Journal of Pain Research

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REVIEW

Biological Markers of Musculoskeletal Pain: A Scoping Review

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Background: Musculoskeletal pain (MSP) is the leading contributor to disability, limiting mobility and dexterity. As research on the determinants of MSP is evolving, biomarkers can probably play a significant role in understanding its causes and improving its clinical management. This scoping review aimed to provide an overview of the associations between biomarkers and MSP.

Methods: This study followed Arksey and O'Malley and PRISMA-ScR recommendations. Keywords related to biomarkers, association, and MSP were searched on PubMed, Embase, Cochrane, and Web of Science databases from inception to September 28th, 2023. Data were systematically retrieved from the retained articles. A narrative synthesis approach – but no quality assessment – was used to map the core themes of biological markers of MSP that emerged from this work.

Results: In total, 81 out of 25,165 identified articles were included in this scoping review. These studies were heterogeneous in many aspects. Overall, vitamin D deficiency, dyslipidemia (or hypercholesterolemia), and cytokines (high levels) were the most studied biomarkers with regards to MSP and were most often reported to be associated with non-specific MSP. Cadmium, calcium, C-reactive protein, collagen, creatinine, hormones, omega-3 fatty acids, sodium, tumor necrosis factor-alpha, and vitamin C were also reported to be associated with MSP syndromes, but the evidence on these associations was sketchier. No conclusions could be drawn as to age and sex.

Conclusions: Our findings suggest that some biomarkers are associated with specific MSP syndromes, while others would be associated with non-specific syndromes. Among all candidate markers, the evidence seems to be more consistent for vitamin D, cytokines and lipids (total cholesterol, triglycerides, low- and high-density lipoproteins). High-quality studies, stratified by age and sex, are needed to advance our understanding on biomarkers of MSP.

Keywords: musculoskeletal pain, biomarkers, scoping review

Introduction

Musculoskeletal pain (MSP) is the leading contributor to disability, limiting mobility and dexterity, and often leads to early retirement from work, lower quality of life and reduced social participation.[1] MSP, especially in its chronic form, is one of the most important causes of disability and generates an enormous burden for health and social care systems globally.[2] While physical exposures at work (eg, manual material handling, repetitive movements) have been known as determinants of MSP for a while, it has become evident in the past 30 years that the causes of MSP are biopsychosocial. These include individual characteristics (eg, age, social deprivation), behavioral factors (eg, smoking, sedentarity), psychological factors (eg kinesiophobia, psychological distress,[3,4] health anxiety[5]), and the psychosocial environment of work (eg job strain, psychological demands).[6–8] Recently, sleep quality, stress, unhealthy diet,[3] and obesity have

Received: 9 April 2024
Accepted: 23 September 2024
Published: 11 October 2024

received much attention in the search for risk and prognostic factors of MSP.[9–13] In a few decades, our understanding of MSP has thus evolved from a strictly biomedical perspective to a much broader approach. However, despite all research efforts, our current understanding of MSP is still very limited.[14]

A biomarker is "a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention."[15,16] Biomarkers play an increasing role in many areas of health research. In oncology, for instance, some proteins related to obesity are known to be involved in the onset of breast cancer;[17] cerebrospinal fluid biomarkers amyloid-β (Aβ 42) and total or phosphorylated *tau* are known to be involved in the pathogenesis of Alzheimer's disease;[18] and some novel biomarkers can highlight the pathophysiology of heart disease.[19] While biomarkers can probably also play an important role in the development of knowledge on the causes and clinical management of MSP, they seem to have been overlooked. For instance, some studies showed statistically significant associations between vitamin D deficiency as circulating levels and low back pain,[20–22] and between biomarkers of inflammation and non-specific low back pain.[23] However, globally, the whole field of study of the biomarkers of MSP remains unexplored. We thus conducted a scoping review to draw the current state of evidence on this topic. The methodology of a scoping review is similar to that of a systematic review in that both follow a structured process, but they are conducted for different reasons and have important methodological differences.[24,25] In contrast to the systematic review, which is useful for answering clearly defined questions[26] and selecting articles for knowledge synthesis in order to achieve greater objectivity, a scoping review provides an overview of an understudied topic, systematically and iteratively combing through the available studies or works on this topic. Its overall objective is to identify and map the available evidence.[24] This objective was well suited to our work, given that most studies that have focused on the biological determinants of MSP have examined biomechanical factors, and that very few have attempted to identify biomarkers. The objective of the current scoping review was thus to provide an overview and mapping of the evidence on the associations between biomarkers and MSP.

