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The Natural History of Modic Changes - a 5- and 15-year Follow-up Study

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Abstract

Modic changes (MCs), defined as bone marrow lesions adjacent to the vertebral endplate seen on MRI, have been associated with back pain. There are different types of MCs, with different histopathological correlates. This community-based study sample comprised 110 men from the Twin Spine Study, with baseline, 5-year, and 15-year follow-up MRIs. Following training and reliability testing, 1320 endplates (T12-S1) were evaluated for MC presence, type, and dimensions at each time point. Results demonstrated that Type 2 Modic Changes (MC2) were the most common type, with approximately half located at the two lowest disc levels. However, Type 1 Modic Changes (MC1) were distributed similarly across the lumbar region. Results suggest that MC1 is a transient phase, with no MC1s at baseline persisting to 15-year follow-up, and most converting to MC2. New MCs mostly occurred in the anterior aspect of the endplate, which may provide clues related to pathogenesis.

Key words

Modic Changes, General Population, Low Back Pain, Natural History, MRI measurement, Reliability

Summary for Lay Audience

Low back pain is a common condition and the leading cause of disability worldwide, placing a heavy burden on affected individuals and society. Currently, the specific pathology underlying a vast majority (85%) of back pain remains unknown severely limiting the development of effective prevention and treatment approaches. Imaging biomarkers and phenotypes (observable traits) associated with LBP may help inform prognosis and provide insights into underlying pathology. In recent years there has been growing interest in one of these specific phenotypes, Modic changes (MCs), defined as bone marrow lesions adjacent to the vertebral endplate as seen on Magnetic Resonance Imaging (MRI). There are different types of MCs, and each has specific histopathological correlates. However, the natural course of these lesions, which this study aims to examine, is not well established.

This community-based study sample comprised 110 men (mean age of 48±8 years) from the Twin Spine Study cohort, shown to be highly representative of the corresponding Finnish population, with baseline, 5-year, and 15-year follow-up MRIs. Images were analyzed at three time points for all participants. Following training and reliability testing, images were evaluated for MC presence, type (MC1, MC2, or Mixed MC), and dimensions (anteroposterior, transverse, and vertical height) at each time point.

This longitudinal study confirmed that MC2 is the most common MC type in men, with MC2, but not other types, mainly located at the lower lumbar endplates. Also, MC1 appears to be a transient phase, with no MC1s at baseline persisting to 15-year follow-up. New MCs mostly occurred in the anterior aspect of the endplate, which may provide clues related to pathogenesis. Complete resolution of MCs can occur, but it is very uncommon.

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Chapter 1

1 Introduction

The focus of this dissertation is to explore the natural history of Modic Changes (MC). The study presented herein may help to better understand the nature and transformation of this imaging biomarker and to inform future research targeting factors that influence these markers, prognostication, and possibly related interventions for Low Back Pain (LBP).

1.1 Low Back Pain Burden and Barriers in Management

Low back pain (LBP) is a prevalent condition. It affects many people at some point in their life and has a point prevalence estimated at 11.9 ± 2.0% and a one-month prevalence of 23.2 ± 2.9% [3–5]. Back pain is the leading cause of disability worldwide [6, 7]. People with this condition seek healthcare services frequently in order to relieve their symptoms, which places a heavy financial burden on both affected individuals and the healthcare and social support system [6, 8]. Most of this burden is related to Chronic LBP defined as LBP persisting for at least three months [9, 10].

Identifying the etiology of LBP is often a challenge, and currently, approximately 85% of LBP cases are classified as ‘‘non-specific LBP’’ and cannot be diagnosed due to the inconsistency between symptoms and observed pathology. This is neither helpful for the patient nor the physician and severely limits the development of effective prevention and treatment approaches [11, 12]. To better understand non-specific LBP, researchers have tried to look at it, not as a disease but a symptom of yet unidentified subgroups or pathologies. MRI is believed to be of importance in identifying contributors to back symptoms [13]. Imaging biomarkers or phenotypes (observable traits) associated with LBP may help inform prognosis and provide insights into underlying pathology [1, 2].

Advancement in MR Imaging created opportunities to learn more about the disc, vertebral body, endplate and facet joints, and their relation to one another. While much

attention has been placed on intervertebral discs, they have limited innervation and do not easily explain LBP. Therefore attention has shifted to other structures, such as the endplate, which is richly innervated [14, 15]. Two main categories of pathology related to the endplate are vertebral signal variations observed on MRI known as Modic changes and endplate structural defects, including Schmorl's nodes, fractures, erosions and calcifications and other endplate defects[16].

1.1.1 Modic Changes, Definition, Prevalence and Distribution

In recent years there has been growing interest in specific phenotypes referred to as Modic changes (MCs) [2]. MCs are defined as bone marrow lesions adjacent to the vertebral endplate seen on Magnetic Resonance Imaging (MRI) [17]. There are three different types of MCs, and each has specific histopathological correlates [18]. Modic et al. were credited with this classification. They defined Type 1 MCs (MC1) as a hypointense signal in T1-weighted imaging (T1WI) and hyperintense signal in T2-weighted imaging (T2WI) representative of bone marrow hypervascularity or edema. Type 2 MCs (MC2) have a hyperintense signal on T1WI and a hyperintense signal on T2WI, reflecting bone marrow fatty degeneration. Type 3 (MC 3) has a hypointense signal in T1WI and a hypointense signal in T2WI corresponding to endplate sclerosis [19]. Mixed type MCs refer to the presence of more than one type of MC within an endplate, as MCs have a variable course and can either change in type or resolve completely over time, and can be present at different stages at the same time [17, 20]. Micro-architectural analysis of MCs showed high bone turnover in MC1 biopsies, with reduced turnover in MC2 and a more stable and sclerotic phase in MC3 [21].

Despite over 30 years of study, much remains unknown or controversial about MCs. In a systematic review, the prevalence of all types of MCs was reported to range from 3-80% in clinical cases and 0.5 to 88% in non-clinical samples [13, 22]. This variation in range could be due to the choice of the study population and the proposed association between MCs and LBP. For example, the prevalence of all types of MCs is reported at 13% in asymptomatic patients in one study and 49% in another study of sciatica patients [23]. Among other factors that could cause inconsistencies in the prevalence in asymptomatic

participants is age. In a study by Takatalo (2021), the mean age of participants from the Northern Finland Birth Cohort was 21.2, and the reported prevalence of all types of MCs was 0.9% [24]. However, in another population-based study with a mean age of 59.2, the prevalence of any type of MCs was 47.1% [25]. Also, as noted, some studies do not differentiate between different types of endplate signal changes [25, 26]. The prevalence of MC1 varies between 3.7% and 69%, and type 2 between 4.3 and 42 % [13].

MCs have been found to be more prevalent at the lower levels (L4-S1) of the lumbar region [27]. Also, they are most often present symmetrically on endplates adjacent to a particular disc [28, 29]. Most MCs have also been found to be on the anterior aspect of lumbar vertebrae [27].

1.2 Association of Modic Changes with Low Back Pain

Many studies have found a strong association between MC1 and LBP [30–32], although this has not been the case for all and controversy remains [13]. Bailly et al. (2014) found an association between MC1s and an inflammatory pain pattern, defined as the presence of at least one of the following three characteristics: maximal pain in the morning, waking at night because of pain, morning stiffness for longer than 60 minutes, and pain during back extension [33]. A decrease in symptom severity has been reported in patients with MC1s that, over time, resolved or converted to other types of MCs, as compared to those that did not [32]. In another study, those with persistent MC1s did not demonstrate improvement in low back pain and function [34]. Moreover, changes in the extent of MC1s have been associated with changes in LBP [35]. Thus, it is important to understand the natural course of MCs.

1.3 Potential Etiological and Pathobiological Factors and Clinical Significance

Modic Changes are considered to have multifactorial pathophysiology including, degenerative, biomechanical, genetic, autoimmune, bacterial and traumatic [15]. MCs are highly connected to disc degeneration (DD); however, DD is not believed to cause MCs by itself [36, 37]. Endplate defects could be another possible etiology of MCs, and can

exist at the same location, but they are mostly related to DD and the exact relation between endplate defects and MCs is not clear [36].

