no occupational driving at any point of their working history. Occupational health care units of the respective work places distributed the study criteria and contact data via their intranets, and the eligible controls could contact the study center (Oulu Deaconess Institute) on a voluntary basis. Institutional Review Board approval and signed, informed consent from each patient were obtained before MR imaging. The study was approved by the ethical committee of Oulu University Hospital.

4.1.2 Patients (II and IV)

Study II consisted of 60 unoperated sciatica patients with a mean age of 45 years (range 23–76 years) with unilateral pain below the knee lasting from three weeks to six months. They had been referred to a randomized controlled trial evaluating the efficacy of periradicular nerve root infiltration for sciatica (Karppinen *et al.* 2001a). At three years (range 2.6–4.0), these patients were called for a prescheduled follow-up MRI assessment. The study protocol was approved by the ethical committee of Oulu University Hospital.

Study IV included 70 patients with a mean age of 48 years [(range 17–75 years) at the time of the first imaging] who underwent lumbar CT and MRI examinations between January 2004 and December 2006 and met the inclusion criteria, and were included after a review of a digital database of a radiology record system. Patients were included if a) both CT and MRI examinations were done within six months from the first imaging, b) MR imaging was performed with a 1.5 T system, and c) CT examination was performed with 16-row multislice CT at our own institution. Two patients with focal metastatic lesions and two patients with lumbar arthrodesis were excluded. Additionally, one technically suboptimal MRI study was excluded. The institutional review board did not require advance approval or individual informed consent, as only patients' images were reviewed.

4.2 Assessments (I and III)

In study I, the self-administered questionnaire included items of occupational history, smoking, alcohol consumption and leisure time physical activity. In addition, body weight (kg), height (m), waist circumference (cm), and body fat percentage (%) were measured. Body Mass Index (BMI) was calculated, and percentage of fat and lean mass was assessed using bioimpedance equipment (Bodystat 1500, Bodystat Ltd., Douglas, Isle of Man, UK). The table of the distribution of selected determinants may be seen in the original article of study I.

In study III, the participants were asked to report the number of previous LBP and leg pain episodes lasting at least 14 days, and to assess the intensity of the pain both during the past week and the past three months with a 10-cm visual analog scale (VAS). Additionally, dichotomous questions were used to assess whether they had experienced LBP ever (vs. never), and whether they had LBP today (at the day of assessment) or not.

4.3 Magnetic resonance imaging

MRI examinations (I–IV) of the lumbar spine were performed using a 1.5 T unit (GE Signa Twinspeed, General Electric Medical Systems, Milwaukee, WI) and a Phased Array CTL Spine Coil (USA Instruments, Aurora, OH).

Imaging sequences in studies I and III were sagittal T1W [repetition time (TR)/echo time (TE) 1809/18 msec] fluid-attenuated inversion recovery (FLAIR) and sagittal T2W (3960/116) fast spin echo (FSE) sequences. Additionally, study III included axial T2W (3960/116) FSE sequences. The inversion recovery time for T1W images was 660 msec, and the number of excitations for both T1W and T2W images was four. Echo train length (ETL) for T1W images was eight, for T2W sagittal images 29 and for T2W axial images 26. The image matrix was 448 x 192 for T1W images, 448 x 224 for T2W sagittal images and 256 x 160 for T2W axial images. Field of view (FOV) for sagittal images was 28 x 28 cm and for axial images 18 x 18. Slice thickness was 4 mm and interslice gap 1 mm.

At baseline, the sequences in study II were T1W (640/14) axial spin echo (SE) and T2W (4000/95) sagittal FSE images. At three years, the imaging sequences included T1W (400/14) sagittal SE images and T2W (4000/95) sagittal FSE images. The technical specifications included ETL of 16, a slice thickness of 4 mm with interslice gaps of 1.0 and 0.5 mm, a FOV of 36 and 20 cm, a matrix of 256x128 and 256x192, and a number of excitations (NEX) of 1 and 2 for sagittal and axial images, respectively.

Study IV included T1W (2060/21) sagittal FLAIR sequences with an inversion time (TI) of 860 ms, echo train length of 6 and the number of acquisitions of 4. The matrix size was 256 x 224, FOV 28 x 28 cm, slice thickness 4 mm and intersection gap 1 mm. T2W (4000/118) sagittal FSE images were obtained with an ETL of 27 and the number of acquisitions of 4. The matrix size was 448 x 224, FOV 28 x 28 cm, slice thickness 4 mm, and intersection gap 1 mm.

4.4 Computed tomography imaging (IV)

The lumbar CT imaging was performed using a 16-slice CT scanner (GE LightSpeed Pro 16; GE Healthcare, Milwaukee, Wisc., USA) with a detector configuration of 16 x 1.25 mm. A standard lumbar spine protocol with a tube voltage of 120 kV, tube current of 100–650 mA and rotation time of 0.8 s was used. Automatic tube current modulation based on patient size and X-ray

attenuation was used. The slice thickness and reconstruction interval was 1.25 mm and 0.625 mm, respectively.

4.5 Image analysis

In all studies (I–IV) the classification of Modic changes was carried out at a workstation on the basis of the T1W and T2W MR images based on the five midsagittal planes. Both the upper and lower endplates at each disc level were graded separately into Modic types MI (low SI in T1W and high SI in T2W images), MII (high SI in T1W and T2W images) and MIII (low SI in T1W and T2W images) (Modic *et al.* 1988a, Modic *et al.* 1988b), and mixed types MI/II and MII/III (Braithwaite *et al.* 1998). In studies I and III, Modic types I and I/II were grouped together, as all lesions containing type I change are assumed to indicate a more active process. Similarly, Modic types II and II/III were grouped together, as they are thought to manifest a more stable and chronic degenerative process. In study II the involvement of one or both endplates, antero-posterior localization, maximal vertical depth (mm), and extent (involvement of the endplate area as quadrants) of Modic changes were also analyzed.

The degree of disc degeneration was graded (studies I and IV) on the T2-weighted sagittal MR images by using the grading system of Pfirrmann *et al.* (2001). In grade I degeneration the nucleus pulposus is homogeneously hyperintense and clearly distinct from the hypointense outer annular fibers. In grade II degeneration the nucleus pulposus is inhomogeneous and horizontal hypointense bands may be present. In grade III degeneration the inner parts of the disc are inhomogeneous and have intermediate signal intensity. In grade IV degeneration the distinction between the inner and outer parts of the disc is lost, and the inner parts of the disc have intermediate or low signal intensity. In grade V degeneration the disc is collapsed. In study II, disc degeneration was graded as normal (no signal changes), grade 1 (slight decrease in signal intensity of the nucleus on T2W images), grade 2 (hypointense nucleus pulposus on T2W images with normal disc height), and grade 3 (hypointense nucleus pulposus on T2W images with disc space narrowing) (Schneiderman *et al.* 1987).

