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SHORT REVIEW

Bone health in type 1 diabetes: focus on evaluation and treatment in clinical practice

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Abstract
Introduction Type 1 diabetes (T1D) is an autoimmune disease with chronic hyperglycemic state, which incidence has been globally rising during the past decades. Besides the well-known diabetic complications such as retinopathy, nephropathy and neuropathy, T1D is characterized also by poor bone health. The reduced bone mineralization, quality and strength lead to vertebral and hip fractures as the most important clinical manifestations. Suppressed bone turnover is the main characteristic of T1D-associated bone disorder.
Results This is thought to be due to hyperglycemia, hypoinsulinemia, autoimmune inflammation, low levels of insulin-like growth factor-1 and vitamin D. Young age of T1D manifestation, chronic poor glycemic control, high daily insulin dose, low body mass index, reduced renal function and the presence of diabetic complications are clinical factors useful for identifying T1D patients at risk of reduced bone mineral density. Although the clinical risk factors for fracture risk are still unknown, chronic poor glycemic control and the presence of diabetic complications might raise the suspicion of elevated fracture risk in T1D. In the presence of the above-mentioned risk factors, the assessment of bone mineral density by dual-energy X-ray absorptiometry and the search of asymptomatic vertebral fracture by vertebral fracture assessment or lateral X-ray radiography of thorax-lumbar spine should be recommended.
Conclusion There is no consensus about the treatment of diabetic bone disorder. However, the improvement of glycemic control has been suggested to have a beneficial effect on bone in T1D. Recently, several experiments showed promising results on using anabolic pharmacological agents in diabetic rodents with bone disorder. Therefore, randomized clinical trials are needed to test the possible use of the bone anabolic therapies in humans with T1D.

Keywords Type 1 diabetes · Bone mineral density · Fracture risk · Pathophysiology · Chronic diabetic complications

Introduction

Type 1 diabetes (T1D) is an autoimmune disease that is triggered in genetically susceptible individuals by environmental factors. The body's own immune system attacks the beta-cells in the islets of Langerhans of the pancreas, destroying or damaging them sufficiently to reduce and eliminate insulin production, leading to the hypoinsulinemia and chronic hyperglycemia [1]. The T1D incidence has been globally rising during the past decades by as much as a 3 % annually. If these trends will continue, the total prevalence of people with T1D will increase in coming years [2].

Chronic hyperglycemia in T1D leads, in course of time, to chronic complications. Besides acute diabetic complications, nowadays, health providers give attention to the

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prevention of disabling chronic complications, such as diabetic retinopathy, nephropathy, neuropathy and precocious atherosclerosis with early cardiovascular disease. Recently, a major interest has been focused on poor bone metabolism in T1D that can represent an overlooked complication of diabetes.

Indeed, there is strong evidence that bones in T1D patients are characterized by decreased mineralization [3, 4], smaller and thinner size [5–11] with reduced bone strength [7–9] and quality [7, 8, 12], which lead to a higher fracture incidence at any site [3, 13–15], predominantly at femoral neck [2]. Moreover, in the presence of diabetes bone healing, following fracture is slower. This explains why in some T1D patients the full recovery after fracture may be delayed [16].

From the pathophysiological point of view, bone metabolism in T1D is characterized by low bone turnover, and in particular by reduced bone formation [17] due to decreased osteoblastogenesis, low osteoblast differentiation, low osteoblast activity (low levels of osteocalcin and reduced mineral apposition rate), low osteoblast number (low osteoblast per surface and osteoid surface) and enhanced osteoblast death [18, 19]. Additionally, slow and short osteoblastic cycle is accompanied by decreased osteoblast lineage selection due to impaired function of bone marrow stromal cells (BMSC) [19]. Osteoclast metabolism appears unaltered or decreased [17, 18].

At the molecular level, it is thought that inhibition of the Wnt/β-catenin signaling and Runx2 activity, which plays a significant role in the control of osteoblastogenesis and bone formation in physiological condition, is responsible for slowing down the osteoblastic metabolism [19, 21]. However, the mechanisms leading to the inhibition of the Wnt/β-catenin signaling and Runx2 activity are still unknown.

It is possible that hyperglycemia with advanced glycation end products (AGEs) [18, 22, 23], hypoinsulinemia [23–25] and autoimmune inflammation [26, 27], well-known characteristics of T1D, play a crucial role in impairing osteoblast differentiation and function. Moreover, the low levels of insulin-like growth factor-1 (IGF-1) [19, 20, 28–31] and vitamin D [32], which also usually accompany diabetes, may be additional factors responsible for poor bone health (see Fig. 1).

