ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2020 September 26; 8(18): 3920-4279

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Semimonthly Volume 8 Number 18 September 26, 2020

World Journal of Clinical Cases

Semimonthly Volume 8 Number 18 September 26, 2020

Contents

World Journal of Clinical Cases

Semimonthly Volume 8 Number 18 September 26, 2020

Contents

World Journal of Clinical Cases

Semimonthly Volume 8 Number 18 September 26, 2020

Contents

World Journal of Clinical Cases

Semimonthly Volume 8 Number 18 September 26, 2020

Contents

ABOUT COVER

Editorial board member of *World Journal of Clinical Cases*, Dr. Li is a Professor at the Nanjing University Medical School in Nanjing, China. Having received his Bachelor's degree from Xuzhou Medical College in 1997, Dr. Li undertook his postgraduate training first at Nanjing Medical University, receiving his Master's degree in 2004, and then at Fudan University, receiving his PhD in 2007. He advanced to Chief Physician in the Department of Anesthesiology at The Affiliated Hospital of Nanjing University Medical School in 2017 and has held the position since. His ongoing research interests involve ultrasound (transthoracic echo and transesophageal echo) in clinical anesthesia and ultrasound-guided limb and trunk nerve block in postoperative pain management. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJCC* as 1.013; IF without journal self cites: 0.991; Ranking: 120 among 165 journals in medicine, general and internal; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Semimonthly

EDITORS-IN-CHIEF
Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
September 26, 2020

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2020 September 26; 8(18): 4010-4016

DOI: 10.12998/wjcc.v8.i18.4010

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

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

Lin-Xia Wang, Guang-Ya Wang, Na Su, Jie Ma, Yu-Kun Li

ORCID number: Lin-Xia Wang 0000-0002-7733-0089; Guang-Ya Wang 0000-0003-0646-6170; Na Su 0000-0003-1112-0756; Jie Ma 0000-0001-8108-9657; Yu-Kun Li 0000-0002-4005-9715.

Author contributions: Wang LX, Li YK, Su N, Ma J and Wang GY collected the data and wrote and edited the manuscript; all the authors approved the publication of the manuscript.

Institutional review board statement: The study was approved by Ethics Committee of Cangzhou Central Hospital.

Informed consent statement: All patients gave informed consent.

Conflict-of-interest statement: The authors declare that there is no conflict of interest.

Data sharing statement: No additional data available.

STROBE statement: The manuscript has been prepared and revised according to the STROBE statement.

Open-Access: This article is an open-access article that was selected by an in-house editor and

Lin-Xia Wang, Yu-Kun Li, Department of Endocrinology, The Third Hospital of Hebei Medical University, Shijiazhuang 050051, Hebei Province, China

Lin-Xia Wang, Guang-Ya Wang, Na Su, Jie Ma, Second Department of Endocrinology, Cangzhou Central Hospital, Cangzhou 061001, Hebei Province, China

Yu-Kun Li, Key Orthopaedic Biomechanics Laboratory of Hebei Province, Shijiazhuang 050051, Hebei Province, China

Corresponding author: Yu-Kun Li, PhD, Professor, Department of Endocrinology, The Third Hospital of Hebei Medical University, No. 139 Ziqiang Road, Shijiazhuang 050051, Hebei Province, China. lykun1962@163.com

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

Manuscript source: Unsolicited manuscript

Received: June 5, 2020
Peer-review started: June 5, 2020
First decision: July 25, 2020
Revised: August 12, 2020
Accepted: August 22, 2020
Article in press: August 22, 2020
Published online: September 26, 2020

P-Reviewer: Georgescu EF, Johansen S, Sato H
S-Editor: Wang JL
L-Editor: Filipodia
P-Editor: Zhang YL

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 β-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

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.