In study II, disc herniations were classified as normal, bulge (a symmetrical extension of the peripheral annulus beyond the margins of the endplates), contained herniations (a focal extrusion of disc material not penetrating the posterior longitudinal ligament), uncontained herniations (an extrusion of disc material through the posterior longitudinal ligament) and sequestration (a

herniated disc fragment not in contact with the parent disc) (Karppinen *et al.* 2001b).

To exclude the MRI findings that may be symptomatic (study III), any presence of disc herniation, nerve root compromise and central spinal stenosis were recorded. The extent of disc herniation was graded as normal, bulging (a circumferential, symmetric disc extension around the vertebral borders), protrusion (a focal or asymmetric extension of the disc beyond the vertebral border, with the disc origin broader than any other dimension of the protrusion) or extrusion (a more extreme extension of the disc beyond the vertebral border, with the base against the disc of origin narrower than the diameter of the extruding material itself and a connection between the material and the disc of origin) (Fardon & Milette 2001). The neural compromise was classified as no compromise, nerve root contact, or compression (Pfirrmann *et al.* 2004). The presence of central spinal stenosis (dural sac cross-sectional area $<75 \text{ mm}^2$ at one level or $<100 \text{ mm}^2$ at two or more levels) was defined according to the criteria of Willen *et al.* (1997).

Endplate sclerosis (IV) was visually evaluated from the CT scans by comparing the MR images and sagittal reconstructed CT scans on a workstation. The presence of endplate sclerosis was defined as yes or no.

To study the capability of MRI in detecting endplate sclerosis within Modic changes (study IV), the endplate signal intensity from the MR images and Hounsfield units (HU) from the CT scans were determined from affected endplates. The largest possible elliptical region of interest (ROI) was fitted within the area displaying a Modic change. For each patient, the area of the ROI was the same in the T1W and T2W MR images and the CT scans. The mean ROI was 60.4 mm^2 (range 30–112 mm^2). To normalize the T1W and T2W signal intensity and the HU values for affected endplates among the patients, the T1, T2 and HU ratios were calculated (T1 ratio=T1W signal intensity for an affected endplate/T1W signal intensity for a normal vertebra, T2 ratio=T2W signal intensity for an affected endplate/T2W signal intensity for liquor signal intensity, HU ratio=HU for an affected endplate/HU for a normal vertebra).

4.6 Statistical analysis

4.6.1 Reliability of Modic changes (I, II and III)

Kappa statistics was used to establish interobserver and intraobserver reliabilities of Modic changes (studies I, II and III) (Landis & Koch 1977). In studies I and III, the interobserver kappa values for the types of Modic changes (N=228 subjects) showed almost perfect agreement between the radiologists, kappa values of different disc levels ranging from 0.85 to 1.00 (mean 0.94). Intraobserver kappa values by disc level ranged from 0.62 to 1.00 (Mean 0.84) (N=120 subjects). In study II, evaluation of Modic changes showed substantial agreement between the radiologists, with a kappa value of 0.64 (N=60) at baseline and at three years. Intraobserver agreement was 0.90 (N=60).

4.6.2 Evaluation of determinants (I)

Logistic regression analysis was used to evaluate the association between selected determinants and 1) type of Modic changes and 2) severe disc degeneration. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated per an increment of one standard deviation unit for each continuous explanatory variable. Analyses were carried out for all lumbar levels combined and separately for changes located at L5–S1.

All subjects were included in the analyses of Modic changes, i.e. either type I or type II at any level (N=228). Subjects who had both type I and type II change at the same or separate level (N=23) were excluded when analyzing determinants of individual Modic types. In the analyses of Modic changes located at L5–S1, subjects who did not have Modic change at L5–S1 but had any Modic change at the upper levels were excluded (N=42). The reference group in the analyses of Modic changes consisted of 100 subjects without any Modic changes, whereas in the analyses of severe disc degeneration the reference group consisted of 163 subjects with at most grade IV degeneration. The age-adjusted analyses were first done separately for each single determinant. Based on these analyses, multivariate analysis was conducted. For the multivariate analysis, only the significant determinants (for either Modic changes or severe disc degeneration) were included.

4.6.3 Natural course of Modic changes (II)

The characteristics of Modic changes were illustrated by frequency tables and crosstabulations. The paired t-test and Wilcoxon signed ranks test were used to analyze the progression in size of Modic changes.

4.6.4 Association of Modic changes with low back and sciatic pain (III)

Logistic regression analysis was used for the evaluation of pain on the type and extent of Modic changes. Odds ratios with 95% confidence intervals were estimated per an increment of one standard deviation unit in each independent variable.

Analyses were done 1) separately for each lumbar level and 2) for all lumbar levels combined. In the classification of Modic changes, Modic type I was prioritized over type II if the subject had separate types of Modic 1) at any single level or 2) at separate levels when lumbar levels were combined. Similarly, extensive Modic change was prioritized over minimal size change. The analyses were adjusted for age and done separately for each pain variable. In a separate analysis, subjects (N=8) with a nerve root compression due to a disc extrusion or central spinal stenosis were excluded because these MRI findings may be symptomatic (Boos *et al.* 1995, Beattie *et al.* 2000, Atlas *et al.* 2005) Univariate analysis of variance was used for checking the effect of confounding upper level Modic changes while analyzing the association of pain with Modic changes at L5–S1.

4.6.5 Comparison of Modic changes and endplate sclerosis (IV)

The characteristics of the Modic changes were illustrated with frequency tables. The difference in age distribution in the study population was evaluated using Student's *t* test. Variations in the T1, T2 and HU ratios were shown graphically as scatter plots. The significance of the difference between the T1, T2 and HU ratios for sclerotic and non-sclerotic Modic changes was determined using a Mann-Whitney test.

5 Results

5.1 Prevalence of Modic changes

In patient populations (studies II and IV), the prevalence of any type of Modic change in relation to the subjects was 65% (39/60) and 51% (36/70), respectively. In study II, 23% (70/300) of the disc levels and in study IV, 20% (82/420) of the endplates were affected. In an occupational cohort (studies I and III), the prevalence in relation to the number of subjects and disc levels was 56% (128/228) and 16% (178/1140), respectively. When the occupational groups were analyzed separately, 55% (87/159) of the train engineers and 59% (41/69) of the sedentary paper mill workers were found to have Modic changes ($P=0.562$). Modic type II change was the most frequent in all studies (I–IV), 65–90% of changes representing this type. Figure 2 shows the distribution of different Modic types in patient population (study IV). Modic changes most typically occurred at L4–5 and L5–S1 (studies I–III), 79–80% of changes being located at these two levels.

