Review

Joint biomarker response to mechanical stimuli in osteoarthritis – A scoping review

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ABSTRACT

Objective: Arthritic cartilage is primed for mechanical damage. Joint biochemical markers (JBM) could provide insight into the impact of mechanical stimulation on joint tissue turnover in osteoarthritis (OA) of potential use in clinical OA research and practice. However, existing studies of the acute impact of physical activities (PA) on JBM often contain risks of substantial bias. The purpose of this scoping review was to critically review and discuss existing reports of acute joint tissue turnover as reflected in JBM in relation to PA in OA and propose considerations for future research.

Design: We searched PubMed, Embase, and Scopus and reference lists for original reports on the acute impact of PA on JBM in human OA. Identified studies were reviewed by two reviewers forming the basis for the discussion of methodology.

Results: Search in databases resulted in nine eligible papers after full-text evaluation. Two additional papers were identified through reference lists, resulting in 11 papers included in this review. Ten investigated knee OA and one investigated hand OA. Biomarkers described were related to turnover of type II collagen, aggrecan, and cartilage oligomeric matrix protein.

Conclusions: The literature is dominated by small, simplistic studies, but suggests that mechanical stimulation can induce acute changes in joint biomarkers. In order to diminish the existing bias in future studies, it is important to recognize methodological considerations e.g. patient and biomarker selection as well as peri-interventional control. Common potential sources of bias include the acute shift in plasma volume due to cardiovascular stress and postural changes.

1. Introduction

Disease modifying treatment for osteoarthritis (OA) is a large unmet medical need [1] and important risk factors include age [2], joint trauma [3] and joint overuse [4,5]. OA can lead to severe pain [6] and functional impairment [7] for which the last resort treatment is joint replacement – a procedure associated with considerable risk of perisurgical complications [8] including bleeding, thrombosis, infection and death. Despite numerous costly and time-consuming clinical trials [9], no disease-modifying drug for OA has yet been approved. Thus, there is a need for tools to optimize clinical development.

Joint biochemical markers (JBM) may provide a perspective on cartilage health status and response to stimuli such as medication [10,11]

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and biomechanical stimulation [12]. JBM are therefore hypothetically suitable candidates for optimizing clinical trials.

JBM can be measured in blood, urine, and synovial fluid and typically relate to essential components of the cartilage extracellular matrix (ECM) including type II collagen, aggrecan, and cartilage oligomeric matrix protein (COMP). The general interest in JBM within OA research is increasing [13] and these have been studied in relation to various biomechanical stimuli [12] as a way of gaining insight into the impact on arthritic cartilage degradation and repair.

OA cartilage is primed for mechanical damage and thus it is plausible that biomechanical stimuli could acutely modulate turnover resulting in altered release of biomarkers [14]. If this concept can be demonstrated, suggested applicable perspectives include proof-of-concept testing of chondroprotective or chondro-anabolic drugs [15], identification of structural progressors [16,17], determination of safe levels of exercise in OA [18] and as determinants to return to sport after joint trauma or surgery [19].

However, previous studies indicate that there are several important caveats to bear in mind when performing and interpreting such studies, which future investigations should consider. Thus, we review the existing reports investigating the acute impact of biomechanical stimulation on JBM in human OA participants. We aimed to provide an overview and to critically review and discuss the methodology used in past studies in order to propose improvements and directions for future clinical research.

2. Methods

2.1. Eligibility criteria

The Joanna Briggs Institute participants/concept/context (JBI PCC) mnemonic was used to develop the following eligibility criteria:

Population: The population included adult human participants with clinically and/or radiologically verified OA in the target joint(s). The population had to be able to perform physical activity (PA), otherwise there were no specific exclusion criteria.

Concept: All research studies that explore the acute impact of PA on JBM of OA were reviewed. The authors defined acute effects as effects detected within minutes up to 24 h after the PA was performed.