Regardless of several basic and clinical studies focused on the pathophysiological aspects of bone health in T1D, there are still unanswered questions about the management of T1D patients at risk of bone disorder. In this review, we will cover the topics regarding the evaluation, identification and management of T1D patients at risk of bone disorder.

What should we do in clinical practice? Management of type 1 diabetic patients at risk of bone disorder

Who is at risk of bone disorder? Clinical risk factors associated with poor bone health in type 1 diabetes

Evaluating T1D patients in clinical practice, it is very important to give answers to the following questions: who is at the risk of bone disorder and who should be evaluated for it? To respond to these questions, adequate algorithms, including clinical factors able to reflect poor bone health in T1D, should be developed.

Clinical factors associated with poor bone health in T1D can be divided into two groups: (1) factors associated with low bone mineral density (BMD), and (2) factors associated with fractures (Table 1).

Clinical factors associated with low BMD

The age of onset of diabetes, disease duration, glycosylated hemoglobin (HbA1c), diabetic complications, daily insulin dose, body mass index (BMI) and renal function can give information about the possible presence of low BMD in T1D.

The age of onset of T1D may be crucial for the acquisition of bone mass. Although data about bone mineralization in children/adolescents are inconsistent, some authors [28, 33] have demonstrated a significant reduction of either lumbar spine or femoral neck BMD in diabetic patients after 2–4 years of follow-up, even having showed normal BMD at baseline. Moreover, early onset of T1D can be a risk factor for smaller bone size [5, 6, 10, 11]. A young age of T1D occurrence, impairing the achievement of the peak of bone mass, might be considered a risk factor for low BMD in T1D patients. However, the majority of studies have found no association between low BMD and duration of T1D [3, 4, 14, 28, 29, 34–39].

The detrimental effect of hyperglycemia on bone and osteoblasts is widely accepted, and it has been demonstrated in vitro studies [18, 22, 23]. However, an association between BMD and poor glycometabolic control, reflected by HbA1c, is not clear in vivo on humans, since only few studies have found a link between poor glycemic control and low BMD [13, 40–42]. These apparent discordances may be due to several reasons. Firstly, in the majority of the studies HbA1c was not evaluated during the previous years of disease, but only during the last 3 months. On the other hand, the lack of a correlation between BMD and HbA1c may also depend on a nonlinear relationship between these variables, hardly detectable by the classic statistics. In the study of Eller-Vainicher et al. [4], a special mathematic