Methods

This scoping review was conducted following the methodology proposed by Arksey and O'Malley[27] and reported according to the PRISMA Extension for Scoping Reviews (PRISMA-ScR).[26] The searches were completed from inception through September 28th, 2023. The final protocol was registered with Open Science Framework (identifier: *10.17605/OSF.IO/MNY86)*.

Eligibility Criteria

In consultation with expert information specialists, a search strategy was built according to the PICOS approach (Participants, Intervention or Exposure, Comparator, Outcomes and Study Design): Participants (P)—no restrictions were made on the human participant population. Intervention (I)/Exposure—any study that addressed the association of biomarkers with MSP was eligible. A biomarker was defined as "a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention".[16] Comparator (C)—we applied no restrictions; Outcomes (O)—we reviewed all papers that reported prevalence, cumulative incidence, or incidence density measures of MSP, including its functional consequences, but specific musculoskeletal diagnoses (eg ankylosing spondylitis, lupus, rheumatoid arthritis) were not included if they were not accompanied by the term "musculoskeletal pain"; Study (S)—all types of studies that evaluated the association between biomarkers and MSP were included. Members of the research team had competencies in English, French, German, and Italian; no language exclusion was required.

Information Sources and Search

With the support of an information specialist, the search strategy was developed and implemented in four electronic databases: PubMed, Embase, Cochrane and Web of Science, from inception to September 28th, 2023. This search combined terms such as 'biomarkers', 'environmental exposures', "biomarkers AND musculoskeletal disorders OR musculoskeletal pain". The final search strategy for each database is presented in Appendix A. CDD and AG sorted

duplicates and removed them using EndNote version 20.1 (Thomson Reuters, 2021). The articles were then exported to the software platform Covidence for the study selection process (Data extraction 2.0 Veritas Health Innovation, Melbourne, Australia).[28]

Selection of Sources of Evidence

To identify relevant studies, screening and selection were carried out in three steps. In the first step, we conducted two pilot searches to standardize the selection process. The selections for confrontations were grouped in two arms.

Then, in the second step, four pairs of reviewers (CDD reviewed all the studies, and AG, SPHH, AKT, and TVP reviewed all the studies altogether) independently screened the papers (titles and abstracts) that were related to biomarkers of MSP. Disagreements over the selection of studies and data collected were resolved by consensus; when consensus was not possible, arbitration was to be made by an expert in musculoskeletal epidemiology (CED).

In the third step, like in the previous one, three pairs of reviewers (CDD with AG, SPHH, or AKT) worked independently to screen the full articles retained in the second step. Most of the articles were obtained through the included databases. For the articles that could not be obtained that way, interlibrary loan services of *Université Laval* and *CHU de Québec-Université Laval* retrieved the papers. In last resort, emails were sent to the corresponding author or journal's office for assistance in retrieving some articles. Disagreements over the selection of studies and the data collected were resolved by consensus; when consensus was not possible, arbitration was to be made by an expert in musculoskeletal epidemiology (CED) or a biomarker expert (CDi).

Titles, abstracts, and full texts were screened using Covidence. Each reviewer used a standard form to gather information on population, intervention/exposure, comparator, outcomes, and study design.

Articles that were irrelevant to the objective were excluded and the result of relevant articles were managed using the Airtable program;[29] the extracted data were recorded in Microsoft Excel (Microsoft Corporation Inc., Seattle, USA).

Data Charting Process and Data Items

Four pairs of reviewers (CDD with SPHH, AKT, AS, or GE) were involved in the data charting and data retrieving processes. Since AS and GE were not involved at the beginning of the selection process, we conducted a training and pilot study with each of them to standardize the information to be collected. This part of the process was done in two steps. First, the included articles were carefully read and key items of relevant information of each paper were identified: publication year, study design, country, population, site of pain, duration of pain, biomarkers, association measurements, and conclusions. Then, data charted by SPHH, AKT, AS, and GE were cross-checked by CDD while making the synthesis of studies, to detect and correct any mistake in extracted data.

We designed specific data charting forms based on the purpose of the study and discussions with the field experts. Pre-tests were conducted by the team before engaging in the formal process. In the presence of important missing information in the papers, the corresponding author was e-mailed to obtain the missing data. Because of time constraints, we defined a time limit of 2 weeks after sending the e-mail to receive the missing data from the authors, after which the missing data were treated as "not available".