Context: All research studies that include an assessment of the impact of PA by changes in serum, synovial fluid or urine biochemical markers of joint tissue turnover in OA were included. Numerical values of the JBM had to be given as well as a grading of the OA by a scientifically acknowledged grading score, often the Kellgren-Lawrence score. The JBM had to be widely accepted as to be related to articular cartilage health. The main effect of PA had to measurable without concurring interventions as e.g. dietary changes.

Types of sources: This review considered all available peer-reviewed published research studies written in a Scandinavian or English language. There were no limitations to their date of publication, country of origin, or setting.

2.2. Information sources

The following electronic databases were searched: PubMed/MEDLINE, EmBase and Scopus. The search was executed on November 20th, 2022.

2.3. Search terms and search strategy

JB and NH undertook a preliminary search to identify controlled terms and keywords in titles and abstracts from relevant literature. Then, an extensive literature search was conducted using the following search phrase: *'Biomarker physical activity osteoarthritis OR Biomarker exercise osteoarthritis OR Biomarker running osteoarthritis OR Biomarker walking osteoarthritis OR Biomarker cycling osteoarthritis OR biochemical marker* *physical activity osteoarthritis OR biochemical marker physical activity osteoarthritis OR biochemical marker exercise osteoarthritis OR biochemical marker exercise osteoarthritis OR Biochemical marker running osteoarthritis OR Biochemical cycling osteoarthritis'*.

2.4. Selection of sources of evidence

Titles and abstracts were screened by two independent reviewers (JB and NH) for assessment according to the inclusion criteria following the PRISMA 2020 guidelines. Duplicates were removed. Then, the full text of selected papers was assessed according to the inclusion criteria by the same two independent reviewers. For both stages, discrepancies between the reviewers were resolved by discussing the context of the articles in questions.

2.5. Data charting process

A data-charting form was jointly developed by the two reviewers, JB and NH, to determine which variables to extract (models, delivery methods, targets, and effects). This data charting form was used to extract data from selected studies. The same two reviewers independently charted the data, discussed the results, and updated, if necessary, the data-charting form to enable the capture of all relevant data to answer the review question. All differences in the charted data were reevaluated by both the reviewers. Data was mostly summarized quantitively through standard numerical values as well as descriptively, when deemed relevant in Table 1. A narrative summary accompanied the charted and/or tabulated results and describes how the results relate to the objectives and questions of the review. Study methods were then critically reviewed in order to identify strengths and limitations and hereby forming the basis for the discussion.

3. Data items

Data on the population, concept, context, and key findings relevant to the review question was extracted. The data-charting form included the following items.

- Author and year of publication
- Participants
- Intervention(s)
- Targets
- Effects

4. Results

Twenty-three papers were initially identified by title and abstract in databases, which resulted in nine eligible papers after full text evaluation. The reference lists of the identified papers were then searched for eligible papers resulting in two additional papers. Thus, 11 papers were included for this review (Fig. 1).

The two largest studies included 40 and 42 participants, respectively, and generally the studies were small (≤20 participants) and the heterogeneity in the study designs was high, in terms of the biomarkers and interventions studied. Ten studies investigated knee OA participants and one studied hand OA. Five knee OA studies investigated the impact of walking, three investigated moderate-high intensity cycling and running, two investigated resistance training, one investigated high intensity endurance and strength and one investigated a mixed low-intensity workout. In the hand OA study, a bout of hand resistance training was investigated. Five studies investigated serum COMP exclusively and three additional studies included serum COMP along with other biomarkers. One study investigated COMP in peri-synovial dialysate. Markers of type II collagen and aggrecan turnover was investigated in four and three studies, respectively. Two studies included a marker reflecting turnover of mixed type I and II collagen turnover (C1,2C) and in a single study type VI collagen degradation (C6M) was investigated.

Table 1
Overview of studies of the acute effects of physical activities on joint biomarkers in OA.

