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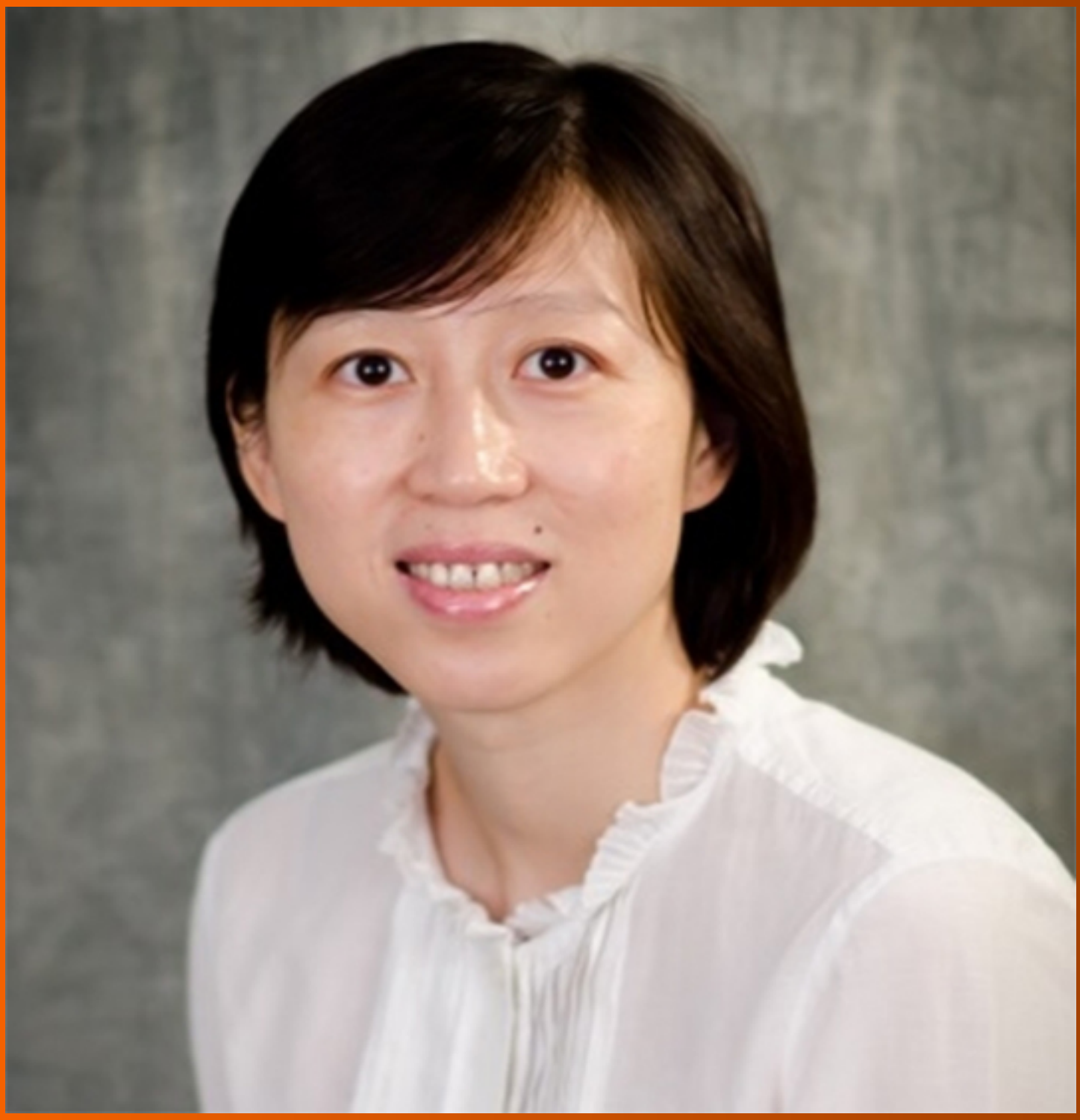

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REVIEW

Bone health in diabetes and prediabetes

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Abstract

Bone fragility has been recognized as a complication of diabetes, both type 1 diabetes (T1D) and type 2 diabetes (T2D), whereas the relationship between prediabetes and fracture risk is less clear. Fractures can deeply impact a diabetic patient's quality of life. However, the mechanisms underlying bone fragility in diabetes are complex and have not been fully elucidated. Patients with T1D generally exhibit low bone mineral density (BMD), although the relatively small reduction in BMD does not entirely explain the increase in fracture risk. On the contrary, patients with T2D or prediabetes have normal or even higher BMD as compared with healthy subjects. These observations suggest that factors other than bone mass may influence fracture risk. Some of these factors have been identified, including disease duration, poor glycemic control, presence of diabetes complications, and certain antidiabetic drugs. Nevertheless, currently available tools for the prediction of risk inadequately capture diabetic patients at increased risk of fracture. Aim of this review is to provide a comprehensive overview of bone health and the mechanisms responsible for increased susceptibility to fracture across the spectrum of glycemic status, spanning from insulin resistance to overt forms of diabetes. The management of bone fragility in diabetic patient is also discussed.

Key words: Bone; Fractures; Type 1 diabetes; Type 2 diabetes; Prediabetes; Diabetes complications; Bone density; Hypoglycemic agents

Core tip: Diabetes mellitus, either type 1 or type 2, is associated with increased fracture risk. Diabetic hyperglycemia and insulin resistance underlie functional alterations of bone cells and bone marrow fat that affect several determinants of bone strength, including bone matrix proteins and bone mass, geometry and microarchitecture.

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Diabetes-related microvascular complications and certain antidiabetic drugs appear to further increase fracture risk, both directly and indirectly. The prevention and management of bone fragility in diabetes includes identification of patients at risk, correction of modifiable risk factors including appropriate choice of antidiabetic drugs and use of antifracture drugs with proven efficacy.

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia leading to serious microvascular and macrovascular complications. In recent years, bone fragility has emerged as a further complication of DM, both Type 1 diabetes (T1D) and type 2 diabetes (T2D). Aim of this review is to provide a comprehensive overview of bone health across the spectrum of glycemic status, spanning from insulin resistance to overt forms of diabetes.

Insulin and bone

Insulin is an anabolic hormone central to the regulation of substrate metabolism in key organs and tissues such as skeletal muscle, the liver and adipose tissue[1]. Both osteoblasts and osteoclasts express the insulin receptor. Insulin stimulates osteoclast formation and promotes proliferation, differentiation and survival of osteoblasts, with an overall balance in favor of bone formation[2]. Studies on insulin receptor knockout mice indicate that insulin signaling is necessary for normal bone acquisition[3,4], likely due to the role of insulin in the regulation of bone energy metabolism. In fact, insulin administration increases ^{18}F-fluorodeoxyglucose ([18F]FDG) uptake by bone in mice, which is markedly reduced in mice lacking the insulin receptor in osteoblasts[5]. Furthermore, activation of the insulin receptor in the growth plate of mice fed with a hypercaloric diet stimulates skeletal growth and growth plate chondrogenesis[6]. Osteoblasts also express the Insulin-like growth factor 1 (IGF-1) receptor[7]. IGF-1 binds both to the IGF-1 receptor and, with lower binding affinity, to the insulin receptor, thus triggering the insulin signaling pathway and exerting osteoanabolic actions.

DM

Depending on the pathogenic mechanism(s) causing chronic hyperglycemia, DM is classified into few main general categories. T1D is distinguished by absolute insulin deficiency due to destruction of pancreatic beta-cells on an autoimmune or idiopathic base. Latent autoimmune diabetes in adults (LADA) is a less common form of autoimmune diabetes that arises in the adult age and is characterized by circulating islet autoantibodies and insulin independence at diagnosis. In T2D, insulin resistance leading to compensatory increase of insulin secretion causes progressive worsening of beta cell function that eventually results in relative insulin deficiency and hyperglycemia. Other forms of DM include monogenic forms (*e.g.*, maturity onset diabetes of the young, MODY), gestational diabetes, and secondary forms either associated with conditions that affect insulin secretion (*e.g.*, pancreatic diseases) or certain drugs (*e.g.*, glucocorticoids and immunosuppressants after organ transplantation). This review will focus on the main diabetes categories, *i.e.* T1D and T2D, as well as on those alterations of glucose metabolism collectively identified as prediabetes[8].

Diabetes and prediabetes: clinical impact on bone

Fracture risk in T1D

Fracture risk is increased in T1D, with a 2- to 6-fold higher risk of fracture as compared with non-diabetic subjects, the risk being greatest in T1D women[9,10]. In a recent analysis that assessed the determinants of fracture risk in T1D adult patients, nearly half of the subjects reported at least one fracture after diabetes diagnosis[11].

Older age, longer T1D duration, age < 20 years at diagnosis and family history of osteoporosis or osteopenia were associated with fracture occurrence.

Fracture risk in T2D and prediabetes

Individuals with T2D have a 1.2- to 3-fold higher risk of fracture as compared with non-diabetic subjects, particularly for hip fractures[9,12], but also for upper arm and ankle fractures[13]. Fracture risk appears to be greater in those with a body mass index (BMI) < 30 kg/m^2 as compared with obese individuals[14], and not to significantly differ by gender[9,15]. Diabetes duration longer than 10 years, low levels of physical activity, use of insulin and systemic corticosteroids and increasing age are also associated with higher fracture risk in T2D[14]. Falls represent another risk factor for fractures, especially in diabetic women[14,16,17]. The association between diabetes, especially T2D, and increased risk of falls is well recognized[18,19] and mainly attributed to diabetes related complications such as therapy-induced hypoglycemic episodes, impaired muscle strength due to sarcopenia, retinopathy-related impaired vision, peripheral artery disease and neuropathy[20,21]. As in a vicious circle, fractures may lead to imbalance, alterations in posture and decreased muscle strength, eventually reducing physical performance and further increasing the risk of falls[22]. Predictive factors of falls and their contribution to fracture risk in T1D patients have not been clearly identified[23].

Despite a clear association between T2D and increased fracture risk[9,19,24], evidence supporting an association between prediabetes and fracture risk is inconsistent. Observations in adolescents suggest that insulin resistance may be detrimental for bone development through puberty, independent of body composition and the level of physical activity[25]. However, no association between insulin resistance and fracture risk was evident after adjustment for BMI and bone mineral density (BMD) in a large cohort of elderly subjects[26]. These findings are consistent with studies that found no statistically significant difference in fracture risk between subjects with or without prediabetes[27,28], but are in contrast with those reporting an association between prediabetes, adjusted for BMI and/or BMD, and lower fracture risk[29].

Assessment of fracture risk in diabetes

Schwartz and colleagues analyzed data from nearly 17,000 older community-dwelling men and women, and found that, for a given T-score and age or FRAX® score (the most widely used fracture risk index), subjects with diabetes had a higher fracture risk than those without diabetes[30]. Similarly, Giangregorio *et al*[31] found that FRAX underestimates the risk of major osteoporotic and hip fractures in individuals with diabetes. Recently, four options have been assessed to enhance the performance of FRAX in patients with DM (using rheumatoid arthritis as a proxy for the effects of DM, trabecular bone score [TBS]-adjustment, reducing the femoral neck T-score input by 0.5 SD, increasing the age input by 10 years)[32]. Although each correction improved the performance of the FRAX tool in predicting fracture risk, no single method was optimal for all fracture outcomes and durations of diabetes.

DIABETIC BONE DISEASE-PATHOPHYSIOLOGY

Several factors might be responsible for the increased fracture risk in diabetic patients. Diabetes-related changes affect bone strength, which in turn depends on different and complex components, *i.e.* BMD, bone microarchitecture and its microenvironment and material properties.

Bone cells

Cellular and molecular components cross-talk to maintain skeletal integrity in an intricate balance that can be altered in DM. It is important to understand alterations in these components, as they have also direct clinical consequences and may represent targets for clinical interventions. Structural elements with a role in physiologic bone formation include support cells like osteoblasts and osteocytes, remodeling cells known as osteoclasts, and non-cellular components like osteoid (hydroxyapatite, collagen, non-collagen-structural proteins) and mineral salts deposited within the matrix. Mesenchymal stem cells (MSC), *i.e.*, the osteoblast precursors, may also differentiate into adipocytes. The fate of MSCs depends on a fine balance between the WNT signaling pathway, which promotes osteogenesis, and the peroxisome proliferator-activated receptor-γ (PPAR-γ) pathway, which promotes adipogenesis[33]. An imbalance between these pathways may result in one cell type predominating over the other. Along with the bone-resorbing osteoclasts, osteoblasts are involved in a fundamental process that lasts the whole human life, bone remodeling, wherein old bone is substituted with new bone to maintain bone strength and mineral

homeostasis, and to repair microdamage[34].

Osteoblasts in T1D

Preclinical studies[25] documented alterations in transcription of osteoblasts promoting genes, in particular Runx2, which is involved in MSC differentiation into pre-OBs and in the regulation of bone matrix protein genes. Some preclinical studies suggested that Runx2 is downregulated by hyperglycemia[35,36], although other studies reported no modification[37,38]. The *Wnt/beta catenin* gene, which is known to promote OB differentiation, is also downregulated[39]. In T1D, low levels of IGF-1, which promotes differentiation of MSCs into OBs[40,41] and bone mineralization[42], may also contribute to reduced bone formation. It is also known that serum from T1D patients decreases collagen production in human OBs when used as a culture medium[43]. Moreover, individuals with T1D have low levels of parathyroid hormone (PTH)[44], which in normal conditions prevents OB apoptosis[45], improves bone density and increases mineralization and enhances, synergistically with IGF-1, osteoblast differentiation into osteocytes[46]. An increase in circulating levels of proinflammatory cytokines such as TNF-a, IL1 and IL6 due to hyperglycemia[47,48], may impair OB proliferation and differentiation *in vitro*[49-53], or even stimulate OB apoptosis[54,55], while inhibiting bone healing *in vivo*[56]. Overall, the evidence suggests that an impairment on OB function and survival may be responsible for reduced bone formation in T1D.