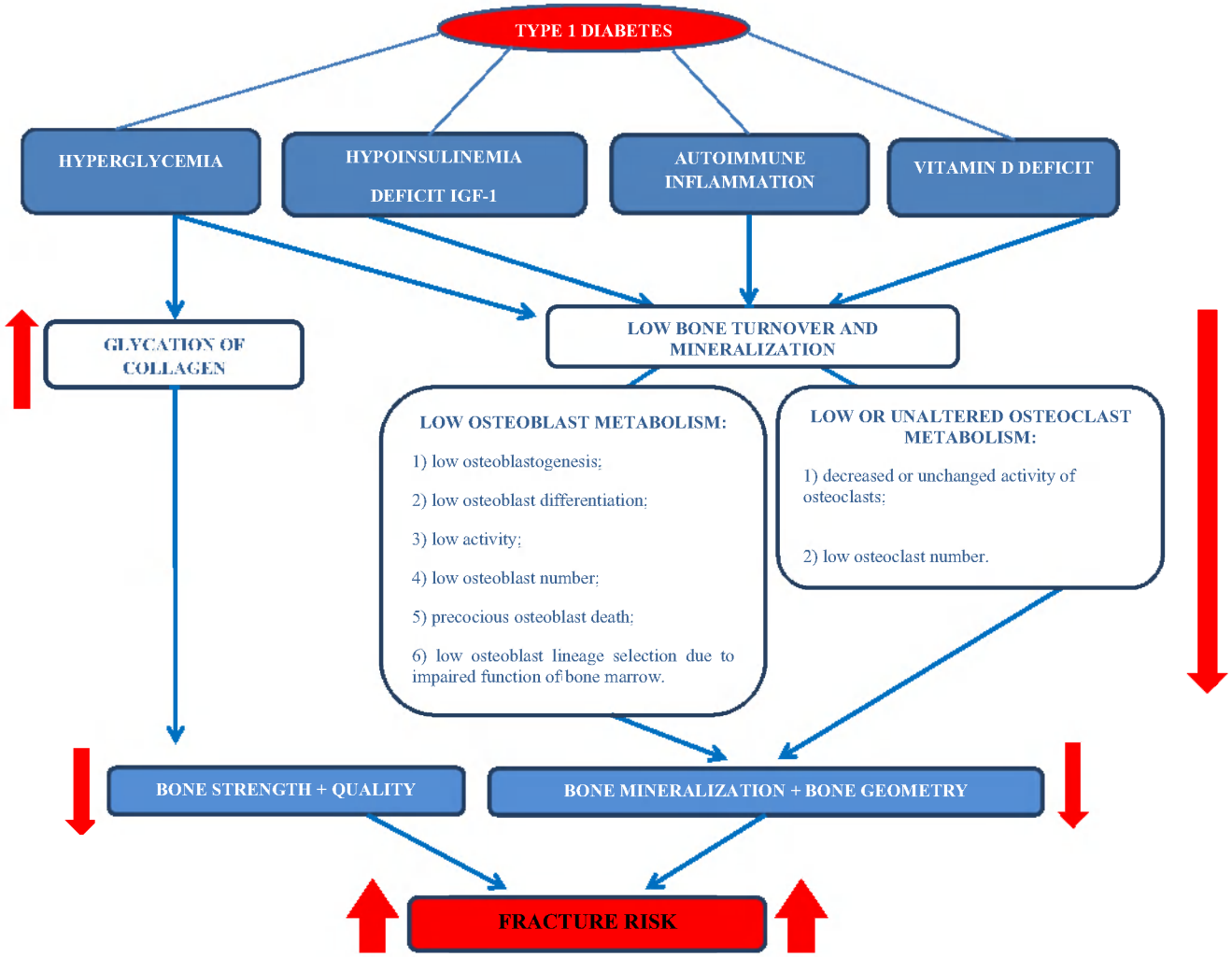

Fig. 1 Pathophysiological aspects of bone disorder in type 1 diabetes. *IGF1* insulin-like growth factor-1. The hyperglycemia with advanced glycation end products (AGEs), hypoinsulinemia and autoimmune inflammation, well-known characteristics of T1D, play a crucial role in impairing osteoblast differentiation and function. Moreover, the low levels of insulin-like growth factor-1 and vitamin D, which also usually accompany diabetes, may be additional factors responsible for poor bone health characterized by decreased mineralization, smaller and thinner size, reduced bone strength and quality, which lead altogether to a higher fracture incidence

Table 1 Clinical risk factors associated with poor bone health in type 1 diabetes

Clinical risk factors for low bone mineralization	Clinical risk factors for fracture risk
Young age of T1D manifestation	Low lumbar spine BMD (only for moderate and severe vertebral fractures)
Poor glycemic control	Poor glycemic control
Presence of diabetic complications	Presence of diabetic complications
Daily insulin dose >0.67 U/kg	
BMI <23.5 kg/m^2	
Renal function <88.8 ml/min	

T1D type 1 diabetes, *BMD* bone mineral density, *BMI* body mass index

approach, such as artificial neural network (ANN), has been applied, which suggested that HbA1c was connected with low BMD through a link with the diabetes complications. Indeed, the diabetic complications are the result of the chronic exposure to high blood glucose of target organs and the finding of an association between chronic complications

and low BMD may also reflect the effect of chronic hyperglycemia on bone. The chronic diabetes complications per se have been suggested to predict low BMD in T1D. The reduced visual function and the presence of diabetic neuropathy may predispose patients to low physical activity, which, in turn, may cause bone loss [35, 43–45]. The presence of diabetic nephropathy with negative calcium balance and reduced vitamin D level was reported to be an early indicator of osteopenia in T1D [43, 44].

Insulin is considered an anabolic agent for bone [24] and, therefore, one should expect BMD to increase with increasing daily insulin dose. On the contrary, in the study of Eller-Vainicher et al. [4] and in the study of Leger et al. [29], patients with diabetes with low BMD had higher insulin dose. This finding could be explained by the following hypotheses. Firstly, it is possible that the need of high insulin dose may reflect the presence of a more severe disease (i.e., a more pronounced inflammatory milieu), leading per se to bone damage. In keeping with these data, a direct correlation between daily insulin dose, HbA1c level [4] and levels of markers of inflammation/oxidative stress [41] has been found. This hypothesis is supported by the ANN analysis [4], showing that insulin dose was strictly connected with HbA1c and then with low BMD, although through diabetes complications. Secondly, higher insulin demands might simply reflect higher insulin resistance and higher autoimmune inflammation at the level of all tissues, including bone. Indeed, recently it has been suggested that in T1D insulin resistance raises the insulin demands, leading to the beta cell stress. In this setting, autoimmunity may be a secondary accelerator operating in patients with particular HLA genotype [46].

