OSTEOPOROSIS AND FRACTURE RISK IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

C. Poiana^{1,2}, C. Capatina^{1,2,*}

“Carol Davila” University of Medicine and Pharmacy - Endocrinology, “C.I.Parhon” National Institute of Endocrinology, Bucharest, Romania

Abstract

Type 2 diabetes mellitus (T2DM) is associated with an increased risk of fragility fractures compared to the general population. The pathogenesis of the elevated fracture risk is multifactorial and still largely elusive. In contrast to primary osteoporosis, in T2DM the bone mineral density (BMD) is increased compared to controls, suggesting that specific alterations in bone quality occur in diabetic patients. Even more, the specific increase in BMD observed in these patients impairs at least in part both the classical diagnosis of osteoporosis by dual-energy X-ray absorptiometry (DXA) and the current fracture risk estimation by FRAX (fracture risk assessment tool). Trabecular bone score (TBS) and TBS-adjusted FRAX could improve fracture risk estimation in patients with T2DM but improved tools are needed in the future as well as specific risk stratification criteria. Decreases in the fracture risk of patients with T2DM can be obtained by optimal diabetes control and standard treatment of osteoporosis (most drugs appear to have similar efficacy in patients with T2DM and primary osteoporosis).

Key words: osteoporosis, diabetes mellitus, fracture, risk.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has an ever increasing prevalence worldwide as well as improved survival, leading to a continuous rise in the number of cases experiencing complications and comorbidities.

Recent studies have shown that T2DM significantly increases the risk for vertebral (1), hip (2) and all non-vertebral fractures (3). This is not only significant at the individual level but also represents a major burden for health services (given the huge numbers of person affected and the costs associated to fracture care). Therefore, it is essential to address both the mechanisms and possible therapeutic interventions suited to decrease fracture risk in patients with T2DM.

Fracture prevalence in DM

T2DM was associated with an increased risk of any fracture [odds ratio (OR) 1.2], hip fractures (OR 1.4) and radius fractures (OR 1.2) (4). The most recent metaanalysis assessing the peripheral fractures in patients with T2DM described an increase in the risk of ankle fractures (RR 1.30) but a decrease in wrist fractures (RR 0.85) (5). One prospective study reported a significantly higher RR for hip fractures (1.82) as well as proximal humerus fractures (1.94) in T2DM women (6).

Most of these studies involved female patients. Studies in men are scarce and a gender difference (with increased hip fracture risk only in women) was suggested (7). In one study the risk of non-vertebral fractures was higher compared to controls only in T2DM men treated with insulin (RR 1.74) (8), but the effect of treatment itself cannot be excluded (see below). In another study on Japanese men those with T2DM had a hazard ratio of 2.76 for fragility fractures compared to normoglycemic men (9). Both longer diabetes duration and poor glycemic control seem associated with a higher fracture risk (10).

Bone mineral density (BMD) in DM

The bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) at femoral neck, hip and spine is higher in T2DM compared to controls. Younger age, male gender and higher BMI are associated with higher BMD levels in T2DM (11). Since fracture risk is increased by low BMD, while in patients with T2DM the BMD is increased, the elevated fracture risk of these patients must be the result of impaired bone quality and/or other diabetes-related fracture risk factors.

Pathogenesis of increased fracture risk in DM

The pathogenesis of the higher fracture rate observed in patients with T2DM, in whom BMD is

*Correspondence to: Cristina Capatina MD, “Carol Davila” University, Endocrinology, 34-36 Aviatorilor blvd., Bucharest, 011863, Romania, E-mail: cristina.capatina@yahoo.com

elevated, remains elusive. A wide range of factors have been involved, from increased rate of falling to distinct bone quality changes in patients with T2DM.