Osteoblasts in T2D

Few studies on OBs from T2D subjects are available. Postmenopausal women with T2D were reported to have higher levels of OB precursor cells than BMI-matched non-diabetic controls. OBs were more immature compared with controls, and Dickkopf-related protein 1 (DKK-1), a regulator produced by bone marrow stromal cells that inhibits OB maturation, was increased[57]. Thus, it appears that individuals with T2D have increased levels of immature OBs, which may explain lower bone quality and higher BMD.

Osteocytes in T1D

In mouse models of T1D, a reduction in osteocyte density and number, and an increase in apoptosis have been reported[58-60]. Sclerostin, an osteocyte-derived protein that inhibits bone formation[61,62] and stimulates OB apoptosis[63], is elevated in adults with long-standing T1D[64] prediabetes[65], or T2D[66]. Surprisingly, however, a large Danish retrospective study of T1D patients found that T1D patients with higher serum levels of sclerostin had a lower incidence of bone fractures[67].

Osteocytes in T2D and prediabetes

As mentioned, osteocyte-derived sclerostin is elevated in adults with T2D and prediabetes[65,66]. In T2D, there is a direct correlation between sclerostin levels, disease duration and glycemic control, and an inverse correlation with bone turnover markers[66,68]. Anti- sclerostin antibodies increased bone mass in diabetic rats[69]. This finding is of particular interest, as an anti-sclerostin monoclonal antibody (romosozumab) is now available for the treatment of osteoporosis in humans[70].

Osteoclasts in T1D

In physiological conditions, the OB-derived receptor activator of nuclear factor kappa-B ligand (RANKL), promotes the differentiation and activation of osteoclasts through the receptor RANK on osteoclast surface. This process is inhibited by osteoprotegerin (OPG), also produced by OBs, which binds to RANKL thereby preventing its interaction with RANK. Patients with T1D and poor glycemic control exhibit more active bone resorption. Consistently, the analysis of peripherally detected osteoclasts in patients with T1D showed a lower sensitivity to inhibitory factors such as OPG[71]. An increased *OPG* gene expression compared to healthy controls has also been reported[72], possibly to compensate for the lower sensitivity to OPG. Other *in vitro* studies, however, showed a reduction in RANKL and its cellular actions in hyperglycemic environments[73] , which could indicate a limited role of RANKL and OPG in the pathogenesis of bone alterations in DM. Finally, a higher concentration of markers of osteoclastic activity (cathepsin K, tartrate-resistant acid phosphatase [TRAP], C terminal telopeptide) has been observed in insulinopenic mice[74,75], although this increase was significant only in the case of severe or long-lasting diabetes. This variability in osteoclastic activation suggests that disease severity and duration may influence the degree of diabetes-induced bone resorption[76,77] .

Osteoclasts in T2D

High glucose levels inhibit osteoclast differentiation and suppress matrix degradation by osteoclasts in animal models of T2D[78]. Accordingly, circulating osteoclast

precursors were found to be increased and more immature in T2D postmenopausal women compared with BMI-matched healthy controls, possibly due to lower RANKL levels[57]. It may be speculated that a lower level of maturation compromises OC activity, leading to decreased bone resorption resulting in higher BMD in T2D.

BMD

BMD in T1D: Low BMD is reported in nearly all studies involving T1D patients of any age compared to non-diabetic controls[79]. The reduction in BMD worsens with longer disease duration[80], poor glycemic control, early age of onset of T1D, and higher insulin dosage[81]. Furthermore, T1D adult patients with microvascular complications have lower BMD than those without microvascular disease[81-86], suggesting a role for bone vascularization in the pathogenesis of diabetic bone disease. Children and adolescents withy T1D have smaller cross-sectional areas and weaker bones despite an increase in bone formation markers, suggesting impaired osteoblast activity during growth[87]. It is likely that an inadequate peak bone mass is reached at the end of the skeletal maturation due to low levels of IGF-1 and the catabolic effects of uncontrolled hyperglycemia during critical growth period[88,89]. Consistently, patients with onset of diabetes before age 10 years reach a lower than average mean near-adult height, adult height being inversely correlated with glycemic control[90].

Altered vitamin D and calcium metabolism due to hyperglycemia may further contribute to reduced BMD in T1D[91]. Reduced BMD, however, might not be the only factor contributing to increased fracture risk. Recent observations suggest that, opposite to what one would expect, BMD does not worsen over time in patients with T1D as compared with nondiabetic individuals[92].

BMD in T2D and prediabetes: Subjects with T2D generally have higher BMD as compared with healthy controls, with significant differences of 0.04 (95%CI: 0.02, 0.05) at the femoral neck, 0.06 (95%CI: 0.04, 0.08) at the hip and 0.06 (95%CI: 0.04, 0.07) at the spine[93]. As insulin is known to exert anabolic effects on bone, high circulating insulin levels may explain the observed increase in BMD in T2D[94]. Accordingly, some studies indicate a positive association between circulating insulin levels and BMD, independent of BMI[95-97]. However, in most studies the positive association between insulin levels or indices of insulin resistance and BMD was lost after adjusting for BMI[26,98-101], implying that the increase in BMD observed in insulin resistant states is mediated by body mass. In fact, obesity has long been considered to be protective towards osteoporosis and osteoporotic fractures, being associated with increased mechanical load stimulating bone formation[102], androgens-to-estrogens conversion in adipose tissue, lower serum levels of sex hormone binding globulin (SHBG)[103], increased circulating leptin[104] and insulin growth factor, and hyperinsulinemia[99]. Recent findings challenge this belief, suggesting that even though BMD increases with body weight, this cannot compensate for obesity-associated greater impact forces during falls. Data from a multiethnic cohort of nearly 2000 pre- or perimenopausal women indicate that higher BMI is associated with higher BMD, but also with lower composite strength indexes[105]. Conflicting data on the association between obesity and fracture risk, with earlier studies demonstrating a protective effect[106-109] and more recent studies indicating an increase in risk[110-114], suggest that BMI is not the only relevant factor in this context, and that body composition and fat distribution may also play a role[115]. Elevated waist circumference and waist-to-hip ratio have been associated with an increased hip fracture risk in a large prospective cohort study[116]. In obese Chinese women, increased fat mass and percent body fat were positively associated with BMD, whereas increased central fat was inversely associated with BMD[117]. Accordingly, visceral adiposity has been associated with increased risk of both vertebral and non-vertebral fractures[118,119]. Central adiposity reflects the amount of visceral adipose tissue (VAT), which is more cellular, vascular, innervated and characterized by the presence of more inflammatory and immune cells, lesser pre-adipocyte differentiating capacity and higher proportion of large adipocytes as compared with subcutaneous adipose tissue (SAT)[120]. VAT is tightly correlated with insulin resistance[121], which, together with low-grade chronic inflammation, possibly mediates the relationship between VAT and increased fracture risk.

In Korean men diagnosed with prediabetes using an oral glucose tolerance test, no significant difference in BMD T-score was found as compared with subjects having normal glucose metabolism[122]. Despite no difference in total body BMD between prepubertal overweight children with prediabetes *vs* non-prediabetic controls (as assessed by OGTT)[123], total body bone mineral content (BMC) was found to be significantly lower in prediabetic children. Inverse associations were found between BMC and markers of insulin resistance and inflammation (C-reactive protein).

Bone turnover

Bone turnover may be assessed by measuring bone turnover markers (BTMs), which reflect the bone resorption and formation processes.

Bone turnover in T1D: In general, both T1D and T2D are considered as states of low bone turnover. Different studies have shown that worse glycemic control is associated with lower bone turnover markers in T1D[124-126], suggesting a negative effect of hyperglycemia on bone turnover. More specifically, patients with T1D exhibit higher sclerostin levels and lower C-terminal telopeptide of type I collagen (CTX) and osteocalcin levels as compared with non-diabetic controls[127].

Bone turnover in T2D and prediabetes: Bone turnover markers are generally reduced in patients with T2D[126,128,129], to a greater extent than patients with T1D[130]. However, not all studies yielded consistent findings. Osteocalcin and CTX are the BTMs most consistently found to be lower in T2D and patients with as compared with subjects without diabetes, whereas sclerostin and osteoprotegerin are generally elevated (Table 1). Conflicting findings have been reported for other markers but, overall, the evidence seems to point towards a suppression of bone formation and bone resorption, both in prediabetes and T2D. Histomorphometric evaluation of bone tissue biopsies from T2D patients confirmed reduced bone turnover[131,132]. The suppression of bone turnover reported in T2D patients is associated with higher risk of vertebral fractures[133,134], independent of BMD. This is consistent with the concept that the impairment in bone strength in T2D is due to impaired material properties, which may be caused by low bone turnover, as well as by elevated concentrations of advanced glycation endproducts (AGEs)[135].

Fewer studies have assessed bone turnover in prediabetes. Impaired fasting glucose (IFG) was associated with lower osteocalcin[128], CTX and N-amino terminal propeptide of T1D procollagen (P1NP)[136,137] in women, and lower CTX and P1NP in men[136], suggesting that, similar to T2D, prediabetes is associated with reduced bone turnover.

Increased bone marrow adiposity

Bone marrow adipose tissue (MAT) has gained increasing attention in recent years as a single anatomic entity, together with its relations with various clinical conditions, including diabetes. MAT consists of MSC-derived adipocytes located within the bone marrow niche. The distribution of MAT around the skeleton is not homogenous, and regulation of marrow adipose depots varies at different skeletal sites. While peripheral depots of MAT (also termed constitutive MAT) rarely change, MAT depots at more central sites (*e.g.*, spine, pelvis and sternum, proximal regions of the long bones) are more diffuse within the red marrow and may increase or decrease in response to environmental or pathological factors (regulated MAT)[138]. Interestingly, hyperglycemia increases the expression of *PPAR* genes, which stimulates differentiation of MSC into bone marrow adipocytes[139]. Similarly, the antidiabetic PPARγ agonists thiazolidinediones (TZDs) are thought to increase fracture risk through promotion of marrow adipogenesis at the expense of osteogenesis[140](Figure 1). Until recently, MAT was thought to be just a reserve of adipose tissue, negatively associated with hematopoiesis, but its complete function has just begun to be revealed. *In vivo* studies using magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) or computed tomography (CT) to assess MAT quantity and composition have helped understand the mechanisms of increased skeletal fragility and metabolic risk associated with several clinical conditions, including diabetes[141].

MAT in T1D: In animal models of T1D, hyperglycemia is associated with increased marrow adiposity and bone loss[37,38,142], whereas no differences in MAT were identified between male patients with T1D and healthy controls[143,144], and neither duration of disease nor glycemic control were related to bone marrow adiposity. This lack of association between MAT and T1D was confirmed in young women with T1D compared with healthy controls[145]. Irrespective of the presence of diabetes, in young women MAT was inversely associated with BMD[145]. Carvalho and colleagues showed that MAT quantity and lipid composition (saturated and unsaturated lipids) were similar between male T1D subjects and controls[144]. There was, however, a significant inverse correlation between MAT saturated lipids and BMD.

MAT in T2D: In T2D men participating in the Osteoporotic Fractures in Men (MrOS) Study, a large epidemiological study of nearly 6,000 men, vertebral MAT was increased as compared with nondiabetic controls, and inversely associate with BMD[146]. Although no differences were detected in total MAT content in postmenopausal women, those with T2D and previous fractures had the lowest MAT

Table 1 Bone turnover markers in prediabetes/insulin resistance and type 2 diabetes

BTM	Meaning	Pre-DM / IR	Ref.	T2D	Ref.
CTX	Bone resorption	↓ or ↔	[136,276,278-280]	↓	[129,132,134,137,281-286]
TRAP	Bone resorption	↑?	[287]	↓ or ↔	[132,281]
uNTX	Bone resorption			↓	[285]
Sclerostin	Inhibition of bone formation	↑	[65]	↑	[284,285,288,289]
OC	Bone formation	↓ or ↔	[128,276-278,280,290]	↓ or ↔	[129,132,134,281,283,285,286,291-294]
P1NP	Bone formation	↓ or ↔	[136,277,280]	↓ or ↔	[88,132,134,137,282,283,285,286]
BAP	Bone formation	Direct association with IR	[295]	↔ or ↓ or ↑	[132,281,284,286,292,294]
ALP	Bone formation	?	?	↔ or ↑	[292-294]
OPG	Inhibition of bone resorption	↑	[296]	↑	[293,296]

BTM: Bone turnover marker; pre-DM: Prediabetes; IR: Insulin resistance; T2D: Type 2 diabetes; CTX: Carboxy-terminal cross-linking telopeptide of type I collagen; OC: Osteocalcin; P1NP: Procollagen type 1 amino-terminal propeptide; TRAP: Tartrate-resistant acid phosphatase; uNTX: Urinary N-telopeptide of type I collagen; BAP: Bone-specific alkaline phosphatase; ALP: Alkaline phosphatase; OPG: Osteoprotegerin; ↑: Increased; ↓: Decreased; ↔: Similar to healthy controls; ?: Unknown.

lipid unsaturation and highest MAT saturation levels independent of age, race, and BMD, highlighting the importance of MAT composition in addition to the degree of marrow adiposity[147]. Furthermore, gender-related differences have been reported in the association between MAT and visceral adipose tissue (VAT)/subcutaneous adipose tissue (SAT) volumes or BMI. While in obese or diabetic women MAT is associated with VAT and SAT[148,149], no such association was found in older men[150]. In men, a negative association between MAT and DXA-derived BMD of femoral neck and total hip was reported. Data on MAT in pre-diabetes is scanty, but a potential relation between hyperglycemia and MAT has been suggested[151].

