REVIEW

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Does metformin administration improve fracture healing? A systematic review of preclinical studies

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Introduction: **Fracture healing plays a critical role in the recovery from bone injuries and functional mobility. However, conditions such as diabetes mellitus increase the vulnerability to disruptions in this process. Diabetes, a systemic inflammatory disorder, is associated with impaired osseus healing and increased fracture vulnerability. Metformin, an oral antidiabetic medication, has shown potential in enhancing fracture healing; however, its clinical effectiveness remains controversial. We aim to elucidate the effects of metformin on fracture healing and explore potential mechanisms of action.**

Methods: **Systematic literature search was performed in PubMed, ScienceDirect, and Google Scholar until January 17, 2024. Criteria encompassed English-language, peer-reviewed articles using in vivo models. This systematic review was conducted in accordance with PRISMA guideline.**

Results: **A total of 7 studies were included in this study. Diabetes impedes fracture healing through inflammation-induced osteoblast cell death, and metformin, commonly prescribed for diabetes, exhibits anti-inflammatory properties. Studies indicated metformin's positive effects on bone repair through AMPK activation, increased collagen production, and enhanced angiogenesis. However, some studies reported inferior bone quality and limited impact on normoglycemic conditions.**

Conclusion: **Metformin emerges as a promising adjunct in fracture healing, particularly in diabetic patients, by promoting osteogenesis and controlling chronic inflammation. Contradictory findings necessitate further research to clarify metformin's effects on bone healing, urging a comprehensive understanding for potential clinical applications and improved patient outcomes.**

Keywords: Metformin, diabetes, fracture healing.

INTRODUCTION

Fracture healing is an essential process for the recovery and mobility of individuals following bone fractures. The susceptibility to disruptions caused by various factors, including as ageing, systemic illnesses, and metabolic irregularities like type 2 diabetes, is evident. Critical to optimising bone healing outcomes, the controlled inflammatory response has a substantial impact on the bone healing process. In addition to other systemic and chronic inflammatory diseases, diabetes impedes the process of bone repair[1].

Fractures were more likely to occur in patients with uncontrolled hyperglycemia, who also exhibited accelerated fracture healing[2]. Despite having a normal bone density, diabetics are more prone to experiencing fractures[3]. It is hypothesised that these arise from modifications in the microarchitectural characteristics that are linked to diabetes[4].

Metformin, a frequently prescribed oral medication for diabetes, has been recognised as a potential therapeutic agent for augmenting the healing process of bone fractures[5]. Metformin is a pharmaceutical agent that reduces hyperglycemia by impeding the synthesis of glucose in the liver[6]. Metformin has osteogenic properties in controlled environments, fostering the growth and specialisation of osteoblasts, according to a number of studies[7]. The ongoing debate surrounds the effectiveness of metformin in facilitating the process of fracture repair, notwithstanding favourable results observed in preclinical investigations.

We aim to evaluate the effect of metformin on bone health due to the increasing prevalence of type-2 diabetes mellitus worldwide, which increases the risk of fractures[7]. The main question to be addressed is the impact of metformin on the process of fracture healing and the specific pathways via which it exerts its therapeutic effects, considering the existing gaps in information.

The aim of this systematic review is to elucidate the influence of metformin on the process of fracture healing. Furthermore, its objective is to ascertain the potential mechanisms through which metformin impacts bone tissue development and expedites the bone regeneration process. The objective of our work is to offer guidance for future research and clinical interventions, ultimately aiming to improve the outcomes of patients with impaired fracture healing.

METHODS

This systematic review adheres to the guidelines outlined by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).

Eligibility criteria

Participants

This systematic review encompasses preclinical in vivo experiments investigating fracture healing in mice or rats.

Interventions

The intervention investigated in this review is metformin in fractured mice or rats.

Outcomes

The results encompass fracture healing assessed using biochemical and radiographic analysis.

Study characteristics

The titles and abstracts were examined to ascertain their pertinence. We employed an extensive array of research approaches, encompassing systematic review, meta-analysis, randomised controlled trials, observational studies, and preclinical trials. We excluded articles for which the full texts were not accessible. Therefore, we selected seven thorough original research papers that are pertinent to the subject.