Infectious causes, either locally or bacteremia, have been proposed for the presence of MCs as bacterial metabolism and cytokines could cause inflammation within the marrow adjacent to the disc [38]. Also, the anaerobic environment and avascularity of the disc impedes recovery and repair. This anaerobic environment and absence of immune response make this area ideal for bacterial growth. It is reported that even minor invasions, such as from tooth brushing damage, could lead to bacteremia, and Propionibacterium acnes (P. acnes), the suspected organism responsible, could enter into the circulation and eventually lead to MCs [13, 23, 39]. Additionally, C-reactive protein (CRP), which is a marker of inflammation, was found to be high in people with MC 1 [40]. Antibiotics were even introduced as a treatment in some cases [41]. Yet, there is also literature that questions this hypothesis explaining the etiology of MCs [15].

Another mechanism suggested for the formation of MCs is an autoimmune response from the nucleus pulposus (NP) getting into contact with bone marrow following endplate damage triggering the expression of cytokines, macrophages and activated T- and B-cells [15, 42, 43]. Genetics also plays a role in DD, endplate defects, and MCs, with one study finding an association between the Vitamin D Receptor and matrix-metalloproteinase-20 (MMP20) genes and MCs [15, 44]

All these etiologies may eventually lead into a common pathological pathway. In such a pathway Toll-like receptor (TLR) appears to play an important role. It is related to TLR2-mediated NF-Kß-responsive gene transcription and production of IL-6 and IL-8. Also, it is known to be a receptor for bacterial cell wall and damage- associated molecular proteins (DAMP) that are considered as “danger molecules” causing mechanical and enzymatic tissue damage [45]. These cytokines and osteoclastic factors, such as RANKL (receptor activator of nuclear factor kappa-B ligand), M-CSF (macrophage colony-stimulating factor), NFATc1(nuclear factor of activating T-cells, cytoplasmic 1), RUNX1(runt-related transcription factor), OSCAR (osteoclast activator receptor), seem to be higher near MCs and interfere with bone marrow composition [46]. The different

types of MCs probably represent different stages of this pathway. For example, following a high bone turnover, possibly due to an inflammatory process, MC1 will form. This pathway is not sequential; thus the progression of all types of MCs may move from one to another or resolution [13].

1.4 Research Rational, Aims and Questions

Further studies of repeated MRI over a longer duration and larger sample sizes are needed to better understand the natural history of MCs and the mechanisms responsible for conversion.

The overarching purpose of the current study was to enhance knowledge of the development of MCs (natural history of Modic Changes) in the lumbar region in men. The specific objectives were to determine the development of MCs at 5-year and 15-year follow-up in terms of changes in occurrence, size, and type.

This dissertation represents the findings of an ambitious, exploratory study to investigate the natural history of Modic Changes and lays the foundation for a subsequent study of the association of MCs with loading factors. We began this project (Chapter 2) with a reliability study on measurements of Modic Changes and specifically on measurement of changes in Modic Changes, to assist decisions on measurement methodology on reading the baseline and follow-up images. The aim of Chapter 3 is to investigate the natural history of Modic Changes in a community-based population. It provides a more inclusive look at how the changes happen over the follow-up period. In this chapter, we will outline how we measured the size of MC in an endplate and how we determined changes in the size of MCs in different dimensions over 5- and 15-years.

Chapter 2

2 Measurement Reliability of Modic Changes

2.1 Introduction

MRI is the imaging method of choice for evaluating patients with LBP as it has excellent soft-tissue contrast, and the images can be viewed in different planes[47]. In recent years there has been growing interest in one of the MRI phenotypes named Modic changes (MCs), defined as bone marrow lesions adjacent to the vertebral endplate seen on MRI. There are different types of MCs, with different histopathological correlates [19]. Modic Change type 1 (MC1) is characterized by hypo-intensity on T1 images and hyper-intensity on T2 images, and it is representative of the inflammatory state. Modic Change type 2 (MC2) is hyperintense on both T1-weighted and T2-weighted images showing yellow or fatty marrow replacement, and Modic Change type 3 (MC3) is hypointense in both T1-weighted and T2-weighted images, corresponding to subchondral sclerosis [19, 20, 48].

Many studies have assessed the intra- and inter-rater reliability of the presence of Modic Changes[47–51]. There are inconsistencies in assessing MCs in longitudinal studies. It has been suggested that pairwise viewing of the image provides us with more reliable results [52]; however, in a general-population study, they suggested non-comparison (independent readings) for studying the course of MCs [50]. Overall, to the author's knowledge, there is no protocol for assessing changes across longitudinal images, although reading the baseline and follow-up images independently or side-by-side (pairwise) could lead to different results. The development of a standardized, reliable protocol is needed. The purpose of the current study was to examine and compare the reliability of independent and pairwise assessments of changes in MC categorization and size to determine the best method for the evaluation of MCs in our longitudinal study.

2.2 Material and Methods

2.2.1 Subjects

Repeated lumbar MR Imaging scans from the Twin Spine Study (TSS) were used to examine measurement reliability. The Twin Spine Study includes a sample of 600 male twins (age 35-70) from the Finnish population [53]. To study the natural history of Modic Changes in this sample, out of the initial sample of 232 twins (116 pairs) shown to be largely representative of the corresponding Finnish population [53], a subsample of 110 men, mean age of 48±8 years, with repeated lumbar MRI were selected that had baseline, as well as 5-year and 15-year follow-up images. For the current study, 20 participants (120 endplates) of these participants' images were randomly selected, including 3 twin pairs (6 subjects).

2.2.2 MRI Data Acquisition

The baseline and 15-year follow-up lumbar MRIs were obtained using 1.5 Tesla Siemens scanners with surface coils, either a Magnetom SP 4000 scanner or a Magnetom Vision scanner (Siemens AG Erlangen, Germany). Sagittal T1-weighted images were acquired using TR/TE times of 650/22 milliseconds and T2-weighted images using repetition and echo times of 2600 milliseconds (ms) and 90 ms, respectively. For the Avanto scanner, the field of view was 320 mm (in axial 348Å (Angstrom) ~384 mm), and the slice thickness and interslice gap were 4 mm and 0.4 mm, respectively. The pixel size of the Magnetom images was 1.02 mm, and the pixel size of the Avanto images was 0.8125 mm. Each subject was lying supine for 30–45 minutes immediately before MRI scanning to minimize the effects of activity and diurnal variations [54]. We used only sagittal images for the current study.

2.2.3 Image Evaluation

We used Horos (a free and open-source code software (FOSS) program distributed free of charge under the LGPL license at Horosproject.org and sponsored by Nimble Co LLC d/b/a Purview in Annapolis, MD USA) for evaluation of DICOM images. This software

can display T1- and T2-weighted MR images simultaneously, which is necessary for detecting and categorizing MCs.

Prior to conducting the study, a set of example MR images depicting various MC types was prepared for teaching and reference purposes. First, an experienced radiologist and spine researcher familiarized themselves with MC classification and measurement and then independently assessed a set of 40 training images, 20 baseline and 20 follow-up images, which they reviewed together afterwards, with discussion and resolution of discrepancies.

We wanted to determine the effects of assessing MCs from baseline and 15-year follow-up images viewed independently or pairwise. Therefore, the spine researcher first independently evaluated the images, including 20 baseline and 20 follow-up scans. Ten days later, the 40 blinded MRIs were placed in random order and assessed again using the MC classification and measurement protocol. Next, ten days later, she repeated the assessments, with the baseline and corresponding 15-yr follow-up scans side-by-side, noting differences in the presence/absence or type of MCs from baseline to follow-up, as well as changes in size. Two weeks later, she viewed the baseline and follow-up scans again side-by-side. In each instance, the observer was blinded to clinical history and any previous measurements. However, due to MRI quality the researcher was able to differentiate baseline from follow-up images.

2.2.4 Modic Change Classification and assessment of dimensions

We evaluated 12 endplates in the lumbar region (T12-S1) for the detection of MCs. Modic classification was used for determining the type (MC1, MC2, MC3 and Mixed MCs) [55]. In sagittal MRI scans, only signal changes extending from the endplate present in more than one sagittal slice were reported as MCs to avoid artifacts.

Quantitative assessment of MC dimensions was recorded in three planes, anteroposterior (AP), transverse and height. For AP assessment, we divided the anterior-posterior diameter of the vertebral body into the anterior, central, and posterior thirds. The location of each MC was determined based on this classification. For measuring the transverse

diameter of MCs, we used 11 sagittal images that represented approximately the entire transverse diameter of the vertebral body. An ordinal scale with 11 points was used to grade the size of each MC, where an MC was deemed to be absent if seen on no slices or only 1 (grade 1). Each grade was the number of slices involved (2-11) [56]. The vertical height of the MC was determined from the slice with the maximum MC height. Vertical height was recorded as one if MC height was less the 25 % of vertebrae body height, two if between 25% and 50%, and if more than 50% (Table 2-1).