ADVANCED GLYCATION END PRODUCTS-BONE MATRIX IN DIABETES

AGEs are protein or lipid complexes formed through non-enzymatic reactions in the presence of high sugar levels. Their accumulation is thought to play a role in aging and some degenerative diseases[152]. In *in vitro* studies, AGEs deposits have been demonstrated in bone matrix, where they may exert a direct toxic effect on OBs[153]. AGEs inhibit bone remodeling and indirectly up-regulate the production of interleukin 6 (IL-6)[154], a catabolic factor that attenuates OBs activity[53] and vascular endothelial growth factor A (VEGF-A) by osteocytes, inducing also their apoptosis[155].

AGEs in T1D: In murine models of T1D, the AGE pentosidine (PEN) in bone is significantly increased, this increase being paralleled by an impairment in bone mechanical properties[156]. Similarly, PEN levels in bone biopsies from fractured T1D patients were higher than in controls[80], and circulating PEN levels are associated with prevalent fractures in T1D[157]. Carboxymethyllysine (CML), another type of AGE that correlates with fracture risk[158], is increased in mouse models of T1D and inversely associated with bone strength[159].

AGEs in T2D and prediabetes: Bone strength in T2D postmenopausal women is reduced as compared with non-diabetic controls, and this reduction appears to be associated with increased AGE accumulation, as indirectly estimated by skin autofluorescence (SAF)[160]. Consistently, increased urinary or serum PEN levels have been associated with greater fracture risk in T2D[161,162]. To the best of our knowledge, no data are available on AGEs and bone health in prediabetes.

Bone geometry and microarchitecture

Bone geometry and microarchitecture contribute to bone strength. Tools such as high-resolution peripheral quantitative computed tomography (HR-pQCT), micro-magnetic resonance (μ-MRI) and TBS acquired through dual-energy X-ray absorptiometry (DXA) are available to study bone structure in diabetes[163,164], offering enough resolution to assess microarchitecture and providing indirect indexes of bone quality.

Bone geometry and microarchitecture in T1D: In rodent models of T1D, deletion of

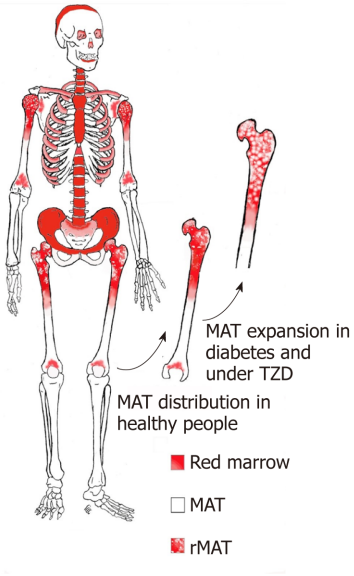

Figure 1 Schematic representation of the anatomical distribution of bone marrow adipose tissue depots. Both hyperglycemia and the antidiabetic drugs thiazolidinediones may induce marrow adipose tissue (MAT) expansion by increasing the expression of peroxisome proliferator-activated receptor genes, which in turn stimulates adipogenesis. rMAT: Regulated MAT (MAT depots that increase or decrease in response to different stimuli).

the insulin receptor from OBs at different stages of maturation leads to anomalous trabecular architecture and higher bone fragility[3,4]. In adults with T1D, trabecular bone quality is lower as compared with non-diabetic age-, BMI-, and sex-matched controls and is negatively associated with insulin resistance, as assessed by the hyperinsulinemic euglycemic clamp[165]. Studies using HR-pQCT demonstrated higher cortical porosity, thicker trabeculae and larger spacing between trabeculae in T1D patients with microvascular complications, compared to those without, and in T1D patients compared with matched non-diabetic controls[166]. Similar findings were reported using μ-MRI[167]. Moreover, using μ-CT in T1D subjects without vascular complications, worse bone quality was found in those who did experience fractures as compared with those who did not[166]. An insufficient peak bone mass at the end of skeletal maturation may result in smaller and shorter bones, a geometry that could favor bone fragility[130]. However, the contribute of altered geometry and defective trabecular and cortical bone to the increased risk of fracture in T1D is yet to be clarified.

Bone geometry and microarchitecture in T2D and prediabetes: The increased fracture risk in T2D may be related to distorted bone microarchitecture, especially in cortical bone[168-170].

Bone micro-indentation allows measuring the bone material strength index (BMSi), which estimates the resistance to crack propagation in bone[171]. BMSi is reduced in patients with T2D as compared to healthy controls[88,93], suggesting a lower resistance to fractures. Increased cortical porosity has been identified as a possible causative factor. Patients with T2D have higher porosity in trabecular bones, as assessed by MRI[170]. Studies using HR-pQCT confirmed a similar trend in porosity. Deficits in cortical bone of T2D patients were more marked in patients with previous fractures compared to those without[169], or present only in T2D patients with microvascular complications compared with patients without complications[169]. In a cross-sectional analysis of nondiabetic postmenopausal women, higher levels of insulin resistance were associated with lower cortical bone volume, independent of age and weight[172]. Consistently, female obese late-adolescents had worse trabecular bone microarchitecture at the radius and tibia as compared with non-obese controls, as well as lower bone volume and estimated bone strength[173]. T2D diabetes and insulin resistance are almost invariably associated with obesity and increased central adiposity, which reflects increased VAT. Studies that explored the relationship between VAT and bone microarchitecture suggest a possible detrimental effect of VAT on bone microarchitecture. Studies have reported a negative impact of VAT on bone microarchitecture, as suggested by a negative association between central adiposity measures and TBS[174,175]. Furthermore, a negative effect of VAT on femoral

cross-sectional area, cortical bone area and bone strength indexes has been reported[176]. On the other hand, higher VAT was associated with improved microarchitecture with the exception of higher cortical porosity at the distal radius in the Framingham osteoporosis study[177]. However, this association lost significance after adjustment for BMI or weight, suggesting that the effects of VAT may not have a substantial effect on the skeleton independent of BMI or weight. In non-diabetic men at the age of peak bone mass, insulin resistance (as assessed by HOMA-IR) was found to be inversely associated with trabecular and cortical bone size, independent of body composition[178]. Overall, these data suggest a detrimental role of hyperinsulinemia on bone microarchitecture and geometry. Central adiposity might have a negative effect on bone microarchitecture, but this possibility needs to be further explored.

Vascular disease: microangiopathy

Diabetic microvascular complications such as retinopathy and neuropathy may indirectly potentiate the fall risk, impairing vision or physical perception. Diabetic microangiopathy may involve all organs, including bone, possibly contributing to bone fragility. Histomorphometric assessments found microangiopathy in 82% of bone biopsy specimens from diabetic patients, and a concomitant reduction of bone marrow capillaries[179]. To date, there is no other direct evidence of bone vascular alteration in humans. In mouse models of T1D, administration of an angiogenic factor to ovariectomized mice led to improvements in bone quality[180]. As mentioned, reduced trabecular BMD, cortical BMD, thinner trabeculae and cortex were reported in T1D patients with known vascular complications, as opposite to T1D patients without complications and non-diabetic controls[166]. Similarly, in a cross-sectional study that assessed peripheral bone microarchitecture, bone strength and bone remodeling in T2D patients with or without diabetic microvascular disease only T2D patients with established microvascular disease displayed lower cortical volumetric BMD and cortical thickness and higher cortical porosity at the radius compared to controls without microvascular disease[181]. Impaired microvascular circulation might lead to hypoxia, which in turn may lead to enhanced adipogenesis within the bone marrow and downregulation of OB differentiation[182].

Pharmacological treatments for diabetes

Metformin. Metformin is widely prescribed for the management of T2D, being recommended as the first-line treatment by international guidelines[8,183]. It reduces hepatic glucose production and improves peripheral insulin sensitivity, thereby enhancing peripheral glucose disposal[184]. Metformin has been shown to promote the osteogenic differentiation of adipose-derived MSC, and in general to exert pro-osteogenic effects in preclinical studies[185-188]. Clinical observations indicate that metformin has a neutral[28,189] or even a favorable effect on fracture risk[12,190,191].

Glucagon-like peptide-1 (GLP-1) receptor agonists (RA): GLP-1 RAs (liraglutide, exenatide, lixisenatide, dulaglutide, semaglutide) are recommended as the best choice for a second agent when combination treatment is needed to achieve glycemic control in patients with T2D in whom atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease predominates[8,183]. By activating the GLP-1 receptor, GLP-1 RAs slow gastric emptying, suppress glucagon secretion while also stimulating glucose-induced insulin secretion[192]. These effects result in the suppression of hepatic gluconeogenesis and increased peripheral glucose disposal. *In vitro*, activation of GLP-1 receptors promotes differentiation of MSC into osteoblasts[193] and inhibits osteoblast apoptosis[194], suggesting an anabolic effect on bone. Studies in rats support these findings[195]. Of note, in animal models of T1D administration of liraglutide significantly improved bone strength and reduced collagen degradation in the bone matrix, although no changes in trabecular no cortical microarchitecture were observed[196]. Case-control studies and metanalyses of population-based studies and randomized clinical trials including patients with T2D treated with GLP-1 RAs indicate no effect on fracture risk[197-199]. However, evidence exist that different GLP-1 RAs may exert opposite effects on fracture risk, which appears to increase or decrease in patients treated with exenatide or liraglutide, respectively[200]. Furthermore, liraglutide was reported to prevent a reduction of BMC after weight loss in obese nondiabetic women, although BMD was not affected[201,202].

Dipeptidylpeptidase 4 (DPP4)-inhibitors: DPP4-inhibitors (sitagliptin, linagliptin, saxagliptin,vildagliptin, alogliptin, *etc*.) exert their action by inhibiting the enzyme DPP-4, which is responsible for the rapid degradation of the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, thereby enhancing glucose-induced insulin secretion[203]. Preclinical studies indicate a possible anti-osteoclastogenic and anti-resorptive effect of DPP4-inhibitors[204,205]. Clinical data

support a neutral[189,206,207] or even favorable[208,209] effect of DPP4-inhibitors on fracture risk. In particular, alogliptin may be associated with a lower risk of bone fracture compared with placebo and other drugs in the same class[210].

Sodium-glucose cotransporter 2 (SLGT2) inhibitors: By inhibiting the renal SGLT2, these drugs (empagliflozin, dapagliflozin, canagliflozin) reduce glucose reabsorption in the kidney, thus increasing urinary glucose excretion and decreasing blood glucose[211]. Associated increases in serum phosphate may lead to changes in PTH and fibroblast growth factor 23 (FGF23) that could affect bone metabolism[212]. Along with GLP-1 RAs, SGLT2 inhibitors are recommended as the best choice for a second agent when combination treatment is needed to achieve glycemic control in patients with T2D in whom atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease predominates[8,183]. Initial reports of increased frequency of bone fractures associated with SGLT2 inhibitors treatment, particularly with canagliflozin, raised concerns about the skeletal safety of these compounds[213]. Furthermore, increased bone turnover and reduced total hip BMD have been reported in patients with T2D treated with canagliflozin[214]. Nevertheless, recent population studies and metanalyses including several thousands of patients consistently failed to demonstrate an association between SGLT2 inhibitor treatment and increased fracture risk in patients with T2D[215-219].

Sulfonylureas and glinides: Sulfonylureas (*e.g.*, glimepiride, gliclazide, glybenclamide) and glinides (*e.g.*, repaglinide) stimulate glucose-independent insulin secretion by binding to specific sites at the β-cell membrane[220,221]. It has been postulated that sulfonylureas do not affect bone directly, but may increase fracture risk by inducing higher rates of hypoglycemic events[222]. Studies that assessed the effect of sulfonylureas and glinides on fracture risk yielded conflicting results, with most studies indicating increased risk[28,189,223-225], but also no effect[191] even decreased risk[12].

Thiazolidinediones (TZDs): TZDs (rosiglitazone, pioglitazone) are insulin-sensitizing agents that exert their action by activating the peroxisome proliferator-activated receptor γ (PPARγ)[226]. Besides enhancing peripheral insulin sensitivity and suppressing hepatic glucose production, activation of PPARγ stimulates adipogenesis and suppresses osteoblastogenesis, thereby reducing the osteoblast pool in the bone marrow[227]. A detrimental effect of TZDs on bone health has been consistently shown. In a cohort study including more than 5000 patients with T2D, current use of TZDs was associated with increased hip fracture risk[190]. Treatment with pioglitazone significantly increased fracture risk compared with placebo in a randomized double-blind, placebo-controlled study[228]. The increase in risk has been confirmed in population-based studies[189] and metanalyses[229], although the impact on bone seems to be more pronounced in women than in men[190,229].

Insulin in T1D: Insulin is the pillar of T1D treatment. As previously discussed, insulin exerts anabolic effects on bone. Intensive insulin treatment has been associated with increased BMD in patients with T1D[82]. Consistently, no association between insulin treatment and single nor multiple fractures was found in a recent study that assessed risk factors for fragility fractures in T1D[230].

