Review article

Nutritional therapy bridges the critical cut-off point for the closed-loop role of type 2 diabetes and bone homeostasis: A narrative review

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ABSTRACT

Currently, osteoporosis-related fractures become the most cutting-edge problem of diabetes-related complications. Rational diet is not only the basis of glycemic management in type 2 diabetes patients, but also the direction of diabetic bone health.

This review highlights the importance of micronutrient supplementation (including calcium, magnesium, zinc, vitamin D, vitamin K, and vitamin C) for patients with T2DM, as well as describing the constructive intermediary role of gut flora between T2DM and bone through nutrients predominantly high in dietary fiber. In addition, it is recommended to combine the Mediterranean dietary pattern with other diversified management approaches to prevent OP. Therefore, this provides a theoretical basis for the potential role of islet β-cells in promoting bone health.

1. Introduction

Osteoporosis (OP) is a systemic bone disorder characterized by decreased bone strength and changes in bone microstructure. OP-caused fractures serve as a pivotal risk factor contributing to escalated rates of morbidity and mortality among the elderly population [1]. A Meta-analysis revealed a global prevalence of 19.7% (*95%CI*: 18.0%–21.4%) for OP, with developing countries 22.1% (*95%CI*: 11.5%–17.7%) exhibiting a higher prevalence than developed countries 14.5% (*95%CI*: 20.1%–24.1%), indicating a pressing global public health concern [2]. The onset of OP could be triggered by various factors, including diabetes mellitus (DM). According to the Global Burden of Disease 2021 diabetes collaborators, it has been found that the number of people suffering from DM globally is up to about 529 million in 2021, with type 2 diabetes (T2DM) accounting for more than 96 per cent of that number, and is projected to grow to about 1.31 billion by 2050 [3]. Although the improvement of medical level has extended the survival time of DM patients, DM has increased the number of elderly patients, accompanied by increased incidence of chronic diseases. Crucially, a systematic review and Meta-analysis has unveiled the worldwide prevalence of OP at 27.67% (*95%CI*: 21.37%–33.98%) among patients with T2DM [4], and
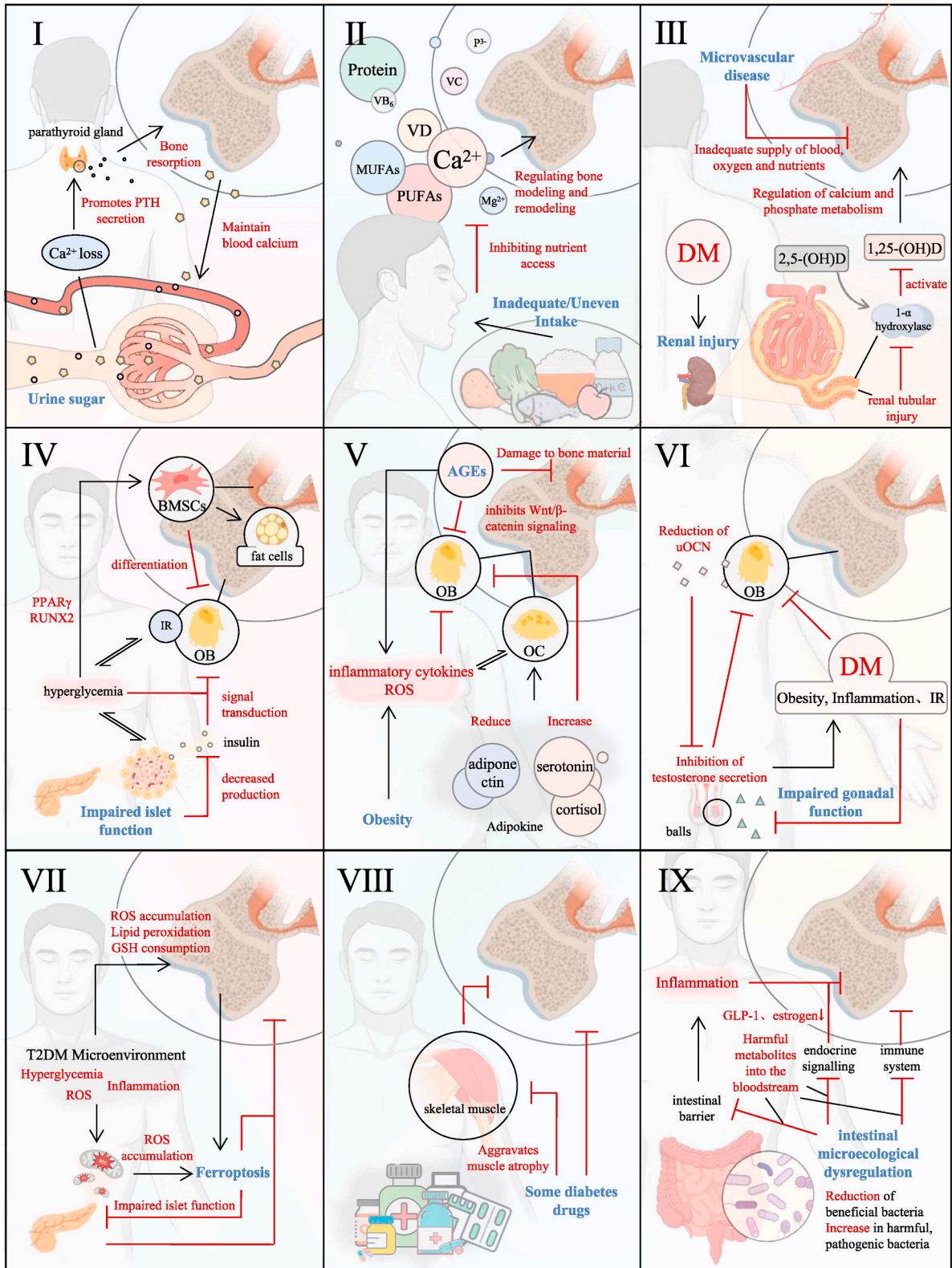

Fig. 1. Direct/indirect effects of T2DM on bone metabolism.

T2DM had been found to be associated with a higher risk of fracture occurrence in several cohort studies [5–7]. However, of greater concern to us is the fact that T2DM affects the efficacy of the skeleton as an endocrine organ, and bone metabolism disorders induced by the patient's chronic hyperglycemic exposure diminish the involvement of bone-derived hormones in various physiological and pathological processes such as cardio residual metabolic health, insulin sensitivity, glucose homeostasis, energy metabolism, and so on [8–10], which is particularly relevant for the development and outcome of diabetic nephropathy [11]. Thus, the complexity of T2DM management is further exacerbated by the inter-crosstalk that exists between the skeleton and other metabolic and organs and tissues, which puts the problem of OP-related fractures at the forefront of T2DM-related complications. Several researches reported that the association may be mediated through various pathways, including chronic hyperglycemia, dietary factors, renal impairment, diminishing pancreatic function, accumulation of advanced glycation end products (AGEs), ferroptosis, medication-related factors, and others, ultimately leading to reduced bone remodeling activity [12–18] and increased OP risk (Fig. 1). On the contrary, maintaining healthy bone homeostasis may benefit osteoblasts (OB) to secrete osteocalcin (OCN) and thus promote the recovery of pancreatic islet function in patients with T2DM (Fig. 2) [19–22].

Hence, in addition to strengthening disease monitoring, patients with T2DM should also consider the management of bone health, ensuring adequate nutrition intake to enhance bone metabolism and subsequently reduce the incidence of OP-related fragility fractures [23]. However, there are few reviews that comprehensively assess the effects of T2DM on bone health through the lens of nutritional therapy currently. Therefore, we aimed to synthesize the scientific evidence and potential mechanisms of the effects of (i) the three major nutrients; (ii) micronutrients (e.g., iron, copper, zinc, magnesium, calcium); (iii) essential vitamins (e.g., vitamin D, vitamin K, vitamin C); (iv) dietary fiber; (v) the four T2DM dietary patterns, and (vi) the integration of the diets with other management modalities on the bone health of patients with T2DM, with the ultimate goal of improving their overall quality of life.

In order to achieve this goal, we took into account the need to have a wider grasp of research progress at home and abroad, so we cited 184 relevant documents using the PubMed database, and two documents published by Chinese people using the Chinese databases CNKI and Wanfang to supplement the overall structure of the article. For search terms, we used "OR" to juxtapose "T2DM" with "osteoporosis", and "AND" to search with the keywords "nutrients, dietary patterns, osteocalcin, intestinal flora, exercise, drugs, epigenetics, smoking and alcohol consumption", respectively. We searched a large amount of relevant literature from 1984 to the present, and finally selected 186 representative articles with high impact factor as references for this review.

1.1. Mechanism I :

T2DM causes urine glucose, Ca^{2+}, and other chemicals to be lost, which stimulates parathyroid glands to release PTH to maintain blood calcium levels, causing bone calcium loss.

1.2. Mechanism II :

Bone strength and function are diminished due to inadequate/unbalanced nutrient intake.

1.3. Mechanism III :

i. T2DM-associated microangiopathy may worsen bone angiogenesis and restrict oxygen, nutrients, hormones, and growth factors, increasing cortical porosity;
ii. Renal tubular damage lowers epithelial 1-alpha hydroxylase activity, and decreases vitamin D activation, which regulates bone metabolism of calcium and phosphate.
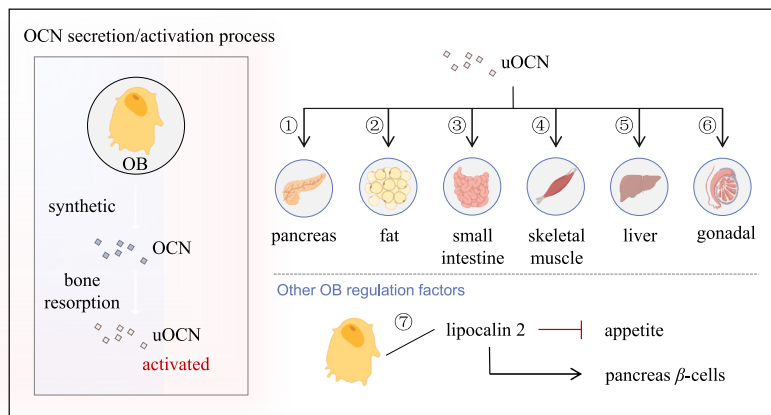

Fig. 2. Potential function of osteocalcin in glucose metabolism regulation.