Study	Study population	N	Kellgren-Lawrence grade	Activity and duration	Biomarker(s) investigated	Conclusions
Andersson et al., 2006 [20]	Knee OA patients Mean age: 55 years Mean BMI: 27.2 kg/m^2 Sex: N/A	7	3	1 h supervised high-intensity endurance and strength exercise	Serum COMP (AnaMar Medical)	Immediate increase from baseline equivalent to 10.5 %. Returned towards baseline within 30 min after exercise.
Bender et al., 2019 [17]	Heberden's hand OA female patients: Mean age: 60.3 years Mean BMI: 26.0 kg/m^2 Bouchard's hand OA female patients: Mean age: 62.8 years Mean BMI: 26.5 kg/m^2	12 Heberden's And 12 Bouchard's	Heberden's group mean: 23.6 Bouchard's group mean: 27.4	Mechanical exercise of the OA hand: 20 repetitions compressing a pressure cuff inflated to 30 mmHg	Serum CPII (type II collagen synthesis) (IBEX Technologies Inc), COMP (Euro-Diagnostica), PIIANP (type II collagen synthesis) (Merck), C1,2C (type I and II collagen degradation) (IBEX Technologies Inc)	Increase in PIIANP, CPII, COMP (magnitude not specified) relative to controls peaking within 15 min after exercise in both groups.
Bjerre-Bastos et al., 2020 [21]	Knee OA patients Mean age: 61.9 years Mean BMI: 26.3 kg/m^2	19	1–3	Ergometer HRmax-test and 30 min of moderate-intensity cycling and running sessions one week apart	Serum ARGS (aggrecan degradation) (Nordic Bioscience)	Decrease (magnitude not specified) from baseline immediately after a maximal heart rate test (HRmax-test). Increased 4.8 % from baseline 2.5 h after running.
Bjerre-Bastos et al., 2021 [15]	Knee OA patients Mean age: 61.8 years Mean BMI: 26.1 kg/m^2 Male/female: 5/15	20	1–3	30 min of moderate-intensity cycling and running sessions one week apart (based on the same study as Bjerre-Bastos 2020 [21])	Serum C2M (type II collagen degradation) (Nordic Bioscience), COMP (AnaMar Medical), PRO-C2 (type II collagen synthesis) (Nordic Bioscience), C6M (type VI collagen degradation) (Nordic Bioscience), and Urine CTX-II (type II collagen degradation) (UrineCartiLaps®)	C2M increased up to 24 % after cycling. PRO-C2 increased 10 % immediately after running. C6M decreased up to 12 % (95%CI: −23 to −4%) and 13 % after running and cycling, respectively. All relative to the background variation
Bjerre-Bastos et al., 2022 [22]	Knee OA patients Mean age: 60.0 years Mean BMI: 27.0 kg/m^2 Male/female: 16/24	40	1–3	20 min of moderate-high intensity cycling and running sessions one week apart	Serum C2M and PRO-C2 (Nordic Bioscience)	C2M decreased up to 30 min after cycling. PRO-C2 increased ~10 % from baseline immediately after cycling and running.
Chu et al., 2018 [23]	Knee OA patients Mean age: 60.3 years Mean BMI: 28.3 kg/m^2 Male/female: 6/10	16	Mean of 2.1	30-min walk	Serum C1,2C (type I and II collagen degradation) and CS846 (aggrecan synthesis) (IBEX)	C1,2C increased 5.5 h after exercise compared to reference samples taken 0,5 h after exercise (magnitude not specified).
Erhart-Hledik et al., 2012 [16]	Knee OA patients Mean age: 59 years Mean BMI: 28.1 kg/m^2 Male/female: 6/11	17	Mean of 2.2	30-min walk	Serum COMP (AnaMar Medical)	COMP trended to increase (4 %) from baseline in serum immediately after the 30-min walk. COMP was reduced 16.3 % from baseline after 5.5 h.
Helmark et al., 2010 [24]	Female knee OA patients Mean age: 66 years Mean BMI: 26.4 kg/m^2	16	Mean of 2.3	Leg-press: 25 sets of 10 repetitions at 60 % of 1 repetition max	Serum COMP (AnaMar Medical) and aggrecan (IDS Nordic), microdialysate COMP and aggrecan and urine aggrecan (IDS Nordic) and CTX-II (Manufacturer N/A) (All samples taken obtained after exercise)	Serum COMP and aggrecan decreased over 4 h after leg press. COMP and aggrecan in peri-articular dialysate as well as urine aggrecan levels also decreased during the 4 h observation period (magnitudes not specified)
Jayabalan et al., 2019 [18]	Knee OA patients Mean age: 63.5 years Mean BMI: 27.7 kg/m^2 Male/female: 7/20	27	2–4	45-min walk	Serum COMP (R&D Systems)	COMP increased 26 % from baseline immediately after the walk.
Jayabalan et al., 2022 [25]	Knee OA patients Mean age: 67.5 years Mean BMI: 27.0 kg/m^2 Male/female: 7/3	10	2–4	Playing golf (walking the golf course)	Serum COMP (R&D Systems)	Increased 62 % from baseline immediately after finishing the golf course.
Mündermann et al., 2009 [26]	Knee OA patients Mean age: 60.7 years Mean BMI: 27 kg/m^2 Male/female: 20/22	42	1–4	30-min walk	Serum COMP (AnaMar Medical)	COMP increased 6.3% from baseline immediately after the walk, reached baseline level 30 min after the walk and decreased −11.1 % from baseline at 5.5 h. Changes in OA patients were similar to non-OA controls
Oguz et al., 2021 [27]	Female knee OA patients Mean age: 51.0 years Mean BMI: 34.76 kg/m^2	11	2–3	20-min walk and 50-min workout including muscle strengthening, balance, stability and stretching	Serum COMP (Sunred Biological Technology)	COMP increased immediately after the walk, not further specified, and increased 11 % after the workout. Both relative to baseline.