TABLE 2-1 Definitions of MC size in the transverse, AP and vertical dimension and Variable of Change

Variables	**Definition**
Transverse	
Small	2 to 4 sagittal slices with MCs
Moderate	5 to 7 sagittal slices with MCs
Large	More than 8 sagittal slices with MCs
AP	
Small	Anterior or central or posterior portion
Moderate	Two portions
Large	All three portions
Maximum MC height	
Small	Less than 25%
Moderate	25% to 50%
Large	More than 50%
Variable of Change	
none	No changes in the size of MC over time
Small increase (+1)	Changes from small to moderate or moderate to large
Large increase (+2)	Changes from small to large
Small decrease (-1)	Changes from moderate to small or large to moderate
Large decrease (-2)	Changes from large to small

AP indicates anteroposterior; MC, Modic Changes

2.2.5 Reliability of Changes

The primary aim of the main study was to assess the reliability of detecting changes in MCs over a period of 5 and 15 years. To find the most reliable method for detecting changes, we assessed baseline and follow-up images independently and pairwise, noting 0 when no change was observed, 1 for an incident (a new MC of any type on a previously normal endplate), 2 for conversion of an MC to another type, and 3 when a MC resolved.

To assess the reliability of change in size, we first selected the endplates that showed the same type of MCs in both baseline and follow-up images at first and second reading of pairwise (n=20) and separate (n=17) viewing. Then we categorized AP, transverse and vertical height of MCs to Small, Moderate or Large (Table 2-1). Any changes from Small to Moderate or Moderate to Large, and vice versa in the follow-up image were considered small changes. Also changes from small to large and vice versa were counted as large changes. These changes could happen in both ways, positive or negative. Furthermore, while we evaluated the changes, we also recorded the endplates that remain the same size (Table 2-1). Also, to better understand the *total* changes in the size of one MC over follow-up, a Sum of Changes (SC) variable was created, taking into account changes in each dimension.

Sum of Changes (SC) = Change in Transverse size + Change in Height + Change in AP size, with changes being either negative (reduction in size) or positive (increase in size). Theoretically, change scores for each dimension of size could range from -2 to +2.

2.2.6 Analysis

Kappa statistics were used to assess intra-rater reliability using the repeated independent and pairwise assessments of MCs on baseline and follow-up images, and inter-method reliability was determined using the first set of independent and pairwise assessments. Kappa is defined as the degree of difference between observed and expected agreement between coders or conditions. For interpreting kappa values, a value less than 0.2 is considered as slight, 0.21 to 0.40 as fair, 0.41 to 0.60 as moderate, 0.61 to 0.80 as substantial, and 0.81 to 1.0 as almost perfect or perfect agreement [57, 58]. Fisher's exact

test was done to assess whether the incident of new MCs is higher in separate viewing in comparison with pairwise viewing.

2.3 Results

MRI of 20 lumbar spines (240 endplates) were assessed 4 times independently. Intra-rater agreement of type, anteroposterior (AP) location, transverse size and vertical height of MCs was found to have substantial to almost perfect agreement using both methods (Table 2-2). However, based on these readings, the intra-rater reliability of separate readings of MC Type was substantial (Kappa (κ) = 0.80, CI=0.75-0.85), while that of pairwise reading was almost perfect (κ = 0.92, CI=0.85-0.99). The inter-method reliability between first reading of independent and pairwise assessments was substantial, as well (κ =0.78, CI=0.73-0.83). In general, as expected, intra-rater reliability of pairwise viewing was better than for separate viewing (Table 2-2).

There were more incident or new MCs noted when assessing images independently (71) in comparison with viewing them side-by-side (54) (Fisher's exact test $p<0.001$, Table 2-3). Similarly, there were more cases of resolving MCs when assessing independently (4) compared with side-by-side (2).

The reliability of changes for pairwise viewing was almost perfect (κ =0.90, CI=0.81-0.99) and that of separate viewing was substantial (κ =0.70, CI=0.61-0.79). Inter-method reliability for detecting changes in MCs in our sample was substantial, as well (κ =0.78, CI=0.73-0.82).

The reliability of changes in the size of MCs that remained the same type from baseline to follow-up (20 endplates for pairwise and 17 endplates for separate viewing) are depicted for pairwise and separate assessments in Table 2-4. In the pairwise viewing we had MCs that did not change type during the 15-year follow-up and all measures of size had moderate to substantial reliability (κ=0.57 to 0.63). When we looked at images separately, there were only 17 endplates with MCs that remained the same type at 15-year follow-up. Except for AP measurements that had slight reliability (κ=0.18), measures had moderate or substantial reliability (κ=0.50 for transverse size and κ=0.59

for height of MCs). The reliability for Sum of Changes in both method was fair (κ=0.27 in separate and κ=0.37 in pairwise viewing).

TABLE 2-2 Reliability of Modic classification and size measurements between pairwise and separate readings of baseline and follow-up images

Variables	Intra-rater reliability (κ) (95% CI)		Inter-method reliability (κ) (95% CI)
	Separate	Pairwise	
MC Type	0.80 (0.75-0.85)	0.92 (0.85-0.99)	0.78 (0.73-0.83)
Anteroposterior Location	0.75 (0.72-0.78)	0.90 (0.87-0.93)	0.75 (0.72-0.78)
Transverse size	0.78 (0.73-0.83)$_{\varepsilon}$	0.89 (0.84-0.94)$_{\varepsilon}$	0.81 (0.76-0.86)$_{\varepsilon}$
Vertical Height	0.79 (0.74-0.84)$_{\varepsilon}$	0.87 (0.82-0.92)$_{\varepsilon}$	0.77 (0.72-0.82)$_{\varepsilon}$
Change in Type	0.70 (0.61-0.79)	0.90 (0.81-0.99)	0.78 (0.73-0.82)
ε indicate weighted Kappa			

TABLE 2-3 Comparison of incident or new Modic Changes detected from independent or pairwise assessments of baseline and 15-year follow-up MR Images

MC Type	Incident or new MCs	
	Independent	Pairwise
MC 1	6	5
MC 2	61	47
Mixed MC	4	2
All	71	54
** The difference in all incident MCs from independent versus pairwise assessments was statistically significant (Fisher's exact test, p<0.001).*		

TABLE 2-4 Reliability of Changes in Type of Modic Changes and Changes in size measurements between pairwise and separate readings of baseline and follow-up images		
Variables	**Intra-rater reliability (κ)**	
	Separate (n=17)	**Pairwise (n=20)**
Changes in AP size	0.18 (0-0.0.37)	0.58 (0.21- 0.95)
Changes in Transverse size	0.50 (0.25-0.75)	0.63 (0.30-0.96)
Changes in Vertical Height	0.64 (0.23-1)	0.57 (0.18-0.96)
Sum of Changes	0.27 (0.06-0.48)	0.37 (0.12-0.62)

2.4 Discussion

This study was purposefully designed to help determine the best method for detecting Changes of Modic changes in follow-up (longitudinal) studies with repeated imaging. Baseline and 15-year follow-up lumbar MR images of randomly selected individuals from a population-based sample allowed Changes of MCs and development of new MCs (incident of new MCs) to be evaluated.

Intra-rater reliability of MC classification has ranged from κ =0.70 to 1.00 in previous studies [17, 49, 59–61], while inter-rater reliability was reported as either substantial [17, 49], or almost perfect [29, 48, 59, 61, 62]. In a study on the reliability of temporal changes using MRI, the inter-rater percent agreement in reporting the absence of MCs was high; however, it was low for reporting the presence of these findings [63]. To this author's knowledge, only two studies assessed the effect of independent versus pairwise viewing of follow-up images in studying changes in MCs, and there are inconsistencies in their results [50, 52]. While one recommended independent viewing for a community-based population [50], the other study found the pairwise comparison method more reliable [29]. Furthermore, almost all prior longitudinal studies on MCs did not report whether they have viewed the repeated images independently or pairwise. The findings from the present study suggest that this may be an important methodological consideration that should be noted. The overall classification of MC type in this study was consistent with other studies [49, 50, 59]. We found substantial intra-rater reliability of MC classification for separate viewing of repeated MRI, and those from pairwise

viewing were almost perfect. As the inter-method agreement in MC classification between assessing images pairwise and separately was substantial (κ =0.78), both methods of image viewing appear to have adequate reliability. However, the reliability of changes in MC type from pairwise viewing was higher than with independent viewing, 0.90 in comparison with 0.70, suggesting this method may be a better way to evaluate change in follow-up studies if the conversion of MCs is of interest.