1.4. Mechanism IV :

    i. Decreased insulin secretion from pancreatic β-cells and insulin receptor resistance in OB cells (Upregulation of Twist2 inhibits Runx2 expression) led to decreased OB proliferation, differentiation, OCN levels, and bone formation;
    ii. Chronic hyperglycemia enhances lipogenic pathways in bone marrow mesenchymal stem cells (BMSCs);
    iii. The hyperglycemic microenvironment stimulates osteocytes to secrete sclerostin and inhibits Wnt signaling, thereby affecting bone formation;
    iv. Hyperglycemic microenvironment accelerates the senescence of osteocytes.

1.5. Mechanism V :

  i. Chronic hyperglycemia induces the formation of AGEs via a non-enzymatic pathway;
    a) AGEs increase the production of inflammatory factors and reactive oxygen species (ROS), which initiates a vicious cycle of inflammation and bone resorption;
    b) AGEs may reduce the expression of insulin growth factor 1 (IGF-1), RUNX2, osteocalcin, and Osterix as well as inhibit endoplasmic reticulum function, thereby negatively affecting OB;
    c) AGEs may stimulate sclerostin expression, suppress Wnt signaling, and affect OB activity;
    d) AGEs accumulation impairs collagen synthesis, impacting bone matrix characteristics and remodeling.
  ii. Obesity increases chronic inflammation, oxidative stress, and adipokine disturbance, leading to decreased lipocalin-2 secretion and increased serotonin and cortisol secretion, which may have a negative impact on bones.

1.6. Mechanism VI :

  i. Obesity, inflammation, insulin resistance, and other factors, resulting in decreased testosterone secretion, increased insulin resistance, inhibited OB proliferation, differentiation, and osteocalcin expression, thereby promoting bone formation by stimulating the proliferation and differentiation of mesenchymal stem cells and osteoblasts;
  ii. Impaired gonadal function results estrogen deficit and increases the activity of the transcription factor *c*-jun in OC precursors, thus activating OC and decreasing GSK3 phosphorylation in OB, inhibiting the Wnt/β-catenin pathway and OB proliferation.

1.7. Mechanism VII :

    i. In the microenvironment of T2DM with impaired glucolipid homeostasis, Fe^{2+} in pancreatic β-cells induces ferroptosis by promoting ROS synthesis via the Fenton reaction, resulting in impaired islet function, which impacts bone metabolism;
    ii. In the microenvironment of T2DM, the oxidation of heme may be catalyzed by the inducible heme oxygenase HO-1 to release large quantities of free unstable iron, generating the Fenton reaction, which forms lipid peroxides and lipid peroxyl radicals, triggering osteoclast ferroptosis and leading to Diabetic osteoporosis; secondly, iron deposition in the bone inhibits the growth of hydroxyapatite, which decreases the tensile strength of bone cell units;
    iii. Activation of osteoblast ferroptosis via the METTL3/ASK1-p38 signaling pathway in high glucose and high fat (HGHF)-induced diabetic bone loss, leading to the development of OP.

1.8. Mechanism VIII :

  i. Medications including sulfonylureas, glargine, and insulin may exacerbate skeletal muscle atrophy and affect bone mass;
  ii. Thiazolidinediones, sodium-dependent glucose cotransporter protein 2 inhibitors, and others have a detrimental effect on bone metabolism, thereby increasing the risk of fracture.

1.9. Mechanism IX :

    T2DM causes gut microbiota imbalance, which results in an increase in harmful metabolites such as lipopolysaccharides and a decrease in beneficial bacterial products such as short-chain fatty acids (SCFAs), contributing to the loss of intercellular binding and causing dysfunctional harmful metabolites of the intestinal barrier to enter the blood circulation.

  a) Causes disorders of the immune system and promotes bone resorption;
  b) Endocrine signaling disruption, such as estrogen and glucagon-like peptide-1 (GLP-1) attenuation, promotes bone resorption, slows bone formation, increases insulin resistance, and induces pancreatic β-cell apoptosis;
  c) Induces systemic low-grade inflammatory responses and facilitates the development of T2DM and OP.

1.10. Osteocalcin modulation

    i. Increased expression of Insulin1 and Insulin2 genes to promote pancreatic β-cell proliferation;

   ii. Promotes lipocalin secretion and increases insulin sensitivity; increases expression of the anti-inflammatory cytokine IL10 and decreases TNF and IL6 secretion;

  iii. Increases GLP-1 expression, which stimulates insulin release;

  iv. Enhances glucose uptake and utilization in skeletal muscle and improves insulin sensitivity;

   v. Promotes hepatic glycogen synthesis, fatty acid oxidation, and enhances insulin sensitivity via the IRβ/P13k/Akt signaling pathway;

  vi. Increases the production of testosterone and insulin secretion.

1.11. Other OB factor regulatory effects

  vii. Lipid transporter protein 2 regulates appetite in the brain and, secondarily, improves glucose tolerance and insulin sensitivity by inducing insulin secretion, which may provide clues on targeted therapies for the prevention/treatment of obesity and T2DM;

2. Macronutrients and micronutrients

The rigidity and flexibility of bone depend on the joint contribution and action of the inorganic and organic phases [24], the ratio of which increases with age, leading to senile bone deterioration [25]. Alteration in organic or inorganic components could potentially impact bone biomechanical properties, consequently affecting the risk of fractures [24]. Therefore, ensuring sufficient nutrient intake is an effective way for maintaining the equilibrium between organic and inorganic components and improving the bone microenvironment.

2.1. Carbohydrates

Carbohydrates are the main macronutrients influencing postprandial blood glucose [26], the material foundation for maintaining bone remodeling [27], and also an important source of energy for OB [12,19,28]. According to the systematic evaluation and Meta-analysis of the Randomized Controlled Trial (RCT), the low GI/GL eating pattern reduced HbA1c in T2DM patients compared with those who chose the high GI/GL control die. This suggests that the combination of "quality" and "quantity" of dietary

Table 1
Protein metabolism in bone.

Functional Effects	Metabolic Effects
Collagen synthesis in bones	Building the bone framework and regulating bone toughness [24]
Synthesis of bone growth factors, hormones, kinases	Regulates bone remodeling and maintains bone homeostasis[[41,43]]
	Insulin-like growth factor 1 (IGF-1):
	• Promote intestinal calcium and phosphorus absorption
	• Involved in calcitriol synthesis
	• Increase the rate of renal phosphate reabsorption
	Osteocalcin (OCN):
	• Regulation of glucose homeostasis
	• Regulation of bone metabolism
	parathyroid hormone (PTH):
	• Maintain blood calcium balance
	• Regulate of bone mass
	Calcitonin (CT):
	• Weaken the PTH-induced increased bone resorption
	Insulin (INS):
	• Regulation of glucose homeostasis
	• Promote OB activity
	Bone alkaline phosphatase (BALP):
	• Hydrolyze phosphatase to provide phosphate for hydroxyapatite deposition
	RANKL-RANK-OPG axis:
	• Regulate OC proliferation and apoptosis
	Sex hormone:
	• Maintain bone formation and bone mass regulation
	Bone morphogenetic proteins (BMP):
	• Regulate the differentiation of BMSCs into bone, cartilage, and fat
Transportation of minerals and micronutrients	Maintain bone calcium, phosphorus, vitamin D, and other mineral concentrations
Endocrine factor expression in bone and skeletal muscle	Participates in the control of glucose and fatty acid metabolism [27]
	IL-6 cytokines:
	• Reduce inflammation
	• Increase glucose uptake by muscles
	• Stimulate OC formation
	Irisin:
	• Promote lipolysis
	• Increase skeletal muscle mass
	• Improve bone condition

carbohydrates is effective in controlling blood glucose through the choice of a low GI/GL diet [29], which alleviates OB insulin-resistant OCN underproduction and fat accumulation due to impaired insulin signaling [27,30,31]. OCN expression, on the other hand, is dependent on the accumulation of the glucose-promoting transcription factor Runx2, which stimulates β-cell proliferation and insulin secretion, improves insulin sensitivity in adipose tissue, liver, skeletal muscle, etc., and regulates glucose homeostasis [19,28]. Dietary carbohydrates play a critical role in the development of T2DM. Elevated glycemia due to excessive carbohydrate not only exacerbates systemic insulin resistance, inflammation, and oxidative stress [30], but also tends to exacerbate the risk of obesity and the effects of mineral loss-induced bone resorption. In addition, the low bone turnover state caused by the inhibition of OB and OC is also the result of the hyperglycemia-induced accumulation of late glycosylation end products [12]. The synergy of these negative effects leads to bone loss and the development of OP, and vicious feedback exacerbates the islet burden.

Recently, much attention has been paid to the effectiveness of the ketogenic diet (KD) in treating diabetes. Meta-analysis showed that a low-carbohydrate diet for up to 6 months achieved higher rates of diabetes remission in adults with T2DM compared to a control diet, suggesting that strict control of carbohydrate intake improved HbA1c and body weight in patients with T2DM [32]. However, several animal experiments have found detrimental effects on bone [33–38], which may be related to the stimulation of OC to promote bone resorption by elevated levels of anti-tartaric acid phosphates [33]. Notably, Notably, the Mate analysis in H Mozaffari comparing high/low carbohydrate intake showed that no association was found between carbohydrate intake and fracture risk ($RR = 1.00$, 95% CI : 0.94–1.05) [39].