Insulin in T2D: Insulin treatment in patients with T2D is initiated when disease progression overcomes the effect of non-insulin agents[8,183]. Thus, patients with T2D started on insulin generally have longstanding diabetes, and may have developed serious complications such as retinopathy-related impaired vision, peripheral artery disease and neuropathy, which in turn are risk factors for falls[20,21]. Insulin use is associated with a 1.4- to 2-fold increase in fracture risk as compared with no insulin use[189,231], and with a 1.6-fold increase in risk as compared with metformin monotherapy[232]. However, not all studies point towards a negative effect of insulin on fracture risk[12,191]. The association between insulin and increased fracture risk despite the anabolic effects of insulin on bone is likely due to the increased risk of falls and hypoglycemic episodes associated with insulin treatment[222].

Surgical treatments for diabetes

Pancreas and islet transplantation in T1D: Beta cell replacement through pancreas or pancreatic islet transplantation is the only currently available cure for T1D in humans, with pancreas transplantation being more often associated with insulin independence and longer graft function. Successful pancreas transplantation provides physiological insulin repletion, without the risk of hypoglycemia associated with exogenous insulin administration. Evidence exists that combined pancreas-kidney transplantation leads to improvements in BMD[233], and that fracture rates in patients with T1D are lower

after transplantation with a simultaneous pancreas–kidney compared with kidney transplantation alone[234], suggesting that T1D remission by pancreas transplantation favorably impacts fracture risk. However, individuals with T1D undergoing pancreas-kidney transplantation also have end-stage renal disease, which strongly affects bone health. A study assessing the effect of diabetes remission following pancreas transplantation alone on bone health in individuals with T1D and preserved kidney function is currently ongoing (NCT03869281).

Metabolic surgery for T2D diabetes: Metabolic surgery is now included as a treatment option for appropriate candidates with T2D[8,235]. Patients undergoing metabolic surgery experience rapid and massive weight loss, which translates into several metabolic benefits, but may be detrimental to bone health. Most available data relate to the Roux-en-Y gastric bypass (RYGB), a restrictive procedure that also involves a malabsorptive component. Sleeve gastrectomy (SG), which has now overcome RYGB and has become the most common bariatric procedure worldwide[236], is a restrictive procedure. Other bariatric procedures, such as the malabsorptive biliopancreatic diversion and the restrictive laparoscopic adjustable gastric banding (LAGB), are being gradually abandoned. Available data indicate that fracture risk after bariatric surgery varies depending on the bariatric procedure, being lowest in patients undergoing LAGB[237] and greatest in those undergoing malabsorptive procedures[238-241], and increases with time after surgery[237,239-242]. However, weight loss-related reductions in BMD have even been reported 6-12 months after minimally invasive bariatric procedures not involving resection of the stomach and/or intestine, such as use of the intragastric balloon or an intraluminal liner implanted into the small intestine[243,244]. Mechanisms underlying the negative effects of bariatric surgery on bone health may involve nutritional factors, mechanical unloading, hormonal factors, and changes in body composition and bone marrow fat[245]. To the best of our knowledge, no studies have specifically addressed the issue of diabetic bone disease in patients with T2D undergoing bariatric surgery.

PERSPECTIVES: POSSIBLE PREVENTIVE AND THERAPEUTIC APPROACHES

Modifiable risk factors for fracture, including factors that affect fall risk and glycemic control should be tackled to reduce fracture risk, although no prospective studies are available to show the antifracture efficacy of preventive lifestyle and/or treatment strategies. Drugs shown to be associated with increased fracture risk in T2D, such as insulin and TZDs[231,232,246] should be avoided, when possible. Strict monitoring should be implemented for T2D patients undergoing bariatric surgery in order to prevent nutritional deficiencies that could worsen weight loss-associated bone loss.

Several alterations in calcium homeostasis have been described in diabetic patients, including reduced intestinal calcium absorption and renal tubular calcium reabsorption, and impaired vitamin D synthesis[247]. It is also recognized that individuals with diabetes, both T1D and T2D, have lower vitamin D levels as compared with non-diabetic controls[248,249]. Overall, these alterations may negatively impact calcium homeostasis and bone mineralization. International guidelines recommend vitamin D supplementation for the prevention and/or treatment of osteoporosis and osteoporotic fractures in men and postmenopausal women[250-252], although recent findings bring into question the efficacy of vitamin D supplementation in preventing fractures or falls, or improving BMD[253]. Vitamin D supplementation was shown to increase bone formation markers[254] and reduce bone resorption markers[255] in postmenopausal women with T2D, not to affect bone turnover markers in patients with T2D and chronic kidney disease[256], and to preserve femoral neck BMD in men with prediabetes[257]. Few data are available about the effect of the use of osteoporosis medications in patients with diabetes.

Stemming from some positive preclinical results[258], few recent human studies have focused the attention on nutrients containing antioxidants such as resveratrol, providing encouraging results in terms of on bone density and on bone loss prevention in obese patients[259] and patients with T2D[260,261] have been reported.

Recently, hyperbaric therapy[262,263] has been shown to promote bone regeneration in animal models of diabetes, but further studies are needed to clarify whether this could be an effective approach in humans.

Raloxifene, a second generation selective estrogen receptor modulator (SERM) indicated for the prevention and treatment of postmenopausal osteoporosis[264], was shown to improve bone material properties (femoral toughness) in diabetes-prone rats[265]. In postmenopausal women, raloxifene may decrease the bone resorption

marker NTX and it has been speculated that it might improve bone quality by reducing AGEs, although no information is available on the effect on reliable bone quality indicators or relevant clinical outcomes such as fracture risk[265]. In a pilot study that assessed the skeletal effects of a third generation SERM, bazedoxifene, in postmenopausal women with T2D, all bone resorption markers decreased significantly after 12 weeks of treatment. Homocysteine and pentosidine, which were used as bone quality markers in this study, were not affected[266].

Little is known about osteoporosis therapies in T1D young patients. As T1D usually manifests in young individuals, it is important to remember that caution must be taken in women during reproductive age, as bisphosphonates are stored and released from bones for long time and may affect fetal skeletal ossification. In elderly, postmenopausal, osteoporotic obese women with T2D treated with long-term bisphosphonates, no difference in spine BMD but a significantly greater decline in BMD in regions of the hip, femoral neck, and forearm were observed as compared with non-diabetic controls[267]. However, the efficacy of these medications must be assessed based on clinically relevant outcomes. Despite being a condition of reduced bone turnover, epidemiological data indicate that diabetes (either T1D or T2D) was shown not to reduce the antifracture efficacy of antiresorptive drugs, which also reduce bone turnover[268].

In a large study on the efficacy of recombinant PTH (rhPTH 1-34, teriparatide), similar reduction in nonvertebral fracture incidence and increase in BMD were observed in postmenopausal osteoporotic women with or without T2D[269].

Denosumab is a RANKL-specific antibody indicated as osteoporosis treatment known to increase particularly cortical BMD. This property might be of particular value, as cortical compartment is the most involved in the diabetic bone. A phase 2 clinical trial to assess the skeletal effects of denosumab in T2D is ongoing (NCT03457818). Interestingly, denosumab was shown to improve hepatic insulin sensitivity in humans[270,271] and, consistently, to reduce fasting plasma glucose in women with diabetes not on antidiabetic medications[272]. Preclinical studies also indicate that denosumab may stimulate human β-cell proliferation[273].

Sclerostin seems to have a central role in the pathogenesis of diabetic bone disease. In mouse models of T1D[273] and T2D[274], administration of anti-sclerostin antibodies seems to reverse the deficits in bone density and micro-fracture healing. No data are currently available on romosozumab, an anti-sclerostin antibody shown to reduce the risk of clinical and vertebral fractures in postmenopausal women with osteoporosis[275].

CONCLUSION

Diabetes has a strong impact on bone health, and skeletal fragility is now recognized as a complication of both T1D and T2D. Fracture risk is greater in patients with T1D, and increases with increasing disease duration. Individuals with T1D have decreased BMD, possibly due to absolute insulin deficiency and the inability of exogenous insulin to mirror endogenous insulin secretion. However, the relatively small reduction in BMD does not appear to completely explain the increase in bone fragility observed in T1D[276-296]. On the other hand, individuals with T2D have either normal or increased BMD, which is in contrast with the increased fracture risk observed in this population. Therefore, it is likely that factors that affect bone quality, rather than bone mass, impact the resistance of T2D bones to fracture (Table 2). Increased non-enzymatic glycation of bone matrix proteins, impaired microcirculation and glucotoxicity itself, *i.e.*, the direct detrimental effect of high glucose on bone cells, may all play a role. Reduced bone turnover and increased bone marrow adipogenesis at the expenses of osteogenesis may also contribute. Despite a clear association between T2D and increased fracture risk, evidence supporting an association between prediabetes and fracture risk is inconsistent, and further studies are needed to clarify whether insulin excess has either a beneficial or rather detrimental effect on bone health. The incomplete understanding of the mechanisms underlying diabetic bone disease makes it difficult to develop reliable tools for fracture risk prediction. To date, no single method is deemed optimal for predicting all fracture outcomes in patients with diabetes[32]. Fracture history and risk factors should be assessed in older patients with DM, and measurement of BMD is recommended, if appropriate for the patient's age and gender[8]. Caution should be used with antidiabetic drugs known to negatively affect bone health, such as TZDs and insulin in patients with T2D. Healthcare professionals involved in the management of T2D patients undergoing bariatric surgery should be aware of the possible detrimental effects on bone health, and implement appropriate nutritional strategies. Due to the lack of randomized

clinical trials to evaluate the efficacy of antifracture drugs in diabetes, and observational data indicating similar efficacy in those with or without diabetes, such drugs should be used according to existing indications.

Future studies should focus on the mechanisms underlying diabetic bone disease, and on preventative and treatment strategies to implement in order to reduce the morbidity associated with fractures in this frail population.

Table 2 Effects of diabetes and prediabetes on bone health

	T1D	T2D	Prediabetes
Fracture risk	↑↑	↑	?
Bone mineral density	↓	↔ or ↑	↔ or ↑
Bone turnover	↓	↓↓	↓?
Bone marrow adiposity	↔	↑	↑?
Bone matrix - AGEs	↑	↑	?
Microarchitecture/geometry	↑ cortical porosity	↑ cortical porosity	↓ trabecular and cortical bone size

AGEs: Advanced glycation endproducts; T1D: Type 1 diabetes; T2D: Type 2 diabetes; ↑: Increased; ↓: Decreased; ↔: Similar to healthy controls; ?: Unknown.

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MINIREVIEWS

Development of therapeutic options on type 2 diabetes in years: Glucagon-like peptide-1 receptor agonist's role intreatment; from the past to future

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Abstract

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia. Type 2 diabetes (T2DM) accounting for 90% of cases globally. The worldwide prevalence of DM is rising dramatically over the last decades, from 30 million cases in 1985 to 382 million cases in 2013. It's estimated that 451 million people had diabetes in 2017. As the pathophysiology was understood over the years, treatment options for diabetes increased. Incretin-based therapy is one of them. Glucagon-like peptide-1 receptor agonist (GLP-1 RA) not only significantly lower glucose level with minimal risk of hypoglycemia but also, they have an important advantage in themanagement of cardiovascular risk and obesity. Thus, we will review here GLP-1 RAsrole in the treatment of diabetes.

Key words: Incretin-basedtherapy; Incretin mimetics; Glucagon-like peptide-1 receptor agonist; Dipeptidyl peptidase-4 inhibitor

Core tip: The prevalence of type 2 diabetes and its complications rising dramatically over the last years. It is well known that diabetes and its complications; especially cardiovascular complications lead to increased morbidity and mortality. Treatment options for diabetes have increased as the pathophysiology was understood. We discuss the incretin-based therapy, especially Glucagon-like peptide-1 receptor agonistsand the beneficial effects on comorbidities besides glucose lowering effect.

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INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia. Depending on etiology; decreased insulin secretion, decreased glucose utilization and increased glucose production contribute to hyperglycemia[1]. There are several distinct types of DM. Type 2 DM (T2DM) accounting for 90% of cases globally[2]. T2DM demonstrate insulin resistance in peripheral tissues, defective insulin secretion particularly in response to glucose stimuli and increased glucose production by the liver as three cardinal abnormalities[2]. Increased lipolysis in fat tissue, increased production of glucagon, incretin hormone deficiency and resistance, increased renal tubular glucose reabsorption and central nervous system role in metabolic regulation also contribute to the pathophysiology of T2DM[3]. The worldwide prevalence of DM is rising dramatically over the last decades, from 30 million cases in 1985 to 382 million cases in 2013[1]. It's estimated that 451 million people had diabetes in 2017[4]. As the pathophysiology was understood over the years, treatment options for diabetes increased. Thus, we will review here Glucagon-like peptide-1 receptor agonist (GLP-1 RAs) role in the treatment of diabetes. We aimed to summarize not only their glucose lowering effect but also their efficacy on the comorbidities come along with diabetes, such as obesity and cardiovascular disease (CVD).

We selected the articles by searching an electronic database (PubMed) with the following terms; glucagon-like peptide 1 agonists, glucagon-like peptide 1 agonists and CVD, glucagon-like peptide 1 agonists and obesity, dipeptidyl peptidase-4 (DPP-4) inhibitors. The articles not related to diabetes, the case reports, abstract only, comments and conference papers were excluded. Only studies in English language were included. Cardiovascular safety trial of each molecule (GLP-1 RA and DPP-4 inhibitor) were also included. All the included articles reviewed for full text.

