Type 2 Diabetes and Osteoporosis: A Guide to Optimal Management

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Context: Both type 2 diabetes (T2D) and osteoporosis are affected by aging and quite often coexist. Furthermore, the fracture risk in patients with T2D is increased. The aim of this article is to review updated information on osteoporosis and fracture risk in patients with T2D, to discuss the effects of diabetes treatment on bone metabolism, as well as the effect of antiosteoporotic medications on the incidence and control of T2D, and to provide a personalized guide to the optimal management.

Evidence Acquisition: A systematic literature search for human studies was conducted in three electronic databases (PubMed, Cochrane, and EMBASE) until March 2017. Regarding recommendations, we adopted the grading system introduced by the American College of Physicians.

Evidence Synthesis: The results are presented in systematic tables. Healthy diet and physical exercise are very important for the prevention and treatment of both entities. Metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonists should be preferred for the treatment of T2D in these patients, whereas strict targets should be avoided for the fear of hypoglycemia, falls, and fractures. Insulin should be used with caution and with careful measures to avoid hypoglycemia. Thiazolidinediones and canagliflozin should be avoided, whereas other sodium-dependent glucose transporter 2 inhibitors are less well-validated options. Insulin therapy is the preferred method for achieving glycemic control in hospitalized patients with T2D and fractures. The treatment and monitoring of osteoporosis should be continued without important amendments because of the presence of T2D.

Conclusions: Patients with coexisting T2D and osteoporosis should be managed in an optimal way according to scientific evidence. (***J Clin Endocrinol Metab*** **102: 3621–3634, 2017)**

The burden of diabetes is increasing as, according to the World Health Organization, ~422 million people are affected globally (1). Type 2 diabetes (T2D) accounts for most people affected and its prevalence increases with age. Osteoporosis affects ~125 million people in Europe, India, Japan, and the United States; it is estimated that one in three women and one in five men over the age of 50 will experience an osteoporotic fracture at some point in life (2). As the prevalence of osteoporosis rises with age, the increasing life expectancy will result in further increases in the global burden of osteoporosis. Both diseases are affected by aging and by changes in lifestyle and they can coexist, especially in the elderly. The true prevalence of their coexistence would be hard to determine, as the fracture risk in patients with T2D is increased and is underestimated by conventional diagnostic

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Abbreviations: aIRR, adjusted incidence rate ratio; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; HOMA-IR, homoeostatic model assessment of insulin resistance; SERM, selective estrogen receptor modulator; SGLT-2i, sodium-dependent glucose transporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione.

criteria for osteoporosis. Interestingly, there is a complex pathophysiological interaction between them: T2D affects bone metabolism and strength in a direct way, certain antidiabetic medications affect bone metabolism, and there is an association between diabetic complications and risk for falls and subsequent fractures (3).

Although many original papers, clinical statements, and guidelines focus on the management of patients with T2D and osteoporosis as separate diseases, their coexistence poses important pathophysiologic, diagnostic, and therapeutic issues that have not been fully elucidated. The aim of this article is to present updated information regarding the prevalence of osteoporosis and fracture risk in patients with T2D, to systematically review effects of medications on both entities, and to provide an individualized guide for the optimal management of patients with T2D and concomitant osteoporosis.

Methods

Search strategies

To identify publications on T2D and osteoporosis, a systematic literature search for human studies was conducted in three electronic databases (PubMed, Cochrane, and EMBASE) until March 2017 and using combinations of the key terms "type 2 diabetes" or "hyperglycemia" or "anti-diabetic agents (each one separately)" and "osteoporosis" or "fracture" or "bone mineral density" or "anti-osteoporotic agents" (each one separately). On the top, a manual search of key journals and abstracts from the major annual meetings in the fields of diabetes, osteoporosis, and endocrinology was conducted. Special attention was paid to papers and guidelines focusing on the management of patients with T2D and osteoporosis. The main search was completed independently by three investigators (S.A.P., A.D.D., and P.G.A.). Any discrepancy was solved by consultation of an investigator who was not involved in the initial procedure (D.G.G.).

Grading of recommendations

We adopted the grading system introduced by the American College of Physicians. Every recommendation is followed by a pair of grading, one grade for the strength of the recommendation and one for the quality of the evidence that supports the specific recommendation. There are three levels of "strength" (strong, weak, insufficient) and three levels of "quality" (high, moderate, low) (4).

Results and Discussion

Osteoporosis and fracture risk in patients with T2D

Both T2D and osteoporosis are negatively affected by aging and lifestyle changes and quite often coexist. Most importantly, several studies have demonstrated that fracture risk is increased in patients with T2D, being higher with longer duration of T2D, poor glycemic control, and when diabetic complications are present (3, 5–8). Interestingly, high fasting glucose variability has also been associated with higher risk for hip fracture (9). On the contrary, patients with impaired glucose tolerance are not at increased risk for fracture and in fact they may be at lower risk (7). It is postulated that this could be the effect of high body mass index (BMI) and insulin resistance, which are often encountered in patients with impaired glucose tolerance (10).

FRAX is a widely used online tool to calculate 10-year fracture risk probability. Its use to guide treatment decisions is reinforced by international societies (11, 12). T2D is not currently included in the FRAX tool and is not considered a secondary cause of osteoporosis, in contrast to type 1 diabetes (13). FRAX is known to underestimate fracture risk in patients with T2D (14), particularly when disease duration is >10 years (15). This is probably associated, at least partly, with the fact that in patients with T2D, bone mineral density (BMD) is generally higher than in nondiabetic patients (16). However, as in the general population, there is significant negative correlation between dual-energy x-ray absorptiometry–derived T-scores and the risk for fracture, even though patients with T2D tend to fracture at higher T-scores compared to the general population (16).

The effect of T2D on bone fragility is complex (3). Patients with T2D, especially those on treatment with hypoglycemic agents and those with complications, such as neuropathy and retinopathy, are at increased risk of falls, which predispose to fractures. Diabetic nephropathy with concomitant secondary hyperparathyroidism and renal osteodystrophy is also associated with augmented fracture risk (17). T2D, through hyperglycemia, oxidative stress, and the formation of advanced glycation end products, has a direct effect on bone metabolism, reducing bone turnover, and disrupting bone formation. Moreover, many patients with T2D have low serum vitamin D concentrations, probably as the result of obesity, low physical activity, and less sun exposure (17). As bone fragility in T2D is associated with high BMD and reduced bone turnover, there have been concerns about the effectiveness of antiosteoporotic medications in patients with T2D. Data so far have been reassuring, showing that bisphosphonates, raloxifene, and teriparatide are effective in increasing BMD both in patients with and without T2D (18, 19). Moreover, teriparatide is equally effective in reducing nonvertebral fractures in patients with T2D (19) and raloxifene in reducing vertebral fractures (18). There are currently no data about the effectiveness of other antiosteoporotic agents.