Besides all the factors described above, some studies [3, 4, 14] have reported low BMI [4] to be associated with low BMD, pointing to the importance of maintaining lean mass and weight in type 1 diabetic patients.

Finally, kidney function seems to be important for femoral BMD not only in general population [47], but also in T1D population [4].

Interestingly, Eller-Vainicher and coauthors [4] have found the thresholds for daily insulin dose, BMI and renal function (>0.67 U/kg, <23.5 kg/m^2, <88.8 ml/min, respectively), below which T1D patients may be at risk of poor bone mineralization. In the absence of these risk factors, the probability to have normal BMD is 84.2 % and measuring BMD may not be necessary. On the contrary, in the presence of all these risk factors the probability to low BMD is 62.9 % and the measurement of BMD might be considered.

Clinical factors associated with fractures

Although low bone mass is a common finding in T1D, it seems that low BMD is of poor fracture prediction in this kind of patients [3, 15], as in other several forms of secondary osteoporosis [48]. T1D patients may have fractures even in the presence of normal BMD values [3, 15]. This fact emphasizes the presence of poor bone quality/strength, beside low bone mineralization, in T1D. On the other hand, Zhukouskaya et al. [15] have assessed the prevalence of asymptomatic morphometric vertebral fractures in T1D population and showed that the more severe vertebral fractures were associated with low lumbar spine BMD. This finding underlines that BMD still remains crucial for fracture event.

Beside BMD, the other BMD-independent clinical factors associated with fractures have not been well studied. Only in one study [14], clinical fractures were associated with HbA1c, while the majority did not show any association between these two variables [3, 15]. As for the association with BMD, this apparent surprising finding may be explained by the fact that only one measurement of HbA1c may not mirror the glycometabolic control during the whole disease duration. The diabetic complications, being a result of high blood glucose level overtime, have been suggested to contribute little to the overall risk of fractures in diabetes [15, 49]. However, in our study [15], T1D patients with vertebral fracture tended to have higher prevalence of diabetic complications, especially retinopathy and neuropathy. Therefore, larger studies are needed to clearly prove whether poor glycemic control, expressed as HbA1c or as diabetic complications, could be considered as clinical risk factor for fractures in T1D, even if it could be highly expectable.

To date it is not clear who should undergo a BMD assessment among T1D patients. If the findings of our studies [4, 15] would be confirmed in other T1D populations, in the presence of diabetic complications (retinopathy, nephropathy, neuropathy) and/or a high daily insulin dose (>0.67 U/kg), low BMI (<23.5 kg/m^2) and reduced renal function and in the presence of clinical features indicating vertebral fractures (kyphosis, back pain, decreased height, etc.), T1D patients should undergo the measurement of BMD and should be searched for the presence of vertebral fractures.

Management of type 1 diabetic patients at risk of bone disorder

Evaluation

There is still no consensus on the correct evaluation and management of T1D patients at risk of bone disorder. However, a possible approach is depicted in Fig. 2.

To exclude other possible causes of osteoporosis, some laboratory tests should be performed including: (1) general exams (blood cell count, serum protein electrophoresis,