In summary, although numerous systematic reviews with Meta-analyses have elaborated on the correlation between carbohydrate intake and T2DM, there is still a lack of high-quality evidence regarding the long-term benefits of low-carbohydrate intake in preventing T2DM and the role of effects on bone metabolism. Therefore, it is now appropriate to take into account the islet function, physical activity, nutritional status, medication use, and other factors of T2DM patients to individualize staple food intake to maintain stable blood glucose and thus reduce the risk of fracture.

2.2. Protein

Dietary protein intake stimulates insulin secretion in T2DM patients with the same effect as carbohydrate intake [40], and its incorporation into the organic matrix of bone as part of the collagen structure [41] is crucial for preventing OP-related fragility fractures [42]. Furthermore, the significance of activating transcription factor 4 in osteoblasts, which facilitates the uptake of amino acids and the synthesis of collagen, has been demonstrated to be crucial for OB differentiation [19]. Thus, dietary amino acids as signaling molecules are essential for bone development and metabolism maintenance (Table 1).

Dietary protein is involved in glucose metabolism and bone homeostasis regulation. However, a systematic review and Meta-analysis of cohort studies revealed that total protein depletion was a risk factor for T2DM ($RR = 1.12$, $95\%CI$: 1.08–1.17) [44]. Overconsumption of dietary protein promotes insulin resistance in obese patients and negatively impacts glucose homeostasis [45]. In addition, previous studies demonstrated that excessive protein intake increases body acid burden, resulting in hypercalciuria bone loss [46], while recent studies have confirmed that dietary acid load is not associated with fracture risk, and modestly increasing dietary protein intake reduces bone loss and hip fracture risk [47–49], which may be related to increased intestinal calcium absorption and stimulation of IGF-1 production [50]. At the same time, we should pay attention to the potential threat posed by the decline in acid buffering capacity in the elderly due to reduced bone and muscle mass and renal impairment [51].

It is believed that the source of the protein has a crucial impact on insulin resistance and bone mass than its quantity. Animal protein consumption is associated with a high risk of T2DM ($RR = 1.14$, $95\%CI$: 1.09–1.19), specifically excessive red and processed meat intake is associated with increased body weight, iron burden, nitrite, and AGEs, etc., whereas plant protein has a protective effect only in women ($RR = 0.92$, $95\%CI$: 0.86–0.97) [44]. Moreover, vegetarian diet that primarily relies on plant protein has the potential to enhance glucose homeostasis to a greater extent in individuals diagnosed with T2DM [52]. The increased abundance of non-protein components, such as antioxidant phytonutrients, fiber, and magnesium in plant protein, may account for this phenomenon [53]. In the study conducted by Liu et al., it was demonstrated that each increase of 0.1 g/kg/d in the intake of animal and white meat proteins, there was a decrease in the loss of BMD at the femoral neck by 5.40 and 9.24 mg/cm^2, and at the rotor by 1.11 and 1.84 mg/cm^2 [49]. Furthermore, vegetarians with a predominantly plant-based protein diet were associated with a reduced BMD and a greater risk of fractures than omnivores [54,55]. Importantly, it may be challenging for older individuals to obtain sufficient protein from a plant-based diet [56].

In summary, it is crucial to ascertain the optimal equilibrium between the consumption of animal and plant proteins in the diet, on the perspective of the individual circumstances of patients with T2DM, which aims to enhance glucose metabolism while simultaneously preserving bone homeostasis.

2.3. Fat

Dietary fats serve as a provider of energy and essential nutrients and precursors of lipid-mediated signaling molecules that influence on the body's metabolic processes. The European guidelines for managing diabetes advocate for the consumption of foods that are mostly rich in monounsaturated and polyunsaturated fatty acids while limiting the intake of saturated fatty acids to no more than 10% of total energy [57]. While the effects of unsaturated fatty acids on glycemic homeostasis are still uncertain, a comprehensive analysis of RCT and Meta-analysis has indicated that increasing polyunsaturated fatty acids has no significant impact on improving glucose metabolism [58]. However, it is worth noting that it could potentially serve as a therapeutic approach for T2DM by influencing bone metabolism [59] and improving lipid profile [60] (Table 2). In addition to other notable aspects, the consumption of unsaturated fatty

acids has been found to contribute to increased levels of high-density lipoprotein cholesterol [60], which serves as a protective factor against OP [61].

T2DM is associated with obesity, which raises the issue of skeletal frailty in T2DM due to obesity factors. T Vilaca et al. reported that obesity-promoted bone mass accumulation was associated with enhanced bone mechanical loading and cytokine or hormone secretion [62], consistent with patients with T2DM exhibiting normal or high BMD but did not reduce their fracture risk [12]. At present, weight loss is still one of the nutritional treatment goals for overweight/obese T2DM patients to improve glycemic control and reduce the risk of cardiovascular morbidity [57]. Notably, a systematic evaluation and Meta-analysis emphasized that obesity management should focus on controlling fat loss and preserving lean body mass to attenuate the increased risk of bone loss and fragility fractures associated with weight loss [63].

In summary, the crosstalk between bone and dietary fat/adipose tissue affects glucose homeostasis and bone remodeling. When aiming to reduce saturated fat intake, it is advisable to substitute saturated fats with unsaturated fatty acids derived from plant-based food sources. Second, although weight loss is associated with negative bone effects, it remains a goal for overweight/obese T2DM patients to improve glycemia and prevent comorbidities, which can be used in combination with equal nutritional supplementation (high protein, calculus, vitamin D, etc.) and individualized exercise strategies (resistance exercise, balance training, etc.) that may alleviate bone damage [63,64].

2.4. Micronutrient

Recently, researchers have been concentrating on the role that micronutrients play in managing T2DM, explicitly emphasizing the effects of chromium, vitamin E, vitamin K, vanadium, and niacin supplementation on glucose-lipid metabolism [65]. However, it is common to overlook the impact of missing/imbalanced micronutrients on bone metabolism and tissue characteristics, thereby increasing the risk of osteoporosis-related brittle fractures [42]. Additionally, causes such as age, medication usage, eating patterns, chronic kidney disease, etc., have been found to be linked to bone injury resulting from deficiencies or excesses of vitamins D, K, and C [66,67].

2.4.1. Osteocyte death from iron metabolism abnormalities in T2DM patients

Ferroptosis is defined by programmed cell death as a result of unchecked iron-dependent lipid peroxidation. The low antioxidant properties of pancreatic β-cells render them susceptible to oxidative stress in the T2DM microenvironment, leading to ROS accumulation and consequently ferroptosis [68]. High glucose and high fat (HGHF)-induced iron overload has been identified as a potential mechanism behind osteocyte ferroptosis, which is mediated by the activation of heme oxygenase-1 [15]. Additionally, OB ferroptosis in the context of OP may be attributed to the METTL3/ASK1-p38 signaling pathway [17].

As ferroptosis has become the focus of contemporary academic research, factors such as Fer-1 [69] and vitamin K [70], 1,3-propanediamine, and reuterin [71] have been utilized as ferroptosis-specific inhibitors. Although the body lacks the mechanism for iron excretion, systemic iron overload can be ameliorated by limiting absorption. Food is the primary source of iron acquisition, and Song et al. found that a high-iron diet overloaded intestinal iron and promoted lipid deposition, oxidative stress, and mitochondrial dysfunction [72], resulting in undesirable alterations in intestinal composition [73]. In contrast, a low-iron diet or iron chelators could effectively delay the glycolipid metabolism level and reduce iron accumulation in T2DM mice [74], which provided a new explanation for the alleviation of ferroptosis by diabetic osteoporosis. However, high body concentrations of ferritin in patients with T2DM attenuate intestinal iron absorption, which may attenuate the role of dietary factors, leading to the current absence of studies in which dietary factors of iron content coordinate iron death in Diabetic osteoporosis. Notably, KD Nupur et al. demonstrated that gut microbiota could inhibit intestinal HIF-2α activity and up-regulate FTN expression through an iron-modulin-independent mechanism,

Table 2
Long-chain polyunsaturated fatty acid regulatory mechanisms on bone and lipid profiles.

Fatty acid type	Effect
Polyunsaturated fatty acid (PUFAs)	Key Ingredients: n-3 PUFAs: Linolenic acid ALA, Eicosapentaenoic Acid (EPA), Docosahexaenoic Acid (DHA) n-6 PUFAs: Linoleic Acid (LA), Arachidonic Acid (AA) Bone Benefits: 1 AA upregulates PPARγ and reduces Runx2 expression to promote the differentiation of BMSCs to adipocytes, thus inhibiting OB production; 2 AA and its metabolite prostaglandin (PGE2) promote RANKL expression to enhance bone resorption; 3 DHA and EPA downregulate PPARγ and increase Runx2 expression to induce OB differentiation; 4 DHA and EPA reduce PGE2 and its receptor secretion and inhibit OC production; 5 The binding of DHA and EPA to PPARγ in MSCs decreases the expression of nuclear factor kappa B-regulated genes TNF, IL-6, and COX2, leading to inhibition of OC production by reduced RANKL; 6 DHA and EPA stimulate OC production by promoting *c*-Fos gene expression through PPARγ; 7 EPA derivative Resolvin E1 maintains OPG/RANKL ratio and regulates OC differentiation; 8 ALA reduces RANK-mediated OC formation by down-regulating OC differentiation markers and histone enzyme K. n-6/n-3 PUFAs： Elevated ratio of n-6/n-3 PUFAs promotes OP development by promoting chronic low-grade inflammation, modulating BMSCs profiles and activating OC generation. Lipid Profiling Benefits： PUFAs improved total cholesterol, triglycerides, HDL cholesterol, C-reactive protein, and other levels.

which regulates host iron metabolism [71]. Among them, increasing the abundance of bifidobacteria reduced by T2DM also combine with iron to reduce the ROS [75], emphasizing the possibility of improving iron metabolism by regulating the gut microbiota through dietary.