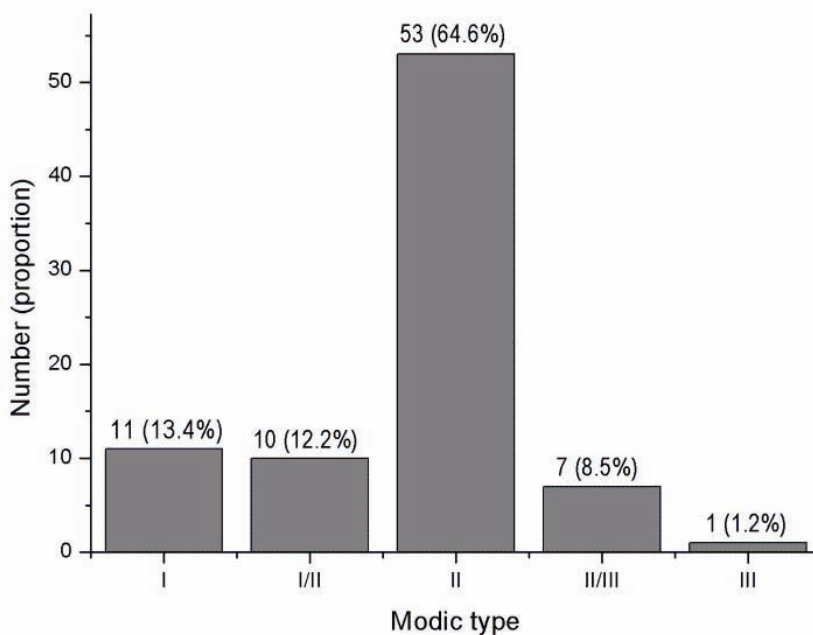


Fig. 2. Distribution of different Modic types in 70 patients with Modic changes (study IV).

5.2 Determinants (I)

5.2.1 Determinants of Modic changes

Modic changes were age-dependent [odds ratio (OR) 1.56; 95% confidence interval (CI) 1.21–1.95]. When all the determinants were included in the univariate age-adjusted analyses, none of the analyzed determinants were associated with Modic type I changes, whereas both weight-related factors (BMI and waist circumference) were associated with type II changes at L5–S1 (OR 1.42; 95% CI 1.03–1.86 and OR 1.48; 95% CI 1.11–1.89, respectively). Similar results were obtained when all lumbar levels were combined. Occupation (train engineers vs. factory workers), duration of exposure to whole-body vibration (years), body fat percentage or alcohol consumption were not significantly associated with Modic changes. The table of the univariate age-adjusted associations of the determinants of Modic changes and severe disc degeneration may be seen in the original article of study I.

In the multivariate model (Table 2), in addition to age, BMI was associated significantly with type II changes at L5–S1. Waist circumference was also significant (OR 1.18; 95% CI 1.05–1.32), but due to collinearity of these two weight-related factors they could not be included in the model simultaneously. Exposure to whole-body vibration was of borderline significance.

5.2.2 Determinants of severe disc degeneration

Severe disc degeneration was age-dependent (OR 1.46; 95% CI 1.13–1.82). When all the determinants were included in the univariate age-adjusted analyses, the duration of exposure to whole-body vibration (OR 1.41; 95% CI 1.05–1.78) and being a train engineer (vs. sedentary factory work) (OR 2.48; 95% CI 1.08–5.67) associated with higher prevalence of grade-five disc degeneration at L5–S1. Mechanical factors (BMI, waist circumference, lifetime exercise), fat percentage, smoking, or alcohol consumption were not significantly associated with severe disc degeneration.

In the multivariate model (Table 2), in addition to age, exposure to whole-body vibration associated with severe disc degeneration at L5–S1.

Table 2. Multivariate models of the predictors of Modic Type II changes and severe disc degeneration, presented for all vertebral levels and for the L5–S1 level separately.

	SD	Modic Type II				Severe disc degeneration ^a			
		All levels ¹ N = 172		L5–S1 ² N = 149		All levels ³ N = 228		L5–S1 ⁴ N = 212	
Determinant		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age	4 years	1.55	1.19–1.94	1.60	1.18–2.05	1.52	1.17–1.90	1.51	1.11–1.94
BMI	3 kg/m ²	2.29	1.05–3.67	2.75	1.31–4.37	1.70	0.64–2.87	1.54	0.39–2.83
Vibration exposure	11 years	1.00	0.95–1.06	1.05	0.99–1.12	1.05	1.00–1.11	1.08	1.01–1.14

The OR per one SD is calculated for each continuous variable. Subjects with both types are not included in the analyses of Type II.

All levels: ¹ 72 with only Modic II changes and ³ 65 with severe disc degeneration

Level L5–S1: ² 49 with only Modic II changes and ⁴ 49 with severe disc degeneration

Subjects with type I changes were excluded from the analyses of type II changes.

The reference group in the analyses of Modic changes consisted of 100 subjects with no Modic changes, and in case of severe disc degeneration of 163 subjects with at most grade IV degeneration.

^a Severe disc degeneration = Pfirrmann grade V

5.3 Characteristics of Modic changes (II)

Modic changes were usually observed in parallel on both sides of the disc (52/300 discs, 34 patients), though in some cases only superior (9/300 discs, 9 patients) or inferior (9/300 discs, 8 patients) margins were involved. Although changes usually affected the whole antero-posterior length of the disc margin (53/300 discs, 38 patients), occasionally only the anterior (8/300 discs, 8 patients) or posterior (9/300 discs, 7 patients) margins of the vertebral body were involved. Vertical depth varied between 3–30 millimeters (mean 11.8 mm). The extent of changes was 25% or less of the endplate area in 22 discs (18 patients), 26–50% in 25 discs (22 patients), and more than 50% in 23 discs (18 patients). The depth and extent of changes were greatest at L4–5 and L5–S1.

5.4 Natural course of Modic changes (II)

Sixty out of 70 discs (86%; 37 patients) with Modic changes at baseline did not alter in Modic type during the three-year follow-up. Figure 3 demonstrates the incidence of new and converted Modic types over the follow-up period. Thirteen out of 230 discs (6%; 13 patients) with no Modic changes at baseline had a new incident Modic change at the three-year follow-up MRI. Ten out of 70 discs (14%; 9 patients) with Modic changes at baseline displayed another type at three years.

Most of converted and new changes were localized at L4–5 or L5–S1 (8 of 10 and 10 of 13, respectively), and co-localized with a symptomatic disc herniation (8 of 10 and 8 of 13, respectively).

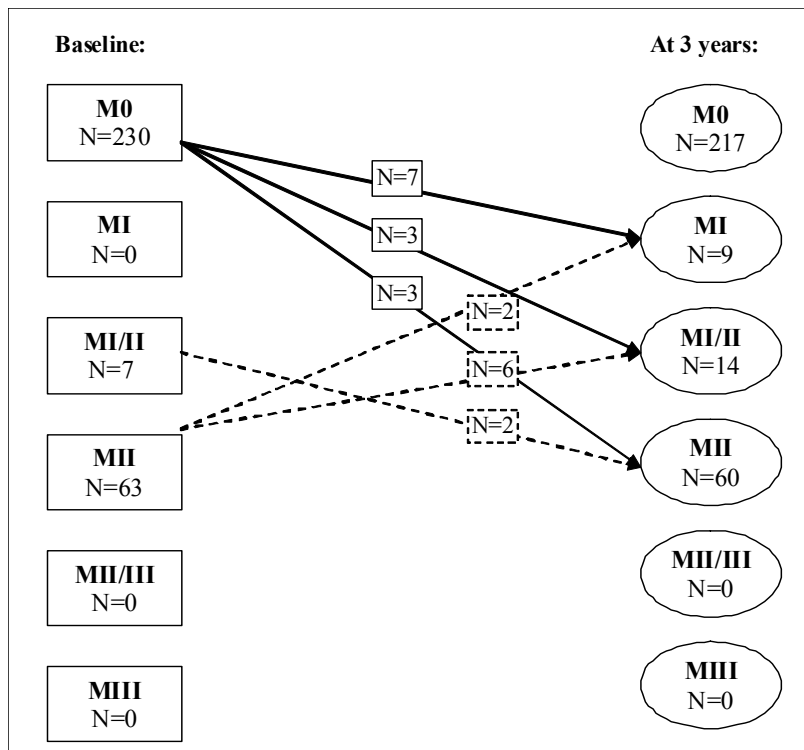


Fig. 3. New (N=13; solid lines) and converted (N=10; dashed lines) Modic changes over the three-year follow-up. All disc levels are presented together (N=300 in 60 patients).