Synthesis of Results

Descriptive statistics were used to summarize quantitative data (eg, age of participants), while frequencies and percentages were used to describe qualitative data (eg, study characteristics, themes). A narrative synthesis approach[30] simplified the mapping of the core themes of biological markers of MSP that emerged from this scoping review. The selected articles were tentatively divided into two tables that reported biomarkers related to specific (Supplementary Table 2) and non-specific (Supplementary Table 3) MSP. Non-specific MSP was defined as MSP not attributable to a recognizable, known specific pathology.[31] Publication details, setting, participants, research methods, tool measurement, biomarkers, type and site of pain, measures of association, and conclusions were extracted. This process was undertaken by the first author (CDD). The extracted information was discussed during meetings with all authors to remove any contradiction, to answer the research question, and describe the factors emerging from the literature. Disagreements were discussed until consensus was obtained; when consensus on the nature of the biomarker was not possible, arbitration was made by a biomarker expert (CDi). During all

our work, if the levels of a given biomarker were not specified explicitly as derived from food, urinary or synovial fluid in the source article, they were considered to have been measured in blood, plasma or serum.

Results

A total of 25,165 articles were identified through database searches, which were reduced to 19,609 after removal of duplicates. The articles were then screened through a reading of study titles and abstracts to determine eligibility and for inclusion in the scoping review. A total of 479 articles were selected by full text reading, and two additional articles were added through hand searches. At the end, 81 articles met inclusion criteria and were retained for data analysis. A detailed flow diagram of study search, screening, and selection results is presented in Figure 1. Of the 81 articles, 38 were considered to report on specific MSP syndromes, 42 on non-specific MSP syndromes and one on both types of syndromes.

Characteristics of Source Evidence

The main characteristics of all included studies are summarized in Figure 2 and Supplementary Table 1. The interest for biomarkers of MSP was quite low before 2005 and seems to be increasing since then. Studies were reported from different locations: 35 were conducted in Asia, 30 in Europe, 13 in North America, two in Australia and one in Africa. The number of participants in a study varied between one (a case report) and 532,985 individuals. There were almost as many studies that used a cross-sectional design (n = 20)[32–51] than studies that used a case–control (n = 19)[39,52–69] or a longitudinal design (n = 18).[70–87] There were 7 congress abstracts,[88–94] 7 systematic reviews or meta-analyses,[21,95–100] three case reports,[101–103] two narrative reviews,[104,105] two letters to the editor,[106,107] one report from a scientific communication,[108] one Mendelian randomization study,[109] and one concise report.[110] The age range of participants differed widely between the studies; the mean age ranged from 7 to 74 years old. Apart from case reports or the scientific communication, six studies included only female participants[42,50,55,66,67,91] and one included only males.[48] The many biomarkers and MSP syndromes studied added to the heterogeneity of data.

Biomarkers Related to Specific MSP Syndromes

Specific pain syndromes were diagnosed by clinical judgement alone,[45,50,57,65] or using different tools with or without clinical examination: the scale of Kellgren and Lawrence for classification of osteoarthritis (OA),[46,50,54,62–64,71,73,77,83,87,92,99,111] questionnaires,[35,37,109] magnetic resonance imaging (MRI), the Modified Stoke Assessment of Spine Score,[82] visual analog scales (VAS)[76,83] and the Western Ontario and McMaster University OA Index (WOMAC).[36] Of the studies that examined the relationships between biomarkers and specific pain syndromes, one estimated the amount of cadmium derived from contaminated foods needed for the development of osteomalacia and osteoporosis,[58] one examined the association between trace elements (lead, manganese, mercury, cadmium, selenium, copper, zinc) and risk of arthritis,[37] one examined the association between serum lipids (lipid profile: total cholesterol, triglycerides, low-density (LDL) lipoprotein, and high-density lipoprotein (HDL)) and glycated hemoglobin (HbA1c) with adhesive capsulitis[61], one examined the association between levels of ferritin, cluster differentiation (CD) 163 protein and pro-inflammatory cytokines with idiopathic arthritis,[105] and one examined the associations between serum cytokines and axial spondyloarthritis.[82] Two studies examined the association between levels of vitamin D and fibromyalgia.[52,87] Four studies examined the association between levels of survivin, vitamin C, sex hormone-binding globulin (SHBG), or 14-3-3η protein with rheumatoid arthritis,[35,74,94,109] and the other 24 studies examined the association between levels of vitamin D, SHBG, autoantibodies (AAbs), CD 40 ligand (CD40L), vascular cell adhesion molecule 1 (VCAM-1), vascular endothelial growth factor (VEGF), immunoglobulin E (IgE), vitamin K, collagen (N-propeptide of collagen IIA (PIIANP)), pentosidine, cartilage oligomeric matrix protein (COMP), total cholesterol, triglycerides, LDL, HDL, interleukin (IL)-6, high-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), cytokines, knee synovial fluid matrix metalloproteinase-13 (MMP-13), tumor necrosis factor alpha (TNF-α), IL-17, fibrinogen, N-telopeptide crosslinks (NTX), calcium, parathyroid hormone (PTH), bone mineral density (BMD), serum hyaluronan (sHA), calcium pyrophosphate dihydrate crystals, albumin, estrogens, synovial fluid uric acid and estradiol, urinary C-terminal cross-linking telopeptide of collagen type II (uCTXII), or fluoride with OA.[36,45–47,50,52,54,55,62–64,66,67,71,83,89,92,95,97,99,101,104,109,111] Data were scattered; no association stood clearly (Supplementary Table 2).

