

Effects of Metformin Alone or in Combination With Insulin on Bone Mineral Density in Osteopenic Patients With Type 2 Diabetes

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Abstract

Background: Patients with diabetes are at risk for osteoporotic fractures. We propose to test the hypothesis that treatment of diabetes mellitus with metformin alone or in combination with insulin affects bone mineral density (BMD) in a positive way possibly via the Wnt/ β -catenin pathway.

Methods: We retrospectively reviewed records of veterans at the Memphis Veterans Administration Medical Center (VAMC) with type 2 diabetes on treatment with metformin alone or in combination with insulin found to have osteopenia by dual-energy X-ray absorptiometry (DXA) between 2002 and 2013. Change in BMD over time was compared with age, race and sex matched controls.

Results: Of 1,662 patients with DXA scans, we had two study groups (13 patients on metformin and insulin; 20 on metformin alone). These patients were compared to age, race and sex matched controls not on metformin, insulin or thiazolidinediones (TZDs). On follow-up (1 - 6 years) of both study groups, there was no statistical difference in average BMD over time compared to controls ($P = 0.172$ in combination group, $P = 0.747$ in metformin alone group). However, there was improvement in BMD over time at the right and left femoral neck in the metformin alone group compared to control (left femur $P = 0.130$; right femur $P = 0.017$).

Conclusions: In this retrospective study, there was a trend towards

improvement in BMD in osteopenic patients with type 2 diabetes treated with metformin. The exact mechanism by which metformin exerts positive effects on bone is yet to be fully elucidated. We propose that metformin may promote bone formation by decreasing sclerostin levels, an inhibitor of the Wnt/ β -catenin pathway. Overall, we surmise that the osteo-anabolic effect of metformin on BMD still needs to be further studied in a larger prospective study.

Keywords: Type 2 diabetes mellitus; Osteopenia; Bone mineral density; Metformin; Insulin; Wnt; T-score; Fracture

Introduction

The incidences of diabetes mellitus and osteoporosis are on the rise globally [1]. It has been increasingly recognized that diabetes adversely affects bone health. According to two meta-analyses, type 2 diabetes patients tend to have normal or slightly higher bone mineral density (BMD) values [2]. However, the incidence of fracture is higher in patients with type 2 diabetes despite frequently reported normal or increased BMD [3]. The increased fracture risk is thought to be related to low bone strength. Bone strength is determined by the integration of both bone mass and bone quality [4]. Since bone mass is thought to be increased in type 2 diabetes, low bone quality is likely to play a larger role in the increased risk of fractures.

Several factors have been suggested to contribute to low bone quality in patients with diabetes. Long-term metabolic effects of hyperglycemia may result in poor bone quality [4]. Hyperglycemia compromises mesenchymal stem cell differentiation resulting in decreased bone formation. Hyperglycemia increases oxidative stress via proinflammatory cytokines such as TNF- α and INF- γ , which may induce apoptosis of osteoblasts. Additionally hyperglycemia increases advanced glycosylated end products (AGEs) further causing deleterious effects on bone [5].

In recent years, it has been proposed that Wnts, a large family of glycoproteins play a major role in regulation of bone mass [6]. Signaling through the Wnt/ β -catenin pathway increases bone mass through promotion of mesenchy-