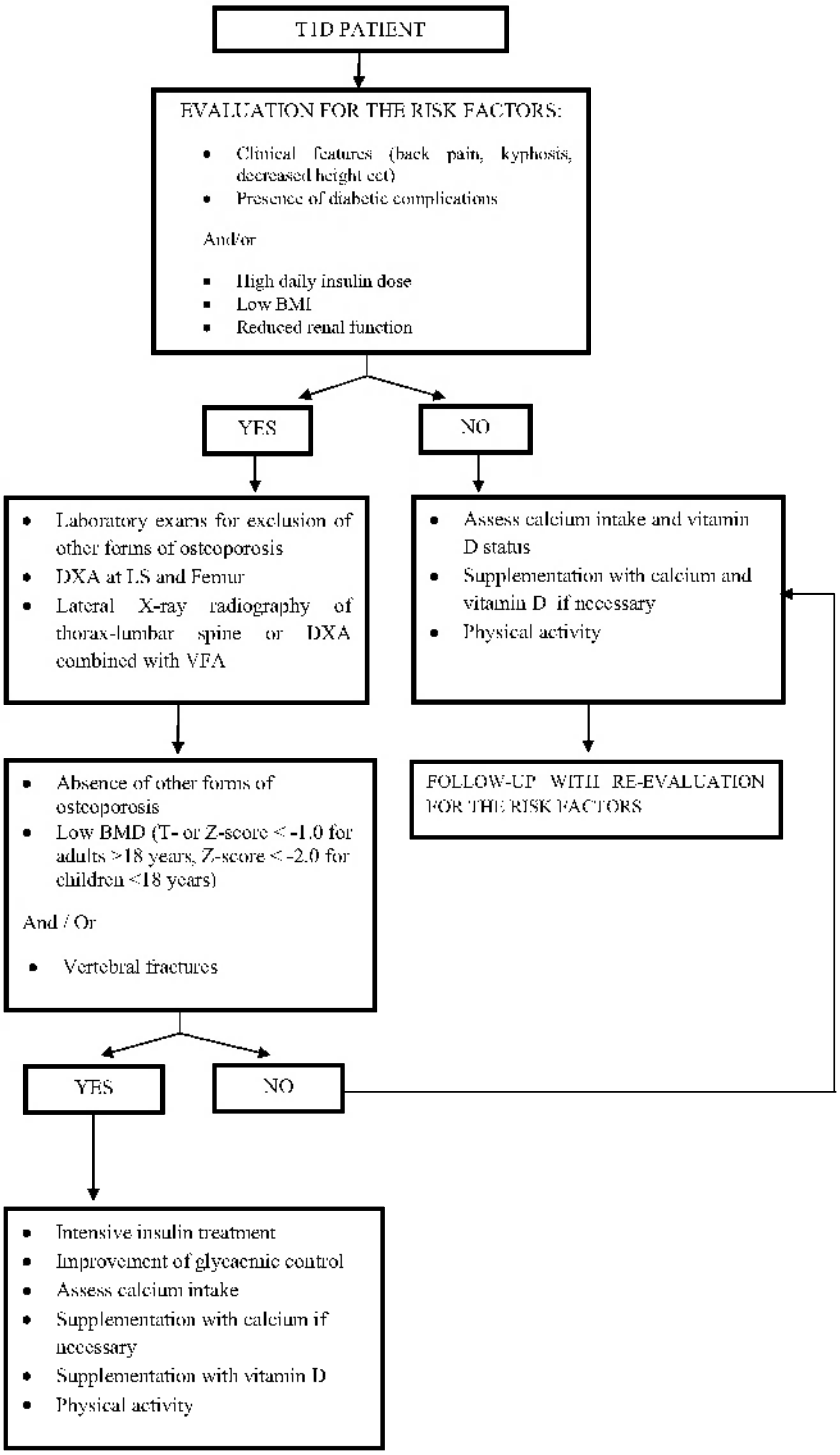

Fig. 2 Proposed flow chart for evaluation, management and treatment of T1D patients at risk of bone disorder. *BMD* bone mineral density, *T1D* type 1 diabetes, *DXA* dual-energy X-ray absorptiometry, *LS* lumbar spine, *VFA* vertebral fracture assessment, *BMI* body mass index

C-reactive protein, liver function with glutamic oxalacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), γ-glutamyltransferase (γ-GT), renal function with creatinine and glomerular filtration rate); (2) mineral metabolism (total serum calcium corrected for albumin, serum phosphate, alkaline phosphatase (ALP), 25-hydroxy-vitamin D (25OHD), 24-h urinary calcium); and (3) thyroid and, in men, testes function (thyroid stimulating hormone, TSH, total testosterone, respectively). Moreover, the possible presence of an associated celiac disease should be excluded in selected patients by performing anti-transglutaminase antibodies. Further laboratory tests may be required, depending on comorbidities and clinical findings [50].

To assess bone mineralization and the presence of vertebral fractures, a dual X-ray absorptiometry scan (DXA)

evaluation at lumbar spine and at femoral neck and lateral X-ray radiography of thorax-lumbar spine or DXA combined with vertebral fracture assessment (VFA) should be performed [50] in the presence of diabetic complications and/or high daily insulin dose, low BMI and reduced renal function.

