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Continuing Education

Connect the Dots

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Diabetes and Endothelial Dysfunction

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Abstract

In patients with diabetes mellitus, endothelial dysfunction is the initial step in the process of atherosclerosis and plays an important role in the development of this condition, leading to diabetic vascular complications. Oxidative stress induced by hyperglycemia and acute glucose fluctuations are associated with endothelial dysfunction through inactivating nitric oxide (NO) by excess production of reactive oxygen species (ROS). Under the condition of insulin resistance, NO production is selectively impaired, whereas endothelin-1 (ET-1) secretion is preferentially activated in endothelial cells, leading to endothelial dysfunction in obese or overweight diabetic patients. On the other hand, endothelial dysfunction might contribute to insulin resistance in skeletal muscle. Reduced NO production through oxidative stress and selective insulin resistance in endothelial cells contributes to decreased glucose uptake by skeletal muscle due to a delayed increase in insulin concentration in the interstitium of the skeletal muscle. Therefore, insulin resistance is further exacerbated through a vicious cycle of endothelial dysfunction and reduced glucose uptake by skeletal muscle. From a clinical perspective, it is important to select an appropriate intervention that is effective in improving endothelial dysfunction for treatment of patients with diabetes mellitus.

In addition to lifestyle modifications, antidiabetic agents that improve insulin sensitivity are anticipated to improve endothelial function and prevent cardiovascular events in patients with diabetes mellitus.

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Diabetic Vascular Complications

Diabetes mellitus is associated with an increased risk of microvascular and macrovascular complications. A recent study has shown that adults aged 50 years or older with diabetes mellitus die 4.6 years earlier, develop disabilities 6–7 years earlier, and spend 1–2 more years in a disabled state than do those without diabetes mellitus in the USA [1]. Microvascular complications, including retinopathy, nephropathy, and neuropathy, and macrovascular complications, including coronary artery disease, ischemic stroke, and peripheral artery disease, are important causes of morbidity and mortality in patients with diabetes mellitus. Macrovascular complications, namely, cardiovascular diseases (CVDs), are associated with increased mortality in patients with diabetes mellitus. CVD is the most common underlying cause of death, accounting for about 45% of deaths in patients with type 1 diabetes mellitus and about 50% of deaths in patients with type 2 diabetes mellitus [2]. It is therefore important to prevent the onset and progression of CVD for better prognosis in the management of patients with diabetes mellitus.

Endothelial dysfunction is the initial step in the pathogenesis of atherosclerosis and plays a key role in the development of this condition, leading to cardiovascular complications [3]. In addition, it has been demonstrated that endothelial function is an independent predictor of cardiovascular events [4]. Diabetes mellitus has been shown to be associated with endothelial dysfunction [5, 6]. For the prevention of CVD in patients with diabetes mellitus, it is therefore important to understand the causative mechanisms linking diabetes mellitus and endothelial dysfunction and to select an appropriate intervention that will effectively ameliorate endothelial function. In this section, the current understanding of the relationship between diabetes mellitus and endothelial function and treatment options are discussed.

Endothelial Function

It had been thought that the vascular endothelium was just a structural barrier separating the blood vessel wall and the inside cavity. In the 1980s, it was revealed that the vascular endothelium functions not only as a barrier but also as an endocrine organ secreting various vasoactive agents such as the vasodilators nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF) and the vasoconstrictors endothelin-1 (ET-1), angiotensin II, and thromboxane A_2 [7]. Thus, the vascular endothelium might be one of the biggest endocrine organs in the human body, with an estimated total weight equal to that of the liver and an estimated total area equal to that of six tennis courts. A healthy endothelium acts as a gatekeeper controlling vascular tone and structure by regulating the balance between vasodilation and vasoconstriction, growth inhibition and growth promotion, anti-thrombosis and pro-thrombosis, anti-inflammation and pro-inflammation, and anti-oxidation and pro-oxidation. Endothelial dysfunction refers to a condition characterized by an inability of the endothelium to maintain vascular homeostasis as a result of an imbalance between endothelium-derived relaxing and contracting factors, leading

to the progression of atherosclerosis. Endothelial dysfunction is an early feature of atherosclerosis and is associated with the development of this condition in human [3]. It is expected that improvement or augmentation of endothelial function may prevent the development and progression of atherosclerosis and consequently reduce cardiovascular events. Therefore, endothelial dysfunction has emerged as a therapeutic target in patients with cardiovascular risk factors such as hypertension, dyslipidemia, and diabetes mellitus and in patients with CVD. NO, one of the various vasoactive agents released from the endothelium, has various anti-atherosclerotic effects including vasodilation, inhibition of platelet aggregation and adhesion, inhibition of leucocyte adhesion, and suppression of vascular smooth muscle cell proliferation. Considering the wide range of anti-atherosclerotic effects of NO, reduced NO bioavailability is generally referred to as endothelial dysfunction.

Diabetes mellitus is associated with endothelial dysfunction. Impaired endothelium-dependent vasodilation has been demonstrated in patients with type 1 and type 2 diabetes [8, 9]. Although the definitive pathogenesis remains unclear, several mechanisms underlying the endothelial dysfunction in patients with diabetes mellitus have been proposed.

Mechanism Underlying the Endothelial Dysfunction in Diabetes

Oxidative Stress

Oxidative stress has been shown to be associated with the pathology of various diseases including diabetes mellitus. Oxidative stress refers to a condition in which the balance of reactive oxygen species (ROS) and the antioxidant system is disturbed in favor of prooxidant ROS. Excessive production of ROS cannot be sufficiently counteracted by the antioxidant defense system, and the deleterious effects of ROS, such as cell proliferation, hypertrophy, apoptosis, and inflammation, become clinically evident. ROS are produced by various oxidase enzymes, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, uncoupled endothelial NO synthase (eNOS), mitochondrial electron transport, cyclooxygenase, glucose oxidase, and lipoxygenase. ROS include superoxide anion (O_{2-}), hydrogen peroxide (H_2O_2), hydroxyl radical (OH), hypochlorous acid (HOCl), NO, and peroxynitrite ($ONOO^-$). O_{2-} is produced by the reduction of molecular oxygen through removal of one electron, and it serves as the precursor of other ROS such as H_2O_2 and OH. In addition, O_{2-} reacts directly with NO and reduces NO bioavailability. In this context, O_{2-} is an important source of oxidative stress associated with endothelial dysfunction. Accumulating evidence has revealed an interaction between oxidative stress and endothelial dysfunction. Excessive O_{2-} reacts directly with NO with high affinity, resulting not only in degradation and inactivation of NO but also in formation of $ONOO^-$, a highly potent oxidant causing lipid peroxidation, DNA damage, and cell death (Fig. 1). In addition, $ONOO^-$ can oxidize the essential eNOS cofactor tetrahydrobiopterin (BH_4) to the biologically inactive trihydrobiopterin (BH_3), leading to a deficiency of BH_4. In the absence of sufficient concentrations of BH_4, eNOS is converted from an NO-producing enzyme into an O_{2-}-generating enzyme. This process is referred to as eNOS uncoupling (Fig. 1) [10]. Under this condition, impaired endothelial function

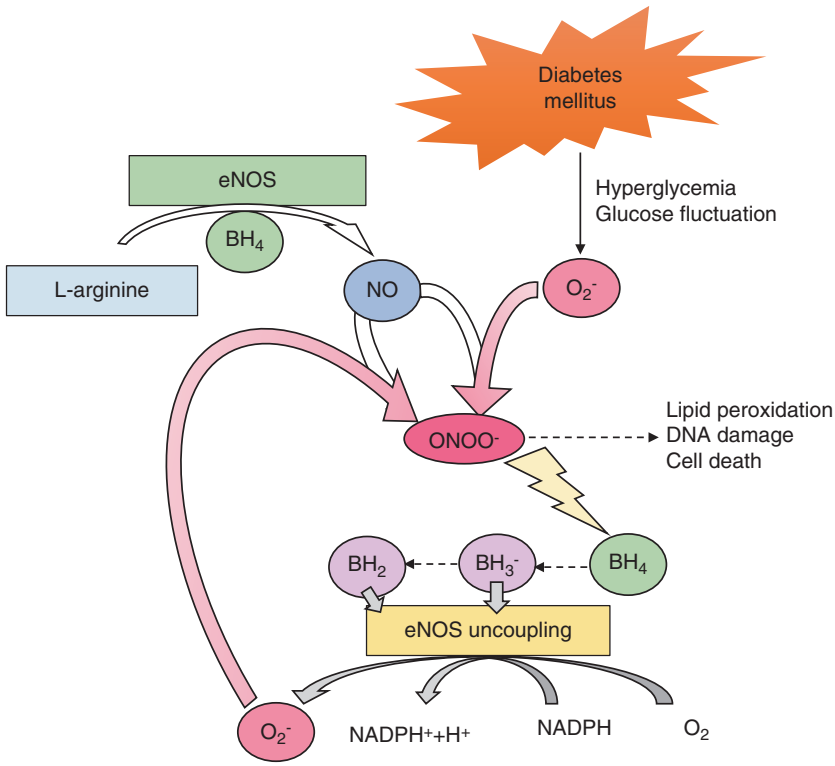

Fig. 1: Putative mechanism of endothelial nitric oxide synthase (eNOS) uncoupling in patients with diabetes mellitus. O_2^- indicates superoxide, BH_4 tetrahydrobiopterin, BH_3 trihydrobiopterin, BH_2 dihydrobiopterin.

is further exacerbated through a vicious cycle of increased oxidative stress and eNOS uncoupling, leading to a further increase in O_{2-} production and a decrease in NO bioavailability. In diabetes mellitus, chronic hyperglycemia is known to be a major contributor to elevated oxidative stress and endothelial dysfunction. In addition, recent studies have demonstrated that acute glucose fluctuations are involved in the mechanism underlying the increased oxidative stress in diabetes mellitus.

Oxidative Stress Induced by Hyperglycemia in Diabetes

Mitochondria are the major intracellular source of O_{2-}. Intracellular glucose oxidation starts with glycolysis, which generates pyruvate for mitochondrial catabolism to form ATP in the cytoplasm. Pyruvate transported into the mitochondria is oxidized to NADH and $FADH_2$ by the tricarboxylic acid (TCA) cycle. NADH and $FADH_2$ serve as donors of electrons used as energy for ATP production through oxidative phosphorylation by the electron transport chain composed of four multiprotein enzyme complexes located in the inner mitochondrial membrane. Electron transfer is coupled with the transfer of protons across the inner mitochondrial membrane. Therefore, electron transfer through the electron transport chain generates a proton gradient by pumping

protons across the inner mitochondrial membrane, providing the energy to drive the ATP synthase. Under the condition of hyperglycemia, NADH and $FADH_2$, electron donors, from the TCA cycle are increased, and the proton gradient across the inner mitochondrial membrane is increased due to the enhanced electron transfer through the electron transport chain and a concomitant increase in the proton pumping. An increase in proton gradient above a certain threshold inhibits electron transport through the electron transport chain, resulting in increased electron leak and O_{2-} generation in mitochondria [11].

Hyperglycemia-induced overproduction of mitochondrial O_{2-} inhibits the activity of the glycolytic enzyme glyceraldehyde-3-phosphate, the activity of which is essential for maintenance of glycolytic flux, thereby resulting in the accumulation of upstream glycolysis intermediates and increased flux of these metabolites into glucose over utilization pathways, including the polyol pathway, hexosamine pathway, protein kinase C (PKC) pathway, and advanced glycation end product (AGE) pathway (Fig. 2) [11]. Increased glucose flux into the polyol pathway consumes NADPH, which is required for regenerating reduced glutathione (GSH), a main intracellular antioxidant. Therefore, intracellular concentrations of reduced GSH are consequently decreased, leading to an increase in intracellular oxidative stress. Shunting of excess intracellular glucose into the hexosamine pathway increases the modification of transcriptional factor through dysregulated protein glycosylation, resulting in altered protein expression. PKC activation induced by hyperglycemia through increased diacylglycerol has various pathogenic consequences including decreased expression of eNOS, increased expression of ET-1, transforming growth factor-β and plasminogen activator inhibitor-1, and activation of NF-κB and NADPH oxidase, leading to impairment of endothelial function. AGE causes functional alterations of intracellular proteins and modifications of extracellular matrix proteins and plasma proteins. In addition, activation of RAGE, a receptor for AGEs, on endothelial cells mediates the production of ROS and activation of NF-κB. Hyperglycemia causes endothelial dysfunction through overproduction of mitochondrial O_{2-} and diversion of glycolytic flux to alternative metabolic pathways.