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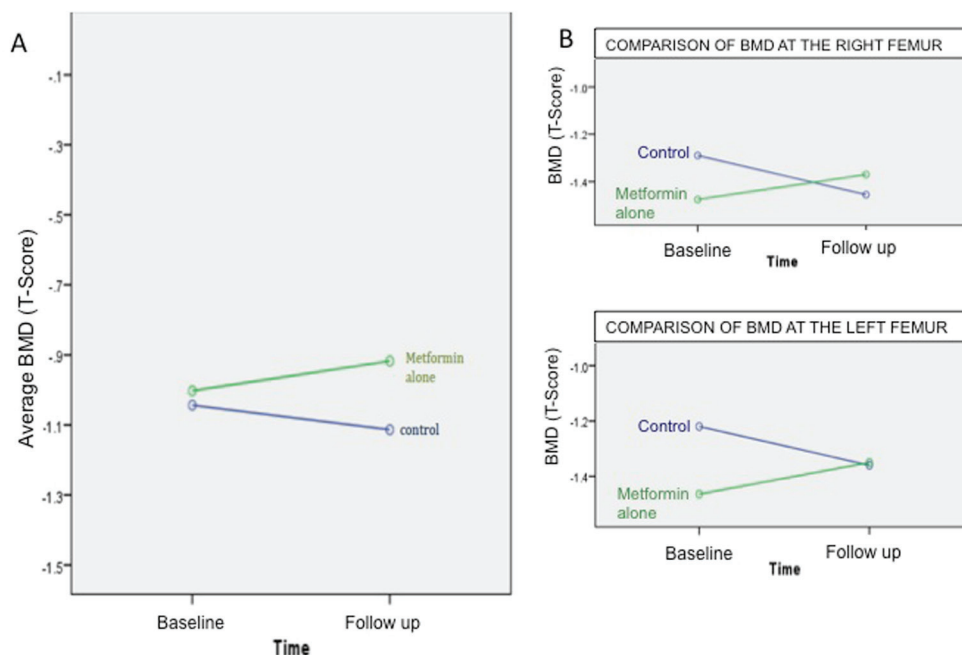


Figure 1. Assessment of the change in BMD over time in patients with type 2 diabetes on metformin alone compared to control. (A) Overall average BMD was not significantly different over time in the metformin alone versus control group ($P = 0.747$). (B) Comparison of BMD at the right and left femur shows improvement in the metformin alone group compared to control over time (right femur $P = 0.017$, left femur $P = 0.130$).

mal stem cell differentiation into osteoblasts as opposed to adipocytes. It also suppresses osteoclastogenesis and inhibits osteoblast apoptosis [7]. Lastly β -catenin decreases bone resorption by increasing osteoprotegerin, a potent inhibitor of osteoclast differentiation [7]. Therefore, it has been surmised that inhibition of Wnt signaling will have deleterious effects on bone. In fact sclerostin a potent Wnt/ β -catenin inhibitor is increased in patients with type 2 diabetes and may contribute to decreased bone mass [8].

In one study comparing the effects of pioglitazone to metformin on sclerostin levels, pioglitazone was associated with increased fractures and higher levels of sclerostin compared to metformin. Therefore, metformin by decreasing sclerostin levels may promote bone formation via the Wnt/ β -catenin pathway [9]. Metformin has also been described to have other beneficial effects on bone. In bilateral ovariectomized rats, metformin was shown to improve bone mass and quality [10]. Metformin also protects osteoblasts from the deleterious effects of hyperglycemia and AGEs [11]. Furthermore, it stimulates osteoprotegerin, which prevents osteoclast activity [12].

The presence of decreased bone density in patients with type 1 diabetes has led to the hypothesis that insulin has anabolic effects on bone [3]. *In vivo* and *in vitro* studies suggest that insulin improves bone formation via proosteoblastic mechanisms. Animal studies show that insulin receptor substrates (IRS) are essential for insulin/IGF-1 receptor signal-

ing. Mice lacking the IRS-1 gene showed severe osteopenia with reductions in osteoblast and osteoclast function resulting in decreased bone turnover [13]. A prospective study on BMD in patients with type 1 diabetes, showed that intensive insulin therapy for 7 years resulted in stabilization of BMD at all sites [14]. These findings suggest that insulin as an anabolic agent, can preserve and increase bone strength through its effects on bone formation [3].

Given that insulin and metformin have positive effects on bone independently, we postulated that metformin alone or in combination with insulin would likely improve BMD in osteopenic patients with type 2 diabetes.

