

## Case Control Study

# Effects of different doses of metformin on bone mineral density and bone metabolism in elderly male patients with type 2 diabetes mellitus

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## Abstract

### BACKGROUND

Diabetes is a chronic disease, which may cause various complications. Patients with diabetes are at high risk of bone and joint disorders, such as osteoporosis and bone fractures. In addition, it became widely accepted that diabetes has an important impact on bone metabolism. Metformin is a commonly used and effective first-line treatment for type 2 diabetes. Some glucose-lowering agents have been found to have an effect on bone metabolism. The present study explored if different doses of metformin have an effect on bone mineral density (BMD) and bone metabolism in type 2 diabetes.

### AIM

To investigate the effects of different doses of metformin on BMD and bone metabolism in elderly male patients with type 2 diabetes mellitus.

### METHODS

A total of 120 elderly male outpatients with type 2 diabetes mellitus who were admitted to our hospital were included in the study from July 2018 to June 2019. They were randomly assigned to an experimental group and a control group with 60 patients in each group. Patients in the experimental group were given high dose metformin four times a day 0.5 g each time for 12 wk. Patients in the control group were given low dose metformin orally twice a day 0.5 g each time for 12 wk. The changes in bone mineral density and bone metabolism before and after

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treatment and the efficacy rate of the treatment were compared between the two groups.

## RESULTS

There was no significant difference in the efficacy rate between the two groups ( $P > 0.05$ ). Before the treatment, there was no significant difference in BMD and bone metabolism between the two groups ( $P > 0.05$ ). However, after the treatment, BMD and bone metabolism were improved in the two groups. Moreover, BMD and 25-hydroxyvitamin D were significantly higher in the experimental group than in the control group, and N-terminal/midregion and  $\beta$ -isomerized C-terminal telopeptides were significantly lower in the experimental group than in the control group (all  $P < 0.05$ ). There was no significant difference in the incidence of adverse reactions between the two groups ( $P > 0.05$ ).

## CONCLUSION

Both high and low dose metformin can effectively control the blood glucose levels in elderly male patients with type 2 diabetes mellitus. However, the benefits of high dose metformin in improving BMD and bone metabolism level was more obvious in patients with type 2 diabetes mellitus.

**Key Words:** Dosages; Metformin; Type 2 diabetes mellitus; Elderly male patients; Bone mineral density; Bone metabolism

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**Core Tip:** In the last two decades, metformin has been a widely used medicine in the treatment of diabetes. It has been proven to have additional benefits in anticancer and antiaging beyond glycemic control. To answer whether it has a positive effect on bone mineral density and bone metabolism, the present study compared the outcomes of bone mineral density and bone metabolism between different doses of metformin in patients with type 2 diabetes. The results supported that a comparatively higher dose of metformin helped to improve bone mineral density and bone metabolism levels in patients with type 2 diabetes.

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## INTRODUCTION

The incidence of chronic diseases has increased due to the improvements in people's living conditions. Type 2 diabetes, as one of the common chronic diseases, is threatening people's health to a considerable degree<sup>[1,2]</sup>. It may raise the risk of osteoporosis, which is mainly caused by the decreased insulin sensitivity or lack of insulin production in elderly male patients. Accordingly, interests of clinical studies are focused on exploring optimum therapies to control the blood glucose levels and meanwhile improve osteoporosis in elderly male patients with type 2 diabetes mellitus<sup>[3,4]</sup>. Currently, metformin is widely used in the treatment of type 2 diabetes. However, there is a contradiction in the statements on different dosages of metformin on bone mineral density (BMD) and bone metabolism in elderly male patients with type 2 diabetes mellitus<sup>[5]</sup>. On this account, the present study analyzed the effects of different dosages of metformin on BMD and bone metabolism in 120 patients with type 2 diabetes.