Effect of antidiabetic medications on bone metabolism

Although lifestyle intervention is the cornerstone of management for patients with T2D, most of those

eventually require pharmacologic therapy. Many agents are available, with different effects on bone metabolism and on the risk of fragility fractures. Metformin, sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase 4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1RA), sodium-dependent glucose transporter 2 inhibitors (SGLT-2i), and insulin are the most commonly used medications. Furthermore, bariatric surgery is now included in the therapeutic armamentarium for T2D. The results of our literature search for human studies examining the effects of antidiabetic agents on bone health are comprehensively presented in Table 1 (5, 20–68). Human clinical studies are included, as are meta-analyses of such studies when they exist. The PRISMA flow diagram detailing the process of identification, assessment, exclusion, and inclusion of such studies is presented in Fig. 1.

Metformin

Metformin primarily decreases hepatic glucose production by inhibiting key enzymes for gluconeogenesis and secondarily enhances peripheral insulin sensitivity. Experimental studies have indicated beneficial effects on bone formation (69), whereas large clinical studies resulted in neutral or positive effects on BMD and fracture risk, in different and various large patient cohorts (5, 20–29). Evidence from randomized controlled trials is missing. However, these observational data are strongly suggestive of a protective metformin profile regarding bone health.

Sulfonylureas

Sulfonylureas are sulfonylurea receptor-1 agonists, which initiate inhibition of the adenosine triphosphate–sensitive K^+ channel and result in depolarization of cell membrane, leading to increased endogenous insulin secretion. With the exception of MrOS study, which suggests that sulfonylureas increase fractures risk in old men with T2D (20), the rest of the studies are indicative of a beneficial or at least neutral effect on fracture risk (5, 20, 21, 25–32). Furthermore, the effect of sulfonylureas on bone metabolism and BMD seem to be neutral, too (25, 31). However, the high risk of hypoglycemic episodes, which can increase the final amount of falls and fractures in these patients, should be taken into consideration (70).

TZDs

TZDs are peroxisome proliferator–activated receptor γ agonists that modulate gene expression, resulting in improved glucose uptake, improved β-cell function, and increased insulin sensitivity. Within a few years of TZDs entering routine clinical use in the treatment of T2D, signals emerged suggesting reduced bone density (47, 48) and increased fracture risk (29, 45) with TZDs compared with other antidiabetic medications. This effect has now been confirmed in randomized studies (36–42, 44, 46) and meta-analyses (35, 43). A meta-analysis of close to 25,000 subjects showed an increased risk of fracture with TZDs in women (odds ratio of 1.94), but not in men (35). The risk was similar with pioglitazone and rosiglitazone, did not vary with age, and was associated with reductions in BMD (35). Other studies have suggested highest risk in women other the age of 65 (41), whereas some studies have also suggested an increased risk in men. A longitudinal follow-up of participants in the ACCORD study using TZDs also showed an increased rate of nonspine fractures in women (but not men) and reductions in risk following discontinuation of the TZD (34). A key part of the mechanism of action of TZDs is the activation of adipogenesis, for which peroxisome proliferator–activated receptor γ is required. Adipocytes and osteoblasts are both derived from mesenchymal stem cells (71), and activation of adipogenesis is known to be associated with suppression of regulators of bone differentiation. In keeping with this, *in vitro* studies have shown reduced expression of bone markers following treatment of mesenchymal stem cells with rosiglitazone (72) and reduced bone differentiation, whereas *in vivo* mouse models confirm reduced bone formation following rosiglitazone treatment (73). Thus, it is likely that the effects of TZDs on bone are closely linked to their metabolic effects, and it is clear now that these medications should be avoided in women with increased fracture risk.

DPP-4i

DPP-4i are oral diabetes medications that inhibit the enzyme DPP-4, which deactivates a variety of bioactive peptides, including glucose-dependent insulinotropic polypeptide and GLP-1; therefore, its inhibition potentially affects glucose regulation through multiple effects. Data from clinical trials so far suggest a potential favorable effect of these agents on bone metabolism, but real evidence is still lacking. The SAVOR–TIMI trial, examining saxagliptin (50), found no effect on fracture risk, whereas a meta-analysis including various medications of this category resulted in a protective effect on prevention of fractures (52). A recent cohort study from South Korea suggested a protective effect of DPP-4i as well (53). A *post hoc* analysis of 20 randomized controlled trials found a slightly higher incidence of fractures with saxagliptin compared with control group (51). Results of neutral effect on fracture risk were recently found in the TECOS trial with sitagliptin (49). Thus, to date more indications for a rather neutral effect of these drugs exist. Further studies are needed to confirm their possible favorable effect.

GLP-1RA

GLP-1RA potentiate glucose-induced insulin secretion and inhibit glucagon release. Furthermore, they delay gastric

Table 1. Effects of Antidiabetic Agents on Bone Health (Human Studies)

