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REVIEW

Bone fragility in patients with diabetes mellitus: A consensus statement from the working group of the Italian Diabetes Society (SID), Italian Society of Endocrinology (SIE), Italian Society of Gerontology and Geriatrics (SIGG), Italian Society of Orthopaedics and Traumatology (SIOT)

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Abstract Bone fragility is one of the possible complications of diabetes, either type 1 (T1D) or type 2 (T2D). Bone fragility can affect patients of different age and with different disease severity depending on type of diabetes, disease duration and the presence of other complications. Fracture risk assessment should be started at different stages in the natural history of the disease depending on the type of diabetes and other risk factors. The risk of fracture in T1D is higher than in T2D, imposing a much earlier screening and therapeutic intervention that should also take into

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account a patient's life expectancy, diabetes complications etc. The therapeutic armamentarium for T2D has been enriched with drugs that may influence bone metabolism, and clinicians should be aware of these effects.

Considering the complexity of diabetes and osteoporosis and the range of variables that influence treatment choices in a given individual, the Working Group on bone fragility in patients with diabetes mellitus has identified and issued recommendations based on the variables that should guide screening of bone fragility and management of diabetes and bone fragility: (A)ge, (B)MD, (C)omplications, (D)uration of disease, & (F)ractures (ABCD&F). Consideration of these parameters may help clinicians identify the best time for screening, the appropriate glycaemic target and anti-osteoporosis drug for patients with diabetes at risk of or with bone fragility.

Introduction

The definition “diabetic bone disease” is used to describe changes in mineral density, bone growth and bone remodelling processes, as well as the increased risk of fracture, associated with the presence of type 1 (T1D) or type 2 (T2D) diabetes. There is increasing evidence that bone should be included among the target organs of diabetes, and that bone fragility is one of the possible complications of the disease. In light of the high prevalence of diabetes among the elderly, this document aims to raise awareness of the association between diabetes and bone fragility among health professionals involved in the treatment of diabetes, osteoporosis and associated complications, and to outline general recommendations for improving the management of patients with diabetes and bone fragility.

Diabetes and fracture risk

Several epidemiological studies have shown that individuals with diabetes have a higher risk of fracture than healthy controls [1]. Recent data indicate an increased risk of any fracture (relative risk [RR]: 1.32; 95% CI 1.17–1.48; $p < 0.001$) in both T1D and T2D [2], generally with a higher risk in T1D. In a meta-analysis of 25 cohort studies, the relative risk in T1D patients was significantly increased by 1.51 times for total fractures, 4.35 for hip fractures, 1.83 for fractures of the upper limb and 1.97 for ankle fractures [2]. A higher prevalence of vertebral fractures (24.4 vs. 6.1%) has also been reported in T1D patients than in controls [3]. The risk of fracture in T1D is increased at all ages and in both sexes, and hip fractures occur 10–15 years earlier than in non-diabetic individuals [4]. T2D is associated with an increased risk of hip fractures (RR 1.79) [5]. No significant associations with forearm or vertebral fractures have been described, whereas wrist and foot fractures are more frequent in T2D patients than in non-diabetic controls [6–8]. Fracture risk is further increased in patients with T2D treated with insulin [9,10], with high HbA1c [11] or with more frequent hypoglycaemic episodes [12].

Bone alterations in diabetes

Bone fragility in T1D can be partially explained by lower lumbar and femoral bone mineral density (BMD) compared to non-diabetic subjects [13]. On the other hand, patients with T2D have a higher BMD than controls [7,14] but also have a significantly higher risk of fracture, even after adjustment for BMD [6,7,15]. The reason for this discrepancy has not been fully clarified, but it is likely that individuals with T2D have poor bone quality, due to alterations in bone remodelling, microarchitecture, strength and composition of the bone matrix and mineral components [16]. Insulin resistance alone is also associated with an increase in BMD [17,18], but it is less clear whether insulin resistance increases the risk of fracture [16].

Pathogenesis of bone fragility in diabetes

The pathogenesis of bone fragility in diabetes is multifactorial and not fully understood. There are many possible mechanisms involved. Chronic hyperglycaemia and the consequent formation of advanced glycation end-products (AGEs) seem to play an important role [19]. Accumulation of AGEs in bone is a physiological occurrence with ageing, but is more accelerated in diabetes [20], where it can contribute to increased bone fragility [21].

A reduction in bone remodelling, mainly estimated using biochemical bone turnover markers (BTM), could contribute to bone fragility in diabetes [19,22] particularly in patients with T2D, who exhibit increased levels of sclerostin, an osteocyte-derived negative regulator of bone formation [20,23]. It has been hypothesised that diabetes compromises the healing of micro-fractures in mechanically loaded bones due to the suppression of bone formation, and that the accumulation of micro-fractures may predispose individuals with diabetes to fractures [24]. Although the suppression of bone remodelling is likely to play a role in determining bone fragility in diabetes, recent evidence indicates that BTMs cannot predict the risk of fracture in T2D [25].

Chronic inflammation and oxidative stress may adversely affect osteogenesis and promote bone resorption [26,27], but further studies are needed to better define their contribution to diabetic bone disease. Furthermore, an increase in adipogenesis could be responsible for the increase in bone marrow adipose tissue observed in patients with T2D [28,29], which has been associated with fracture risk in men and trabecular volumetric BMD in

women [28]. In patients with T1D the amount of bone marrow adipose tissue does not appear be increased [30].

Finally, hypovitaminosis D is common in both T1D and T2D patients [31],

Diabetes-specific risk factors for fracture (A•B•C•D & F•G)

Age

Type 1 diabetes. Fracture risk in T1D is increased at all ages, even in children [48], and increases further with age [4]. Young age is not a protective factor against the risk of fracture associated with T1D.

Type 2 diabetes. The association between fracture risk and T2D seems to be stronger at younger ages, especially for hip fracture [32]. However, the risk of hip fracture throughout lifetime remains higher than in non-diabetic individuals, up to 40–70% higher in older T2D patients [5,15].

BMD

Although BMD has been shown to underestimate the risk of fracture in both T1D and T2D, a reduction in BMD remains an independent risk factor for fractures [33]. However, it should be noted that, for the same T-score and age, the risk of fracture is higher in T2D patients compared to non-diabetic controls [34]: a given T-score in a woman with T2D corresponds to a fracture risk equal to that of a non-diabetic woman with a T-score lower of about 0.5 units [34]. It is therefore possible for a woman with T2D to experience a fracture event even in the presence of a T-score that is not in the range of osteoporosis.

Complications of diabetes

Typical complications of diabetes such as peripheral neuropathy and impaired balance [35], diabetic retinopathy [15] and impaired renal function [36] have been associated with an increased risk of falls and fracture.