Nonetheless, several studies have reported the potential impact of adjunctive treatment involving dietary iron restriction on iron parameters in individuals with diabetes. While the effect may be moderate, further investigations are warranted to address the existing knowledge gap regarding dietary determinants related to iron content that may help mitigate iron-related mortality in individuals with T2DM.

2.4.2. Osteocyte death from copper metabolism abnormalities in T2DM patients

Copper is an essential trace element, and excessive concentrations produce cytotoxicity. In recent years, Tsvetkov et al. have shown that copper death occurs through the direct binding of copper to the lipoylated components of the tricarboxylic acid cycle [76]. It has been shown that serum copper levels are higher and associated with elevated markers of oxidative stress and inflammation in patients with T2DM compared to healthy subjects [77], and the generated ROS induces lipid peroxidation that damages OB structure, reduces the number of OCs, and interferes with bone metabolism [78]. However, how excess copper contributes to the development of Diabetic osteoporosis is yet to be corroborated and may be a new pathogenetic mechanism.

Concerning dietary factors, copper has a dual antioxidant/pro-oxidant effect due to differences in intake, with excess intake predisposing to copper toxicity leading to insulin resistance [79]. A animal study found that pancreatic α/β-cell neogenesis could be induced by feeding low-copper diets containing copper chelators [80]. However, the effect of a low-copper diet on diabetic osteoporosis is not well established.

2.4.3. Zinc

T2DM is usually associated with polyuria zinc loss, leaving the body in a state of zinc deficiency, and the mechanism of action of zinc supplementation in alleviating glycolipid abnormalities and modulating antioxidant impairment in T2DM has been consistently demonstrated in long-term studies [65,81,82]. Secondly, zinc is not only a component of bone tissue but also a bone protective factor that counteracts the development of OP and is essential for bone collagen matrix synthesis, mineralization, and bone turnover [83].

According to a Meta-analysis, dietary zinc supplementation effectively improved bone turnover markers (uOCN, BALP, etc.) and increased BMD [83]. However, Skalny AK et al. reported that zinc uptake regulates OB proliferation and differentiation through stimulatory effects on Wnt/β-catenin cascade activity and mediated by upregulation of cAMP-PKA-CREB, MAPK/ERK and IGF-1/IGF-1R/Akt/GSK3β/β-catenin signaling pathways as well as promoting OPG expression and inhibiting RANKL signaling while inhibiting bone resorption [84]. In addition, an animal study showed that combined zinc and vitamin D supplementation favored calcium absorption in rats and slowed the development of OP by down-regulating the OP-related factors M-CSFR and RANKL [85].

Notably, it has also been reported that short-term zinc supplementation in zinc-deficient rats failed to normalize bone mass or cortical and cancellous bone microarchitecture [86], suggesting that early zinc supplementation in T2DM has a preventive and protective effect on OP occurrence.

2.4.4. Magnesium

The loss of Mg^{2+} in T2DM patients contributes to the elevation of inflammatory factors, exacerbating the vicious cycle of inflammation and oxidative stress in the body [87], and affects the activity of insulin-transduction-related phosphatase group enzymes and bone health [88].

Mg^{2+} acts as a co-factor to promote OB cell attachment, differentiation, and mineralization [89], approximately 60% of which is deposited in bone. Altering the magnesium status of the body may be regulated by direct stimulation of OB proliferation and differentiation or indirect effects on the major regulators of calcium homeostasis (PTH, vitamin D) [90], but no short-term effects of magnesium were found in a study evaluating the effects of magnesium in conjunction with vitamin D on glycemic and bone turnover markers in obese or overweight patients [91].

In addition, it is still worth paying close attention to the antagonistic effects of excess magnesium supplementation with calcium and mineralization defects resulting from the effects of excess magnesium supplementation on bone metabolism and parathyroid function are noted [90], and more importantly to intestinal micro-ecological imbalances [73]. Meanwhile, further research is needed to investigate the effects of elevated magnesium levels on bone mass.

2.4.5. Combined role of calcium and vitamin D in the bones of patients with T2DM

About 99% of the body's calcium is stored in bones and teeth and is responsible for tissue mineralization in the form of hydroxyapatite. Calcium homeostasis is mainly regulated through 1,25-(OH)$_2$D signaling and plays a crucial role in insulin resistance and secretion [92]. Dietary calcium supplementation in T2DM patients not only compensates for pathological bone calcium loss due to glycemia and complications but may also alleviate therapeutically-activated bone loss due to, for example, KD [35], veganism [93], and weight loss [64], and effectively improves patients' bone structure and metabolic homeostasis.

The role of vitamin D in regulating calcium homeostasis, bone mineralization, reducing inflammatory responses, and improving insulin sensitivity has been demonstrated. In an RCT, bioactive vitamin D supplementation was found to significantly reduce DM progression. Secondly, BMD and serum OCN concentrations at the lumbar spine and femoral neck were significantly increased in the vitamin D-supplemented group compared with the placebo group [94], which is consistent with the finding by Chen Xue et al. of the potential benefit of maintaining adequate vitamin D status in the body in terms of preventing microvascular complications of T2DM [95]. In addition, vitamin D may alleviate T2DM by modulating the ferroptosis signaling pathway [96], thereby combating the

development of OP.

According to a recent RCT evaluating the effect of whether or not to take vitamin D supplements on β-cell function in 243 Chinese pre-DM people, calcium combined with vitamin D supplementation effectively improves pancreatic β-cell function, increases insulin secretion, and positively affects glucose metabolism in patients with early-stage T2DM [97], while daily supplementation with calcium (1000–2000 mg) and vitamin D (400–800 IU) could reduce the risk of any fracture by 6% (*RR* = 0.94, *95%CI*: 0.89–0.99) and the risk of hip fracture by 16% (*RR* = 0.84, *95%CI*: 0.72–0.97) [98]. Furthermore, in a clinical observation, the use of vitamin D combined with calcium supplementation in postmenopausal T2DM patients was shown to improve bone loss and biochemical indices, as well as muscle strength effectively [99].

2.4.6. Vitamin K

Vitamin K may improve insulin sensitivity and glycemic balance by promoting intestinal homeostasis, regulating vitamin K-dependent proteins, inhibiting intestinal inflammation [100,101], improving calcium absorption, regulating OCN, and promoting bone mineralization [102], which demonstrated that adequate intake of vitamin K may have a crucial role in regulating diabetic bone damage.

Systematic evaluation and Meta-analysis showed that vitamin K supplementation reduced the risk of fracture in women who were postmenopausal or had OP (*OR* = 0.42, *95%CI*: 0.27–0.66) compared to controls (taking placebo, etc.), and that vitamin K_2 dosage may be associated with increased in OB activity and inhibition of OC-induced bone resorption [103] and be involved in the carboxylation of OCN [42]. An experimental study of Chinese older adults by Zhang et al. showed that vitamin K_2 supplementation at 90 µg/d can effectively alleviate bone loss in postmenopausal women [104] and confirmed its efficacy and safety in a Meta-analysis [105].

Recently, Chen et al. demonstrated in both in vivo and vitro experiments that vitamin K_2 significantly attenuates ferroptosis and enhances the osteogenic capacity of BMSCs through the AMPK/SIRT1 pathway, which improves the development of T2DM-based OP [70].

2.4.7. Vitamin C

Currently, study reported that the effectiveness of supplemental vitamin C in the adjunctive management of T2DM is low. Das UN's study suggested that the effect of vitamin C on T2DM may be protected by promoting the production of prostaglandin 1, prostacyclin, and endothelial nitric oxide, as well as anti-inflammatory and antioxidant effects by modulating the content of essential fatty acids and by enhancing lipoxin A4 [106]. Furthermore, a Meta-analysis of an RCT showed that short-term improvement in glycemic metabolism in patients with T2DM [107]. Nonetheless, there is still a lack of evidence from high-quality studies demonstrating that vitamin C supplementation improves glycemia in patients with T2DM.

Vitamin C is an essential cofactor in promoting collagen formation and OB synthesis and differentiation. Meanwhile, it can inhibit bone resorption of OC in an inflammatory environment [108]. Several population-based studies have demonstrated that vitamin C supplementation has a positive impact on improving BMD and reducing fracture risk [109,110] and its effects may be associated with reduced levels of circulating total lipocalin and the inflammatory factor vascular cell adhesion molecule-1, further explaining the potential for dietary supplements of vitamin C would reduce the risk of inflammation and the development of OP in DM patients [111].

In summary, patients with T2DM should focus on monitoring micronutrient deficiencies such as zinc, magnesium, calcium, vitamin D, vitamin K, and vitamin C in the T2DM microenvironment, which, although they are not the most effective dietary factors for alleviating T2DM, are more critical in preventing the development of Diabetic osteoporosis. Secondly, we should also consider that the combined supplementation effects of micronutrients may be antagonistic or synergistic, e.g., combined zinc and vitamin C supplementation may be more favorable for calcium absorption, antagonistic effects of excess magnesium and calcium. It is worth noting that cell death due to disturbed iron and copper metabolism, which usually occurs in T2DM, may be an additional mechanism for the development of OP. In contrast, diet is still the primary source of iron and copper acquisition, and it may be possible to reduce their parameters by restriction, etc., but more experiments are still needed to fill this gap.