Authors, Year (Study Name), (Reference)	Sample Information	Follow-Up	Bone Formation	Bone Resorption	Bone Mineral Density	Fractures
Metformin						
Napoli N, 2014 (MrOS) (20)	881 T2D/5994 total (M)	9.1 ± 2.7 y				↔
Colhoun HM, 2012 (21)	206,672	9 y				↔
van Lierop AH, 2012 (22)	71 (M)	24 wk	↓	↓		
Borges JLC, 2011 (23)	688	18 mo			↔ (vs rosi)	
Kanazawa I, 2010 (24)	55	1 y	↔		↔ (vs. pio)	
Zinman B, 2010 (ADOPT) (25)	1605 (689 F, 916 M)	12 mo	↓	↓		
Home PD, 2009 (RECORD) (26)	4447	5.5 y				↔ (vs TZDs)
Solomon DH, 2009 (27)	30,000	10 mo				↓ (F, vs TZDs)
Melton LJ, 2008 (5)	1964	Retrospective				↓
Monami M, 2008 (28)	1945	4.1 ± 2.3 y				↔
Kahn SE, 2006 (ADOPT) (29)	4360	4 y				↓ (vs TZDs)
Vestergaard P, 2005 (30)	124,655 (Cs)/373,962 (Ct)	Retrospective				↓
Sulfonylureas						
Gilbert MP, 2015 (LEAD-3) (31)	746	52 w			↔	
Napoli N, 2014 (MrOS) (20)	881 T2D/5994 total (M)	9.1 ± 2.7 y				↔/↑
Colhoun, 2012 (21)	206,672	9 y				↔
Zinman B, 2010 (ADOPT) (25)	1605 (689 F, 916 M)	12 mo	↓	↓		
Dormuth CR, 2009 (32)	84,339	9 y				↓ (vs TZDs)
Home PD, 2009 (RECORD) (26)	4447	5.5 y				↔ (vs TZDs)
Melton LJ, 2008 (5)	1964	Retrospective				↔
Monami M, 2008 (28)	1945	4.1 ± 2.3 y				↔
Kahn SE, (ADOPT) (29)	4360	4 y				↓ (vs TZDs)
Vestergaard P, 2005 (30)	124,655 (Cs)/373,962 (Ct)	Retrospective				↓
Thiazolidinediones						
Choi HJ, 2016 (33)	207,558	5–8 y				↑
Schwartz AV, 2015 (ACCORD) (34)	6865	4.8 y (mean)				↑ (F)
Zhu ZN, 2014 (35)	24,554 (22 RCTs)	Meta-analysis				↑ (F)
Bilezikian JP, 2013 (36)	225 (F, rosi)	52 wk		↑	↓	
Bone HG,2013 (37)	156 (F, pio)	12 mo	↔	↔	↔	
Xiao WH, 2013 (38)	70 (pio)	3 mo	↓	↔		
Colhoun HM, 2012 (21)	206,672	9 y				↑ (rosi and pio)
van Lierop AH, 2012 (22)	71 (M)	24 wk		↑		
Borges JLC, 2011 (23)	688 (rosi)	18 mo			↓ (vs metf)	
Harsløf T, 2011 (39)	53 (F, rosi)	14 wk	↓	↑	↓	
Gruntmanis U, 2010 (40)	111 (rosi)	6 mo	↔	↑		
Habib ZA, 2010 (41)	19,070	Retrospective				↑ (F, >65 y, >1 y treat)
Kanazawa I, 2010 (24)	55 (pio)	1 y	↓		↓	
Zinman B, 2010 (ADOPT) (25)	1605 (689 F, 916 M)	12 mo	↓	↑		
Dormandy J, 2009 (PROactive) (42)	5238 (pio)	34.5 mo (mean)				↑ (F, >65 y, >1 y treat)
Dormuth CR, 2009 (32)	84,339	9 y				↑ (vs SUs)
Home PD, 2009 (RECORD) (26)	4447	5.5 y (mean)				↑ (vs metf and SUs)
Loke YK, 2009 (43)	13,715 (10 RCTs)	Meta-analysis			↓ (F)	↑ (F)
Glintborg D, 2008 (44)	30 (PCOS F)	16 wk	↓	↔	↓	
Meier C, 2008 (45)	1020 (Cs)/3728 (Ct)	Retrospective				↑
Berberoglu Z, 2007 (46)	56/26 (F, rosi)	12 wk	↓	↔		
Grey A, 2007 (47)	50 (F, rosi)	14 wk	↓	↔	↓	
Kahn SE, 2006 (ADOPT) (29)	4360	4 y (median)				↑ (F, vs metf and SUs)
Schwartz AV, 2006 (48)	666	4 y			↓ (F)	
DPP-4i						
Josse RG, 2017 (TECOS) (49)	14,671	43,222 person-y				↔
Choi HJ, 2016 (33)	207,558	5–8 y				↓ (vs TZDs)
Mosenzon O, 2015 (SAVOR-TIMI) (50)	8280/8212 (saxa)	2.1 y (median)				↔
Hirshberg B, 2014 (51)	9156 (saxa, 20 RCTs)	Pool analysis				↑
Monami M, 2011 (52)	11,880/9175 (28 RCTs)	Meta-analysis				↓
GLP-1RA						
Paschou SA, 2016 (53)	28 (lira)	8 wk	↔	↔	↔	
Gilbert MP, 2015 (LEAD-3) (31)	746 (lira)	52 wk			↔	
Iepsen EW, 2015 (54)	37 (lira)	52 wk	↑	↔	↔	
Su B, 2015 (55)	11,206 (16 RCTs)	Meta-analysis				↑ (exe)/↓ (lira)
Mabilleau G, 2014 (56)	2918/1337 (7 RCTs)	Meta-analysis				↔
Bunck MC, 2011 (57)	61 (exe)	44 wk	↔		↔	
SGLT-2i						
Bilezikian JP, 2016 (58)	716 (cana)	104 wk	↑	↑	↓ (hip)	

(*Continued*)

Table 1. Continued

Authors, Year (Study Name), (Reference)	Sample Information	Follow-Up	Bone Formation	Bone Resorption	Bone Mineral Density	Fractures
Tang HL, 2016 (59)	30, 384 (cana, dapa, empa, 38 RCTs)	Meta-analysis (24–160 wk)				↔
Watts NB, 2016 (60)	10,194 (nine studies)/ 4327 (CANVAS)/5867 (pooled)	Various studies included				↑ (cana)
Bays HE, 2014 (61)	376 (cana)	12 wk	↔	↑		
Bolinder J, 2014 (62)	182 (dapa)	102 wk	↔	↔	↔	↔
Kohan DE, 2014 (63)	252 (dapa)	104 wk				↑
Ptaszynska A, 2014 (64)	3281 (dapa, 12 studies)	Pool analysis				↔
Ljunggren O, 2012 (65)	165 (dapa)	50 wk	↔	↔	↔	↔
Insulin						
Napoli N, 2014 (MrOS) (20)	881 T2D / 5994 total (M)	9.1 ± 2.7 y				↑
Colhoun HM, 2012 (21)	206,672	9 y				↔
Bunck MC, 2011 (57)	61	44 wk	↔		↔	
Monami M, 2008 (28)	1945	4.1 ± 2.3 y				↑ (M)
Vestergaard P, 2005 (30)	124,655 (Cs)/373,962 (Ct)	Retrospective				↔
Ivers RQ, 2001 (66)	3654	2 y				↑
Nicodemus KK, 2001 (67)	32,089 (F)	11 y				↑
Schwartz AV, 2001 (68)	657 T2D/9654 total (F)	9.4 y				↑ (foot)