Increased falling rate

An increased risk of falls is present in elderly patients with T2DM compared to healthy elderly individuals (12). Several risk factors for falls are present in diabetic patients including visual loss due to diabetic retinopathy, neurological and cognitive impairment, comorbidities-especially cardiovascular, risks associated with medication use (hypoglycemia, hypotension). Falling frequency is an essential determinant of fracture risk therefore increased awareness of falling risk factors, optimal disease control and intensive patient education are needed. However, the overall risk of fracture in T2DM women is still increased after controlling for confounding factors including frequency of falls (13). Therefore other bone abnormalities associated with decreased bone strength (e.g altered microarchitecture, turnover etc), specific to diabetic patients have been suggested.

Microarchitectural changes and bone strength

Few histomorphometric data from patients with T2D are available. The bone microarchitecture assessed by high-resolution peripheral quantitative computed tomography (HRpQCT) offers conflicting results. In some studies it is similar to controls (for distal radius and tibia) (14), while in other studies an increased cortical porosity is observed (15). Bone microindentation testing (measuring the resistance of subperiosteal bone to penetration at the proximal tibia as a measure of bone strength) reveals decreased bone resistance in T2DM compared to controls (14). However, due to difficulties in obtaining bone histomorphometry in clinical settings, easier and widely available methods of investigating bone structure are needed. This is even more important in patients with T2DM in whom BMD is a poor marker for fracture risk.

Bone quality can be indirectly assessed with the use of trabecular bone score (TBS), a noninvasive method of investigating the bone microarchitecture based on the DXA image of the lumbar spine. The mean TBS is lower in T2DM compared to controls, especially in poorly-controlled patients (16), and this is correlated to an altered bone microstructure and a higher risk of fracture (17). Since TBS is widely available it might be a useful predictor of fracture risk in these patients. Currently no validating studies or specific cutoffs for

fracture risk prediction are available but these are strongly needed.

Bone turnover

Biochemical markers of bone turnover are significantly lower in T2DM patients compared to controls. Serum levels of bone resorption markers [C-terminal cross-linked telopeptide of type-I collagen (CTX) and tartrate-resistant acid phosphatase TRAP5b], and formation markers (e.g. osteocalcin) are all decreased in T2DM (18). Sclerostin, an osteocytic protein that inhibits osteoblast activity, is present in higher concentrations in the serum of patients with T2DM compared to controls, positively correlated with VF (19).

Pathogenesis of impaired bone quality

The pathogenesis of bone quality alterations in diabetic patients is most likely multifactorial. Chronic hyperglycemia might exert a detrimental effect on bone quality by means of high levels of advanced glycation end products (AGE) resulted from the non-enzymatic transformation of multiple proteins (especially collagen). Serum levels of AGE are higher in T2DM and positively correlated with new and prevalent VF (20). AGE progressively accumulate in the bone matrix and impair bone cells homeostasis (21).

Bone microvascular damage could also worsen bone strength: T2DM patients with microvascular disease have lower cortical thickness and increased cortical porosity at the radius (22). DM is also associated with a mild chronic inflammatory state and the increased levels of cytokines might exert significant antiosteoblastic or resorptive effects (23).

Excessive adipose tissue, especially that with visceral disposition (associated with insulin resistance, frequently observed in T2DM) might also contribute. Obesity, frequently associated in T2DM patients, is associated with higher risk of fracture (24), despite the fact that the increased mechanical loading conferred by high body weight and fat mass has a positive effect on bone formation and has classically been viewed as beneficial for bone function. Excessive adiposity affects bone homeostasis possibly through secretion of adipokines and inflammatory factors that increase bone turnover (25). Hyperinsulinaemia secondary to insulin resistance is positively correlated to BMD (26). Therefore in the early phases of the disease the combined effect of all these factors on bone health is variable but in late disease the additional deleterious effects of AGEs and microvascular damage lead to reduced bone strength and increased fracture risk (27).