Oxidative Stress Induced by Acute Glucose Fluctuations in Diabetes

Blood glucose levels are strictly regulated within a narrow range in normal subjects. However, in patients with diabetes mellitus, a rapid and large increase in blood glucose levels in the postprandial phase is observed. Recent studies have demonstrated that the postprandial acute hyperglycemia may play a significant role in the pathogenesis of diabetic vascular complications through increased oxidative stress, reduced NO bioavailability, and consequent endothelial dysfunction [12]. Glucose fluctuations induced by intermittent high glucose might be more deleterious to endothelial cells than a constant high glucose concentration. In in vitro studies, intermittent high glucose has been demonstrated to enhance apoptosis of endothelial cells via the activation of PKC and NADPH oxidase, suggesting the involvement of oxidative stress in endothelial cell injury [13, 14]. In addition, a recent clinical study has demonstrated that glucose fluctuations, obtained from continuous glucose monitoring system data by calculating the mean amplitude of glycemic excursion (MAGE), are associated with increased oxidative stress in patients with type 2 diabetes [15].

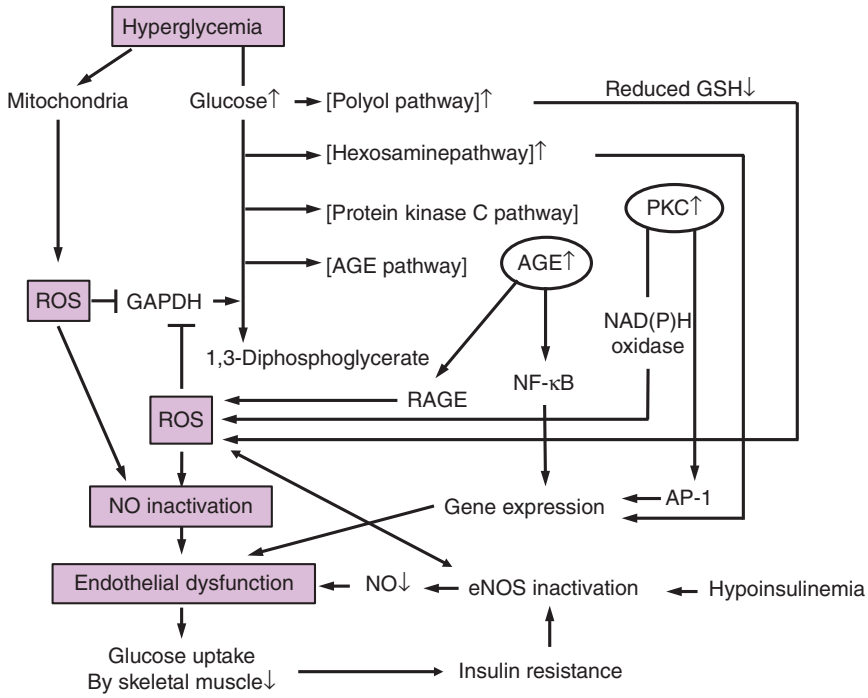

Fig. 2: Putative mechanisms of hyperglycemia-induced endothelial dysfunction in patients with diabetes mellitus. *ROS* indicates reactive oxygen species, *GAPDH* glyceraldehyde-3-phosphate, *eNOS* endothelial nitric oxide synthase, *AGE* advanced glycation end product, *RAGE* receptor for AGEs, *AP-1* activator protein-1.

Monnier et al. reported that the mean urinary excretion rate of 8-iso $PGF_{2\alpha}$, an oxidative stress marker, strongly correlated with MAGE, whereas there were no significant correlations between the urinary excretion rates of 8-iso $PGF_{2\alpha}$ and any other glucose control parameters, including HbA_{1c} and fasting plasma glucose [15]. In addition, Torimoto et al. reported that there was a significant association between glucose fluctuations and endothelial dysfunction in patients with type 2 diabetes [16]. MAGE significantly correlated with reactive hyperemia index, a marker of endothelial function, measured by using peripheral arterial tonometry in patients with type 2 diabetes [16]. Although the precise molecular mechanisms for enhanced oxidative stress and consequent endothelial cell injury by glucose fluctuations have not been fully elucidated, a possible explanation is that constant high glucose may facilitate cellular metabolic adaptations against high glucose-induced toxic effects by consistent feedback, whereas such adaptations may be reduced during intermittent exposure to high glucose due to the absence of consistent feedback, resulting in higher glucose toxicity. HbA1c has been used as a clinical marker of glycemic exposure and as a therapeutic marker of glycemic control in treatment of patients with diabetes mellitus. However, HbA1c serves as a time-averaged measure of glycemic exposure without any information regarding glycemic variability and fluctuations. Recent large randomized trials have demonstrated the lack of significant reduction in cardiovascular events with intensive glycemic control using HbA1c

as a therapeutic parameter of glucose control. In the treatment of patients with diabetes mellitus, attention should be paid to not only fasting plasma glucose and HbA1c levels but also postprandial hyperglycemia in order to protect the endothelium from oxidative injury for the prevention of vascular complications in patients with diabetes mellitus.

Selective Insulin Resistance in Diabetes

In addition to its essential glucose and lipid metabolic actions, insulin has several important vascular actions including NO production in endothelial cells. Insulin stimulation of endothelial cells through binding to its cognate receptor on the endothelial cell surface phosphorylates insulin receptor substrate (IRS), which stimulates phosphoinositide 3-kinase (PI 3-kinase)/Akt pathway. Akt directly phosphorylates eNOS at Ser^{1177}, resulting in activation of eNOS and increased NO production (Fig. 3). Insulin also stimulates the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway and downstream release of the vasoconstrictor ET-1 in endothelial cells, which is independent of the PI 3-kinase/Akt pathway (Fig. 3). Under the condition of insulin resistance in endothelial cells, insulin-induced activation of the PI 3-kinase/Akt pathway and the downstream phosphorylation of eNOS are selectively impaired due to the decreased endothelial IRS function, whereas the MAPK/ERK pathway is unaffected and preferentially activated due to the compensatory hyperinsulinemia, resulting in decreased NO production and increased ET-1 secretion, a characteristic of endothelial dysfunction. It has been demonstrated that the vasodilatory effect of insulin is enhanced under the condition of ET-1 blockade in patients with type 2 diabetes but not in healthy control subjects [17]. Insulin resistance causes endothelial dysfunction through the selectively impaired PI 3-kinase/Akt pathway due to impaired IRS function and enhanced stimulation of the MAPK/ERK pathway due to compensatory hyperinsulinemia in endothelial cells.

Insulin Resistance in Skeletal Muscle Associated with Endothelial Dysfunction

Skeletal muscle plays an important role in glucose homeostasis through insulin-induced glucose uptake. Insulin has to be delivered to the interstitium of skeletal muscle for stimulating glucose uptake by the skeletal muscle. Insulin itself acts in an NO-dependent fashion to increase interstitial insulin concentration by dilating terminal arterioles to increase the number of perfused capillaries and microvascular exchange surface area (microvascular recruitment), dilating larger resistance vessels to increase total limb blood flow, and promoting trans-endothelial transport of insulin to the interstitium of skeletal muscle [18]. Therefore, endothelial dysfunction induced by oxidative stress and selective insulin resistance in endothelial cells causes impairment of vasodilation and insulin transport across the endothelium through reduced NO bioavailability, leading to insulin resistance in skeletal muscle due to a delayed increase in insulin concentration in the interstitium and a consequent decrease in glucose uptake by skeletal muscle. Results of both animal and human studies support the association of insulin resistance with impaired vasodilator action

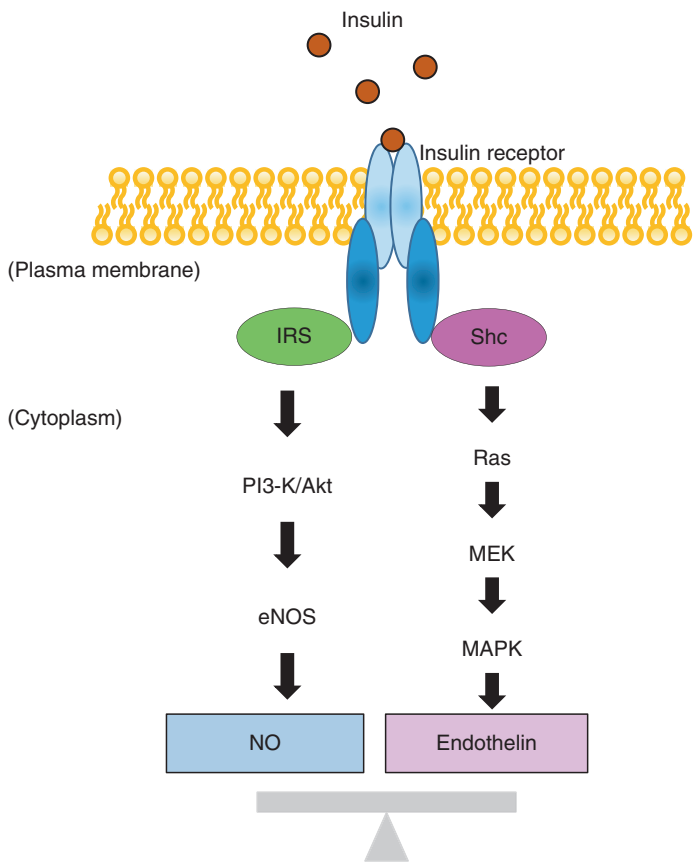

Fig. 3: Distinct signaling pathways mediating insulin effects on nitric oxide (NO) and endothelin. *IRS* indicates insulin receptor substrate, *PI* 3-k phosphoinositide 3-kinase, *eNOS* endothelial nitric oxide synthase, *MEK* mitogen-activated protein kinase kinase, *MAPK* mitogen-activated protein kinase.

and impaired glucose uptake in skeletal muscle [19, 20]. In clinical studies, skeletal muscle blood flow response to insulin was shown to decrease in diabetic and obese subjects compared with that in lean subjects [19]. In in vivo studies, eNOS knockout mice have been shown to exhibit insulin resistance through decreased muscle blood flow and glucose uptake by skeletal muscle [20]. Therefore, insulin resistance is further exacerbated through a vicious cycle of endothelial dysfunction induced by selective insulin resistance and reduced glucose uptake by skeletal muscle (Fig. 4).

Current Treatment Targeting Endothelial Dysfunction in Diabetes Mellitus

From a clinical perspective, early detection of endothelial dysfunction and early intervention for maintaining endothelial function in a healthy condition are important for the prevention of future cardiovascular events in patients with cardiovascular risk factors. Therefore, in the management of patients with diabetes mellitus, it is important to select an appropriate intervention that effectively improves endothelial function for the prevention of diabetic vascular complications.

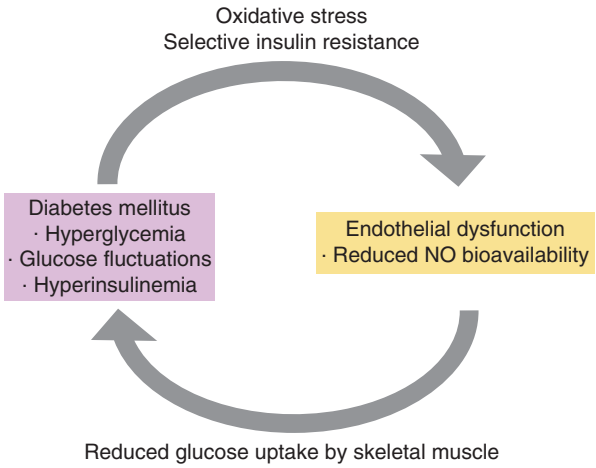

Fig. 4: A vicious cycle of endothelial dysfunction and diabetes mellitus.