Abbreviations: ↓, decrease; ↑, increase; ↔, neutral; cana, canagliflozin; Cs, cases; Ct, controls; dapa, dapagliflozin; empa, empagliflozin; exe, exenatide; F, female; lira, liraglutide; M, male; metf, metformin; PCOS, polycystic ovary syndrome; pio, pioglitazone; RCT, randomized controlled trial; rosi, rosiglitazone; saxa, saxagliptin; SU, sulfonylurea.

emptying and reduce appetite, inducing clinically significant weight loss. They have been demonstrated to successfully control glucose levels and promote weight loss without increasing the risk of fractures. Recent experimental data from ovariectomized rats indicated that GLP-1RA exendin exerts a favorable effect on various bone parameters (74), with no significant differences in BMD observed with exenatide in humans in an early study, after weight loss (57). A meta-analysis of clinical trials found no effect of treatment on fractures as serious adverse events (56), whereas a later meta-analysis resulted in a protective effect of liraglutide and a negative effect of exenatide (55). However, none of the studies included was powered for bone outcomes. A recent randomized study including obese nondiabetic women showed that after 52 weeks of treatment with a long-acting GLP-1RA, for weight maintenance after 12% loss through a low-calorie diet, increased bone formation by 16% and prevented bone loss (54). A randomized, placebo-controlled, double-blinded, crossover trial with liraglutide in patients with T2D did not find any effect of treatment either on bone mineral density or bone markers. The treatment period in this study was shorter than in the previously described study (53). However, similar lack of an effect on BMD was found in a subgroup analysis of the LEAD-3 trial with a follow-up period of 52 weeks (70). The initial results of GLP-1RA effects on bone metabolism sound promising, but they should be interpreted with caution and in the context of the trials that were not designed for studying bone outcomes.

SGLT-2i

Glucose is physiologically reabsorpted in the proximal tubule of the kidney from glomerular filtrate via sodium-glucose cotransporters. SGLT-2i inhibit these cotransporters, resulting in loss of glucose calories in urine and reduction of glucose concentrations (75). Several agents are available with common ("class effect") and different characteristics. Regarding bone health, it has been shown that canagliflozin might exert negative effects on bone density, bone resorption, and fracture risk at the hip (58, 60, 61). This resulted in revision of the label of this drug and addition of a new warning by the US Food and Drug Administration in September 2015. With the exception of one study with dapagliflozin (63), empagliflozin and dapagliflozin have not been shown to exert significant changes in BMD, bone markers, or fracture risk, and therefore they seem to present a rather neutral effect on bone metabolism (59, 62, 64, 65). However, the concerns raised from studies with canagliflozin inevitably affect the whole class. Further studies are needed to elucidate the mechanisms of bone loss and the real safety profile among these newly used medications.

Insulin

No specific randomized controlled trial has been designed so far to investigate the effect of insulin treatment on bone health. However, it has been almost consistently shown that patients who are treated with insulin present in general an increased prevalence of fractures (21, 22, 29, 31, 61, 73–75). The long term of the disease, the presence of more diabetes complications, and the increased risk of falls both because of the above but also of the hypoglycemic events due to insulin therapy may altogether contribute to the increase of fractures. In the Blue Mountain Eye Study, longer duration of