## MATERIALS AND METHODS

### Participants

A total of 120 elderly male patients with type 2 diabetes mellitus who visited The Third Hospital of Hebei Medical University's outpatient clinics were included from July 2018 to June 2019. All of them meet the diagnostic criteria for type 2 diabetes and received necessary examinations including routine blood test, coagulation test, transcranial Doppler test and head computed tomography scan. According to the sequences of hospitalization admission, they were assigned to an experimental group and a control group with 60 patients in each group. The age range was 61 to 83 ( $72.12 \pm 5.68$ ) years for the experimental group and 62 to 84 ( $72.57 \pm 5.63$ ) years for the control group. Patients in the experimental group had 2 to 15 years ( $8.84 \pm 2.35$ ) of disease duration, and patients in the control group had 3 to 16 years ( $8.99 \pm 2.15$ ) of disease duration. There was no significant difference in general information in patients between the two groups ( $P > 0.05$ ).

### Inclusion criteria

Patients who meet any of the following diagnostic criteria were included in the study: Fasting blood sugar  $\geq 7.0$  mmol/L; two-hour postprandial glucose  $\geq 11.1$  mmol/L; normal random glucose  $\geq 11.1$  mmol/L based on 2017 Guideline for the Prevention and Management of Type 2 Diabetes<sup>[6]</sup>. Additional criteria included patients without previous history of cerebral hemorrhage or cerebral infarction complicated with hemiplegia. Patients who were diagnosed with tumors were excluded from the study. All the participants signed an informed consent statement, and the study was approved by our hospital ethics committee.

### Methods

Metformin (0.5 g, Cat. # H32021625, Suzhong Pharmaceutical Group Co., Ltd., Taizhou, China) was administrated to patients in both groups. In the experimental group, metformin was dosed at 0.5 g four times daily with 2 g total daily dose. In the control group, metformin was initially dosed 0.5 g twice daily with or after meals and the maximum daily dose was 1 g. The treatment lasted for 12 wk in both groups.

### Measurements

Clinical effectiveness was compared between the two groups according to the levels of blood glucose. The effectiveness was defined as stabilization of fasting and postprandial blood glucose levels to the normal range without complications. Effective blood glucose control was defined as blood glucose levels close to the normal range without severe complications. Ineffectiveness was defined as blood glucose levels that were still high<sup>[7,8]</sup>. BMD for lumbar vertebra of L1-4 and hip was measured by dual-energy X-ray absorptiometry (Horizon DXA system, Manufacturer: Hologic, Inc., USA, Model: Discovery A) before and after the treatment. Bone metabolic markers were compared between the two groups. Levels of N-terminal midfragment of osteocalcin,  $\beta$ -isomerized C-terminal telopeptides and 25-hydroxyvitamin in the blood were measured by Infinite F50 ELISA reader. The incidence of complications was observed in the duration of medication.

### Data processing

Data that were counted or measured in the study were statistically analyzed using SPSS19.0. The  $\chi^2$  test was used to evaluate a relationship between two categorical variables, and the counted data was expressed as a percentage. Student *t* test was used for measured data. A *P* value  $< 0.05$  was considered statistically significant.

## RESULTS

### Efficacy of treatment

There was no significant difference in the treatment efficacy between the two groups (Table 1).

### Changes in BMD and bone metabolic markers

There was no significant difference in the levels of BMD and bone metabolic markers between the two groups before the treatment ( $P > 0.05$ ). After the treatment, levels of BMD and bone metabolic markers were improved. To be specific, levels of BMD and

Table 1 Comparison of efficacy between the two groups, *n* (%)

Groups	Well-controlled	Effectively-controlled	Ineffective	Overall efficacy
Control group	38	19	3	57 (95.00)
Experimental group	40	18	2	58 (96.67)
$\chi^2$				0.349
<i>P</i> value				> 0.05

25-hydroxyvitamin D were higher in the experimental group than in the control group (all  $P < 0.05$ ). However, levels of N-terminal midfragment and  $\beta$ -isomerized C-terminal telopeptides were lower in the experimental group than in the control group (all  $P < 0.05$ , Table 2).

