Maturitas xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Diabetes and bone health

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ARTICLE INFO

Article history:
Received 3 April 2013
Accepted 8 April 2013
Available online xxx

Keywords:
Diabetes
Osteoporosis
Fractures
Thiazolidinediones

ABSTRACT

The increasing prevalence of diabetes especially type 2 diabetes worldwide is indisputable. Diabetics suffer increased morbidity and mortality, compared to their non-diabetic counterparts, not only because of vascular complications, but also because of an increased fracture incidence. Both types 1 and 2 diabetes and some medications used to treat it are associated with osteoporotic fractures. The responsible mechanisms remain incompletely elucidated. In this review, we evaluate the role of glycemic control in bone health, and the effect of anti-diabetic medications such as thiazolidinediones, sulfonylureas, DPP-4 inhibitors, and GLP-1 agonists. In addition, we examine the possible role of insulin and metformin as anabolic agents for bone. Lastly, we identify the current and future screening tools that help evaluate bone health in diabetics and their limitations. In this way we can offer individualized treatment, to the at-risk diabetic population.

Contents

Abbreviations: AGEs, advanced glycation endproducts; BMD, bone mineral density; CAH, congenital adrenal hyperplasia; DM, diabetes mellitus; DPP-4, dipeptydil petptidase-4; DXA, dual-energy X-ray absorptiometry; FRAX, fracture risk assessment tool; FSH, follicle stimulating hormone; GH, growth hormone; GIP, gastric inhibitory polypeptide; GLP, glucagon like peptide; IGFBP3, insulin-like growth factor binding protein 3; IGF-1, insulin like growth factor 1; LH, luteinizing hormone; PCOS, polycystic ovarian syndrome; PPAR-gamma agonists, peroxisome proliferator-activated receptor gamma; SHBG, sex hormone binding globulin; PTH, parathyroid hormone; TZDs, thiazolidinediones.

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http://dx.doi.org/10.1016/j.maturitas.2013.04.004

1. Introduction

The diabetes pandemic is growing at a fast pace worldwide. Osteoporosis is a skeletal disorder characterized by low bone mineral density (BMD), changes in bone architecture with proportional loss of osteoid and bone mineral, and predisposition to fractures. In 2000 it was estimated that 9 million osteoporotic fractures occurred worldwide, associated with significant disability and mortality [1]. There is a growing body of evidence that both types 1 and 2 diabetes mellitus (DM), predispose to osteoporotic fractures.

Recent studies report that diabetics are at higher risk for hip [2–6], proximal humerus [3,4], foot [3] and all non-vertebral fractures [3–5,7]. Several parameters that need to be considered in the association of diabetes, BMD and fracture risk include: diabetes type, age of onset, body mass index, level of glycemic control, medication affecting bone metabolism (Table 1), and vitamin D deficiency, which is more prevalent in diabetics [8]. The responsible mechanisms remain incompletely elucidated. In this review we discuss current evidence concerning diabetes and bone health.

2. Diabetes and bone mineral density

According to a review and meta-analysis by Vestergaard, BMD was increased in type 2 DM, and decreased in type 1 DM, compared with controls. Body mass index (BMI) was a major determinant for BMD, and one might conclude that the higher BMI had a protective effect against fractures. On the contrary, the meta-analysis showed that hip fracture risk is increased in both type 1 and type 2 diabetics [9]. For a given BMD, diabetic bone appears to be weaker and more likely to fracture. Alternatively, patients with type 2 DM could be suffering more fractures despite having stronger bones if they are falling more. Diabetics may fall more frequently for several reasons including: impaired proprioception due to peripheral neuropathy, visual impairment from diabetic retinopathy, macular edema, cataracts, and changes in accommodation associated with rapid fluctuations in glycemia, lightheadedness from hypo- and hyperglycemia or postural hypotension. In Verstergaard's study the relative risk for hip fracture was 6.9, but the relative risk that one would expect according to BMD was only 1.4. Many factors could contribute to this. One could be that the onset of DM in adolescence can cause decreased peak bone mass. A study indicates that women with type 1 DM exhibit low BMD early in life with significant differences already present in the post-teenage years [10]. Bone does not turn over uniformly and is susceptible to non-enzymatic glycation. Advanced glycation end-products (AGEs) in bone collagen can account for increased fracture risk associated with aging and DM [11]. Furthermore, the fact that racial and ethnic differences are associated with differences in glycation and the level of hemoglobin A1c (HbA1c), raises the question as to whether different races can be more susceptible to collagen glycation and thus to increased risk for fracture for the same BMD and plasma glucose levels. The Diabetes Prevention Program studied 3189 patients with impaired glucose tolerance, and after adjusting for factors affecting glycemia, the mean HbA1c levels were higher in blacks and Hispanics, for the same plasma glucose levels, compared to whites [12]. Whether this leads to differences in the risk of microvascular, macrovascular or bone complications remains to be determined in future studies.

