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Osteoporosis and bone fractures in patients with diabetes mellitus



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Abstract

Patients with diabetes mellitus are at an increased risk of bone fractures. While in type 1 diabetes (in which the risk is increased by an average of six times) the major reason is low bone mass, patients with type 2 diabetes are at an increased risk (which is about twice the risk in the general population) despite increased bone mineral density (BMD) and this is caused by inferior quality of bone.

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Introduction

Osteoporosis is a systemic disease of the skeleton characterised by low bone mass, impaired microarchitecture of the bone and the resulting increased risk of fracture, with the latter being the most important in terms of clinical significance. Fracture risk assessment is currently the mainstay of diagnostic evaluation of osteoporosis [1].

The metabolic changes resulting from diabetes mellitus considerably affect bone metabolism and increase the risk of fractures. In patients with type 1 diabetes the impaired bone formation is a result of absolute deficiency of insulin and insulin-like growth factor-1 (IGF-1), which leads to lower values of peak bone mass. In type 2 diabetes, obesity, the increased load on bone and insulin resistance resulting in hyperinsulinaemia all lead to increased bone formation. In spite of that, however, the risk of fractures, especially peripheral fractures, is still increased in these patients. In both types of diabetes, bone displays inferior quality and strength [1].

The pathogenesis of bone changes in patients with diabetes mellitus

When analysing the underlying mechanisms of bone changes in patients with diabetes, the differences in the pathogenesis of type 1 vs. type 2 diabetes should be taken into account, especially in terms of endogenous insulin secretion by pancreatic beta cells. Insulin is an anabolic hormone which acts on bone through insulin receptors expressed by osteoblasts: IRS-1 and IRS-2 (IRS, *insulin-like substrate*). Stimulation of IRS-1 affects bone turnover, while stimulation of IRS-2 shifts the balance between bone formation and resorption towards the former. Insulin stimulates osteoblast proliferation, inactivates p27 (responsible for osteoblastogenesis), promotes collagen synthesis and increases glucose uptake [2].

Type 1 diabetes mellitus

In type 1 diabetes, autoimmune processes lead to the destruction of pancreatic β cells, which results in absolute insulin deficiency, which coupled with hyperglycaemia (see below) negatively affects the bone. In type 2 diabetes, on the other hand, insulin secretion is not only preserved but is also excessive for several years. The development of hyperglycaemia is determined by the co-existence of insulin resistance (which leads to compensatory hyperinsulinaemia) and insulin secretion defect [3]. In type 2 diabetes, the stimulatory effects on bone formation co-exist with the negative effects of hyperglycaemia.

In type 1 diabetes, the deficiency of insulin and IGF-1, which is present since the diagnosis (in adolescence or childhood), leads to impaired bone formation, abnormal mineralisation, abnormal bone microarchitecture, increased fragility of the bone and reduced peak bone mass [2]. The persistently poor metabolic control in adolescents with type 1 diabetes increase the risk of osteoporosis in adult life [4]. The premenopausal reduction of bone mineral density (BMD) in women with type 1 diabetes increases the risk of postmenopausal osteoporosis [5].

The co-existence of other autoimmune diseases (Graves' disease with hyperthyroidism, coeliac disease with calcium malabsorption) is an additional risk factor for osteoporosis and increased fracture risk in type 1 diabetes [6].

Bone mineral density is also affected by genetic factors. The $\alpha 1$ type 1 collagen (COL1A1) gene polymorphism in patients with type 1 diabetes is associated with reduced BMD at femoral neck and reduced serum vitamin D levels versus controls [7]. On the other hand, vitamin D receptor gene polymorphism has little effect on BMD in type 1 diabetics [8].

Interestingly, children and adolescents with type 1 diabetes have an increased concentration of osteoprotegerin compared to controls. Osteoprotegerin is a protein belonging to the family of tumour necrosis factor receptors (TNFR) capable of binding with receptor activator of nuclear factor kappa B ligand (RANKL), which prevents RANKL from binding to receptor activator of nuclear factor kappa B (RANK) and results in the suppression of osteoclastogenesis. Elevated osteoprotegerin in patients with type 1 diabetes may be the body's response to increased bone resorption. Osteoprotegerin is also elevated in diabetic nephropathy, cardiovascular disease and it shows a positive correlation with HbA_{1c}, blood pressure and age [9, 10].

Type 2 diabetes mellitus

In type 2 diabetes, hyperinsulinism coupled with insulin resistance increases bone mass through effects on bone formation via IRS-1 and IRS-2 surface receptors on osteoblasts and by reducing the concentration of sex-hormone binding globulin (SHBG), which leads to increased concentrations of oestradiol and testosterone. Additionally, in obesity, which usually accompanies type 2 diabetes, peripheral conversion of androgens to oestrogens by adipose tissue aromatase is increased and these hormones exert protective effects on bone. As a result, increased BMD is observed in type 2 diabetics [2, 11].