Inclusion and exclusion criteria

Articles meeting the following criteria were included: original peer-reviewed articles published only in English, utilising mice or rat models in vivo, and published between January 1, 2010, and January 17, 2024. Review articles and remarks were not considered. The following conditions determined the exclusion criteria for papers: intended non-unions, non-healing, or non-stabilized fractures; presence of critical-sized defects; additional fractures of other bones in the same animal; isolated fractures of other bones; absence of fractures; species other than mice or rat; and models designed to induce osteitis or other infections.

Information sources

A thorough literature search was conducted using many online journal databases, such as PubMed, ScienceDirect, and Google Scholar. No language restrictions were applied. In addition, the search also encompassed grey literature sources, such as conference abstracts and theses. The search was carried out in October 2023.

Search strategy

The search strategy employed the keywords ‘Metformin, ‘Bone’, ‘Fracture’, ‘Healing’. The Boolean operations AND, OR, and NOT were utilised. After removing unnecessary research, we evaluated the titles and abstracts of the remaining papers. The full-text studies were examined based on the indicated eligibility criteria. Furthermore, the bibliographies of the chosen study were additionally scrutinised to locate supplementary works that may be integrated. Three independent researchers were recruited to conduct article screening and subsequent data analysis.

Evidence and quality appraisal

The studies were subjected to thorough examination using the Oxford Centre for Evidence-Based Medicine levels of evidence. The clinical data was subsequently categorised into five distinct groups, denoted as I to V, with Ia being the most substantial degree of evidence.

RESULTS

Literature search

At first, a total of 61 items were obtained during the initial search. After eliminating duplicate publications and evaluating abstracts, a total of 29 research studies remained. Seven studies were chosen according to the predetermined criteria for inclusion.

Study characteristics

This review included a total of 7 studies. There are a total of seven animal experiments involved in the inquiry. All experiments conducted using mice or rats. The data about the study features, experimental conditions, and variables were collected and examined. The study’s attributes are documented in Table I.

Risk of Bias assesesment

All studies were assessed using SYRCLE’s risk of bias tool. Table was shown in Table II.

Table I. — Characteristics of the study.

Authors	Year	Country	Subject	Sample sizes	Bone Injury Model	Daily Dose	Follow up duration	Study Result	Study Design
Guo et al.[8]	2023	United States	12-week-old MKR and WT mice BMSC cell culture	Not mentioned	- Femoral close fracture - Radius non-union fracture - Femoral drill hole	200mg/kg for 14 days	31 days	Metformin reverses the delay of bone healing and remodelling of hyperglycaemic mice at cellular level by increasing proliferation and differentiation of BMSC, but has no significant effect on normal blood glucose level mice	Experimental
Jeyabalan et al.[7]	2013	England	16-week-old female C57BL/6 mice post-OVX Wistar Rats	9 OVX mice in each group 10 rats in each group	Femoral fracture	OVX Mice: 100mg/kg Rats: 200-240mg/kg	28 days	Metformin has no significant effect on bone loss induced by ovariectomy in mice	Experimental
Khan et al.[9]	2015	India	WT and diabetic mice	Not mentioned	No fracture	350mg/kg	31 days	Metformin improved trabecular microarchitecture and increased bone strength and periosteal cells through AMPK pathway which activates PGC-1a expression and subsequently increases osteoblast differentiation	Experimental
La Fontaine et al.[15]	2016	United States	14-week-old male ZDF rat	12 lean rats (lean group) 12 diabetic rats (DM group) 12 diabetic rats treated metformin (DM + Metformin group).	Femoral fracture	300mg/kg	42 days	Diabetes decreases biomechanical properties in rats, and metformin causes adverse effect on the fracture load even more	Exerimental
Ruan et al.[5]	2023	China	8-week-old male wild-type mice 10-week old female post-OVX mice BMSC and BMM cell culture	20	Femoral fracture	150mg/kg	42 days	Metformin promotes angiogenesis in vitro and in vivo by inhibiting YAP1/TAZ in endothelial cells which increases formation of type H vessels and in turn helps in bone healing	Experimental

Table I. — Characteristics of the study - continued.