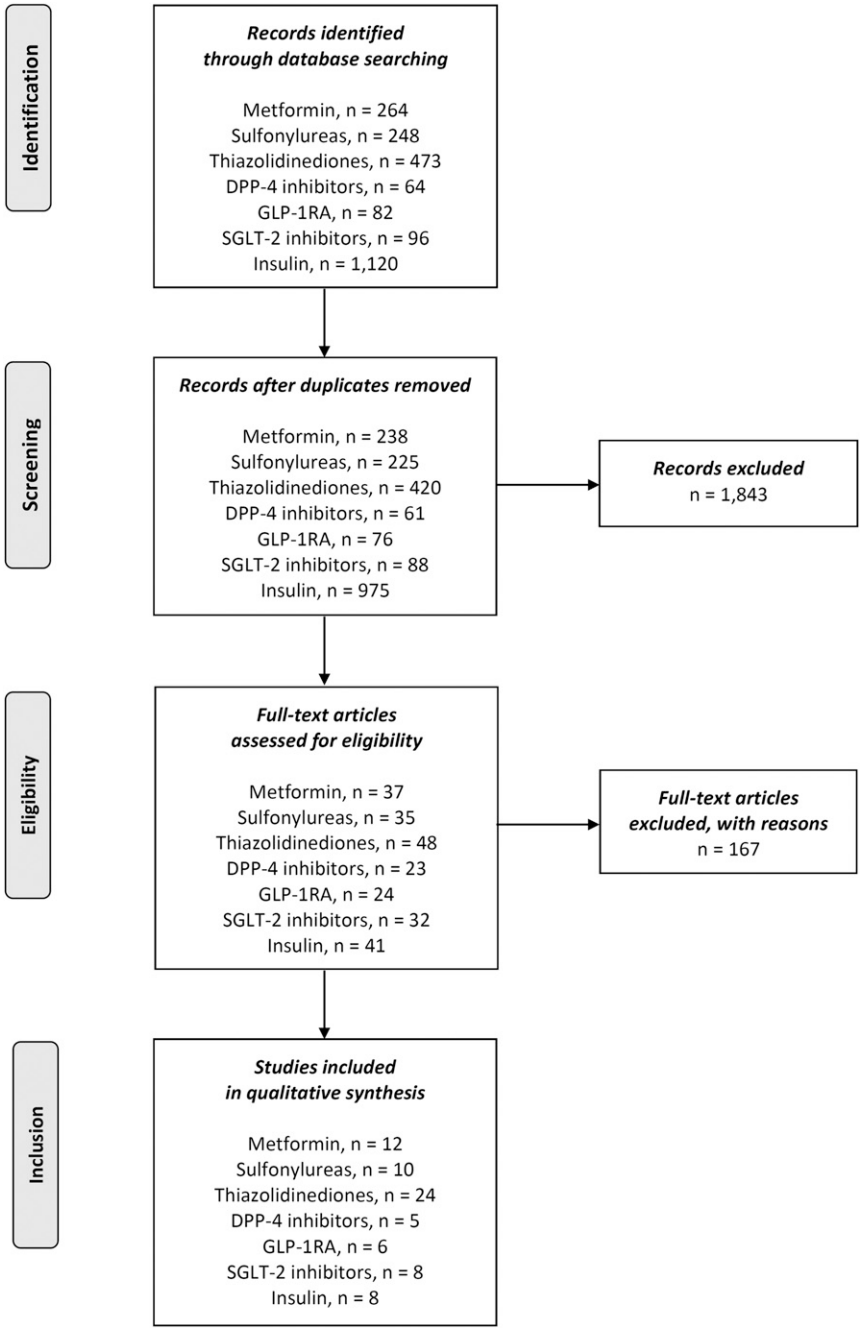

Figure 1. PRISMA flow diagram detailing selection of human studies for inclusion, regarding the effects of antidiabetic agents on bone health.

diabetes, the presence of diabetic retinopathy, and cataract were associated with increased fracture risk (73). The question of whether insulin itself impairs bone quality needs further investigation, even if the higher incidence of fractures with insulin was maintained after adjusting for a broad number of other parameters in a large study (28).

Bariatric surgery

Bariatric surgery is now a well-established therapeutic option for adults with T2D and BMI $\geq$ 35 kg/m^2. In fact, this is the most effective treatment of substantial weight loss with durable results and significant reduction in abdominal obesity, as well as better glycemic control requiring less medication. However, after surgery, life-long lifestyle support and medical monitoring is necessary, as nutritional deficiencies, hyperinsulinemic hypoglycemia, osteoporosis, and bone fractures need to be carefully balanced with the metabolic benefits (76, 77). Indeed, recently published studies revealed that patients undergoing bariatric surgery are more likely to have fractures than are obese or nonobese controls, and this risk remains higher after surgery (78). Fracture risk seems to be increased 1 to 2 years after surgery and is more clearly associated with biliopancreatic diversion than with Roux-en-Y gastric bypass or sleeve gastrectomy (79).

Effects of antiosteoporotic medications on the incidence of T2D and glucose metabolism

Bisphosphonates, denosumab, teriparatide, strontium ranelate, and selective estrogen receptor modulators (SERMs) (raloxifene and bazedoxifene) are currently the only agents approved for the treatment of osteoporosis. There are only scarce data about their effects on glycemia in patients with T2D and few data about their effect on glucose metabolism in individuals without T2D. The results of our literature search for human studies examining the effects of antiosteoporotic medications on the incidence of T2D and glucose metabolism are comprehensively presented in Table 2 (80–108). Studies conducted in patients with glucocorticoid-induced osteoporosis were not included. The PRISMA flow diagram detailing the process of identification, assessment, exclusion, and inclusion of such studies is presented in Fig. 2.

Bisphosphonates

Two studies fulfilled eligibility criteria (80, 81). A large (n = 35,998) retrospective open cohort study with data from primary care from the United Kingdom showed a reduced risk of developing T2D in individuals exposed to bisphosphonates (median follow-up time, 42 months),

Table 2. Effects of Antiosteoporosis Medications on Glucose Metabolism (Human Studies)

	Patients Without Diabetes						Patients With T2D				
Drug Category/ Author, Year (Reference)	N/Duration (mo)	Fasting Glucose	Postprandial Glucose	HbA1c	HOMA-IR	New-Onset Diabetes	N/Duration (mo)	Fasting Glucose	Postprandial Glucose	HbA1c	HOMA-IR
Bisphosphonates (general)											
Toulis 2015 (80)	35,988/42					Decrease					
Yang 2016 (81)	9664/50					Neutral					
Alendronate											
Vestergaard 2011 (82)	55,090					Decrease					
Schwartz 2013 (83)	3084/48	Neutral				No					
Chan 2015 (84)	1011					Decrease					
Zoledronic acid											
Schwartz 2013 (83)	3537/36	Neutral				No					
Passeri 2015 (85)	24/12	Neutral									
Denosumab											
Schwartz 2013 (83)	3535/36	Neutral				No					
Passeri 2015 (86)	14/3	Neutral	Neutral	Decrease	Neutral						
Lasco 2016 (87)	48/6	Neutral			Neutral	No					
Teriparatide											
Anastasilakis 2008 (88)	25/6	Neutral	Neutral		Neutral						
Passeri 2015 (85)	14/18	Neutral									
Celer 2016 (89)	23/6	Increase			Increase	No					
Strontium ranelate											
Atteritano 2016 (90)	40/12	Neutral				No					
SERMs											
Raloxifene											
de Valk-de Roo 1999 (91)	15/24	Neutral									
Barret-Connor 2003 (92)	2449/48	Neutral		Neutral			108/48	Neutral		Neutral	
Cangacci 2002 (93)	34/6	Neutral	Neutral								
Cangacci 2003 (94)	14/6	Neutral									
Carr 2005 (95)	9/2	Neutral									
Cuccinelli 2002 (96)	21/3	Neutral	Neutral								
Francucci 2005 (97)	12/25	Neutral									
Murase 2006 (98)	10/3	Neutral		Neutral	Neutral		10/3	Neutral		Neutral	Neutral
Hadjadj 2007 (99)							18/6			Decrease	
Lasco 2004 (100)	12/12	Neutral	Neutral								
Lee 2003 (101)	16/12	Neutral									
Matsumura 2010 (102)							43/12	Neutral		Neutral	
Groverprez 2013 (103)	8/3	Decrease			Decrease						
Mori 2013 (104)							144/6	Neutral		Neutral	
Nagamani 2008 (105)	20/3	Neutral	Neutral		Neutral						
Van Pelt 2014 (106)	33/6	Neutral	Neutral								
Sumino 2010 (107)	15/12	Neutral									
Basedoxifene											
Yoshii 2015 (108)							20/3	Neutral		Neutral	Neutral

Abbreviation: HOMA-IR, homeostatic model assessment of insulin resistance.