Risk factors for fractures in DM

As shown above, BMD measurement is likely to grossly underestimate the fracture risk of patients with T2DM because it is not able to capture the specific bone alterations present in patients with T2DM (impaired bone quality, cortical porosity, low bone turnover). The association between classical clinical risk factors for osteoporotic fractures and incident fractures is similar in subjects with and without DM (28). However, other factors, specific to the population with DM need to be taken into account and improved tools for fracture-risk prediction are urgently needed.

Inadequate glycemic control is clearly associated with impaired bone quality: fracture risk is positively correlated to the serum HbA1c level, disease duration, presence of diabetes complications (10, 29).

Insulin use (associated with increased risk of hypoglycemia, more advanced disease or complications) has also been associated with an increased risk of non-vertebral fracture in diabetic men (8). Also, some other therapeutic options for the treatment of diabetes (see below) have been associated with increased risk.

As mentioned above, the falling history is of particular importance in T2DM patients.

Predicting Fracture Risk in Patients with T2DM

The use of classical fracture risk assessment tools underestimates the risk of major osteoporotic fractures in T2DM. For a given T-score and age or for a given FRAX score (fracture risk assessment algorithm), diabetic individuals had a higher fracture risk than controls. Also, at similar fracture risk a diabetic patient has a significantly higher T-score than controls. (30) The contribution of age in predicting fractures is also decreased in DM (hazard ratio 2.59 in non-diabetics compared to 1.64 in DM) (31).

TBS, although still lacking clear stratification criteria, appears more useful in T2DM. Significantly lower TBS and higher TBS-adjusted FRAX scores are found in T2DM patients with prevalent VF compared to those without VF (32). TBS is an independent predictor of fracture, even after adjustment for classical FRAX items (33). Current FRAX algorithm is not a highly accurate tool for patients with T2DM: for this subgroup of patients additional specific items might be included or a totally different specific tool for diabetic patients might be needed. To date, surrogate measures have been proposed for a more accurate appreciation of fracture risk in these patients such as using rheumatoid arthritis as a proxy for T2DM or decreasing the actual

BMD of the patient with T2DM by 0.5 standard deviations (SD) (34).

Antidiabetic treatment and fracture risk

Although optimal diabetes control is essential for decreasing the risk of complications, some of the antidiabetic drugs have been associated with increases in fracture risk. Thiazolidinediones (rosiglitazone and pioglitazone) increase the fracture risk (combined RR 1.4) for a wide range of fractures excepting hip and possibly vertebral fractures (35) and decrease BMD at the lumbar spine, total hip and forearm (36).

The most widely used biguanide drug, metformin, has osteogenic effects in culture (37), but in clinical studies the BMD at hip and lumbar spine is reduced during metformin treatment (38). The data regarding the effect on fracture rate are contradictory (39, 40). Overall metformin does not seem to have substantial clinical effects on bone health but randomized studies are clearly needed to clarify this.

The use of sulfonylureas was associated with an increased risk of hip fracture (OR 1.46) (41) despite earlier studies suggesting, on the contrary, a decrease in hip fractures rate associated with their use. (4) A possible explanation is that the increase in risk noted in some studies is related to possible drug-induced hypoglycemia (OR for fractures 2.42) (41).

Hypoglycemia, most common in insulin-treated T2DM cases, is associated with falls and consequently bone fractures (42). For newer products, associated with less hypoglycemia (eg insulin glargine), the risk of fractures is less (43). Chronic insulinotherapy has been associated with an increase in fracture prevalence (8) while others could not confirm this effect (4). The confounding effects of hypoglycemic episodes frequency, disease duration and severity cannot be excluded.

In older patients with T2DM, canagliflozin (a sodium glucose cotransporter 2 SGLT-2 inhibitor) showed small but significant reductions in total hip BMD and increases in bone formation and resorption biomarkers (44) as well as an increase in the global incidence of falls and fractures (45). However, a recent metaanalysis reported no conclusive association between SGLT-2 inhibitors use and fracture risk in T2DM (46).

Glucagon-like peptide-1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors do not significantly alter the fracture risk in large clinical studies (47).