Considering the associations of endothelial dysfunction with hyperglycemia, glucose fluctuations, and insulin resistance, lifestyle modifications and pharmacological therapies aiming at lowering glucose level without hypoglycemia, flattening glucose fluctuations, and improving insulin sensitivity may be beneficial for the restoration of endothelial function and prevention of cardiovascular events.

Insulin Therapy

Intensive glycemic control with insulin therapy effectively reduces microvascular complications and cardiovascular events in patients with type 1 diabetes [21]. For patients with type 1 diabetes, in whom insulin resistance does not predominate and a healthy energy balance is achieved, insulin therapy may be safe and beneficial to the endothelium because of the absence of selective insulin resistance in the PI 3-kinase/Akt pathway, leading to increased production of NO in endothelial cells. However, the effect of insulin therapy on endothelial function in patients with type 2 diabetes is still controversial and may be dependent on the achieved metabolic control level [22]. It is possible that high-dose insulin therapy in obese or overweight diabetic patients with insulin resistance who are refractory to its glucose-lowering effect due to excess nutrient supply and positive energy balance may be harmful to the endothelium through an imbalance between impaired PI 3-kinase/Akt pathway and enhanced MAPK/ERK pathway activation caused by selective insulin resistance in endothelial cells, leading to endothelial dysfunction.

Antidiabetic Agents

An antidiabetic agent exerts its glucose-lowering effect by increasing pancreatic insulin secretion and/or ameliorating insulin sensitivity in peripheral tissues. Sulfonylureas, insulin secretagogues, could potentially have an effect similar to that of high-dose insulin therapy and could be harmful

to endothelial function in obese or overweight diabetic patients with insulin resistance due to the selective insulin resistance in endothelial cells.

Considering the reciprocal relationship between insulin resistance and endothelial dysfunction, antidiabetic agents that improve insulin sensitivity are anticipated to have beneficial effects on endothelial function through restoration of PI 3-kinase/Akt signaling and downstream NO production. Thiazolidinediones, insulin sensitizers, have been shown to improve endothelium-dependent vasodilation [23, 24]. In addition, thiazolidinediones have been demonstrated to increase the expression and plasma level of adiponectin, which directly stimulates NO production from endothelial cells through activation of the PI 3-kinase/Akt pathway in patients with insulin resistance or type 2 diabetes [25, 26]. Metformin, another insulin-sensitizing agent, has also been shown to improve endothelium-dependent vasodilation with significant association with improvement of insulin resistance assessed by the homeostasis model (HOMA-IR) in patients with type 2 diabetes [27]. Therefore, pharmacological therapies targeting insulin resistance may have beneficial effects on endothelial function through improving insulin sensitivity and increasing NO production in endothelial cells in diabetic patients with insulin resistance.

Antidiabetic agents that decrease the postprandial rise in blood glucose levels are also anticipated to have beneficial effects on endothelial function through decreased oxidative stress and a consequent increase in NO bioavailability. Glinides, dipeptidyl peptidase 4 (DPP-4) inhibitors, and α-glucosidase inhibitors are antidiabetic drugs that improve the control of postprandial glucose levels. These antidiabetic agents have been shown to improve postprandial endothelial function [28–31]. However, there are conflicting reports showing that α-glucosidase inhibitors, glinides, and DPP-4 inhibitors have no significant beneficial effects or even have adverse effects on endothelial function in patients with type 2 diabetes [28, 32, 33]. Although the precise reasons for the discrepancy of the results remain unknown, some explanations, including differences in the vascular beds assessed for endothelial function, subject selection, and treatment period, have been postulated. As for glinides and DPP-4 inhibitors, there is a possibility that increased insulin secretion through their pharmacological actions could be harmful to endothelial function in obese or overweight diabetic patients due to the selective insulin resistance in endothelial cells.

Other Treatment

In patients with type 2 diabetes, other cardiovascular risk factors such as hypertension and dyslipidemia are highly prevalent. Therefore, a multiple risk factor intervention approach is important for the prevention of cardiovascular events in patients with type 2 diabetes. The Steno-2 study demonstrated that an intensified and targeted multifactorial intervention including behavior modifications and polypharmacologic therapy aimed at controlling several modifiable risk factors reduced the risk of cardiovascular and microvascular events by about 50% compared with a conventional strategy [34]. In the management of other risk factors in patients with type 2 diabetes, it is also important to select an appropriate intervention that will be expected to improve endothelial function, including administration of antihypertensive agents such as angiotensin-converting

enzyme inhibitors and angiotensin II type I receptor blockers [35, 36], administration of statins [37], and lifestyle modifications such as aerobic exercise and body weight reduction [38, 39].

Conclusions

In patients with diabetes mellitus, endothelial dysfunction is the early feature of atherosclerosis and plays an important role in the development of this condition, leading to diabetic vascular complications. Oxidative stress induced by hyperglycemia and glucose fluctuations causes endothelial dysfunction through inactivating NO by excess production of ROS. Selective insulin resistance in the PI 3-kinase/Akt pathway and impaired downstream NO production in endothelial cells may also contribute to endothelial dysfunction, whereas endothelial dysfunction might contribute to insulin resistance. Insulin potentially regulates its own delivery to skeletal muscle in an NO-dependent fashion at multiple steps. Reduced NO production through oxidative stress and selective insulin resistance in endothelial cells causes insulin resistance in skeletal muscle due to a delayed increase in insulin concentration in the interstitium of skeletal muscle. It is clinically important to break out of the cycle of endothelial dysfunction and insulin resistance in obese or overweight diabetic patients for the prevention of cardiovascular events. In addition to lifestyle modifications such as aerobic exercise and body weight reduction, antidiabetic agents that improve insulin sensitivity are expected to ameliorate endothelial function. Although an intervention targeting the reduction of oxidative stress is theoretically attractive, clinical studies in which the effects of antioxidants on cardiovascular events in patients with diabetes mellitus were investigated have revealed disappointing outcomes. Further studies are needed to develop clinically safe and effective treatment strategies targeting oxidative stress for the prevention of cardiovascular events in patients with diabetes mellitus.

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2

Diabetes and Osteoporosis

Ippei Kanazawa, Toshitsugu Sugimoto

Abstract

Accumulating evidence has shown that the risk of osteoporotic fracture is increased in patients with diabetes mellitus independently of bone mineral density. Thus, diabetes-related bone disease is now recognized as one of diabetic complications. Collagen cross-links of advanced glycation end products (AGEs), dysfunction of osteoblasts with low bone turnover, as well as abnormal microstructure of trabecular and cortical bone are involved in bone fragility in diabetes mellitus. Circulating levels of AGEs and homocysteine are increased in patients with diabetes, and AGEs and homocysteine directly inhibited the differentiation of osteoblasts. In addition, these induce the apoptosis and regulate expression levels of sclerostin and RANKL in osteocytes, which play important roles of bone remodeling. Moreover, several antidiabetic drugs affect bone metabolism and fracture risk. Therefore, the underlying mechanism of diabetes-related bone fragility is very complex and not still fully understood. In this review, we described effects of diabetes on bone metabolism and the risk of fracture based on the recent evidence.

Keywords: Diabetes-related bone disease Osteoporosis Fracture Bone formation Advanced glycation end products

Introduction

Diabetes mellitus is known to cause various complications such as neuropathy, retinopathy, nephropathy, and atherosclerosis, resulting in the deterioration of quality of life and life prognosis. Accumulating evidence has shown that the risk of osteoporotic fractures, such as hip and vertebral fractures, is significantly increased in not only type 1 diabetes mellitus (T1DM) but also type 2 (T2DM). Vestergaard reported a meta-analysis [1] showing that patients with T1DM had slightly

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decreased bone mineral density (BMD) at the lumbar and hip (*z*-score −0.22 and −0.37, respectively) and that T2DM patients had higher BMD at the lumbar and hip (*z*-score +0.41 and +0.27, respectively). Based on these BMD values, the estimated fracture risks were 1.42-fold in T1DM and 0.77-fold in T2DM, respectively. However, the risks of hip fracture compared to nondiabetic controls were 6.94-fold in T1DM and 1.4-fold in T2DM, respectively. Another meta-analysis also showed that hip fracture risks of T1DM and T2DM patients were increased to 6.3-fold and 1.7-fold, respectively, compared to nondiabetic controls [2]. Furthermore, we previously demonstrated that the presence of T2DM was an independent risk factor for prevalent vertebral fractures in Japanese men and women (odds ratio, 4.7 for men and 1.9 for women) after adjusting for age, body mass index, and lumbar BMD [3]. In addition, we tested usefulness of calcaneal quantitative ultrasound (QUS), which is thought to be able to evaluate bone quality of microarchitecture. However, QUS was also not associated with the risk of vertebral fracture in patients with T2DM [4]. These findings suggest that BMD and QUS may not reflect bone fragility in T1DM and T2DM and that measurements of BMD and QUS may lead to underestimate the actual risk of fracture. Therefore, bone mass reduction-independent fracture risk exists in diabetic patients, and impaired bone quality may be a major cause of diabetes-related bone fragility. Estimation of bone mass and microarchitecture by BMD and QUS is not useful in diabetic patients.

Increased Collagen Cross-Links of Advanced Glycation End Products in Diabetes

Advanced glycation end products (AGEs) are generated by sequential nonenzymatic chemical glycoxidation of protein amino groups. AGEs accumulate in various tissues including bone, kidney, brain, and coronary artery atherosclerotic plaques with aging. AGEs have a pivotal role in the development of complications in patients with diabetes, because hyperglycemia and oxidative stress accelerate AGE formation. Among AGEs, pentosidine is a well-characterized compound and is considered a good predictor for the development of micro- and macro-vascular complications in diabetic patients. Previous studies have shown that serum pentosidine levels in patients with diabetes were significantly higher than those in healthy subjects. Saito et al. previously reported that spontaneous diabetic rats displayed significant increases in pentosidine cross-links in bone, which was linked to impaired mechanical properties despite normal bone mass [5]. These findings clearly support the pathophysiology of bone fragility with normal BMD, which is seen in diabetic patients.

Because previous studies have shown that circulating pentosidine levels are significantly correlated with content of pentosidine in cortical bone, serum and urine pentosidine levels could be used as a surrogate marker for its content in bone as well as bone strength. Indeed, our previous study showed that elevated serum pentosidine levels were significantly associated with prevalent vertebral fracture in postmenopausal women with T2DM [6]. Schwartz et al. also reported an observational cohort study showing that higher urine pentosidine was associated with increased clinical fracture incidence in elderly patients with T2DM, but not in those without it [7]. In addition, a recent clinical study using bone biopsy in patients with T1DM showed that pentosidine content in trabecular was significantly and positively associated with HbA1c levels and increased

in T1DM patients with fracture [8]. Therefore, accumulation of pentosidine cross-links in bone may be a major cause of impaired bone quality in patients with diabetes.

Dysfunction of Osteoblasts and Osteocytes in Diabetes

Bone tissue is constantly renewed by a balance between osteoblastic bone formation and osteoclastic bone resorption. Several clinical studies and meta-analyses have revealed that bone formation markers, especially serum osteocalcin, which is a marker of bone formation and produced by mature osteoblasts, were significantly decreased in patients with diabetes compared to nondiabetic subjects [9]. We and others previously demonstrated that serum osteocalcin levels were significantly increased after intensive glycemic control in T2DM, while bone specific alkaline phosphatase (BAP), which is a marker of early stage of differentiated osteoblasts, was significantly decreased [10]. Moreover, the ratio of osteocalcin/BAP was significantly associated with prevalent vertebral fracture in T2DM patients [11]. These findings suggest that derangement of osteoblast maturation may be involved in the risk of fracture in diabetic patients. On the other hand, osteocytes account for 90–95% of bone cells, and recent studies have shown that osteocytes play multifunctional roles in orchestrating bone remodeling by regulating both osteoblast and osteoclast functions. Sclerostin is specifically expressed in osteocytes and inhibits osteoblastic function and bone formation by antagonizing canonical Wnt signaling pathway. We previously showed that elevated serum sclerostin levels were associated with an increased risk of vertebral fractures in T2DM patients independently of BMD and bone turnover [12], suggesting that dysfunction of osteocytes also may contribute to the bone fragility in diabetes. In contrast, there are inconsistent results about bone resorption markers. Several studies showed that they are higher in patients with diabetes than those in nondiabetic subjects, while a meta-analysis demonstrated that C-terminal cross-linked telopeptide (CTX) was significantly lower in diabetic patients [9]. It is thus considered that bone resorption may be relatively elevated in patients with diabetes compared to decreased bone formation.

