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Biomarkers to Monitor Efficacy of Exercise Programs in Multimorbid Osteoarthritis Patients: Is Inflammation the Clue?

Programme zur Steigerung der körperlichen Aktivität bei multimorbiden Arthrosepatienten: Entzündungsparameter als Biomarker?

REVIEW

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Summary

› **Osteoarthritis (OA) is a pro-inflammatory,** degenerative disease of the joints. Since the osteoarthritis risk profile overlaps with that of other lifestyle-related diseases, such as obesity, type 2 diabetes mellitus (T2DM), or cardiovascular disease, affected individuals are often multi-morbid. Physical activity has been demonstrated to be a valuable preventive and therapeutic tool in OA and also in almost all other lifestyle-related diseases. Thus, affected individuals might benefit from an exercise program in multiple respects. To monitor efficacy of such training interventions, a set of reliable biomarkers, preferentially such that can be assessed from easily accessible biological fluids, in particular urine or blood, would be desirable.

› **In this short review,** we give an overview of potential blood and urine biomarkers that might be used to monitor efficacy of exercise interventions in osteoarthritis patients, with a specific focus on multi-morbidity. Currently, the most-extensively studied markers are inflammation-related factors, such as C-reactive protein (CRP) or interleukin-6 (IL-6), but also metabolic markers, for example the adipokines adiponectin, leptin, and resistin, and products of cartilage decay, such as C-telopeptide of type II collagen (CTX-II), or cartilage oligomeric protein (COMP). Finally, recent studies also point to circulating microRNAs (miRNAs) as potential biomarkers in OA, suggesting that they might also have the potential to be studied in the context of training interventions.

KEY WORDS:
Degenerative Joint Disease, Lifestyle-Related Diseases, Physical Activity, Blood and Urine Markers

Zusammenfassung

› **Arthrose (engl. osteoarthritis, OA)** ist eine entzündliche Gelenkserkrankung. Da das OA-Risikoprofil mit dem für andere Zivilisationskrankheiten wie Adipositas, Typ 2-Diabetes oder Herz-Kreislauferkrankungen überlappt, sind die betroffenen Individuen häufig multimorbid. Körperliche Aktivität ist nachweislich eine sehr effektive präventive und therapeutische Maßnahme sowohl bei OA als auch bei anderen Zivilisationskrankheiten. Somit könnten betroffene Patienten/-innen in vielfältiger Hinsicht von einem Bewegungsprogramm profitieren. Um die Effizienz von Trainingsinterventionen zu überwachen, wäre ein Set von gut verfügbaren Biomarkern wünschenswert, präferentiell solche, die aus leicht zu gewinnenden Körperflüssigkeiten wie Blut oder Urin bestimmt werden können.

› **In diesem kurzen Übersichtsartikel** fassen wir den derzeitigen Kenntnisstand zu potentiellen Blut- und Urin-Biomarkern zusammen, welche in Zukunft dazu dienen könnten, die Effizienz von Trainingsprogrammen bei multimorbiden OA-Patienten/-innen zu evaluieren. Momentan sind verschiedene Entzündungsmediatoren am besten untersucht, insbesondere das C-reaktive Protein (CRP) und Interleukin-6 (IL-6). Zudem rücken metabolische Faktoren, z. B. die Adipokine Adiponectin, Leptin und Resistin, aber auch Produkte der Knorpeldegeneration, wie das C-Telopeptid des Typ II-Kollagens (CTX-II) oder cartilage oligomeric protein (COMP) in den Fokus. Schließlich deuten neuere Forschungsergebnisse an, dass auch zirkulierende microRNAs (miRNAs) interessante OA-Biomarker sein könnten, was im Kontext von Trainingsinterventionen weiter untersucht werden sollte.