Citation: Wang LX, Wang GY, Su N, Ma J, Li YK. Effects of different doses of metformin on bone mineral density and bone metabolism in elderly male patients with type 2 diabetes mellitus. *World J Clin Cases* 2020; 8(18): 4010-4016
URL: https://www.wjgnet.com/2307-8960/full/v8/i18/4010.htm
DOI: https://dx.doi.org/10.12998/wjcc.v8.i18.4010

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[1,2]. 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[3,4]. 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[5]. 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 ± 5.68) years for the experimental group and 62 to 84 (72.57 ± 5.63) years for the control group. Patients in the experimental group had 2 to 15 years (8.84 ± 2.35) of disease duration, and patients in the control group had 3 to 16 years (8.99 ± 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 ≥ 7.0 mmol/L; two-hour postprandial glucose ≥ 11.1 mmol/L; normal random glucose ≥ 11.1 mmol/L based on 2017 Guideline for the Prevention and Management of Type 2 Diabetes[6]. 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[7,8]. 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, β-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 χ^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)
χ^2				0.349
P 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 β-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[9,10]. 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[11,12]. 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[13].

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 β-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[14,15]. 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^2		N-MID, ng/mL	β-CTx, pg/mL	25(OH)D, ng/mL
		Lumbar L_{1-4}	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[a]	0.76 ± 0.15[a]	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[ab]	0.93 ± 0.20[ab]	10.68 ± 4.24[ab]	310.64 ± 146.83[ab]	25.96 ± 6.91[ab]

[a]$P < 0.05$ *vs* before the treatment;
[b]$P < 0.05$ *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[16].

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[17]. 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[18,19]. 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[20].

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 β-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.

REFERENCES

1 **Shi C**, Sun L, Bai R, Wang H, Liu D, Du J. Comparison of a twice daily injection of insulin aspart 50 with insulin aspart 30 in patients with poorly controlled type 2 diabetes. *Curr Med Res Opin* 2019; **35**: 1091-1096 [PMID: 30550344 DOI: 10.1080/03007995.2018.1558853]

2 **Chen Z**, Li G. Sodium-Glucose Co-Transporter 2 Inhibitors Compared with Sulfonylureas in Patients with Type 2 Diabetes Inadequately Controlled on Metformin: A Meta-Analysis of Randomized Controlled Trials. *Clin Drug Investig* 2019; **39**: 521-531 [PMID: 31041606 DOI: 10.1007/s40261-019-00781-w]

3 **Brooks LK**, Kalyanaraman N, Malek R. Diabetes Care for Patients Experiencing Homelessness: Beyond Metformin and Sulfonylureas. *Am J Med* 2019; **132**: 408-412 [PMID: 30472322 DOI: 10.1016/j.amjmed.2018.10.033]

4 **Peng Y**, Chen SH, Liu XN, Sun QY. Efficacy of different antidiabetic drugs based on metformin in the treatment of type 2 diabetes mellitus: A network meta-analysis involving eight eligible randomized-controlled trials. *J Cell Physiol* 2019; **234**: 2795-2806 [PMID: 30145806 DOI: 10.1002/jcp.27097]

5 **Tseng CH**. Metformin and risk of chronic obstructive pulmonary disease in diabetes patients. *Diabetes Metab* 2019; **45**: 184-190 [PMID: 29804817 DOI: 10.1016/j.diabet.2018.05.001]

6 **Zeng S**, Gan HX, Xu JX, Liu JY. Metformin improves survival in lung cancer patients with type 2 diabetes mellitus: A meta-analysis. *Med Clin (Barc)* 2019; **152**: 291-297 [PMID: 30173870 DOI: 10.1016/j.medcli.2018.06.026]

7 **Hwang SH**, Kim MC, Ji S, Yang Y, Jeong Y, Kim Y. Glucose starvation induces resistance to metformin through the elevation of mitochondrial multidrug resistance protein 1. *Cancer Sci* 2019; **110**: 1256-1267 [PMID: 30689265 DOI: 10.1111/cas.13952]

8 **Peters AS**, Wortmann M, Fleming TH, Nawroth PP, Bruckner T, Böckler D, Hakimi M. Effect of metformin treatment in patients with type 2 diabetes with respect to glyoxalase 1 activity in atherosclerotic lesions. *Vasa* 2019; **48**: 186-192 [PMID: 30421661 DOI: 10.1024/0301-1526/a000762]