Osteoporosis Therapy in Patients with Type 2 Diabetes

Studies specifically evaluating the antifracture efficacy of current antiosteoporotic drugs in patients with T2DM have not been published yet. Since osteoporosis in T2DM is a low bone-turnover condition (different from the widely prevalent postmenopausal osteoporosis), antiresorptive medications might not be a pathogenetically-targeted option. However, a metaanalysis evaluating the efficacy of some frequently used antiosteoporotic drugs (bisphosphonates, raloxifene and teriparatide) revealed a therapeutic efficacy similar to that obtained in non-diabetic patients with osteoporosis (48). Randomized control trials are needed to assess the fracture-preventing effect of antiosteoporotic drugs in patients with T2DM.

For denosumab no such analysis is available yet. In a phase 3, randomized, double-blind, placebo-controlled single-dose study on 250 osteoporotic patients, although not designed for the analysis of the subgroup of patients with diabetes, the increase of lumbar spine BMD was similar to that obtained in patients without T2DM (49). Since in animal studies denosumab induced human beta-cell proliferation both *in vitro* and *in vivo*, the possibility of using it in the future as a treatment for diabetes itself has been raised (50).

In conclusion, T2DM is associated with a higher risk of vertebral and hip fractures. Since fracture risk is present at higher BMD (hence at higher T scores) in T2DM, there is an absolute need to better clarify the pathogenetic mechanisms, fracture risk markers and treatment indication criteria for these patients. Fracture risk assessment tools that include the specific alterations of bone quality in T2DM are needed in order to allow a better selection of patients to be treated for osteoporosis. Optimal glycemic control should be aimed for, but the specific (sometimes detrimental) effect of certain antidiabetics on fracture risk must also be acknowledged. Further clinical data are needed to support the fracture risk reduction effect of available treatment strategies.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Wang J, You W, Jing Z, Wang R, Fu Z, Wang Y. Increased risk of vertebral fracture in patients with diabetes: a meta-analysis of cohort studies. *International orthopaedics*. 2016; 40(6): 1299-307.
2. Norris R, Parker M. Diabetes mellitus and hip fracture: a study of 5966 cases. *Injury*. 2011; 42(11): 1313-1316.
3. Rathmann W, Kostev K. Fracture risk in patients with newly diagnosed type 2 diabetes: a retrospective database analysis in primary care. *Journal of diabetes and its complications*. 2015; 29(6): 766-770.
4. Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. *Diabetologia*. 2005; 48(7): 1292-1299.