SCHLÜSSELWÖRTER:
Degenerative Gelenkserkrankung, Zivilisationskrankheiten, Körperliche Aktivität, Blut- und Urinmarker

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Introduction

Physical exercise has been shown to exert a beneficial preventive and therapeutic effect on almost all pathologies. In a lot of cases, exercise-based therapeutic programs can be superior to a pharmacological therapy, or they can complement medication in an advantageous manner. This general positive effect independent of the specific disease in question is presumably based on the fact that physical activity influences a broad variety of signal transduction pathways and gene expression patterns in most tissues and organs in the body, such as the cardiovascular, the respiratory, and the musculoskeletal system, and many more, in contrast to pharmacological therapy that usually tackles only one or a few specific molecular pathways in a limited number of tissues and organs. Against this background, several authors have attributed the term "multipill" or "polypill" to physical exercise (for review, see (28)). ›

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The prevalence of lifestyle-related diseases, such as osteoarthritis (OA), obesity, type 2 diabetes mellitus (T2DM) and cardiovascular diseases has been continuously increasing over the last few decades. There are some obvious reasons for this phenomenon, specifically social factors, such as altered lifestyles and workplace settings, demographic reasons, as well as the developments of modern medicine and healthcare systems. It has been known for quite a long time that specifically patients diagnosed with one or more of these lifestyle-related diseases benefit to a great extent from programs aiming at boosting their daily amount of physical activity. Interestingly, in many cases, there is a direct correlation between the degree of physical adaptation, such as increases in muscle force or maximal oxygen consumption, and the overall health benefit, i.e. the degree of risk reduction (for review, see (26)).

Based on literature data on dose-effect relationships, several medical societies have published recommendations for individual lifestyle-related diseases, for example for OA or T2DM patients. However, the fact that most of these patients are multi-morbid, suffering from more than one of the pathologies in question, has hardly been addressed so far. Multi-morbidity is mainly the effect of overlapping risk profiles, for example between obesity and T2DM, or obesity and OA.

Interestingly, however, a recent study analyzing training recommendations published by the different medical societies for the most common lifestyle-related diseases came to the conclusion that there was surprisingly little difference (12), suggesting that a standardizing training program ("One fits all."), perhaps supplemented by some disease-specific elements in a modular manner, might be an efficient and cost-effective strategy for the design of exercise-based preventive and therapeutic programs for these patients.

To evaluate efficacy of such a program, subjective criteria, such as personal perception of individual health, and objective criteria, such as physiological data (blood pressure, resting heart rate), imaging analysis (such as radiological assessment in OA), or functional tests (maximum force or endurance power) can be implemented. However, most of these tests are time-consuming and/or expensive. In addition, for OA patients, physiological and even radiological data do not very well correlate with subjective health or pain perception. Thus, specifically with regard to OA patients with comorbidities, identification of reliable biomarkers would be desirable to monitor and improve efficacy of specific exercise regimens.

In general, such biomarkers can be assessed from the synovial fluid of affected joints themselves. This method might be highly sensitive and allow the detection of OA-related changes at early stages of the disease, however, in clinical practice, it would be desirable to also have biomarkers available that can be analyzed from easily accessible biological fluids, such as urine or blood. So far, little is known on potential interrelationships of biomarker concentrations in these different biological compartments. Some initial research suggests that while there might be some degree of correlation for individual markers, this might not be the case for others (for review, see (32)).

In the following, we will briefly sum up current knowledge on potential blood and urine biomarkers to monitor training adaptation in multi-morbid OA patients diagnosed with one or more further comorbidities, specifically lifestyle-related diseases such as obesity, T2DM, or cardiovascular disease. Since low-grade systemic inflammation is a specific and common feature of most of these patients, we will particularly focus on inflammation-related markers, but will also briefly address the issues of metabolic markers, such as adipokines, and OA-specific markers, and proteins related to cartilage decay, specifically since inflammation, metabolism, and musculoskeletal / joint decay are closely linked to and intertwined with OA pathogenesis, particularly in multimorbid patients. Finally, recent studies suggest that circulating microRNAs (miRNAs), in particular such that have been functionally linked to inflammation, metabolism, or cartilage decay, might also have the potential to serve as OA biomarkers.

