*Marta Toboła, Magdalena Osińska, Ada Sawicka

Diabetes mellitus, osteoporosis and bone fractures

Cukrzyca, osteoporoza i złamania kości

Department of Geriatrics, Internal Medicine and Metabolic Bone Diseases, Centre of Postgraduate Medical Education, Warsaw
Head of Department: Associate Professor Marek Tałałaj, MD, PhD

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S u m m a r y

The prevalence of osteoporosis and diabetes mellitus (DM) is alarming. Both diseases have similar molecular mechanisms and genetic predispositions. Patients with type-1 DM (T1DM) have reduced bone mineral density (BMD), which may partly explain increased fracture risk. Most patients with type-2 DM (T2DM) show normal or increased BMD but higher risk of fractures. Conventional diagnostic methods used in patients suspected for osteoporosis, such as the fracture risk assessment tool (FRAX) and DXA measurements are not sufficient in patients with DM.

Anti-diabetic therapies can additionally enhance fracture risk or reduce the incidence of low energy fractures. Thiazolidinediones reduce bone formation, and increase bone resorption. The drugs increase risk of fractures, that is further increased with duration of treatment. Insulin slightly increases fracture rate, possibly due to frequent episodes of hypoglicemia resulted in falls. Metformin has a positive effect on osteoblast differentiation and decreases fracture rate in T2DM patients. It is important to verify all risk factors for fracture in every individual diabetic patient and take into account this assessment when anti-diabetic therapy is chosen.

S t r e s z c z e n i e

Częstość osteoporozy i cukrzycy (DM) jest alarmująca. Obie choroby mają zbliżone mechanizmy molekularne i predyspozycje genetyczne. Pacjenci z cukrzycą typu 1 (T1DM) charakteryzują się obniżoną gęstością mineralną kości (BMD), co częściowo tłumaczy zwiększone ryzyko złamań. Większość pacjentów z cukrzycą typu 2 (T2DM) ma normalną lub podwyższoną BMD, ale wyższe ryzyko złamań kości. Konwencjonalne metody diagnostyczne wykorzystywane u pacjentów podejrzewanych o osteoporozę, takie jak ocena ryzyka złamań (FRAX) i pomiary przy pomocy DXA, są niewystarczające u pacjentów z DM.

Leki przeciwcukrzycowe mogą dodatkowo zwiększyć lub zmniejszyć częstość złamań niskoenergetycznych. Tiazolidinediony redukują tworzenie tkanki kostnej oraz zwiększają jej resorpcję. Leki zwiększają ryzyko złamań, które wzrasta w miarę wydłużania czasu terapii. Insulina nieznacznie zwiększa częstość złamań, prawdopodobnie z powodu większej liczby epizodów hipoglikemii, która sprzyja upadkom. Metformina wywiera korzystny wpływ na różnicowanie się osteoblastów i zmniejsza częstość złamań u pacjentów z T2DM. Ważne jest, aby weryfikować obecność czynników ryzyka złamań u każdego pacjenta z cukrzycą i uwzględnić wyniki tej oceny przy wyborze terapii przeciwcukrzycowej.

Conflict of interest
Konflikt interesów
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Address/adres:
*Marta Toboła
Department of Geriatrics,
Internal Medicine and Metabolic Bone Diseases
Centre of Postgraduate Medical Education
ul. Czerniakowska 231, 00-416 Warszawa
tel. +48 (22) 584-11-47
kl.geriatrii@szpital-orlowskiego.pl

INTRODUCTION

The prevalence of osteoporosis and diabetes mellitus is alarming. In the United States, 50% of elderly individuals are osteoporotic and 20% of population have either diabetes or prediabetic condition. It was found that both diseases had similar features including molecular mechanisms and genetic predispositions (1). Bone and energy homeostasis are under the control of the same regulatory factors, including insulin, bone derived hormone – osteocalcin, peroxisome proliferator-activated receptor-γ (PPAR-γ), as well as gastrointestinal hormones, such as glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide (GLP).

Insulin exerts an anabolic effect on bone tissue due to its structural homology to insulin-like growth factor-I (IGF-I), interacting with the IGF-I receptor present on osteoblasts (2). It was shown that lower serum IGF-I concentrations are associated with a higher number of vertebral fractures in postmenopausal women

with type 2 diabetes (3, 4). On the other hand insulin increases bone resorption by reducing an expression of osteoprotegerin (OPG) – a decoy receptor for receptor activator of nuclear factor kB ligand (RANKL) and stimulates bone turnover (5-8).