5. Vilaca T, Walsh J, Eastell R. Discordant pattern of peripheral fractures in diabetes: a meta-analysis on the risk of wrist and ankle fractures. *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2019; 30(1): 135-143.
6. Schwartz AV, Sellmeyer DE, Ensrud KE, Cauley JA, Tabor HK, Schreiner PJ, Jamal SA, Black DM, Cummings SR. Older women with diabetes have an increased risk of fracture: a prospective study. *J Clin Endocrinol Metab*. 2001; 86(1): 32-38.
7. Ahmed LA, Joakimsen RM, Berntsen GK, Fonnebo V, Schirmer H. Diabetes mellitus and the risk of non-vertebral fractures: the Tromsø study. *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2006; 17(4): 495-500.
8. Napoli N, Strotmeyer ES, Ensrud KE, Sellmeyer DE, Bauer DC, Hoffman AR, Dam TT, Barrett-Connor E, Palermo L, Orwoll ES, Cummings SR, Black DM, Schwartz AV. Fracture risk in diabetic elderly men: the MrOS study. *Diabetologia* 2014; 57(10): 2057-2065.
9. Iki M, Fujita Y, Kouda K, Yura A, Tachiki T, Tamaki J, Sato Y, moon JS, Hamada M, Kajita E, Okamoto N, Kurumatani N. Hyperglycemic status is associated with an elevated risk of osteoporotic fracture in community-dwelling elderly Japanese men: The Fujiwara-kyo osteoporosis risk in men (FORMEN) cohort study. *Bone* 2019; 121: 100-106.
10. Compston J. Type 2 diabetes mellitus and bone. *J Intern Med*. 2018; 283(2): 140-153.
11. Ma L, Oei L, Jiang L, Estrada K, Chen H, Wang Z, Yu Q, Zillikens MC, Gao X, Rivadeneira F. Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. *European journal of epidemiology* 2012; 27(5): 319-332.
12. Roman de Mettelinge T, Cambier D, Calders P, Van Den Noortgate N, Delbaere K. Understanding the relationship between type 2 diabetes mellitus and falls in older adults: a prospective cohort study. *PloS one*. 2013; 8(6): e67055.
13. Bonds DE, Larson JC, Schwartz AV, Strotmeyer ES, Robbins J, Rodriguez BL, Johnson KC, Margolis KL. Risk of fracture in women with type 2 diabetes: the Women's Health Initiative Observational Study. *J Clin Endocrinol Metab*. 2006; 91(9): 3404-3410.
14. Farr JN, Drake MT, Amin S, Melton LJ, 3rd, McCready LK, Khosla S. *In vivo* assessment of bone quality in postmenopausal women with type 2 diabetes. *Journal of bone and mineral research*. 2014; 29(4): 787-795.
15. Paccou J, Ward KA, Jameson KA, Dennison EM, Cooper C, Edwards MH. Bone Microarchitecture in Men and Women with Diabetes: The Importance of Cortical Porosity. *Calcified tissue international*. 2016; 98(5): 465-473.
16. Dhaliwal R, Cibula D, Ghosh C, Weinstock RS, Moses AM. Bone quality assessment in type 2 diabetes mellitus. *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2014; 25(7): 1969-1973.
17. Silva BC, Bilezikian JP. Trabecular bone score: perspectives of an imaging technology coming of age. *Arquivos brasileiros de endocrinologia e metabolismo*. 2014; 58(5): 493-503.
18. Kacso A, Goia-Socol M, Hazi G, Tomoaia G, Kacso IM,