Table 1
Classes of medications and their effect on bone mineral density and fracture risk.

Medications	Bone mineral density	Fractures
Thiazide	↑	↓
Loop diuretics	↓	↑
Hyperglycemia/diabetes	↑ Type 1 DM ↑ Type 2 DM	↑
TZDs	↓	↑
Metformin	↑ In rodent and in vitro	More data needed
Sulfonylurea	↔	↓
GLP-1 agonist	↑ In rodent	More data needed
DDP-4 inhibitors		
Insulin	↑ In rodent and in vitro	↑

3. Glycemic control

There is evidence that the level of glycemic control is associated with bone health. A deficit in osteoblasts is the cornerstone of diabetic osteopenia. Hyperglycemia impairs osteoblast function [13]. The association of vitamin D and bone health is well established. Diabetics are prone to vitamin D deficiency [8], and moreover, poor glycemic control, has been shown to impair the response of osteoblasts and osteoclasts to 1,25 $(OH)_2$ vitamin D3, in type 2 diabetics [14]. In a study with 75 premenopausal white type 1 diabetic women, with matched controls, poor glycemic control was associated with decreased BMD at all bone sites except spine with low bone formation markers (osteocalcin), but with normal bone resorption markers (N-telopeptide), suggesting uncoupled turnover favoring resorption [15]. The findings regarding bone turnover markers are similar in type 2 diabetics [16]. Some studies suggest that improvement in glycemic control can result in increased bone turnover markers, of resorption and formation, in both male and female diabetics, possibly mediated by increased levels of insulin like growth factor-1 (IGF-1) [16]. One study suggests, that improvement of poorly controlled type 2 DM decreased bone turnover, increasing osteocalcin but also decreasing markers for bone resorption [17]. Thus, bone turnover seems to be altered by glycemic control, but the exact effect of hyperglycemia is not well established and further research is needed. In addition, bone turnover can be affected by many other factors and there can be wide inter-subject variability. However, what is very interesting is the potential role of bone as an endocrine organ and osteocalcin acting as regulating hormone for insulin secretion from pancreatic beta cells. Evidence from studies suggests that higher osteocalcin is associated with an improved metabolic profile, less insulin resistance in patients without diabetes and lower HbA1c in diabetics [18–20]. Evidence from rodent models show that infusion of osteocalcin increases insulin secretion reduces serum glucose and improves glucose tolerance [21]. Thus, the low osteocalcin levels in diabetics could be associated with hyperglycemia itself, rather than a marker for bone formation. In this case, serum alkaline phosphatase and procollagen type 1 N-terminal propeptide can be used as more reliable bone formation markers. Bone metabolism may also be affected by late complications of diabetes, like renal failure with impaired 1-α-hydroxylation of 25 (OH) vitamin D. One additional factor leading to decreased bone mass in patients with DM may be the increased urine calcium excretion, associated with a functional hypoparathyroidism, as seen in a study by Thalassinos et al. [22]. In this study of 59 type 1 and type 2 diabetics with normal renal function, 24 h urinary calcium, parathyroid hormone (PTH) and serum calcium were measured under both poor and good glycemic control. In both groups urinary calcium was found to be elevated and improved glycemic control resulted in a significant reduction. With poorly controlled DM, considerably more type 1 diabetics had PTH levels below the detection limit with lower calcium, compared to type 2 diabetics. After improved control only urinary calcium continued to be higher, whereas PTH and calcium levels normalized. These results suggest that during poor glucose control, increased urinary calcium secretion with a component of "functional hypoparathyroidism", especially in type 1 diabetics, can be one of the factors leading to decreased BMD with DM [22].

Please cite this article in press as: Antonopoulou M, et al. Diabetes and bone health. Maturitas (2013), http://dx.doi.org/10.1016/j.maturitas.2013.04.004