Smieszek et al.[11]	2018	Poland	4-month-old male Wistar rats rASC culture	With cranial defect (n = 18); without cranial defect (n = 18), each divided into control (n = 6), 100 mg/kg metformin (n = 6), and 250 mg/kg (n = 6)	Cranial defect	100 mg/kg 250 mg/kg	4 weeks	Metformin promotes the osteogenesis of rASCs, increases formation of mineralized extracellular matrix rich calcium and phosphorous deposits, In vivo, metformin accelerated bone healing and formation of mature tissue at a fracture site in rat cranial defect model.	Experimental
Zhu et al.[12]	2023	China	8-week-old male rats Neutrophils isolated from C57BL/6 mice	40 divided into 4 groups (n = 10): the control group, the high glucose group, the high glucose with DNase I treatment group, and the high glucose with metformin	Femur	150 mg /kg	28 days	Metformin promotes bone growth through increasing osteogenesis by inhibiting hyperglycaemia-induced NET formation	Exerimental

AMPK= AMP-activated protein kinase; BMM = bone marrow-derived macrophages; BMSC= Bone Marrow Stromal Cells; DM = diabetes mellitus; MKR = hyperglyacemic mouse model; NET = Neutrophil Extracellular Trap; OVX = ovariectomy; rASC = rat adipose-derived multipotent mesenchymal stromal cells; WT = wild type; ZDF = Zucker diabetic fatty.

Table II. — SYRCLE's risk of bias tool assessment result.study.

Author(s)	Selection Bias			Performance Bias		Detection Bias		Attrition Bias	Reporting Bias	Other
	Was the allocation sequence adequately generated and applied?	Were the groups similar at baseline or were they adjusted for confounders in the analysis?	Was the allocation to the different groups adequately concealed during?	Were the animals randomly housed during the experiment?	Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	Were animals selected at random for outcome assessment?	Was the outcome assessor blinded?	Were incomplete outcome data adequately addressed?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could result in high risk of bias?
Guo et al.[8]	UC	Y	UC	Y	UC	Y	UC	Y	Y	Y
Jeyabalan et al.[7]	UC	UC	UC	Y	UC	Y	UC	Y	Y	Y
Khan et al.[9]	UC	Y	UC	UC	UC	Y	UC	Y	Y	Y
La Fontaine et al.[15]	UC	UC	UC	Y	UC	Y	UC	Y	Y	Y
Ruan et al.[5]	UC	Y	UC	Y	Y	Y	UC	Y	Y	Y
Smieszek et al.[11]	UC	Y	UC	Y	Y	Y	UC	Y	Y	Y
Zhu et al.[12]	UC	UC	UC	Y	UC	Y	UC	Y	Y	Y

DISCUSSION

Diabetes mellitus impedes fracture healing by reducing the creation of new bone cells (osteoblastogenesis) due to reduced expression of genes that regulate osteoblast development[8]. Individuals with diabetes experience persistent inflammation. An increased inflammatory condition initiates osteoblast apoptosis and extends the longevity of osteoclasts[9].

The process of fracture healing consists of several separate stages: hematoma formation, granulation tissue production, bony callus formation, and bone remodelling. Metformin is the primary medication recommended for the treatment of diabetes. Research has demonstrated that it decreases the likelihood of fractures in individuals with diabetes when compared to those who use alternative antidiabetic medications[10]. Metformin exhibits anti-inflammatory properties and enhances the resolution of chronic inflammation in individuals diagnosed with diabetes[9]. Our study findings indicate that metformin enhances bone healing by employing several pathways during distinct phases of the fracture healing process.

With the exception of the studies conducted by Jeyabalan et al. and La Fontaine et al., all other research findings concur that metformin efficiently stimulates adenosine monophosphate-activated protein kinase (AMPK), a crucial component in the process of osteogenesis. It enhances the balanced development of bone marrow stromal cells, promoting the formation of osteoblasts and suppressing their transformation into adipocytes. The observed effects include increased cellular proliferation and the development of bone tissue, as evidenced by the enhanced production of type 1 collagen, alkaline phosphatase activity, and expression of bone-morphogenetic protein-2. Furthermore, it enhances the activity of PGC-1a.[5,9,11–13] Mu et al. conducted a study showing that metformin increases the phosphorylation of AMPKa, a component of AMPK found in bone tissue, primary osteoblasts, and osteoclasts[14].