- Georgescu CE. Effect of Experimental Dysglycemia on Under-Carboxylated Osteocalcin Production in Human Primary Osteoblast-Like Cell Cultures. *Acta Endocrinologica-Bucharest*. 2018; 14(1): 11-15.
19. Ardawi MS, Akhbar DH, Alshaikh A, Ahmed MM, Qari MH, Rouzi AA, Ali AY, Abdulrafee AA, Saeda MY. Increased serum sclerostin and decreased serum IGF-1 are associated with vertebral fractures among postmenopausal women with type-2 diabetes. *Bone* 2013; 56(2): 355-362.
20. Yamamoto M, Yamaguchi T, Yamauchi M, Yano S, Sugimoto T. Serum pentosidine levels are positively associated with the presence of vertebral fractures in postmenopausal women with type 2 diabetes. *The Journal of clinical endocrinology and metabolism*. 2008; 93(3): 1013-1019.
21. Li Z, Li C, Zhou Y, Chen W, Luo G, Zhang Z, Wang H, Zhang Y, Xu D, Sheng P. Advanced glycation end products biphasically modulate bone resorption in osteoclast-like cells. *American J of physiology-Endocrinology and metabolism* 2016; 310(5): E355-66.
22. Shanbhogue VV, Hansen S, Frost M, Jorgensen NR, Hermann AP, Henriksen JE, Brixen K. Compromised cortical bone compartment in type 2 diabetes mellitus patients with microvascular disease. *European journal of endocrinology / European Federation of Endocrine Societies* 2016; 174(2): 115-124.
23. Sun M, Yang J, Wang J, Hao T, Jiang D, Bao G, Liu G. TNF- α is upregulated in T2DM patients with fracture and promotes the apoptosis of osteoblast cells *in vitro* in the presence of high glucose. *Cytokine* 2016; 80: 35-42.
24. Tanaka S, Kuroda T, Saito M, Shiraki M. Overweight/obesity and underweight are both risk factors for osteoporotic fractures at different sites in Japanese postmenopausal women. *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2013; 24(1): 69-76.
25. Stojanovic SS, Arsenijevic NA, Djukic A, Djukic S, Simonovic SZ, Jovanovic M, Pejnovic N, Nikolic V, Zivanovic S, Stefanovic M, Petrovic D. Adiponectin As A Potential Biomarker of Low Bone Mineral Density in Postmenopausal Women with Metabolic Syndrome. *Acta Endocrinologica-Bucharest* 2018; 14(2): 201-207.
26. Barrett-Connor E, Kritiz-Silverstein D. Does hyperinsulinemia preserve bone? *Diabetes care*. 1996; 19(12): 1388-1392.
27. Shanbhogue VV, Mitchell DM, Rosen CJ, Bouxsein ML. Type 2 diabetes and the skeleton: new insights into sweet bones. *The lancet Diabetes & endocrinology*. 2016; 4(2): 159-173.
28. Fraser LA, Pritchard J, Ioannidis G, Giangregorio LM, Adachi JD, Papaioannou A, Leslie WD. Clinical risk factors for fracture in diabetes: a matched cohort analysis. *Journal of clinical densitometry: the official journal of the International Society for Clinical Densitometry*. 2011; 14(4): 416-421.
29. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes--a meta-analysis. *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2007; 18(4): 427-444.
30. Schwartz AV, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, Donaldson MG, Cauley JA, Harris TB, Koster A, Womack CR, Palermo L, Black DM. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. *JAMA*. 2011; 305(21): 2184-2192.
31. Leslie WD, Morin SN, Lix LM, Majumdar SR. Does diabetes modify the effect of FRAX risk factors for predicting major osteoporotic and hip fracture? *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2014; 25(12): 2817-2824.
32. Choi YJ, Ock SY, Chung YS. Trabecular Bone Score (TBS) and TBS-Adjusted Fracture Risk Assessment Tool are Potential Supplementary Tools for the Discrimination of Morphometric Vertebral Fractures in Postmenopausal Women With Type 2 Diabetes. *Journal of clinical densitometry*. 2016;19(4):507-514.
33. McCloskey EV, Oden A, Harvey NC, Leslie WD, Hans D, Johansson H, Barkmann R, Boutroy S, Brown J, Chapurlat R, Elders PJ, Fujita Y, Gluer CC, Goltzman D, Iki M, Karlsson M, Kindmark A, Kotowicz M, Kurumatani N, Kwok T, Lamy O, Leung J, Lippuner K, Ljunggren O, Lorentzon M, Mellstrom D, Merlijn T, Oei L, Ohlsson C, Pasco JA, Rivadeneira F, Rosengren B, Sornay Rendu E, Szulc P, Tamaki J, Kanis JA. A Meta-Analysis of Trabecular Bone Score in Fracture Risk Prediction and Its Relationship to FRAX. *Journal of bone and mineral research*. 2016; 31(5): 940-948.