AGEs have a physiological function and act through their receptors. Because receptor for AGEs (RAGE) is expressed in osteoblasts and osteocytes, there is a possibility that AGEs directly affect bone formation and bone remodeling. Our *in vitro* studies have shown that the combination of high glucose and AGEs inhibited the mineralization of osteoblastic cell line, MC3T3-E1 [13], and that AGEs inhibited the osteoblastic differentiation or mineralization of mouse stromal ST2 cells and human mesenchymal stem cells by decreasing osterix expression, increasing transforming growth factor (TGF)-β expression, and suppressing endoplasmic reticulum stress proteins [14, 15] (Fig. 1). Moreover, high glucose and AGEs significantly increased the expression of sclerostin in osteocyte-like MLO-Y4 cells [16]. In contrast, AGEs decreased the expression of receptor activator of nuclear factor κB ligand (RANKL) in the cells. Furthermore, AGEs induced apoptosis of osteoblasts and osteocytes. Taken together, AGEs directly inhibit osteoblastic differentiation and bone formation and indirectly by increasing sclerostin expression in osteocytes as well as contribute to low turnover of bone remodeling by decreasing RANKL expression.

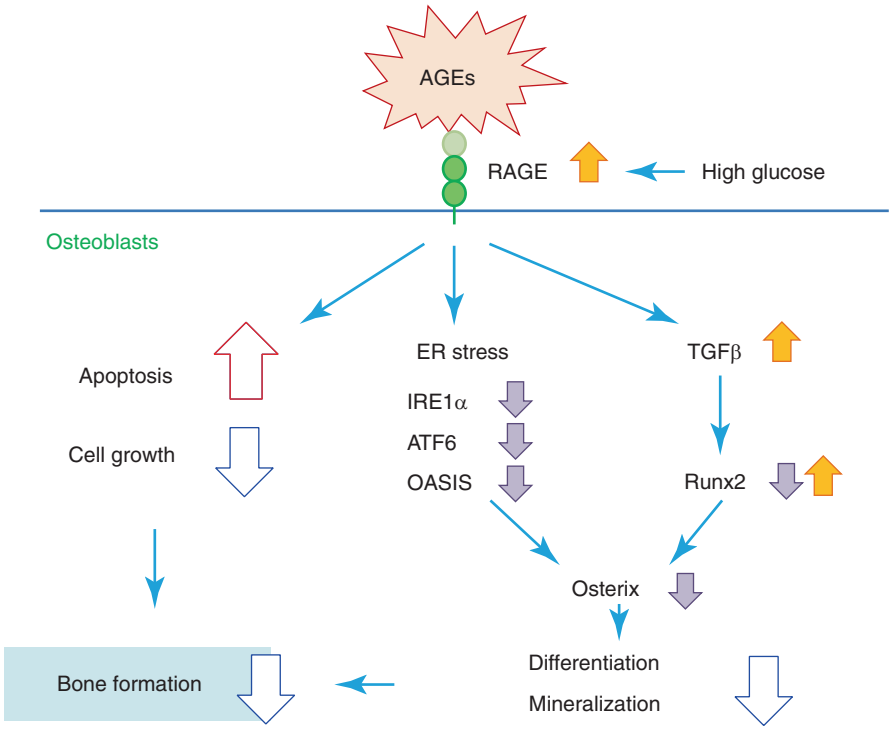

Fig. 1: Direct effects of advanced glycation end products (AGEs) on osteoblasts. Receptor for AGEs (RAGE) is expressed in osteoblast, and AGEs act as physiological molecules. AGEs induce apoptosis and suppress cell growth of osteoblasts. AGEs inhibit the differentiation and mineralization of osteoblasts through ER stress and TGFβ expression, resulting in decreased bone formation.

Homocysteine (Hcy) is a sulfur-containing amino acid formed by the demethylation of methionine, and high plasma Hcy levels are often caused by aging, lifestyle-related diseases such as diabetes, as well as vitamin B12 and folate insufficiency. Hcy has been shown to be an independent risk factor for cardiovascular disease, and several studies have previously shown that hyperhomocysteinemia increases the risk of osteoporotic fracture independently of BMD, suggesting that the deterioration of bone quality may be a dominant cause of Hcy-induced bone fragility. Li et al. previously showed that plasma Hcy levels were significantly increased in patients with T2DM than those in nondiabetic subjects and that higher plasma Hcy levels were associated with the incidence of vertebral fractures and hip fractures in patients with T2DM [17]. Although the mechanism underlying Hcy-related bone fragility in diabetes is still unclear, there are several studies including ours on effects of Hcy on osteoblastic function and collagen cross-links [18, 19]. Diet-induced hyperhomocysteinemia decreased bone quality *in vivo*, and Hcy directly affected osteoblastic lineage cells such as bone marrow stromal cells and osteoblasts. It has been shown that Hcy induces the apoptosis of osteoblastic cells by increasing oxidative stress. In addition, Hcy suppresses the expression of the collagen cross-linker lysyl oxidase and increases the

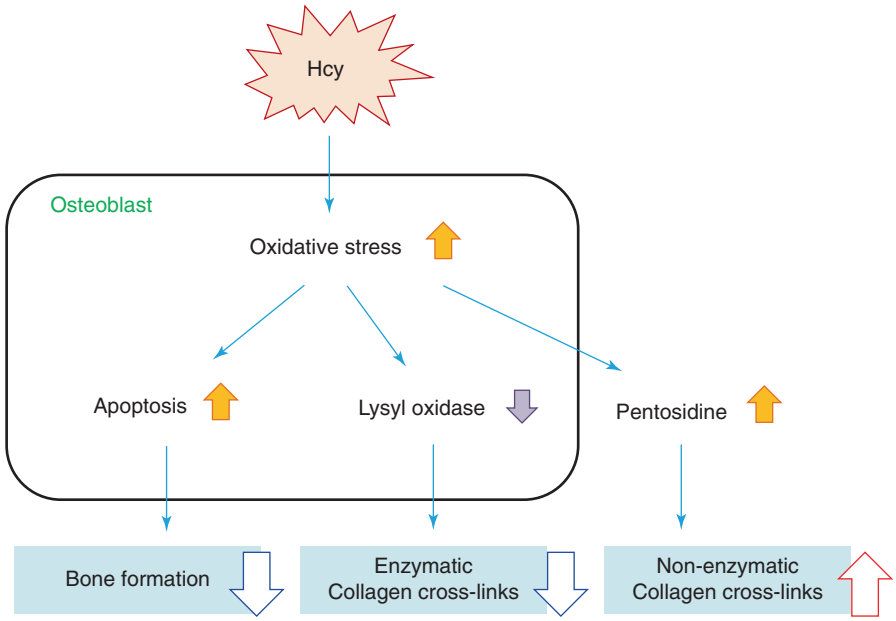

Fig. 2: Effects of homocysteine (Hcy) on osteoblasts. Hcy increases intracellular oxidative stress in osteoblasts and induces apoptosis. Hcy suppresses the expression of lysyl oxidase, which is the most important enzyme for collagen cross-links, and increases the extracellular pentosidine accumulation.

accumulation of extracellular pentosidine in osteoblasts. These findings suggest that Hcy may impair viability and function of osteoblasts as well as deteriorate bone stiffness by inhibiting formation of enzymatic collagen cross-links and increasing nonenzymatic pentosidine cross-links in bone matrix (Fig. 2). Moreover, we previously showed that Hcy increased oxidative stress and induced apoptosis of osteocytes by increasing NADPH oxidase 1 (Nox1) and Nox2 expressions although detail of the mechanism is still unclear [20]. Thus, the dysfunction of osteocytes by Hcy may be involved in the bone fragility in diabetes.

Insulin action is important for osteoblastic differentiation, collagen synthesis, and bone formation. Osteoblast-specific insulin receptor gene knockout mice displayed a remarkable reduction in bone volume due to decreased bone formation and deficient numbers of osteoblasts [21]. Blocking insulin signaling suppresses osteoblastic proliferation, induces its apoptosis, and inhibits the differentiation and mineralization of osteoblasts by decreasing a Runx2 inhibitor, Twist2. These results are supported by the clinical finding that patients with T1DM have lower BMD and an increased risk of fragility fracture and can develop early-onset osteoporosis as well as poor bone healing and regeneration after injury. Insulin-like growth factor (IGF)-I is also known to have an anabolic effect on bone. IGF-I is expressed in osteoblasts and promotes osteoblastic differentiation and bone remodeling by autocrine and paracrine pathways in the microenvironment. Circulating IGF-I is mainly produced in the liver via regulation by growth hormone and diet and acts in an endocrine manner on bone as well. Significant reduction in bone mass and deficient mineralization were observed in osteoblast-specific knockout mice of IGF-I receptor, and liver-specific IGF-I

gene-null mice showed a marked reduction in bone volume, periosteal circumference, and medial lateral width [22]. Moreover, several laboratory studies have shown that the stimulatory actions of IGF-I on osteoblasts are blunted by high glucose or AGEs and that high glucose significantly impairs the proliferative and functional responses of osteoblastic cells to IGF-I. AGEs also significantly decreased IGF-I secretion in osteoblasts. Thus, high glucose concentrations or AGEs may cause the resistance of osteoblasts to IGF-I actions in local environment. Therefore, IGF-I signaling is important for maintaining bone mass and strength in diabetic patients, and decreased IGF-I levels may be involved in the diabetes-related bone fragility. Indeed, we have previously shown that serum IGF-I level was positively associated with serum osteocalcin levels and inversely with the number of prevalent vertebral fractures in postmenopausal women with T2DM [23].

Abnormal Microstructure of Bone

Previous clinical studies using high-resolution peripheral quantitative computed tomography (HR-pQCT) have shown that cortical porosity is associated with the independent risk of fracture in T2DM patients. Burghardt et al. showed that T2DM patients had 10% higher trabecular volumetric BMD and higher trabecular thickness in the tibia compared to nondiabetic subjects, whereas cortical porosity in the distal radius was significantly 50% higher in T2DM than controls [24]. Furthermore, pore volume of the tibia showed similar trend, but not significant. In addition, HR-pQCT images of the distal radius and tibia showed that T2DM patients with fracture had severe intracortical porosity as well as extremely dense trabecular bone in the peripheral region adjacent to the cortex. Recently, several studies demonstrated consistent results. Therefore, increased cortical porosity may be involved in the fragility fracture in T2DM. However, the underlying mechanism is unknown. Osteocytes exist in the cortex, and it is considered that apoptosis of osteocytes may lead to increased pore volume of cortical bone. As described above, AGEs and Hcy induce the apoptosis of osteocytes. Thus, further studies are necessary to examine the association of AGEs and Hcy levels with cortical porosity.

Trabecular bone score (TBS) is a texture parameter that quantifies local variation in the gray level distribution of dual-energy X-ray absorptiometry images. Although TBS is not a direct physical measurement of bone microarchitecture, it is associated with bone microarchitecture of trabecular and stiffness of vertebra independently of BMD. Because of no need of further invasive examinations, TBS attracts widespread attention to physicians. Several studies showed that TBS was significantly decreased in patient with T2DM, while BMD was increased [25]. Thus, abnormal distribution of trabecular may be involved in the increased risk of fracture in diabetes. HbA1c levels and insulin resistance were reported to be associated with TBS; however, the mechanism of low TBS with high BMD is still unknown. A few clinical studies recently showed the usefulness of TBS to access the risk of fracture in patients with diabetes. Further longitudinal studies are needed to use TBS in clinical settings.

Taken all together, collagen cross-links of AGEs, dysfunction of osteoblasts with low bone turnover, and abnormal microstructure of trabecular and cortical bone are involved in bone fragility in diabetes mellitus (Fig. 3).