In the only previous study assessing changes in the size of MCs, they observed that the AP size of MCs is significantly affected by the method of evaluation (independent vs pairwise) [52]. Our findings were consistent with theirs, and in assessing the reliability of change in AP size, the Kappa for separate viewing was lower than for pairwise viewing (0.17 (slight) and 0.57 (moderate), respectively). Overall, changes in size appear to be more reliable in pairwise viewing of images.

Our measurement reliability for evaluating change in size was low with wide confidence intervals using both methods. However, this could be due, in part, to the small sample (low number of endplates that remained the same type, 20 pairwise and 17 separate). This is also the same for the sum of changes. A bigger sample of endplates remaining the same type is needed to better assess the reliability of change in size and sum of changes. As such, changes in MC size need to be viewed with caution.

We expected that the method used to view repeated images would affect the detection of MCs. Viewing the images side-by-side could be beneficial in detecting more subtle changes in the size of MCs, as the eye may be more likely to detect such changes when directly comparing images. On the other hand, when there is a small area of signal variation on only the baseline or the follow-up image, the reader may be less likely to report it as a notable MC, than if viewing the finding on a separate image independently. This is supported by the finding that incident or new MCs were reported more commonly when viewing images separately (71) than viewing repeated images side-by-side (54) and statistically significant. Furthermore, the disappearance of MCs was higher in separate viewing (4) in comparison with pairwise (2). However, as we do not have a gold standard for determining change, we cannot say which method's assessments are more valid.

Another possible bias relates to the expectation of a higher prevalence or worsening of MCs with ageing at follow-up when assessing the scans side-by-side. Yet, such a bias was not supported by the findings of the current study as fewer incident MCs were found when viewing baseline and follow-up images side-by-side as compared to viewing them independently.

There are several limitations of the reliability study that should be considered. First, although the number of endplates is relatively large (n=120), the sample of 20 subjects' images is modest. It would be important to see whether the study findings replicate with a larger sample to have greater confidence in recommending the side-by-side method for widespread use in assessing MC changes from repeated imaging. Second, the spine researcher underwent proper training, reviewing a training image set with an experienced radiologist, including independent readings followed by discussion and resolution of all discrepancies, but this study did not specifically investigate inter-rater reliability. It is possible that others' assessments and reliability may differ. Third, in our statistics, we did not account for any residual correlation between twins or among the discs, which may have affected results. Furthermore, the image quality of the early generation 1.5T MR images and the 15-year follow-up images, may have influenced measurement reliability. However, these effects may be expected to have influenced the reliability of both assessment methods similarly. Finally, the unavoidable differences in image quality between baseline and 15-year follow-up images, allowing them to be differentiated, may have created bias both on seeing more details in the 15-year follow-up images and if there were expectations related to MC development.

In conclusion, the results of the current study led to the decision to evaluate changes of MCs in the main study (Chapter 3) by viewing the repeated images side-by-side. According to our results, in longitudinal studies with the aim of identifying changes in types and sizes of MCs, reading the images side-by-side appears to be more reliable than assessing the images independently.

Chapter 3

3 The Natural History of Modic Changes - a 5- and 15-year Follow-up Study

3.1 Introduction

Low back pain is a common condition and the leading cause of disability worldwide, placing a heavy burden on affected individuals and society [6]. Currently, the specific pathology underlying the vast majority (85%) of back pain remains unknown, which severely limits the development of effective prevention and treatment approaches [6, 11]. Imaging biomarkers or phenotypes (observable traits) associated with LBP may help inform prognosis and provide insights into underlying pathology [1, 2].

In recent years there has been growing interest in specific spine imaging phenotypes referred to as Modic Changes (MCs) [2], defined as bone marrow lesions adjacent to the vertebral endplate seen on Magnetic Resonance Imaging (MRI) [17]. There are three different types of MCs, and each has specific histopathological correlates [28]. Modic et al. (1988) are credited with this classification. They defined Type 1 MCs (MC1) as a hypointense signal in T1-weighted imaging (T1WI) and hyperintense signal in T2-weighted imaging (T2WI) representative of bone marrow hypervascularity or edema. Type 2 MCs (MC2) have hyperintense signal in T1WI and hyperintense signal in T2WI, reflecting bone marrow fatty degeneration; and Type 3 (MC3) have hypointense signal in T1WI and hypointense signal in T2WI corresponding to endplate sclerosis [19]. As MCs have a variable course, over time, they can either change in type or resolve completely and can be present at different stages at the same time. Therefore, Mixed type MCs (Mixed MC) refer to the presence of more than one type of MC within an endplate [17, 20].

While several longitudinal studies have assessed the natural course of MCs, most are limited by highly selected study samples of patients with symptomatic back conditions [23, 32], and may not be representative of the natural history of MCs in the general population [28]. In a community-based study of 72 overweight (BMI 29.3 kgm^{-2} ± 7.9

kgm^{-2}) participants from a weight loss clinic, the natural history of MCs was investigated [28]. However, since higher BMI has been associated with the presence of more MCs [64], the external validity of the study is limited. In another longitudinal study of a sample from the general Danish population, different types of MCs were not distinguished [65], and, therefore, the natural course of MCs could not be determined.

Thus, further studies of repeated MRI over a longer duration with larger sample sizes representative of the general population are needed to better understand the natural history of MCs and the mechanisms responsible for conversion. The aim of this study was to address this need through the study of a population-based sample of men with repeated imaging at 5- and 15-year follow-up.

3.2 Methods

3.2.1 Study Sample

The study sample was a subset of participants from the Twin Spine Study, a multidisciplinary and multinational research project that focused on the effects of environmental, behavioural, and constitutional factors on spinal degeneration, pathology, and pain. The first wave of data collection was in 1991, when baseline data were collected, with final follow-up data on a subset collected in 2009 [53]. The original Twin Spine Study subjects were 232 monozygotic (MZ) twin males recruited from the Finnish Twin Cohort, born prior to 1958. They were selected based only on exposure to specific common behavioral or environmental factors (e.g., occupational demands, exercise, or sports participation) without regard to back pain history. There was an 82% volunteer rate [66]. The study sample was found to be highly representative of the Finnish Twin Cohort, representing of the Finnish population [53, 66]. The selected population was compared to all MC male pairs that were alive at the time of selecting these participants, and no significant difference was found in the level of leisure-time physical activity, education, outdoor vs. indoor work, shift work or work monotony. Also, the amount of smoking, occupation category, and social class did not significantly differ. No significance was found in work-capacitating neck, shoulder or back pain and sciatica history. The only

differences were the current work status and physical loading at work, that could be due to the criteria for selecting the participants [66]. Five years after the baseline study, 75 pairs were examined again, and ten years later, 116 participants were still alive and able to travel to the study center to be reexamined approximately 15 years after their baseline evaluations [67]. The sample for the current study included 110 men (age 35-69 at baseline) out of 150 randomly selected from those with baseline images who participated in repeated MRI at 5-year follow-up and attended a 15-year follow-up. Characteristics of 108 subjects of the 110 included in the current study sample (we found two additional twins MRI admissible) have been reported previously. Their baseline mean (SD) height, weight, and BMI was 174.8 (7.0), 79.5 (11.2), and 26.0 (2.9), respectively [68]. These characteristics were also previously published on 232 baseline MZ twin males, and the figures were almost similar to the selected participants (mean (95%CI) height, weight, and BMI were 175.0 (173.9-176.1), 79.3 (77.6-81.1), and 25.9 (25.4-26.4), respectively)[69]. Among the 110 participants, there were 24 pairs (48 participants). Prior lumbar spinal surgery was an exclusion criterion.