ROLE OF INCRETINS IN GLUCOSE HOMEOSTASIS

Glucose is the most important physiologic substance involved in the regulation of insulin secretion from the pancreas[5-7]. Glucose has a dose-dependent effect on the beta cells. It's well known that oral glucose administration has a greater effect on insulin release than intravenous glucose administration[8-10]. Known as the incretin effect. In a study, insulin secretion was detected 26% lower in response to IV administration than oral administration[10]. This increased response to oral glucose shows that glucose absorption from the gastrointestinal tract may cause secretion of some hormones which have an effect on B-cell sensitivity[5-10]. GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are the major incretin hormones in humans[11]. GIP is produced in the K-cells and these cells are located predominantly in the proximal parts of the intestine, especially in the duodenum. GLP-1 is produced by the L-cells which distally situated especially in the ileum. L-cells also found in the colon in high density[12]. Both K-cells and L-cells can be situated throughout all parts of the intestine. It's also detected that there is a population of cells which contain both GLP-1 and GIP[13]. Secretion of incretin hormones is correlated with food intake and the driving factor is the presence of nutrients in the lumen, not distension since loading of water does not cause a significant increase in GLP-1 and GIP concentrations[14-16]. The incretins are cleaved by the enzymeDPP-4 and lose their biologic activity[1,2].

INCRETIN EFFECT IN DIABETES MELLITUS

The incretin effect found substantially reduced or even absent in patients who have T2DM and hyperglycemia[17-19]. As the fasting plasma glucose level increases above the level defining diabetic state (126 mg/dL), incretin effect seems to start to reduce[20].

This reduced effect is universal with the possible exception of East Asians[21].

T2DM patients almost completely lost response to GIP[22]. Because much of the incretin effect in healthy individuals is mediated by GIP, lack of activity may explain the reduced incretin effect in T2DM patients[20]. Besides this; the substantial insulinotropic activity of GLP-1 retains in these patients and GLP-1 activity related to dose and concentration, linearly[23-25]. However, GLP-1 insulinotropic effect is reduced compared with healthy individuals; a result of reduced B-cell mass, most likely[25,26]. The effects of GLP-1 on appetite, gastrointestinal motility, food intake, and suppression glucagon secretion are retained[23,27]. Parenterally given GLP-1 significantly increase insulin secretion, suppress glucagon secretion and normalize glucose concentration[22].

INCRETIN-BASED THERAPY IN T2DM

As the research in the field of diabetes progressed and the pathophysiologic processes were understood, new therapeutic options were invented. Incretin-based treatment is one of them. Practically, DPP-4 inhibitors or GLP-1 RAs can be used for this therapeutic approach. Besides that, GLP-1 gene transferring has studied in animal models and it was showed that GLP-1 gene transfer may be an alternative to GLP-1 infusion or multiple daily or weekly injections, in the future[28,29].

There are several GLP-1 agonists used in daily clinical practice. Some of them are listed below in Table 1[30]. All of the GLP-1 agonists administered by subcutaneous injection but semaglutide also has an oral form[31]. On the other site, all of the DPP-4 inhibitors are given orally. Alogliptin (25 mg, once daily), linagliptin (5 mg, once daily), saxagliptin (5 mg once daily), sitagliptin (100 mg, once daily) and vildagliptin (50 mg, twice daily) are the DPP-4 inhibitors used in daily clinical practice[32].

GLP-1 RA and DPP-4 inhibitors are important therapeutic options for patients with T2DM[33]. European Association for the Study of Diabetes and the American Diabetes Association recommend these agents as the second line for the treatment of T2DM[34]. The glucose-lowering effect of these agents with minimal risk of hypoglycemia is well studied. They also have a favorable effect on body weight and blood pressure[35-43]. The efficacy of GLP-1 RAs is greater than DPP-4 inhibitors, in general[44]. While patients who receive GLP-1 RA experience significant weight loss, the effect of DPP-4 inhibitors on body weight is neutral[44,45]. In a systematic review of comparative effectiveness of GLP-1 RAs, it was concluded that GLP-1 RAs are similar or more effective than oral glucose-lowering agents in improving glycemic parameters. In the same review, GLP-1 RAs found to provide similar or less decrease in Hba1c level compared with insulin therapy, with less hypoglycemia[46].

CARDIOVASCULAR OUTCOMES OF INCRETIN-BASED THERAPY IN T2DM

After the meta-analysis, published by Nissen and colleagues in 2007, suggesting that rosiglitazone (an anti-diabetic agent) was associated with increased risk of myocardial infarction (MI) among T2DM patients, United States Food and Drug Administration (FDA) mandated the conduct of large, randomized, placebo-controlled cardiovascular safety trials for all new anti-diabetic agents[47,48]. FDA defined the standards of these studies[48]. Several large randomized controlled trials (RCT) have been completed since that time. The RCT examined saxagliptin for cardiovascular safety established an unexpected increased risk of hospitalization for heart failure among patients randomized to saxagliptin[49,50]. The RCT's examined other DPP-4 inhibitors didn't establish such results[51-59]. Vildagliptin haven't been studied in RCT for examining cardiovascular safety.

Because the GLP-1 RAs promote weight loss, reduce blood pressure, decrease myocardial and vascular inflammation and decrease platelet aggregation behind their effect on blood glucose level, they thought to reduce cardiovascular risk[60,61]. Cardiovascular safety was established for the whole class in the RCTs of cardiovascular outcomes with GLP-1 RAs (liraglutide, semaglutide, lixisenatide, and extended-release exenatide). Besides that, the results for cardiovascular efficacy was mixed[62-65]. Among these RCTs in two studies (SUSTAIN 6 and LEADER) a significant reduction in three-point major adverse cardiovascular events (non-fatal stroke, non-fatal MI and cardiovascular mortality) was shown[63,64]. Questions emerged after these varying findings about the generalizability of the trials to the drug class. The data available from the RCTs of cardiovascular outcomes with GLP-1 RAs was synthesized in a meta-analysis to examine the overall effect on cardiovascular efficacy and

Table 1 Glucagon-like peptide-1 receptor agonist

Drug	Administration	Phase 3 clinical trial
Exenatide	Twice daily (5 μg or 10 μg)	Amigo
Liraglutide	Daily (0.6 mg or 0.8 mg or 1.2 mg)	Leader
Exenatide ER	Weekly (2 mg)	Duration
Lixisenatide	Daily (10 μg or 20 μg)	Getgoal
Dulaglutide	Weekly (0.75 mg or 1.5 mg)	Award
Semaglutide	Weekly (0.5 mg or 1.5 mg)	Sustain
Albiglutide	Weekly (30 mg or 50 mg)	Harmony

safety[66]. According to this meta-analysis; cardiovascular safety appointed for all GLP-1 RAs, use of GLP-1 RAs was associated with a significant 10% relative risk reduction for the three-point major adverse cardiovascular events, also associated with risk reduction in cardiovascular mortality of 13% and all-cause mortality of 12% compared with placebo[66]. Likewise, it was determined in a retrospective epidemiological study that patients who treated with exenatide were less likely to have CVD, CVD related and all-cause hospitalizations[67]. The trial of cardiovascular outcomes in patients with T2DM on albiglutide was completed in 2018 and it was shown that albiglutide was both as safe as placebo in terms of cardiovascular outcomes and superior to placebo in efficacy even in short period of time (1.6 years)[68].

The effect of incretin-based therapy on atherosclerosis was examined in a meta-analysis of RCTs. Incretin-based therapy showed significant improvement of carotid intima media thickness in the long term (2 years) but it has failed to show this effect in 1 year follow up[69].

Certain experimental studies examined incretin receptors on vascular smooth muscle cells and showed their role in causing atherosclerosis[70,71]. Also, the efficacy of DPP-4 inhibitors on improvement of endothelial function was shown[72].

It was generally shown in observational studies that there is a relationship between hyperglycemia and CVD but reduced CVD by reducing hyperglycemia haven't confirmed in clinical trials[73-78]. Moreover, one trial terminated early because in the intensive glycemic treatment arm, all-cause mortality was increased and, in each subgroup, it was associated with hypoglycemia[74,79]. It's an important point that GLP-1 RAs and DPP-4 inhibitors have a glucose lowering effect with less hypoglycemia (GLP-1 RAs are more potent than DPP-4 inhibitors)[35-44].

According to the recent meta-analysis, GLP-1 RAs are seemed to be cardio-protective as a whole class[80]. They have pleiotropic actions on cardiovascular risk factors with a direct effect on the cardiovascular system (Table 2)[69,80,81].

A recently published review in which several preclinical studies were examined, it was concluded that using GLP-1 agonists improve functional outcome after ischemic stroke. It's unknown whether these results are valid for humans in clinical practice[82].

THE EFFECT OF INCRETIN-BASED THERAPY ON BODY WEIGHT

Obesity is an important risk factor and comorbidity of T2DM, and it also elevates cardiovascular risk. Obesity must also be managed for effective treatment of T2DM. GLP-1 RAs were studied in several trials and it was established that GLP-1 RAs cause significant weight loss in T2DM patients with obesity[46,83,84]. The effect of DPP-4 inhibitors on weight in neutral[44,45,83]. Although GLP-1 RA's cost and administration route may be limitations for generalized acceptance, they may also offer a reasonable alternative choice for obese patients (liraglutide 3 mgr.) without diabetes who don't achieve weight-loss goals with lifestyle modification alone[84].

CONCLUSION

T2DM is a chronic disorder which comes along with several comorbidities like obesity, CVD, kidney disease, hypertension, *etc*. As long as the pathophysiologic process of DM was understood over the years, several new therapeutic options emerged. Individualizing care gained importance in the last years for the management of DM. It's important to manage obesity, hypertension, hyperlipidemia

Table 2 Cardiovascular effect of glucagon like peptide-1 receptor agonists

Anti-atherosclerotic effect	Decrease matrix metalloproteinase 2; decrease vascular smooth muscle cell proliferation
Improves endothelial function	Increase nitric oxide-induced vasodilation; decrease oxidative stress
Anti-inflammatory effect	Suppress human macrophagesby inhibition of protein kinase C
Decrease infarct/injury size	Decrease glucose-induced apoptosis; decrease intracellular calcium overload
Modifies risk factors	Improve glycemic control; decrease body weight; decrease blood pressure; decrease low-density lipoprotein

and total cardiovascular risk together with lowering glucose level with minimal risk of hypoglycemia. GLP-1 RAs not only significantly lower glucose level with minimal risk of hypoglycemia but also, they have an important advantage in the management of cardiovascular risk and obesity.

All GLP-1 RAs are administered parenterally but semaglutide also can be given orally by now. Besides that, it was showed that GLP-1 gene transfer may be an alternative to GLP-1 injections, in the future.

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MINIREVIEWS

Competences for self-care and self-control in diabetes mellitus type 2 in primary health care

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Abstract

The purpose of the guidelines of self-care and self-control of type 2 diabetes mellitus proposed by the Brazilian Ministry of Health is to strengthen and qualify users and health care professionals through the integrality and longitudinality of care with this disease. This article aims to present the self-care and self-control of people with type 2 diabetes mellitus in objective terms, taking into account the current recommen-dations based on scientific evidence and also from the subjective point of view, that is, emphasizing the aspects related to experience and subjectivity of these people. Next, we present the essential skills for self-care and self-control of users and professionals working in primary health care.

Key words: Diabetes mellitus type 2; Self-care; Primary health care

Core tip: This article aims to present the self-care and self-control of people with type 2 diabetes mellitus under the objective point of view, taking into account the current recommendations based on scientific evidence, and also from the subjective point of view, emphasizing the aspects related to experience and the subjectivity of these people. Next, we present the essential skills for self-care and self-control of users and professionals working in primary health care.

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INTRODUCTION

Type 2 diabetes mellitus (DM2) is currently a global epidemic. Incidence and prevalence are increasing in developing and newly industrialized countries. Its impact on public health worldwide consists of social problems, such as reduced quality of life and reduced survival of people with DM2, and economic problems, such as reduced productivity and high treatment costs[1].

Among the several types of diabetes, DM2 accounts for 90%-95% of cases. It is characterized by an imbalance of the metabolism of carbohydrates, lipids, and proteins and is associated with a deficiency in the secretion and/or action of the hormone insulin secreted by the pancreas. As a consequence, there is a decrease in tissue sensitivity or insulin responsiveness and an increase in blood glucose levels. As a way to combat the complications of hyperglycemia, the goal of treatment is to achieve normal blood glucose levels[2].

An individual with DM2, if not properly treated and controlled, may develop acute complications, such as hypoglycemia, hyperglycemia, and chronic progressive changes in the retina, kidneys, and peripheral nerves, and may trigger atherosclerotic lesions of the heart, brain, and peripheral members[2].

Due to the requirement of constant glycemic control, chronicity, and lack of cure, the person with DM2 remains linked to the health system for decades and needs continuous attention focused on the integral care provided by family health and family support nucleus in actions to promote, monitor, and prevent complications of DM2. The complexity of care for people with DM2 requires an interdisciplinary approach with health professionals open to dialogue and willing to plan appropriate consultations and interventions to the specific needs of people with DM2 that are centered on the actions of self-care and glycemic control[3].