Inflammation Markers

OA, particularly in multi-morbid and/or older patients, is a "pro-inflammatory" disease. On the one hand, cartilage degeneration promotes inflammatory processes. On the other hand, in multi-morbid patients, comorbidities, such as obesity, T2DM, or cardiovascular diseases trigger processes of permanent, systemic, low-grade inflammation (11, 19, 24). This persistent inflammation is, at least in part, the result of a pathological metabolic situation: In obese patients, large amounts of pro-inflammatory cytokines are released from adipose tissue, and there is even evidence indicating that in non-obese individuals, isolated hyperglycemia and hyperinsulinemia drive inflammation (metaflammation) (35). Permanent inflammation then promotes degenerative processes in the musculoskeletal system, such as skeletal muscle, but most likely also in joint cartilage (5). As a whole, several studies suggest that in multi-morbid patients, low-grade inflammation associated with other pathologies appears to be an independent risk factor for OA, eventually driving a vicious circle of cartilage decay and inflammation (for review, see (17)). In addition, in older people, even when non-obese and generally healthy, a similar systemic, low-grade inflammation is regularly observed (inflammaging). Even though the causes of this inflammatory response are not entirely understood, its effects on the musculoskeletal system strongly resemble the ones seen in multimorbid patients (for review, see (10)).

Thus, while the molecular mechanisms of this complex interplay between chronic disease, metabolism, aging and inflammation are only partially understood, it appears to be clear that there is no single factor initiating or driving low-grade inflammation, but a complicated network of signal transduction and gene regulation processes in various tissues and organs. If there is something like a central factor, linking OA, obesity, metabolic syndrome, and inflammation, however, this might be overall muscle integrity (for review, see (5)).

As mentioned, exercise is considered a "polypill" in the context of a broad variety of chronic diseases and specifically multimorbidity. Its positive preventive, therapeutic, and rehabilitative effect has been known for a long time. Even though there are also conflicting results (21), specifically when younger and/or healthy people were analyzed (6, 15), more and more data suggest that at least in multi-morbid and/or older subjects, regular exercise exerts an anti-inflammatory effect (16, 23, 27, 33, 38), which might be one of the reasons for its positive effect on overall health outcome in these patients. As a whole, these data suggest that molecular mediators of inflammation, such as pro-inflammatory cytokines, might be suitable biomarkers for OA diagnosis and prognosis, and might even allow monitoring and supervision of therapeutic interventions, such as exercise-based regimens. However, while levels of a broad variety of inflammation markers, such as pro-inflammatory cytokines, are indeed strongly elevated in synovial fluid from affected joints and correlate with severity and progression in OA and in rheumatic disease in general, it is difficult to reliably assess pro-inflammatory factors from more easily accessible biological fluids, such as urine or blood (for review, see (1, 32)).