Abbreviations: BMI = Body Mass Index, N/A = Not applicable, OA = Osteoarthritis
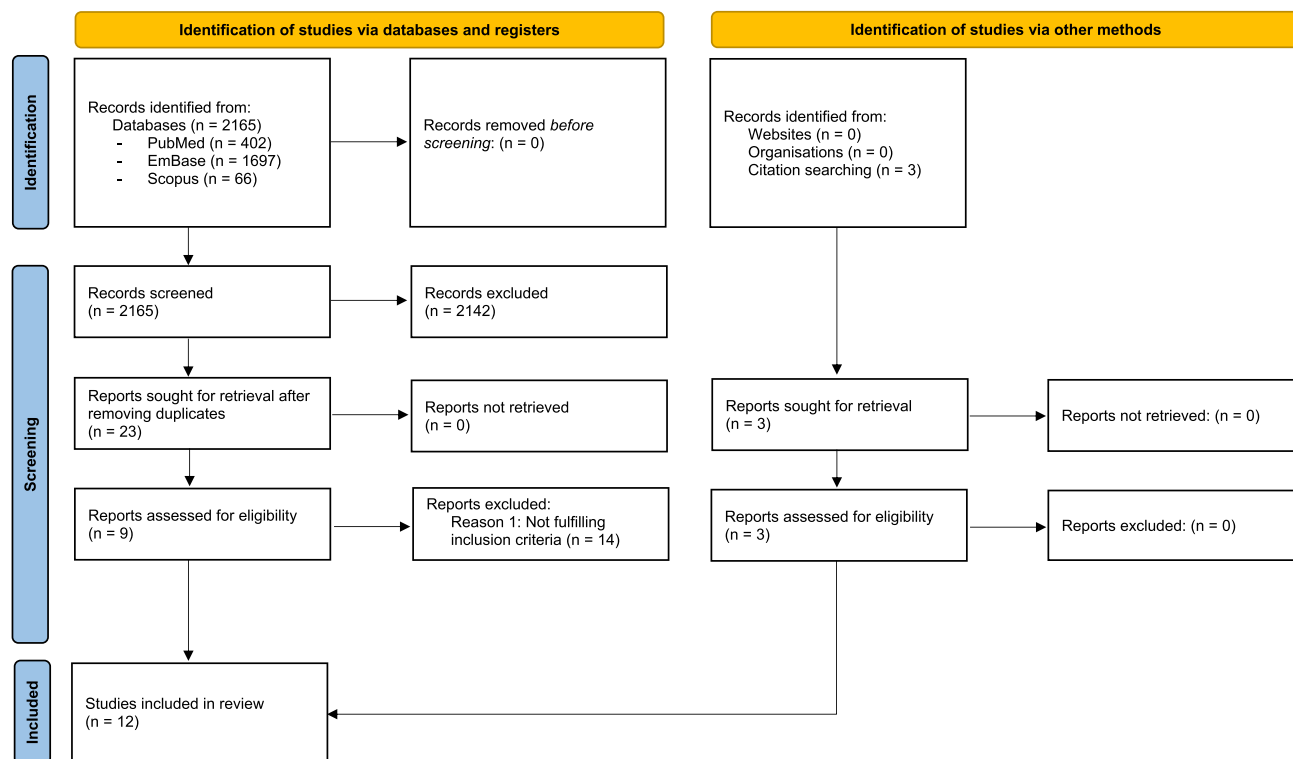
Fig. 1. A PRISMA flow chart of the paper identification process. 23 papers were identified by title and abstract of which nine fulfilled the inclusion criteria after full-text assessment. Reference lists of the included papers were searched for additional references, resulting in three papers. Thus, 12 papers were included.