5.5 Association of Modic changes with low back and sciatic pain (III)

5.5.1 Lumbar level vs. pain symptoms

Associations of pain with Modic changes (type I or II) by disc level are presented in Table 3. Having any Modic change at any of the levels associated with an increased number of LBP episodes and with higher LBP scores during the past week and the past three months. At specific disc levels, associations of pain

symptoms with Modic changes were seen only at L5–S1, changes being associated with a higher number of previous LBP and sciatica episodes, and with a higher LBP score during the past week. Modic changes at the upper lumbar levels (L1–2 to L3–4) or at L4–5 did not associate significantly with any pain variables.

Table 3. Association of pain with any Modic change (type I or II), presented by lumbar disc level for all 228 subjects.

Pain variable	Mean (SD)	L1–2 to L3–4 ¹ N = 34		L4–5 N = 56		L5–S1 N = 86		Any level ² N = 128	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Low back pain									
Pain episodes	4.3 (15.3)	1.05	0.73–1.38	0.98	0.65–1.31	2.28	1.44–3.15	2.62	1.47–3.86
VAS (1 week)	1.7 (2.2)	0.93	0.59–1.35	0.98	0.69–1.30	1.36	1.06–1.70	1.47	1.13–1.87
VAS (3 months)	2.3 (2.1)	1.13	0.78–1.55	1.03	0.74–1.36	1.22	0.94–1.54	1.51	1.17–1.90
Sciatic pain									
Pain episodes	2.9 (9.4)	0.84	0.30–1.42	0.62	0.02–1.26	1.44	1.01–1.89	1.29	0.87–1.73
VAS (1 week)	1.3 (2.1)	0.68	0.32–1.13	0.91	0.63–1.23	1.24	0.95–1.56	1.22	0.93–1.56
VAS (3 months)	1.7 (2.2)	1.02	0.67–1.43	0.97	0.69–1.30	1.12	0.85–1.42	1.33	1.02–1.69

The OR per one SD adjusted for age is calculated for each pain variable. The number of Modic changes at each disc level is given.

¹Disc levels L1–2, L2–3 and L3–4 are combined.

²Modic changes at any of the levels from L1–2 to L5–S1.

VAS = Intensity of pain on a 10-cm Visual Analog Scale.

5.5.2 Type of Modic changes vs. pain symptoms

Type I Modic changes associated with a higher number of previous LBP episodes, higher LBP scores during the past week and past three months, and a higher sciatic pain score during the past three months (Table 4). At L5–S1, the associations were similar. At the upper levels, analyzed separately, no association of pain symptoms with Modic type I was found.

Type II changes associated with a higher number of previous LBP episodes and higher LBP scores during the past week and past three months (Table 4). At L5–S1, type II changes associated with a higher number of previous LBP episodes.

Table 4. Association of pain variables with Modic types I and II at L5–S1 and at all levels combined.

Pain variable	Modic Type I				Modic Type II			
	L5–S1 N = 28 ²		Any level ¹ N = 56 ²		L5–S1 N = 58 ²		Any level ¹ N = 72 ²	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Low back pain								
Pain episodes	2.24	1.26–3.27	2.53	1.24–3.90	2.21	1.33–3.14	2.51	1.36–3.74
VAS (1 week)	1.63	1.17–2.19	1.69	1.23–2.24	1.23	0.91–1.60	1.37	1.00–1.80
VAS (3 months)	1.37	0.94–1.85	1.67	1.23–2.20	1.14	0.83–1.50	1.38	1.02–1.80
Sciatic pain								
Pain episodes	1.43	0.93–1.96	1.26	0.83–1.72	1.38	0.95–1.83	1.26	0.83–1.70
VAS (1 week)	1.45	1.06–1.92	1.34	0.98–1.77	1.09	0.78–1.44	1.11	0.80–1.48
VAS (3 months)	1.39	1.00–1.85	1.52	1.13–1.98	0.95	0.66–1.29	1.14	0.82–1.51

Subjects with a Modic change of a given type are compared to subjects with no Modic changes at the corresponding level(s). The OR per one SD adjusted for age is calculated for each pain variable. The number of Modic changes (type I or II) at each disc level is given.

¹Modic changes at any of the levels from L1–2 to L5–S1.

²Number of subjects in the comparison groups, i.e. with no Modic changes, is 142 at L5–S1 and 100 for any level.

VAS = Intensity of pain on a 10-cm Visual Analog Scale.

5.5.3 Effect of confounding factors on pain variables

Eight subjects had nerve root compression due to a disc extrusion. One of these subjects also had central spinal stenosis at the herniation level. When these eight subjects were excluded from the study population, the results were analogous to those for the whole study population (i.e., Modic changes at L5–S1 and Modic type I lesions associated with pain symptoms). Moreover, Modic changes at the upper levels did not have an effect on the results when analyzing the association of pain with Modic changes at L5–S1.

5.6 Comparison of Modic changes and endplate sclerosis (IV)

5.6.1 Prevalence of endplate sclerosis within Modic changes

Thirty-one out of 82 (38%) endplates with Modic changes had sclerosis in CT (Table 5). No sclerosis was observed in CT in the absence of Modic changes in

MRI. Endplate sclerosis was adjacent to the endplate and usually localized in the same area with a Modic change. Table 5 presents the occurrence of different Modic types in MRI compared with endplate sclerosis in CT. Of the specific Modic types, mixed I/II and II/III, and the only type III change were associated with sclerosis. Modic changes were most typically sclerotic at L5–S1, 58% (19 of 33 endplates) of the changes being sclerotic at this level.

Table 5. Number of different types of Modic changes (levels and endplates pooled; N = 420) and the number (proportion) of endplate sclerosis within changes.