3. Dietary fiber and gut microbiota

The gut microbiota is a complex, dynamic, spatially heterogeneous ecosystem that collectively maintains the normal physiological dynamic balance of the human body. Animal studies using transplanted fecal microorganisms in germ-free mice have shown that gut microbiota play an important role in bone metabolism [112–114] and blood sugar regulation [115,116]. Additionally, the composition and abundance of healthy microbiota reflect the intestinal mucosal barrier effect, the production of major metabolites such as SCFAs, and the promotion of unbound secondary bile acid formation, which are common factors for alleviating T2DM and promoting bone health.

Patients with T2DM are usually accompanied by a moderate gut microbiota imbalance, with downregulation of beneficial bacteria and an increase in harmful and conditionally pathogenic bacteria, which not only induces low-grade intestinal inflammation to promote insulin resistance [117,118] but also leads to a dysregulation of the gut-bone axis [119], accelerating the progression of diabetic bone damage.

In interactions involving host-gut microbiota, diet becomes a key determinant of gut microbiota composition and function [120], especially dietary fiber, which may alter the production of beneficial metabolites in the gut microbiota [121]. According to a systematic review and meta-analysis, high fiber intake in T2DM patients significantly improved gut microbiota and increased the production of short-chain fatty acids (SCFA) [122], which not only effectively controlled blood glucose, lipids, body weight, and inflammation and reduced the risk of all-cause mortality [123], but also regulated the balance of immune, metabolic and endocrine

systems involved in bone homeostasis [119] (Fig. 3). Secondly, a study of the effects of using different sources of calcium in combination with inulin and lactose on intestinal metabolism and bone in post-ovariectomy rats found that inulin supplementation resulted in increased intestinal SCFAs output, decreased pH, increased abundance of Allobaculum and Bifidobacterium, which indicated beneficial effects on the vertebral bone [124]. Another study showed that administration of oligo-fructose/oligo-galactose significantly attenuated high-fat diet-induced bone loss in mice [125].

3.1. Dietary fiber and gut microbiota [73,120,121,126–128]

i. Maintain the integrity of the intestinal barrier:
   a) As a substrate for the energy supply of gut cells and flora;
   b) Maintains intestinal barrier integrity and prevents intestinal infections by regulating the immune system and physiological changes of gut microbiota.
ii. Improvement of the intestinal microbiological environment:
   a) Regulates the composition and metabolism of bacterial colonies, improves gut microbiota diversity and provides a fermentable carbon source;
   b) Immunomodulation, physiological changes, and maintenance of the anaerobic environment of the gut are exerted primarily through gut microbial fermentation;
   c) Combined with micronutrient (Ca, Zn, etc.) delivery to the distal colon favors the prevention of intestinal infections;
   d) Increases bioavailability of some micronutrients (vitamin A, vitamin B_1, vitamin C, Ca, Zn, Mg, etc.);
   e) a shorter intestinal transit time, improved fecal consistency and weight;
   f) β-oxidation is exerted through the use of butyrate to maintain an anaerobic environment.

3.2. Gut microbiota and T2DM [118,129–132]

i. SCFAs enhance intestinal anti-inflammatory capacities and modulate over-immunity by inhibiting histone deacetylase (HDAC), activating G protein-coupled receptor (GPR), and regulating Toll-like receptors (TRL);
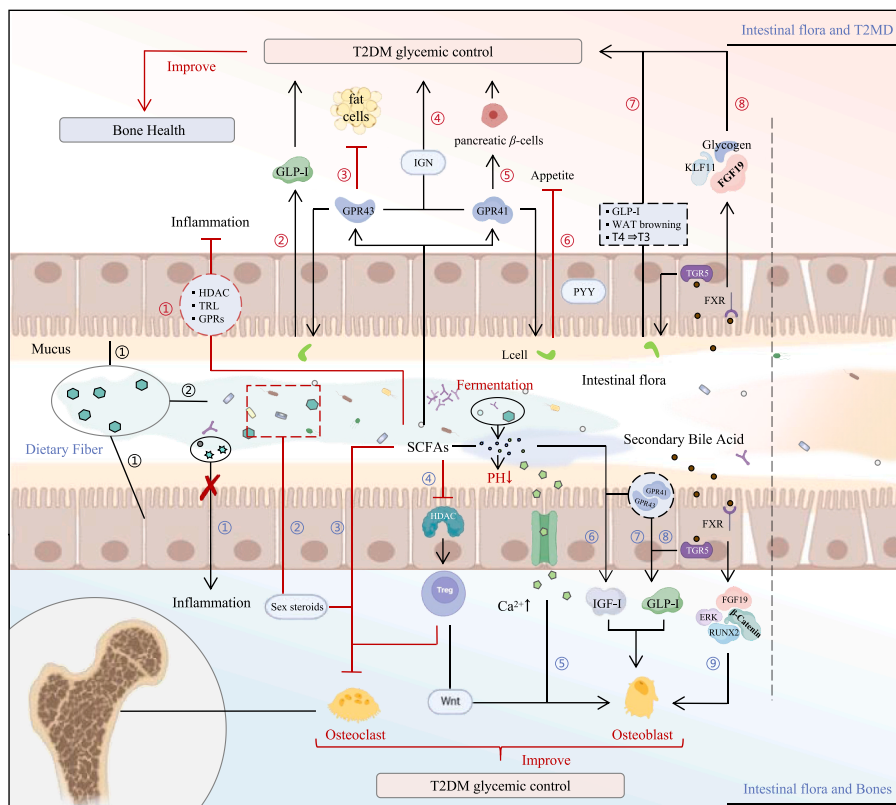

Fig. 3. Closed-loop effects of dietary fiber and gut microbiota on glycemic control and bone health in patients with T2DM.

ii. Activation of GPR43 by SCFAs leads to increased GLP-1 secretion, which in turn improves islet function and insulin sensitivity;

iii. GPR43 regulates energy metabolism, leading to increased energy expenditure and inhibition of fat accumulation;

iv. SCFAs reduce appetite, body weight, and hepatic glucose output by promoting GPR41, GPR43 regulation of intestinal gluco-neogenesis (IGN) expression;

v. SCFAs activate GPR41 to promote pancreatic β-cell secretion;

vi. GPR41 upregulates secretion of peptide YY (PYY) by intestinal L-cells, promotes satiety and alleviates insulin resistance;

vii. Secondary bile acids increase GLP-1 levels via GTR5, which in turn promotes insulin secretion; Promotes thyroxine activation; Improvement of energy metabolism by activation of TGR5/cAMP signaling induces white adipose tissue (WAT) browning;

Table 3
Benefits of four T2DM eating patterns in bone metabolism.

Eating patterns	Osteo-metabolic effect
Low-carbohydrate eating patterns	Supply of carbohydrates [32]: <26%: Low-carbohydrate diet (LCD) <10%: ketogenic diet (KD) Animal experiments: 1 LCD impairs bone mass and trabecular microstructure in aged mice [38]; 2 KD results in a lower rate of differentiation of BMSCs into OB, which in turn impairs longitudinal growth, BMD and mechanical properties in mice [35]; 3 KD activation of OC promotes bone resorption, which in turn damages the cancellous and cortical bone structure of mouse long bones, leading to bone loss [33]; 4 KD impairs cone microstructure and compressive stiffness in mice [36]; (No exploratory mechanism) 5 KD may impair bone mass and mechanical properties in rats by inhibiting osteogenesis and enhancing osteoblastic processes [37]. Bone benefits: There are no adequate experimental designs for human studies to demonstrate the adverse effects of KD on bone [134,135].
Mediterranean eating patterns	Dietary structure [136]: Large amounts: olive oil, grains, pulses, nuts, fruits and vegetables, spices, herbs Moderate amounts: dairy, wine, poultry, eggs, fish/seafood Small amounts: processed meat, red meat, sweets Beneficial ingredients [137]: 1 Phytochemicals (phenolic compounds, phytosterols, antioxidants, fiber); 2 Unsaturated fatty acids (MUFA, PUFA); 3 Vitamins, minerals (vitamin A, vitamin B, vitamin C, Vitamin E, calcium, potassium, magnesium, etc.); 4 Probiotics. Bone benefits [41,138–140]: 1 Provide high quality protein, calcium and trace elements for bone formation and metabolism; 2 Antioxidant, anti-inflammatory and alkalinizing properties increase bone formation, inhibit bone resorption and reduce trabecular separation; 3 Increase alkaline phosphatase activity and calcium deposition, and controls OB proliferation and maturation; 4 Reduce bone resorption and calcium loss caused by saturated fatty acids, high sodium content; 5 Decrease the likelihood of ferroptosis in osteocytes.
Vegetarian eating patterns	Surplus portion [102,141]: • ALA, PUFA, fiber, carotenoids, vitamin B, vitamin E, vitamin C, vitamin K, potassium, magnesium, manganese, copper, etc. Lack of risk [102,141]: • Protein, EPA, DHA, vitamin B_{12}, vitamin D, Iron, Zinc, Iodine, Calcium, etc. Bone benefits [55,93,142]: 1 Higher incidence of bone turnover markers and accelerated bone renewal; 2 Lack of protein, calcium, vitamin D and other nutrients that maintain bone mass and density: 3 Low bioavailability and need for higher intake to maintain bone health; 4 The anti-inflammatory and antioxidant effects of the surplus components have positive effects on calcium absorption and bone metabolism.
Intermittent fasting	Fasting methods [143,144]: • Time-restricted eating: Eating only during specific periods (4–12h) in 1 day, with overnight fasting extended for at least 12h. • Alternate-day fasting: 1 day of fasting alternating with 1 day of casual or adequate eating (<25% energy expenditure). • Regular fasting: 2 days per week of fasting (25 per cent of energy consumption) and the remaining 5 days of free-feeding. Bone benefits [144]: 1 The net effect of metabolic changes induced by lifestyle/behavioral changes on bone outcomes is unclear; 2 Reduced energy intake and weight loss may have a negative impact on bones; 3 Indirect negative impact on bones as a result of the independent effect of reduced physical activity; 4 The contribution of compositional changes in muscle, fat, and bone to bone effects is uncertain; 5 Frequent metabolic shifts cause acute insulin resistance at the first meal after fasting Low concentrations of C-terminal cross-linking telopeptide of type I collagen and OCN, gastrointestinal hormones (GPI, GLP-1) affect bone health by enhancing insulin secretion; 6 Focus on time constraints rather than quality and quantity of food; 7 Increased gut microbial abundance positively affects bone by influencing metabolite (SCFAs, etc.) production, improving nutrient bioavailability, and modulating immune hormones; 8 Time-restricted eating induced changes in circadian rhythms are indirectly associated with improved bone outcomes.

viii. Secondary bile acids enhance insulin sensitivity by enhancing glycogen synthesis via FXR, enhancing the expression of the transglucose-regulated recording factor Krueppel-kike factor (KLFF11), and inducing the expression of an endocrine fibroblast growth factor 15 (FGF15, human homolog, FGF19), thereby increasing energy expenditure and improving insulin sensitivity.

