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Review

Effects of diabetes drugs on the skeleton

Christian Meier [a,*], Ann V. Schwartz [b], Andrea Egger [a], Beata Lecka-Czernik [c,d]

[a] Division of Endocrinology, Diabetes and Metabolism, University Hospital, Basel, Switzerland
[b] Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA
[c] Department of Orthopedic Surgery, Center for Diabetes and Endocrine Research, University of Toledo College of Medicine, Toledo, OH, USA
[d] Department of Physiology and Pharmacology, Center for Diabetes and Endocrine Research, University of Toledo College of Medicine, Toledo, OH, USA

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ABSTRACT

Type 2 diabetes is associated with increased fracture risk and the mechanisms underlying the detrimental effects of diabetes on skeletal health are only partially understood. Antidiabetic drugs are indispensable for glycemic control in most type 2 diabetics, however, they may, at least in part, modulate fracture risk in exposed patients.

Preclinical and clinical data clearly demonstrate an unfavorable effect of thiazolidinediones on the skeleton with impaired osteoblast function and activated osteoclastogenesis. The negative effect of thiazolidinediones on osteoblastogenesis includes decreased activity of osteoblast-specific transcription factors (e.g. Runx2, Dlx5, osterix) and decreased activity of osteoblast-specific signaling pathways (e.g. Wnt, TGF-β/BMP, IGF-1). In contrast, metformin has a positive effect on osteoblast differentiation due to increased activity of Runx2 via the AMPK/USF-1/SHP regulatory cascade resulting in a neutral or potentially protective effect on bone.

Recently marketed antidiabetic drugs include incretin-based therapies (GLP-1 receptor agonists, DPP-4 inhibitors) and sodium-glucose co-transporter 2 (SGLT2)-inhibitors. Preclinical studies indicate that incretins (GIP, GLP-1, and GLP-2) play an important role in the regulation of bone turnover. Clinical safety data are limited, however, meta-analyses of trials investigating the glycemic-lowering effect of both, GLP-1 receptor agonists and DPP4-inhibitors, suggest a neutral effect of incretin-based therapies on fracture risk. For SGLT2-inhibitors recent data indicate that due to their mode of action they may alter calcium and phosphate homeostasis (secondary hyperparathyroidism induced by increased phosphate reabsorption) and thereby potentially affect bone mass and fracture risk. Clinical studies are needed to elucidate the effect of SGLT2-inhibitors on bone metabolism. Meanwhile SGLT2-inhibitors should be used with caution in patients with high fracture risk, which is specifically true for the use of thiazolidinediones.

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* Corresponding author at: Division of Endocrinology, Diabetes and Metabolism, University Hospital Basel, Missionsstrasse 24, CH-4055 Basel, Switzerland. Fax: +41 61 264 97 96.
E-mail address: christian.meier@unibas.ch (C. Meier).

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Introduction

Type 2 diabetes is associated with increased fracture risk despite the fact that patients with diabetes have higher bone mineral density as compared to non-diabetic individuals [1–3]. The mechanisms underlying the detrimental effects of diabetes on skeletal health are only partially understood. It is assumed that determinants of fracture risk are multifactorial including diabetes-related microvascular complications, fall risk and alterations associated with chronic hyperglycemia [4]. As documented in preclinical models hyperglycemia may alter calcium and vitamin D metabolism resulting in impaired bone mineralization [5,6]. Furthermore, chronic hyperglycemia may result in deposition of advanced glycosylation end-products in bone collagen (such as pentosidine) contributing to impaired bone quality [7,8] and higher fracture risk [9,10]. Several studies suggest that skeletal dynamics are reduced in type 2 diabetes [4] with decreased osteoblast function as documented by reduced biochemical markers of bone formation [11] and lower bone formation rate in a histomorphometric study [12]. Several pathophysiological changes in diabetics might contribute to decreased bone formation. They include interference of advanced glycosylation end-products with osteoblast development [13], function [14] and attachment to collagen matrix [15], increased levels of osteocyte-derived sclerostin [16–18], and hyperglycemia-induced suppression of osteogenic differentiation of marrow-derived progenitor cells diverting osteoblastic precursor cells to a metabolically stressed adipogenic pathway that induces synthesis of a hyaluronan matrix that recruits inflammatory cells and establishes an inflammatory process contributing to bone demineralization [19].

Antidiabetic drugs are indispensable for glycemic control in most type 2 diabetics. However before discussing potential benefits or risks of antidiabetic drugs on bone metabolism it seems evident that optimal glycemic control *per se* is an important contributing factor for improvement of skeletal integrity in diabetic patients. This notion is supported by several studies showing increased fracture risk in patients with poor glycemic control and reduced risk in patients on intensive glycemic control.

