Editorial

ANNALS OF MEDICINE & SURGERY

OPEN

Metformin: pioneering a path forward in knee osteoarthritis care?

Muhammad Wajeeh Anis, MBBS[a], Arham Iqbal, MBBS[a], Mohammad Ijlal Younus, MBBS[a], Ali Aamir, MBBS[b], Waheedullah Khalid, MBBS[c,*]

Osteoarthritis (OA) is a prevalent chronic articular disease characterised by cartilage degeneration, which results in a progressive reduction in cartilage mass owing to the loss of chondrocytes. This degeneration initiates a cycle of inadequate bone remodelling and concurrent destruction by inflammatory mediators. Symptoms commonly include severe pain, inflammation, and swelling that significantly affect daily activities[1]. Recent epidemiological data indicate a substantial global burden, with an estimated 240 million individuals worldwide experiencing symptomatic OA. Among individuals aged older than or equal to 60 years, ~10% of men and 18% of women are affected. According to recent findings from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), the age-standardised point prevalence and annual incidence rate of symptomatic, radiographically confirmed hip and knee OA had experienced notable increases since 1990, with rates of 3754.2 [Uncertainty Index (UI) 3389.4–4187.6) and 181.2 (UI 162.6–202.4)] per 100 000, respectively[2].

Current treatment landscapes

OA stands out among chronic aging conditions due to its limited options for effective therapies, none of which have demonstrated efficacy in slowing disease progression. Traditionally, management, as outlined by the American Academy of Orthopaedic Surgeons, has primarily relied on non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroid injections, with knee replacement surgery emerging as the sole viable option for advanced cases[3]. However, recent research published in the literature has uncovered a new facet: alongside its known antidiabetic properties, metformin has shown promise in mitigating the advancement of OA[4].

Metformin is a widely utilised pharmaceutical agent known for its significant benefits in glucose metabolism and the prevention of diabetes-related complications[5]. From a physiological standpoint, metformin has been observed to effectively decrease hepatic glucose production. However, not all of its effects can be solely attributed to this mechanism, as emerging evidence suggests a prominent role of the gastrointestinal tract, the gut microbial communities, and the tissue-resident immune cells[6]. At the molecular level, outcomes vary depending on the dosage and duration of metformin treatment, leading to discernible disparities between acute and long-term administration. Metformin operates through both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent pathways, inhibiting mitochondrial respiration, potentially inhibiting mitochondrial glycerophosphate dehydrogenase, and involving mechanisms associated with the lysosome. Over the past decade, our understanding of the effects of metformin on glycaemic control has evolved from a simplistic perspective attributing its efficacy solely to AMPK activation in the liver, to a significantly more intricate view acknowledging its multifaceted modes of action[7,8]. Therefore, exploring the novel effects of metformin may hold promise for the treatment of OA.

Recent research findings

According to a study published in April 2023, metformin attenuates OA by targeting chondrocytes, synovial macrophages, and adipocytes. This study concluded that metformin protects against knee OA, possibly by reducing apoptosis and catabolism of chondrocytes as well as by suppressing infiltration and inflammation by synovial macrophages[9]. This finding was supported by a systematic review published in November 2022, which found consistent evidence across pre-clinical and human studies supporting the beneficial effects of metformin on chondroprotection, immunomodulation, and pain reduction in knee OA[10]. Another study, published in September 2020, analysed metformin in relation to OA associated with destabilisation of the medial meniscus (DMM) surgery in experimental mice. Significant synovial hyperplasia and osteophyte formation were observed at both 6 and 12 weeks post-DMM surgery. However, metformin therapy administered either before or after DMM surgery markedly reduced these pathological changes, resulting in a significant reduction in cartilage degeneration and mitigating the progression of OA[11]. Therefore, the aforementioned study suggests that metformin administered shortly after knee injury can limit the development of OA in injury-induced animal models.

[a]Dow International Medical College, [b]Dow Medical College, Karachi, Pakistan and [c]Ariana University, Kabul, Afghanistan

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Department of Medicine, Ariana University, Kabul, Afghanistan. E-mail: waheedullahkhalid@gmail.com (W. Khalid).

Annals of Medicine & Surgery (2024) 86:4333–4335

Received 19 April 2024; Accepted 17 June 2024

Published online 24 June 2024

http://dx.doi.org/10.1097/MS9.0000000000002318

Table 1

Summary of clinical studies on metformin and osteoarthritis.

Author	Study design	Participants	Findings
Li *et al.*[6]	Randomised control trial	Patients with knee osteoarthritis	Metformin attenuates osteoarthritis by targeting chondrocytes, synovial macrophages, and adipocytes
Lim *et al.*[7]	Systematic review	Pre-clinical and human studies	Evidence supports beneficial effects of metformin on chondroprotection, immunomodulation and pain reduction in knee osteoarthritis
Li *et al.*[8]	Experimental mouse model	Mice with destabilization of the medial meniscus	Metformin administration reduces synovial hyperplasia and osteophyte development after knee injury
Feng *et al.*[9]	Experimental model	Animal model of osteoarthritis	Metformin mitigates cartilage degeneration by modulating AMPK/mTOR signalling pathways
Yan *et al.*[10]	Laboratory-based experimental study	Chondrocytes from osteoarthritis patients	Metformin treatment inhibited microRNA-34a while promoting SIRT1 expression in OA chondrocytes
Zheng *et al.*[11]	Laboratory-based experimental study	Synovial M1 macrophages isolated from osteoarthritis patients	Metformin attenuates the inflammatory response via the regulation of synovial M1 macrophages in osteoarthritis

AMPK, AMP-activated protein kinase; OA, osteoarthritis.