The risk of fracture is particularly high in patients with T1D with eye, kidney, neurological, or cardiovascular complications [37,38]. Likewise, diabetes complications in T2D patients, especially if multiple, are associated with a higher risk of fracture [35,39].

Duration of disease and drugs

A longer duration of disease is associated with a high risk of fracture [40], both in T1D [37] and T2D [9,41]. A further aspect to consider is drug therapy. In T2D patients, the use of certain hypoglycaemic drugs (as discussed in detail in the section “Diabetes therapy”) has been associated with an increased fracture risk [42]. Polypharmacy (four or more drugs; the use of more drugs with an increased risk of drug interactions) increases with age and is another important risk factor for falls [43] (Supplementary Table 1). Finally, many drugs have a negative effect on bone and can cause loss of bone mass and/or increase the risk of fracture (Supplementary Table 1) [44].

Fractures (previous)

Previous fractures are a known risk factor for osteoporotic fractures [45,46]. The same applies to T2D, where the risk of hip fracture increases by more than 450% and the risk of fractures is 390% higher in patients with a previous major fracture [47]. The presence of a previous vertebral fracture also increases the risk of nonvertebral fractures in patients with T2D [48]. The results of a large cohort study that included both T1D and T2D subjects indicate that the ability of traditional risk factors to predict osteoporotic fractures is not influenced by the presence of diabetes [49].

Fatty liver disease

Emerging evidence indicates that non-alcoholic fatty liver disease (NAFLD), which is extremely prevalent among individuals with type 2 diabetes [50], might be a risk factor for fragility fractures despite normal BMD [51]. Of note, presence and severity of NAFLD have been associated with reduced BMD in children and adolescents [52]. These observations need further validation in patients with diabetes, but should prompt physicians to perform even more accurate fracture risk assessment in those with NAFLD.

Glycaemic control

Poor glycaemic control seems to affect both bone quality and fracture risk. In general, there is a progressive increase in the risk of fracture in patients with higher HbA1c (especially those with HbA1c >9% [4.9 mmol/mol]) [11]. Patients with T1D and poor glycaemic control (HbA1c > 8% or 63.9 mmol/mol) are 1.4 times more likely to experience a non-vertebral fracture from a low energy trauma than those with good glycaemic control (HbA1c ≤ 7% or 53 mmol/mol) [38]. Consistently, literature data suggest that a better glycaemic control can prevent bone loss in T1D [53].

Conversely, in T2D a recent case–control analysis found no association between poor glycaemic control (HbA1c > 8% or 63.9 mmol/mol) and the risk of non-vertebral fractures from low-energy trauma [38].

Hypoglycaemia is associated with an increased risk of fracture, both in T1D [54] and T2D [55]. It is plausible that a more aggressive therapeutic approach increases the risk of hypoglycaemic episodes and consequently the risk of falling and fracture [36,56].

Current recommendations

The 2018 Italian Standards of Care in Diabetes by the Italian Diabetes Society do not provide specific recommendations for screening and fracture prevention in diabetes, with the exception of the recommendation that pioglitazone should not be used in elderly people at risk of bone fracture [57]. The American Diabetes Association (ADA) Standards of Medical Care in Diabetes issued in 2020 acknowledge that fracture risk is significantly higher in individuals with T1D or T2D, in both sexes and in all age groups, and recommend the assessment of fracture history and fracture risk factors in elderly patients with diabetes [58]. Measurement of BMD (DXA) is recommended if appropriate for patient age and gender. Fracture prevention strategies, according to the ADA, are the same as those applied to the general population, and include vitamin D

supplementation. Finally, the ADA recommends caution when using medications associated with fracture risk, such as thiazolidinediones (TZDs) and sodium-glucose linked transporter-2 (SGLT-2) inhibitors.

In 2018, the International Osteoporosis Foundation (IOF) working group on Bone and Diabetes proposed an algorithm for the identification and management of patients with diabetes and increased fracture risk (Fig. 1), based both on the evidence available at the time and expert opinion [59].

Challenges in diagnosis and treatment

The algorithm issued by the IOF (Fig. 1) should guide screening and treatment timing for primary or secondary fracture prevention. However, we believe that providing further indications may help clinicians apply this algorithm, and guide therapeutic choices according to patient clinical characteristics, stage of disease and on the type of diabetes.

Starting from an algorithm published some years ago [60], we identified some variables that should guide the screening and choice of hypoglycaemic and anti-osteoporotic treatment: (A)ge, (B)MD, (C)omplications (C), (D)uration of disease, & (F)ractures or, in short, ABCD&F. As shown in Fig. 3, taking into account these parameters may help clinicians identify the best time for screening, the appropriate glycaemic target and anti-osteoporosis drug for patients with diabetes at risk of or with bone fragility.

Recommendations

Risk assessment and diagnosis of bone fragility (Table 1)

The techniques used for the measurement of BMD and fracture risk assessment in the general population are, respectively, DXA, prescribed in Italy according to the criteria in Supplementary Table 2, and the Fracture Risk Assessment Tool (FRAX®). DXA-derived BMD, together with fracture history assessment, is widely used in clinical practice and was shown able to predict fracture risk over 20–25 years in post-menopausal women [61]. FRAX® is available online (http://www.shef.ac.uk/FRAX/). The trabecular bone score (TBS) is a recently developed analytical tool that reanalyses the spatial dynamics of pixel intensity variations at the level of the lumbar spine, as measured by DXA, defining a quantitative index that reflects the microarchitecture of trabecular bone. Vertebral morphometry is a quantitative method for the diagnosis of vertebral fractures based on the measurement of vertebral heights though X-Ray or DXA.

According to the International Society for Paediatric and Adolescent Diabetes (ISPAD), assessment of BMD using DXA can be considered as early as late adolescence, particularly in the presence of coeliac disease. The choice