compared with age-, sex-, and BMI-matched controls, and interestingly this was independent of sex and [adjusted incidence rate ratio (aIRR) 0.52; 95% confidence interval (CI), 0.48 to 0.56; $P < 0.0001$]. This reduction was independent of sex, BMI, and the specific agent used. It must be emphasized that there was a negative association between the incidence of T2D and the duration of exposure to bisphosphonates. An increased risk of T2D was found with 1 to 2.5 years of bisphosphonate use (aIRR, 1.67; 95% CI, 1.47 to 1.90) and a decreased risk with >2.5 years of treatment (aIRR range, 0.13 to 0.81). Neither patients exposed to bisphosphonates nor controls had a diagnosis of T2D prior to study entry (80). The other retrospective cohort study tested the association between exposure to antiresorptive therapy and the newly diagnosed T2D. The vast majority involved exposure to bisphosphonates (5% exposure to raloxifene). No significant effect on the incidence of T2D was found by exposure to antiresorptive therapy, after a mean period of 4.2 years [3.7% in the new antiresorptive therapy users (n = 9664) and 4.2% in nonusers (n = 23,976); adjusted hazard ratio, 1.01; 95% CI, 0.87 to 1.16] (81).

Alendronate. Three studies (one randomized placebo-controlled study and two case-control studies) fulfilled eligibility criteria. The largest (n = 6151) study was the Fracture Intervention Trial, a randomized placebo-controlled study, in which postmenopausal women were assigned to alendronate at 5 mg/d for 2 years and 10 mg/d thereafter (n = 3084) or placebo (n = 3067). No difference in fasting glucose concentrations or in the incidence of diabetes was observed between the two groups after 4 years of follow-up (83). In a large retrospective case-control study, patients exposed to alendronate for three or more times (n = 1011) showed a reduced incidence of T2D, compared with no treatment

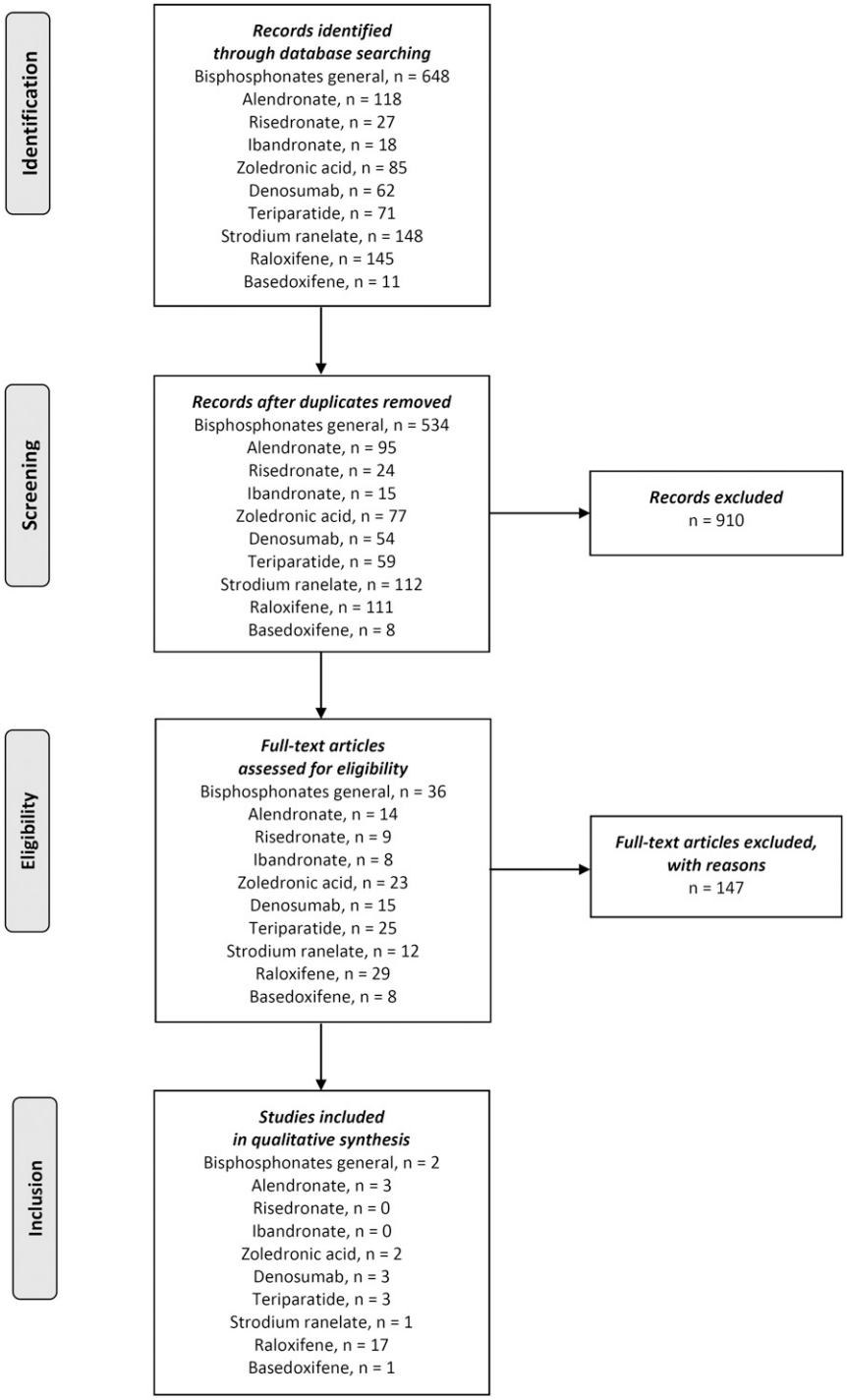

Figure 2. PRISMA flow diagram detailing selection of human studies for inclusion, regarding the effects of antiosteoporosis medications on glucose metabolism.