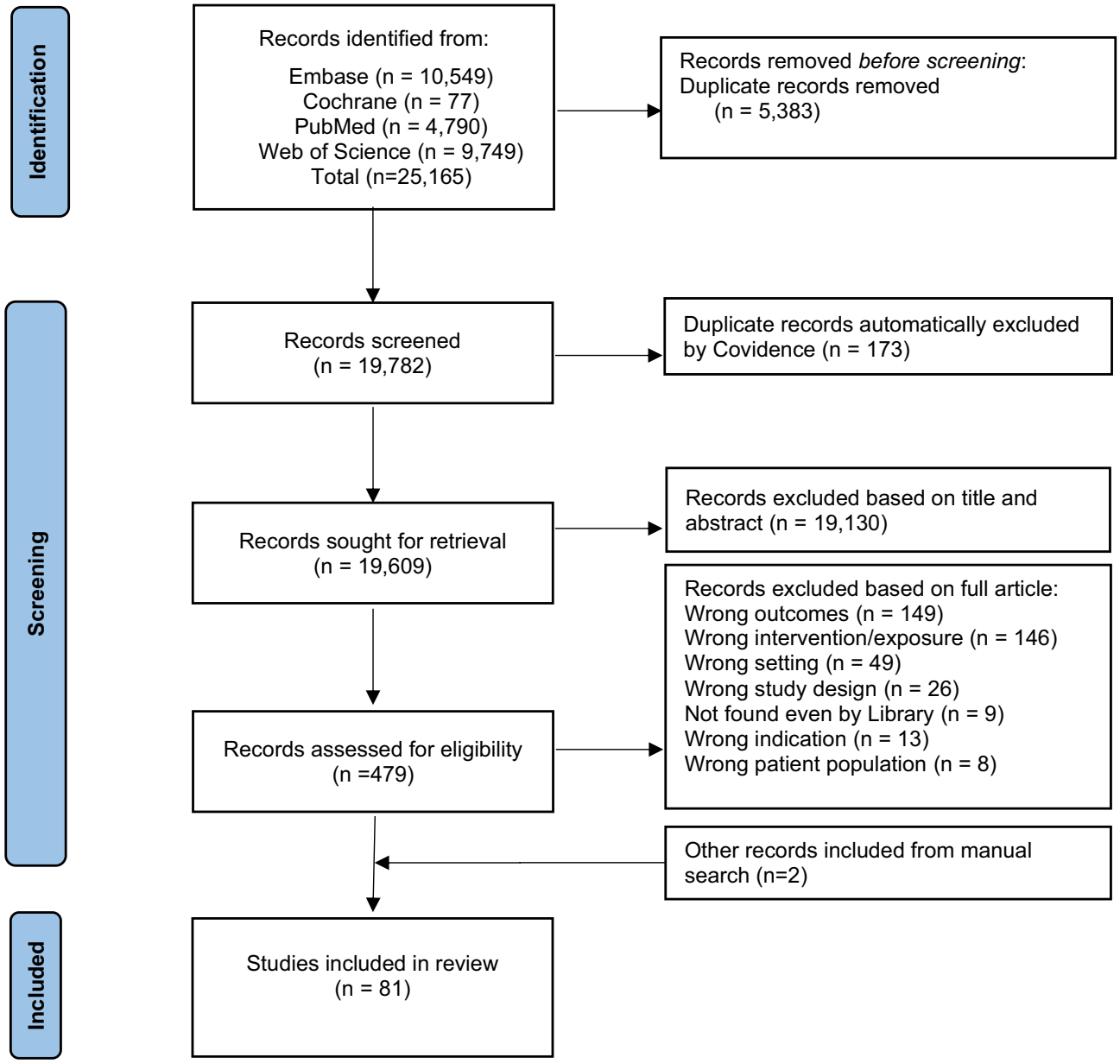

Figure 1 Flow chart of the scoping review.