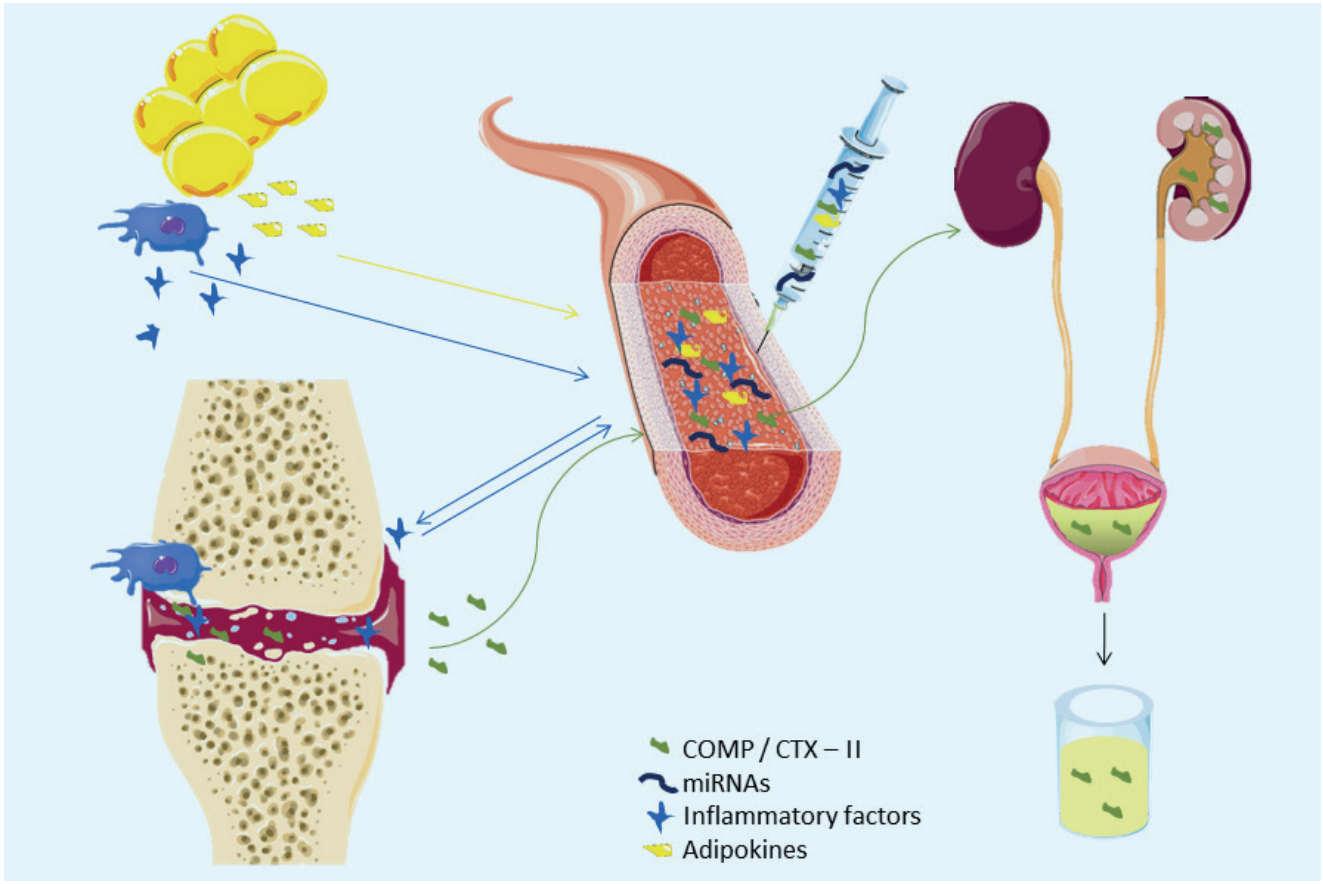

Figure 1

Schematic overview of potential biomarkers in multi-morbid OA patients. Inflammatory cells (shown in bright blue), and also fat cells (yellow) in adipose tissue and inflamed joints (green) produce inflammatory factors, such as pro-inflammatory cytokines (bright blue symbols). The latter again promote inflammation in diseased joints as part of a vicious circle. In addition, pro-inflammatory factors stimulate CRP production by the liver (not shown). Furthermore, adipose tissue secretes adipokines (yellow), which also promote inflammation and possibly cartilage degradation. Degenerating joint cartilage releases products of cartilage decay, such as COMP and CTX-II (green), which can be determines from patients' urine. In addition, specific miRNA species (dark blue) whose concentration is altered both in OA and in response to exercise, might serve as biological markers to monitor efficacy of training interventions in (multi-morbid) OA patients. The figure was prepared using elements from Servier Medical Art (https://smart.servier.com).