3.2.2 MRI Acquisition

At baseline and follow-up, 1.5 T Siemens scanners with surface coils were used, including a Siemens Magnetom at baseline and a 5-year follow-up (Magnetom SP 4000, Siemens AG Erlangen, Germany), and a Siemens Avanto scanner at 15-year follow-up. For the baseline imaging, the field of view was 260 mm, and the slice thickness and interslice gap were 4 mm and 0.4 mm for sagittal images, with sagittal T1-weighted images using TR/TE times of 650/22 and T2-weighted images using repetition and echo times of 2600 millisecond (ms) and 90 (ms), respectively. For the Avanto scanner, the field of view was 320 mm (in axial 348Å (Angstrom) ~384 mm), and the slice thickness and interslice gap were 4 mm and 0.4 mm. The pixel size of the Magnetom images was 1.02 mm, and the pixel size of the Avanto images was 0.8125 mm. Each subject was lying supine for 30–45 minutes immediately before MRI scanning to minimize the effects of physical activity and diurnal variations [54].

3.2.3 Assessment of Modic Changes

MRI evaluations were performed on a PC workstation using Horos (a free and open-source code software (FOSS) program that is distributed free of charge under the LGPL license at Horosproject.org and sponsored by Nimble Co LLC d/b/a Purview in Annapolis, MD USA), and Image J (an open-source, Java-based imaging program developed by Wayne Rasband of the Research Services Branch, National Institute of Mental Health, in Bethesda, Md) [70]. Both Horos and Image J can simultaneously display multiple T1- and T2-weighted images for comparison and allow quantification of MCs.

The lumbar MRI scans (T12-S1) were analyzed for MC presence and type (MC1, MC2, or Mixed MC), and anteroposterior (AP), transverse and vertical size (Figure 3-1). We used the traditional Modic classification system for determining MC type [19]. We only noted vertebral marrow lesions that extended from the endplate in more than two adjacent sagittal slices to exclude imaging artifacts.

Each participant had 11 sagittal T2-weighted images that represented approximately the entire transverse diameter of the vertebral body. The transverse size was rated as none if MCs were absent or present in only one sagittal slice, small if present in 2 to 4 slices, moderate if in 5 to 7 slices, and large if MCs spanned more than eight sagittal slices [56] (Table 2-1) .

The AP diameter of an MC was assessed by dividing the AP diameter of the vertebral body into thirds representing the anterior, central, and posterior portion using the sagittal view in MRI. The location of each MC was determined based on this classification. The AP size of a MC was rated as none if there was no MC; small if only one portion included an MC; moderate if the MC involved two of the three portions; and large if the anterior, central, and posterior portions of the vertebral body were involved [56] (Table-2-1).

For measuring the height of MCs in the sagittal images, the slice with the greatest height was selected. Vertical height was recorded as 0 = no MCs, 1= small if <25% of vertebral

height, 2 = moderate if 25% to 50% of vertebral height, and 3 = large if the MC extended over 50% of the vertebral height (Table 2-1).

3.2.4 Changes in the Size of Modic Changes

As the study focused on the development of Modic Changes throughout time, changes in size were recorded for MCs that remained from one time to the next. The change in size of the MC, included transverse, anteroposterior and vertical height. Changes were recorded as none = 0, small = 1, or large = 2, as described in Table 2-1, and could be either positive or negative depending on whether the size had increased (+) or decreased (-). Changes were examined across three timeframes, baseline to 5 -year follow-up, 5-year to 15-year follow-up, and baseline to 15-year follow-up.

To better understand the *total* changes in the size of one MC through time, a Sum of Changes (SC) variable was created, taking into account changes in each dimension. The Sum of Changes signified the amount of change in each MC using an ordinal scale from -6 to +6 using the following equation:

Sum of Changes (SC) = Change in Transverse size + Change in Height + Change in AP size, with changes being either negative (reduction in size) or positive (increase in size).

3.2.5 Measurement Training and Reliability Assessment

As explained in Chapter 2, prior to conducting the current study, a spine researcher was trained in assessing and measuring MCs by an experienced radiologist. A set of 30 images were read separately by the spine researcher and radiologist, followed by a discussion and resolution of discrepancies. Another set of 40 images (20 baseline and 20 15-year follow-up) were assessed as noted in the previous chapter to select the most reliable method for viewing images. Viewing images side-by-side showed almost perfect reliability in MC categorization (κ =0.92) and size measurements (κ =0.87-0.90) [58]. Also, measurements of change were more reliable in pairwise viewing for types of MC(κ =0.90), and size of MC (κ =0.57 to 0.63). Therefore, the pairwise (comparison) viewing method was selected for our longitudinal study of changes in MCs.

3.2.6 Analysis

The natural history of Modic change was explored at each spinal level and at each time point using descriptive statistics. Statistical analyses were conducted using the Fisher's exact test to identify the association of the presence of MCs between upper and lower endplate.

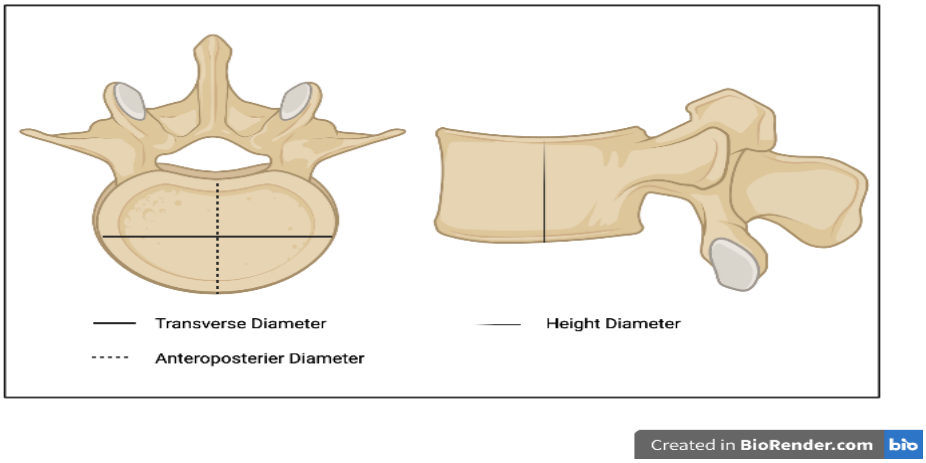

Figure 3-1 Planes for measurement of size in Modic Changes

3.3 Results

The study included 110 of the Twin Spine Study participants who completed both the 5- and 15-year follow-up and had MR Images available. The mean age at baseline was 48±8 years, with a range of 35 to 64 years of age. All participants were males.

3.3.1 Prevalence of Modic Changes

We evaluated 1,320 vertebral endplates (110 participants) for the presence and type of MCs at three time points over 15 years. At baseline, MCs were present in 214 endplates (16.21%) in 78 participants (70.9%), with the majority being Type 2 (involving 191 endplates in 71 participants). All participants were reimaged after 5 and 15 years, with MCs present on 273 (20.68 %) and 509 (38.56%) endplates, respectively (Table 3-1). The

majority of MCs were Type 2 at all time points, located mostly at the two lowest disc levels (L4-L5 and L5-S1). However, the other Types of MCs were distributed similarly across the lumbar region (Figure 3-2).

Table 3-1 Prevalence (%) of Modic Changes in the lumbar vertebral endplates examined (n=1320) at each time point

	No MC	**MC1**	**MC2**	**Mixed MC**
Baseline	1106 (83.8)	16 (1.2)	191 (14.5)	7 (0.5)
5-year follow-up	1047 (79.3)	13 (0.9)	248 (18.8)	12 (0.9)
15-year follow-up	811 (61.4)	40 (3.0)	428 (32.4)	41 (3.1)