3.3. Gut microbiota and bones [119,128,133]

i. The balance of intestinal microbiota can enhance the integrity of the intestinal barrier, preventing pathogenic bacteria and harmful substances from entering and causing inflammation, which in turn stimulates the occurrence of OC;

ii. Some gut microbiome could participate in regulation of sex hormone levels to inhibit bone loss;

iii. SCFAs directly inhibit OC differentiation by increasing glycolysis occurs;

iv. SCFAs promote bone formation by inhibiting HDAC activity to increase Treg cell differentiation, inhibit bone resorption and activate Wnt signaling pathway;

v. SCFAs promote passive intestinal Ca^{2+} transport by decreasing the intestinal pH and increasing the calcium solubility;

vi. SCFAs enhanced bone formation by stimulating the production of insulin-like growth factor 1 (IGF-1);

vii. SCFA promotes GLP-1 secretion by stimulating GPRs to activate L-cells;

viii. Some of the secondary bile acids converted by gut microbiota increase GLP-1 secretion via TGR5 and promote bone formation; leads to calcitonin secretion by parathyroid cells and inhibits bone resorption;

ix. Partial secondary bile acids converted by gut microbiota promote bone formation by FXR upregulate Runx2 expression, enhance extracellular signal-regulated kinase (ERK) and β-linker protein signaling, and promote bone formation by FGF15.

Thus, high dietary fiber intake is negatively associated with diabetic osteoporosis. The European Dietary Management of Diabetes recommends a dietary fiber intake of at least 35 g/d, with grains, vegetables, legumes, seeds, nuts, and whole fruits recommended as sources of dietary fiber [57].

In summary, gut microbiota plays an important mediating role in T2DM and bone metabolism, so maintaining a good symbiotic relationship between the human body and gut microbiota is beneficial in delaying the development of T2DM and the onset of OP. It is worth noting that dietary fiber can exert beneficial effects on blood glucose regulation and bone health in T2DM patients by improving the gut microbiota.

4. Recommended safety of diabetic eating patterns for bone

A multi-food mutual benefit diet integrates the value of each nutrient's contribution and provides a more comprehensive assessment of the effects of several currently popular diabetes eating patterns on bone metabolism (Table 3).

4.1. Low-carbohydrate eating patterns

A systematic evaluation and Mate analysis of RCTs showed that short-term low-carbohydrate eating patterns were effective in alleviating T2DM symptoms, reducing HbA1c, body weight and triglyceride levels [32], and that KD was associated with significantly lower HbA1c values compared to LCD [145]. Although KD may have advantages in reducing body weight and promoting muscle strength preservation, there is insufficient evidence of positive/negative effects of low-carbohydrate eating patterns on human bone health, and the efficacy and gut microbiota composition of KD in patients with long-term T2DM is insufficient due to adherence is inconclusive [146]. However, study focusing on LCD demonstrated clinical deterioration in quality of life and LDL cholesterol in patients when dietary control was achieved for up to 12 months [32].

In addition, a low-carbohydrate intake is usually accompanied by a lower fiber effect. It is recommended to choose an ideal low-carbohydrate and high-fiber diet to maintain intestinal health. However, current recommendations based on the management of DM diets in Europe do not recommend the use of KD for weight loss as it can lead to micronutrient deficiency, hypoglycemia, ketoacidosis and is even associated with higher mortality [57].

Therefore, further studies on the long-term effects of low-carbohydrate diets are needed to assess their combined effects on T2DM and bone metabolism.

4.2. Mediterranean eating patterns (MD)

MD is a plant-based diet [136], and synergism with the rest of the food-derived components of its dietary structure is an effective way to improve insulin sensitivity, lipid profiles, and anti-inflammatory, antioxidant and antithrombotic properties in patients with T2DM [137]. Furthermore, a recent study suggesting nut consumption as a dietary strategy for the management of T2DM and related complications [147] further supports the validity of MD.

A Meta-analysis found that high adherence to MD was associated with a 21% (RR = 0.79, $95\%CI$: 0.72–0.87) reduction in hip fracture risk and was positively associated with BMD of the spine and femoral neck [148]. A study by V Benetou et al. showed that each 2-point increase in the MD score reduced the risk of hip fracture in older adults by 4% (HR = 0.96, $95\%CI$: 0.92-0.9) [149], while higher scores were positively associated with the consumption of olive oil, fruit and vegetables, legumes and fish, and negatively associated with red meat [150]. In addition, the ability of extra virgin olive oil to reduce the risk of OP-related fractures was confirmed in an observational cohort study of long-term olive oil consumption in older adults at high cardiovascular risk [151]. Moreover, in an

experimental study, it was also found that moderate red wine consumption decreased serum hepcidin levels and increased iron bioavailability in patients with T2DM, while phenolic substances in red wine inhibited intestinal iron absorption [140], thereby effectively reducing the risk of ferroptosis in patients with T2DM. Notably, a cohort held by Mitchell et al. of Swedish men and women included in a survey of 5,0755 men and women who were scored on the MD diet found that a reduced risk of hip fracture was directly associated with adherence to the MD diet and was not mediated by T2DM or BMI [152].

MD is an effective modulator of the immune system-gut microbiota [153] and is essential for improving glucose metabolism and bone homeostasis-related SCFAs fermentation metabolite production in T2DM patients [154].

It is also important to focus on the synergistic effect of physical activity as an intrinsic feature of the Mediterranean style [155] on bone protection in T2DM patients.

4.3. Vegetarian eating patterns

In recent years, the search for health or the perception of animal pain has led to a growing trend towards vegetarian diets [156]. A 24-week study by Kahleova et al. comparing the benefits of a vegetarian diet with a traditional diabetic diet in improving DM found that 43% of patients on a vegetarian diet reduced their reliance on medication, compared with only 5% of the control group, and the benefits were even more remarkable when exercise was taken into account [157]. Subsequent investigations provided additional evidence to support the positive psychological impacts [158].

Regarding bones, vegans have lower BMD and bone health-related biomarkers (lysine, selenoprotein P, n-3 fatty acids, calcium, vitamin A, etc.) compared to omnivores [55]. Furthermore, in a large prospective cohort study of 25,518 vegetarians with a follow-up of 17.6 years, vegetarians ($HR = 1.25$, $95\%CI$: 1.04–1.50) and vegans ($HR = 2.31$, $95\%CI$: 1.66–3.22) had a significant risk of hip fracture compared with meat eaters, while the risk of total and leg fractures was even more pronounced in vegans [159]. Additionally, another large prospective cohort based on the UK Biobank showed that vegans have a higher risk of hip fracture than the meat-eaters is partly due to a lower BMI, so adequate nutrient intake and weight management are recommended [160]. Hence, some scholars have posited that due to the progressive enhancement in the nutritional value of vegan diets, taking into account the numerous advantages associated with plant-based diets, it is feasible to address the issue of low bioavailability and inadequate levels of certain nutrients in order to prevent adverse impacts on bone metabolism [102].

However, a step forward is needed to monitor vegetarian eating patterns in the long term to exclude potential adverse effects associated with specific nutrients, exploit their potential health effects, and consider their role in managing patients with T2DM.

4.4. Intermittent fasting

Sustained weight loss of 5% is an effective way to improve glycemic control and reduce drug dependency in overweight/obese T2DM patients, and restricting energy within a defined time window and allowing patients to choose food outside this window is more likely to improve adherence and avoid the risk of malnutrition [143], which are reasons why dietary adjuncts to Intermittent Fasting (IF) energy deprivation have come to the fore.

Several systematic evaluations and Meta-analyses have shown that IF effectively increased fat mobilization, modulated leptin and lipocalin metabolism levels, reduced inflammatory responses, and induced the reconstitution of gut microbiota, which resulted in reduced insulin resistance and improved β-cell function [143,161], with one IF intervention for more than 1 year demonstrating maximal benefit in terms of improvement in BMI, HbA1c, and fasting blood glucose levels in patients with T2DM [162].

A study held by Clayton DJ et al. found that short-term 24-h strict energy restriction did not affect bone resorption or bone formation markers [163]. An RCT showed that a time-restricted eating program for up to 6 months was effective in reducing body weight and showed some bone protection, while an alternate-day fasting program had no adverse effects on bone [144], which were confirmed in an RCT of a 6-week time-restricted eating program in older adults, which was safe, well tolerated and did not affect lean body mass, bone density or nutrient intake [164]. In contrast, the Muslim month of Ramadan, a one-month Time-restricted eating program, has been shown to be beneficial to bone health, as dietary changes during Ramadan result in reduced mean PTH levels [165].