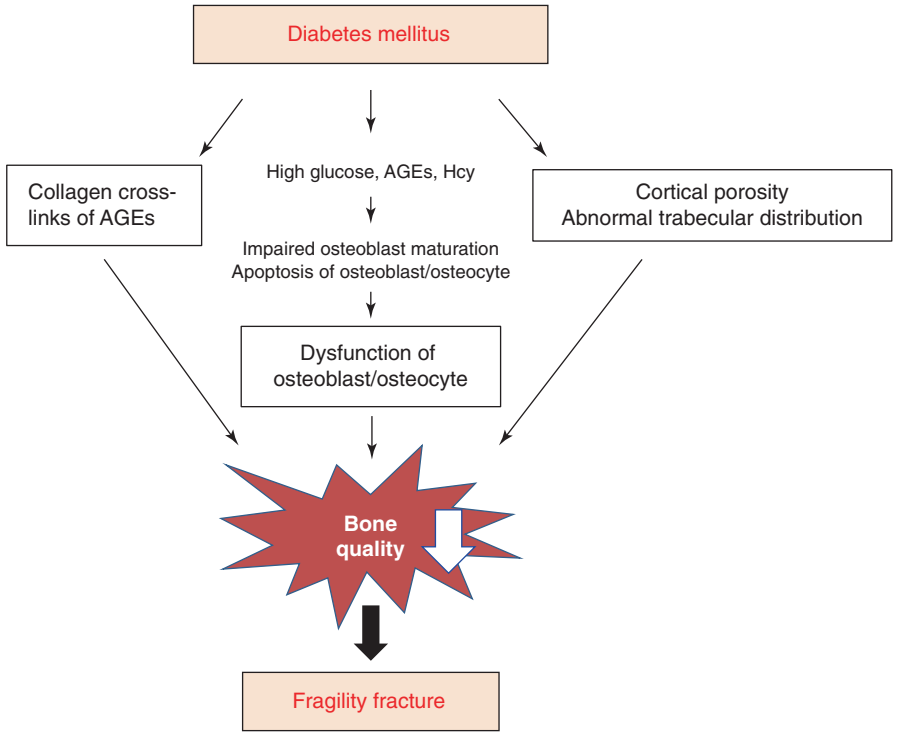

Fig. 3: Pathophysiology of diabetes-related bone fragility. Chronic hyperglycemia and increased oxidative stress by diabetes promote collagen cross-links of advanced glycation end products (AGEs). Hyperglycemia, AGEs, and Hcy inhibit osteoblastic differentiation and maturation and induce apoptosis of osteoblasts and osteocytes, resulting in dysfunction of osteoblast and osteocyte. Diabetes increases cortical porosity and abnormal trabecular distribution. These pathways contribute to the deterioration of bone quality and fragility fracture.

The Risk of Fall

Fragility fracture occurs after low-energy trauma such as falls and bumps, which wouldn't hurt a person with healthy bones, in patients with osteoporosis. It has been shown that diabetic patients have increased risk of falls. Thus, the increased risk of fracture is caused by not only weakened stiffness of bone itself but also high incidence of falls. It is suggested that loss of body weight, diabetic neuropathy, autonomic neuropathy, diabetic retinopathy with visual disturbance, renal dysfunction, insulin use, and hypoglycemia, etc. are associated with the increased risk of fall. Sarcopenia is one of diabetic complications, and the presence of sarcopenia is also an important risk factor for the risk of fall. Like the dysfunction of osteoblasts, insulin and IGF-I action and pentosidine accumulation are associated with loss of muscle mass. Insulin and IGF-I are well known to have anabolic effects on muscle mass. Indeed, we previously showed that parameters of residual insulin secretion and serum IGF-I levels, but not HbA1c, are significantly and positively associated with skeletal muscle mass index in T2DM even after adjustment for age, duration of

diabetes, renal function, and HbA1c [26, 27]. In addition, our *in vitro* studies have shown that AGEs directly inhibit myogenesis of myoblastic cells [28]. Previous lots of studies have revealed that vitamin D insufficiency and deficiency are associated with the increased risk of fall and muscle mass reduction, and supplementation of vitamin D decreases the incidence of fall. We previously reported that active vitamin D and eldecalcitol, which is an analogue of active vitamin D and is an available drug for the treatment of osteoporosis, enhanced myogenesis of myoblastic cells and protected against AGE-induced inhibition of myogenesis [28]. Since diabetic patients frequently have vitamin D insufficiency and deficiency, vitamin D status is very important for diabetes-related bone fragility regarding strength of bone and muscle.

Osteoporosis and sarcopenia are aging-related diseases associated with the deterioration of muscle and bone strength, resulting in frailty in elderly people. Sarcopenia and osteoporosis are traditionally viewed as separate entities that increase in prevalence with aging. However, accumulating evidence indicates that some pathological conditions such as accumulated AGEs and decreased IGF-I are involved in both diseases as described above. Recent studies have shown an interaction between muscle and bone tissues that has been recognized as the muscle-bone axis. Previous studies have shown that muscle tissue secretes various hormones called myokines and that bone also secretes various hormones such as osteocalcin. We have previously shown that osteoglycin (OGN) is an important factor linking muscle to bone. OGN is a small leucine-rich proteoglycan and initially isolated from bovine bone as an inducer of matrix mineralization. Our *in vitro* studies demonstrated that OGN suppressed the early stage of osteoblastogenesis, but enhanced the differentiation and mineralization of late-stage osteoblasts [29]. Also, we found that AGE treatment inhibited the expression of OGN in myoblasts and that active vitamin D recovered the AGE-induced suppression of OGN and sequentially inhibited osteoblastic differentiation [28].

Therefore, there are several common factors affecting bone and muscle as well as their interaction (Fig. 4). Especially, AGEs are important aggravating factors for the increased risk of fracture due to diabetes-related bone fragility and muscle weakness (Fig. 5).

Treatments for Diabetes-Related Bone Fragility

A prospective population-based cohort study, the Rotterdam study, previously showed that HbA1c levels are associated with the incidence of fracture in T2DM patients [30]. Cox proportional hazard regression models adjusted for age, sex, height, and weight indicated that patients with inadequately controlled diabetes (HbA1c ≥ 7.5%) had 47–62% higher fracture risk than control subjects without diabetes (hazard ratio 1.47) and adequately controlled diabetes (HbA1c <7.5%, hazard ratio 1.62). Other groups also reported that poor controlled diabetes is associated with the increased risk of fracture although cutoff point is different from the Rotterdam study. Therefore, controlling blood glucose below 7.5% seems to be required for diabetes-related bone disease.

We and others previously reported that intensive glycemic control for 1–2 months significantly increased serum osteocalcin levels, while BAP was decreased [10], suggesting that lowering blood glucose can improve impaired osteoblastic maturation and reduce the risk of fracture in diabetes. However, of surprise, the action to control cardiovascular risk in diabetes (ACCORD)

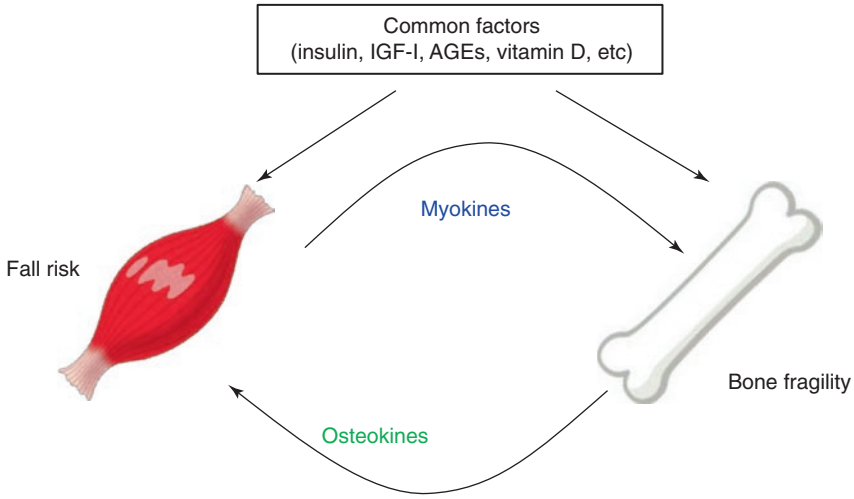

Fig. 4: Muscle function is involved in diabetes-related bone disease. Several common factors such as insulin, insulin-like growth factor (IGF)-I, AGEs, and vitamin D affect bone and muscle tissue. Muscle and bone are associated with each other through myokines and osteokines.

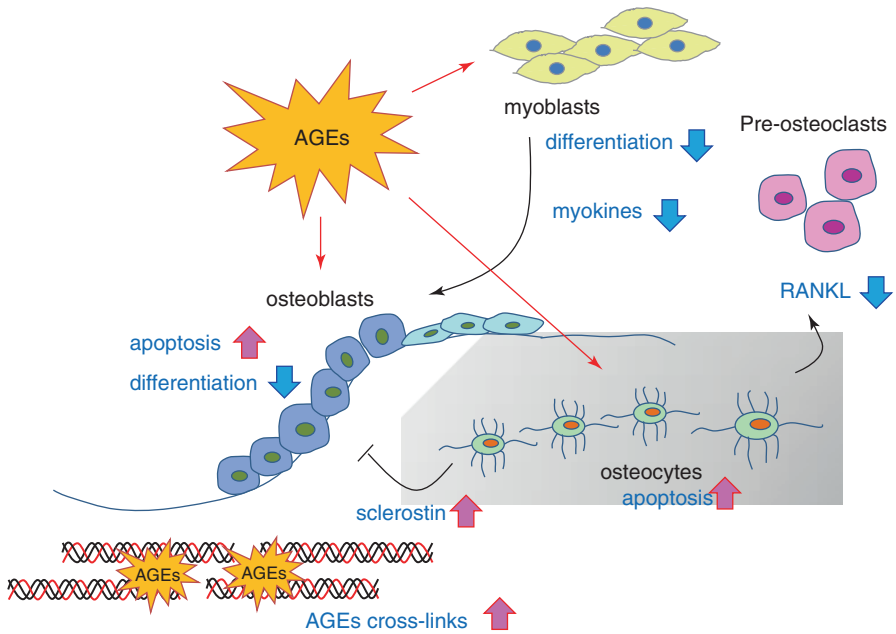

Fig. 5: Multifacet effects of advanced glycation end products (AGEs) on bone metabolism. AGEs induce apoptosis of osteoblasts and inhibit osteoblastic differentiation. AGEs induce apoptosis of osteocytes, enhance the expression of sclerostin, and decrease the expression of receptor activator of nuclear factor κB ligand (RANKL) in osteocytes, leading to inhibiting differentiation of osteoblasts and osteoclasts as well as decreasing bone turnover and remodeling. AGEs inhibit the differentiation of myoblasts and suppress the expression of myokines, resulting in suppression of osteoblastic differentiation. Production of AGE cross-links in bone matrix is promoted by diabetic condition.

randomized trial revealed that intensive therapy targeting HbA1c < 6.0% did not affect 2-year percent change in BMD or the incidence of fracture (nonspine, hip, ankle, foot, proximal humerus, and distal forearm) or fall compared to standard therapy targeting HbA1c < 7.5% [31]. Several studies have shown that some antidiabetic drugs affect bone metabolism and fracture risk. Among them, insulin treatment and thiazolidines are known to be associated with the risk of fracture. Several studies including ours demonstrated that patients treated with insulin had higher risk of fracture [32]. In the ACCORD trial, many participants of intensive therapy received insulin treatment and had body weight gain and increased risk of hypoglycemia, which may affect bone metabolism and fracture risk. Therefore, approach of glycemic control should be considered, and further intervention trials are necessary to find out how we should treat diabetic patients with long-term diabetic duration in terms of reduction of fracture risk. On the other hand, peroxisome proliferator-activated receptor γ (PPARγ) is known to be a negative regulator of osteoblastogenesis. Activation of PPARγ inhibits the commitment of multipotential mesenchymal stem cells to osteoblastic lineage and induces adipogenesis. Indeed, several studies and meta-analyses have shown that treatment with thiazolidines decreases BMD and increases the risk of fracture in elderly women, but not men [32–34]. Treatment with sodium glucose cotransporter 2 (SGLT2) inhibitors is concerned to increase the risk of fracture because SGLT2 inhibitors increase calcium excretion along with glucose excretion in urine and induce loss of body weight, both of which may have negative impacts on bone. Although further studies are mandatory, we should take care of bone health when SGLT2 inhibitors are used. In contrast, several studies showed that incretin, especially glucose-dependent insulinotropic polypeptide (GIP), and dipeptidyl peptidase-4 (DPP-4) inhibitors as well as metformin may have favorable effects on bone. We previously demonstrated that serum DPP-4 levels were associated with the risk of multiple vertebral fractures in T2DM [35], and a meta-analysis showed that patients treated with DPP-4 inhibitors had lower incidence of fracture compared to other treatments [36]. Metformin is reported to enhance the differentiation of osteoblasts *in vitro* [37] and increase bone mass *in vivo* [38]. Several epidemiological studies showed that metformin treatment is associated with low risk of fracture. However, we don't have strong evidence about the effects of DPP-4 inhibitors and metformin on the risk of fracture in diabetic patients thus far.