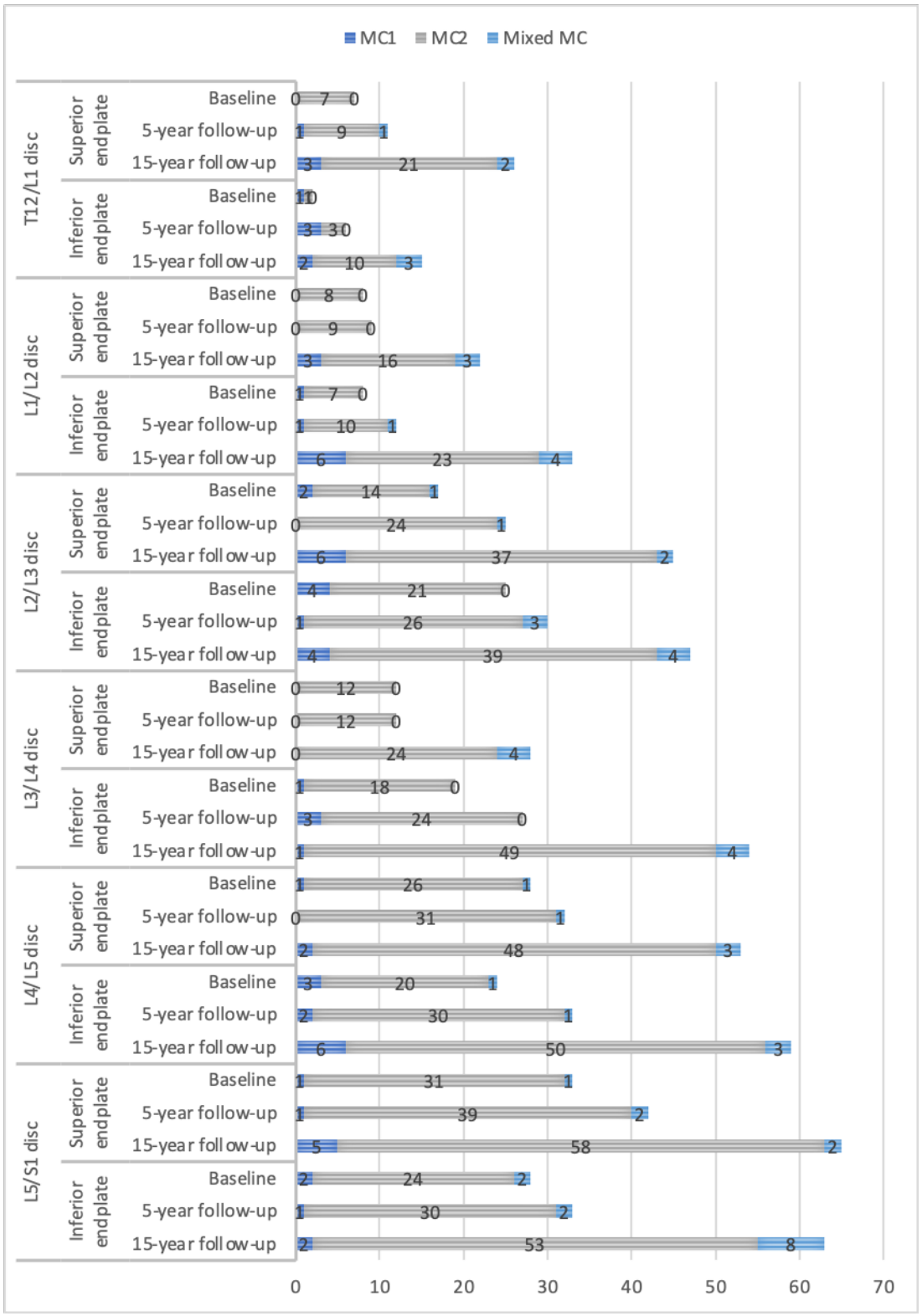

Figure 3-2 Distribution of Modic Changes across the lumbar region

3.3.2 Distribution of Modic Changes between Superior and Inferior Endplates

Overall, at baseline, there were 109 MCs present in the endplate superior to the disc and another 105 MCs in the inferior endplates. Out of 214 endplates with MCs at baseline, 116 (53.4%) showed the same type of MCs on both sides of a disc.

At 5-year follow-up of the 273 MCs observed, 131 were located on superior endplates and 142 on inferior endplates. One hundred forty-eight endplates of 273 (54 %) showed the same type of MCs on both sides of the disc.

Ten years later, at the 15-year follow-up, out of 509 endplates with MCs, 294 (57%) endplates had the same type of MC on either side of the disc. In addition, 237 endplates showed MCs on the superior endplate and 272 on the inferior. Overall, at all timelines, the presence of MCs was not significantly different between the cranial and caudal endplates (Fisher's exact test, $p>0.05$).

3.3.3 Evaluation of the Location and Size of Modic Changes

Of all MCs at baseline, 66 (30%) were located only anteriorly, 13 (6%) only centrally, and 13 (6%) only posteriorly on the endplate. MCs were present across two regions in 29 (13%) cases, and 93 (42%) MCs spanned all three regions. At 5-year and 15-year follow-up, the pattern was similar, with MCs most frequently spanning all three regions in 134 (49%) and 260 (51%), respectively, followed by MCs that were present only in the anterior region of the endplate in 79 (28%) and 119 (23%), respectively (Table 3-2).

Regarding the transverse size of MCs, at baseline, MCs were most often of small size (49%), as was the case at 5-year (52%) and 15-year follow-up (41%). At the same time, as illustrated in Table 3-3, the percentage of endplates with moderate and large MCs increased from baseline to 15-year follow-up (Table 3-2).

MCs were mainly <25% (n=89, 42%) to up to 50% (n=96, 44%) of the height of the vertebra at baseline, which was also the case at 5- and 15-year follow-up (Table 3-2).

Table 3-2 Transverse size, Anteroposterior location, and Height of MCs by time point			
Variables	**Timeline**		
	Baseline, n (%)	**5-year follow-up, n (%)**	**15-year follow-up, n (%)**
Transverse size			
Small	105 (49.0)	142 (52.0)	210 (41.2)
Moderate	60 (28.0)	77 (28.2)	160 (31.4)
Large	49 (22.5)	54 (19.7)	139 (27.3)
Anteroposterior location			
Anterior (only)	66 (30.8)	79 (28.9)	119 (23.1)
Central (only)	13 (6.0)	8 (2.9)	9 (1.7)
Posterior (only)	13 (6.0)	15 (5.4)	46 (9.1)
Anterior and central	11 (5.1)	16 (5.8)	31 (6.0)
Anterior and posterior	2 (0.9)	2 (0.7)	15 (2.9)
Central and posterior	16 (7.4)	19 (6.9)	30 (5.8)
Anterior, central, and posterior	93 (42.4)	134 (49.0)	260 (51.0)
Height of MC			
<25% of vertebral height	89 (42.5)	121 (44.3)	243 (47.7)
25% to 50% of vertebral height	96 (44.8)	121 (44.3)	219 (43.0)
>50% of vertebral height	29 (13.3)	31 (11.2)	47 (9.1)

3.3.4 Incidence of Modic Changes

Sixty-nine of 1106 endplates (6%) with no MCs at the baseline had new incident MCs (new MCs of any type on previously normal endplates) at the 5-year follow-up, with 58 (84%) of them being MC2. The occurrence of MC2 was most frequently only in the anterior region of the endplate, as observed in 22 (37%) or with an anterior component,

as seen in another 25 (36%) (Table 3-3). Similarly, 6 (75%) MC1s appeared in the anterior region (Table 3-3). All new MC1s in the 5-year follow-up had normal endplates at baseline (Figure 3-3).

At the 15-year follow-up, 266 of 1104 (25%) endplates without any MCs at 5-year follow-up developed new MCs. Out of 206 new occurrences of MC2, 66 (32%) were in the anterior region (Table 3-3). Eighty-five percent of new MC1 in 15-year follow-up had normal endplates ten years earlier. The other 15% had converted from MC2s. Also, 7 out of 8 de novo MC1s at 5-year follow-up and 30 out of 39 (77%) de novo MC1s at 15-year follow-up were either purely located on the anterior location of the endplate or had an anterior component.

Table 3-3 The type and location of incident Modic Changes at follow-up

Location at the endplate	At 5-year follow-up			At 15-year follow-up		
	MC1(%)	MC2 (%)	Mixed MC (%)	MC1(%)	MC2 (%)	Mixed MC (%)
Anterior	6 (75.0)	22 (37.9)	0 (0.0)	13(37.1)	66 (32.0)	6 (24.0)
Central	1 (12.5)	1 (1.7)	0 (0.0)	1 (2.8)	4 (1.9)	0 (0.0)
Posterior	0 (0.0)	7 (12.0)	0 (0.0)	4 (11.4)	27 (13.1)	2 (8.0)
Anterior and central	0 (0.0)	4 (6.9)	0 (0.0)	4 (11.4)	10 (4.8)	2 (8.0)
Anterior and posterior	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	7 (3.4)	0 (0.0)
Central and posterior	0 (0.0)	3(5.1)	1(33.3)	3 (8.5)	14 (6.8)	2 (8.0)
Anterior, central, and posterior	1 (12.5)	20 (24.4)	2(66.6)	10 (28.5)	78 (37.8)	13 (52.0)

3.3.5 Natural History of Modic Changes

Out of 214 endplates with MCs at the baseline, 151 (150 MC2 and one Mixed type) did not alter in type during the 15-year follow-up. Baseline type 1 Modic lesions were

uncommon, with a total of 16 lesions observed in 12 participants. Of these 16 lesions, at 5-year follow-up, one resolved, seven changed to MC2s and 3 to Mixed Type Modic Changes. The MC1 that resolved was of small transverse and AP size and moderate height. Of the 5 MC1s at both baseline and 5-years, all resolved at 15-year follow-up (Figure 3-3).