Biomarkers Related to Non-Specific MSP

Non-specific pain syndromes were also diagnosed by clinical judgement alone or using different tools with or without clinical examination: the scale of Kellgren and Lawrence for classification of OA, and the WOMAC; the Örebro MSP Questionnaire (OMPQ),[81] the American College of Rheumatology criteria for fibromyalgia,[48,79] the Wong-Baker Faces Pain Rating Scale[53] and Pfirrmann grading system.[38,49] Of the studies that examined the relationship between biomarkers and non-specific MSP, one examined the relationship between deficiency in vitamin D and unexplained arthralgia;[112] one examined the relationship between urinary cadmium and arm and foot pain;[78] two studies explored the association between serum vitamin D, vitamin C, and spinal pain;[35,51] two studies examined the relationships between urinary cadmium, serum vitamin D, and leg pain;[53,78] and two other studies examined the association between serum vitamin D and anti-cyclic citrullinated peptide antibody (anti-CCP), and arthralgia.[110,112] Four studies[32,43,56,78] explored the association between neck pain and various biomarkers in blood (albumin, calcium, ferritin, globulin, lipoprotein, cholesterol, triglycerides, and vitamin D) and urinary cadmium. Five studies examined the relationships between lipids

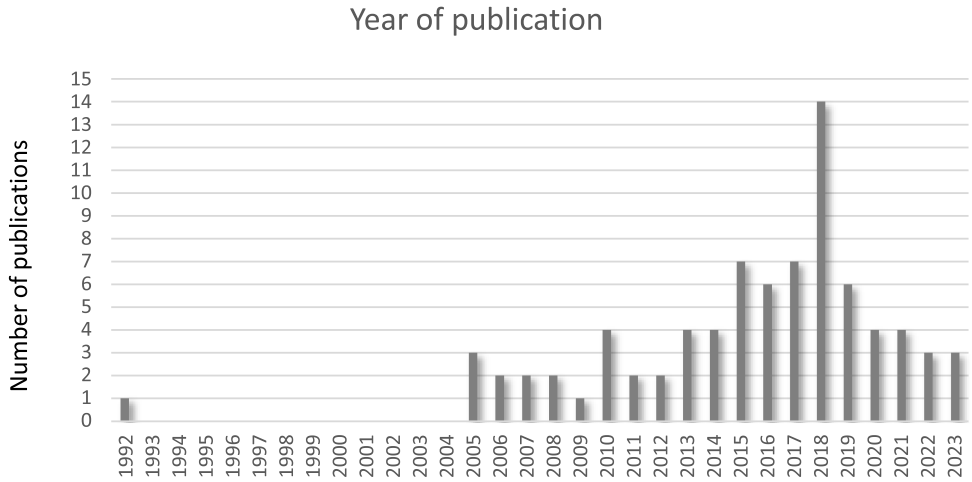

Figure 2 Biomarkers of musculoskeletal pain: scoping review key data.

(total cholesterol, triglycerides, LDL, HDL) and omega-3 fatty acids in blood and urinary cadmium and vitamin D, and MSP in shoulders;[41,78,79,96,100] and six others assessed the relationships between levels of COMP, CRP, hyaluronate of synovium inflammation, glycosaminoglycan, keratin sulphate epitope 5D4, tyrosine, lysine, leucine – 40 (YKL-40), osteocalcin, IL-6, type I collagen (CTX-I), vitamin D and urinary cadmium, and knee pain.[44,47,60,78,79,91] Nine studies assessed the relationship between uric acid, calcium, estradiol, hemoglobin, phosphate, cortisol, dehydroepiandrosterone sulfate, follicle-stimulating hormone (FSH), hormone levels (gonadotrophins) such as total testosterone, luteinising hormone (LH), SHBG, vitamin D in blood and urinary cadmium with chronic MSP in general.[39,40,48,78,81,88,98,106,108] The remaining 12 studies examined the associations between levels of cortisol, creatinine, CRP, sodium, vitamin D, cholesterol, and spinal pain.[21,42,49,52,57,68,75,85,87,91,102,103] Vitamin D seemed to have been more often studied in relation to non-specific MSP than any other biomarker (Supplementary Table 3).

Synthesis of Results

Overall, there was much variation in the nature and site of MSP considered and the biomarkers studied. Several studies did not conduct multivariate analyses and when they did, the most frequent variables included in the regression models were sex, age, socioeconomic condition, depression, and other comorbidities. In addition to the evaluation of the associations and the case studies considering specific MSP, many studies evaluated the association of several biomarkers with OA. These studies concluded that high levels of PIIANP and AAbs were useful to facilitate the diagnosis of OA, and that higher levels of collagen, COMP, estrogens, IgE, IL-17, pentosidine and urinary CTX were positively associated with OA.[47,55,60,63,66,99,104] Vitamin D deficiency was found to play an important role in the diagnosis of OA,[87] to be associated with knee OA,[50] and to be positively and significantly associated with arthralgia.[112] For specific MSP, high TNF-α levels was identified as a marker of systemic inflammation, but it did not seem to have major effects on OA and knee function.[45] Individuals exposed to high doses of cadmium developed osteomalacia and osteoporosis.[58]