A complete list and overview of the papers is provided in Table 1 in order of appearance (alphabetical order).

COMP was the most commonly assessed JBM, evaluated in eight out of the eleven reports identified. Various markers of collagen type II turnover were also common, in addition to markers of aggrecan turnover and in the case of Bjerre-Bastos et al. (2021), a marker of collagen type VI was evaluated.

Andersson et al. [28] found an increase from baseline in serum COMP (10.5U/L to 11.6U/L equivalent to 10.5 %, p = 0.018, SD not reported) immediately after exercise and COMP returned towards baseline within 30 min after exercise. The main strengths of this study were the inclusion of participants with definite structural OA and a follow-up of 6 h after exercise with frequent sampling. The main limitations were the relatively small sampling size and the absence of standardized rest prior to exercise and first sample taken.

Bender et al. [17] found increase in PIIANP, CPII, COMP (magnitude not specified) peaking within 15 min after exercise in both groups (Heberden's and Bouchard's). This study's strengths were the control groups, the frequent sampling and the minimal influence of exercises on the cardiovascular system. The main limitations were the absence of male patients and of comparison between erosive and non-erosive hand-OA.

Bjerre-Bastos et al. [21] (2020) found that serum ARGS decreased (magnitude not specified) from baseline immediately after a maximal heart rate test (HRmax-test). ARGS increased from baseline after running (4.8 %, SD 9.1). The strengths were multiple exercise interventions with standardized intensity by % of HRmax, frequent sampling and the consideration of background variation in statistical analysis. The study limitations were the inclusion of participants with doubtful OA (KL 1) and the absence of standardized rest prior to exercise and first sample taking.

Bjerre-Bastos et al. [15] (2021) found increase in serum C2M up to 24 % (95 % confidence interval(95%CI): 7–40 %) after cycling relative to the background variation, 10 % (95%CI: 1.5–19.5 %) increase in serum PRO-C2 immediately after running relative to the background variation and decreased C6M decreased 12 % (95%CI: −23 to −4%) and 13 % (95%CI: −22 to −2%) 2 h after running and cycling, respectively, relative

to the background variation. Strengths and limitations were equal to Bjerre-Bastos 2020, as the report was based on the same trial.

Bjerre-Bastos et al. [22] (2022) found decrease in serum C2M (7 %, SD 2.4) up to 30 min after cycling and increase in serum PRO-C2 between 8.5 % (SD 4.4) and 13 % (SD 4.8)) during and immediately after cycling and running. The study's strengths were inclusion of a relatively high number of patients (40), a standardized rest period prior to exercise and first sample taken and frequent blood sampling. The main limitation was the inclusion of participants with bilateral doubtful OA (KL 1).