9 **Šálek T**, Adamíková A. Cystatin C measurement leads to lower metformin dosage in elderly type 2 diabetic patients. *Basic Clin Pharmacol Toxicol* 2019; **124**: 298-302 [PMID: 30218617 DOI: 10.1111/bcpt.13132]

10 **Feng WH**, Bi Y, Li P, Yin TT, Gao CX, Shen SM, Gao LJ, Yang DH, Zhu DL. Effects of liraglutide, metformin and gliclazide on body composition in patients with both type 2 diabetes and non-alcoholic fatty liver disease: A randomized trial. *J Diabetes Investig* 2019; **10**: 399-407 [PMID: 29957886 DOI: 10.1111/jdi.12888]

11 **Du Q**, Wu B, Wang YJ, Yang S, Zhao YY, Liang YY. Comparative effects of sitagliptin and metformin in patients with type 2 diabetes mellitus: a meta-analysis. *Curr Med Res Opin* 2013; **29**: 1487-1494 [PMID: 23927568 DOI: 10.1185/03007995.2013.833090]

12 **Pratley RE**, Fleck P, Wilson C. Efficacy and safety of initial combination therapy with alogliptin plus metformin versus either as monotherapy in drug-naïve patients with type 2 diabetes: a randomized, double-blind, 6-month study. *Diabetes Obes Metab* 2014; **16**: 613-621 [PMID: 24400655 DOI: 10.1111/dom.12258]

13 **Bolinder J**, Ljunggren Ö, Johansson L, Wilding J, Langkilde AM, Sjöström CD, Sugg J, Parikh S. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Diabetes Obes Metab* 2014; **16**: 159-169 [PMID: 23906445 DOI: 10.1111/dom.12189]

14 **Wu D**, Li L, Liu C. Efficacy and safety of dipeptidyl peptidase-4 inhibitors and metformin as initial combination therapy and as monotherapy in patients with type 2 diabetes mellitus: a meta-analysis. *Diabetes Obes Metab* 2014; **16**: 30-37 [PMID: 23803146 DOI: 10.1111/dom.12174]

15 **Amin NB**, Wang X, Jain SM, Lee DS, Nucci G, Rusnak JM. Dose-ranging efficacy and safety study of ertugliflozin, a sodium-glucose co-transporter 2 inhibitor, in patients with type 2 diabetes on a background of metformin. *Diabetes Obes Metab* 2015; **17**: 591-598 [PMID: 25754396 DOI: 10.1111/dom.12460]
16 **Ismail TA**, Soliman MM, Nassan MA. Molecular and immunohistochemical effects of metformin in a rat model of type 2 diabetes mellitus. *Exp Ther Med* 2015; **9**: 1921-1930 [PMID: 26136915 DOI: 10.3892/etm.2015.2354]
17 **Wang C**, Liu F, Yuan Y, Wu J, Wang H, Zhang L, Hu P, Li Z, Li Q, Ye J. Metformin suppresses lipid accumulation in skeletal muscle by promoting fatty acid oxidation. *Clin Lab* 2014; **60**: 887-896 [PMID: 25016691 DOI: 10.7754/clin.lab.2013.130531]
18 **Ke WC**, Wu Q, Gu YX. Relationship between bone metabolism markers and bone mineral density in elderly patients with type 2 diabetes mellitus. *Jianyan Yixue* 2017; **32**: 86-89 [DOI: 10.3969/j.issn.1673-8640.2017.02.004]
19 **Wang P**, Jang GL. Relationship between serum insulin and bone mineral density and bone metabolism indexes in elderly patients with type 2 diabetes mellitus. *Shandong Yiyao* 2017; **57**: 71-73 [DOI: 10.3969/j.issn.1002-266X.2017.14.021]
20 **Zhou TT**, Feng ZP. Relationship between bone mineral density and bone metabolism indexesin in postmenopausal female patients with type 2 diabetes complicated with osteoporosis. *Zhongguo Guzhi Shusong Zazhi* 2019; **25**: 29-32 [DOI: 10.3969/j.issn.1006-7108.2019.01.06]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com