34. Schacter GI, Leslie WD. DXA-Based Measurements in Diabetes: Can They Predict Fracture Risk? *Calcified tissue international*. 2017;100(2):150-164.
35. Bazelier MT, de Vries F, Vestergaard P, Herings RM, Gallagher AM, Leufkens HG, van Staa TP. Risk of fracture with thiazolidinediones: an individual patient data meta-analysis. *Frontiers in endocrinology*. 2013; 4: 11.
36. Billington EO, Grey A, Bolland MJ. The effect of thiazolidinediones on bone mineral density and bone turnover: systematic review and meta-analysis. *Diabetologia*. 2015; 58(10): 2238-2246.
37. Cortizo AM, Sedlinsky C, McCarthy AD, Blanco A, Schurman L. Osteogenic actions of the anti-diabetic drug metformin on osteoblasts in culture. *European journal of pharmacology*. 2006; 536(1-2): 38-46.
38. Dutta M, Pakhetra R, Garg M. Evaluation of bone mineral density in type 2 diabetes mellitus patients before and after treatment. *Medical journal, Armed Forces India*. 2012; 68(1): 48-52.
39. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, o'Neill MC, Zinman B, Viberti G. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *The New England journal of medicine* 2006; 355(23): 2427-2443.
40. Monami M, Cresci B, Colombini A, Pala L, Balzi D, Gori F, Chiasserini V, Marchionni N, Rotella CM, Mannucci E. Bone fractures and hypoglycemic treatment in type 2 diabetic patients: a case-control study. *Diabetes care*. 2008; 31(2): 199-203.
41. Rajpathak SN, Fu C, Brodovicz KG, Engel SS, Lapane K. Sulfonylurea use and risk of hip fractures among elderly men and women with type 2 diabetes. *Drugs & aging*. 2015; 32(4): 321-327.
42. Stepka M, Rogala H, Czyzyk A. Hypoglycemia: a major problem in the management of diabetes in the elderly. *Aging (Milan, Italy)*. 1993; 5(2): 117-121.
43. Pscherer S, Kostev K, Dippel FW, Rathmann W. Fracture risk in patients with type 2 diabetes under different antidiabetic treatment regimens: a retrospective database analysis in primary care. *Diabetes, metabolic syndrome and obesity: targets and therapy*. 2016; 9: 17-23.
44. Bilezikian JP, Watts NB, Usiskin K, Polidori D, Fung A, Sullivan D, Rosenthal N. Evaluation of Bone Mineral Density and Bone Biomarkers in Patients With Type 2 Diabetes Treated With Canagliflozin. *J Clin Endocrinol Metab*. 2016; 101(1): 44-51.
45. Watts NB, Bilezikian JP, Usiskin K, Edwards R, Desai M, Law G, Meininger G. Effects of Canagliflozin on Fracture Risk in Patients With Type 2 Diabetes Mellitus. *J Clin Endocrinol Metab*. 2016; 101(1): 157-166.
46. Tang HL, Li DD, Zhang JJ, Hsu YH, Wang TS, Zhai SD, Song YQ. Lack of Evidence for a Harmful Effect of Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors on Fracture Risk among Type 2 Diabetes Patients: A Network and Cumulative Meta-Analysis of Randomized Controlled Trials. *Diabetes, obesity & metabolism* 2016;18(12):1199-1206.
47. Driessen JH, Henry RM, van Onzenoort HA, Lalmohamed A, Burden AM, Prieto-Alhambra D, Neef C, Leufkens HG, de Vries F. Bone fracture risk is not associated with the use of glucagon-like

- peptide-1 receptor agonists: a population-based cohort analysis. *Calcified tissue international* 2015; 97(2): 104-112.
48. Anagnostis P, Paschou SA, Gkekas NN, Artzouchaltzi AM, Christou K, Stogiannou D, Vryonidou A, Potoupnis M, Goulis DG. Efficacy of anti-osteoporotic medications in patients with type 1 and 2 diabetes mellitus: a systematic review. *Endocrine* 2018; 60(3): 373-383.
49. Pitale S, Thomas M, Rathi G, Deshmukh V, Kumar P, Reddy S, Shetty N, Kakar A, Babhulkar S, Mody B, Chacko J, Acharya S, Joglekar S, Halbe V, Kravits BG, Waterrhouse B, Nino AJ, Fitzpatrick LA. A randomized placebo-controlled trial of the efficacy of denosumab in Indian postmenopausal women with osteoporosis. *Indian J Endocrinol Metab.* 2015; 19(1): 148-154.
50. Schmitz F, Roscioni S, Lickert H. Repurposing an Osteoporosis Drug for beta Cell Regeneration in Diabetic Patients. *Cell Metab.* 2015; 22(1): 58-59.