So far, in plasma or serum, C-reactive protein (CRP) and interleukin-6 (IL-6) appear to be the most reliable inflammatory markers in (multi-morbid) OA (31, 36). CRP is produced in the liver in response to a broad variety of pro-inflammatory stimuli, specifically IL-6 (for review, see (8)). Furthermore, with regard to other (non-OA) patient cohorts, recent meta-analyses suggest that these two proteins might be suitable markers to monitor the progress of exercise therapies, in particular in T2DM and CVD (cardiovascular disease) patients (13, 15, 16, 21, 27, 38), and in older subjects (23, 33), but there are also data suggesting no association (21). By contrast, in healthy, inactive subjects, data on CRP and IL-6 levels in response to both endurance and resistance training interventions are inconsistent (6), suggesting that determination of inflammation markers to evaluate the success of exercise programs might only be useful in pathological situations which are associated with chronic, low-grade inflammation, or in the elderly, but not in young, healthy, sedentary people. Nevertheless, taken together, these data suggest that in OA patients with comorbidities, CRP and IL-6 might be suitable markers to monitor the efficacy of exercise therapy.

Metabolic Markers

Adipokines are produced by cells of white adipose tissue and released into the circulation. They regulate inflammation and metabolism, thus linking these two processes. The best-characterized adipokines are adiponectin, leptin, and resistin. Their concentration is elevated in obese and diabetic subjects (for review, see (14)). The fact that obesity is an OA risk factor also in non-weight-bearing joints, such as the phalanges of the hand, allowing the conclusion that OA might not just be a simple "biomechanical-inflammatory" disease, but also have "inflammatory-metabolic" causes, sheds light on adipokines as potential OA markers, due to their proposed function as mediators between inflammation and metabolism. Thus, adipokines might further promote OA progression indirectly by promoting general and systemic inflammation, but probably also directly by stimulating mechanisms known to be involved in cartilage decay, such as MMP (matrix metalloproteinase) production (for review, see (34)).

Some recent studies could indeed demonstrate that plasma and serum adipokine concentrations are elevated in OA patients. De Boer et al. (9) found distinctly higher levels of adiponectin, leptin, and resistin in serum of knee OA patients when compared to healthy controls. In addition, there was a, however weak, correlation with synovial inflammation, but not with cartilage damage, as assessed by biochemical and histochemical methods. A further study could demonstrate a positive correlation of serum adiponectin levels with radiological assessment of OA (7). ›

Finally, some recent studies have aimed at defining an OA-specific metabolome in biological fluids. The results suggest that while in synovial fluid, it is indeed possible to define an OA-related metabolome that correlates with disease severity, this might not be an option in other bodily fluids, such as urine, plasma, or serum. However, in these compartments, there might still be a set of a few metabolites, particularly select amino acid and lipid species or their metabolites, which might be worth to be checked out for their potential as small-molecule OA biomarkers (for review, see (18, 29, 30)).

Biomarkers of Cartilage Decay

Cartilage decay and enhanced cartilage turnover result in the release of cartilage proteins into the circulation, implicating cartilage components as potential biomarkers for OA. In addition, proteases involved in cartilage decay, particularly MMPs, have been discussed as potential biomarkers.

So far, most studies in this direction have focused on cartilage oligomeric protein (COMP) in serum (sCOMP), and C-telopeptide of type II collagen (CTX-II) in urine (uCTX-II). Saberi Hosnijeh et al. (31) carried out a meta-analysis and found a strong association of these two markers with both incidence and progression of knee and hip OA, with the exception of sCOMP in hip OA progression, for which data are still inconclusive. Specifically, sCOMP and uCTX-II levels were higher in OA patients when compared to healthy controls and correlated with radiologically assessed severity of disease (3, 31). Particularly uCTX-II might be an interesting marker in clinical practice, since urine is a bodily fluid that can be obtained in a non-invasive manner. In addition, a very recent meta-analysis (3) demonstrated strong correlation between the different grades of Kellgren-Lawrence classification of knee OA (KL 1-4), a score based on radiological assessment, and sCOMP levels, indicating that this marker might also be suitable to monitor a subtle slowdown in disease progression, as might be expected in response to a training intervention.