Vitamin D deficiency was found to be associated with many non-specific MSP syndromes,[79,106] including knee pain[44,91] and spinal pain,[35,51] although some other studies did not identify such associations.[68] Dose–response patterns were found in the relationship between vitamin D deficiency and leg pain.[53] High levels of cadmium,[78] calcium,[40] creatinine,[102] CRP,[47,85] omega-3 fatty acids,[41] lipids (total cholesterol, triglycerides, LDL, and HDL),[32,33,49,61] sodium,[102] and vitamin C[35] were found to be associated with miscellaneous MSP. In one study, patients with shoulder pain had significantly lower levels of omega-3 fatty acids compared to healthy controls.[41] No conclusions could be drawn on age and sex for specific as well as non-specific MSP.

Table 1 presents a synthesis of the results of all the studies included in this review. Of all biomarkers, vitamin D has been the most often studied in relation to MSP, and in the vast majority of studies (18 of 20 – 90%) the reported inverse associations were statistically significant. Studies on CRP levels provided mixed results (4 of 7 reporting significant

positive associations – 57%), while those on cytokines (9 of 9 – 100%) and lipids (8 of 12 – 67%) that may have caused dyslipidemia and hypercholesterolemia, reported mostly significant positive associations. Studies on other biomarkers were less numerous, and their results did not point to a clear direction.

Discussion

Summary of Evidence

Our scoping review provides a synthesis of the existing evidence regarding biomarkers studied in relation to MSP syndromes, a research question that can provide very important leads to a better understanding of the causes of MSP, but that has not been assessed thoroughly yet. The wide search strategy led to the inclusion of 81 papers. The literature was heterogeneous in many aspects, including the type of publication, the study design, the MSP syndromes and biomarkers considered and their measurements, and the analyses conducted. Lower levels of vitamin D, higher levels of lipids (total cholesterol, triglycerides, LDL, and HDL) and cytokines were the biomarkers found most consistently associated with MSP.

The interest for biological markers of MSP is recent. For decades, research on the determinants of MSP has mainly focused on biomechanical and psychosocial variables, with psychological factors having been identified as strong predictors of MSP and their consequences.[113] Our scoping review identified clearly that the majority of the studies that have looked at biomarkers of non-specific MSP have focused on vitamin D. Indeed, vitamin D deficiency has been found to be associated with OA, knee pain, leg pain, neck pain, and spinal pain. While cadmium, CRP, cytokines, lipids, ferritin, and vitamin C, to name but a few, were reported to be associated with specific and non-specific MSP, the evidence is more sketchy on these associations. Draper-Rodi et al[114], in their scoping review on predictors of non-specific low back pain, identified two possible reasons that could explain the recent interest in biological prognostic factors: 1) there might be variation in classification of factors, eg, sleep disorders could be classified as biological rather than psychological; and (2) as diagnoses of MSP were not made traditionally using biomarkers, it may be time to include biological factors more explicitly as predictors of some diseases. Although these two reasons were mentioned in relation to low back pain, they also apply to other MSP, since biomarkers have been much neglected in many MSP syndromes.

We noticed that most of the biomarkers that were found to be associated with specific pain syndromes were also found to be associated with non-specific pain syndromes, except anti-CCP, hemoglobin, and survivin. We also noticed that high levels of cadmium derived from contaminated food, which were involved in the occurrence of osteomalacia,[58] were associated with five sites of non-specific MSP: arm, foot, leg, neck, and shoulder. Even if this relationship is not well documented in the literature, it can be hypothesized that since cigarette smoke is a source of cadmium[115,116] and that cigarette smoking is associated with MSP,[9] cadmium might play a mediating role between cigarette smoking and MSP.

Association Between Vitamin D and MSP

Many studies in our review found associations between vitamin D deficiency and specific and non-specific MSP. Vitamin D deficiency is uncommon in sunny countries.[52] Most of the included studies were conducted in non-sunny countries, where vitamin D deficiency is a common health problem, which prevalence has increased substantially in recent years.[117] For instance, the prevalence of vitamin D deficiency in the US general population is 25%, and more than 40% in the elderly population.[118] Since vitamin D plays an important role in the constitution of bones, it is not surprising that its deficiency would be associated with arthralgia and spinal pain.[36,71,87,97,112] Some authors examined changes in levels of vitamin D and found these changes to be correlated with widespread MSP.[34,50,79,88]

Association Between Inflammatory Markers and MSP

Besides the fairly high consistency of a relationship between vitamin D and MSP, this scoping review also highlighted associations between several inflammatory biomarkers and MSP: CRP, cytokines (COMP, IL-6/IL-10, TNF-α, IL-17) with specific MSP: axial spondyloarthritis,[82] idiopathic arthritis,[105] and OA in general. For non-specific MSP, we noted that high levels of serum COMP and plasma IL-6 were associated with knee OA[60] and that high serum levels of hs-CRP