The purpose of the guidelines of self-care and self-control of DM2 proposed by the Brazilian Ministry of Health is to strengthen and qualify care to users and to health professionals through the integrality and longitudinality of care with this disease. Thus, users with DM2 and health professionals who work in primary care should have competencies for self-care and self-control in this pathology. According to Cyrino[4], competence is a person's ability to mobilize different knowledge to master specific problematic situations faced in daily life and to develop attitudes and practices.

To achieve the goals detailed by the Strategy for the Care of People with Diabetes Mellitus published in the Basic Care Book number 36 of the Ministry of Health[5], it is proposed that primary care professionals adopt the approach of person-centered health with DM2[6,7]. This approach allows primary care professionals to use objective methods such as anamnesis, physical examination, and laboratory tests as well as subjective methods for analyzing and understanding feelings and ideas, the effects of DM2 on one's life, and expectations of treatment[8]. Thus, health professionals, in addition to the epidemiological and pathophysiological knowledge of DM2, must understand the psychosocial aspects of people; have pedagogical skills, communication skills, listening, understanding, and negotiating with the interdisciplinary health team[9]. On the other hand, people with DM2 must have the skills and autonomy to assume self-care and self-control.

In this way, this article aims to present the self-care and self-control of people with DM2 under the objective point of view, taking into account the current recommendations based on scientific evidence, and also from the subjective point of view, emphasizing the aspects related to experience and the subjectivity of these people. Next, we present the essential skills for self-care and self-control of users and professionals working in primary health care.

SELF-CARE AND SELF-CONTROL OF PEOPLE WITH DM2 UNDER THE OBJECTIVE POINT OF VIEW

Self-care and self-control are shown as possibilities for the person with DM2 to reduce the repercussions caused by the disease. Self-care is understood as the set of activities that involve dietary, corporal, drug, and glucose monitoring practices performed by

the patient to promote his health, minimizing hypoglycemia and excessive weight gain. Self-control is the monitoring of the conditions of health and disease by the subject himself, according to objective parameters obtained by biochemical tests of blood glucose and glycohemoglobin[4].

The main goal of self-management and self-control of people with DM2 is metabolic control and includes tests for fasting blood glucose and glycated hemoglobin[10]. Glycated hemoglobin is the gold standard that provides an index of glycemic control for 6 to 12 wk[11], dosed quarterly until reaching control and then every 6 mo [3]. In order not to increase the risk of hypoglycemia or other complications of treatment, the patient aims to reach values lower than or equal to 6.5 a 7.0[1,10] .

The monitoring of the annual lipid profile (triglycerides, total cholesterol and its fractions) is of fundamental importance for the control of DM2, since this indicator is associated with cardiovascular diseases, obesity, and arterial hypertension, which may favor the development of insulin resistance and metabolic syndrome[10].

Blood pressure should be measured query, with ideal targets for systolic pressure < 130 mmHg and diastolic blood pressure of < 80 mmHg. In addition, ophthalmologic evaluations, urinary albumin excretion, and comprehensive examination of feet should be made after the diagnosis in order to avoid retinopathies, nephropathies, ulcers, and amputations, respectively[10].

For self-care and self-management of DM2 in order to maintain glycemic control, to avoid acute complications, and to reduce the risk of long-term complications, it is recommended that people with D2M regularly participate in medical appointments and care health monitoring of biochemical and blood pressure tests, weight and abdominal circumference measurements, as well as evaluation of drug treatment, diet, and physical activity[10]. But not enough people attend consultations regularly, making necessary adherence to self-care and self-control, which begins with the incorporation of dietary practices and physical activity prescribed by professionals in primary health care.

Behavioral modification related to dietary practices is a requirement imposed by the disease, and the selection of foods and fractionation of meals, energy consumption for the purpose of reducing or avoiding weight gain, and decreased consumption of trans and saturated fats, cholesterol, and sodium should be reviewed. These modifications improve insulin resistance and decrease plasma glucose, abdominal circumference, and visceral fat levels by improving the metabolic profile with reduced levels of low-density lipoprotein, triglycerides and increased high-density lipoprotein[12,13].

As for the body practices, 150 min per week of aerobic physical activity of moderate intensity is recommended. These activities include walking, cycling, running, swimming, and dancing, preferably three times a week, provided that there is no medical contraindication. Exercise improves glycemic control, reduces glycated hemoglobin and cardiovascular risk, contributes to weight reduction, and improves self-esteem[1]. When associated with changes in eating habits, important components of maintenance of glycemic control and weight loss programs are important[10].

When the desired glycemic levels have not been reached after the use of dietary measures and exercise, antidiabetic medicinal products should be used. Some people with DM2 will require insulin therapy soon after the diagnosis and many throughout the treatment[1].

SELF-CARE AND SELF-CONTROL OF PEOPLE WITH DM2 FROM THE POINT OF VIEW OF THEIR EXPERIENCE AND SUBJECTIVITY

The subjects should be prepared and motivated from diagnosis to take the treatment. Although people are adaptable to the realization of self-care and self-control, compliance with these practices is not so easy for most people with DM2. At the moment the disease is discovered, the structure of daily life and the forms that sustain it are interrupted. First, ruptures occur with the new limits of normal daily life, as behaviors performed before being sick must be changed, potentially leading to deep breaks in one's biography and self-concept. Finally, in the various segments of daily life, due to the care they need, people with DM2 must mobilize resources to face the changed situation[14].

At this stage, the person may be faced with the obstacle of food (one of the most difficult to overcome), the non-acceptance of DM2, fear of insulin, a lack of knowledge about the disease and self-care, the need for commitment and discipline, unfavorable financial situation, and the emotional component involved with feeding[4,15].

Thus, living with the limits imposed by a diagnosis of DM2 is full of conflicts,

ruptures, questioning, and nonconformity. Knowing the experience and the subjectivity of these people, of the meanings attributed to them by the disease, favor the identification of limiting aspects and the way in which they articulate different aspects that interact in the production of self-care and consequently in self-control.

Some studies seek to approach the subject and his experience with the disease, taking into account the vision and participation in the management of care[16] treatment adherence[17], the involvement of friends and family in the treatment[18], as well as support or self-help groups and social networks[19].

The experiences of individuals with the disease are socially shared, and their analysis is possible when expressed as subjective narration, that is, the conscious or unconscious mind of people. Thus, one approach to the subjective questions is the social representations, understood as complex subjective productions, because they have an impersonal aspect, in the sense of belonging to all; they are the representation of others, belonging to other people or to another group and are also a personal representation, perceived effectively as belonging to the ego[20].

Social representations play a fundamental role in the dynamics of social relations by understanding and explaining reality, guiding behaviors and practices, explaining and justifying behaviors in a situation or with partners, and defining identity[21]. The author emphasizes a clear relationship between social representation, identity, and the behavior of people.

It is necessary, then, to understand the social representations in which people with DM2 are anchored and the social identities that underlie them. With this intention, Amorim *et al*[22,23] investigated the identity representations of users with DM2 of a basic health unit, located in Belo Horizonte, Brazil. From the guiding question: "what comes to mind when I speak, I am diabetic", the speeches were categorized and interpreted by the technique of content analysis and theories of social representation and social identity. As a result of this research, some people with DM2 studied are considered normal, others accept the disease, there are those who are dissatisfied, and others lead a life with difficulty. The "normal" participants coexist with illness in a positive way and minimize the impact of DM2 on their identity when they experience the process of normalization of illness and care, in which the changes and adaptations required to the treatment become routine and are incorporated into daily life. Participants who "accept the disease" do not ideally accept their chronic illness. The ideal acceptance of a disease consists of a psychological state in which the illness is part of the perception of reality and is not perceived as a factor that limits the person. The unfavorable attitudes of the "non-conforming" participants, the information about the risks of the disease and the image of danger that they elaborate on the illness, help to understand the sense that the participants attribute to the "diabetic being". Participants who think that they "have a life fraught with difficulties" face obstacles in taking care of themselves, culminating in negative feelings and attitudes about the disease. It is possible that people with "distressed" DM2, not feeling confident about the future and facing adversity, do not make sustained efforts to achieve their goals, neglecting self-control and self-care. Thus, the obstacles faced by participants who think they are "accepting the disease, think they are "discontented" and "have difficulties" when they put into practice self-care, especially in relation to food, should be understood by the team that works in primary health care, biomedical logic[22,23].

The social representations about the feeding of these people with DM2 were investigated. Some respondents indicated that the person with DM2 should eat healthy. Others relied on the quality of food, representing it as "eating vegetables and fruits" and "avoiding sweets." There are still those whose speech was based on eating little, worrying about the quantities of food eaten. There are those who represented eating as not eating too much, focusing on the frequency of feeding, as they consider that breaking down the food in many meals is not appropriate. Others focused their speech on selective food intake, specifically those that do not harm the body. Finally, others considered that food does not imply following a specific diet[24,25].

In analyzing the social representations of the diet of people with DM2 as they represent their identity and its implications for glycemic control, it was found that adequate HbA1c values of the participants considered to be "normal" are adequate and are related to the actions of self-care, allowing to infer about the effectiveness of feeding. Proper nutrition improves insulin resistance, decreases the levels of plasma glucose and waist circumference, and improves metabolic visceral fat profile of triglycerides and cholesterol. People who think they have a normal life represent eating in the categories eating healthy, eating reduced, eating vegetables and fruits, and divert from sweets[26].

The particular way in which the participants who judge "accepting the disease", "having difficulties", and "nonconformists" perform the self-care related to the alimentary practice is derived from the different processes of subjectivation in which each one of them relies on to construct its social representations on the identity and

feeding and consequently have mean values of HbA1c above normal values. Participants who "accept the disease" are based on "no" to represent their diet: do not eat too much and do not eat at all. Participants who "have a life with difficulties" represent their eating in the negative categories: do not eat too much, do not eat at all, and do not follow the diet. A participant who represents eating in eating vegetables and fruits, unlike normal people, has difficulty putting their thinking into practice. "Nonconformists" represent their food in the negative categories: not eating much and not eating at all. Two participants represented their diet in eating vegetables, but in practice they eat the forbidden foods[26].

USER ABILITIES REQUIRED FOR SELF-CARE AND SELF-CONTROL

The adherence of people with DM2 to self-care and self-control therapies is still low in developed countries, with around 50%, and it is estimated that in developing countries this percentage is lower, compromising the effectiveness of the treatment[27].

Due to the complexity of self-care and self-control in DM2, Cyrino[4], based on the literature and the joint evaluation with specialists in the area, defined a list of competencies required by people with DM2 to conduct the treatment. A total of 47 skills classified in the fields of knowledge - technical dimension of illness and know-how-practical dimension were elaborated, contemplating the general notions about DM2 and its complications, glycemic self-control, self-care in acute complications, and self-care in drug treatment.

In addition to the knowledge and skills portrayed in the competency roll, it is necessary to consider the attitudes and the necessary awareness that influence the user's behavior and consequently the health improvement[28]. For Sousa *et al*[29] the increase in knowledge when correlated significantly with attitude is associated with the predisposition to assume self-care.

In order to verify the knowledge and attitudes of people with DM2 who participated in a self-care education program, Rodrigues *et al*[30] used the instruments validated for use in Brazil, the Diabetes Knowledge Questionnaire and the Diabetes Attitude Questionnaire. The Diabetes Knowledge Questionnaire covers issues related to knowledge about basic physiology, hypoglycemia, food groups and their substitutions, management of DM2 in the course of another disease, and general principles of care. The Diabetes Attitude Questionnaire presents issues that include stress associated with DM2, treatment receptivity, treatment confidence, personal efficacy, health perception, and social acceptance[30]. After applying these two instruments, Rodrigues *et al*[30] concluded that although participants had a good level of knowledge, they still did not change their attitude towards coping with the disease.

As knowledge does not always lead to a change in attitude towards the daily demands that treatment imposes on daily life, it is necessary to listen to the feelings, the hidden complaints of the person with DM2. In this line of reasoning, according to which the subjective perspective of the patient is considered and valued, Cyrino[4] developed a study with the objective of knowing the skills developed by users with DM2 of a health service for self-care and self-control in DM2, from their testimonials. A set consisting of 98 competences derived from the knowledge of the experience of those who live the disease was raised, distributed in the fields of knowledge, know-how and know how to be and know how to communicate. The competences related to psychological and social difficulties to self-care were expressed by people with DM2, showing differences in conceptions about the disease and care among health professionals and their patients[4].

To know the skills of people with DM2 for self-care, a scale containing 27 items was developed and validated, assessing physical abilities (vision, touch, dexterity, and manual ability), mental abilities (reading, attention, memory, discrimination and classification of knowledge within certain situations, judgment of certain situations, and conceptualization of a system of actions to act in certain situations), and motivational and emotional capacities[31,32]. This scale of identification of the competence of the person with DM2 for self-care (ECDAC) allows a qualitative and quantitative evaluation of the capacities of people with DM2 for the exercise of the self-care actions necessary for the maintenance of health[33]. The deficiencies in the physical, mental, and motivational capacities pointed out by the ladder provide subsidies for the planning and implementation of intervention methods based on the person-centered approach, favoring a global and individualized assistance practice.

ABILITIES OF HEALTH PROFESSIONALS NECESSARY FOR SELF-CARE AND SELF-CONTROL

The complexity involved in self-care and self-management of people with DM2 requires an approach of interdisciplinary care with family health strategy professionals and family health support nucleus open to dialogue, with the ability to communicate, employing person-centered care and valuing the objective and subjective aspects. In this sense, it is recommended that these professionals overcome the biomedical paradigm of being the experts responsible for curing diseases and help people achieve health and normality[34], through a systemic and comprehensive view of the individual, family, and community in the promotion, specific protection, rehabilitation, and care, working with creativity and critical thinking[35].