Chu et al. [23] found increased serum C1,2C 5.5 h after exercise compared to reference samples taken 0.5 h after exercise (percentual magnitude not specified). One strength was a rest period prior to exercise and first sample taken while the main limitations was using a sample drawn 0.5 h after exercise as reference.

Erhart-Hledik et al. [16] found a trend of increase (4 %, no SD reported) from baseline in serum immediately after the 30-min walk. COMP was reduced 16.3 % (no SD reported) from baseline after 5.5 h. Strengths of the study was that participants rested prior to exercise and first sample taken. The main limitation was the infrequent sampling.

Helmark et al. [29] found serum levels of COMP and aggrecan to decrease over approximately 4 h after leg press exercise in patients with knee OA. COMP and aggrecan in peri-articular dialysate (obtained via microdialysis) as well as urine aggrecan levels also decreased (magnitudes not specified). The paper's strengths were the inclusion of different types of specimen and rest prior to exercise and first sample taken. Limitations were the absence of baseline samples taken prior to exercise.

Jayabalan et al. [18] (2019) found increased COMP from 935 ng/ml (SD: 422 ng/ml) to 1164 ng/ml (SD: 665 ng/ml) equivalent to a 26 % increase after 45-min walk. The strengths of this study were the large sample size and rest period prior to exercise and first sample taken. This study also suffers of limitations like the lack of standardization of walking speed which was self-selected by the study participants. The inclusion of participants with KL 4 can be considered both a strength and a limitation, as KL 4-knees contain denuded areas thus potentially reducing the

amount of stimulated cartilage, while on the other hand it is interesting to gain insight into JBM response in this late stage OA.

Jayabalan et al. [25] (2022) found an increase of serum COMP from 813 ng/ml (SD: 191 ng/ml) to 1321 ng/ml (SD: 310 ng/ml) equivalent to a 62 % increase immediately after finishing the golf course. The inclusion of a control group and cross-over were the two major strengths of this study while the small number of participants was a key limitation. To test real-life activity such as golf can be considered as an originality.

Mündermann et al. [26] found a 6.3 % increase in COMP immediately after 30 min of walking. COMP levels returned to baseline 30 min after the walk and continued to decrease to −11.1 % from baseline at 5.5 h. No difference in COMP changes where found between OA patients and non-OA controls.

Oguz et al. [27] found increased serum COMP immediately after the walk, not further specified, and increased COMP (11 %, SD 7.9) after the workout. The inclusion of participants with definite radiographic OA (KL 2 and 3) was a strength and the low number of participants and self-selected walking speed were the main limitations.

5. Discussion

For this review we identified 11 studies investigating the acute impact of PA on JBM. The studies were generally simplistic, heterogeneous in design and modest in size. COMP and markers of type II collagen degradation were most frequently investigated.

5.1. Impact of physical activity on markers of cartilage degradation

The majority of the studies investigating markers of cartilage ECM degradation found an increase of these JBM in response to PA. In contrast, Erhart-Hledik et al. did not find any increase in average serum COMP after a walking exercise [16]. Their results are unusual as five studies found 10–62 % COMP increase in immediate response PA involving the OA joints. There is no obvious explanation why Erhart-Hledik and colleagues did not find any increase in COMP, but it may be explained by the small samples size combined with the known high individual variation in serum COMP, and it is worth noting, that COMP decreases in some participants. Another explanation could be the PA intensity. While Erhart-Hledik investigated only 30 min walking, the other studies tested more intensive PA including playing golf or 50 min workout.

COMP is relatively consistently seen to peak acutely in serum in immediate response to exercise and then gradually return to baseline concentrations during subsequent rest [28,30]. This trajectory of COMP change in serum is similar to that reflecting hemoconcentration in response to exercise, which has been demonstrated in OA [22] and thus hemodynamics may partly confound the acute COMP increase. Further, there is no difference in response when comparing changes in relation to a bout of walking exercise in OA versus non-OA controls [26].