Khan, Zhu, Guo, and Ruan et al. utilised micro-CT scanning to evaluate bone regeneration post-fracture. Consensus was reached among all participants that samples subjected to metformin treatment consistently exhibited superior healing outcomes across all time intervals[5,9,11,12]. The data suggests that metformin could serve as a viable alternative treatment for fractures in diabetic people.

Ruan et al. suggested that metformin has the potential to improve bone regeneration via stimulating angiogenesis, namely the development of type H capillaries. Metformin was discovered to enhance the growth of endothelial cells and increase the production of vascular endothelial growth factor in sites of bone fractures[5].

In contrast to previous research, Jeyabalan et al. discovered that metformin has no substantial impact on bone loss in mice induced by ovariectomy, a disease marked by reduced levels of oestrogen. Ovariectomy replicates the consequences of menopause in women afflicted with osteoporosis. Irrespective of the timing, the administration of metformin medication did not have any impact on the activity of AMPK, a crucial element in bone formation. Metformin administration for a short duration leads to the phosphorylation of AMPK in the liver, but has minimal impact on AMP phosphorylation in bone. The researchers determined that metformin does not stimulate the production of gene markers that are unique to osteoblasts[7].

Guo et al. demonstrated that metformin promotes bone repair in mice with high blood sugar levels, but does not affect mice with normal blood sugar levels[9]. These findings indicate that metformin primarily targets the normalisation of increased blood glucose levels, rather than directly influencing the bone repair process.

La Fontaine et al. observed that while metformin facilitates bone repair, the resulting bone integrity is inferior when compared to individuals without diabetes[15]. These findings indicate that hyperglycemia, which refers to elevated blood sugar levels, continues to impact the bone healing process despite treatment with metformin. On the other hand, metformin can have a negative impact on the strength and structure of bones, resulting in decreased mechanical qualities of newly developed bone following a fracture.

Metformin plays a crucial role in adipose-derived stem cell (ASC) research, particularly in the context of diabetes treatment. This assertion is substantiated by a study carried out by Zhang et al., which examined this particular molecule. ASCs have been discovered to exhibit a twofold impact on their capacity to produce bone tissue under particular circumstances. Metformin functions as a protective measure in a hyperglycemic setting, preserving the ability of ASCs to undergo osteogenesis, the process of converting these stem cells into bone cells. This preventive effect is especially crucial in circumstances of heightened blood glucose levels linked to diabetes. In addition, metformin enhances the osteogenesis process in ASCs in the context of osteoporosis caused by diabetes[16].

SYRCLE's risk of bias tool was used in this study. Several domains showed widespread unclear

risks, such as allocation concealment, blinding of caregivers, and blinding of outcome assessors. Lack of reporting is the main reason of these unclear risks. Variations in the species and age of study subjects, different bone injury models, and different metformin dosing regimens prevented the high-quality meta-analysis to be conducted.

We noticed divergent outcomes, particularly with the specific attributes that metformin influences in the bone regeneration process. The observed disparities can be attributed to variations in methodology, duration of treatment, and therapeutic levels of metformin. Eventhough the current evidence is still preclinical and mixed, the findings of our analysis offer the use of metformin as a promising candidate to improve bone repair.

We acknowledge some studies about metformin in bone defects or osseointegration models were excluded by study design. Latest researches in non-union fracture models and combination therapy may have been published since our search period. Therefore, further in vivo research and well-designed clinical trials are necessary to provide continuous emerging evidence and authenticate the efficacy of metformin as a supplementary treatment for the process of bone fracture repair.

CONCLUSION

In conclusion, preclinical studies show metformin holds promising medication as an advantageous adjunctive therapy in the context of bone fracture healing. It promotes the repair of fractures in diabetes by increasing the generation of fresh bone tissue, improving the microstructure of the bone, and managing chronic inflammation. Persistent inconsistencies in the data require further and larger investigation whether in animals or humans to achieve a more definitive understanding of the effect of metformin on bone regeneration, in order to improve patient therapy.

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