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Review

The effect of anti-diabetic drugs on the musculoskeletal system in women

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Abstract

Diabetes mellitus is a chronic endocrine disorder caused by absolute or relative lack of insulin, which subsequently leads to hormonal and metabolic changes in the body. Since patients receive continuous long-term anti-diabetic treatment, there was a chance to analyze the effect of anti-diabetic drugs on bone tissue in type 2 DM (T2DM) patients. The results of the studies indicate that the bone metabolism is the most adversely affected by treatment with thiazolidinediones and canagliflozin from the group sodium-glucose co-transporter-2 inhibitors, while dipeptidyl peptidase-4 (DPP-4) inhibitors and insulin have a positive effect on it, and, finally, glucagon-like peptide-1, biguanides and sulfonylureas have rather a slight impact on the bone tissue.

Keywords: DPP-4 inhibitors, insulin, metformine, osteoporosis, SGLT2, thiazolidinediones.

Introduction

Diabetes mellitus (DM) is one of the most common human diseases and one of the three pathologies often causing early disability and high mortality. Chronic hyperglycemia have an adverse effect on the cardiovascular, urine, nervous and other human body systems [1].

IDF Diabetes Atlas (2019) counts around 463 million people suffering from DM worldwide. One of the rapidly growing complications of diabetes is a disorder of phosphorus–calcium metabolism and bone condition, manifested by early osteoporosis [2]. Recent studies have shown that the impaired bone structure integrity in patients with T2DM may be associated with hypoglycemic drugs [3].

Thiazolidinediones

The thiazolidinediones, oral hypoglycemic drugs include rosiglitazone and pioglitazone. These medications improve insulin sensitivity and are administered for T2DM treatment [4]. However, the results of the clinical and experimental studies show that thiazolidinediones adversely impact the bone structure [5–7]. ADOPT studies have shown that peri- and postmenopausal women taking rosiglitazone, experienced a higher risk of fractures. Based on the studies it was found that an increased risk of fractures in women is not associated with the difference in peri- and post-menopausal estrogen level [8]. The study of sex differences in the side effects of thiazolidinedione therapy have found that women were twice likely to have an increased risk of fractures [9]. The results of another randomized placebo-controlled study have demonstrated that post-menopausal women with no T2DM and no osteoporosis, after 14 weeks of rosiglitazone therapy, experienced a significant decrease in the level of bone formation markers in the acetabulofemoral joint [10]. Besides, one more study data have shown that despite high bone mineral density, patients with T2DM have an increased risk

of fracture from thiazolidinedione therapy due to impaired stem cell differentiation and effects on osteoblastogenesis [11].

SGLT2i

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are a new class of drugs used in the complex treatment of T2DM. Their main mechanism lies in the effect on the excretory renal function, causing increased excretion of glucose in the urine, thereby reducing blood glucose levels. [12]. One among the major negative effects caused by SGLT2i, there are genitourinary infections and bone fractures when treated with canagliflozin [13]. The effect of SGLT2i on calcium–phosphorus metabolism and bone tissue in T2DM patients have not been fully investigated yet [7, 5, 14]. Till now, CANVAS clinical study have demonstrated an increased incidence of bone fractures with canagliflozin, which raises the level of bone resorption markers due to weight loss. It raises the level of beta-carboxy-telopeptide, a fragment of type 1 collagen, composing 90% of bone tissue. Therefore, it can be assumed that an increase in telopeptide levels during treatment with canagliflozin may lead to osteoporotic changes [15, 16]. Some studies also indicate that the canagliflozin reduces estradiol levels in women [17].

Though not all SGLT2i medications have a proven negative effect on the bone matrix, still some studies have shown the correlation of dapagliflozin and empagliflozin treatment and increased level of bone metabolism markers [18–20].

Dipeptidyl peptidase-4 (DPP-4) inhibitors

The class of dipeptidyl peptidase-4 inhibitors (DPP-4i) is associated with less risk of fractures compared to thiazolidinediones and sulfonylureas [21]. Even in the case of long-term use, the risk of fractures is low according to a retrospective cohort study [22].

On the contrary, DPP-4i can improve bone metabolism. In an animal study [23], sitagliptin contributed to the improvement of bone mineral density while affecting the intestinal hormones GIP (glucose-dependent insulinotropic polypeptide), which is involved in bone homeostasis and increases intracellular calcium, enhances collagen and alkaline phosphatase syntheses [24, 25].