In T1D patients with low BMD (T or Z score <-1.0 at lumbar spine or femoral neck for adults >18 years; Z score <-2.0 at lumbar spine o femoral neck for children <18 years) and/or with vertebral fractures, an appropriate treatment should be considered [50].

Treatment approach in clinical practice

The best approach to treat patients with T1D-related bone disorder is still not clear. Due to the lack of data on the possible therapeutic options on humans, most recommendations that can be given to the T1D patients at risk and with manifested bone disorder derive from the good clinical practice and from the experience of the physician rather than from evidence-based guidelines.

Since hypoinsulinemia and hyperglycemia play an important role in damaging bone, insulin treatment accompanied by reduction of glycaemia seems to be the pivotal point in treatment and prevention of bone disorder in T1D. In the prospective study of Campos Pastor et al. [44], although the statistical significance was not reached, a BMD increase was associated with the improvement of glycemic control in T1D patients on intensive insulin treatment after 7 years of follow-up. However, the insulin treatment with reduction of hyperglycemia, probably, is not enough for bone health, since an elevated fracture risk is still present in T1D even after initiation of intensive insulin treatment. This may be due to several reasons. Firstly, insulin treatment may be beneficial for bone mineralization but not sufficient for the restoration of bone quality/strength [9]. Secondly, to avoid the risk of hypoglycemia, it is not possible to reduce the glycaemia to the values of subjects without diabetes. Therefore, it is possible that even a slight chronic hyperglycemia may be sufficient for damaging bone. Finally, the other additional factors besides hyperglycemia (i.e., autoimmune inflammation, deficit of IGF-1 and vitamin D), interfering with the bone health in T1D, are probably scarcely or not influenced by the correction of the glycometabolic control. However, intensive insulin treatment, being a standard treatment of T1D, with improvement of glycemic control should be taken into consideration in all patients. Insulin with reduction of hyperglycemia would be beneficial not only for bone but also for prevention of chronic diabetic complications.

In case of prescription of any other drugs, besides insulin (for example, insulin-sensitizing drugs, metformin, in order to reduce insulin resistance), it should be taken in consideration the possible influence of this drugs on bone metabolism. Some in vitro studies suggest that metformin may have a direct osteogenic effect by stimulating proliferation and differentiation of rat osteoblast-like cell lines [51]. On the other hand, Hegazy [52] has found neither osteogenic nor osteoporotic effect of metformin. If further studies will confirm the anabolic effect of metformin on bone, this agent could be useful for treating both osteoporosis and T1D diabetes, at least in patients in whom a certain grade of insulin resistance is associated with the autoimmune damage of β-cells.

Any deficiency of calcium and vitamin D should be corrected in T1D patients with bone disorder. Although there are no specific guidelines for calcium supplementation in diabetic patients, daily calcium uptake varies from 800 to 1000–1200 mg for children and adults, respectively [53]. It should be assumed ideally through the diet, but supplementation can be used if dietary uptake is inadequate or cannot be optimized. In the last years, awareness has been raised about daily dietary calcium intake and calcium supplementation. Some studies have created a lot of controversy, since they have suggested that a high calcium intake could be associated with a higher incidence of cardio-vascular disease, myocardial infarction and possible stroke [54]. However, this association between calcium supplementation and mortality has been studied on aged subjects. Nevertheless, taking into consideration the advances in the treatment and follow-up of T1D and that T1D patients live longer nowadays, the correct calcium supplementation becomes relevant when T1D patients become elder. At this regard, recent meta-analysis of prospective cohort studies [55] has found a U-shaped relationship between dietary calcium intake and cardiovascular mortality. Both lower and higher 800 mg/day of calcium intakes were gradually associated with a higher risk of cardiovascular mortality. For all-cause mortality, a threshold effect at calcium intakes of about 900 mg/day has been observed. Moreover, use of calcium supplements was not significantly associated with cardiovascular mortality in comparison with non-use of any supplements. Thus, the recommendations for calcium intake should consider the individual characteristics and should focus only on patients with low calcium intake [55].