Modic type	Sclerosis				Total
	Yes		No		
	N	%	N	%	
I	2	18.2	9	81.8	11
I/II	9	90.0	1	10.0	10
II	12	22.6	41	77.4	53
II/III	7	100.0	0	0.0	7
III	1	100.0	0	0.0	1
Total	31	37.8	51	62.2	82

5.6.2 Capability of MRI in detecting endplate sclerosis

The T1W or T2W signal intensities did not differ in endplates with type I or II Modic changes with or without sclerosis (Figs. 4A–D). Type II Modic changes with sclerosis had statistically higher HU values (Mean, 2.1; SD 0.6) than did changes without sclerosis (Mean, 1.0; SD 0.2) ($P < 0.001$) (Fig. 4F). Additionally, sclerotic type I Modic changes tended to have higher HU values (Mean, 2.8; SD 0.7) than type I changes without sclerosis (Mean, 1.1; SD 0.1) ($P = 0.056$) (Fig. 4E).

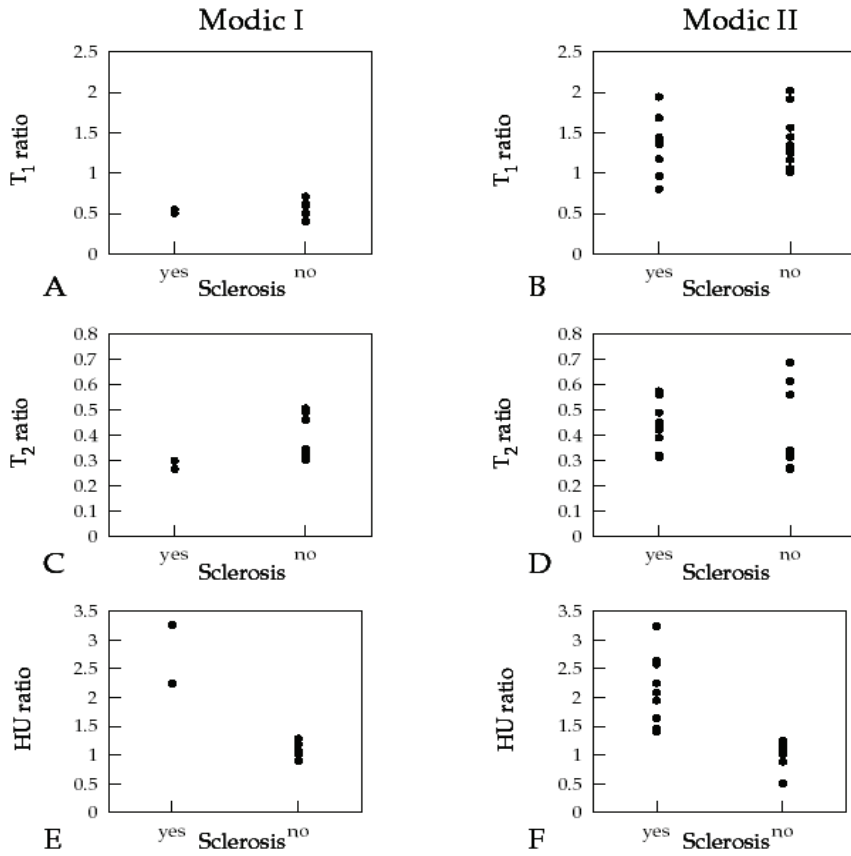


Fig. 4. Scatter plots A–F show the variation in normalized T1- and T2-weighted signal intensity and HU values at the endplates with type I or II Modic changes with or without sclerosis.

6 Discussion

Modic changes are bone marrow signal intensity changes adjacent to the endplates of the degenerated intervertebral discs in magnetic resonance imaging. In recent years, they have come into focus in the search for the source of back pain symptoms. The present study evaluated the determinants of Modic changes and the association of Modic changes with low back pain symptoms in an occupational cohort. The prevalence and the natural course of Modic changes was investigated in a longitudinal follow-up MRI study. In addition, comparisons were made between computed tomography and magnetic resonance imaging to evaluate the presence of endplate sclerosis on different types of Modic changes, and further to assess the capability of MRI in detecting endplate sclerosis within these changes.

In the present study, Modic changes were a common MRI finding both among patients and middle-aged working males. In addition to age, weight-related factors were associated with Modic changes. Modic changes converted from one type to another during a three-year follow-up period, and type II changes were less stable than previously assumed. A considerable proportion of Modic changes were sclerotic as observed in CT. Modic changes were always found in combination with a degenerative intervertebral disc and thus they are assumed to be a specific phenotype of degenerative disc disease. Finally, Modic changes were associated with pain symptoms – especially changes located at L5–S1 and type I Modic changes.

6.1 Determinants of Modic changes

The present study showed that age and weight-related factors (BMI and waist circumference) are associated with Modic changes. Previously, it has been shown that a multitude of factors determine the risk of disc degeneration including age, genetic inheritance and loading history (Adams & Roughley 2006). However, there is only limited information about the determinants of Modic changes. In addition to age (Modic *et al.* 1988b, Karchevsky *et al.* 2005), body weight (Karchevsky *et al.* 2005, Leboeuf-Yde *et al.* 2008), heavy physical work (Kjaer *et al.* 2006), smoking (Kjaer *et al.* 2006) and male gender (Karchevsky *et al.* 2005) have shown associations with Modic changes.

Modic changes occur adjacent to the degenerated intervertebral discs (de Roos *et al.* 1987, Modic *et al.* 1988b). The prevalence of Modic changes has been found to increase with age (Modic *et al.* 1988b, Karchevsky *et al.* 2005) and they are

uncommon in younger individuals (Kjaer *et al.* 2005b). Similarly, a close association between age and the prevalence of changes was found in this study as evidence of their degenerative etiology.

Weight-related factors were associated with Modic changes but not with disc degeneration. Previously, obesity has been suggested as a risk factor for disc degeneration, but the results have remained controversial (Heliövaara 1987, Riihimäki *et al.* 1990, Harrington *et al.* 2001, Liuke *et al.* 2005). In a population-based study, overweight in combination with hard physical work was significantly associated with the prevalence of Modic changes (Leboeuf-Yde *et al.* 2008). In another patient study, Modic changes were associated with increasing weight, but not with BMI (Karchevsky *et al.* 2005). In Finland, obesity (BMI at least 30 kg/m²) has increased in all age groups and in both men and women. Currently, more than 20% of the population is obese. (Aromaa & Koskinen 2004.) Although weight-related factors were found to be associated with an increased likelihood of Modic changes, the influence of weight reduction on degenerative disease, both clinical symptoms and progression of degenerative imaging findings, is unknown.

This study showed a significant association between lifetime leisure exercise activity and all Modic changes at L5–S1 in the multivariate analyses (data not shown). However, when type I and II changes were analyzed separately, no significant association remained. There is only limited knowledge about the association of physical activity and Modic changes. In a Danish population-based cohort, exposure to high-level physical activity at leisure time did not differ between subjects with “Modic changes and disc degeneration” vs. those with “only disc degeneration”. However, exposure to occupational physical load was significantly higher in the subgroup of “Modic changes and disc degeneration” compared to “only disc degeneration” group. (Kjaer *et al.* 2006.) Videman *et al.* (1995) detected a relation between vigorous exercise and lumbar degenerative changes among former Finnish elite athletes. However, they did not evaluate Modic changes separately. Recent studies on identical twins have shown that 70% of intervertebral disc degeneration can be attributed to familial factors rather than to the mechanical environment (Sambrook *et al.* 1999). However, the endplate is a weak link of the spine in compression, and always fails before the intervertebral disc, even if the latter is injured before loading commences (Brinckmann 1986). The author speculates that mechanical loading damages the endplate and may lead to activation of degeneration. This may first be visible in MR images as a more

active Modic type I lesion, and if the mechanical loading continues, it converts to a more stable type II lesion (Modic *et al.* 1988b).