Primary outcome

The primary outcome measure was improvement in BMD (as measured by T-score) at the lumbar spine and at the left and right femoral necks.

Materials and Methods

We conducted a retrospective review of the computerized patient record system (CPRS) at the Memphis Veterans Administration Medical Center (VAMC). We included patients with type 2 diabetes on metformin alone or in combination with insulin diagnosed with osteopenia according to the

World Health Organization (WHO) criteria by dual-energy X ray absorptiometry (DXA) at baseline, and with a follow-up DXA scan for comparison. We excluded patients on prior or current treatment with medications that can improve BMD such as bisphosphonates, denosumab or teriparatide. We also excluded patients on TZDs or other antidiabetic agents besides insulin and metformin. Lastly, we excluded patients with type 1 diabetes, fractures or osteoporosis or no follow-up DXA scan. The study was approved by the institutional review board at the Memphis VAMC.

Statistical analysis

Standardized data collection was obtained using the computerized medical records at the VAMC. Osteopenia was defined according to WHO criteria as a BMD between 1 and 2.5 standard deviations (SD) below that of the young adult mean (i.e. T-score between -1 and -2.5). Osteoporosis was defined by the WHO criteria as a BMD ≥ 2.5 SD below that of the young adult mean (i.e. T-score of ≤ -2.5). Improvement in BMD was defined as a less negative or more positive T-score. Variables between groups were compared using *t*-tests. Estimated marginal means was used to assess for change in BMD over time comparing baseline BMD to follow-up. Multi-regression analysis was used to control for confounding variables. P-value < 0.05 was considered statistically significant and confidence intervals were reported to reflect goodness of fit. These analyses were done using SPSS.

Results

About 1,662 patients were found to have DXA scans; however, only 13 patients were included in the metformin and insulin combination study group. The mean age was 59.7 ± 7.2 with a mean body mass index of 31.6 ± 4.6 kg/m². Of the 13 patients, 23.1% were female; 7.7% Asian, 15.4% African American and 76.9% were Caucasian. These patients were age, race and sex matched with a control group of osteopenic patients with type 2 diabetes on other antidiabetic agents besides insulin, metformin or TZDs. On follow-up (1 - 6 years), there was no statistically significant difference in average BMD in the study group over time ($P = 0.172$) compared to the control group. Comparison of HbA1C values demonstrated significantly higher values in the combination study group (7.81 ± 1.45) than the control (5.89 ± 0.71) groups ($P < 0.01$).

We also compared 20 osteopenic patients with type 2 diabetes on metformin alone to age, race and sex matched patients with DXA scans at baseline and at follow-up. At baseline, the metformin group had a mean age of 61.8 ± 8.1 , 30% were African American and 15% were female, and the rest were Caucasian males. In this group we found that on

average the BMD did not change over time ($P = 0.747$); however, there was improvement in the BMD at the right and left femoral necks (right femur $P = 0.017$, left femur $P = 0.130$) (Fig. 1).

Discussion

In a retrospective chart review in the Memphis VAMC, our data show that we are not able to demonstrate a significant improvement of BMD in both osteopenic patients with type 2 diabetes on insulin and metformin compared to control. The small number of patients and retrospective nature limit the study. Furthermore, the significantly worse HbA1C values in the combination group suggest that the inability to control the diabetes may have played a role, diminishing improvement in BMD.

In the metformin alone group we were able to demonstrate some improvement in BMD at the right and left femur over time in osteopenic patients with type 2 diabetes compared to control. The exact mechanism by which metformin exerts positive effects on bone is not known. We propose that metformin may promote bone formation by decreasing sclerostin levels, an inhibitor of Wnt/ β -catenin pathway. Metformin also protects osteoblasts from the deleterious effects of hyperglycemia and AGEs. Overall, we conclude that these findings may be of clinical significance and should be followed with prospective, randomized and controlled studies.

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Conflict of Interest

There are no potential conflicts of interest.

Disclaimer

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