There were 7 Mixed Type MCs present at baseline (in 4 participants). Three of these, converted to type 2 (in 2 participants). Of the four remaining Mixed Type MCs (in 2 participants), three endplates showed no change in size, and one showed an increase in transverse and AP size (Table 3-4 and Figure 3-3).

More than 55% of MCs remaining as type 2 at follow-up, had the same transverse, AP and vertical size at 5- and 15-year follow-up. While there were various changes in different directions happening in the size of MC2s throughout the 15-year follow-up, most changes were positive, indicating an increase in the size of MCs (Table 3-5).

To better understand the natural history of MC2, we used the Sum of Changes in transverse, anteroposterior and vertical height of each MC2 over the follow-up period. The measurement of the central tendency of Sum of Changes is shown in Table 3-6. Even though, as mentioned before, most MC2s remained the same size as at baseline, the mean for Sum of Changes over 15- year follow-up was 1.0 ± 1.1, which is suggestive of a small increase in the size of MCs over time. Also, as is evident in Table 3-6, the mean increased over time by 0.2 ± 1.0 during the first 5 years and 0.9 ± 1.5 over the next 10 years.

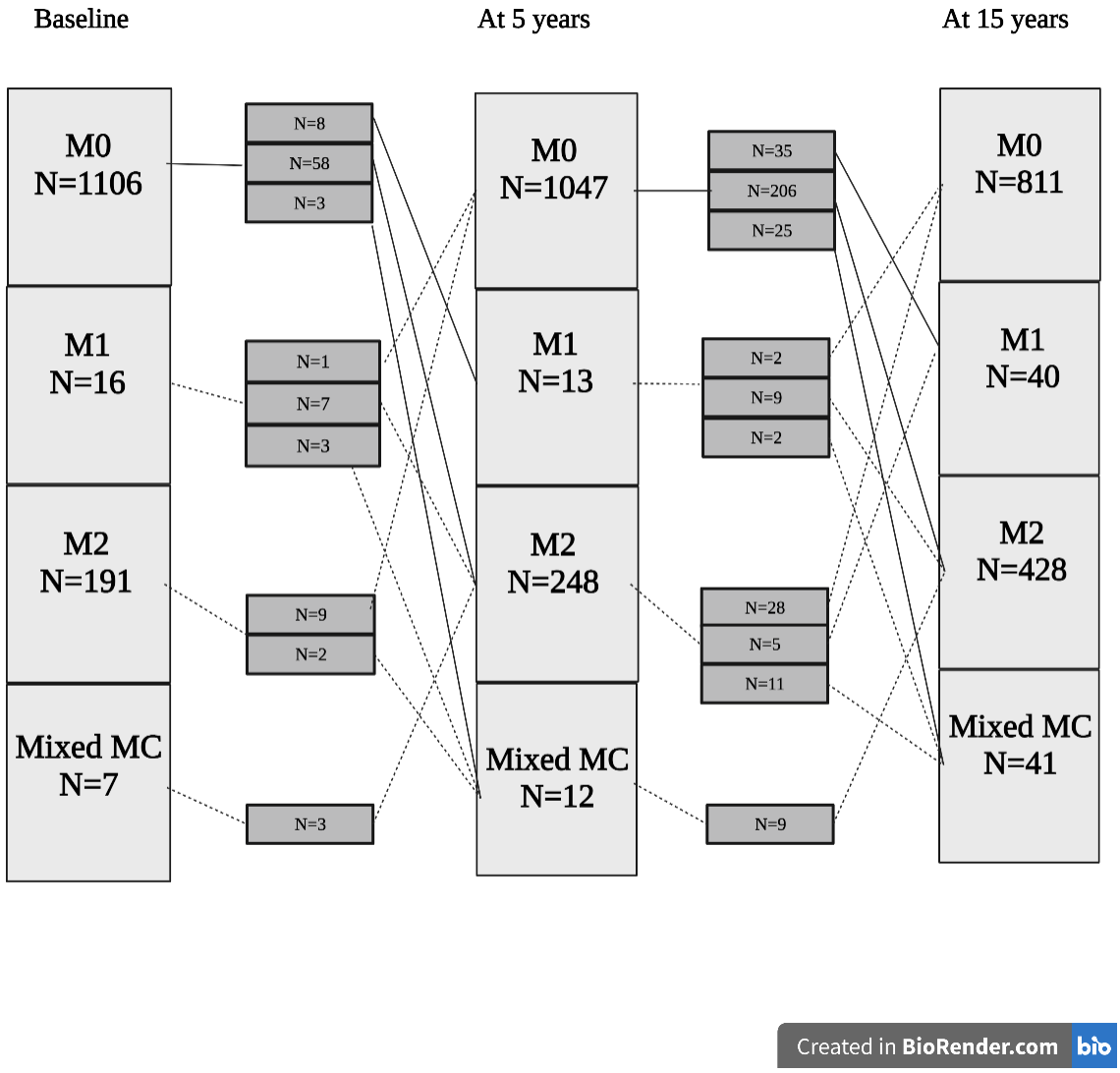

Figure 3-3 conversion and incident Modic Changes throughout time. Solid lines signify the incident from normal endplates and dotted lines show the conversion of one type of MC to another.

Table 3-4 Development of MCs and changes in type throughout time (n=1320 endplates)

Changes from Baseline to 15-year Follow-up			Modic Type at Baseline				
				No MC	MC1	MC2	Mixed MC
			Total	1106	16	191	7
At 15-year follow-up	Modic Type	No MC	811	783	0	24	0
		MC1	40	37	1	1	1
		MC2	428	254	12	157	5
		Mixed MC	41	28	3	9	1

Table 3-5 Development of MC 2 over 15 years

Changes in time	Aspect of size	Increase n (%)		Decrease n (%)		Remained the same size
		small (+1)	*Large (+2)*	*Small (-1)*	*Large (-2)*	
Baseline to 5-year follow-up n= 180	***Transverse***	18 (10.0)	0	3 (1.6)	2 (1.1)	157 (87.2)
	AP	8 (4.4)	13 (7.2)	3 (1.6)	0	156 (86.6)
	Height	26 (14.4)	3 (1.6)	28 (15.5)	1 (0.5)	122 (67.7)
5-year to 15-year follow-up n= 204	***Transverse***	49 (24.0)	21(10.2)	8 (3.9)	2(0.9)	124 (60.7)
	AP	24 (11.7)	20 (9.8)	4 (1.9)	3 (1.4)	153 (75.0)
	Height	58 (28.4)	3 (1.4)	29 (14.2)	2 (0.9)	112 (54.9)
Baseline to 15-year follow-up n= 157	***Transverse***	41 (26.1)	20 (12.7)	6 (3.8)	3 (1.9)	87 (55.4)
	AP	23 (14.6)	27 (17.1)	3 (1.9)	1(0.6)	103 (65.6)
	Height	42 (26.7)	3 (1.9)	21 (13.3)	1(0.6)	90 (57.3)

Table 3-6 The Sum of Changes in Type 2 MCs over each follow-up period			
Follow-up	**Sum of Changes in MC 2**		
	Mean (SD)	**Min**	**Max**
Baseline to 5-year follow-up (n= 180)	0.2 (1.0)	-2.0	5.0
5-year to 15-year follow-up (n= 204)	0.9(1.5)	-4.0	5.0
Baseline to 15-year follow-up (n= 157)	1.0 (1.5)	-5.0	6.0

3.4 Discussion

LBP is a major global public health concern and has significant costs to both the sufferers and the healthcare system. To better understand the contributors to spinal pain underlying pathology, MRI phenotypes of Modic Changes (MC), have received research and clinical interest. As Modic classification has been shown to be reliable and reproducible, with the exception of MC3 [71], endplate calcification, we decided to focus on MC1, 2, and Mixed type MCs. In a community-based study of men, we evaluated endplates for MC presence, type (MC1, MC2, or Mixed MC), and dimensions (anteroposterior, transverse, and vertical height) at baseline, 5- and 15-year follow-up. The aim of this longitudinal study was to provide insight into the development and pathogenesis of MCs. This longitudinal study confirmed that MC1 appears to be a transient phase, with no MC1s at baseline persisting to 15-year follow-up. New MCs mostly occurred in the anterior aspect of the endplate. In addition, MC2 is the most common MC type in men, with MC2, but not other types, mainly located at the lower lumbar endplates.