(the relative risk for developing T2D in nonexposed group was 1.21; 95% CI, 1.03 to 1.41). However, the significance of this association was diminished in patients older than 65 years or with hypertension or dyslipidemia. Notably, even though both study groups had osteoporosis, a potential effect of other baseline risk factors, such as family history of diabetes, BMI, and physical activity, could not be excluded (84). In a nationwide cohort study in Denmark, alendronate use was associated with a reduced risk of developing T2D (hazard ratio, 0.71; 95% CI, 0.59 to 0.85). This effect was dose-dependent (for one or more defined daily doses per day; hazard ratio, 0.22; 95% CI, 0.12 to 0.41). However, patients receiving alendronate were compared with the general population and, therefore, a significant effect of weight and mostly BMI, which is negatively associated with osteoporosis but positively associated with the development of diabetes, was not taken into consideration. Interestingly, in this study, patients exposed to antiresorptive drugs had been diagnosed less frequently with diabetes even before starting treatment, which further supports differences in the baseline risk for T2D between the two study groups (82).

Risedronate. No study fulfilled eligibility criteria.

Ibandronate. No study fulfilled eligibility criteria.

Zoledronic acid. Two studies fulfilled eligibility criteria. The largest (n = 6151) study was the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial, a randomized placebo-controlled trial in which postmenopausal women with osteoporosis were assigned to zoledronic acid 5 mg/y for 3 years (n = 3537) or placebo (n = 3576). No difference in fasting glucose concentrations or in the incidence of diabetes was observed between the two groups after 4 years of follow-up (83). The other was a prospective study (n = 24) in which zoledronic acid (5 mg/y) did not affect glucose metabolism after 12 months (85).

Denosumab

Three prospective studies fulfilled eligibility criteria. The largest (n = 7076) study was the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months trial, a randomized placebo-controlled study in which postmenopausal women were assigned to

denosumab 60 mg every 6 months (n = 3535) or placebo (n = 3541). No difference in fasting glucose concentrations or in the incidence of diabetes was observed between the two groups after 3 years of follow-up (83). In 48 women with postmenopausal osteoporosis, administration of 60 mg of denosumab did not affect fasting plasma glucose concentrations and homoeostatic model assessment of insulin resistance (HOMA-IR) after 24 weeks (87). Another small prospective study (n = 14), in which an oral glucose tolerance test was performed at 4 and 12 weeks after injection of 60 mg of denosumab, did not show any effect on fasting, postprandial glucose concentrations, or HOMA-IR, despite a slight reduction in hemoglobin A1c (HbA1c) (86).

Teriparatide

Three prospective studies in postmenopausal women with osteoporosis fulfilled eligibility criteria. One study showed that teriparatide treatment (20 μg/d) increased fasting glucose and HOMA-IR index in 23 postmenopausal women after 6 months of treatment (89). In another small study (n = 14), neither teriparatide nor zoledronic acid affected glucose metabolism after 18 and 12 months, respectively (85), as another small study (n = 25) showed in which teriparatide did not affect glucose metabolism (fasting and postprandial glucose, as well as HOMA-IR levels) after 6 months of treatment (88), despite the fact that a transient mild adverse effect on stimulated glucose levels occurs 1 hour after the first administration of teriparatide, as demonstrated by the same group (109).

Strontium ranelate

One study fulfilled eligibility criteria, which did not show any effect of strontium ranelate in 40 postmenopausal women with osteoporosis with respect to fasting plasma glucose concentrations, after 12 months of treatment. It also did not affect hemostasis factors or lipid profile (90). However, strontium ranelate has been associated with increased risk for cardiovascular events, and the European Medicines Agency has issued a warning against its use in patients at high risk for cardiovascular events, that is, in patients with a history of ischemic heart disease, peripheral artery disease, cerebrovascular disease, and in those with uncontrolled hypertension (110). This might be particularly relevant in patients with T2D.

SERMs

Raloxifene. Seventeen studies, 12 randomized-controlled and 5 observational prospective studies, fulfilled eligibility criteria. Twelve studies were conducted in postmenopausal women without diabetes (91, 93–97, 100, 101, 103, 105–107), three were conducted in those with T2D (99, 102, 104), and two were conducted in both diabetic and nondiabetic postmenopausal women (92, 98). Only one study in T2D showed a decrease in HbA1c levels (99), and two studies in patients without diabetes showed an increase in insulin sensitivity (94, 101) and a decrease in fasting glucose concentrations (only in patients with high insulin resistance) (101). In 14 studies no significant effect of raloxifene on glucose metabolism was noticed (91, 92, 94–98, 100, 102, 104–107).

Bazedoxifene. Regarding the effect of bazedoxifene, one prospective study fulfilled eligibility criteria, according to which, in 20 postmenopausal women with T2D, bazedoxifene (20 mg/d) did not affect fasting plasma glucose concentrations, HbA1c, or HOMA-IR after 12 weeks of treatment (except for a slight and transient decrease in HOMA-IR at 4 weeks) (108).

In conclusion, data so far indicate that antiosteoporotic medications have minimal, if any, effects on glucose metabolism, whereas the finding of a reduction in the risk of developing diabetes with bisphosphonates users warrants further investigation in well-designed studies.

Practical guide for the optimal management of T2D in patients with concomitant osteoporosis

Targets

Glycemic control is usually assessed by measuring HbA1c, which correlates with the average blood glucose concentrations during the past 2 to 3 months. The American Diabetes Association and European Association for the Study of Diabetes consensus guidelines recommend a general HbA1c target of <7% (111). However, this therapeutic target should be personalized and should be modified from time to time even for the same patient. Therapeutic targets are determined by the patient's and disease's features (111, 112). In patients with T2D and osteoporosis, longer duration of T2D, presence of clinical cardiovascular disease, recurrent severe hypoglycemia episodes, or hypoglycemia unawareness should indicate a higher HbA1c target (≤7.5% to 8%) to avoid hypoglycemia and falls, which will further increase the risk of fracture (*Strong Recommendation, Low-Quality Evidence*) (66–68, 111, 112). Additionally, most patients with T2D present hypertension and are treated with several antihypertensive agents. Proper control of blood pressure with careful consideration of avoiding hypotension is of great importance in order again for falls to be avoided. Furthermore, proper vision of these patients with at least annual tests by fundoscopy and referral to ophthalmologists if needed, as well as at least annual neuropathy assessment, should be taken into careful consideration (*Strong Recommendation, Low-Quality Evidence*) (66–68, 111–113).