The data on the effects of leptin, secreted by white adipose tissue, on bone metabolism are conflicting. Leptin seems to stimulate osteoblasts (through surface receptors) and bone formation and from the other side, to increase bone resorption (through effects on the central nervous system) [12].

Glycaemic control and the type of treatment play an important role in the preservation of bone mass. BMD in patients with type 2 diabetes treated with insulin is increased compared to patients on oral antidiabetic treatment due to the anabolic effects of insulin on bone [13].

Bone mineral density may also be affected by the equally frequently used antihypertensive and lipid-lowering treatment in diabetic patients. Loop diuretics increase urinary calcium loss, while thiazide diuretics reduce calciuria. Some studies have demonstrated a beneficial effect of statins on increasing BMD [6].

Aetiologic and pathogenetic factors common to both types of diabetes mellitus

Hyperglycaemia resulting from impaired secretion and/or action of insulin acts on bone tissue cells through

advanced glycation end-products (AGEs), which thanks to the presence of specific surface receptors lead to increased production of interleukin-6 (IL-6) through osteoblast line cells. IL-6 stimulates osteoclasts to commence bone resorption. The accumulation of AGEs in collagen leads to inferior bone quality and strength. Furthermore, glycated collagen inhibits expression in osteoblasts [14]. Hyperglycaemia impairs gastrointestinal calcium absorption by increasing gastroparesis [15]. In the general population, fasting glucose levels (as well as glucose levels following glucose load) shows a positive correlation with osteoporotic fracture risk [16].

The development of osteoporosis in both types of diabetes is also promoted by the co-existence of chronic microvascular complications, which also affect the bone marrow blood vessels [17]. The presence of peripheral and autonomic neuropathies is associated with bone changes of Charcot's neuroarthropathy type, in which increased blood flow and the formation of arteriovenous shunt lead to increased bone resorption. The increased bone damage in patients with diabetic neuropathy may be related to overexpression of nuclear factor kappa B (NF- κ B), leading to increased release of proinflammatory cytokines, such as TNF- α and interleukin-1 β , which stimulates osteoclast synthesis [18]. Reduced BMD is seen in patients with type 1 and type 2 diabetes alike, with co-existent Charcot's neuroarthropathy, while only in patients with type 1 diabetes low BMD precedes the development of neuroarthropathy [19].

In both types of diabetes, a negative calcium balance is observed, which is caused by insufficient supply of dietary calcium, intestinal absorption abnormalities and hypercalciuria secondary to hyperglycaemia. Low serum magnesium, a frequent finding in diabetes, especially in poorly controlled diabetes, leads to abnormal bone metabolism [7, 20].

Physical activity, increased ingestion of calcium and a higher body mass index (BMI) increase BMD in patients with type 2 diabetes, while older age and increased content of zinc in the diet are risk factors of osteopenia [21].

Bone fractures in patients with diabetes mellitus

Despite the differences in the pathogenesis of bone changes and BMD values between patients with type 1 diabetes and patients with type 2 diabetes, an increased risk of bone fractures is observed in both types of diabetes [22]. The Nurses' Health Study has demonstrated an increased risk of femoral neck fracture in women with type 1 and 2 diabetes compared to non-diabetic women. After considering BMI, physical activi-

ty, menopausal status, hormone replacement therapy use, vitamin D and calcium supplementation and smoking status, the relative risk of femoral neck fracture was 6.4 (3.9–10.3) in women with type 1 diabetes *versus* non-diabetics and 2.2 (1.8–2.7) in women with type 2 diabetes *versus* non-diabetics. Patients with a longer duration of diabetes were at a higher risk of fracture compared to women with a shorter duration of diabetes [23]. Similar results were obtained in a meta-analysis of several studies evaluating the risk of femoral neck fracture in diabetes [24]. Data on spinal fractures and forearm fractures in patients with diabetes are sparse and contradicting.