PATOPHYSIOLOGY OF OSTEOPOROSIS IN DIABETES MELLITUS

A complex and heterogenous molecular pathophysiology seems to underlie osteoporosis and fracture risk in diabetes-related bone disease. Diabetes mellitus (DM) was found to induce the overexpression of many cytokines and hormones, such as sclerostin, gremlin, angiotensin II (Ang-II), parathyroid hormone (PTH), interleukin-6 (IL-6) and tumor necrosis factors (TNFs) but it also sequesters the over expression of vitamin D and neurotransmitters required for growth of osteoblasts (1). DM is responsible for the upregulation of PPAR-γ, fatty acid binding protein, tumor necrosis factor-α (TNF-α) and for increased availability of mesenchymal stem cells for adipocyte formation at the cost of osteoblast formation (9-12). For this reason DM is considered responsible for the deposition of lipids in the bone marrow, expansion of marrow cavity, diminishing of bone microcirculation, and the reduction of osteoblast number available for bone formation (13-15).

Serum osteocalcin concentration has been reported to be negatively correlated with hemoglobin A1c (HbA1c) level (16). In patients with DM osteocalcin, both in bone and serum, has been found to be incompletely carboxylated, and undercarboxylated osteocalcin has been negatively implicated in energy metabolism and glucose control (17, 18). Higher levels of undercarboxylated osteocalcin were suggested to be linked to increased risk of hip fractures (19).

Recent human cross-sectional studies confirm that bone turnover is attenuated in type 2 diabetes mellitus (T2DM). Sclerostin, an inhibitor of bone formation, was shown to be increased in patients with T2DM, independent of gender and age. Positive correlation was documented between sclerostin level and both duration of T2DM and HbA1c, and negative correlations between sclerostin and bone turnover markers (13).

Decreased bone quality in patients with T2DM is partly combined with advanced glycation end products (AGEs) – highly reactive glucose metabolites, which are implicated in forming additional cross-links between collagen fibres in bone. It results in excessive stiffness and in fragility of bone tissue (20, 21). AGEs accumulate in various tissues including bone, interfere with normal tissue function, as well as increase inflammation and cellular damage. AGEs have been identified as a biomarkers of increased fracture risk. Accumulation of pentosidine, one of the AGEs, in cortical and trabecular bone tissues was reported to exert negative impact on bone strength (22-24), while higher levels of the endogenous secretory receptor for AGEs (esRAGE) – a decoy AGE receptor – have protective effects on fracture risk in diabetes (25).

DIABETES MELLITUS AND RISK OF FRACTURES

Significant associations between diabetes mellitus and fracture risk were documented. Patients with T1DM are characterized by reduced BMD, which may partly explain increased fracture risk. Most patients with T2DM show normal or increased BMD (at the spine and femoral neck) but, in spite of this, higher fracture risk (26). The meta-analysis of the published data showed that younger age, higher body mass index, male gender, and higher HbA1c were positively associated with higher BMD values in patients with T2DM (27). The results of 16 studies performed in the US and Europe revealed that T2DM was associated with over two-fold increase in risk of hip fractures in men (relative risk [RR] = 2.8) and women (RR = 2.1) (1). Studies conducted on a Japanese population indicated that T2DM patients, both men and women have increased rate of vertebral fractures (28). The results of Rotterdam Study documented that individuals with T2DM were characterized by 69% higher risk of non-vertebral fractures compared to those without diabetes, despite having higher BMD at the femoral neck and lumbar spine (29). It was shown that glycemic control at the HbA1c level of 7.5% was associated with higher BMD but also with higher risk of all types of osteoporotic fractures (30). Obese Japanese men with T2DM and HbA1C of 9% and above had three times increased risk of vertebral fractures compared with men with diabetes and normal BMI, despite equal or even higher BMD values (16). Human histomorphometric studies revealed that bone turnover in older T2DM patients was diminished. Low bone turnover could result in higher BMD together with decreased bone quality (31).

Bone mineral density in patients with T1DM is only modestly reduced (estimated -0.22 spine Z-score, -0.37 hip Z-score) but relative risk of hip fractures is as high as 6.3 (32). The incidence of hip fractures among women with T1DM, included in the Nurses Health Study, was reported as 383 per 100,000 over a follow up period of 2.2 million person-years. This means a 6-fold increase from the overall incidence of hip fractures in the population, reported at 63 per 100,000, and a 2.5-fold increase from the incidence of hip fractures in type 2 diabetics (33).

Conventional diagnostic methods used in patients suspected for osteoporosis, such as the fracture risk assessment tool (FRAX) and DXA measurements are not sufficient in the case of diabetes (1). Patients with DM have increased risk of falls due to microvascular (retinopathy, neuropathy) and macrovascular complications. They are characterized by diabetic neuropathy-mediated muscle atrophy and muscle weakness. Diabetic retinopathy may result in loss of vision, while heart failure as well as polyneuropathy promote the rate of falls (34).