The efficacy of vitamin D on T1D-related bone damage has been examined only minimally in animal models. In rat model of T1D, low femoral BMD has improved significantly after treatment with 1α-hydroxyvitamin D3 [32]. Nevertheless, since vitamin D deficiency is related to mineralization defects and increased PTH levels [56, 57], the correction of vitamin D deficit state seems to be crucial. Given the low number of foods containing large amount of vitamin D, and variations in exposure to sunlight, which are the main sources of vitamin D, the supplementation with vitamin D is generally required and can be achieved with

daily, weekly or monthly dosing frequencies [56]. According to the some guidelines regarding the prevention and treatment of vitamin D deficiency [57], vitamin D deficient subjects should be supplemented with vitamin D3 at dose of 600–1000 U/day for children and 1500–2000 U/day for adults, in order to maintain 25OHD levels above 30 ng/ml (75 nmol/l). The obese patients (because of accumulation of vitamin D in the adipose tissue), patients with malabsorption syndromes and patients assuming medications affecting vitamin D metabolism (e.g., antiepileptic drugs, glucocorticoids, AIDS drugs, antifungals, cholestyramine) require higher doses of vitamin D about 3000–6000 U/day.

Finally, weight-bearing physical activity has been recently demonstrated to have a positive effect on bone mineral acquisition in children with T1D, similarly to what happens in children without T1D [58]. Thus, weight-bearing sports, including ball games, jumping activities or gymnastics should be encouraged in T1D children to optimize bone mineral acquisition during growth and potentially prevent the development of osteoporosis later in life [58].

Pharmacological treatment

With regard to pharmacological intervention, there are no trials specifically designed to evaluate antifracture efficacy of antiosteoporotic drugs in T1D. Since T1D-related osteoporosis is characterized by a reduced bone turnover, the treatment with antiresorptive drugs might be not the best choice. However, studies performed on patients with type 2 diabetes have shown that the magnitude of change in BMD with alendronate treatment compared with placebo was similar in women with and without diabetes [59], and that the diabetic state does not affect the fracture-preventive potential of bisphosphonates [60]. Nevertheless, evidence is limited to recommend bone-specific drugs, such as bisphosphonates (BPs) in young adults with secondary osteoporosis due to diabetes, since T1D patients include prevalently children and young adults [50]. Moreover, caution must be taken in prescribing BPs to women during reproductive age, since BPs are known to be stored and released from bones for long periods of time and have shown to affect fetal skeletal ossification in rat models. The effects of BPs on bone growth in infants in the long terms are still unknown [50].

Denosumab, a human monoclonal anti-receptor activator of NF-κB ligand (RANKL) antibody, is a novel alternative antiresorptive drug, which, at variance with BPs, is not stored in bones. Denosumab markedly increases BMD either at trabecular or cortical compartment and reduces vertebral and non-vertebral fractures [61]. One peculiarity of this drug is that it increases particularly cortical BMD [62], which makes it a rather intriguing option in T1D-related bone disease, which is characterized by a markedly damaged cortical compartment. Unfortunately, neither animal nor clinical studies are available so far demonstrating the efficacy of denosumab in diabetic patients.

The anabolic therapy with parathyroid hormone, which is known to increased bone apposition, and to a lesser extent also bone resorption, seems to be an interesting option for T1D-related osteoporosis. Motyl et al. [63] have studied the effect of PTH treatment in diabetic rodents, showing increasing bone mineralization by promoting remodeling and reducing diabetes-induced osteoblast apoptosis, and making the conclusion that intermittent PTH therapy might be an option to promote bone formation and resorption, which are both depressed in diabetic patients. To date, however, no data on humans are available on the possible usefulness of PTH anabolic therapy in T1D patients.

Since bone metabolism in diabetes is characterized by the inhibition of the Wnt/β-catenin signaling [19, 21], and sclerostin, an inhibitor of Wnt/β-catenin pathway, is increased in T1D [64], anti-sclerostin antibodies could represent a good solution from a pathophysiological point of view for T1D-related osteoporosis. Romosozumab (AMG-785), a human monoclonal anti-sclerostin antibody, has shown a large, rapid, transitory increase in bone formation markers and moderate but sustained decrease in bone resorption markers resulting in a strongly positive balance in bone turnover (anabolic window). This uncoupling between bone apposition and resorption explains the rapid gain in BMD observed in postmenopausal women with low bone mineral density, which is significantly greater than with alendronate and teriparatide (1–34 PTH), either at spine or hip [62, 65]. Recently, the anti-sclerostin antibodies have been experimented also in diabetic rats resulting in enhanced bone mass and strength and accelerated bone defect repair via potent anabolic bone effect [66]. This drug, however, is currently undergoing the phase 3 studies for assessing its efficacy on fracture risk.