Table 1 Synthesis of Studies on Associations Between Biomarkers and Musculoskeletal Pain (MSP)

Biomarker	Number of Articles	Specific Biomarker Reported	MSP Syndromes Studied	Number of Studies Reporting a Statistically Significant Association of Biomarker with MSP	Number of Studies Reporting no Statistically Significant Association of Biomarker with MSP
Vitamin D	26[a]	Hypovitaminosis D, Vitamin D deficiency, osteomalacia,	Arthralgia, back pain, knee pain, knee osteoarthritis (OA), neck pain (chronic), generalized (widespread) MSP, spinal pain, fibromyalgia, OA, nonspecific MSP, idiopathic MSP	18	2
Lipids (total cholesterol, LDL-C, HDL-C[b], non-HDL-C[c], triglycerides, ApoB[d] levels)	13	High levels of LDL and non-HDL (hypercholesterolemia)	Rheumatoid arthritis, general MSP (chronic), shoulder pain (rotator cuff, primary frozen, adhesive capsulitis), neck pain, knee pain, hand pain, hip pain, spinal pain, back pain, modic change	8	4
Cytokines[e] (IL-1B, IL-2, IL-1, IL-6, IL-10, IL-18, IL-31, Th1, Th2, and Th17, ESR[f], TNF-α[g])	10	High concentrations	Axial spondyloarthritis, knee, lumbar OA, knee OA	9	0
CRP[h]	9	High levels	Rheumatoid arthritis, low back pain (chronic), sciatic pain (acute), general MSP (chronic), knee pain, knee OA, lumbar OA	4	3
COMP[i]	8	High levels	Axial spondyloarthritis, knee, OA (knee, hip, low back)	5	0
Collagen (PIIANP, urinary CTX-II[j], C-telopeptide of type I collagen, fibrinogen, estrogen)	7	High levels	OA (knee, hip)	6	0
Calcium	6	Hypercalcemia, osteomalacia	Neck pain, low back pain, OA, general chronic MSP	2	2
Hormones (gonadotrophins, sex hormone-binding globulin, parathyroid hormone)	5	High levels of gonadotrophins, low levels of sex hormone	Neck pain, low back pain, OA (back pain), rheumatoid arthritis, ankylosing spondylitis, general MSP, idiopathic MSP	2	2
Uric acid and blood urea	4	Inappropriate secretion, Hyperuricemia	Back pain, OA, general chronic MSP, knee OA	4	0

Albumin	3	n.a.	Neck pain, chronic neck pain, OA	0	2
Telopeptide (urinary N-telopeptide)	3	High levels	Neck pain (pseudoarthrosis), knee pain, osteoarthritis	1	1
Cadmium	3	High levels	Chronic MSP (back, knee, shoulder, leg, neck, foot, arm), arthritis, OA, degenerative arthritis, rheumatoid arthritis, psoriatic arthritis	3	0
Cortisol	2	Low levels	Low back pain, MSP	2	0
Epitope	2	Relatively low frequency of the shared epitope	Knee pain, arthralgia	1	0
Creatinine	2	Low levels	Back pain, general chronic MSP	0	1
Ferritin	2	Low levels	Chronic MSP	2	0
Autoantibodies	1	High or low levels	Knee OA	1	0
CD 40L[k]	1	High levels	Knee OA	1	0
VCAM[l]	1	High levels	Knee OA	1	0
VEGF[m]	1	n.a.	Knee OA	0	0
Omega-3 fatty acids	1	Low levels	Shoulder pain (rotator cuff tears)	1	0
Pentosidine	1	High levels	Knee OA	1	0
14-3-3η[n]	1	High levels	Rheumatoid arthritis	1	0
FGF-23[o]	1	High levels	Knee OA	1	0
IgE[p]	1	High levels	Knee OA	1	0
Hemoglobin Alc	1	n.a.	Adhesive capsulitis	0	0
Survivin	1	High levels	Arthralgia	1	0
Vitamin C	1	Hypovitaminosis C	Spinal pain, arthritis	1	0
Vitamin K	1	Deficiency	Knee osteoarthritis	1	0
Sodium	1	Hyponatremia	Back pain	1	0

(*Continued*)

https://doi.org/10.2147/JPR.S472934

Table 1 (Continued).