Other researches in T2DM patients treated with DPP-4i have shown a low-risk of upper limb fractures [26]. I Barchetta study demonstrates a positive effect of DPP-4i on the vitamin D level in patients with T2DM, which enables to consider its positive effect on bone metabolism as well [27].

Insulin

It is known that insulin drugs should be used with caution to avoid hypoglycemia [19, 20, 28]. An increased incidence of bone fracture in DM patients taking insulin is because these patients usually have a long history of diabetes, they experience more diabetic complications and a much higher risk of hypoglycemia, associated with a higher frequency of falls [29]. Meanwhile, insulin remains the drug of choice for DM patients with existing limb fractures for better glycemic control [19]. Also, insulin preparations affect osteoblast differentiation and proliferation, which in turn produce osteocalcin [28]. The study have shown the osteocalcin effect (namely of its two forms – carboxylated and non-carboxylated) on the β-cells of the pancreas, in terms of improvement of insulin sensitivity and β-cell function [30].

Sulfonylureas

A class of sulfonylurea drugs can also lead to hypoglycemia, especially in elderly patients [5]. Hypoglycemic conditions are accompanied by the increased risk of falls and, consequently, fractures, but it is not the result of a direct impact of medications on bone resorption [31].

Study results show that this class of drugs, similar to insulin, contributes to bone health since they stimulate insulin secretion, which in turn promotes osteoblast differentiation, as described above [28]. One research has

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also shown a beneficial effect of glimepiride on bone tissue formation while activating phosphoinositide 3-kinases and v-akt murine thymoma viral oncogene homolog, which improves osteoblast differentiation [32].

Biguanides

A class of biguanides, especially metformin, has a direct osteogenic effect on bones. It influences osteoblast differentiation and bone matrix synthesis, meanwhile promoting osteoblast proliferation through AMP-activated protein kinase (AMPK) [33–35].

Therefore, it can confirm the osteoanabolic properties of metformin [5].

GLP-1 ra

Glucagon-like peptide-1 receptor agonists (GLP-1 ra) play a part in increasing insulin secretion due to incretin hormone function in response to food intake, which helps to suppress glucagon secretion [5]. Experimental studies found that native glucagon-like peptide 1 does not have a direct influence on osteoblasts, but affects osteogenic differentiation indirectly while being present in bone marrow stromal cells [36].

Some study demonstrated that liraglutide significantly reduces the risk of bone fractures, whereas exenatide treatment was associated with an increased risk of accidental bone fractures [37]. A randomized cohort study, based on the effect of liraglutide on bone mass in overweight women and controls, also proved its benefit. The results showed that in the group of women who took liraglutide, the bone mass increased by 16% [38]. A cohort study revealed that the use of GLP-1 ra is not associated with a reduced risk of bone fractures compared with other anti-hyperglycemic drugs [39].

One of the side effects of GLP-1 ra treatment can be nausea, vomiting, and diarrhea, these are likely to lead to malabsorption of minerals and nutrients, which adversely affects bone physiology. [40].

It also should be reminded and emphasized to diabetic patients that aerobic exercises have a positive contribution to bone metabolism. This is evidenced by studies focused on comparing changes in arm strength and bone metabolism after 6 months in non-insulin-dependent patients. Training on aerobic exercises on the treadmill helps to improve markers of bone metabolism and grip strength in patients with diabetes [41].

Conclusions

The constant use of anti-diabetic drugs can influence the musculoskeletal system. Thus, despite the high hypoglycemic efficiency, the thiazolidinediones cause disorders in stem cell differentiation, especially adversely affecting women, due to their age-related estrogen decrease. According to the latest studies, the group of SGLT2i also harm bone tissue. Though it's only concerning canagliflozin, taking which increases the frequency of fractures, whereas dapagliflozin and empagliflozin do not cause such an effect. Based on the studies, insulin and sulfonylureas have a good influence on calcium metabolism. The main disadvantage associated with these drugs is the risk of hypoglycemia, which can lead to falls and fractures. Osteogenic agents include biguanides, GLP-1 ra, and DPP-4i indirectly act on bone metabolism through bone marrow stromal cells. The biguanide group takes part in the osteoblastic process by osteoblast differentiation, DPP-4i improve metabolism in bone tissue itself, and GLP-1 ra, although indirectly, acts on bone metabolism through bone marrow stromal cells.

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