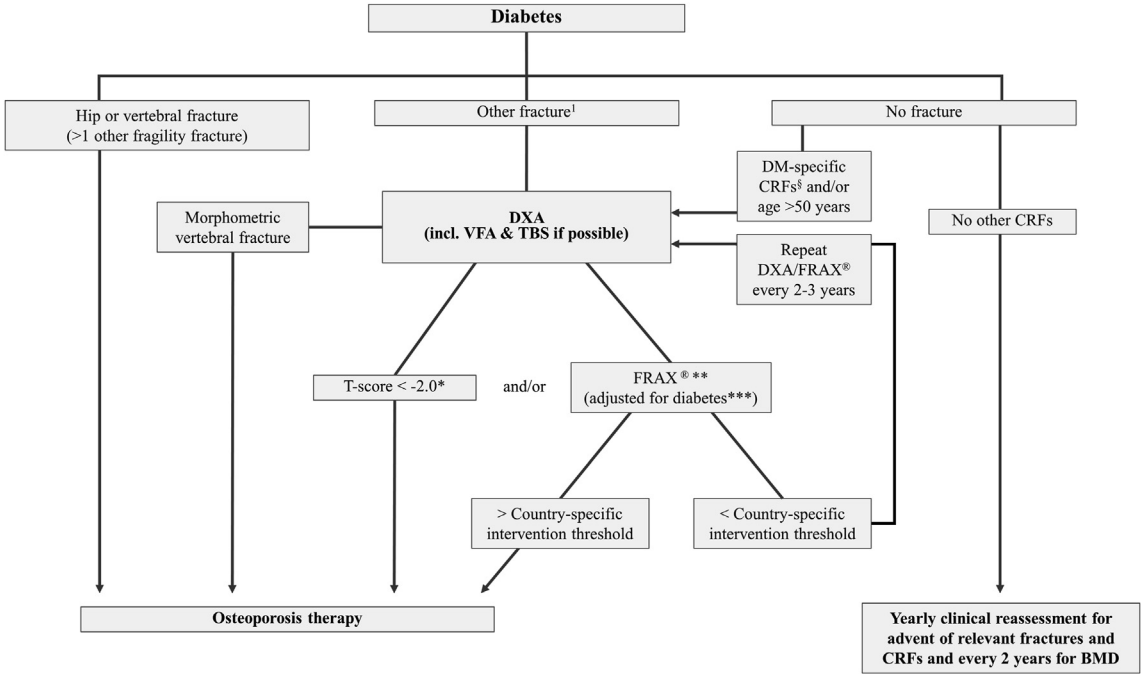

Figure 1 Fracture risk evaluation in patients with diabetes. *In diabetes, fracture risk at T-score < −2 equivalent for non-diabetes at T-score < −2.5 (see text). **Depending on country-specific guidelines for therapies. ***For example, with TBS and/or "rheumatoid arthritis" – yes. [§]Diabetes-specific clinical risk factors: • Diabetes duration >5 years, • Diabetes medication: insulin, thiazolidinediones (TZDs), possibly sodium-glucose co-transporter-2 (SGLT2) inhibitors, • HbA1c > 7.0% or 53 mmol/mol, • Microvascular complications: peripheral and autonomic neuropathy, retinopathy, nephropathy. [1]In certain countries, humerus or pelvis fractures are also sufficient to initiate therapy; otherwise, more than non-vertebral non-hip fragility fracture could be required to initiate therapy; alternatively, a non-vertebral non-hip fragility fracture should prompt further exams to evaluate fracture risk. Modified from Ref. [59], under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/).

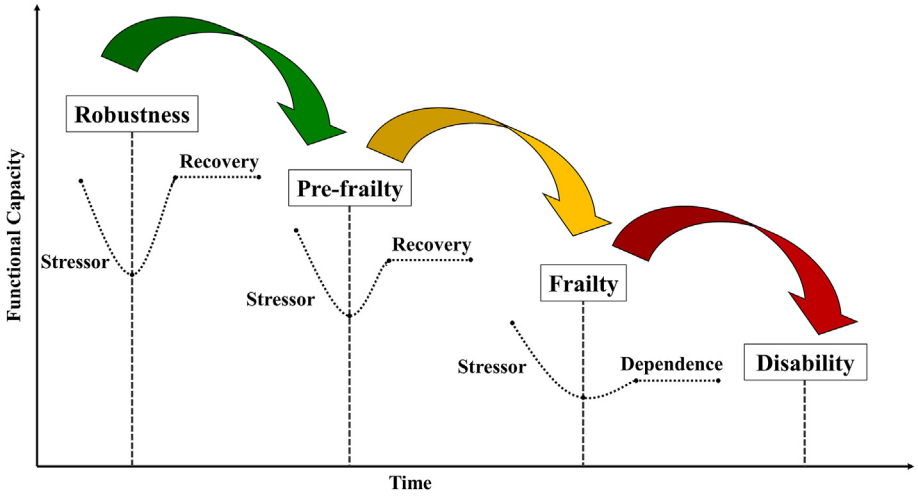

Figure 2 Frailty as a chronic condition leading to disability.

to perform DXA at a young age also depends on the presence of other risk factors affecting fracture risk, including glycaemic control (HbA1c) and the presence of microvascular complications [62–64]. Other risk factors for fracture in T1D are glycaemic control in the previous 5 years (HbA1c threshold ≥7.9% or 62.8 mmol/mol), duration of illness ≥26 years and family history of fragility fractures. These factors should always be investigated to prompt proper screening and adopt a targeted therapeutic strategy in T1D patients. T1D-related complications appear 5–10 years after disease onset and after puberty. In the absence of evidence to establish a specific age threshold based on disease duration for performing DXA, it is important that diabetologists inform families and patients of the importance of early diagnosis and treatment.

TBS may be useful but its role needs to be validated, while there is no evidence for FRAX®.

In T2D, BMD is 5–10% higher than in the non-diabetic population [6] and the risk of fracture can be underestimated by DXA alone. It has been proposed that a correction factor of 0.5 should be applied in the interpretation of T-score in T2D [34]. Thus, in a patient with diabetes, the risk of fracture corresponding to a T-score < -2.0 is equivalent to that of a person without diabetes with a T-score < -2.5. In the clinical evaluation of a patient with T2D, FRAX® (selecting the option for rheumatoid arthritis (RA) [59,65]) or TBS can also be also used.

The risk of fracture appears to be neutral in patients newly diagnosed with T2D, perhaps due to putative protective factors such as an increased fat mass or hyperinsulinaemia preceding the onset of diabetes; and increases significantly only after 5 years of diabetes [40]. Assessment of BMD should therefore be carried out in all patients with T2D diagnosed for at least 5 years. The frequency of assessments is determined by the algorithm shown in Fig. 1. The presence of disease duration >5 years requires further investigations such as DXA and TBS, including the assessment of vertebral fractures by X-ray or VFA. Regardless of DXA assessment, it is important, especially in patients with long disease duration, to assess the risk of fracture with medical history and FRAX® during follow-up visits. If the results of the assessment are above the indicated thresholds, it is suggested to monitor the patient by repeating DXA and FRAX® at regular 2-3-year intervals [59].

Regardless of the type of diabetes, fracture risk assessment questionnaires should be regularly used in the outpatient setting.

A radiological diagnosis may also take advantage of images acquired for other clinical problems, such as chest X-ray, CT or MRI performed for other reasons. This approach may be particularly useful during hospitalisation.

For T2D patients undergoing metabolic-bariatric surgery, the European Association for the Study of Obesity (EASO) states that DXA should be performed before surgery and every two years thereafter to monitor BMD in patients undergoing gastric bypass, biliopancreatic diversion or duodenal switch. However, EASO recognises that performing DXA prior to surgery can be difficult and the reliability of results poor in patients with severe obesity [66].