While there is currently no evidence of detrimental effects of IF on bone health, the impact of IF on bone remains insufficiently understood. Furthermore, the long-term benefits of IF and the consequences of regular fasting on bone health have yet to be investigated. Hence, it is imperative to conduct additional assessments of the impact of various IF regimes on bone results.

In summary, various eating patterns, including low-carbohydrate, Mediterranean, vegetarian, and intermittent fasting, have been demonstrated to be effective in managing blood glucose levels in individuals with T2DM. However, there is few research examining the impact of low-carbohydrate diets and intermittent fasting on bone health. Furthermore, vegetarian diets have been associated with lower BMD and an increased risk of hip fractures. Consequently, strategies aimed at promoting the MD appear to offer greater public health benefits in terms of improving bone health in individuals with T2DM compared to the aforementioned eating patterns.

5. Integration of eating nutrition with other management practices

In order to alleviate T2DM and control the development of OP, we should not limit ourselves to the single benefit brought by dietary factors, but use a total of "5-horse carts" including diet, exercise, drugs, education, monitoring and the latest research concepts to jointly pull the improvement measures of T2DM and its OP and other complications in a more efficient direction, in order to jointly safeguard the health interests of T2DM patients.

5.1. Integration of the "5-horse carts" management approach

Focusing on the education of T2DM patients about knowledge, attitudes and practices, as well as long-term monitoring, is an important safeguard concerning diet, exercise and medication. And following diet as a foundational following diet as a foundational therapeutic principle and combining it with the synergies brought about by exercise and medication is an effective means of managing the condition and bones of patients with T2DM. As reported by Faidon Magkos and Liru Chen, dietary management combined with physical activity is an important factor in the alleviation of T2DM and OP, with an emphasis on personalized high-intensity strength training and low-impact weight-bearing exercise as strategies for OP management [166,167]. However, when dietary control is lacking, the only remaining physical activity loses the benefits of glycemic management in most patients [166], and the question of whether exercise training has a cumulative effect on medication in patients with OP was also raised in a systematic evaluation with Meta-analysis [168]. However, it is worth our attention that when choosing T2DM drugs, we should consider the second impact effect on bone. As we mentioned in Fig. 1, drugs such as thiazolidinediones and sodium-dependent glucose cotransporter protein 2 inhibitors may have exacerbated OP progression [18]. In contrast, a population-based cohort study shed light on the need to also consider second-impact effects on T2DM when using OP medications. The cohort matched the final enrolment of 4301 denosumab users with 21,038 bisphosphonate users and found that the use of denosumab reduced the risk of developing T2DM ($HR = 0.68$, $95\%CI$: 0.52–0.89), suggesting that there may be an additional benefit to glucose metabolism with denosumab [169].

5.2. Integration of nutritional therapy and epigenetics

Epigenetics has been shown to play a key role in the gene regulation of several metabolic diseases such as DM and OP [170]. However, the reversible nature of its regulation makes alterations in epigenetically related genes and proteins mediated by dietary factors possible new therapeutic targets. As we mentioned in Fig. 3, the production of microbial metabolites originating from the diet inhibits the activity of core epigenetic enzymes such as histone HDAC, which in turn promotes bone formation [119], and diet can alter the expression of RUNX2 through the regulation of miR-221-3p and miR-222-3p [171]. However, based on the importance of weight control in the management of T2DM, we found that in a 2-year clinical trial that included 538 overweight or obese adults randomly assigned to four dietary intervention groups with varying proportions of macronutrients, results showed that participants assigned to the low-fat diet group who also exhibited higher DNAm levels on the CPT1A gene had a greater reduction in plasma total triglycerides compared to participants assigned to the Participants in the high-fat diet group had greater reductions in total plasma triglycerides compared to those assigned to the high-fat diet group [172]. In addition, excessive intake of either SFA or PUFA increased the overall level of methylation in adipose tissue in healthy populations, but the heterogeneity of the loci of action of SFA (125) versus PUFA (1, 797) as well as the overlap of methylation of only 47 genes further supports the differential effect of diet on epigenetic changes [173]. Therefore, the strong correlation between dietary factors and DNA methylation makes the "precision diet" an effective means of preventing and treating T2DM and obesity in the future [174].

In summary, emerging data support the potential effectiveness of diet, drugs and lifestyle for the prevention and treatment of T2DM and bone metabolism-related diseases. This is especially true for DNA methylation and miRNAs, as they can counteract aberrant epigenetic regulation.

5.3. Integration of nutritional therapy and lifestyle

In patients with T2DM, smoking not only increases the risk of all-cause mortality also aggravates OP and glycemic control [175, 176]. However, moderate alcohol consumption (10–14 g/d) reduces the risk of T2DM by 18% [177] and showed a J-shaped relationship between alcohol consumption and OP and hip fracture in a systematic evaluation and dose-response Meta-analysis in a prospective cohort study, but moderate alcohol consumption (0–22 g/d) was associated with a reduced risk of OP and hip fracture, which may contribute to the production of CT as well as to the slowing age-related bone loss by reducing bone remodeling [178]. When referring to the interaction between alcohol and nutritional therapy, although moderate alcohol consumption increases the motivation for dietary fat and protein, the increased protein intake partially offsets the risks associated with excess dietary fat [179]. In particular, the positive effects of moderate alcohol consumption on gut microflora have been associated with the polyphenols, microbes, fiber and melanoidins that red wine and beer are rich in [180,181].

In summary, based on the response of patients with T2DM to other management modalities, we should give equal or even higher importance to the process of developing personaliezd diets. To this end, we should focus on the synergistic effects of medication choice on T2DM and OP, and avoid the management complications associated with smoking and excessive alcohol consumption. In addition, more reliable evidence is needed to address the opportunities and challenges of using "precision diets" to prevent and manage T2DM and OP.

6. Discussion and outlook

To date, as the effects of COVID-19 continue to unfold, the impact of the global industrial chain and the socio-economic status of human beings have led to varying degrees of decline in adherence to care for patients with T2DM. Food shortages and lower incomes have had a particularly pronounced impact on dietary changes between social groups, potentially forcing households in low- or middle-income countries to shift from nutrient-rich fruits, vegetables, and products of animal origin to consumption patterns based on starchy staples [182], a shift that reduces food diversity and micronutrient intake in developing countries with a high prevalence of

T2DM, which makes it difficult to maintain patients' condition and bone health. More interestingly, however, is the bidirectional causal relationship between T2DM and COVID-19 found by Hongbao Cao et al. using genetic correlation and Mendelian randomization analyses of 33,153 patients with COVID-19 and 74,124 patients with T2DM, mainly in Europe [183]. The management of T2DM sexual OP in such an era will be a great challenge.

Thus, unhealthy dietary behaviors, lifestyles and zeitgeist are the main drivers of the global epidemic of T2DM, but dietary management remains fundamental in controlling the progression of T2DM and has been largely focused on controlling glycemic homeostasis only by means of diets and medications, thus ignoring T2DM-induced OP, which can lead to fracture. However, this may be attributed to the current lack of randomized controlled trials to determine the optimal management of diabetic osteoporosis, as well as stemming from the dependence of fracture predictors on BMD to the point of underestimating the impact of T2DM on the risk of fracture occurrence [18], resulting in the inability of clinicians and researchers to correctly assess the quality of the skeleton in patients with T2DM in order to enhance the benefits of clinical care. Predictably, caregivers will also be less likely to take the reverse recovery thinking by bone and pancreatic β-cells further into account. Despite the difficulties and ambiguities in the management of skeletal care for patients with T2DM, sound dietary recommendations remain the most basic, effective, and important approach to care today, and the cornerstone in the road to figuring out the best way to manage it. More importantly, when it comes to nutritional guidelines for patients with DM, although diabetes associations in China, the United States, Canada, Europe, and Japan maintain different attitudes toward food choices based on national conditions, they are all shallow when it comes to skeletal nutritional support, with less mention of vitamin or micronutrient adequacy goals [184,185].

Therefore, in order to emphasize the goal of adding vitamin or micronutrient adequacy in national dietary nutritional guidelines for patients with T2DM and the urgent need to preserve the quality of life of patients in this day and age, this paper provides an excerpt from the progression of T2DM to OP (e.g., Fig. 4), describing the ways in which nutritional therapy can prevent the onset of OP from developing and alleviate T2DM through the maintenance of homeostasis of bone metabolism and, thus, providing innovative dietary recommendations.