However, COMP was also found to acutely increase in the hand OA study by Bender et al. [17] in which any hemoconcentration must be considered negligible. COMP is found in multiple tissues, but as articular tissue is the main origin [31,32], the increase in serum is likely due to clearance from the joints and peri-synovial lymphatic drainage, but it must be considered that non-cartilage tissue could contribute.

The increase in COMP is most likely due to mobilization of existing and not newly formed fragments, as the increase occurs within 15 min. However, the studies by Chu [23] and Erhart-Hledik [16] et al. suggest that these changes are still relevant. Acute increase in degradation markers is associated with structural progression over 5 years and although higher amounts of mobilizable biomarkers do not necessarily reflect evoked tissue degradation, they could indicate higher degree of exercise-evoked turnover reflecting tissue maintenance. Therefore, we suggest that the use of type II collagen derived biomarkers would be more reliable markers for definite cartilage breakdown, as the natural turnover in cartilage is known to be minimal [33]. A set of studies explored this approach [15,22].

Bjerre-Bastos et al. (2021) investigated two types of exercise with different degrees of mechanical stimulus, but found no increase in marker of type II collagen degradation, C2M [22]. A single preceding study investigated serum C2M and urine CTX-II in response to similar interventions finding increase in C2M following cycling and no changes in CTX-II [15]. Thus, the results are ambiguous. However, the most recent study [22] was relatively well powered, carried out with a robust methodology and therefore the most credible result is that type II collagen degradation is not acutely affected by this type of controlled PA. Although CTX-II is an established OA JBM, urine may not be ideal for detection of acute changes due to the delay in renal filtration, and further, CTX-II is known to be affected by substantial diurnal variation [34]. Logically, a serum-based marker of type II collagen degradation, such as C2M, should be better suited. The inclusion of knees with a KL grade of 1 is a weakness of the study and may partly explain the ambiguous results, but another obvious explanation may simply be the resilience of type II collagen in the cartilage reflecting overall great resilience of the arthritic cartilage to mechanical stress from a JBM perspective. Studies have indicated the low turnover and high conservation of the type II collagen component of cartilage [33]. Thus, although there is undoubtedly loss of cartilage over years, acute degradation of an essential and specific molecule of the cartilage, such as type II collagen, does not seem to be evoked by mechanical stress.

An interesting study of hand exercise in hand OA by Bender et al. [17] found increase in COMP, but no increase in a marker of both type I and type II collagen cleavage, C1,2C. This suggests, that exercising arthritic joints can evoke increase in a non-collagenous marker of cartilage degradation without an accompanying increase in collagen marker of cartilage degradation.

In nine studies, increases in biomarkers reflecting cartilage degradation were detected in response to exercise. Chu et al. [23] found increase in serum C1,2C and Helmark et al. [29] found increased urine aggrecan, but these two studies do not reflect changes from pre-exercise levels, as they did not include a baseline sample.

Bjerre-Bastos (2020) [21] found marker of aggrecan degradation, serum ARGS, to increase 5 % in response to a bout of running, and as described, several studies found another non-collagen marker, COMP, to increase 10–62 % in response to mechanical loading of arthritic joints. ARGS and COMP are both thought to reflect cartilage degradation, and ARGS is even used as a pharmacodynamic marker in the therapeutic development of OA drugs [10].

Does increase in ARGS and COMP reflect accelerated breakdown of cartilage ECM? Although Mündermann et al. [26] found no difference in the response to a walking exercise between knee OA subjects and non-OA controls this is speculative and may be the case, but there are important limitations and potential biases to consider. The impact of exercise on ARGS has only been investigated in the one study by Bjerre-Bastos et al. [21], and considering the sample size and the minute changes observed, the results must be regarded as being associated with great uncertainty and solely hypothesis-generating. However, Helmark et al. [29] found an increase in urinary aggrecan, so it is plausible that aggrecan degradation is affected by biomechanical stress. ARGS is strictly speaking a degradation marker, but one could hypothesize that ARGS release is part of the natural tissue maintenance, and as such this would be one half of tissue turnover, rather than a pathological event. Aggrecan formation has only been investigated in a single study [23] and never in combination with a degradation marker, thus little is known about the turnover balance of aggrecan in relation to mechanical stimuli. The above leads to speculation of whether the turnover of ARGS in relation to PA turns pathological in OA.

