

Vertebral Bone Mineral Measures and Psychological Wellbeing Among Individuals with Modic Changes

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Abstract:

Purpose: This case-control pilot study examined whether vertebral bone mineral measures were associated with the presence of chronic low back pain (CLBP) and Modic changes (MCs), and to compare psychological wellbeing and inflammation among individuals with CLBP and MCs, compared to individuals with no history of low back pain and without MCs.

Methods: Eleven individuals with MRI-defined MCs in the lumbar spine and CLBP (cases) and 10 individuals with no history of CLBP or MCs (controls) responded to standard questionnaires regarding pain characteristics and psychological health. Bone mineral density (BMD) was measured with postero-anterior and lateral-projection dual energy X-ray absorptiometry (DXA) to estimate areal BMD (aBMD) and apparent volumetric BMD (ap.vBMD). High sensitivity serum C-reactive protein (hsCRP) was measured as an index of inflammation.

Results: While there was no difference between the groups in measures of depression, anxiety and stress, cases reported significantly greater pain catastrophizing attitudes ($P < 0.01$). hsCRP concentrations did not differ between groups ($P = 0.54$). Among the 7 cases where MCs were identified between L3–4, significantly higher mean aBMD was observed at the affected vertebral level, compared to the adjacent, unaffected, cephalad level ($P = 0.01–0.04$), but not when ap.vBMD was calculated ($P = 0.36$).

Conclusions: Vertebral BMD is not reduced among individuals with CLBP and MCs compared to a control group, although pain catastrophizing attitudes are increased among individuals with CLBP and MCs.

Keywords: Modic change, bone mineral density, hsCRP, psychological health

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Introduction

Increased attention is being directed towards the relationship between chronic low back pain (CLBP) and vertebral structural changes characterised by bone marrow lesions adjacent to the vertebral endplate, known as vertebral endplate signal (Modic) changes (MCs). These are MRI-detected abnormalities in vertebral subchondral bone extending from the vertebral endplate involving hypervascularization (type 1), replacement of vertebral haematopoietic elements with fat (type 2), and bone sclerosis (type 3). MCs, which are strongly associated with degenerative intervertebral disc disease,¹ represent a specific subgroup of people with back pain, as they are closely associated with the experience of low back pain.² This is in contrast to the finding of degenerative disc disease in the absence of MCs which are poorly associated with the self-report of low back pain.³

Although the exact aetiology of MCs remains uncertain, two pathways linked to intervertebral disc degeneration have been proposed in the literature: biomechanical, due to abnormal mechanical stresses transferred through the vertebral body; and biochemical, expressed through pro-inflammatory mediators within the intervertebral disc which become particularly significant in situations of disc herniation.^{4,5} The sequelae via both pathways may have important implications for bone health,⁶ specifically bone mineral density (BMD), although this issue has not been studied in detail. While intervertebral disc degeneration has been associated previously with changes in the distribution of intra-vertebral bone mass⁷ and therefore is likely to have implications for vertebral bone strength, this has not been linked explicitly with MCs. Similarly, while mechanisms of inflammation-mediated bone loss are well recognised, an association with MCs has not been studied, despite recent data highlighting increased concentrations of high sensitivity C-reactive protein (hsCRP) in patients with type 1 MCs.⁸ Furthermore, the personal impact of CLBP per se on health-related behaviours and wellbeing, may also have negative implications for bone health.⁶

While a number of factors might account for an association between BMD and CLBP, the behavioural sequelae of CLBP such as activity avoidance and poor psychological wellbeing, leading to increased depression, anxiety and stress, are likely to exert a

significant influence on bone health. In particular, depression has been linked to reduced BMD through cortisol dynamics.⁹ Pain catastrophizing attitudes, common among individuals who experience chronic musculoskeletal pain, have been linked to passive coping behaviours and depression, and increase the risk of poor outcomes from CLBP,¹⁰ which may have implications for bone health.⁶ In the context of MCs, the association between CLBP and BMD may be more pronounced and therefore have implications for surgical interventions commonly undertaken for these disorders, such as discectomy, arthrodesis, and total disc replacement.¹¹⁻¹³ For example, the combination of inflammation associated with type 1 lesions and the clinically-observed high levels of pain, disability and poor psychological wellbeing in patients with CLBP and MCs may strengthen the relationship between CLBP and BMD.⁶ While some clinical characteristics of individuals with CLBP and MCs have been reported previously,^{3,8} these have not specifically addressed BMD and psychological wellbeing, nor the combination of these factors with inflammation. Therefore, the aim of this case-control pilot study was to examine whether vertebral bone mineral measures were associated with the presence of CLBP and MCs, and to compare psychological wellbeing and inflammation among individuals with CLBP and MCs, compared to individuals with no history of low back pain and without MCs.