A recent cohort study explored the association between glycemic control as measured by serum hemoglobin A1c (HbA1c) levels and the risk of hip fracture in type 2 diabetics aged over 65 years and observed a linear relationship between HbA1c and hip fracture risk. After adjustment for various contributing factors hip fracture risk was 24–31% higher among diabetics with HbA1c levels above 9% than among patients with HbA1c levels of 6–7% [20]. These data are in line with some but not all previous studies confirming a detrimental effect of poor glycemic control on fracture risk [21–23]. In contrast, however, this relationship could not be observed in the ACCORD trial, a clinical trial investigating type 2 diabetics randomized either to intensive or standard treatment strategies. The lack of significant effect of glycemic control on the occurrence of non-vertebral fractures (and falls) might be attributed to the small difference in effective diabetes control between patients with intensified treatment strategy (HbA1c 6.4%) and standard treatment (HbA1c 7.5%) [24]. Although reducing hyperglycemia is mandatory not only for skeletal health but also in decreasing the onset and progression of microvascular complications, individualized treatment is necessary, balancing the benefits and risks of glycemic control based on the patient's age and health status [25]. Drug-induced hypoglycemic episodes need to be avoided which in addition to diabetic complications (neuropathy, retinopathy) may increase the risk of falls and fractures.

This review summarizes the effects of antidiabetic drugs on bone metabolism and fracture risk (Table 1). Preclinical and clinical data of both, insulin sensitizers (metformin, thiazolidinediones) and insulin secretagogues are discussed with specific focus on the skeletal effects of recently marketed drugs such as incretin-based therapies (GLP-1 receptor agonists, DPP-4 inhibitors) and SGLT2-inhibitors.

Metformin

Metformin is most commonly used to increase insulin sensitivity in diabetic patients. Biguanides decrease hepatic glucose production and increase glucose uptake in muscle. Metformin is considered by the World Health Organization an essential medicine satisfying the criteria of the public health relevance, evidence on efficacy and safety, and comparative cost effectiveness (www.who.int/medicines). Metformin mechanism of insulin sensitization includes activation of hepatic and muscle AMP-activated protein kinase (AMPK), which results in suppression of fatty acid synthesis and stimulation of fatty acid oxidation in liver and increase in muscle glucose uptake [26]. AMPK also decreases expression of sterol-regulatory element-binding-protein 1 (SREBP-1), a transcription factor involved in adipocyte differentiation and pathogenesis of insulin resistance, dyslipidemia and diabetes. Animal studies indicate that metformin has a positive effect on osteoblast differentiation due to increased activity of osteoblast-specific Runx2 transcription factor via AMPK/USF-1/SHP regulatory cascade [27] and it has a negative effect on osteoclast differentiation and bone loss after ovariectomy by decreasing RANKL and increasing osteoprotegerin levels [28]. Interestingly, in rodent models metformin can prevent the adverse effects of TZDs on bone by either inducing re-ossification of bone after rosiglitazone treatment or preventing rosiglitazone effects when applied in combination with rosiglitazone [29].

There are few clinical studies investigating the effect of metformin on bone and fracture risk. Metformin was compared with a sulfonylurea (glyburide) and with a thiazolidinedione (rosiglitazone) in the ADOPT trial, discussed in more detail in the section on thiazolidinediones [30]. The primary endpoint of this trial was time to monotherapy failure. Fractures were identified as adverse events. Fracture incidence was similar in those assigned to metformin or glyburide. One-year changes in the bone resorption marker CTX were similar in women (difference in 12-month change: +2.0%) and modestly greater in men (−8.4%) in those assigned to metformin compared with a sulfonylurea [31]. The metformin group had greater decreases in levels of the bone formation marker P1NP (difference in 12-month change: −9.4% women; −19.5% men), compared with the sulfonylurea group.

Most observational studies on metformin have found no effect on fracture risk although three studies have reported reduced risk [32–34]. Metformin use was associated with lower fracture risk,

Table 1
Antidiabetic drugs and their effect on fracture risk.

Target	Mode of action	Class of drugs	Drugs	Fracture Risk
Insulin	Sensitizers	Biguanides	Metformin	↓
		Thiazolidinediones	Pioglitazone, rosiglitazone	↑
	Secretagogues	K + ATP	Sulfonylureas	Neutral
		GLP-1 analogs	Liraglutide	Neutral - ↓
			Exenatide	Neutral - ↑
		DPP-4 inhibitors	Sitagliptin, etc.	Neutral - ↓
Other	α-glucosidase inhibitors		Acarbose, miglitol, voglibose	?
	Amylin analog		Pramlintide	?
	SGLT2 inhibitors		Canagliflozin, dapagliflozin	(↑)

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