Biomarker	Number of Articles	Specific Biomarker Reported	MSP Syndromes Studied	Number of Studies Reporting a Statistically Significant Association of Biomarker with MSP	Number of Studies Reporting no Statistically Significant Association of Biomarker with MSP
Copper, fluoride, lead, manganese, selenium, zinc, mercury	1	High levels	Arthritis, OA, degenerative arthritis, rheumatoid arthritis, psoriatic arthritis, intervertebral disc degeneration	1	0
Serum angiotensin-converting enzyme (ACE), ionized calcium	1	High levels	Intervertebral disc degeneration	1	0
Short-chain fatty acids (SCFAs)	1	Higher serum levels	Arthritis	1	0

Notes: [a]The total of articles includes some that did not report any association measures. [b]LDL: Low-density lipoprotein. [c]HDL: High-density lipoprotein. [d]ApoB: Apolipoprotein B. [e]IL: Interleukin; Th: T helper. [f]ESR: Erythrocyte sedimentation rate. [g]TNF-α: Tumor necrosis factor alpha. [h]hs-CRP: High sensitivity C-reactive protein. [i]COMP: Cartilage oligomeric matrix protein. [j]PIIANP: N-propeptide of type IIA procollagen; CTX-II: C-telopeptide of cross-linked collagen type II. [k]CD 40L: Cluster of differentiation or antigen ligand 40. [l]VCAM: Vascular cell adhesion molecule. [m]VEGF: Vascular endothelial growth factor. [n]14–3-3η: Synovial inflammation marker that is released into synovial fluid and peripheral blood in rheumatoid arthritis and erosive psoriatic arthritis. [o]FGF-23: Fibroblast growth factor-23. [p]IgE: Immunoglobulin E.

were associated with acute sciatic pain.[85] It must, however, be remembered that several studies did not adjust for putative confounders, which imposes caution on interpretation of their results.

Strengths and Limitations of the Review

One important strength of our review is the exhaustive coverage of the literature that we have conducted with an all-encompassing research strategy. We have mapped the literature on the biomarkers of MSP with no restriction on publication dates. Therefore, a wide range of publications was used as a source of information for our analysis. Also, this scoping review was registered, supporting the transparency of our research process. The team included several specialists in various related fields and used sophisticated tools: Covidence and Airtable for selecting articles and extracting the core information. Data extraction was done by several pairs of reviewers, experts in scoping reviews, and the process was standardized in various pilot studies, which allowed us to secure the validity of our conclusions.

Despite these strengths, one important limitation of this scoping review is the lack of quality assessment of the articles. This is a common limitation of scoping reviews since the conclusions are to be only descriptively summarized,[119–121] and it is in line with the objective of this study ie to draw a map of the literature on this understudied topic. Another limitation is that, since the term "biomarker" is very broad and we wanted to focus on the definition of Puntmann et al,[15,16] articles not referencing the term "biomarker" were automatically eliminated. We then proceeded to write a strategy that would eliminate all articles focusing on traditional determinants of MSP. Even so, our search for biomarkers of MSP was likely not exhaustive. Also, as the line between specific and non-specific MSP is often blurred, our classification was approximative and often time complicated by mixes of syndromes not always clearly defined. It was also noted that few studies stratified the results by age and biological sex. Considering that many biological processes differ along these variables, it would be more appropriate to consider stratification on age and sex, when possible. Finally, the fact that several biomarkers can be measured in different fluids (blood, serum, urine) using different methods adds another level of heterogeneity of data and of complexity in interpretating them. Despite these limitations, our scoping review lays the ground for further research into biomarkers involved in the development and persistence of MSP.

Clinical Implications

Current knowledge on MSP, especially related to non-specific syndromes, is very limited, and the clinical management of this condition is difficult and often unsuccessful. The identification of biomarkers of MSP would provide a rapid important advance to pain measurement – offering possibilities to objectivize MSP and improve prognostic modelling – a better understanding of widespread pain syndromes and, on a longer term, eventually, new possibilities to prevent and treat MSP.

Conclusion

MSP is a major public health problem, and much research has established that its causes are biological as well as psychosocial. This scoping review synthetized the evidence on the associations between several biomarkers and MSP. Despite the lack of quality assessment, we found a wide heterogeneity of type of reports, study designs, measures of variables and type of analyses, and we identified some biomarkers that seem to stand stronger, most notably vitamin D, lipids, and some markers of inflammation such as CRP. Given the large number of candidate markers to explore as to their relationship with MSP, these ones may warrant the next efforts. High-quality studies, stratified by age and sex, are needed to advance our understanding of the relationships between biomarkers and MSP.

Acknowledgments

We thank Frederic Bergeron, librarian at Université Laval, for his help with the search strategy.

Funding

The researchers did not receive any grant from a commercial, public, or not-for-profit funding agency to perform this study.

Disclosure

All authors declare that they have no conflicts of interest to report in this work.

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