Methods

Participants

Community-dwelling adults experiencing CLBP (pain duration ≥ 3 months) in conjunction with the presence of MRI-defined MCs in the lumbar spine (cases, $n = 11$), and individuals with no history of LBP in the past year and no evidence of MRI-defined MCs in the lumbar spine (controls, $n = 12$) were recruited for this study. Cases were recruited from primary and secondary healthcare facilities, while controls were recruited from the community. The following exclusion criteria were applied during screening to eliminate known osteoporosis risk factors and other potential confounders of BMD data: aged ≥ 55 years, BMI < 18 or > 28 kg/m², history of lumbar spine surgery, history of metabolic bone disease, commencement of menopause or underwent hysterectomy prior to 45 years, history of protracted (> 6 months)



exposure to medications known to affect BMD, other current condition associated with systemic inflammation, regular smoking for at least 12 months within the last 10 years, excessive alcohol intake (>3 units/day) for at least 12 months within the last 10 years. All participants provided written informed consent and the study was approved by institutional Human Research Ethics Committees.

Identification of MCs

All cases had a previously-acquired lumbar MRI assessed by a radiologist (DF) to confirm the presence of MCs, using the Nordic protocol, for which reliability has been established.¹⁴ All controls had a spinal MRI taken at a single imaging provider upon entering the study to exclude the presence of MCs. Each control MRI was reviewed by the same radiologist using the Nordic protocol. Two controls were subsequently excluded due to the identification of MCs, such that the total number of controls included in the study was $n = 10$.

Questionnaire data

All participants responded to the catastrophizing subscale of the Coping Strategies Questionnaire (CSQ-CAT) to measure pain catastrophizing attitudes¹⁵ while depression, anxiety and stress were measured with the 21-item Depression Anxiety Stress Scale (DASS21).¹⁶ The CSQ-CAT consists of 6 items rated on a 7-point scale and the internal consistency of the subscale is reported to be high ($\alpha = 0.85$).¹⁷ The DASS-21 has three sub-scales (depression, stress and anxiety) each consisting of seven items measured on a 4-point scale. The internal consistency ($\alpha = 0.92$ – 0.95) and reliability ($r = 0.65$ – 0.78) of the DASS-21 have been established previously.¹⁸ Cases also responded to questions about LBP-related pain intensity in the last month using a numeric rating scale (NRS),¹⁹ and CLBP-related disability using the Oswestry Disability Index (ODI). The ODI contains 10 questions, each with six ordinal responses. Internal consistency of the ODI in adults is reported to range from $\alpha = 0.71$ – 0.87 .²⁰

Bone densitometry

Areal BMD (g/cm^2) of the lumbar was acquired with a Hologic Discovery A densitometer (Hologic Inc, Bedford, MA) in standard postero-anterior (PA) and

lateral projections using the high definition scanning mode. Scans were analysed using Hologic software version 12.6.1 to derive BMD at each vertebral level L1–L4 in the PA projection and L2–L4 in the lateral projection. Total spine BMD was calculated automatically as the mean BMD of the included levels from each projection. Apparent volumetric BMD (ap.vBMD; g/cm^3) was derived from the lateral scan data using the Hologic width-adjustment feature.

Inflammation

Serum high sensitivity C-reactive protein (hsCRP) was measured 24 hours after the cessation of any analgesic or anti-inflammatory medications and withholding of alcohol, consistent with a previous study.⁸ HsCRP concentration was measured using a Siemens Healthcare Diagnostics reagent run on a BNII Nephelometer (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The assay had a measurement range of 0.175–1100 mg/L .

Data analysis

Questionnaire and other data were compared between groups using independent t-tests for normally distributed data and Mann-Whitney U tests for data which were not normally distributed. Among cases with MCs at levels L3–L4, bone mineral measures were compared between the affected vertebral level and the immediately adjacent, unaffected cephalad level (either L3 or L2) using paired t-tests (data were normally distributed). The one case which had a Modic change identified at L2 was excluded from this within-subject analysis since comparative BMD data acquired from lateral-projection DXA cannot be measured accurately at L1. To examine any difference in total spine BMD between cases and controls, which might identify any systemic spinal bone deficits, a one-way ANCOVA was performed, adjusting for age, height and mass (data were normally distributed). Data were analysed using SPSS Statistics 17.0.