Within this context, Torres *et al*[36] developed a training program for primary health care professionals for DM2 education. The competency role required by people with DM2 to conduct the treatment developed by Cyrino[4] was adapted and applied, including questions related to pathophysiology, nutrition, physical exercise, and insulin therapy, to assess the knowledge of the professionals of basic health units concerning self-care. The difficulties identified by the professionals pointed out the need for continuing education and supported the planning and development of the educational program in DM2. For the professionals' training, the work workshops modality was used to motivate the exchange of experiences and knowledge and reflection on the obstacles they experienced in their daily lives when caring for people with DM2.

In order to overcome these obstacles, primary health care professionals should value the individual's own experience, his subjectivity, his conceptions of illness[17,37], as well as his beliefs[38,39]. By living the disease in their everyday experience, the subject mobilizes knowledge and attributes meanings to master specific problematic situations, developing the skills (*i.e.* attitudes and practices related to self-care and self-control in DM2)[4].

Thus, in practicing the person-centered approach, health professionals should have the ability to distinguish the disease from the experience of the disease, so that they find methods of health promotion and preventive care more appropriate to the world of the person, varying according to the person, the moment, and the question of health care. The use of qualitative methodologies provides an in-depth understanding of the broad context of understanding the subjective issues of the person being treated[40].

After this stage, health professionals and the person in care should work together on a joint problem management plan to define goals, care priorities, and care roles[40]. To apply problem solving requires the ability to recognize the problem, ability to generate alternative solutions, and insight to select an appropriate option[41].

This pathology requires a holistic view of the health-disease process by the health professional, with the apprehension of the subject in its biopsychosocial dimension, integrating preventive, promotional, and coordinated assistance actions, for a more comprehensive understanding of the disease and to favor more effective interventions and accession. A structured intervention in multidisciplinary teams for the effective development of programs of education and health promotion of these patients and relatives is fundamental[42].

The abilities for self-care and self-control in DM2 of users and health professionals are illustrated in Table 1.

CONCLUSION

People with diabetes face obstacles, often filled with social representations. The rules to be followed by these individuals should be adapted to deal with the restrictions, prohibitions, and difficulties that act as contingency to put into practices the desired behavior.

So, to ensure the effectiveness in meeting the people with DM2, the experience of listening, the ability to communicate and understand the subjective aspects of people and the context in which they operate, is a key skill to be developed by health professionals in primary health care. A change in the behavior of health professionals is possible to be motivated by the institution in which it is linked as well as by an internal involvement mediated by the self-conscience of its professional activity.

On the other hand, people with DM2 should have knowledge about the disease, motivation and positive attitude from diagnosis to self-control and self-care, and support from the social network and family. Participation in the educational process should be active, this essential condition to ensure effective results for better

Table 1 Abilities for self-care and self-control in diabetes mellitus type 2

Abilities for self-care and self-control in diabetes mellitus type 2	User	Health professionals
	Physical abilities	Interdisciplinary approach
	Mental abilities	
	Motivational abilities	Person-centered approach
	Emotional abilities	

acceptance of the disease, treatment adherence, metabolic control, and quality of life.

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ORIGINAL ARTICLE

Retrospective Study

Comparison of awareness of diabetes mellitus type II with treatment's outcome in term of direct cost in a hospital in Saudi Arabia

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Abstract

BACKGROUND

Saudi Arabia is among the top 10 countries with the highest prevalence of diabetes. Cost of prevention and the indirect cost must be calculated to increase the awareness of society and to emphasize disease prevention and limit further complications.

AIM

To understand the importance of awareness and the impact on the expenditure of diabetes mellitus and treatments outcomes.

METHODS

A prospective descriptive and comparative survey was carried out among patients with diabetes mellitus in Saudi Arabia.

RESULTS

One hundred and one participants were included in the study of which 40% were female and one third were above the age of 50. The mean of the first HbA1c reading was 6.95, and the median was 7. The mean of the second reading of HbA1c was 7.26, and the median was 7. The mean body mass index was 32.1, and the median was 30.9. The average yearly cost of the medication was 995.14 SR. Comparing participants who think that a healthy low-sugar diet can affect blood sugar with those who do not, showed a statistically significant difference when cost was considered (*P* value = 0.03). Also, when comparing the group of participants who know when to take their oral hyperglycemic medicine and their yearly direct cost and those who do not know when to take it, by using independent sample T test, showed significant statistical difference (*P* value = 0.046).

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CONCLUSION

It is essential for the governments to invest in ways to prevent and help in the early detection of such an expensive disease by performing national screening and education programs. Many pharmaco-economic studies can be done to help the decision-maker in our hospitals think about strategies to help the patient to be physically fit by offering gymnasium or places to walk or contract.

Key words: Middle East; Diabetes; Lifestyle; Hypoglycemic

Core tip: This study evaluated diabetic patients' compliance to hypoglycemic medications, dietary control, and their impact on cost effectiveness. It shows that lack of compliance has negative impact on patients' therapeutic outcomes, which in turn affects cost of medications and management of diabetic complications. Further educational campaigns are important among diabetic patients in order to reduce negative health consequences and economic outcomes.

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INTRODUCTION

Diabetes mellitus (DM) is a non-communicable metabolic degenerative disorder associated with a high risk of chronic complications and comorbidities[1]. Obesity and many other inabilities could lead to diabetes if they happen in pre diabetic patients[2].

Around 422 million people are diagnosed with DM, and 80% of diabetes deaths occur in low- and middle-income countries. Approximately 1.5 million deaths in 2012 were directly caused by diabetes worldwide, while 2.2 million deaths were caused by higher blood glucose level due to the increases of risk of cardiovascular disease in the same year. The prevalence of the disease increased dramatically many fold during the last 3 decades, aligning with the increase of prevalence of obesity, overweight, and physical inactivity[3]. If no drastic actions are taken, the number of people living with diabetes is expected to reach 552 million by 2030[4-6]. Cost of prevention and indirect cost must be calculated to increase the awareness of society and to emphasize the importance of disease prevention and limiting further complications[7]. Saudi Arabia is among the top 10 countries with the highest prevalence of diabetes[8-10]. Early prevention can limit the complications and their impact on the person's quality of life, reducing the cost with positive impact on the Health system[11]. Most countries spend between 5% and 20% of their total health expenditure on diabetes[12,13]. Fourteen percent of the population in the Eastern Mediterranean Region has diabetes[14], approximately 35 million people. The expected prevalence of diabetes in Middle East and North America (MENA) will be 60 million in 2030[15,16].

The sixth edition of the International Diabetes Federation Diabetes Atlas reports that only 2.5% of global health expenditure on diabetes is spent in the MENA Region[17]. The anticipated prevalence for diabetes 2010-2030 in the Gulf countries are: United Arab Emirates 18.7%-21.4%, Kingdom of Saudi Arabia 16.8%-18.9%, Bahrain 15.4%-17.3%, Kuwait 14.6%-16.9%, and Oman 13.4%-14.9%[18,19]. The recent and rapid socio-economic development of the Gulf Cooperation Council countries has been associated with this rising prevalence.

"The prevalence of obesity in adults of 30-60 years in Saudi Arabia increased by 1.5% for women and 4.1% for men annually between 1992 and 2005. In Qatar and Kuwait, 35% and 36% of male; and 45% and 48% of female adults were found to be obese"[20]. Equally alarming are the numbers for younger age cohorts: In Kuwait, 21% of males and 18% of females aged 10-19 years were obese[21-23].

The statistics of World Health Organization in Saudi Arabia in 2016 showed that the rate of diabetes in males was higher than that in females. Also, the level of overweight females was higher than that in males, and the rate of physical inactivity

was higher among women 67.7%, while in men it was 52.1%[24].

The purpose of this study was to describe the relationship between direct medical costs and individual demographic characteristics, different regimen of treatment, and glycemic control. Here, we include the monthly cost of medications and the pharmacy average consumption of each oral hypoglycemic medication listed in the formulary. In addition, awareness of these patients of the disease and the role of lifestyle modifications in addition to oral hypoglycemic medication are explored. Lack of sufficient awareness will lead to high treatment cost with low therapeutic outcomes.

MATERIALS AND METHODS

A prospective descriptive and comparative face-to-face survey was carried out among patients with DM in Saudi Arabia. The study included both genders of patients visiting the primary care medical center. Patients aged between 35 to 75 years who were on oral hypoglycemic were selected within the inclusion criteria. Pregnant women were excluded from the study. The prices and quantities of average monthly ordering costs of the medicine were collected from the institution.

A random convenience sample of patients following up with the chronic disease clinic (CDC) were selected for this study to help ensure a representative sample. The participants were males and females from different backgrounds and educational and socio-economic levels. The total number of patients registered to follow up in December 2016 was 371, among which 196 patients were not able to come to the appointment and therefore considered as no shows. Among the remaining, 112 patients were involved in this study. The sample size for the study was calculated using raosoft online calculator (http://www.raosoft.com/samplesize.html), with a margin of error of 9%, confidence interval of 96%, and response distribution of 50%, and the population number of patients is 371 was used.

A structured questionnaire was used to collect data. The questionnaire was translated into Arabic, the national language of Saudi Arabia, to ensure proper understanding of the questions. The questionnaire was collected by the researcher. The questionnaire was divided into two parts. The first section included questions about the respondents socio-demographic data including, gender, age range, onset of the disease, medical history, and the and the regimen of the hyperglycemic medication. The second part was used to determine the level of knowledge about DM type 2 by checking the awareness of disease, their knowledge about its complications, and how far they are trying to control it by healthy diet and exercise. After finishing the data collection process, data were extracted as an Excel file, and then data were copied on SPSS (version 24, Armonk, NY, United States). Responses were coded and entered into SPSS for analysis using basic frequencies, descriptive, independent samples *t*-test.

Ethical standards for conducting the study were maintained as follows: (1) Confidentiality of all patients guaranteed; (2) Patients' information obtained from the survey was confidential; and (3) Patients can withdraw from the study at any time.

RESULTS

A total of 112 questionnaires were collected, of which 11 responses were incomplete and hence excluded from the study. At the end, a total of 101 responses out of 112 received responses were adopted for the study. Socio-demographic characteristics are listed in Table 1.

Health status of respondent

One third of the participants had only DM (30.7%) as past medical history. More than half (63.4%) suffered from DM with other cardiovascular comorbidities, and 5.9% had diabetes with other diseases.

During 2015 to 2016, the last subsequent two reading of HbA1c of intervals from 3-9 mo were recorded from patients' files, the mean of the first reading was 6.95, and the median was 7. The mean of the second reading of HbA1c was 7.26, and the median was 7. The mean body mass index (BMI) was 32.1, and the median was 30.9.

Lifestyle behavior

Among all participants, 36.6% were not doing any exercise, the remaining (n = 65) were classified according to the type of exercise they do, which was mostly walking 55.4%. About one forth (25.7%) of 952 of the people doing exercise said they do it daily, and 13% said they exercised once a week. The mean was 2.7, and the median of

Table 1 Socio-demographic characteristics

Characteristic	Frequency	Percentage
Gender		
Male	61	60.4
Female	40	39.6
Age		
30-39	12	11.9
40-49	22	21.8
50-59	34	33.7
60-69	27	26.7
70-79	6	5.9
Onset of the disease		
< 1	7	6.9
1-5	37	36.6
6-10	28	27.7
> 10	29	28.7
Regimen of treatment		
No medicine, only healthy lifestyle	2	2
Single therapy	51	50.5
Double therapy	35	34.7
Triple therapy	13	12.9

the time to exercise per week was 2. Around one third (33.7%) of the participants exercised between 30 to 59 min every time they exercised, while 36.6% did not do any exercise at all.

In their daily diet, more than half of the participants ate three meals/d (60.4%), 25.7% ate two meals/d, 9.9% ate four meals/d, 3% ate one meal/d, and 1% ate five meals/d. Concerning preferred food, 53.5% prefer mixed refined carbohydrates and complex carbohydrates, 31.7% said they prefer refined carbohydrates, 12.9% prefer protein-based diet, and 2% prefer complex carbohydrates only. About their daily consumption of dates, their answers varied between 5.9% did not eat any dates, to 1% eating 22 dates/d. The mean of their consumption was 6.12 dates/d and the median was 5.

General awareness of participants

Approximately 75% of participants believe that healthy diet can help control blood sugar level, 11.9% did not know, while 12.9% did not believe that it has an effect on blood sugar and suggested that diabetes is a result of if emotional and genetic factors. More than half of the participants (51.5%) were not following any healthy low sugar diet. As regard to exercise, 67.3% believe that it can lower blood sugar level, and 32.7% did not believe that it has any direct effect on blood sugar but did think it is good for general health. Most of the participants (93%) know when to take their oral hyperglycemic medication, while 8% did not know exactly the correct time to take their medicine either before or after food. Around half of them (45.5%) will skip their tablet if ever missed, 35.6% will take the tablet once they remember, 10.9% will double the next dose, and 7.9% said they did not have an idea what to do if ever they missed their oral hyperglycemic medications.

Regarding hypoglycemic symptoms, one third of them (28%) did not know how to deal with them, and 73% knew how to deal with them. More than half of them (63.4%) never visited a diabetic educator. Sixty-five percent said they have full awareness of the disease, while around one third of participants (34.7%) think they are not aware enough. The average yearly direct cost of the hyperglycemic medication of the participants (without any medicine used to treat its complications) was 995.14 SR. The median was 614.4SR with results of being widely distributed. Only two of the participants were not on any medicine because they do not adhere to the regimen (yearly cost is zero), and they were instead following a strict healthy diet and exercise only. The maximum yearly direct cost was 3417 SR, and this patient was taking 6 mg of Glimeperide once a day and 50 mg of Vildagliptine twice a day.

