METFORMIN AS A PROMISING ANTI-AGING AGENT IN THE TREATMENT OF OSTEOARTHRITIS

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Abstract
Osteoarthritis (OA) is traditionally considered an age-related disease. Therefore, repurposing drugs with the potential to reduce cell senescence is a justified therapeutic strategy. Such is the case of metformin, the most widely used antidiabetic medicine with well-known pharmacokinetics, acceptable toxicity, and beneficial metabolic effects. Metformin could significantly impact processes associated with aging and OA such as cellular senescence, inflammaging, mitochondrial dysfunction and impaired nutrient sensing. The aim of the present narrative review is to unveil the potential of metformin to modify disease course in light of aging osteoarthritic joints. The drug has pleiotropic effects on chondrocyte and extracellular matrix metabolism and may provide through AMPK-dependent and -independent pathways a meaningful improvement of OA. Mostly preclinical and retrospective cohort studies have shown that metformin exposure could lead to the regulation of cartilage homeostasis, symptomatic relief of pain and postpone surgery for those suffering from OA. Randomized control trials are warranted to justify the preliminary expectations.

Keywords: osteoarthritis; aging; metformin; cellular senescence

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Osteoarthritis (OA), a leading cause of disability and poor quality of life in the elderly [1], is one of the most significant health challenges for the modern aging society. Among others, advanced age is the most prominent risk factor for the onset and development of OA [2]. Historically, the term «osteoarthritis» was introduced to denote a common finding in clinical practice: tender and deformed joints in the elderly resulting from “wear and tear” of articular cartilage. However, this concept has undergone a tremendous shift in recent years due to our better understanding of pathogenic mechanisms [3]. We are now very aware that osteoarthritis is a condition that affects the entire joint and its adjacent tissues resulting in a syndrome of joint failure. Simultaneously with the major pathogenic breakthrough, new diagnostic tests are being actively developed and studied in the form of innovative biomarkers reflecting joint remodelling processes. Importantly, the expectations from the new therapies with orthobiologics, small molecules, and stem cells have not been met [4]. The area with the most unsatisfactory progress seems to remain non-surgical disease management. Importantly, the expectations from the new therapies with orthobiologics, small molecules, and stem cells have not been met [4].

Since the novel therapeutic options did not bring about any major effect on disease modification, researchers and clinicians were increasingly turning to repurpose relatively old synthetic drugs with pleiotropic use in diverse conditions. Such is the case of metformin, the most widely used antidiabetic medicine with well-known pharmacokinetics, acceptable toxicity, and beneficial metabolic effects. This drug has recently been suggested to attenuate the effects of aging by influencing essential pathological processes such as cellular senescence, impaired protein homeostasis, mitochondrial dysfunction, altered intercellular transmission, telomere attrition, epigenetic alterations, stem cell dysregulation, etc. [5].
Search strategy
For the purpose of the present narrative review, we adapted the recommendations of Gasparyan et al. [6], implementing a systematic approach to finding relevant articles. Thus, a search in the PubMed (MedLine) and Scopus databases was performed on 20.10.2022 and 23.10.2022 using the terms “osteoarthritis” and “metformin” to retrieve 67 and 413 articles, respectively. After the exclusion of irrelevant and duplicate articles and all reviews, 15 original research papers were selected and included in the “rationale for metformin use in osteoarthritis” section of the review. To provide contextual background, research articles and reviews were included that relied upon data from diverse database searches and previous knowledge of both authors.

Osteoarthritis as an age-related condition
OA is traditionally considered an age-related disease [2] since signs and symptoms occur predominantly in individuals after the fourth decade of life. The relationship between age and knee OA has been suggested to be non-linear with a sharp rise in incidence between 50 and 75 years of age [7]. In fact, OA pathogenesis is inextricably linked to pathological aging phenomena such as accumulation of oxidative stress, “inflammaging”, cellular senescence, mitochondrial impairment, dysregulated nutrient sensing, and energy metabolism, decreased autophagy, and alterations in cell signalling attributable to age-related changes in the extracellular matrix [8].

Inflammaging is an age-related condition characterized by elevated levels of blood inflammatory markers and associated with high susceptibility to chronic morbidities such as osteoarthritis [9]. Altered metabolic homeostasis plays a central role in promoting inflammation during the advancement of age. Other key factors are genetic susceptibility, gut microbiota, chronic infections, and intrinsic immune cell defects.

Key hallmarks of aging are immunosenescence and inflammaging [10]. Those processes are related to immune dysfunction and inflammation that occur with aging and include remodelling of immune system microarchitecture, resulting in unfavorable changes in the aging immune-competent cells and lymphoid organs [11]. Furthermore, inflammaging and cellular senescence in general are driven by dysregulated nutrient sensing [12], the ability of cells to recognize and respond to fuel substrates. A key regulator of cellular metabolism is 5’ adenosine monophosphate (AMP) activated protein kinase (AMPK) which is a heterotrimeric enzyme composed of a catalytic subunit (α) and two regulatory subunits (β and γ) [13]. AMPK activity is thought to reduce matrix catabolic responses to inflammatory cytokines (interleukin[IL]-1β and tumor necrosis factor[TNF]-α) [14] and the capacity of TNF-α and IL-8 to induce type X collagen expression [15]. Importantly, it is found to decrease in chondrocytes of aged mice and those with OA, as well as in injured bovine cartilage [16]. Additionally, AMPK activity is decreased in human OA articular chondrocytes and cartilage [15]. Therefore, AMPK pharmacologic activation may lead to a substantial change in the cellular environment resulting in regulation of nutrient-sensing homeostasis and a significant delay of inflammaging.