Summary

In summary, it has been shown that the risk of fracture is significantly increased in both T1DM and T2DM. Thus, diabetes-related bone disease is one of important diabetic complications. Recent studies elucidate the mechanism of diabetes-related bone fragility, collagen cross-links of AGEs, dysfunction of osteoblasts with low bone turnover, and abnormal microstructure of trabecular and cortical bone. Also, sarcopenia associated with the risk of fall is important for protecting diabetic patients from osteoporotic fractures. In both T1DM and T2DM, BMD is not necessarily a good marker for the bone fragility and that BMD measurement seems to be less useful in diabetic patients. It is therefore an urgent task to seek suitable surrogate markers for diabetes-related bone disease, for example, HR-pQCT, TBS, and pentosidine levels in serum and urine. Because of no

evidence that treatments for diabetes can improve diabetes-related bone fragility and reduce the risk of fracture, the use of anti-osteoporotic drugs should be positively considered for diabetic patients with the increased risk of fracture such as presence of fracture, low BMD including osteopenia, poor glycemic control, long duration of diabetes, treatments with insulin and thiazolidines, and sarcopenia.

Disclosure Summary The authors have nothing to disclose.

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3

Glycemic Goals

Nicholas H. E. Mezitis, Spyros G. E. Mezitis

Abstract

Diabetes mellitus represents a profound fuel utilization disorder, which finds its expression through a convenient biochemical marker, namely an aberrant blood glucose concentration. Our understanding of this illness, classically viewed as a perturbation in the insulin–glucose relationship, now includes an appreciation of the plethora of proinflammatory metabolites identified and the damage a surfeit of these potentially toxic substances can wreak on the vascular endothelium. Nevertheless, blood glucose continues to be viewed as an adequate representation of the circulating fuel mix, since it and its related markers (HbA1c, fructosamine) are easily measured. Restoring euglycemia is considered the goal of our management, in the expectation that it reflects restoration of a global eumetabolic state. The definition of *euglycemia* has been the focus of professional societies and of the research community, in their quest to establish targets for diabetes management with an eye on patient safety and on the prevention of complications, primarily vascular in nature. This chapter considers both the goals selected and the data supporting these choices.

Keywords: Diabetes mellitus pathophysiology: • Glucose toxicity • Insulin therapy • Hypoglycemia • Vascular complications • Glycemic goals, targets, control, • Metabolic memory • DM 2, DM 1, Diabetes in Pregnancy, Prediabetes • Fasting glucose, Postprandial glucose, HbA1c • Glucose fluctuations • Combination Therapy • Circadian cycle • Somogyi phenomenon • 'Dawn' phenomenon • oGTT • Trials: • DCCT • EDIC • WESDR • Kumamoto • DIGAMI • UKPDS • ACCORD • DPP • Clinical Practice Guidelines with Glycemic Targets from Professional Societies: • American

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The core issue in diabetes management, reflected upon and debated since the introduction of insulin therapy, has been that of "control." Pioneers and luminaries in the field have variously agreed on parameters for glycemia and have subsequently argued over the necessity and advisability of all-out efforts to attain them [1, 2]. Central to the argument has been the putative correlation of glycemia with diabetes complications, with increasing levels reflecting increased risk.

For many years, the acceptance of the validity of the axiom that "tight control" is a prerequisite for health and longevity dominated the field of management and was credited with the positive outcomes in the group of survivors represented by the recipients of the Joslin medal [3].

In the era of evidence-based medicine, it has become necessary to justify the increasing expenses involved in employing an expanding armamentarium of sophisticated medications and novel glucose monitoring and drug delivery systems. Proof from clinical trials, that compulsive efforts to achieve glycemic targets benefit morbidity and mortality as expressed by fewer complications, is deemed imperative, if support for present policies is to be sustained.

The first major trial to be initiated with these objectives in mind was the Diabetes Control and Complications Trial (DCCT) conducted between the years 1983–1993 in patients with type 1 diabetes [4]. The 1,441 study participants were followed for an average of 6.5 years. A primary "prevention" cohort with early diabetes (1–5 years) was selected based on the absence of retinopathy and albuminuria in order to assess the benefits of "intensive" glycemic control on *avoiding the appearance* of diabetic eye disease. A secondary "intervention" cohort with diabetes of 5–15 years duration was selected based on the presence of background diabetic retinopathy and microalbuminuria, in order to assess the benefits of "intensive" glycemic control on *arresting the progression* of retinopathy.

Intensive intervention in the DCCT involved attaining fasting (premeal) capillary glucose (CBG) levels 70–120 mg/dL and postprandial (2 h) levels below 180 mg/dL. The goals selected related to the criteria for diagnosis of diabetes mellitus on the standard 2 h 75 g oGTT for nonpregnant adults in 1983 [5]. Treatment modalities in this group consisted of multiple daily injections of insulin (MDI) or continuous subcutaneous insulin infusion (CSII) via insulin pump. Frequent monitoring of CBG (at least four times daily) was required of participants with close supervision by study personnel in monthly meetings and in follow-up telephone support sessions. Education in diet and exercise principles was emphasized.

Conventional therapy in the DCCT permitted insulin administration one to two times daily with once daily glucose monitoring and less frequent (once every 3 months) interaction with study personnel. Emphasis was on avoiding excessive *symptomatic* excursions in glycemia (hypo- or hyper-), rather than on specific targets for their glucose levels.

Monitoring in the DCCT included, apart from CBG records and HbA1c, fundus photography, determinations of 24 h urine albumin excretion, nerve conduction studies, autonomic nerve testing, and clinical evaluation. The intensive therapy cohorts sustained an average HbA1c of 7.2% during the study, as opposed to an average HbA1c of 9.1% in the conventional therapy groups.

Significant outcome differences favoring the intensive therapy groups made it necessary to *terminate the study prematurely*. The primary prevention therapy group saw a 76% reduction in adjusted mean risk for retinopathy, a 34% reduction in microalbuminuria, a 44% reduction in albuminuria, and a 69% reduction in clinical neuropathy. Progression of complications was slowed in the corresponding secondary intervention therapy cohort as well (54% for retinopathy, 43% for microalbuminuria, 56% for albuminuria, 57% for clinical neuropathy). Both peripheral and autonomic neuropathy benefited in the intervention group. Importantly, these benefits in risk reduction in both intensive therapy groups were evident among subgroups as well. Subgroups were defined according to baseline covariates, including age, gender, duration of diabetes, percentage of ideal body weight, level of retinopathy, mean blood pressure, presence of clinical neuropathy, HbA1c at screening, and albuminuria.

Support for the DCCT conclusions, namely that tight glycemic control in type 1 diabetes reduces the risk of onset and progression of microvascular complications, had been previously provided by preliminary results from the Stockholm Diabetes Intervention Study (SDIS), published in 1988 [6]. For that trial, 102 patients with a diagnosis of IDDM, using the terminology of the period, who had nonproliferative retinopathy and unsatisfactory blood glucose control, were randomized to "intensified conventional treatment (ICT)" or "regular treatment." Already at 18 months in the 5 year study the HbA1c was significantly better in the ICT group ($p = 0.00005$) and this translated into risk reduction for progression of retinopathy ($p = 0.024$), microalbuminuria ($p = 0.023$), and peripheral neuropathy (p between 0.0005 and 0.047). These benefits came at the expense of frequent occurrence of hypoglycemia in the ICT group ($p = 0.003$).

The final results from the DCCT and SDIS studies, both published in 1993, popularized intensive insulin therapy as a means to achieve tight glycemic control in diabetes mellitus. Guidelines from professional organizations advocated that these principles be uniformly applied to both Type 1 and Type 2 diabetes, even though the latter group had not been studied in either trial. Moreover, Type 2 diabetes was predominantly associated with macrovascular disease and this complication had not been investigated. Concerns regarding hypoglycemia, hyperinsulinemia, and weight gain all contributed to the controversy.

The Kumamoto Study in Japan [7] proposed to provide answers to the issues of intensive insulin therapy in type 2 diabetes. 110 patients were recruited to replicate the DCCT trial design with an "intensive therapy" group (>2 insulin injections/day) and a "conventional therapy" group (1–2 insulin injections/day). Glycemic targets for the intensive therapy group were fasting glucose <140 mg/dL, 2 h postprandial glucose <200 mg/dL, and HbA1c < 7%. Goals on the conventional therapy group were to avoid symptomatic hypo- or hyperglycemia. Follow-up was for a 6 year period.

The benefits of tight glycemic control with intensive therapy for the onset and progression of diabetic retinopathy, nephropathy, and neuropathy in Type 2 diabetes was confirmed.

The validity of extrapolating the DCCT results to the general population required confirmation in a population-based cohort, since they represented outcomes in a select group of volunteers.

The desired support came from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) [8], which was funded by the National Eye Institute and began in 1979. It involved all

persons with Type 1 (996) and Type 2 (1370) diabetes in an 11-county area in southern Wisconsin and sought to identify the incidence of retinopathy and other diabetes complications, including the level of health care delivery and the presence of risk factors (poor glycemic control, smoking, and hypertension) in this population. Comparison with DCCT was made with the WESDR Type 1 group which met DCCT criteria for the primary (39) and secondary (111) cohorts and underwent a 4-year follow-up assessment. The DCCT and WESDR groups were comparable for age, gender, BMI, blood pressure, and insulin dose. Once again, the severity of retinopathy was found to be related to higher glycosylated hemoglobin levels, among other factors, supporting the relevance of DCCT findings for all patients with Type 1 diabetes mellitus.

The question that remained to be answered was that of the relationship of levels of glycemia to complications of diabetes, since hypoglycemia was and continues to be a major concern in any intensive therapy regimen. The DCCT Research Group addressed this issue in a retrospective analysis of data from their original trial correlating HbA1c results to retinopathy progression [9]. A continuously increasing risk, importantly even for HbA1c levels < 7%, was demonstrated (Fig. 1). Statistically, a 10% reduction in HbA1c translated into a 39% decrease in retinopathy progression *without a threshold value*.