### Complications in the two groups

Complications occurred in three patients in the control group during the administration of medication including nausea in one patient, dizziness in one patient and gastrointestinal reactions in one patient. Comparatively, complications were reported in two patients in the experimental group during the administration of medication including dizziness in one patient and nausea in one patient. These complications disappeared after discontinuation of the study medicines, which did not have an effect on the treatment efficacy. Therefore, there was no significant difference in the incidence of complications between the two groups ( $P > 0.05$ ).

## DISCUSSION

Risk of osteoporosis is increased with the development of type 2 diabetes. Osteoporosis may occur in patients with type 2 diabetes for a variety of reasons. First, type 2 diabetes makes blood glucose higher than normal for a long time, which means a large amount of glucose is excreted in the urine, and islet function is influenced gradually. Furthermore, a large amount of calcium and phosphate ions in serum is excreted out of the body by osmotic diuretics. In that, the decreased blood calcium and phosphate concentrations may lead to osteocyte dysfunction<sup>[9,10]</sup>. Second, the poor blood glucose control may cause accumulation of glycosyl compound that may further promote oxidative stress and then lead to osteopenia and myelosuppression. All of this may have adverse effects on osteoblast and bone formation<sup>[11,12]</sup>. In another way, physical activity is not low in elderly male patients. Microstructure impairment at subchondral bone is more likely to occur resulting from bone disorders where the bone remodeling process occurs too frequently. This increases the possibility of fracture. Metformin as the first-line treatment for type 2 diabetes shows good efficacy in lowering blood glucose. Meanwhile, it greatly improves BMD in patients with type 2 diabetes, and its role in bone tissues is now increasingly being mentioned and discussed<sup>[13]</sup>.

The present study examined the effect of different dosages of metformin on BMD and bone metabolism in elderly male patients with type 2 diabetes mellitus. The results showed that there was no significant difference in the treatment efficacy between the two groups ( $P > 0.05$ ). Before the treatment, there was no significant difference in BMD and levels of bone metabolism markers between the two groups ( $P > 0.05$ ). However, BMD and levels of bone metabolism markers were improved in the two groups after the treatment. To be specific, BMD and levels of 25-hydroxyvitamin D were higher in the experimental group than in the control group and levels of N-terminal midfragment and  $\beta$ -isomerized C-terminal telopeptides were lower in the experimental group than in the control group (all  $P < 0.05$ ). It revealed that a high dosage of metformin can help to improve osteoporosis as well as control blood glucose in elderly male patients with type 2 diabetes mellitus.

Metformin can promote the osteogenic differentiation and mineralization of induced mesenchymal stem cells, which are derived from pluripotent stem cell and can differentiate into many cell types such as adipocytes, osteoblasts and chondrocytes. Its effect on differentiation can be regulated by cellular transcription factors<sup>[14,15]</sup>. Several animal experiments reported that metformin may enhance and induce osteogenic differentiation of mesenchymal stem cells. *In vitro* studies revealed that metformin may increase type I collagen synthesis, alkaline phosphatase activity,

**Table 2 Comparison of levels of bone mineral density and bone metabolic markers between the two groups**

Groups	n	BMD, g/cm <sup>2</sup>		N-MID, ng/mL	β-CTx, pg/mL	25(OH)D, ng/mL
		Lumbar L <sub>1-4</sub>	Hip			
Control group						
Before the treatment	60	0.71 ± 0.13	0.62 ± 0.09	19.35 ± 8.14	498.57 ± 210.02	9.54 ± 3.67
After the treatment	60	0.88 ± 0.17 <sup>a</sup>	0.76 ± 0.15 <sup>a</sup>	15.54 ± 5.23	376.27 ± 157.45	17.97 ± 5.74
Experimental group						
Before the treatment	60	0.73 ± 0.11	0.64 ± 0.08	20.41 ± 8.13	504.74 ± 237.41	9.23 ± 2.84
After the treatment	60	1.04 ± 0.25 <sup>ab</sup>	0.93 ± 0.20 <sup>ab</sup>	10.68 ± 4.24 <sup>ab</sup>	310.64 ± 146.83 <sup>ab</sup>	25.96 ± 6.91 <sup>ab</sup>