Results

Among the 11 cases, MCs were identified at 21 vertebral endplates (Table 1). Descriptive characteristics of the cohort and questionnaire data are summarised in Table 2. There was no difference in hsCRP concentrations between the groups. While no differences in DASS21 scores were observed between the



Table 1. Frequency (%) of Modic change (MC) types 1–3 identified among the cases (N = 11).

Vertebral level endplate	MC1	MC2	MC3	Total
L2	1 (100)			1 (100)
L3	1 (100)			1 (100)
L4	1 (16.7)	4 (66.7)	1 (16.7)	6 (100)
L5	2 (22.2)	7 (77.8)		9 (100)
S1	2 (50.0)	2 (50.0)		4 (100)
Total	7 (33.3)	13 (61.9)	1 (4.8)	21 (100)

groups, the cases reported significantly greater pain catastrophizing attitudes.

Vertebral bone mineral measured we compared between the affected and adjacent, unaffected, cephalad vertebral level among cases (Table 3). Of the 7 cases where MCs were identified between vertebral levels L3–L4, a significantly-higher mean BMD was observed at the affected level compared to the adjacent, unaffected cephalad level when acquired in the PA (paired difference (95% CI): 0.08 (0.002, 0.15) g/cm²) and lateral (0.12 (0.04, 0.20) g/cm²) projections, but not when a width-adjustment correction was applied (0.08 (–0.12, 0.28) g/cm³).

No significant difference was observed between cases and controls for adjusted mean (standard error) total lumbar spine BMD acquired in the PA [1.09 (0.03) and 1.05 (0.03) g/cm², respectively; adjusted mean difference (95% CI): 0.04 (–0.05, 0.12) g/cm²] and

lateral [0.80 (0.02) and 0.75 (0.02) g/cm², respectively; adjusted mean difference (95% CI): 0.05 (–0.03, 0.12) g/cm²] projections, nor when a vertebral width adjustment was applied [0.22 (0.01) and 0.21 (0.01) g/cm³, respectively; adjusted mean difference (95% CI): 0.003 (–0.02, 0.02) g/cm³].

Discussion

Vertebral BMD was measured in both PA and lateral projections in this study. Lateral-projection DXA has several advantages over PA-projection. First, it enables measurement of predominantly metabolically-active trabecular bone in the vertebral body without the overriding influence of the cortical-rich posterior elements of the vertebral body. Second, lateral projection-DXA is less affected by degenerative spinal structural changes and aortic calcification, which can artificially inflate the vertebral BMD measures. Third, an apparent volumetric measure of BMD can be derived from lateral-projection scans. The apparent volumetric density measure is more closely related to true volumetric density than areal BMD measures and has greater diagnostic sensitivity for bone fragility.²¹ Areal BMD measured in PA and lateral-projections at vertebral levels where MCs were present was significantly higher compared to the adjacent, unaffected cephalad vertebral level. While previous data point to a segmental peak in areal BMD at L3 followed by a slight decline at L4,²² our data

Table 2. Descriptive and clinical characteristics of the groups.

Descriptor	Case	Control	Mean difference (95% CI)	Mann-Whitney U test P-value
N [frequency of male (M) and female (F)]	5 M; 6 F	4 M; 6 F	–	–
Age [years]	44.4 (6.0)	41.1 (8.3)	3.4 (–3.4–10.1)	–
Height [cm]	175.1 (9.9)	172.6 (6.7)	2.5 (–5.2–10.2)	–
Mass [kg]	78.4 (16.1)	75.9 (15.4)	2.5 (–11.9–16.9)	–
Lifetime history of LBP [years]	12.6 (11.9)	–	–	–
Usual intensity of pain in last month, median (IQR) [possible range 0–10]	6 (2)	–	–	–
ODI [%]	37.1 (13.5)	–	–	–
CSQ-CAT [possible range 0–24]	11.2 (6.1)	2.7 (3.3)	8.5 (3.9–13.0)*	–
DASS21—depression [possible range 0–42]^	4.6 (4.3)	2.4 (3.1)	2.1 (–1.3–5.6)	0.19
DASS21—anxiety [possible range 0–42]^	3.2 (4.8)	1.6 (2.1)	1.7 (–1.7–5.1)	0.62
DASS21—stress [possible range 0–42]	9.8 (7.5)	7.8 (6.4)	2.0 (–4.3–8.4)	–
hsCRP [mg/L]^	2.2 (2.9)	1.1 (1.1)	1.1 (–1.1–3.2)	0.54

Notes: *Significant difference ($P < 0.05$). Data are expressed as the mean (SD) with the corresponding mean difference and 95% confidence interval (95% CI), unless indicated otherwise. Where data were not normally distributed (indicated with ^), the results of the non-parametric test are included.