Metformin: an old friend with a new face
Chemically, metformin (1,1-dimethylbiguanide hydrochloride) is a biguanide containing two coupled guanidine molecules with additional substitutions [9,17]. Although metformin’s mechanism of action is thought to be attributable to the suppression of hepatic glucose production, the drug exhibits beneficial effects beyond glycemic control. Importantly, it has shown a reduced incidence of macrovascular complications in T2DM that could not solely be explained by its antiglycemic effects [18].

Metformin has a good safety profile with an insignificant risk for hypoglycemia and could be combined with other antidiabetic agents, including insulin. In addition, through the reduction of appetite and hyperinsulinemia, drug intake could lead to beneficial weight reduction in patients with T2DM [19]. Metformin remains the good old player in the modern treatment of T2DM. As suggested by recent evidence, metformin pleiotropic actions are not fully understood, as several targets and signalling pathways have been proposed [20].

Recent research has shown that metformin not only suppresses inflammatory response by improvement of metabolic proinflammatory parameters such as hyperglycemia, hyperinsulinemia, insulin resistance, and dyslipidemia but also has a direct anti-inflammatory effect itself [21]. Numerous studies have suggested that metformin suppresses chronic inflammation by inhibiting nuclear factor-κB (NFκB) through AMPK-independent and -dependent pathways [22,23,24].

The rationale for metformin use in osteoarthritis
Used as a frontline treatment for type 2 diabetes mellitus (T2DM), metformin is implicated in the treatment of diverse conditions associated with OA such as obesity, metabolic syndrome and prediabetes, and polycystic ovary syndrome [25].
Therefore, its beneficial effect on OA may be attributable to favorable metabolic changes and a reasonable question to consider is whether metformin impacts osteoarthritis “per se” or secondary due to confounding phenomenon.

A theoretical basis for the action of metformin in OA has been recently advanced based on preclinical research and retrospective registry-based studies. Metformin was shown to reduce apoptosis rate and catabolic processes in chondrocytes and diminish inflammation mediated by synovial macrophages [26]. Furthermore, two metformin targets, AMPK and growth differentiation factor 15, were associated with hip OA and its risk of development [27]. Another two studies showed that the AMPK/SIRT1 pathway implicated in cholesterol accumulation and autophagy was mitigated by metformin to preserve osteoarthritis chondrocytes [28] and protect against extracellular matrix degradation [27]. Evidence has suggested that metformin also influences the process of cellular senescence by activating AMPK dependent autophagy pathway [29]. AMPK-dependent pathways to impact proinflammatory processes and cellular senescence are summarized in Figure 1.

In experimental mouse models of advanced OA, metformin was found to suppress ferroptosis and pyroptosis in OA chondrocytes resulting in the reduction of disease alterations such as chondrocyte degradation, subchondral sclerosis and abnormal angiogenesis in the subchondral bone [30,31]. On another note, change in the microarchitecture of subchondral bone is a characteristic feature in patients with OA. In the process of bone remodelling, osteoclasts play the central role and metformin may attenuate their activity [32]. Metformin in combination with physical exercise prevents articular damage progression and metabolic dysfunction in estrogen-deficient and obese mice [33].

The proinflammatory cytokines most commonly associated with OA are IL-1β and TNF-α, produced by activated chondrocytes and synovial cells [34]. Both inflammatory mediators have procatabolic effects on cartilage metabolism by reducing collagen and proteoglycan production and increasing aggrecan release through the induction of degradative proteases [34]. IL-1β and TNF-α also induce chondrocytes and synovial cells to express additional inflammatory mediators such as IL-8, IL-5, nitric oxide, and prostaglandin E2. IL-1β actions are partially mediated by the SIRT3/PINK1/Park signaling pathway that was found suppressed by metformin in primary murine chondrocytes [35].

Data from the Osteoarthritis Initiative, a prospective cohort study, showed that metformin intake might have a favorable effect on long-term outcomes in patients with knee OA and obesity [36]. In a retrospective study, Lu et al. suggested that metformin therapy, prescribed for T2DM, in combination with a selective COX-2 inhibitor for OA pain was related to lower rates of arthroplasty. The authors hypothesized this could be due to the synergistic anti-inflammatory effect of the combination [37]. Real-world data from retrospective registry-based studies showed that metformin intake was linked to a reduction in knee pain in OA patients [38] and lower risk for total knee arthroplasty (TKA) with accumulative effectiveness over time in those with T2DM or obesity [38,39]. On contrary, Barnett et al. found no association between exposure to metformin and OA onset in patients with T2DM [40].

Conclusions
OA is commonly associated with other conditions characteristic of a sedentary lifestyle. Repurposing metformin may provide symptomatic relief and postpone surgery for those suffering from OA, a progressive disease leading to joint failure. While preclinical and retrospective studies have established a theoretical basis for metformin use in OA, randomized control trials are still warranted to elucidate metformin disease-modifying potential and place in the management of the disease.

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