Another issue that arose related to the "metabolic memory" for management choices made in the past, allowing for later changes in the regimen. To investigate this concern, subjects completing the DCCT in 1993 were offered the opportunity to volunteer for a follow-up observational study, where all participants were managed with the original intensive therapy protocol. The majority of subjects (1,375 of 1,421) elected to continue in the new Epidemiology of Diabetes Intervention and Complications (EDIC) study [10]. Results reported in 2014 confirmed that despite the convergence of glycemic control after the DCCT study for both the intensive therapy and conventional therapy treatment groups to HbA1c ca. 8%, differences in the development and

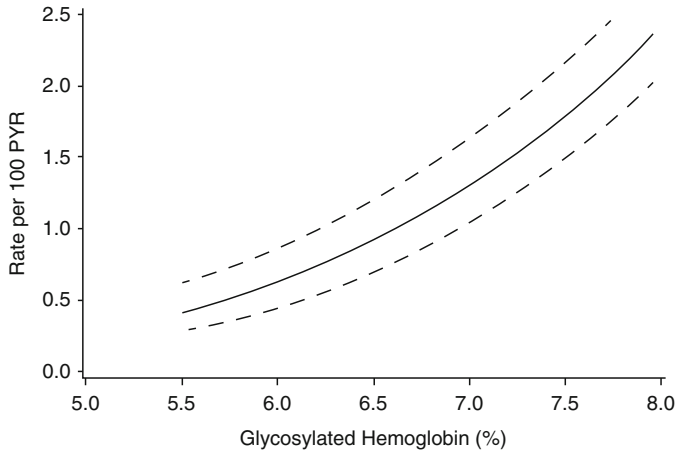


Fig. 1: The absolute risk of sustained retinopathy progression (hazard rate per 100 patient-years) in the combined treatment groups as a function of the updated mean HbA1c during follow-up in the DCCT, estimated from a Poisson regression model with 95% confidence bands: rate vs values of HbA1c [9].

progression of retinopathy, nephropathy, and neuropathy were still evident 10 years later, based on initial therapy (DCCT) assignment. Good glycemic control, once achieved, unequivocally conferred long-term benefits (Fig. 2).

Furthermore, another analysis of the DCCT and EDIC data for glucose variability using the mean amplitude of glycemic excursions (MAGE) index [11] failed to show a relationship to complications by EDIC year 4, underscoring the undisputed importance of long-term glucose control expressed by the HbA1c, as a predictor of small vessel complications [12].

The microvascular benefits described were mirrored by macrovascular outcomes [13]. Lower levels of HBA1c were associated with a lower incidence of cardiovascular events, i.e., fatal or nonfatal myocardial infarction or CVA (MACE), suggesting a salutary and sustained role of intensive diabetes control on the development and progression of atherosclerosis (Fig. 3).

Other studies have attempted to address the same question, namely if good glycemic control protects from macrovascular complications. The long-term (8 years) results from the Kumamoto study, which included 110 individuals with Type 2 diabetes, showed clear benefit in the intensive therapy versus the conventionally treated group on cardiovascular, cerebrovascular, and peripheral vascular events, but did not have the power (N) to achieve statistical significance [14].

The Kumamoto investigators' exploration of the mechanisms through which hyperglycemia mediates vascular damage revealed an association with increased production of reactive oxygen species and lipid peroxidation, as demonstrated by measurements of the marker 8-hydroxy-deoxy-guanosine in the urine [15].

Other important trials also sought to demonstrate the importance of good glycemic control in avoiding macrovascular complications. The United Kingdom Prospective Diabetes Study (UKPDS) with 5,000 newly diagnosed Type 2 diabetes patients and the Diabetes Mellitus Insulin

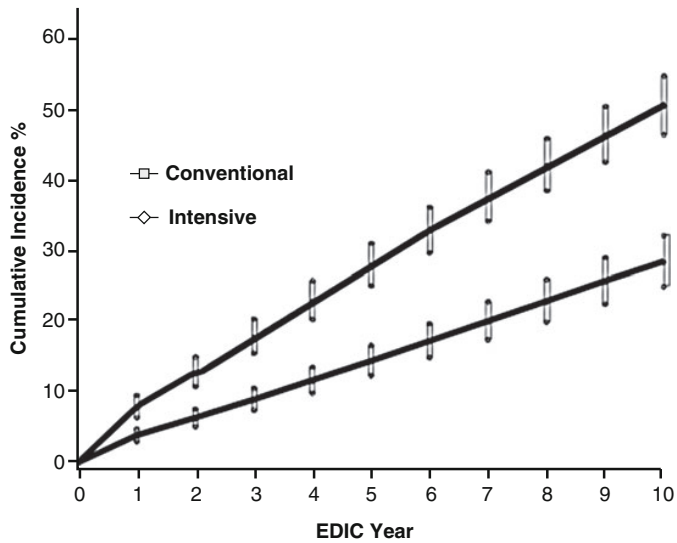


Fig. 2: After adjustment for diabetic retinopathy (*DR*) severity at DCCT closeout, the cumulative incidence of further DR progression during the first 10 years of EDIC follow-up is shown (*Top curve*: conventional therapy; *Bottom curve*: intensive therapy) [10].

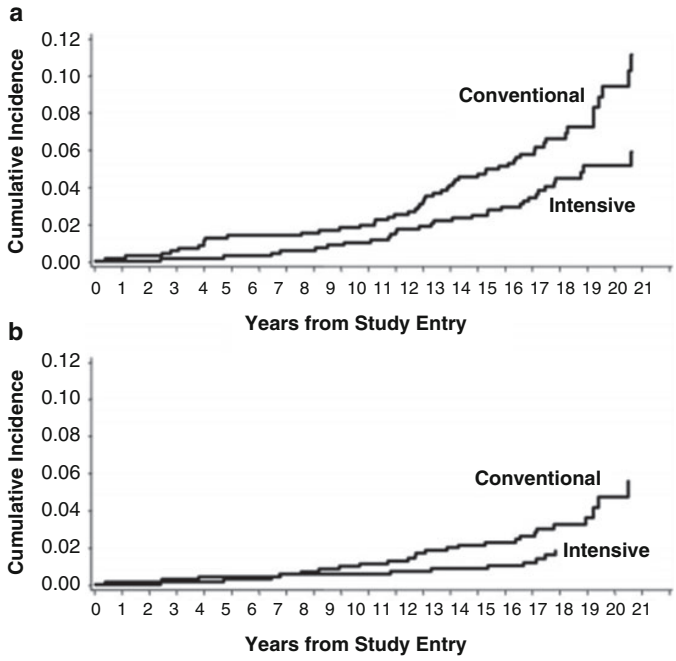


Fig. 3: DCCT/EDIC Trial: cumulative incidence of clinical CVD outcomes (**a**) Any qualifying primary outcome event. (**b**) MACE [70].

Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study in Scandinavia with 620 patients studied an outpatient and an inpatient population respectively.

In the UKPDS [16], a continuous association between the risk of myocardial infarction and the level of glycemia was documented, albeit less pronounced than that for microvascular complications (Fig. 4)

In the DIGAMI study [17], patients admitted to the coronary care unit and treated with intravenous insulin had 31% lower mortality at 1 year follow-up, compared to the group treated with multiple daily injections (Fig. 5)

Other trials have followed to further elucidate the relationship of glycemic control and cardiovascular risk in the ever-increasing population of patients with Type 2 diabetes mellitus. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [18] was conceived specifically with this goal in mind and aspired to provide a definitive answer by recruiting 10,251 patients in 77 clinical centers across the United States and Canada. Study participants were adults with a median HbA1c of 8.1%. Cardiovascular disease or "anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, current status as a smoker, or obesity)" were prerequisites for inclusion in the study. Random assignment to an intensive therapy group targeting an HbA1c < 6.0% or a standard therapy group with an HbA1c goal between 7.0% and 7.9% followed. Metformin, insulin secretagogues, thiazolidinediones, disaccharidase inhibitors, incretins, and "insulins" were used either as single agents or in combination regimens. Interestingly,

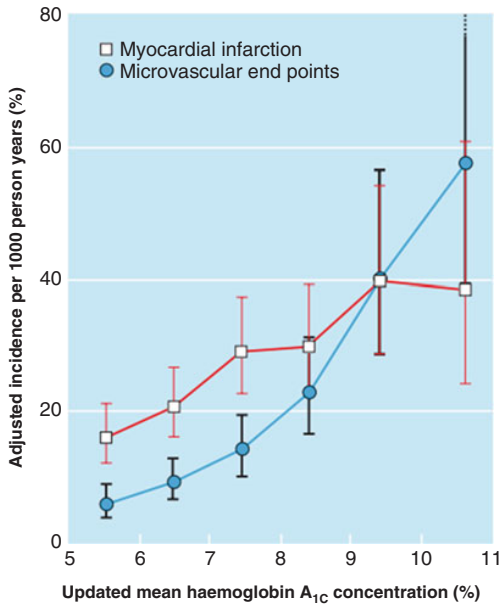
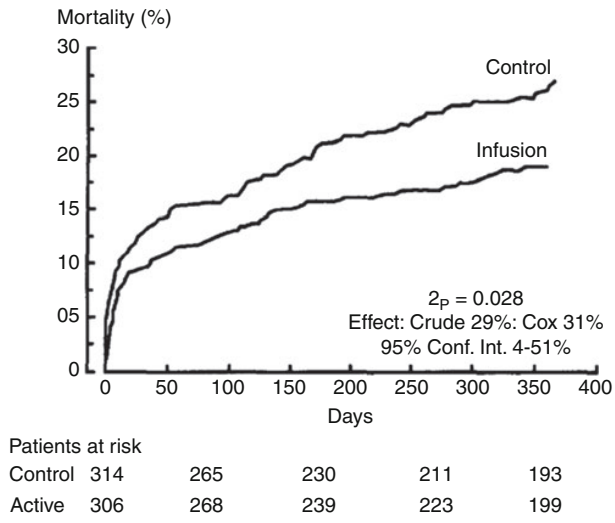


Fig. 4: Incidence rates and 95% confidence intervals for myocardial Infarction and microvascular complications by category of updated HbA1C concentration, adjusted for age, sex and ethnic group, expressed for white men aged 50-54 years at diagnosis and with mean duration of diabetes of 10 years [16].



Patients at risk

Control	314	265	230	211	193
Active	306	268	239	223	199

Fig. 5: Actuarial mortality curves in the patients receiving insulin-glucose infusion and in the control group during 1 year of follow-up. Numbers below the graph = number of patients at different times of observation. Active = patients receiving infusion conf. Int. = confidence interval [17].

the number of subjects exposed to combinations of four or five classes of oral agents with (526) or without (539) insulin was significantly greater in the intensive therapy group compared to the standard therapy group (36 and 67, respectively). Rosiglitazone was used liberally in the intensive therapy group (91.2% vs. 57.5%) and the important distinction of insulins versus insulin analogues was not reported. Adding to complexity of evaluation, some subjects were further assigned to intensive versus standard antihypertensive treatment and some were assigned to a combination of statin and fibrate therapy with lipid control in mind.

The ACCORD trial was interrupted for the diabetes management arm after data at 3.5 years showed that incidence of death (from any cause and from cardiovascular causes) was greater (5.0% vs. 4.0%) in the group targeting a glycated hemoglobin level less than 6.0%.

This study has reignited the debate over the advisability and necessity of "tight" glycemic control in Type 2 diabetes mellitus. Many other trials [19] have subsequently targeted the issue of cardiovascular outcomes in therapy for Type 2 diabetes mellitus (Table 1).

In particular, after the controversial meta-analysis by Nissen [20, 21] associating cardiovascular complications with the use of rosiglitazone, all oral agents for diabetes treatment under consideration for FDA approval are to include data on cardiovascular outcomes. Drugs already on the market are following suit with their own studies.

The focus on vascular complications of diabetes mellitus, however, must not distract our attention from the profound effects of hyperglycemia on other systems such as collagen [22, 23], bone [24, 25], and the immune system [26]. Effects on telomere length have wider implications [27].

Telomeres are specialized DNA-protein structures at the end of all chromosomes, which shorten with cell division triggering cell senescence once mean length reaches a critical value. Telomere "attrition" relates both to DNA polymerase inability to fully copy chromosomal strand ends and to the inefficiency of DNA repair mechanisms operating in these regions of the genome.

Table 1: Clinical trials enrolling people with type 2 diabetes with cardiovascular outcomes as the primary endpoint [19].