Table 3. Vertebral bone mineral measures of affected levels and adjacent, cephalad unaffected levels among cases.

Projection for BMD measure	Level	Mean (SD)
Postero-anterior (PA) (g/cm ²)	Affected	1.14 (0.12)
	Unaffected	1.06 (0.07)
Lateral (g/cm ²)	Affected	0.84 (0.15)
	Unaffected	0.73 (0.11)
Width-adjusted lateral (g/cm ³)	Affected	0.28 (0.19)
	Unaffected	0.20 (0.03)

of higher areal BMD at affected levels (usually L4) do not support this finding. This may be related to increased degenerative spinal conditions associated with MCs present at L4,¹ and the observed positive association between areal BMD and intervertebral disc degeneration.²³ Further, the absence of any difference between the groups in the concentration of hsCRP and depression scores would likely render the influence of any inflammation-mediated bone loss and depression-mediated bone loss, respectively, to be negligible. While Rannou et al⁸ identified differences in hsCRP between individuals with type 1 and type 2 MCs; we are unable to verify this finding in our data due to the low sample size of type 1 cases. Nonetheless, our data support their finding of no difference in serum hsCRP concentrations between individuals with type 2 MCs and controls.

Our finding of no significant difference in ap.vBMD between affected and unaffected lumbar vertebrae is consistent with recent volumetric BMD data derived from computed tomography (CT).²⁴ Further, in contrast to areal BMD data reported by Singer et al,²² CT-derived segmental volumetric BMD is lowest at L3, over the range of T1–L5,²⁵ which supports our data. The absence of any difference in ap. vBMD between the affected and unaffected vertebrae suggests that local MCs do not negatively influence bone density. However, given this sample size we are unable to comment regarding the association between vertebral BMD and the type of Modic change. This may be an important area for future research. The association between MCs and bone quality remains uncertain, although this represents an important area of research given the role of bone quality in determining bone strength, independent of BMD. While MCs have been associated with bone tissue changes measured histologically, little research

has been conducted to elucidate their influence on bone micro-architecture, for example measured using micro-CT. Furthermore, given that MCs are usually localised to the subchondral bone adjacent to the vertebral endplate, measurement of whole vertebral body BMD by DXA may mask any subregional changes in vertebral BMD.²¹ Measurement of subregional BMD profiles among individuals with MCs may be warranted, particularly in light of recent findings which substantiate the use of lateral-projection DXA in this context and point to improved diagnostic sensitivity of this approach for vertebral fragility.²¹

Individuals with MCs reported greater pain catastrophizing attitudes, consistent with data comparing individuals with and without CLBP, including those with inflammatory-mediated CLBP,^{26,27} yet other psychological characteristics (depression, stress, anxiety) were not different between the groups, supporting the notion that not all CLBP experiences are linked to poor psychological states. Mean values for the DASS subscales suggest both cases and controls fall within the normal ranges for depression, anxiety and stress.²⁸ Catastrophizing and depression are considered co-existent yet independent predictors poor outcomes for CLBP. Our data are consistent with a recent study indicating individuals with CLBP may demonstrate one of either factors,¹⁰ nonetheless, the authors highlighted that the additive effect of both catastrophizing and depression has a significantly greater influence on poor outcomes compared to presence of either factor in isolation. It may be that a combination of depression and catastrophizing is needed before BMD is negatively influenced in the context of CLBP and MCs. While the influence of depression on BMD has been established previously,⁹ the influence of catastrophizing should be examined in a larger study.

This study was initiated as a pilot and therefore the sample size represents a limitation to the interpretation of the data presented. A larger study should now be undertaken to verify the findings in this pilot project. Nonetheless, novel and clinically relevant data are reported which may provide a framework for larger studies. Future studies should examine the association between different types of MCs and BMD and, as well as the association with bone micro-architecture, and the association between MCs and psychological wellbeing.



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Author Contributions

Conceived and designed the experiments: AMB, PBO, JDW. Analysed the data: AMB. Wrote the first draft of the manuscript: AMB, PBO. Contributed to the writing of the manuscript: AMB, PBO, DF, JDW. Agree with manuscript results and conclusions: AMB, PBO, DF, JDW. Jointly developed the structure and arguments for the paper: AMB, PBO, JDW. Made critical revisions and approved final version: AMB, PBO, DF, JDW. All authors reviewed and approved of the final manuscript.

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Disclosures and Ethics

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