Therapeutic algorithm

Lifestyle intervention with medical nutrition therapy and exercise forms the cornerstone of therapy of T2D and coexistent osteoporosis. Modest weight loss, a Mediterranean-style diet rich in monounsaturated fats and long-chain omega-3 fatty acids, as well as nuts and seeds, appropriate intake of calcium and vitamin D with careful consumption of fatty milk products, and limited intake of alcohol and sodium are an ideal medical nutrition therapy for both entities. Regarding exercise, intense walking at least 150 minutes per week could combine the moderate-intensity aerobic type of exercise indicated for T2D with the weight-bearing exercise indicated for osteoporosis. Of course, cessation of smoking is very important for these patients and such counseling should be a routine component of diabetes and osteoporosis care (*Strong Recommendations, High-Quality Evidence*) (111, 114).

Eventually, most patients require pharmacologic therapy. Metformin should be the first-line pharmacologic therapy, sometimes even initiated at diagnosis concurrently with lifestyle intervention (5, 20–30, 111). If HbA1c remains over target (usually ≥7%) after 3 months, then a second agent should be added. Of the following six treatment options, that is, sulfonylureas, TZDs, DPP-4i, SGLT-2i, GLP-1RA, or basal insulin, that represent the current general second-line treatment on patients with T2D (presenting also as options for monotherapy if metformin is contraindicated or not well tolerated) (111), sulfonylureas, DPP-4i, or GLP-1RA should be rather preferred in patients with osteoporosis (*Weak Recommendation, Moderate-Quality Evidence*) (5, 20–68, 70–75). Except for the presence of osteoporosis, the second agent choice should be based of course on various patients, disease, and drug characteristics. In routine clinical diabetes practice the ABCDE algorithm, namely age, body weight, complications and comorbidities, diabetes duration, and expense, is very helpful (111–113). Insulin should be used with caution and with careful measures to avoid hypoglycemia (*Weak Recommendation, Moderate-Quality Evidence*) (20, 21, 28, 30, 57, 66–68). TZDs (29, 34–48, 71–73) and canagliflozin (58, 60, 61, 75) should be avoided, whereas other SGLT-2i are less well-validated options (59, 62–65) (*Strong Recommendation, High-Quality Evidence*). If the addition of a third agent is needed, this should be decided again in the same context (5, 20–68, 70–75, 111–113).

The effect of antiosteoporotic medications on the incidence of T2D and on glucose metabolism should be taken into consideration as well. The existing data show no real effect, whereas the finding of reduction in the risk of developing diabetes with bisphosphonates users warrants further investigation in well-designed studies (80–110) (Table 2). In general, both the treatment and the monitoring of osteoporosis should be continued as indicated by international guidelines (12) without important amendments because of the presence of T2D (*Strong Recommendation, High-Quality Evidence*) (Fig. 3).

Management of hospitalized patients with fracture

Insulin therapy is the preferred method for achieving glycemic control in hospitalized patients with T2D and fracture, as it is for all hospitalized patients with hyperglycemia (111). Oral or injectable hypoglycemic agents other than insulin should be discontinued at the time of hospital admission and insulin therapy should be initiated. Sliding scale insulin therapy has been broadly used in the past, but it should be avoided. The treatment option of choice is a scheduled subcutaneous insulin regimen including basal insulin, in combination with short-acting insulin administered before meals. During surgery for fracture, continuous insulin infusion (also known as variable rate insulin infusions) may be required, but subcutaneous basal insulin along with subcutaneous bolus insulin to prevent hyperglycemia during the perioperative period could be an

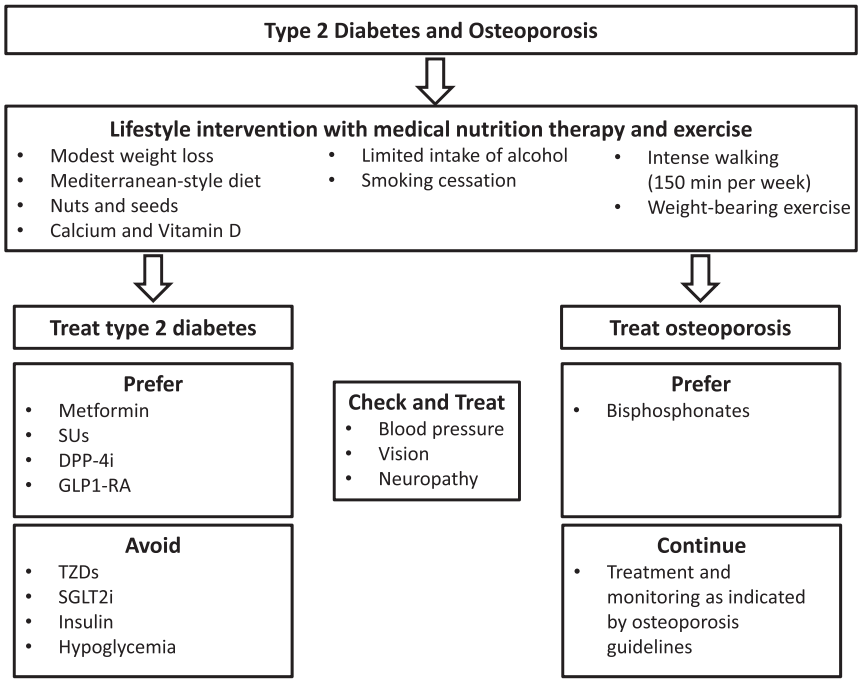

Figure 3. Algorithm for optimal management of patients with T2D and coexisting osteoporosis.

alternative choice. In the postsurgical setting, basal insulin with or without bolus (depending on eating) should be initiated after continuous insulin infusion (115, 116) (*Strong Recommendation, Moderate-Quality Evidence*).

Conclusion

Both T2D and osteoporosis are affected by aging and changes in lifestyle. These two clinical entities quite often coexist and the medications used for each one affects the course of the other. Healthy diet and physical exercise are very important for the prevention and treatment of both. Metformin, sulfonylureas, DPP-4i, and GLP-1RA should be preferred for the treatment of T2D in patients with osteoporosis, whereas strict targets should be avoided for the fear of hypoglycemia, falls, and fractures. Insulin should be used with caution and with careful measures to avoid hypoglycemia. TZDs and canagliflozin should be avoided, whereas other SGLT-2i are less well-validated options. Because no evidence currently exists for any detrimental effect of antiosteoporosis medications on glucose metabolism and taking also into consideration a possible beneficial effect of bisphosphonates, the treatment and the monitoring of osteoporosis should not be modified because of the presence of T2D.

Acknowledgments

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