miRNAs

MicroRNAs (miRNAs) are short, non-coding RNA molecules that regulate expression of specific target genes via a complex set of post-transcriptional mechanisms. In most cases, this leads to gene expression silencing, however, activation of gene expression is also possible. Besides operating within the cells they had been produced in, microRNAs can also be released into the circulation, rendering them interesting candidates for easily accessible biomarkers, especially since their concentrations can be determined via qPCR analysis in a timely and cost-effective manner (for review, see (37)).

Some recent studies suggest that circulating miRNAs might also serve as biomarkers for OA diagnosis and monitoring. There might even be something like an OA-specific miRNA signature (25). Interestingly, most of the so-far identified candidate miRNA, or, more exactly, their target mRNAs have been implicated in inflammatory signaling, metabolic control, or cartilage decay, thus providing a link to the abovementioned protein markers (for review, see (20)).

Several circulating miRNAs have even been correlated with both OA disease severity and progression in a clinical setting. Examples include a recent study in which serum miRNA levels were analyzed in a large cohort of OA patients, with knee or hip joint replacement as primary outcome. Using microarray screening analysis, the authors could demonstrate that particularly levels of miRNAs let-7e, -454, and 885-5p correlated with disease severity and were associated with future total joint arthroplasty (2). Furthermore, Ntoumou et al. (25) performed high density resolution miRNA microarray analysis with serum samples from a small cohort of primary OA patients compared to a healthy control group. The authors identified a large set of candidate miRNAs, and further analyzed miRNAs 140-3p, -33b-3p, and -671-3p, which have been predicted to be involved in the regulation of metabolic processes. These candidate miRNAs, and probably others, might also be useful to monitor efficacy of training programs in multimorbid OA patients in the future.

Conclusions and Perpectives

Osteoarthritis is a pro-inflammatory disease. Especially multi-morbid patients might benefit from exercise programs, addressing not only their OA, but also potential comorbidities, such as obesity, T2DM, or cardiovascular diseases. Recent results suggest that a standardized training program ("One fits all."), perhaps in combination with some disease-specific elements in a modular manner, might be an efficient and cost-effective strategy for this patient cohort.

However, the efficacy of such a program has not been evaluated so far. For a sensitive, unbiased, standardized assessment, implementation of biomarkers, preferentially such that can be determined from easily accessible biological fluids, such as urine or blood, is desirable. However, as Mobasheri et al. (22) state, there are still no OA biomarkers apt to be used in routine clinical practice, despite the fact that there are promising approaches to get there. Nevertheless, several markers, specifically pro-inflammatory cytokines, adipokines, markers of cartilage decay, and circulating miRNAs, have successfully been used in evaluating early, exploratory clinical trials.

In addition, the fact that some of these markers have already been employed to monitor the efficacy of training studies in other patient cohorts looks promising. However, particularly in the context of training therapies and/or multi-morbidity, it is still not clear which biomarkers are most conclusive (4). Thus, further studies are warranted which should aim to systematically analyze candidate biomarkers in the context of standardized training therapies.

In addition, in the context of routine clinical practice, a problem might be that current laboratory detection methods for some of the most promising markers, particularly ELISA analysis, might be too elaborate, time-consuming and expensive, prompting the need to refine and adapt them. Taken together, we can conclude that biomarkers to monitor training therapy in multimorbid OA patients are definitely within sight, with the most promising candidates being proinflammatory factors, or molecules linked to metabolism and cartilage decay. However, further studies, specifically with larger patient cohorts and modified detection strategies, have to be done before such protocols can be implemented in clinical routine.

Conflict of Interest
The authors have no conflict of interest.

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