Several experiments on animal models have been focused also on the reduction of autoimmune inflammation and on the treatment with recombinant IGF-1 (rhIGF-1), to improve bone mineralization and quality in T1D. Treatment with tumor necrosis factor-α (TNF-α)-specific inhibitors reduces diabetes-induced increases in osteoblast apoptosis [18]. Fowlkes et al. [24] have showed favorable effect of rhIGF-1 in promoting new bone formation and in improving bone biomechanical properties in T1D diabetic rodents. To date, however, no studies are available on the possible therapeutic use of TNF-α-specific inhibitors and rhIGF-1 in humans with T1D.

Preventive measures

In T1D patients without bone disease and with or without risk factors discussed above (see also Fig. 2), some preventive measures should be taken into consideration.

To maintain a good bone health, such general recommendations as an adequate calcium intake, vitamin D supplementation and physical activity, if necessary, should be given to all T1D patients. Then, the optimization of diabetic treatment with improvement of glycemic control and the annual screening for diabetic complications (nephropathy, retinopathy and neuropathy) should be performed to prevent and minimize the risk factors for bone disorder in T1D. Subsequently, a re-evaluation of the risk factors, a further measurement of BMD by DXA and a re-assessment of the presence of asymptomatic vertebral fractures by lateral spinal X-ray radiography, should be considered after 24 months in T1D patients with elevated risk of bone damage and/or fracture.

A possible flow-chat for the evaluation, management and treatment of T1D patients at risk or with manifested bone disorder is depicted in Fig. 2.

Which way should we proceed? Conclusion and future prospects

In summary, T1D is characterized by poor bone health, which should be recognized as a diabetic complication among the other well-known complications such as retinopathy, nephropathy, neuropathy. Slow bone turnover is the main characteristic of T1D-associated bone disorder, which leads to reduced mineralization, reduced quality and strength of bone, with consequent fracture event as the most important clinical manifestation. Although, during the last decade, many studies both on animals and humans have been focused on the pathogenesis of T1D-related bone damage and on the risk factors for the identification of T1D patients at risk of bone disorder, several questions still remain to be answered.

Firstly, since BMD represents a poor clinical tool for fracture prediction, as it often happens in case of secondary osteoporosis [48], we need to develop some methods, which is easy to perform in clinical practice and able to predict fracture risk in T1D patients. Trabecular bone score (TBS), being an indirect measure of bone quality [67] and easily obtainable through DXA, has been shown to predict better than BMD the fracture risk in patients with some forms of secondary osteoporosis [48, 68, 69]. To date, besides TBS, other techniques, such as micro-computed tomography and nuclear magnetic resonance (MRI), have been proposed to directly evaluate bone micro-architecture. However, such techniques are impractical for routine clinical management. Indeed, MRI has recently arisen as a useful tool to measure bone structure in vivo. In particular, high-resolution MRI techniques have introduced new perspectives for trabecular bone architecture characterization by non-invasive non-ionizing methods. This promising approach is able to quantify morpho-functional changes in both aging and pathology. In this particular context, fractal lacunarity seems to be the proper tool to characterize trabecular bone architecture as it is able to describe both discontinuity of bone network and sizes of bone marrow spaces, whose changes are an index of bone fracture risk [70]. Therefore, prospective studies are needed to investigate the usefulness of these novel promising techniques in the prediction of fracture risk in T1D.

Secondly, it is possible that a good glycemic control may exert a beneficial effect on bone but it is not clear how strict we should maintain glycemic control and below which level we should lower HbA1c to prevent or improve bone disorder in T1D. Therefore, we need prospective studies focused on the changes of bone metabolism/mineralization/fracture risk after intensification of insulin treatment (for example, through insulin pump), which is known to lead to a notable improvement of glycemic control.

Finally, it is not clear yet what kind of drugs should be used in osteoporotic T1D patients who fail to improve notwithstanding a good glycemic control and supplementation of calcium/vitamin D. Some promising results seem to come from the use of anabolic pharmacological agents in diabetic rodents with bone disorder. Therefore, randomized clinical trials are needed to understand whether it could be the case in humans.

Conflict of interest Volha V. Zhukouskaya, Cristina Eller-Vainicher, Alla P. Shepelkevich, Yulia Dydyshko, Elisa Cairoli and Iacopo Chiodini declare that they have no conflict of interest.

Ethical approval All the studies cited in the current mini review involving human participants and/or animal models have received ethical approval.

Informed consent All human participants before entering in the research gave their informed consent.

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