In accordance with the fundamental nutritional principles of T2DM, it is advisable to tailor the consumption of staple foods to the individual's comprehensive health status. This approach aims to prevent excessive carbohydrate intake and consider the potential
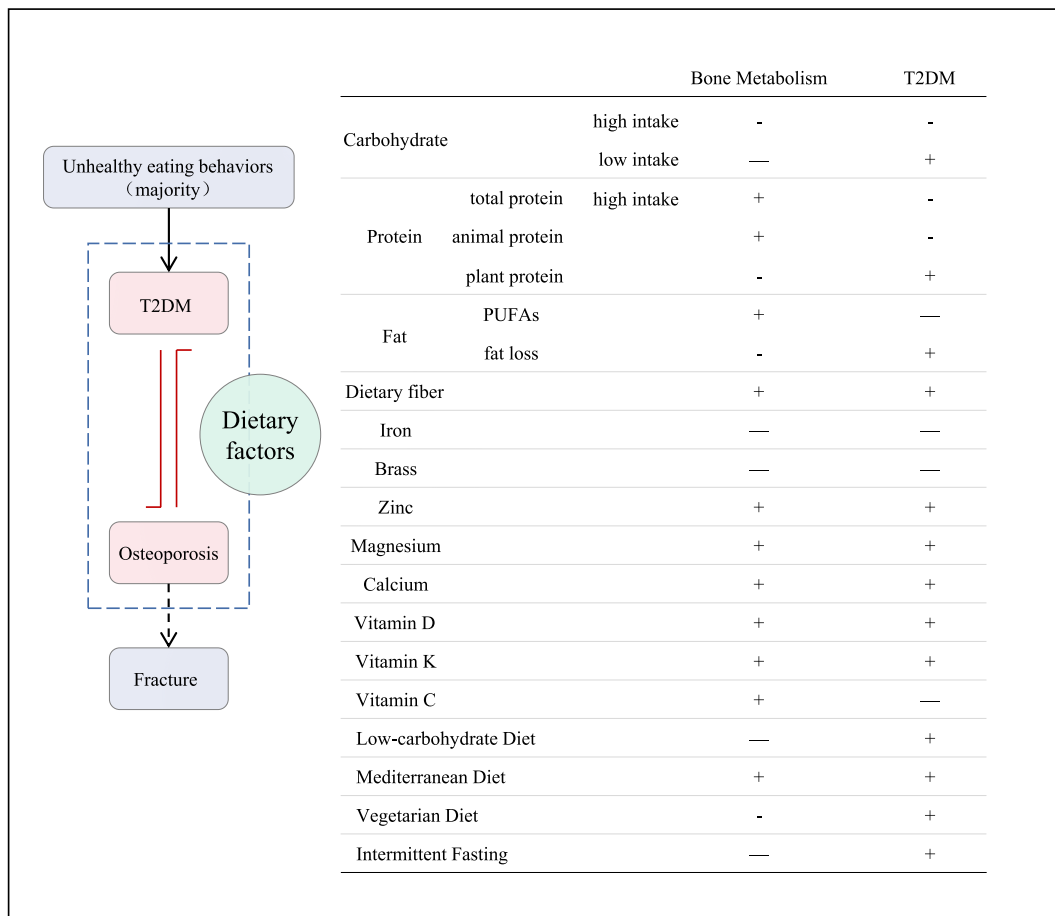

			Bone Metabolism	T2DM
Carbohydrate		high intake	-	-
		low intake	—	+
Protein	total protein	high intake	+	-
	animal protein		+	-
	plant protein		-	+
Fat	PUFAs		+	—
	fat loss		-	+
Dietary fiber			+	+
Iron			—	—
Brass			—	—
Zinc			+	+
Magnesium			+	+
Calcium			+	+
Vitamin D			+	+
Vitamin K			+	+
Vitamin C			+	—
Low-carbohydrate Diet			—	+
Mediterranean Diet			+	+
Vegetarian Diet			-	+
Intermittent Fasting			—	+

Fig. 4. Comparison of the pros and cons of dietary supplementation in T2DM and bone metabolism.
Notes: Pros: +, Cons: , To be studied: , →: Promote, ⊣: Inhibit.

impact of low carbohydrate consumption on bone health. Additionally, it is important to avoid excessive reduction of animal protein intake solely for glycemic control. Instead, a dietary protein pattern that effectively manages blood glucose levels while regulating bone health should be pursued. At the same time, the intake of unsaturated fatty acids and dietary fiber should be increased to regulate the intra-organic environment, including blood glucose, lipids, body weight, inflammation, bone metabolism, and other intra-organism environments, to create a benign closed-loop effect. However, weight loss is associated with adverse bone effects, which can be mitigated with adequate nutrients and individualized exercise strategies. Focusing on micronutrient supplementation, such as calcium, magnesium, zinc, vitamin D, vitamin K, vitamin C, etc., is significant in compensating for bone loss in T2DM and promoting the balance between the organic and inorganic phases of the bone. Moreover, it has also been emphasized that dietary nutrient intake, especially high in fiber, exerts beneficial effects in alleviating T2DM and promoting bone health by regulating gut microbiota. Furthermore, strategies that promote the Mediterranean eating pattern have greater public health benefits in ameliorating bone damage in T2DM than low-carbohydrate diets, vegetarian diets, and intermittent fasting patterns.

However, a "one-size-fits-all" dietary intervention strategy will not achieve the best results in disease prevention and treatment, and patients' confidence to follow their personal preferences is indeed a key factor for long-term maintenance. Therefore, we should also focus on the T2DM patients' own preference in choosing their dietary patterns and make necessary dietary recommendations for the corresponding patterns. For low-carbohydrate dietary patterns, we emphasize the importance of choosing an ideal low-carbohydrate rich in fiber and long-term monitoring of changes in micronutrients, blood glucose and bone metabolism in vivo to prevent the negative effects of the lack of long-term health evidence. Considering the multiple benefits of a plant-based diet, we recommend obtaining adequate amounts of essential amino acids and n-3 PUFAs from soy and its products, grains, nuts/seeds in combination with each other, as well as from algae and mushrooms, actively supplementing with supplements such as calcium, vitamin D, and vitamin B_{12}, and catabolizing phytic acid by heat treatment in order to rectify the low bioavailability and low content of some of its nutrients [102]. Although intermittent fasting is uniquely better for patient compliance, the effects on bone metabolism should still be monitored over time. At the same time, in order to respond to clinical needs, we can provide "precision nutrition" according to the variability of the individual's response to diet. In addition, when managing T2DM and its OP complications, we should focus on the integration of other management modalities of diet and nutrition, develop a good lifestyle, control smoking and alcohol, and strengthen physical activity, so as to maintain the health interests of patients with T2DM through the "5-hourse carts" of diet, exercise, medication, education, and monitoring.

The limitations of this study are that it is a narrative review and therefore selection bias and information bias cannot be excluded. And while this study explores nutritional recommendations in the context of T2DM-induced OP, a current national cohort study based on 580,127 Swedish patients with T2DM in a 1:1 matched cohort showed a proportion of less than 0.1% change in fracture risk explained by T2DM [186]. However, we believe that the long-term hyperglycemic effects of T2DM, dietary changes, and gut flora dysbiosis leading to disturbances in bone metabolism can be explained, which is consistent with the cohort's categorization of risk factors as low BMI, prolonged duration of T2DM, insulin therapy, and low physical activity. In addition, this study focuses on the key role of nutritional therapy in relation to T2DM and bone and does not address the impact of specific foods, other comorbidities and type 1 diabetes (which carries a higher risk of fracture [5]). And the integration of nutritional therapy with other management modalities is only briefly described, without going into detail to compare multiple medications, exercise modalities and delving into the mechanisms of macronutrient and micronutrient effects on epigenetics. It should be acknowledged that we only discussed the potential role of OCN on pancreatic β-cell recovery in T2DM, as well as mentioning lipid transporter protein 2, and failed to adequately evaluate the remaining osteogenic hormones. Therefore, future studies should consider a stronger multivariate design in order to more fully characterize them in the context of the actual or suffering from other complications.

Moreover, it is clear from the comprehensive analysis in this review that certain aspects of diets related to bone metabolism remain under-explored in academia. Therefore, there is an urgent need for more rigorous trials to determine the potential benefits of dietary interventions for T2DM and bone health.

1. To investigate the individual effects of carbohydrate intake on bone health and to track the long-term effects of low-carbohydrate diets;
2. To find a balance point for animal/plant protein intake to improve blood glucose metabolism while maintaining bone health;
3. To assess the potential of unsaturated fatty acids to alleviate T2DM;
4. To examine the effects of altered dietary iron and copper intake on organismal iron and copper metabolism in T2DM patients and to determine if copper death is an additional pathogenesis of Diabetic osteoporosis;
5. More high-quality evidence is required to evaluate the effectiveness of vitamin C in treating T2DM;
6. To monitor long-term vegetarian eating patterns and eliminate potential adverse reactions related to certain nutrients, exploring their potential benefits between T2DM and bone metabolism homeostasis;
7. More adequate research evidence is needed to evaluate the effects of various IF programs on bone outcomes;
8. To substantiate the article's claim, additional research is required to ascertain how changes in uOCN levels influence T2DM outcomes;
9. This paper only addresses a subset of the dietary factors contributing to bone health caused by T2DM; subsequent discussions still require refinement;
10. High-quality research evidence is needed to assess the impact of the use of T2DM medications versus OP medications for both diseases;
11. More robust evidence is needed to address the opportunities and challenges of using the Precision Diet to prevent and control T2DM and OP.

7. Conclusion

There is no evidence to recommend a specific diet to prevent the development of OP due to T2DM, and the carbohydrate intake, the ratio of animal-to-vegetable protein intake should be adjusted based on the patient's individual situation, and the willingness of the eating pattern should be selected according to the necessary dietary recommendations. However, this paper highlights that patients with T2DM can be protected against the development of OP by supplementation with calcium, magnesium, zinc, vitamin D, vitamin K, vitamin C, high dietary fiber and adopting a Mediterranean dietary pattern in combination with individualized exercise strategies, control smoking and limit alcohol consumption in order to prevent the development of osteoporosis and, in doing so, provide a theoretical basis for the potential role of pancreatic β-cells as a means of improving bone health.

Data availability statement

No data was used for the research described in the article.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Jia Zeng: Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization. **Ying Qian:** Writing – review & editing, Writing – original draft, Conceptualization. **Jizhuo Yang:** Writing – review & editing, Writing – original draft. **Xinqiang Chen:** Writing – review & editing, Writing – original draft, Conceptualization. **Chuanwen Fu:** Writing – review & editing, Writing – original draft, Conceptualization. **Zhuohang Che:** Writing – review & editing, Writing – original draft. **Yuemei Feng:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Jianzhong Yin:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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