In this study, there was a trend between smoking (assessed as pack-years) and a higher prevalence of Modic changes at L5–S1, but no association with severe disc degeneration. Previously, there is only one study of the effect of smoking on Modic changes, where self-reported hard physical work in combination with heavy smoking was strongly associated with Modic changes (Kjaer *et al.* 2006). Although an association between smoking and disc degeneration was observed in an earlier study on Finnish twins (Battie *et al.* 1991), the association between smoking and disc degeneration was not confirmed in a later study (Battie *et al.* 1995). At the moment, the author is unable to either disprove or support the hypothesis that smoking is a risk factor for degenerative imaging findings. The study on the effect of smoking on Modic changes should be replicated in other population-based cohorts.

Another environmental factor, alcohol, has been associated with many organ abnormalities and cognitive deficits. There are no studies about the effects of alcohol on Modic changes. However, there is evidence that moderate alcohol consumption may reduce the risk of intervertebral disc degeneration (Zhang *et al.* 2008). This study found no association between alcohol consumption and Modic changes or disc degeneration. It therefore seems likely that alcohol does not have deleterious effects on the intervertebral discs.

Occupation (train engineers vs. sedentary factory work) or the duration of exposure to whole-body vibration was of borderline significance for type II Modic changes located at L5–S1. Interestingly, whole-body vibration was associated with severe disc degeneration, but only at L5–S1. There is evidence of an association between vibration and degenerative spinal changes (Videman & Battie 1999) but this could not be confirmed in a high-quality twin study with discordant occupational driving exposure (Battie *et al.* 2002). Although the findings of this study indicate that exposure to whole-body vibration may accelerate disc degeneration (and possibly Modic changes), we cannot wholly exclude a chance finding.

Based on the findings of this study, the determinants of Modic type I and II changes are different. The determinants of type I remain unidentified, whereas age and weight-related factors (BMI, waist circumference) were related to type II changes. This may be partly explained by the low number of subjects with type I changes. However, type I changes are also associated with an ongoing degenerative process which converts over time to type II or normal bone marrow

(Modic *et al.* 1988b). Finally, the influence of determinants may also vary at different stages of the degenerative process.

The strength of the study of the determinants is based on the occupational cohort consisting of train engineers and sedentary factory workers of similar age range. Additionally, all train engineers were full-time train drivers from Northern Finland, which ensured a very similar exposure to whole-body vibration. The factory workers consisted of paper mill and chemical factory workers from the same area with only sedentary job and no vibration exposure.

The limitations of the study are based on its cross-sectional nature, which is a common problem in epidemiological studies. Even if selected determinants can be reasonably well assessed retrospectively, their temporal relation to the development of Modic changes or disc degeneration cannot be demonstrated. The effect of age, and perhaps of genetic factors, may also dilute the effect of environmental determinants. Furthermore, there were no precise measurements of whole-body vibration exposure. When studying lifetime effects, such precision is not feasible due to variations in train models and railway conditions.

According to the results of this study, besides age, the determinants of Modic changes and disc degeneration are different. Weight-related factors, which add the load of the lumbar spine, seem important in the pathogenesis of Modic changes, whereas whole-body vibration was associated with severe disc degeneration.

6.2 Prevalence and characteristics of Modic changes

The prevalence of Modic changes in this study varied between 51 and 65% (studies I–IV) according to the study population. Previously, the prevalence of Modic changes among patients with degenerative disc disease of the lumbar spine has been reported to vary between 19 and 59% (de Roos *et al.* 1987, Modic *et al.* 1988b, Toyone *et al.* 1994, Weishaupt *et al.* 2001, Schmid *et al.* 2004, Karchevsky *et al.* 2005, Kjaer *et al.* 2005a, Albert & Manniche 2007). The prevalence rates in studies I, III and IV (51–56%) were in accordance with previous findings, whereas the prevalence in study II (65%) was higher than observed earlier. However, when the prevalence of Modic changes in study II was reported in relation to lumbar disc levels (23%), it accorded with the previous findings in patient populations (20–50%) (de Roos *et al.* 1987, Modic *et al.* 1988b, Karchevsky *et al.* 2005). The high prevalence in relation to the subjects in study II may be explained by the study population consisting of only sciatica patients, as Modic changes are known to appear after disc herniations (Albert & Manniche 2007). Modic changes have been

observed to be a more common MRI-finding in patients with LBP compared to non-clinical populations (Jensen *et al.* 2008). Furthermore, Modic changes are uncommon in asymptomatic individuals without disc degeneration (Weishaupt *et al.* 1998, Kjaer *et al.* 2006).

Type II Modic change was the most frequent in all studies (I–IV), 65–90% of changes being of this type. There is disagreement as to whether type I or II Modic change is the most common in the lumbar spine. The predominance of type II has been found in several studies, as it has been observed to constitute up to 80% of Modic changes in the lumbar spine (de Roos *et al.* 1987, Modic *et al.* 1988b, Braithwaite *et al.* 1998, Schmid *et al.* 2004, Karchevsky *et al.* 2005), and this is supported by the results of the present study. This may be explained by the finding that type I Modic changes have been observed to convert to type II or normal bone marrow, whereas type II Modic changes are usually associated with a more stable degenerative process (Modic *et al.* 1988b). Other studies have suggested that type I is a more common Modic type and may account for up to 71% of Modic changes (Weishaupt *et al.* 2001, Kjaer *et al.* 2005a). The differences in prevalence rates between studies of Modic changes and the frequency of each Modic type might be explained by differences in the definition of changes. The different prevalence and distribution of Modic types may also result from differences in the study populations and inclusion criteria.

An association of Modic changes and intervertebral disc degeneration was confirmed in the present study. All discs adjacent to a Modic change had at least grade III disc degeneration (studies I and III). In addition, changes occurred most commonly at L4–5 or L5–S1 (studies I–III), as previously observed (Modic *et al.* 1988b, Karchevsky *et al.* 2005). New and interesting findings were that the depth and the extent of changes were also greatest at L4–5 and L5–S1. These findings may be related to the biomechanics of the lumbar spine. L5 is the largest of all movable vertebrae and it carries the weight of the upper body (Moore 1999). The vertical depth of Modic changes was observed to vary between 3 and 30 mm, in accordance with earlier findings (Modic *et al.* 1988b). Changes were usually identified at both sides of the disc margin, and they usually involved the whole antero-posterior length of the disc margin, which accords with previous findings (Modic *et al.* 1988b). However, Chung *et al.* (2004) suggested that the distribution of changes was more in the anterior than the posterior endplate of the vertebra. The inconsistent results may be explained by the difference in the definition of Modic changes, as these authors also included very small changes located at the corners of the vertebral bodies. Inflammatory spondyloarthropathias may lead to signal

intensity alterations in the insertion of the annulus fibrosus-longitudinal ligament complex that may be mimicking Modic changes (Jevtic *et al.* 2000, James & Davies 2006).