Recent research has provided valuable insights into the underlying causes of OA. These studies have revealed certain markers and signalling pathways, such as the AMPK/mTORC1 pathway, that play a crucial role in the development of OA. Consistent with these findings, a study conducted in January 2020 examined the impact of metformin on an experimental model of OA. The results showed that metformin effectively mitigated cartilage degeneration by modulating the AMPK/mTOR signalling pathway[12]. These findings strongly suggest that metformin holds great promise as a potential treatment for OA, offering hope for improved outcomes in patients suffering from this condition.

Data from a recent study suggest that metformin modulates chondrocyte senescence and proliferation through the microRNA-34a/SIRT1 pathway, indicating its potential as a novel strategy for treating OA. According to this study, metformin treatment at 1 mM inhibited microRNA-34a while promoting SIRT1 expression in OA chondrocytes. Both miR-34a mimics and siRNA targeting SIRT1 suppressed SIRT1 expression in chondrocytes. MTT and colony formation assays revealed that metformin enhanced chondrocyte proliferation, which was diminished by the introduction of miR-34a mimics or siRNA-SIRT1. Furthermore, western blot results demonstrated that metformin suppressed the expression of senescence-associated protein P16, pro-inflammatory cytokine IL-6, and catabolic gene MMP-13, while elevating the expression of anabolic proteins such as collagen type II and Aggrecan. These effects can be attenuated by transfection with miR-34a mimics[13]. Moreover, another study published in March 2023 demonstrated that metformin inhibits the M1 polarisation of synovial sublining macrophages, which promotes synovitis and exacerbates OA, thus reducing cartilage loss. In this study, metformin prevented the secretion of pro-inflammatory cytokines by M1 macrophages, suppressed the inflammatory response of chondrocytes cultured in conditioned medium (CM) from M1 macrophages, and attenuated the migration of M1 macrophages induced by interleukin-1ß (IL-1ß)-treated chondrocytes *in vitro*[14]. Overall, this study highlights the therapeutic potential of metformin in targeting synovial M1 macrophages in OA.

Clinical implications and future directions

Combining metformin with disease-modifying anti-rheumatic drugs (DMARDs) and implementing early intervention strategies after joint injury may offer significant benefits in slowing knee OA progression and improving long-term outcomes[15]. To support this conclusion, it is necessary to reference a retrospective, matched-cohort study conducted in Taiwan, which demonstrated that patients with and type 2 diabetes mellitus (T2DM) who received combination therapy comprising COX-2 inhibitors and metformin exhibited lower rates of joint replacement surgery compared to those not receiving such therapy. This observed reduction in joint replacement surgery rates may be attributed to the combination therapy's more pronounced decrease in pro-inflammatory factors compared with individuals not undergoing metformin therapy[16]. A critical link emerges between these findings and the broader discourse on integrating metformin into OA management strategies, particularly for patients with diabetes who are at risk for knee OA. This integration is supported by various studies, as summarised in Table 1, which further advocates the inclusion of metformin in comprehensive OA treatment protocols. Despite these promising results, not all studies have reached consistent conclusions. Potential influencing factors include incomplete adjustment for confounding variables and limitations in the accuracy of OA diagnostic modalities. In addition, the exclusive examination of metformin administration in diabetic cohorts, without a detailed exploration of dosage regimens and treatment durations, may introduce variability in the interpretation of study outcomes[17]. Current clinical studies predominantly focus on patients with diabetes, probably because of metformin's primary role in glycaemic control, thereby limiting its direct evaluation in non-diabetic populations for osteoarthritis prevention. Therefore, future research should explore the optimal dosing regimens, long-term effects, and potential synergies with existing therapies. Additionally, investigating the role of metformin in specific OA subtypes and elucidating its broader implications on joint health are essential for advancing OA management strategies.

Conclusion

Recent research has highlighted the potential of metformin to attenuate cartilage degeneration, modulate inflammatory pathways, and target key cellular processes implicated in OA pathogenesis. These findings suggest that metformin may serve as a valuable adjunct therapy, particularly in diabetic patients at risk of knee OA, and could potentially offer benefits in slowing disease progression and improving long-term outcomes. With

continued research and exploration, metformin has the potential to revolutionise the management of OA and enhance the quality of life of millions of individuals worldwide, including people with diabetes or metabolic abnormalities, and those experiencing age-related joint cartilage degeneration.

Ethical approval

Ethics approval was not required for this editorial article.

Consent

Informed consent was not required for this editorial article.

Source of funding

The authors did not receive any funding for this work.

Author contribution

M.W.A.: conceptualization; supervision; writing—original draft. A.I.: conceptualization; supervision; writing—original draft. M.I.Y.: conceptualization; writing—original draft. A.A.: conceptualization; visualisation; writing—original draft; writing—review and editing. W.K.: conceptualization; writing—original draft.

Conflicts of interest disclosure

One of the authors, Ali Aamir, declares a conflict of interest, as he is currently serving as a reviewer for the Annals of Medicine and Surgery. The other authors have no conflicts of interest to declare.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Muhammad Wajeeh Anis, Arham Iqbal, Ali Aamir.

Data availability statement

Data sharing is not applicable to this article.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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