Finally, it should be borne in mind that "traditional" risk factors (Supplementary Table 2) are useful to estimate the risk of fragility fracture even in patients with diabetes, regardless of the type of diabetes [49]. Thus, traditional risk factors, together with diabetes-specific risk factors, should be investigated during each follow-up diabetes visit.

Management

Lifestyle interventions

Nutrition At every stage of life, adequate intake of nutrients such as calcium and vitamin D with diet contributes to bone health and reduces the risk of osteoporosis and subsequent fractures [67–70]. To date, there is insufficient evidence to issue specific nutritional guidelines for frail

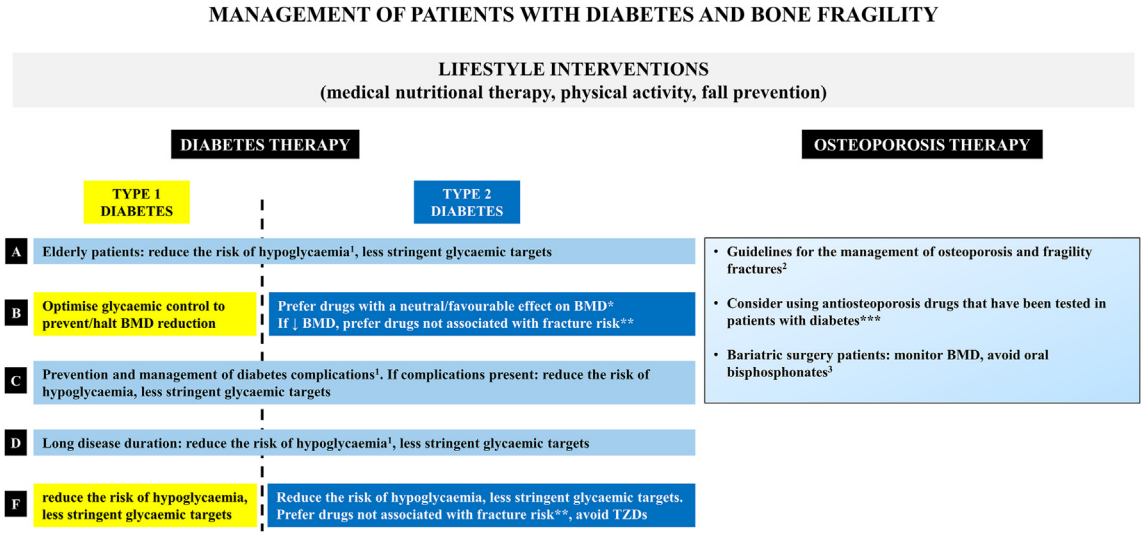

Figure 3 Management of patients with diabetes and bone fragility. A, age, B, bone mineral density (BMD), C, complications, D, duration of disease and drugs, & F, fractures. (G)lycaemic control is key in each of these aspects. *metformin, GLP1 receptor agonists, DPP4 inhibitors; ** GLP1 receptor agonists, DPP4 inhibitor; drugs associated with fracture risk in type 2 diabetes: sulfonylureas, insulin, canagliflozin (?); *** alendronate, risedronate, denosumab, teriparatide. [1]Associazione Medici Diabetologi (AMD) - Società Italiana di Diabetologia (SID) - Italian Diabetes Care Standards 2018. http://www.siditalia.it/clinica/standard-di-cura-amd-sid [57]. [2]Nuti R et al. Guidelines for the management of osteoporosis and fragility fractures. Intern Emerg Med. 2019; 14 (1):85–102 [141. [3]Busetto L et al. Practical Recommendations of the Obesity Management Task Force of the European Association for the Study of Obesity for the Post-Bariatric Surgery Medical Management. Obes Facts 2017; 10:597 [66].

elderly people with T2D. The limited evidence available suggests that protein-rich, high-calorie diets can prevent weight loss and malnutrition in the elderly. However, studies have not specifically addressed frailty [71].

Dietary advice emphasising restriction of food variety and quantity can lead to malnutrition in elderly patients with diabetes, especially in the context of anorexia of ageing [72]. Among overweight adults with T2D, significant weight loss may also result in bone loss, although this appears to be limited (less than 1% after 4 years), has only been observed in men and the fracture rate was not increased [73,74]. In frail elderly individuals, intentional weight loss leads to muscle and bone depletion [75,76], which can be prevented or limited by the association of caloric restriction with a physical activity programme, particularly endurance or combined aerobic and endurance [77–79].

Physical activity Physical inactivity contributes to the reduction of muscle strength, mass and function (i.e. sarcopenia), which in turn appears to be a crucial factor for frailty in elderly patients. The combination of diabetes and physical inactivity accelerates the development of sarcopenia, thus worsening glycaemic control and disability. Physical therapy seems to be more important in improving functional capacity than medical nutritional therapy in the elderly as compared to younger patients. The combination of aerobic and endurance training seems to be the best training mode [80,81]. Specific guidelines have been proposed for the promotion of training interventions for older adults with T2D [82]. A risk assessment should be performed before recommending training programmes for more frail adults. Type of activity and timing should be considered in relation to the pharmacological regimen, particularly hypoglycaemic agents associated with an increased risk of hypoglycaemia [83].

Prevention of falls and frailty in the elderly patient (Table 2)

Individuals with diabetes and eye, neurological and vascular complications - and poor physical health in general - are more likely to fall. As a corollary, effective fall prevention strategies should be developed to prevent fractures in individuals with longstanding diabetes or diabetes complications.

In elderly patients with diabetes, frailty is a pre-disability condition that, if not recognised, can lead to dreadful consequences such as geriatric syndromes, hospitalisation, severe disability, and premature death (Fig. 2). Early diagnosis of frailty in elderly people with diabetes is essential to implement preventative strategies and timely, individualised interventions to prevent falls, maintain mobility, delay the appearance of frailty and disability.

Comprehensive geriatric assessment Given the syndromic nature of frailty, comprehensive geriatric assessment (CGA) should be used to identify geriatric syndromes and the most appropriate therapeutic goals. It has been demonstrated that CGA-based programmes lead to improved functional outcomes and quality of life, reduced use of health services and reduced mortality in older people [84,85]. Several scientific societies recommend that treatment strategies should be based on CGA programmes, repeating the patient's assessment yearly, and whenever there is a change in clinical conditions or drug therapy [82,86].

Drug therapy in elderly individuals with comorbidities, frailty and diabetes should be reviewed periodically and,

Table 1 Risk assessment and diagnosis of bone fragility.

The presence of traditional risk factors for osteoporotic fractures, as well as the presence of diabetes-specific risk factors, should be investigated at each follow-up diabetes visit, regardless of the type of diabetes.