PHARAMACOTHERAPY AND FRACTURES

Thiazolidinediones (rosiglitazone, pioglitazone) increase insulin sensitivity via activation PPAR-γ. Extensive clinical evidence indicate that these drugs cause bone loss and increase fracture risk (35-37). Thiazolidinediones (TZDs) impair the differentiation of osteoblast precursors and reduce bone formation. TZDs increase adiposity of bone marrow, promote osteoclast differentiation, and diminish aromatase activity leading to increased bone resorption. Retrospective studies on 84,339 diabetic patients in Canada concluded that both women and men receiving TZDs have increased risk of fractures, that is further increased with duration of treatment. Of the two evaluated drugs pioglitazone was found more strongly associated with fractures than rosiglitazone (38). Observational studies based on the UK General Practice Research Database (GPRD), which included a large population of older individuals, showed that therapy with TZD and its duration were associated with significant increase in nonvertebral fractures independent of patient sex and age. The TZD monotherapy was associated with increased risk of peripheral fractures regardless of sex and type of TZD (39). Another study on the GPRD population suggested that prior fracture increased the risk of the next fracture occurrence. Among the persons with prior fracture exposure to TZD, either rosiglitazone or pioglitazone, increased fracture rate by 43% similarly in men and women and the duration of exposure increased this risk even further (40). A meta-analysis of 10 randomized trials indicated that TZDs double the fracture rate in women with T2DM but not in men. It was found that that prolonged use of TZDs (> 25 prescriptions) increased mainly the risk of non-vertebral fractures, and that fracture risk is increased even in young women without other risk factors for osteoporosis (41).

Incretin analogs and DPP4 protease inhibitors are the new groups of anti-diabetic drugs that enhance the mechanism by which enteric hormones stimulate insulin release from β-cells and inhibit glucagon production in the liver (42). Glucose-dependent insulinotropic peptide (GIP), and glucagon-like peptides (GLP-1 and GLP-2) are released by gut endocrine cells in response to nutrient intake. Osteoblasts and osteoclasts express receptors for both GIP and GLP incretins.

A number of studies indicate that GLP-2 acts as an antiresorptive hormone in bone tissue (43), while GIP can act both as an antiresorptive and anabolic hormone (44, 45). Experimental studies showed that mice deficient in GLP-1 receptor develop cortical osteopenia and have more fragile bones as well as increased quantity of osteoclasts and increased bone resorption (46). The treatment of T2DM patients with incretin mimetic exenatide did not decrease BMD and did not have any effect on levels of serum bone turnover markers (47). A meta-analysis of 28 clinical trials, including 20,000 patients, showed that treatment with DPP-4 inhibitors was associated with a reduced risk of fractures (odd ratio 0.60) compared to placebo (48).

Insulin-treated older diabetic women, included in The Studies of Osteoporotic Fractures, had more than double the risk of foot fractures (multivariate adjusted RR = 2.66) compared with non-diabetics and non-insulin user diabetics (49). Studies among the Rochester cohort confirmed that insulin slightly but significantly increased fracture rate (50). It was suggested that treatment with insulin could increase fracture rate due to longer lasting disease, more diabetic complications, and more frequent episodes of hypoglicemia resulted in frequent falls (1).

Sulfonylureas (e.g. glyburide) comprise a class of drugs which activate sulfonylurea receptors on the surface of pancreatic β cells and stimulate exocytosis of insulin from vesicles. Evidence from The ADOPT and The Rochester studies indicate that glyburide therapy does not have any effect on bone mass and fracture risk, however glyburide therapy decreased serum levels of bone formation marker P1NP (35, 50, 51).

Metformin is the most commonly used drug to increase insulin sensitivity in diabetic patients. Biguanides decrease hepatic glucose production and increase glucose uptake in muscles. Metformin activate hepatic and muscle AMP-activated protein kinase (AMPK), which results in suppression of fatty acid synthesis, stimulation of fatty acid oxidation in the liver and increase in muscle glucose uptake (52). 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, dislipidemia and diabetes. Animal studies indicate that metformin has a positive effect on osteoblast differentiation due to increased activity of osteoblast-specific Runx2 transcription factor (53). It has also a negative effect on osteoclast differentiation and bone loss after ovariectomy by decreasing RANKL and increasing osteoprotegerin levels (54). Human studies of the Rochester cohort suggest that metformin decreases fracture risk in T2DM patients (hazard ratio 0.7), but the ADOPT study did not demonstrate beneficial effects of metformin on fracture risk (37, 50).

CONCLUSIONS

Both type-1 and type-2 diabetes mellitus increase the risk of bone fractures. The anti-diabetic therapies can additionally enhance fracture risk (TZDs and insulin), may not affect this risk (sulfonylurea) or even reduce incidence of low energy fractures (metformin).

It is important to verify all risk factors for fracture in every individual diabetic patient and take into account this assessment when anti-diabetic therapy is chosen.

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