When comparing participants who think a healthy low-sugar diet can affect blood sugar level with their yearly direct cost (mean of yearly direct cost is 952.8 SR) and

those who think low-sugar diet has no effect on their blood sugar level (mean of yearly direct cost is 1334.6 SR) the difference is statistically significant. This is when using independent sample *t*-test, with *P* value = 0.03. Comparing participants who know when to take their oral hyperglycemic medicine and their yearly direct cost (the mean of direct cost = 976.7 SR) and those who did not know (the mean of direct cost = 1209.1 SR) by using independent sample *t* -test, showed significant statistical difference with *P* value = 0.046.

On the other hand, when comparing the yearly cost between the group of participants who are following low sugar diet and those who are not following such a diet, it showed no significant statistical difference by independent sample *t* -test with *P* value = 0.656. Also, there was no statistically significant in the yearly direct cost between the group of participants who think exercise can lower blood sugar level and those who think it has no effect on blood sugar with *P* value = 0.141.

Comparing male and female genders regarding lifestyle showed a statistically significant difference between the number of dates consumption with a *P* value = 0.003 by Levene's test for Equality of Variance by Independent Samples Test. Also, when comparing the type of food preferred as refined carbohydrates and the awareness of participants about the importance of a healthy diet on blood sugar level *versus* gender the *P* value = 0.004 and 0.009, respectively, by using Linear-by-Linear association Chi square test. Using the same type of test to compare gender *versus* physical activity, the *P* value = 0.002. Using Chi square test to compare gender *versus* full awareness of disease, the *P* value = 0.078. When comparing gender *versus* how to deal with hypoglycemic attack with *P* value = 0.026 by using Linear-by-Linear Association. On the other hand, there was no significant statistical difference for gender *versus* following healthy diet and visiting diabetic educator.

Awareness of a healthy lifestyle

The mean HbA1c for the second reading of the participants who said a low-sugar diet can help to decrease blood sugar level *versus* participants who said there is no effect of a low-sugar diet on blood sugar-level was 7.04 *versus* 7.98, respectively, which was statistically significance different (*P* value = 0.007) by independent sample test. On the other hand, there was no relationship between awareness of the significance of healthy diet and BMI levels. The mean BMI of the participants who said the healthy low-sugar diet can lower blood sugar level was 31.6 and the mean of those who said it has no effect on the blood sugar level was 31.8 (independent sample *t* test, *P* value = 0.951).

Thirty-eight percent of the participants were not following a low-sugar diet, although they had the awareness of the impact of a healthy low-sugar diet on blood sugar results. Eight-point nine percent of participants were not following such a diet because they did not have an idea if low-sugar diets had an effect or not. The significant statistical difference according to Pearson chi-square asymptotic significance had a *P* value of 0.001.

Regarding the awareness of the importance of exercise, the mean BMI of the participants who think exercise can lower blood sugar level was 32.05, and the mean of those who said it had no effect on the blood sugar level was 32.20 (independent sample *t*-test, *P* value = 0.695). When comparing the second HbA1c reading between people who think exercise would improve blood sugar level (the mean is 7.11) and those who think it would not (mean is 7.57), it was statistically significant (*P* value = 0.049, Levene's test for equality of variance descriptive data). Of those patients who think exercise could decrease blood sugar, 41.1% of them did not exercise, 10 of 68 exercised once/wk, and only 16 of 68 exercised daily. On other hand, 10 out of 33 who did not think exercise has an effect on blood glucose level do exercise daily for general health only, not because of its importance on blood sugar level. While 28.7% (19 out of 66) think they have full awareness of the disease, they do not think exercise can lower blood sugar level.

Visiting diabetic educator

Among participants who have visited a diabetic educator, 48.6% will skip the missed dose (18 out of 37), 32.4% will take it once remember, and 18.9% of them will double the next dose to compensate for the missed one. There was no statistically significant difference between the people who ever visit diabetic educator and their daily preferred type of food (*P* value = 0.832). Data taken from the pharmacy and supply department in the hospital where the study was conducted showed that the direct cost of diabetes is 133258620 SR.

Participants who are aware of the importance of a low sugar diet have better HbA1c (7.04) in comparison to those who do not have this awareness (HbA1c = 7.98) (*P* value = 0.007). There is, however, no significant difference in BMI between participants who have an awareness of healthy diet (31.6) and not (31.8). Both

categories are obese. On the other hand, participants who are aware of the importance of exercise have better a HbA1c result (mean of HbA1c is 7.11) in comparison to those who did not have this awareness (mean of HbA1c is 7.57) (P value = 0.049, Levene's test for equality of variance descriptive data). These data will encourage us to increase their awareness in order to give better HbA1c results.

DISCUSSION

This study explored participant awareness of DM and the importance of a healthy lifestyle (diet and physical activity) and its impact on their health from a financial and therapeutic point of view. The main past medical history among participants is diabetes with other cardiovascular diseases. Since diabetes is associated with many comorbidities, it is recommended that individuals maintain a healthy lifestyle and HbA1c levels below 7.0%[25]. The International Expert Committee recommended that persons with HbA1c level between 6.0 and 6.5% were at particularly high risk and might be considered for diabetes prevention interventions[26,27]. As mentioned in results, HbA1c score worsened instead of improving during the treatment course, which reflected some defect in the chain of treatment. United Kingdom Prospective Diabetes Study and Diabetes Control and Complications Trial demonstrated that improving HbA1c by 1% for diabetic patient cuts micro-vascular complications risk by 25%[28]. In addition to other research that has also shown that people with type 2 diabetes who reduce their HbA1c level by 1% are 19% less likely to suffer cataract, 16% are less likely to suffer heart failure and 43% are less likely to suffer amputation or death due to peripheral vascular disease[29,30]. Diabetic patients must be encouraged to lose weight, be more physically fit, and follow a healthy diet and active lifestyle to minimize their risk of complications and increase their quality of life. A high BMI score is associated with substantially shorter healthy and chronic disease-free life expectancy. Physical inactivity has been identified globally as the fourth leading risk factor for mortality. It becomes increasingly important to identify high-risk populations and to implement strategies to delay or prevent diabetes onset[31]. It is recommended to all individuals with diabetes to have physical activity as part of the therapy plan[32]. The recommendation is to exercise at least 150 min/wk. It is recommended to do at least 30 min of moderate or vigorous physical activity 5 d of the week. To lose weight or maintain weight loss, they might need to do 60 min or more of physical activity 5 d/week[33].

In this study, the results are far away from the international recommendations; participants were not following the correct duration and frequency of exercise. Studies have shown that weight loss of 5%-7% improves blood glucose control in type 2 diabetes, reduces cardiovascular risk factors, reduces insulin resistance, contributes to weight loss, and improves well-being[34,35]. Another way of lowering BMI and controlling blood sugar is to follow a healthy diabetic diet, it is one of the most important services that should be offered to diabetic patients. The recommendation is to limit refined carbohydrates and processed meals. They should focus on high fiber diet and complex carbohydrates like vegetables. Complex carbohydrates are digested slowly, thus preventing the body from producing too much insulin. Carbohydrate counting is a way to plan meals. It has a bigger impact on blood sugar levels than fats and proteins. Some studies have shown that eating too much protein, especially animal protein, may actually cause insulin resistance. A key factor in diabetes is a healthy diet that includes protein, carbohydrates, and fats[36]. According to this study's results, when compared with the recommended diabetic diet, most of the participants preferred to eat carbohydrates with a smaller number of meals. This result when compared with another study conducted in Iran in 2015, showed that consumption of 24.2 g of one type of dates (approximately two dates) at the snack time did not cause significant alterations in blood glucose level[37]. However, as sugar caused the same effect on blood glucose, these snacks may not be considered very healthy for patients with type 2 diabetes, even though they have good content of minerals, vitamins, fiber, and antioxidants[38,39].

Lack of knowledge among participants regarding hyperglycemic medicine affects the incidence of hypoglycemic reactions, which is considered as indirect cost. Unfortunately, many studies from both developed and developing countries have reported that diabetes knowledge is generally poor among diabetic patients[40-43]. Health care clinic programs to increase patients' awareness about DM and to keep them educated and motivated are essential in order to improve their understanding, compliance, and management and, thereby, their ability to cope with the disease. According to Canadian guidelines for diabetes care, they recommend that all people with diabetes who are able should be taught how to self-manage their diabetes and

offered timely diabetes education that is tailored to enhance self-care practices with comprehensive programs. Incorporate behavioral/psychosocial interventions, as well as knowledge and skills training with shared decision making, and problem-solving skills are more likely to improve a diabetic's glycemic control[44-46]. Education of diabetics is one of their rights to be offered in the healthcare system to enhance their treatment outcomes and to minimize the side effect and complications. In this study, the yearly direct cost was higher with the group of participants who had less awareness about the impact of a healthy low-sugar diet on blood sugar level and the group of participants who did not know how to take their oral hyperglycemic medications. But the difference was not statistically significant between the yearly direct cost and those of participants who said they were on diabetic diet (maybe due to their misunderstanding of the best type of carbohydrate and portion recommended), number of meals, dates consumption, and other techniques of a diabetic diet. The same result was found for yearly direct cost and the group of participants who think exercise can lower blood sugar level, which was maybe due to the improper and insufficient time of exercise that does not follow the guideline recommendations mentioned above.

Although around 60% of both genders never visited a diabetic educator, they are almost the same in the awareness of healthy diet and its impact on blood sugar level. Men prefer refined carbohydrates + complex carbohydrates (which are healthier) compared to half of women who mainly prefer refined carbohydrates. The male participants consumed more dates than women, and this difference was highly statistically significant (P value = 0.003). With all of this similarities and differences, there was no significant difference in the yearly cost of both genders.

The rise in diabetes in the gulf region has been linked to many different factors, including diet, exercise, and lifestyle changes due to rapid economic change, increased fast food, and sedentary lifestyle[47]. In Saudi Arabia, for example, the consumption of meat for each person had increased by 2.2% per year between 1993 and 2003, while fiber rich food has decreased[48]. The dietary regime in the Gulf Cooperation Council region has moved away from "predominantly consuming dates, milk, fresh vegetables and fruit, whole wheat bread, and fish to mostly foods rich in high saturated fats and refined carbohydrate diets coupled with a low dietary fiber intake"[49].

In conclusion, poor awareness and limited diabetic education service were considered barriers to get better treatment outcomes. Male patients were more likely to be aware about the disease and adhere more to physical activity than females. There is a greater need for primary care providers to offer continuous diabetes awareness to the public whenever possible to provide the knowledge of preventing disease progression as it is global endemic disease with rapidly increasing prevalence. According to the World Health Organization, it can be prevented and managed through diet and physical activity. The burden of diabetes is huge worldwide; this study showed that the standards of diabetes care in the region can be improved. It may be useful to consider some of the interventions applied worldwide. These could potentially be as effective, and there is a degree of overlap. For example, the use of patient education by small group or a one-on-one setting education programs, diabetes specialist nurses, and self-glucose monitoring appear to be potentially useful and are relatively well-developed components of systems elsewhere.

It is essential for the governments to invest in ways to prevent and help in the early detection of such an expensive disease by performing national screening and education programs. Many pharmaco-economic studies can be done to help the decision maker to think about strategies to help the patient to be physically fit by offering gymnasiums or places to walk or to have a contract with a specialized gym to refer them there. Even if this seems costly, it has a good economic impact.

ARTICLE HIGHLIGHTS

Research background

Saudi Arabia is among the top 10 countries with the highest prevalence of diabetes. Cost of prevention and indirect cost must be calculated to increase the awareness of the society and to emphasize the importance of disease and limiting further complications.

Research motivation

Diabetes complications are the most expensive medical consequences encountered during diabetes management. Lack of patient education regarding lifestyle changes and medication use leads to treatment failure, which adds burden to both patients and the government.

Research objectives

The purpose of this study was to describe the relationship between direct medical costs and individual demographic characteristics, different regimen of treatment, and well glycemic control. Here, we include the monthly cost of medications and the pharmacy average consumption of each oral hypoglycemic medication listed in the formulary. In addition, awareness of these patients of the disease and the role of lifestyle modifications in addition to oral hypoglycemic medication are explored. Lack of sufficient awareness will lead to high treatment cost with low therapeutic outcomes.

Research methods

A prospective descriptive and comparative face-to-face survey was carried out among patients with diabetes mellitus in Saudi Arabia. The study included both genders of patients visiting the primary care medical center. Patients aged between 35 to 75 years who were on oral hypoglycemic were selected within the inclusion criteria. Pregnant women were excluded from the study. The prices and quantities of average monthly ordering costs of the medicine were collected from the institution.

Research results

Results of this study show a lack of proper counseling about lifestyle changes and medication use among patients with diabetes. This study urges other researchers to focus on patient counselling techniques and the barriers diabetic patients encounter during therapy.

Research conclusions

This study shows that there is a lack in patient education about the proper way to manage diabetes, which affects money expenditure on diabetic management. This study proposes the use of well-structured techniques by diabetic educators that include organized follow up plan and utilization of modern technology to reduce diabetic complications and improve quality of life.

Research perspectives

Future research should focus on the utilization of social media in promoting diabetes education in both diabetic and pre diabetic patients.

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