T1D	T2D
•T1D patients have low BMD and high risk of fracture at an early age DXA remains the gold standard for the diagnosis of osteoporosis; being a technique that involves low X-ray emission, it can also be performed in paediatric patients, when the reference physician deems it appropriate. •Densitometry by DXA should be performed: o in all T1D patients after the age of 50 years, or o even earlier in those with diabetes-specific risk factors such as: • micro- or macrovascular complications, • suboptimal glycaemic control (HBA1c >8% or 63.9 mmol/mol) • family history of fragility fractures • celiac disease o As already indicated by the International Society for Pediatric and Adolescent Diabetes (ISPAD), a DXA scan should be considered in late adolescence, especially if the patient also has celiac disease. Note: in patients aged <50 years, the z-score should be used instead of the T-score. •It is important to investigate previous fractures and risk factors for bone fragility (intake of calcium, vitamin D, malabsorption, etc.) during each clinical assessment. •Vertebral morphometry can be performed either by RX or DXA in a semi-quantitative way. This assessment should be reserved to patients with: o clinical history of intense spinal pain, o fragility fractures in other bone sites. o patients with spine or hip T or Z-score < −2.0 •FRAX® and DeFRA can be useful for estimating the risk of fracture, but there are no specific thresholds for T1D.	•Patients with T2D have normal or increased BMD compared to healthy individuals of the same age •BMD should be measured in all T2D patients with: o Age >50 years o Previous fragility fracture o Chronic therapy with thiazolidinediones or canagliflozin o General risk factors, independent of diabetes •A correction factor of 0.5 can be applied in the interpretation of T-score (for example < −2.0 should be considered as < −2.5). •In T2D patients undergoing bariatric surgery with a malabsorptive component, DXA should be performed before surgery and every two years thereafter to monitor BMD •FRAX® can be used in the clinical evaluation of patients with diabetes, selecting the option for rheumatoid arthritis •The Trabecular Bone Score showed a very good sensitivity in predicting the risk of fracture in T2D but further studies are needed to validate its use in clinical practice •Vertebral morphometry can be performed either by RX or DXA in a semi-quantitative way. This assessment should be reserved to patients with: o T-score < −2.0 o clinical history of intense spinal pain, o fragility fractures in other bone sites. o disease duration >5 years o use of a TZD

A vertebral fracture diagnosis can be made using images acquired for other clinical problems such as a chest X-ray, CT or MRI [85,86].

where appropriate, de-intensification of therapy should be considered.

Multimodal interventions The rationale for such interventions lies in the complex framework underlying frailty. The results of the MID-Frail study (The Multi-modal Intervention in Diabetes in Frailty), indicate that an individualised endurance exercise programme in conjunction with nutritional education is associated with beneficial effects on the functional status of frail and prefrail participants, with lower health care costs [87].

Education Health professionals involved in the management of patients with diabetes should inform patients and caregivers about the association between diabetes and fracture risk and stress the importance of preventing and managing hypoglycaemic episodes. Ideally, treatment regimens should be adjusted to a patient's self-management skills, and patient education should take into account any functional and mental limitations, comorbidities and social situations.

Diabetes treatment (Table 3)

For the pharmacological treatment of diabetes, Italian physicians should refer to the Italian Diabetes Care Standards of the Italian Diabetes Society [57], and to the recent Consensus Report of the ADA/EASD [88]. Here we provide a brief overview of the effects of hypoglycaemic drugs on bone. The assessment of ABCD&F risk factors may be useful to guide therapeutic choices (Fig. 3).

Insulin Insulin has an anabolic action on bone. In patients with T1D, intensive insulin treatment started at disease onset has been associated with increased BMD and reduced bone resorption markers [53], and no association has been found between insulin treatment and fracture risk [62].

On the contrary, some studies have shown a higher risk of fracture in insulin-treated T2D patients than non-insulin-treated patients [9,10]. Among elderly male patients, the risk is higher in those with tighter glycaemic control (HbA1c <6.5% or 47.5 mmol/mol) [89], probably because more aggressive insulin therapy is associated with a higher risk of hypoglycaemia. Moreover, in subjects with T2D treated with insulin the risk of falling is almost four times higher [41] and, in patients with foot ulcers, insulin therapy has been associated with recurrent falls [90]. It is possible that differences in the effects of insulin therapy in T1D and T2D are due to the fact that, generally, insulin treatment in T2D is initiated in the late stages of the disease, often when the complications of diabetes have already emerged and patients are older. Overall, all these factors increase the risk of falls and fractures.

Metformin Metformin is a largely used medication with low risk of hypoglycaemia. In large cohort studies, metformin treatment in T2D patients has shown a protective

Table 2 Prevention of falls and frailty in the elderly patient.

- Elderly patients with T2D are at high risk of frailty, with subsequent disability and adverse events, and should undergo an assessment of frailty and/or pre-frailty before starting specific treatments.
- A multidimensional geriatric assessment should be granted to all patients, conducted according to the principles of "comprehensive care", aimed to provide individualised interventions with respect to a person's needs, and provided in an integrated multidisciplinary manner (interdisciplinary).
- The multidimensional geriatric assessment should be repeated annually and whenever acute or sub-acute changes in a patient's general health status occur, with the aim of optimising interdisciplinary management.
- Elderly patients with T2D could benefit from multimodal interventions, which are effective in reducing the risk of fragility and disability.
- Exercise programmes, particularly multi-component programmes, should be encouraged, as these are effective in improving glycometabolic control, reducing the risk of sarcopenia and falls, mitigating physical and cognitive decline, and improving functional capacity and quality of life.
- In light of the high risk of hypoglycaemia, it is not recommended to aim at stringent glycaemic control. Glycaemic targets should be individualised based on frailty status, comorbidities, polypharmacotherapy, quality of life and life expectancy.

effect on hip fracture risk of, with a 20−30% lower risk than insulin [39,91] and sulfonylureas or TZDs [39,92]. Other cohort studies have reported a neutral effect of metformin on the risk of hip fracture in elderly subjects with T2D [10,93].

Sulfonylureas (and glinides) Sulfonylureas stimulate insulin secretion, regardless of blood glucose levels, increasing risk of hypoglycaemia. There is little data on the effects of sulfonylureas on bone metabolism. In the ADOPT study, fracture rate was higher than with metformin, but lower than with rosiglitazone [92]. Other studies [10,42], although not all [39,93,94], showed an increased risk of fracture in patients treated with sulfonylureas.

Table 3 Diabetes treatment.