<sup>a</sup>*P* < 0.05 *vs* before the treatment;

<sup>b</sup>*P* < 0.05 *vs* the control group after the treatment. 25(OH)D: 25-hydroxyvitamin D; β-CTx: β-isomerized C-terminal telopeptides; BMD: Bone mineral density; N-MID: N-terminal midfragment.

extracellular calcium deposition and osteocalcin synthesis and may repair bone lesions in rats with diabetes<sup>[16]</sup>.

Moreover, metformin can inhibit osteoclast differentiation and reduce the activity of C-terminal propeptides of type I collagen. Metformin's effect on bone metabolism is realized through several ways in patients with diabetes mellitus including activating the extracellular signal-regulated kinase and AMP-activated protein kinase signaling pathway, changing the expression of bone morphogenetic proteins and nitric oxide and influencing osteoblasts<sup>[17]</sup>. When used at high doses, metformin can reduce blood glucose, inhibit advanced glycation end product deposition, relieve injuries to the thigh and induce the osteogenic differentiation<sup>[18,19]</sup>. Similarly, the present study revealed that the relationship between osteoporosis and blood glucose levels should be taken into consideration in addition to usage of osteogenic promoting agents in the treatment of type 2 diabetes complicated with osteoporosis in elderly patients. In this way, the treatment efficacy will be improved greatly in these population<sup>[20]</sup>.

## CONCLUSION

In conclusion, both high and low dose metformin can effectively control blood glucose in elderly male patients with type 2 diabetes mellitus. Comparatively, a high dosage of metformin may help to improve BMD and bone metabolism. However, the influence of high metformin concentration in inhibiting bone formation should be cautioned. Further studies are needed to assess the optimum dosage of metformin.

## ARTICLE HIGHLIGHTS

### Research background

Patients with diabetes mellitus may develop skeletal complications including osteopenia, osteoporosis and even fracture. Although metformin is used as an antidiabetic rather than an antiosteoporotic medicine, it is essential to examine the effects of metformin on bone metabolism because it is a widely used medication to treat diabetes in this population.

### Research motivation

By comparing different doses of metformin on bone metabolism and bone mineral density (BMD) in patients with type 2 diabetes, the optimal dose of metformin will be estimated to achieve the benefits of bone protection beyond glycemic control.

### Research objectives

The aim of this study is to compare the effects of a high dose *vs* low dose of metformin on BMD and bone metabolism in patients with type 2 diabetes mellitus.



### Research methods

One hundred and twenty patients with type 2 diabetes were enrolled in the study. They were assigned to a high dose metformin group (2 g daily) and a low dose metformin group (1 g daily) with 60 patients in each group for 12 wk. Changes in BMD and bone metabolism as well as the efficacy of the treatment were compared between the two groups before and after treatment.

### Research results

The results showed that there was no significant difference in the treatment efficacy between the two treatment groups. After the treatment, levels of BMD and bone metabolic markers were improved. To be specific, levels of BMD and 25-hydroxyvitamin D were higher in the high dose metformin group than in the low dose metformin group. However, levels of N-terminal midfragment and  $\beta$ -isomerized C-terminal telopeptides were lower in the high dose metformin group than in the low dose metformin group.

### Research conclusions

A high dosage of metformin can help to improve osteoporosis as well as control blood glucose in elderly male patients with type 2 diabetes mellitus.

### Research perspectives

The effects of metformin on BMD and bone metabolism should be further evaluated in long-term observational studies with large sample sizes.

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