5.2. Impact of exercise on JBM of cartilage formation

Four studies investigated JBM reflecting formation of cartilage extracellular matrix components; PIIANP and CPII in one study, CS846 in one study and PRO-C2 in two studies. Marker of type II collagen formation,

PRO-C2, increased transiently in acute response to exercise – a change that could be confounded by hemoconcentration [22]. However, Bender et al. [17] found two other markers of type II collagen formation, PIIANP and CPII, to increase within 15 min of hand exercise, supporting an actual increase in serum biomarkers of type II collagen formation in response to mechanical stimulation of arthritic joints. PRO-C2 is also a pharmaco-dynamic marker which have been shown to be modulated by pharmacological induced cartilage formation [35]. Thus, increase in formation markers could reflect a natural repair-response. Alternatively, the increase in formation markers could be speculated to reflect fragment-mobilization originating in ongoing activity in osteophyte tissue, which has been shown to have increased turnover [36].

6. Considerations for future research

Future studies should aim to produce results applicable in clinical practice and clinical research and methods should be carefully considered taking known sources of bias into account. In the light of the known rapid response in some structural JBM, such as COMP, in response to load, rest prior to the intervention seems mandatory to reduce noise from prior PA. Based on the results of Bjerre-Bastos 2022 [22], indicating a relevant influence of plasma volume changes in studies of acute changes in circulating JBM, study design should accommodate the potential influence of plasma volume changes. These can be easily estimated [22] and if the JBM kinetics are known, adjustments can be made for these changes. Several previous studies have included knee OA participants with KL 1, but as KL 1 reflects questionable structural OA, exclusion of these should be considered. Conversely, a few studies included participants with KL 4, and although KL 4 represents definite and severe structural knee OA, there is a risk that there is little remaining cartilage to mechanically stimulate, leading to less release of relevant protein fragments for measurement. Thus, ideally, only KL 2 and 3 are included.

Future studies should aim for adequate power, which is feasible, as there is existing data available in the literature to estimate expected changes and standard deviation for most JBM. Increased focus should be on markers specific for joint tissue e.g. that relate to type II collagen and aggrecan. Shear stress and compressive load has fundamentally different impact on cartilage [37] and studies including different types of mechanical stress are thus warranted.

As reflected in this review, past studies suggest considerable variation and heterogeneity in individual JBM response. Thus, prospective follow-up could provide valuable information about responders versus non-responders [16,23]. If possible, matched samples should be taken from synovial fluid and serum, and serum should be collected many times and over a long period of time for detailed trajectories. Nocturnal sampling could rationally be considered, as there is known diurnal variation [34, 38], but the activity in joint tissue at night is largely unknown. Finally, many existing studies lack a non-OA control group, a such should be included if the desire is to make inference about osteoarthritis pathology. Alternatively, the acute response in JBM in relation to exercise, such as leg-press, of target leg versus control leg in subjects with unilateral knee OA could be an interesting approach.

7. Conclusion

The existing literature on the impact of mechanical stimulation on structural joint biochemical markers is dominated by small, simplistic studies, but suggests that mechanical stimulation can induce acute changes in biomarkers reflecting joint tissue turnover. However, it remains uncertain exactly which processes these changes reflect. There are interesting perspectives for research into the effect of exercise on JBM of cartilage turnover, but in order to optimize progression in this research field a number of factors, including potential sources of bias, which are described in this review, should be considered in future studies, especially the intensity-dependent shift in plasma volume induced by physical activity.

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