- In patients with early onset T1D, maintaining stringent glycaemic targets with intensive insulin therapy may have a favourable effect on BMD. In general, good glycaemic control can contribute to better bone health.
- In patients with T2D and risk factors for fracture, TZDs and SGLT-2 inhibitors (canagliflozin) should be used with caution, and drugs with a neutral or favourable impact on bone (e.g. metformin, incretins) should be preferred.
- TZDs should be used with great caution in elderly subjects with or at risk of osteoporosis, falls or macular oedema, and should be avoided in case of risk of bone fracture.
- In frail patients with long duration of disease, complications and/or increased risk of fracture, particular caution should also be exercised in the use of drugs that may lead to hypoglycaemia, such as insulin, sulfonylureas or glinides. In these instances, it may be appropriate to maintain less stringent glycaemic targets.
- In elderly patients with diabetes, it is advisable to simplify the therapeutic regimen in the case of recurrent episodes of severe hypoglycaemia or high glycaemic variability, or when cognitive impairment occurs following an acute event.
- In patients with T2D undergoing bariatric surgery, strict monitoring should be implemented to prevent nutritional deficiencies that could worsen the loss of bone mass associated with weight loss.

Thiazolidinediones TZDs such as pioglitazone and rosiglitazone exercise their function by activating PPARγ, stimulating adipogenesis and suppressing osteoblastogenesis. Substantial evidence indicates that treatment with TZDs is associated with a reduction in BMD and an increased risk of fracture, especially in women [95,96].

SGLT-2 inhibitors Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin all belong to this class. SGLT2 inhibitors reduce the reabsorption of glucose filtered by the kidney, causing an increase in glycosuria that results in a reduction in blood glucose levels. Treatment with empagliflozin, dapagliflozin [97] or ertugliflozin [98] does not appear to change the risk of fracture in patients with T2D. Initial data on canagliflozin showed a significant increase in the incidence of fractures compared to placebo, but subsequent analyses and, more recently, the CREDENCE study, indicate a neutral effect on bone [99]. Real world data on fracture risk in patients treated with SGLT2 inhibitors do not show an increase in fracture risk in patients treated with SGLT2 inhibitors compared to subjects treated with GLP-1 analogues [100] or DPP-4 inhibitors [101].

GLP-1 receptor agonists and DPP-4 inhibitors Acting only when blood glucose increases as a result of carbohydrate intake with food, incretin drugs (GLP-1 analogues and DPP-4 inhibitors) do not cause hypoglycaemia. GLP-1 analogues and DPP-4 inhibitors have a favourable or neutral effect on BMD [102]. Liraglutide has been reported to counteract the decline in BMD induced by weight loss [103]. Data available to date indicate that GLP-1 agonists are not associated with fracture risk [104,105]. With regard to DPP-4 inhibitors, two large RCTs, the SAVOR-TIMI 53 study on saxagliptin [106] and the TECOS study on sitagliptin [107] showed no association between DPP-4 inhibitors and fracture risk.

In brief, maintaining stringent glycaemic targets with intensive insulin therapy may have favourable effects on BMD in patients at the early stages of T1D. However, in frail patients with long disease duration, complications and/or increased risk of fracture, drugs that can lead to hypoglycaemia, such as insulin and - for T2D - sulfonylureas or glinides, should be used with particular caution. In these cases, it may be appropriate to maintain less stringent glycaemic targets. In addition, in patients with T2D and risk factors for fracture, TZDs should be avoided while canagliflozin should be used with caution [58]. In order to prevent hypoglycaemia, hypotension and drug interactions due to polypharmacy in elderly patients with diabetes, it is advisable to simplify the therapeutic regimen in the case of recurrent severe hypoglycaemic episodes or high glycaemic variability, or when cognitive impairment occurs following an acute event [43].

Metabolic-bariatric surgery Available data indicate that the risk of fracture after bariatric surgery varies depending on the procedure, being lower in patients undergoing

LAGB [108] and greatest in those undergoing malabsorption procedures [109,110] and increases with time after surgery [108,109,111]. However, reductions in BMD associated with weight loss have also been reported 6–12 months after minimally invasive bariatric procedures that do not involve resection of the stomach and/or intestine, such as intragastric balloon or endoluminal lining of the small intestine [112,113]. The mechanisms underlying the negative effects of bariatric surgery on bone health probably involve nutritional factors, mechanical unloading, hormonal factors and changes in body composition and bone marrow fat [114].

Prevention and treatment of bone fragility (Table 4)

Prevention is primarily based on the correction of risk factors (diet, physical activity, adequate calcium intake through diet) or correction of modifiable factors (cigarette smoking, alcohol abuse, environmental risk factors for falls), which are recommended for all subjects [115].

Data on vitamin D and calcium intake in diabetes are scarce and mainly on T1D, with conflicting results [116]. Calcium supplements should only be recommended for individuals who may be at risk of inadequate calcium intake from the diet at a daily dose of 0.5–1.2 g [117]. A daily dose of 400–800 UI of vitamin D (up to 4000 UI per day) are recommended by Endocrine Society.

Fall risk assessment and appropriate fall prevention measures should be included in the treatment of elderly patients with diabetes.

Table 4 Prevention and treatment of bone fragility.

- Adequate calcium intake according to Dietary Reference Values by age should always be recommended for patients with diabetes, particularly in patients with T1D during bone growth in order to achieve an adequate peak bone mass.
- In both forms of diabetes vitamin D deficiency is a common finding. Vitamin D should therefore be administered at a dosage sufficient to reach the target values (30 ng/ml). As in all non-diabetic individuals, it is recommended to follow the dosages indicated in the summary of product characteristics of the chosen drug. In the case of cholecalciferol, do not use boluses exceeding 100,000 IU and do not exceed 200,000 IU per month. Use calcitriol only in case of renal insufficiency.
- Particular attention should be paid to the prevention of falls.
- Nutritional programmes aimed at weight reduction should always be associated with physical activity in order to improve insulin resistance, prevent sarcopenia, improve motor coordination and reduce the risk of falls.
- Drug therapy is based on the use of anti-resorption drugs such as bisphosphonates (alendronate, risedronate, ibandronate, zoledronate), denosumab or anabolic drugs such as teriparatide.
- Anti-resorptive or anabolic therapy should be used following the criteria and treatment thresholds suggested by the International Osteoporosis Foundation (Fig. 1).
- In Italy, reimbursement of anti-resorptive or anabolic drugs is regulated by the “note 79” by the Italian Medicines Agency (AIFA), which grants free access to patients with diabetes and:
  - T-score < -3.0 at spine or hip (primary prevention).
  - Previous osteoporotic fractures (secondary prevention).
- The choice of the drug is based on AIFA criteria, a patient's clinical characteristics and life expectancy.

Phrmacological treatment

The drugs used to treat osteoporosis exert their effect either by reducing bone resorption (bisphosphonates, SERMs, and denosumab), or by stimulating bone formation (teriparatide, abaloparatide, romosozumab). All these drugs have been shown to reduce the risk of vertebral fractures and, in some cases, anabolic agents have also been shown to reduce the risk of non-vertebral fractures, including hip fractures.