6.3 Natural course of Modic changes

Before the significance of different Modic types can be evaluated, a better understanding of the natural course of these changes is needed. In the original study, Modic *et al.* (1988b) observed that five of six patients with a type I change converted to a type II over a 14- to 36-month interval. The authors found that type I changes can also revert back to normal, whereas type II changes usually do not alter with time, thus associating with a more stable and chronic degenerative process. (Modic *et al.* 1988b.) Later, Braithwaite *et al.* (1998) suggested that Modic changes can convert from one type to another, presenting different stages of the same pathological process.

After the initial report of Modic *et al.* (1988b), the dynamic process of Modic type I changes have been confirmed. Mitra *et al.* (2004) found that 52% of type I changes converted into type II and 40% increased in size, while only 8% of type I changes remained stable during a 12- to 72-month follow-up period. In a recent study, only 11% of type I Modic changes remained stable during an 18- to 72-month follow-up period (Luoma *et al.* 2008).

The stability of type II Modic change is questioned by the results of the present study. During a three-year follow-up period, 14% of Modic changes at baseline converted to another type, 80% of the conversions being from type II to either type I or mixed type I/II. This finding was recently supported by a case report of two patients with conversion of type II change into type I (Marshman *et al.* 2007). These findings suggest that type II Modic change may not be as stable as previously assumed. An acute ongoing process in some type II changes may cause the conversion of yellow marrow to red, resulting in type I or type I/II Modic change. This was supported by the progression of disc degeneration (loss of signal or disc height or even disc collapse in two cases).

A limitation of the study was that spondylolisthesis and instability were not evaluated as they may be associated with conversions of a Modic change to another type. Modic changes have been reported to be associated with segmental hypermobility in the dynamic flexion-extension MR images (Toyone *et al.* 1994). These findings need to be confirmed in future studies assessing the natural history of Modic changes.

6.4 Modic changes and low back pain

This study showed that Modic changes at L5–S1 and Modic type I lesions are more likely to be associated with pain symptoms than other types of Modic changes or changes located at other lumbar levels. Previously, a wide spectrum of disc abnormalities, including disc degeneration, disc bulging, disc protrusion, and annular tears, have been found in a substantial percentage of healthy volunteers (Boden *et al.* 1990, Jensen *et al.* 1994, Boos *et al.* 1995, Stadnik *et al.* 1998). In contrast, disc extrusions, nerve root compression and Modic changes are rare in asymptomatic volunteers (Jensen *et al.* 1994, Boos *et al.* 1995, Weishaupt *et al.* 1998, Kjaer *et al.* 2006). In recent years, Modic changes have come into focus as a source of back pain symptoms.

In accordance with previous findings, this study showed that Modic type I changes are associated with pain symptoms. In a study of 74 patients with disc degeneration, Toyone *et al.* (1994) observed that 73% of patients with type I change had significant LBP, as opposed to only 11% of patients with type II. In a longitudinal study of LBP patients, a positive trend was found between the evolution of type I to type II change and symptom improvement (Mittra *et al.* 2004). In the Danish study of 412 subjects of 40-year-old Danes, a strong association of Modic changes with LBP during the past year, especially for Modic type I, was observed (Kjaer *et al.* 2006). Recently, Albert and Manniche (2007) reported similar results as they showed that type I changes were more strongly associated with LBP than type II changes. The correlation of Modic changes with pain induced by discography has also been studied, but the results have remained controversial (Braithwaite *et al.* 1998, Sandhu *et al.* 2000, Weishaupt *et al.* 2001, Kokkonen *et al.* 2002).

A new and interesting finding in the present study was that both Modic type I and II lesions at L5–S1, but not at upper levels, are associated with the occurrence and intensity of LBP. This is the first study to assess the role of lumbar levels in relation to Modic changes and LBP. The author speculates that the association of LBP symptoms with L5–S1 level might be due to mechanical factors, but the pathophysiology of this phenomenon needs further investigation.

Disc extrusions and nerve root compression are observed to be rare in asymptomatic volunteers (Jensen *et al.* 1994, Boos *et al.* 1995, Weishaupt *et al.* 1998). Boos *et al.* (1995) showed that the only substantial morphologic difference between symptomatic patients and asymptomatic matched controls was the presence of neural compromise (83% vs. 22%). Therefore, in this study nerve root

compression due to a disc extrusion was considered a confounding factor in the pain analyses. However, the results were analogous when these subjects were excluded from the analyses.

According to the results of this study, Modic changes at L5–S1 and Modic type I lesions are more likely to be associated with pain symptoms than other types of Modic changes or changes located at other lumbar levels. This is the first study to assess the role of lumbar levels in relation to Modic changes. The author is aware of a potential bias related to multiple comparisons, but the results are consistent, and in the author's opinion they are not chance findings. However, the results are valid only on group-level. In the future, larger studies are needed to verify the current findings.

6.5 Comparison of MRI and CT in detecting Modic changes

This is the first study to investigate Modic changes in MRI compared with multislice CT examination. It has been suggested that only type III Modic changes are visible in plain film radiography with endplate sclerosis (Modic *et al.* 1988a, Modic *et al.* 1988b). Interestingly, the results of this study are somewhat different, as it was found that not only type III changes, but also other Modic types, especially mixed Modic changes (I/II and II/III), showed endplate sclerosis in CT. However, endplate sclerosis could not be detected in MR images in the quantitative analysis.

A new and important finding in our study was that 90% (9 out of 10) of mixed type I/II and all seven mixed type II/III changes in MRI showed sclerosis at the endplates in question in CT. The corresponding proportions of sclerotic endplates for type I, II and III Modic changes were 18% (2 out of 11), 22% (12 out of 55) and 100% (1 out of 1), respectively. Modic *et al.* (1988a, 1988b) were the first to introduce the appearance of bone sclerosis in MRI. They suggested that type III Modic changes are presented by decreased signal intensity on both T1- and T2-weighted images, which appears to correlate with extensive bone sclerosis in plain film radiography (Modic *et al.* 1988a). Conversely, type I and II Modic changes showed no definite correlation with sclerosis in plain film radiography (Modic *et al.* 1988b). Mixed Modic types were not evaluated separately.