In type 1 diabetes, the increased risk of fractures may result from reduced BMD, while in type 2 diabetes, it may be a consequence of poorer bone quality, impaired micro- and macroarchitecture and the increased tendency to fall. The risk of fractures in diabetes is also affected by the underlying disease, its course, incidence of hypoglycaemic episodes, especially if they are not preceded by prodromal symptoms, and diabetic complications, both microvascular and macrovascular. Cardiovascular complications (stroke, transient ischaemic attacks, myocardial infarction, heart failure) considerably impair motor performance in diabetic patients. Also type 2 diabetes related obesity limits the patient's motor activity and contributes to the development of osteoarthritis, which interferes with ambulation. Poorer motor activity is the cause of increased risk of falls, leading to extraspinal fractures. The higher risk of falls and the resulting fractures in patients with diabetes may also result from the presence of diabetic retinopathy or cataracts, which impair visual acuity. In patients with co-existing sensory motor neuropathy and diabetic foot, balance disorders are observed [25]. Patients with advanced diabetic nephropathy develop secondary hyperparathyroidism leading to increased calcium resorption from bone [26].

Patients with diabetes more frequently require medication, which may result in increased risk of falls (e.g. β -blockers, sedatives: benzodiazepines, barbiturates, antidepressants, antiparkinsonian drugs, opioids).

Similarly, certain drugs used in the treatment of diabetes may affect bone mass status and the risk of fractures. Thiazolidinediones (nuclear PPAR- γ agonists which reduce insulin resistance), which are used in the treatment of type 2 diabetes, exert anti-osteoblastic effects, leading to osteoblast and osteocyte apoptosis [27]. Rosiglitazone increases the risk of foot and upper extremity fractures in women, as demonstrated in such studies as ADOPT (A Diabetic Outcome Progression Trial) [28]. Metformin used in patients with type 2 diabetes (which reduce insulin resistance and hyperinsulinism) similarly to thiazolidinediones does not increase the risk of bone fractures [29].

Treatment of osteoporosis in patients with diabetes mellitus

In all patients with type 1 diabetes of long duration and in lean women with complications of type 2 diabetes screening for osteoporosis is recommended [1].

Remembering the effects of hyperglycaemia on the development of bone changes in diabetic patients it is very important to achieve the level of glycaemic control in accordance with the Polish Diabetes Society guidelines ($HbA_{1c} \leq 6.5\%$). In many patients with type 2 diabetes, initiation of insulin therapy may be beneficial due to the anabolic effects of insulin on bone [1].

Patients with diabetes require supplementation of **calcium** (1000–1500 mg/day) and **vitamin D** (800–2000 IU/day) [1]. The diabetic diet they follow may limit the ingestion of dairy products and lead to calcium deficiency. This results in increased parathormone secretion and calcium resorption from bone. Vitamin D deficiency in patients with diabetes may be a result of decreased dermal synthesis, impaired formation of its active metabolite in the kidneys and reduced number and affinity of vitamin D receptors in target organs. In patients with type 2 diabetes with microvascular complications, vitamin D deficiency is more prevalent, while data on the relationship between insulin treatment and hypovitaminosis D are conflicting [30, 31].

Management of osteoporosis in diabetes should be commenced early in order to reduce the risk of fractures. The National Osteoporosis Foundation (NOF) recommends a threshold for therapeutic intervention when BMD T-score is less than -1.5 SD. Drugs which have proved useful in such management include drugs approved for the treatment of osteoporosis in the general population [1].

Bisphosphonates suppress bone turnover by reducing bone resorption by osteoclasts, which increases BMD and reduces fracture risk. Alendronate sodium increases BMD in elderly women with type 2 diabetes. Over a 3-year follow-up of elderly women with diabetes, there has been an increase in BMD of 6.6% in the lumbar spine and of 2.4% in the hip. Alendronate sodium was well tolerated [32]. No strong clinical evidence exists, however, on the effect of bisphosphonates on the incidence of fractures.

Contraindications to bisphosphonates in diabetes include: autonomic neuropathy in the gastrointestinal tract and renal failure. The new intravenous formulations of bisphosphonates (ibandronate, zoledronate) may be an alternative if contraindications to oral treatment exist [33].

Selective oestrogen receptor modulators may also be useful in patients with diabetes complicated by osteoporosis. However, due to the reduced incidence of fractures observed in the general population only with

no effect on extraspinal fractures, they are preferred, at least in the general population, in early postmenopause, when femoral neck fractures are not so prevalent as in the old age [34].

Other drugs with potentially beneficial effects on bone in diabetes include **strontium ranelate** and **teriparatide** (recombinant human parathyroid hormone 1-34). In addition to the antiresorptive action, these drugs exert anabolic effects, stimulating bone formation (which is reduced in patients with insulin deficiency). However, no clinical evidence is available to support their efficacy in patients with diabetes.

A very important element of osteoporosis prevention and treatment strategy in patients with diabetes consists in the inclusion in the patient education programme of information about complications, screening tests, lifestyle and physical activity advice [1]. The knowledge of the possibility of osteoporosis in patients with diabetes allows for the implementation of early prevention, diagnostic evaluation and, if necessary, treatment.

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