Bisphosphonates currently approved for the treatment of osteoporosis as first-line drugs are: alendronate, risedronate, ibandronate and zoledronate [115]. They differ according to the formulation and recommended therapeutic regimen, varying from daily, weekly, monthly or yearly. All regimen types have been shown to reduce both vertebral and hip fractures, varying between 40% and 60% [118–121]. Available data support the efficacy and the safety of bisphosphonates in people with diabetes [122,123].

SERMs (raloxifene and basedoxifene) are associated with a 30–50% reduction in the risk of vertebral fracture in post-menopausal women [124,125]. Post-marketing data confirmed that bisphosphonates and raloxifene are equally effective in subjects with T1D, T2D or normoglycaemia [126].

Denosumab is a monoclonal antibody that exerts an anti-resorptive effect through by binding RANK, thus preventing its interaction with the RANK receptor [69]. The anti-fracture efficacy of this dose has been demonstrated for vertebral fractures (−68%), hip fractures (−40%) and non-vertebral fractures (−20%) in post-menopausal women during 3 years of therapy [127]. Within the few evidence available, it should be noted that a post-hoc analysis of the “Freedom” registration study showed a reduction in fasting blood sugar levels *vs.* placebo in patients with diabetes treated with denosumab [128].

Among anabolic drugs, Teriparatide has shown a strong anti-fracture effect in both RCT and real-world studies [129,130]. Teriparatide might even be more effective in reducing clinical fracture in patients with diabetes (−77%) than in non-diabetic patients (−48%) [130]. Teriparatide, by increasing both bone formation and, to a lesser extent, bone resorption, could be of particular benefit in diabetes bone disease, which is characterised by reduced bone turnover.

Therapeutic approach

All patients about to start anabolic or anti-reductive therapy should receive vitamin D supplementation in order to reach the serum target of >30 ng/ml.

The therapeutic choice and intervention thresholds should be based on the recommendations of the International Osteoporosis Foundation.

Primary prevention

Patients with T-score < -2.0 or meeting the treatment threshold of the FRAX algorithm should start anti-resorptive therapy with first-line drugs like bisphosphonates or denosumab (first choice if intolerant to bisphosphonates or renal impairment).

Secondary prevention

In patients with a fragility fracture, besides bisphosphonates and denosumab the use of teriparatide should be considered, as teriparatide has shown strong anabolic action and reduced risk of fracture in patients with diabetes [131,132].

It would be advisable, where possible, to start therapy with teriparatide in order to "unblock" bone turnover. Followed by an anti-resorptive agent. Patients with long life expectancy might be prescribed denosumab in light of the data on its safety and long-term efficacy [133] in non-diabetic patients.

According to the guidelines issued in October 2019 by a coalition of scientific societies led by the American Society of Bone and Mineral Research, patients with a fragility fracture, either vertebral or hip fracture, should be started on anti-resorptive therapy and vitamin D supplementation as early as possible during hospitalisation [131].

Management of patients with diabetes and fragility fractures

Surgical treatment of fractures in patients with diabetes

The coexistence of diabetes and osteoporosis makes people with fragility fractures more vulnerable to complications. Individuals with T1D or T2D with surgically treated fractures, and particularly those with complications, are more likely to experience delays in wound and fracture healing and postoperative complications, such as surgical wound infections, malunion and reintervention [134–136]. Men and women with T2D have a 28% and 57% higher risk of death after a hip fracture than subjects without diabetes [137]. Furthermore, patients with diabetes hospitalised for a hip fracture are at increased risk of postoperative cardiac events, and exhibit a longer length of stay [135].

Diabetic neuropathy, if present, may impact haemodynamic and respiratory stability and may prompt the need for longer monitoring after surgery.

Surgical management of fractured patients with diabetes (Fig. 4) requires accurate planning to define a stable fixation strategy in light of the increased risk of pseudoarthrosis. Whenever possible, closed reduction techniques (intramedullary nailing, percutaneous fixation) are preferable to open surgery, as the first decrease the risk of bacterial infections. If open reduction is necessary, abundant irrigation of the fracture site is recommended to minimise the risk of contamination.

As for the postoperative period, it should be borne in mind that the normal healing process of skin and tissue lesions is impaired in people with diabetes [138]. This makes them more prone to the development of chronic wounds, such as ulcerative lesions of the lower limb that, as a result of complications secondary to infections, can even lead to amputation. Delayed wound healing may also predispose to the development of infections, which are up to four times more frequent in patients with diabetes as compared with healthy subjects. It is also important to maintain good glycaemic control in the perioperative period, since perioperative hyperglycaemia is associated with an increased risk of surgical site infections in orthopaedic surgery [139,140]. Glycaemic targets during hospitalisation differ depending on the clinical setting, being 140–180 mg/dl, based on the estimated risk of hypoglycaemia, in critically ill patients, in the Intensive Care Unit. For non-critically ill patients, the goal is to maintain preprandial glycaemic values < 140 mg/dl, postprandial values < 180 mg/dl or random values < 180 mg, if achievable without increasing the risk of hypoglycaemia.

In the case of fragility fractures in elderly patients with diabetes, early mobilisation reduces the risk of ulcerative and pressure lesions due to an altered blood supply secondary to diabetic vascular complications.

Management of elderly patients with diabetes and fragility fractures: orthogeriatric models

Originally developed for acute management of the most vulnerable fractured patients, the orthogeriatric model now covers the entire management pathway of fractured patients, including programmes for the prevention of new fractures. Not all components of the orthogeriatric pathway are available everywhere.

Depending on the context, three main orthogeriatric models can be identified: counselling, integrated care and rehabilitation. The first two refer to acute management and differ in the role of the geriatrician, who is a consultant or is fully responsible for the management of the fractured patient, respectively. The orthogeriatric rehabilitation model is applied to fractured patients undergoing hospital rehabilitation and is of value in subjects with relevant comorbidities, such as diabetes and associated complications. It is important to emphasise the central role of the CGA and, subsequently, of individualised multidisciplinary management and social-healthcare integration.

The objectives and clinical content of orthogeriatric models vary according to the context and time of the intervention. Aspects that deserve special attention are listed in Box 1.

Patients with diabetes are particularly at risk of medical complications due to diabetes-associated comorbidities, such as alterations in renal function. Therefore, patients with diabetes appear to be the ideal target for orthogeriatric care.

Finally, hospitalisation should also be an opportunity to search for possible diabetes complications and other chronic conditions not previously diagnosed, to plan the diagnostic and therapeutic pathway, particularly in patients with a history of falls in the absence of an identified cause.