There have been few reports in the literature in which reactive bone sclerosis has appeared hypointense in T1W and hyperintense in T2W MR images. In a study on MRI features of osteoblastoma (Shaikh *et al.* 1999), low signal intensity reactive sclerosis was observed in both T1W and T2W images. A

histopathological examination of reactive sclerosis with this behavior showed heavy matrix mineralization. Reactive sclerosis accompanied by marrow edema appeared hypointense in T1W and hyperintense in T2W images. In the histopathological examination these cases were associated with increased fibrovascular tissue within the marrow and a perivascular infiltration of lymphocytes and plasma cells. (Shaikh *et al.* 1999.) The same association has been observed in inflammatory arthropathy. In an acute stage of the process, non-sclerotic changes with low signal intensity in T1W and high signal intensity in T2W images are seen in the anterior disco-vertebral junction. As the process becomes chronic, sclerotic changes (shiny corners in plain film radiography) with high signal intensity in T1W and T2W images are seen, reflecting the healing process of the lesion. The reactive new bone formation probably occurs in previously inflamed areas. (Jevtic *et al.* 2000, James & Davies 2006.)

In this study, endplate sclerosis observed in CT could not be detected in MR images in the quantitative analysis. The T1- or T2-weighted signal intensities did not differ in endplates with type I or II Modic changes with or without sclerosis. However, as assumed, the HU values of sclerotic Modic changes were higher than in those without sclerosis. This finding is explained by the difference within the imaging modalities used. CT is superior to MRI for evaluation of reactive or sclerotic bone formation. Because of the lack of mobile protons, bone sclerosis yields no detectable signal in MRI. Furthermore, signal intensity in MRI depends on the fat/water content within bone trabeculae. (Vogler & Murphy 1988, Vanel *et al.* 2000.)

From the histopathologic point of view, osteosclerosis is defined as a qualitative increase in bone volume. The sclerosis may be fully or partly mineralized. If the sclerosis is partly mineralized, the amount of water is increased and there is less calcium deposition compared with fully mineralized sclerosis (Ott 1996). The sclerosis seen in plain film radiography and in CT of type III Modic changes is a reflection of dense mineralized bone within the vertebral body rather than the marrow elements (Modic *et al.* 1988b).

The sclerosis seen in most of the mixed Modic types and in some type I and II changes may be related to a regenerative process of the bone marrow. This finding is indirectly supported by the result of this study, as no sclerotic bony endplates were observed in CT in the absence of Modic changes in MRI. Modic changes are thought to be a reflection of the degenerative process within the bone marrow (Modic *et al.* 1988b), and the sclerotic Modic changes may be related to the

healing process with new bone formation. However, the clinical importance of this finding remains to be studied.

A limitation of the study was its retrospective nature. The patients were referred for a variety of clinical problems and exact clinical correlation was not attempted. However, our purpose was to document and quantify this new finding with MRI and CT examinations. High-dose ionizing radiation prevents application of CT in prospective studies and non-patient populations. MRI has become the first imaging modality in patients with LBP, because it provides a non-invasive precise morphologic appraisal of the lumbar spine and permits direct relation of morphologic findings to LBP. Despite these shortcomings, the author believes that the results are important because they can improve diagnostic yield in patients with LBP in the future.

In conclusion, endplate sclerosis existed in all types of Modic changes in CT, especially in mixed Modic types, and not only in type III changes, as previously assumed. Endplate sclerosis with Modic changes was not detected in MRI, which may depend on the amount of trabeculae and mineralization of the bone marrow.

6.6 Future prospects

During the last two decades, our understanding of the vertebral bone marrow changes adjacent to the endplates of degenerated intervertebral discs has increased. However, the need for further research remains. Areas of future research should mainly include the mechanism, natural history and relationship to symptoms. Three hypotheses of the mechanism - biomechanical, biochemical and infective – have been proposed. To date, however, the evidence supporting these hypotheses or their possible interplay in the pathogenesis of Modic changes is not clear. According to the current literature, including this thesis, type I Modic changes are likely to be associated with LBP symptoms. However, the prognostic significance of these changes, including conversions into different types, in relation to a patient's symptoms needs to be confirmed. Therefore, further studies with longer follow-up periods, more frequent MRI studies and larger sample sizes will be required.

Isolating a subgroup of patients with type I Modic changes could be of therapeutic and economic interest. In a recent study, LBP patients with Modic type I change tended to have better short-term efficacy following intradiscal steroid injections than those predominantly with type II changes (Fayad *et al.* 2007). In addition, surgical studies have suggested that patients with type I changes who

undergo lumbar fusion for LBP do better than those without changes or with type II (Vital *et al.* 2003). These authors speculate that disappearance of type I changes may be an indicator of successful fusion and stabilization. However, with the current knowledge, it is probably premature to assume that the bone marrow changes are themselves a prognostic finding or indicative of a need for a specific intervention. In the future, a controlled study of patients with type I changes with randomization to different forms of therapy might be helpful to determine whether the evolution of these changes can be altered by therapeutic interventions, or whether it is dependent on the natural history of the degenerative process.

7 Summary and conclusions

The results of this thesis indicate that Modic changes are a specific phenotype of degenerative intervertebral disc disease. It is important for radiologists to recognize and differentiate these changes from other bone marrow signal intensity changes that exist in vertebral bodies. Physicians treating low back pain patients should also be familiar with the appearance, the natural course and the association of Modic changes with LBP symptoms. The main conclusions of the present study are summarized as follows:

1. Besides age, the determinants of Modic changes and disc degeneration may be different. Weight-related factors seem to be important in the pathogenesis of Modic changes, whereas whole-body vibration is associated with severe disc degeneration.
2. Modic changes are a common MRI finding in patients with degenerative disc disease. They can change from one type to another, and type II changes may be less stable than previously assumed.
3. Modic changes at L5–S1 and Modic type I lesions are more likely to be associated with pain symptoms than other types of Modic changes or changes located at other lumbar levels.
4. Endplate sclerosis exists in all types of Modic changes in CT, especially in mixed Modic types, and not only in type III changes, as previously assumed. Endplate sclerosis with Modic changes is not detected in MRI, which may depend on the amount of trabeculae and mineralization of the bone marrow.

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Original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:

- I Kuisma M, Karppinen J, Haapea M, Niinimäki J, Ojala R, Heliövaara M, Korpelainen R, Kaikkonen K, Taimela S, Natri A & Tervonen O (2008) 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* 9:51.
- II Kuisma M, Karppinen J, Niinimäki J, Kurunlahti M, Haapea M, Vanharanta H & Tervonen O (2006) A three-year follow-up of lumbar spine endplate (Modic) changes. *Spine* 31:1714–1718.
- III Kuisma M, Karppinen J, Niinimäki J, Ojala R, Haapea M, Heliövaara M, Korpelainen R, Taimela S, Natri A & Tervonen O (2007) Modic changes in endplates of lumbar vertebral bodies: prevalence and association with low back and sciatic pain among middle-aged male workers. *Spine* 32:1116–1122.
- IV Kuisma M, Karppinen J, Haapea M, Lammentausta E, Niinimäki J & Tervonen O (2009) Modic changes in vertebral endplates: a comparison of MR imaging and multislice CT. *Skeletal Radiol* 38:141–147.

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ISBN 978-951-42-9060-2 (Paperback)

ISBN 978-951-42-9061-9 (PDF)

ISSN 0355-3221 (Print)

ISSN 1796-2234 (Online)