Previously, a cross-sectional study on MCs was conducted utilizing baseline data from the entire group of 600 participants in the Twin Spine Study, from which the sample for the current study was drawn. The prevalence and distribution patterns of MCs and their

association with age were investigated, and they found MCs in 55.6% of lumbar spines and they were prominently Type 2 (29.2% of participants). Type 1 were only present in 6.4% of the population [56]. As our 110 baseline study participants were a small subgroup of this larger study, as expected, we found a similar prevalence, with MC2s being present in 63% and MC1s in 10% of the population. Findings on the prevalence of MCs in the general population are inconsistent. Some groups have reported it as high as 56% [27] and 47.1% [25]. On the other hand, it has been stated as rare in other studies [17, 22, 24, 72]. It can be justified by the positive association between age and the prevalence of MCs and age difference in these studies [62, 73], as studies with low prevalence had relatively younger participants [24, 72].

As observed in previous studies [23, 27, 28, 62], we found that MC2s were mainly present in the endplates of the lower lumbar levels. However, this is not true for other types of MCs. Similarly, MCs in the cervical spine were mostly found at the lower of cervical spine levels[74]. As intrinsic or extrinsic loading factors could affect the lower levels of both cervical and lumbar spine more[75], we speculate that there may be a relation between MC2 and loading factors.

It has been reported that MCs typically extend across the whole anteroposterior length of the endplate [17] There are many studies that reported MCs to be primarily present anteriorly to endplate [13, 29, 62, 76]. While we found that the majority of MC (42-51 %) are extended through the endplate, the anterior portion of the endplate was more prone to having MCs than any other portion, and the incident of MCs are mostly in the anterior part. This observation supports similar findings by Modic et al. (1988), who suggested MCs extend anteroposteriorly [77]. This finding could provide clues to MC pathogenesis and the relation of MCs to flexion-extension forces [62].

The longest prior longitudinal study of MCs, to this author’s knowledge, is a 10-year follow-up study that did not differentiate different types of MCs [78]. In another study, Mitra et al. (2012) investigated the course of MC1 in 44 symptomatic patients with follow-up images conducted at different times, from less than a year to more than four years. Their results show that in follow-up images after shorter intervals, the number of

partially converted MC1s, which may be counted as Mixed type MCs, are higher than complete conversion. Moreover, when the interval between images is more than 48 months, almost half are converted fully to MC2 [32]. Our longer follow-up study demonstrated that only 31% of MC1s persisted after five years, and none after 15 years, and all converted to different Modic types, providing clues to the life span of MC1. In the current study, the 69% that did not persist as MC1 at 5-year follow-up converted to either type 2 or Mixed type MCs. The complete resolution of MC1 was rare in our study and was only found at one endplate after five years and two endplates after 15 years. One study found a 39.6% increase in the size of MC1 in their participants over 12-72 months [32]. While our follow-up study was longer, and we expected to see an increase in MC1 size, changes in the size of persistent MC1s at 5-year follow-up were variable and were not always positive. These findings were consistent with previous findings that MC1 has a dynamic process [32, 55]. Therefore, we speculate that MC1s are an unstable phase of MCs, which eventually convert to MC2 in a period of 15 years.

Another observation in our study was a decrease in the number of MC 1 in a 5-year follow-up, from 16 to 13, despite the fact that we had an overall increase in the number of MC1 from baseline to 15-year follow-up, from 16 to 40. To the author's knowledge, no other longitudinal studies reported a decrease in the number of MC1 in the follow-up studies. Given the relatively small sample and the low presence of MC1, and as that the reliability of change *in type* was almost perfect (K=0.92), the decrease in number could be a chance finding. It could also be explained by Mixed type MCs. Mixed type MCs could be a transition phase from MC1 to MC2. It is possible that some of MC1s are in transition, and they may have read as Mixed type MC. Despite this, even a similar number of MC1s after five years was surprising given the large increase to 40 at 15-year follow-up.

As stated previously, Mixed type MCs suggest a transition phase. Modic et al. (1988) observed 5-6 patients with MC1 converted from type 1 to 2 over a 14 to 36-month follow-up, and they suggested a connection between type 1 and 2 changes [55]. We observed that MC1, 2 and even normal endplates could appear later as Mixed type MCs and at the end are mostly converted to MC2. Also, we saw no transition of Mixed type

MC to normal endplate. We concluded that Mixed type MCs represent a transition phase during the conversion of MC1 to MC.

Consistent with other studies, we found MC2 was the most common type [2, 19, 27, 79]. Overall, even though MC2 seems to be a stable phase in the natural history of MCs, there are still changes happening in size or even type of these MCs. We noticed changes in all aspects of size in MC2 both including increases and decreases, and rarely resolution of MC2s. However, over time, the mean Sum of Changes appeared to be positive. We reached the conclusion that MC2 can change over time, although at a slower and lower rate than MC1. However, given the low reliability of changes in size and sum of changes these results should be viewed by caution.

Few studies regarding the natural history of MCs exist, and most have selection bias related to the recruitment of symptomatic participants [17, 28, 32, 65, 80]. Our study population was selected with no regard to the history of LBP and is largely representative of the general population of Finnish men [53]. Additionally, to our knowledge, our study is the first to assess the development of MCs at three time-points, allowing us to investigate changes over 15 years. However, as MCs seem to be more prevalent in males [15], we cannot make the assumption that our findings apply equally to women. A few limitations of the present study must be considered. First, the study population size was small, yielding a small number of MC1s and Mixed type MCs and the sample comprised only males. It would be valuable to investigate a larger population-based sample of both sexes to gain a better understanding of these less common MC types. Second, while this is the first study of which we are aware to include three time points per participant, having more follow-up time points would allow further analysis of the timing and evolution of MCs. Third, in our analysis we counted the twins as individuals and did not account for any residual correlation between the twins or among the discs. Fourth, although the challenge is present in every long-term longitudinal study, the quality of the images varied between the 5- and 15-year follow-up, and this may influence the detection of smaller MCs in earlier states. Furthermore, we did not have access to axial images in all planes in these images. Having access to different planes could help us have a more precise measurement.

Overall, different factors appear to play a role in the development of the different types of MCs and the conversion from one type to another. Understanding the disease course of MCs and the potential causes for the conversion from one type to the another in the general population could have implications on interventions targeting MCs and LBP. Our 15-year longitudinal study confirmed that MC1s are transitory and convert to MC2, or Mixed type, which is likely a conversion state from type 1 to 2, over a period of 15 years. MC1s are most commonly associated with LBP [13], and a positive association has been found between extent of MCs and LBP symptoms[32]; Therefore, it is important to identify the risk factors that are associated with their development, which may have implications for prevention or resolution. Additionally, patients with LBP and positive MC1 have been shown to respond less favorably to conservative treatment compared to those without MCs [81], which could indicate a LBP phenotype with implications for management.

Our study findings were consistent with earlier studies' finding that MC type 2 was the mostly prevalent. In addition, we found it was the only type that was more prevalent in the lower disc levels. The current study also showed that the anterior aspect on the endplate seemed to be more prone to the incident of new MCs. As load mass found to have significant effects on anteroposterior shear [82], loading can be suggested as an etiological factor of MCs, especially type 2. Finally, the slow growth in the size of MC2, and the conversion of MC2 to MC1, Mixed and rarely to normal endplates are all suggestive of the dynamic status of MC2. As MC2 can affect the response to surgical treatment and cause poor fusion rate[15], it is important to understand whether this change in size is associated with the associations and what factors cause these conversions over time.

In conclusion, this longitudinal study demonstrated that MC2s are mostly located in the lower lumbar levels of the spine and the incidence of new MCs most frequently occurs in the anterior portion of endplates. As MCs are found to be an important element in the degenerative process of the lumbar spine and MC2 is the most common type [13], it is important to find out more about what causes these changes, and their tendency to locate

anteriorly may provide helpful clues. This study also enhanced knowledge of the natural history of MC1 and Mixed type MCs and their life span.

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