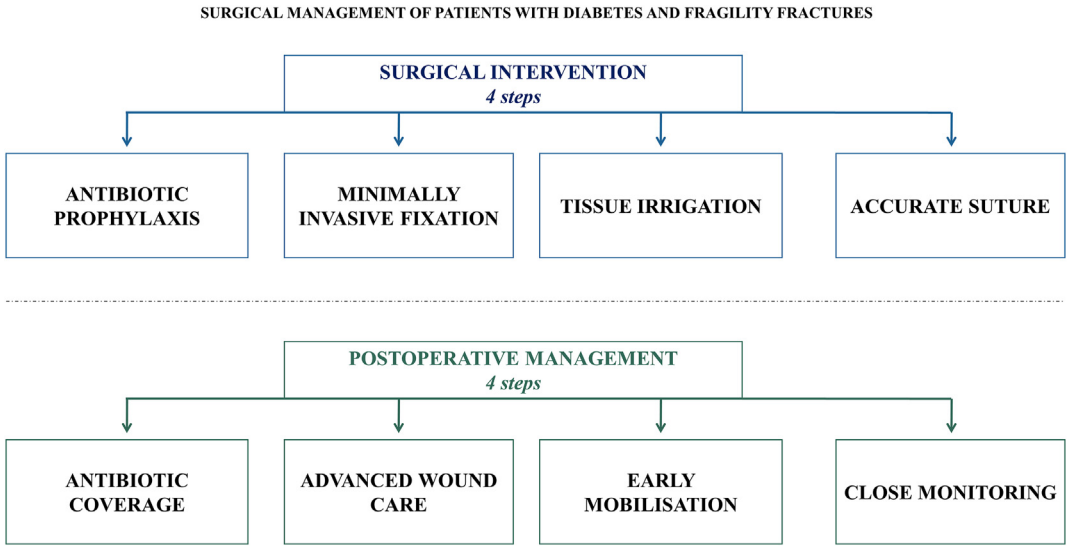

Figure 4 Surgical management of patients with diabetes and fragility fractures.

Box 1
Aspects to be considered in orthogeriatric care.

- Hydration and nutrition, especially at the time of admission and in the perioperative phase.
- Prevention and screening of phlebitis.
- Reduction of catheter indwell time
- Mobilisation and prevention of pressure ulcers.
- Blood pressure monitoring in individuals at-risk and in the perioperative phase
- Anaemia prevention and screening.
- Metabolic and electrolyte balance.
- Acid and base balance in patients at risk.
- Limiting the number of drugs and the risk of interactions.
- Screening for potential adverse drug reactions.
- (Prevention and) for postoperative cognitive decline.
- Prevention and early diagnosis of infectious complications.

Conclusions

Bone fragility is a typical complication of diabetes that can affect patients of different ages and with different disease severity depending on the type of diabetes, the duration of the disease and the presence of other complications. T1D occurs early, leading to a high risk of complications that usually appear after puberty and 5–10 years after onset. For this reason, screening for fractures, with careful medical history and DXA, should be considered as early as at the final stage of adolescence (ISPAD Guidelines). In T1D, special attention should be paid to a long disease duration, complications or suboptimal glycaemic control, which are associated with an increased risk of fracture. Patients with

prediabetes or newly diagnosed T2D are not at increased risk of bone fragility probably due to the anabolic effect of hyperinsulinaemia. However, β cell function slowly decreases leading to overt hyperglycaemia, which results in glucotoxicity and inflammation, production of reactive oxygen species and AGEs, causing organ damage and increasing the risk of complications. At this stage, the properties of bone minerals and bone resistance are compromised.

Patients with T2D aged >50 years or younger patients who already have a fragility fracture or other risk factors related to diabetes (complications, poor glycaemic control, long disease duration) should undergo BMD measurement by DXA or other screening methods (FRAX®, TBS) and possibly morphometric assessment. It is important to achieve stricter glycaemic control in young patients and less stringent targets in the elderly to avoid the risk of hypoglycaemia and, consequently, falls. The therapeutic choice should fall on drugs with a neutral/positive effect on bone metabolism, avoiding TZDs, sulfonylureas and aggressive intensification of insulin treatment in the elderly. Modern treatment models such as orthogeriatric models should guide the inpatient pathway and home care of fractured elderly patients with diabetes. It is important to consider that both T1D and T2D patients need an adequate intake of calcium and vitamin D. Osteoporosis therapy should be initiated for a T-score < -2.0 or in the presence of a vertebral or hip fracture. Among the available drugs, anti-resorptive drugs such as alendronate or denosumab and anabolic drugs such as teriparatide are supported by clinical evidence in patients with diabetes. It is imperative that patients with diabetes and reduced bone mass or fragility fractures undergo not only clinical treatment but also fall prevention pathways. In patients undergoing a hip fracture, anti-osteoporotic treatment should be initiated during hospitalization, a strict monitoring of laboratory tests and further bone assessment should be carried on through a fracture liaison service model of care. It is mandatory that both primary and secondary fracture prevention measures include frailty and falls assessment and care.

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Search strategy and selection criteria. A literature review was conducted through October 15th, 2020 on MEDLINE, EMBASE and Cochrane Database by using the following MeSH terms: (Diabetes) AND (Fractures, Bone) OR (Bone) OR (Bone Density) OR (Bone Remodeling); (Insulin Resistance) AND (Fractures, Bone) OR (Bone) OR (Bone Density) OR (Bone Remodeling); (Fractures, Bone) AND (Hypoglycemic Agents) OR (Insulin) OR (Metformin) OR (Liraglutide) OR (Exenatide) OR (Canagliflozin); OR (Pioglitazone); OR (Rosiglitazone); (Glimepiride); (Gliclazide); (Glibenclamide); (Sitagliptin); (Linagliptin); (Saxagliptin); (Alogliptin); OR (Bariatric Surgery); (Diabetes) AND (Fractures, Bone) AND (Diet) OR (Calcium) OR (Vitamin D) OR (Exercise); (Diabetes) AND (Frailty); (Diabetes) AND (Diphosphonates) OR (Alendronate) OR (Risedronic Acid) OR (Zoledronic Acid) OR (Ibandronic Acid) OR (Selective Estrogen Receptor Modulators) OR (Raloxifene) OR (Bazedoxifene) OR (Denosumab) OR (Teriparatide); (Diabetes) AND (Orthopedic Procedures) OR (Peroperative Complications) and the following free text search terms: (GLP-1 agonist); (Lixisenatide); (Albiglutide); (Dulaglutide); (Semaglutide); (SGLT-2 inhibitors); (Empagliflozin); (Ertugliflozin); (Dapagliflozin); (Thiazolidinedione); (Dipeptidyl peptidase 4 inhibitor); (Sulphonylureas); (Fracture Risk Assessment); (Comprehensive Geriatric Assessment); (Musculoskeletal); (Calorie Restriction); (Fall); (Surgical Complications). Cohort studies, observational prospective and retrospective studies, randomized clinical trials and systematic reviews written in English were considered for inclusion and their relevance assessed by at least two independent reviewers for each Society. Narrative reviews and reference lists from the retrieved journal articles were also examined. Relevant national or international guidelines were also considered. Case reports and case series were excluded.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2021.01.019.

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