Study Completed	Intervention	Enrollment (n)	Completion
ORIGIN	Insulin glargine	12,537	2012
SAVOR	DPP-4 inhibitor: saxagliptin	16,492	2013
EXAMINE	DPP-4 inhibitor: alogliptin	5,384	2013
TECOS	Dpp-4 inhibitor: sitagliptin	14,000	2015
ELIXA	GLP-1 RA: lixisenatide	6,000	2015
In progress			
EMPA-REG OUTCOME	SGLT-2 inhibitor: empagliflozin	7,097	2015
LEADER	GLP-1 RA: liraglutide	9,340	2015
ASCEND	Aspirin/omega-3 fish oil	15,480	2016
CANVAS	SGLT-2 inhibitor: canagliflozin	4,407	2017
EXSCEL	GLP-1 RA: weekly exenatide	14,000	2018
TOSCA IT	TZD or SU (stroke study)	3,371	2018
CAROLINA	DPP-4 inhibitor: linagliptin	6,00	2018
REWIND	GLP-1 RA: dulaglutide	9,622	2019
DEVOTE	Insulin degludec	7,638	2016
DECLARE	SGLT-2 inhibitor: dapagliflozin	17,150	2019
VERTIS	SGLT-2 inhibitor: ertugliflozin	3,900	2020
Total		**152,418**	

Unfortunately, telomeric DNA is particularly prone to oxidative damage such as that associated with hyperglycemia. The study by Salpea et al. demonstrated that leukocyte telomere length was on average 780 base pairs shorter in study subjects with diabetes mellitus Type 2 compared to controls without diabetes mellitus, "*representing a biologic age gap of approximately 24 years*" [28].

The impact of hyperglycemia, with the associated metabolic perturbations (i.e., increased circulating levels of triglycerides, free fatty acids, superoxide radicals) accompanying fluctuations in this marker, unquestionably wreaks havoc throughout the body and results in accelerated aging (progeria), an acquired immune deficiency state, and premature death.

In view of the pandemic scale of hyperglycemia in the population worldwide [29 Table 2] and with an impressive panoply of medications targeting all aspects of fuel economy in the body, it remains to make an informed choice in matching therapy to the appropriate patient.

Customization of therapy is the key to successful outcomes in the management of diabetes. In-depth knowledge of the patient, including their social circumstances, diet preferences, and obstacles to achievement of goals, is a prerequisite to planning treatment.

The American Diabetes Association [30], the American Association for Clinical Endocrinology with the Endocrine Society [31], the European Association for the Study of Diabetes [32], and other professional organizations have all published clinical practice guidelines specifying targets for glycemia in patients with diabetes mellitus. The Diabetes Prevention Program (DPP) trial [33] has demonstrated the efficacy of intervention in the population with prediabetes as well. Of note, as of 2011 the HbA1c is not simply an index of glycemic control in management, but has also been globally accepted as an independent diagnostic criterion for diabetes mellitus [34].

Efforts to achieve glycemic goals are associated with adverse effects as well. These may be side effects associated with the drugs used, but they also include hypoglycemia [35] and weight gain. In the DCCT trial, for example, 65% of patients in the intensive therapy group had at least one episode of hypoglycemia requiring assistance during their participation, compared to 35% with similar experiences in the conventionally treated subjects group [36]. In addition, after 6.5 years in the study, 33.1% of subjects in the intensive therapy group were identified as overweight, compared to 19.1% in the group managed with conventional therapy [37].

The hospitalized patient [38] is particularly vulnerable to hypoglycemia with the emphasis on accelerating control for shortened hospital stays and the mismatch between meals and insulin schedules. Likewise, the risks of hyperglycemia associated with recovery, healing, and superinfection [39] underscore the importance of cogent algorithms for insulin management [38, 40; Fig. 6], rather than ad hoc "sliding scales" [41].

The key to achieving targets for glycemia (Table 3) is the annotated record of capillary blood glucose results with preprandial (fasting) and postprandial sampling (Fig. 7). Values at both time points are of importance, with the understanding that glycemic variability [43, 44], its peaks and troughs (Fig. 8), relates to tissue damage and malfunction [45–48], and should guide modifications in therapy [49].

The first step in diabetes management is to dose medications to a level avoidinghypoglycemia. This prevents the Somogyi phenomenon [50], otherwise known as "rebound" event, which destabilizes the profile for many hours and confuses dosing decisions.

Table 2: Multivariate-adjusted prevalence† of prediabetes and prevalence change for the U.S. population aged 12 years and older by sociodemographic characteristics and BMI, NHANES, 1999–2010 [29].

Characteristic	Prevalence (95% CI) by survey periods			Absolute prevalence change		
	T1 (1999–2002)	T2 (2003–2006)	T3 (2007–2010)	T2–T1	T3–T2	T3–T1
Overall population	28.3 (26.0–30.6)	28.1 (25.9–30.3)	34.3 (32.7–35.9)	−0.2	6.2***	6.0***
Adults aged ≥ 18 years	30.2 (27.8–32.6)	29.9 (27.5–32.3)	36.5 (34.7–38.3)	−0.3	6.6***	6.3***
Age (years)						
12–17	13.3 (10.1–16.5)	14.6 (11.6–17.6)	17.9 (13.4–22.4)	1.3	3.3	4.6
18–44	20.1 (17.0–23.2)	19.6 (17.3–21.9)	25.6 (23.0–28.2)	−0.5	6.0**	5.5*
45–64	36.7 (33.4–40.0)	36.6 (31.6–41.6)	45.5 (41.9–49.1)	−0.1	8.9**	8.8**
≥65	44.7 (41.5–47.9)	44.4 (40.0–48.8)	48.2 (46.0–50.4)	−0.3	3.8	3.5
Sex						
Male	34.7 (31.4–38.0)	33.4 (30.3–36.5)	38.8 (36.6–41.0)	−1.3	5.4*	4.1*
Female	22.1 (20.2–24.0)	23.0 (20.9–25.1)	30.0 (27.9–32.1)	0.9	7.0***	7.9***
Race/ethnicity						
Non-Hispanic white	28.0 (25.2–30.8)	27.5 (24.7–30.3)	33.9 (31.7–36.1)	−0.5	6.4***	5.9**
Non-Hispanic black	24.0 (20.6–27.4)	27.6 (24.5–30.7)	36.0 (31.8–40.2)	3.6	8.4**	12.0***
Mexican American	34.4 (30.5–38.3)	30.3 (26.6–34.0)	37.8 (33.9–41.7)	−4.1	7.5*	3.4
PIR						
<1	28.2 (23.6–32.8)	28.9 (25.1–32.7)	39.4 (36.0–42.8)	0.7	10.5***	11.2***
1–2.9	27.7 (25.1–30.3)	28.6 (25.9 –31.3)	34.8 (32.7–36.9)	0.9	6.2***	7.1***
≥3	28.7 (25.6–31.8)	27.5 (24.3–30.7)	32.5 (30.1–35.0)	−1.2	5.0*	3.8
BMI (kg/m^2)						
<25.0	19.5 (16.7–22.3)	19.5 (16.8–22.2)	27.9 (25.0–30.8)	0.0	8.4***	8.4***
250.–29.9	30.8 (27.8–33.8)	29.6 (26.5–32.7)	35.7 (32.9–38.5)	−1.2	6.1**	4.9*
≥30.0	35.5 (32.4–38.6)	36.1 (32.9–39.3)	40.5 (37.1–43.9)	0.6	4.4	5.0*

P values were calculated from *t* test. †Estimated from a logistic regression model, controlling for age, sex, race/ethnicity, PIR, and BMI. Individuals for other racial/ethnic groups are included in the denominator but their separate estimates are not presented.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

The second step is to establish control of the fasting blood glucose, which is influenced both by the timing of the preceding evening's meal and by the "dawn phenomenon" [51], in which insulin counter regulatory hormones unchecked promote excessive glycogenolysis.

The third step is to ensure a match between balanced diet and medication, with an emphasis on timing of meals and timing and dosing of drugs, carefully taking pharmacokinetics and drug interactions into consideration [52].

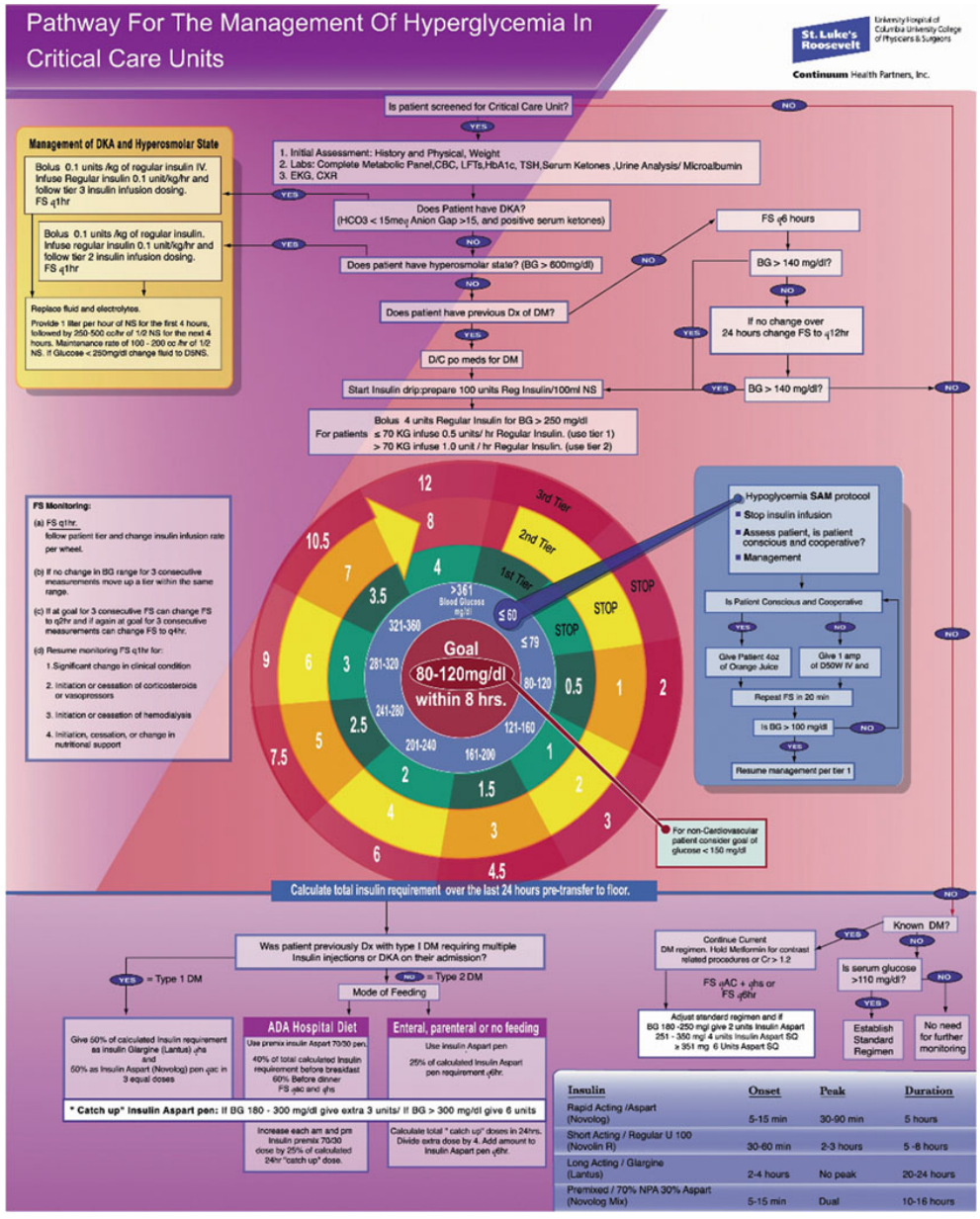


Fig. 6: Pathway for the management of hyperglycemia in critical care units [38].

Adjustments for exercise are key considerations, particularly for patients using insulin and calculating carbohydrate ratios and sensitivity factors [53].

In pregnancy, optimization of glycemic control (Fig. 9) is of particular importance for birth outcomes [53] and for sequelae of " metabolic memory" impacting both the mother and her

Table 3: Summary of glycemic recommendations for nonpregnant adults with diabetes [42].

A1C	<7.0%[a]
Preprandial capillary plasma glucose	80–130 mg/dL[a] (7.2–4.4 mmol/L)
Peak postprandial capillary plasma glucose[b]	<180 mg/dL[a] (<10.0 mmol/L)

[a]More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawarencess, and individual patient considerations
[b]Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes

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DATE	Before Breakfast	2 Hours After Breakfast	Before Lunch	2 Hours After Lunch	Before Dinner	2 Hours After Dinner	Before Bed	3.00 A.M
COMMENTS								
COMMENTS								
COMMENTS								
COMMENTS								
COMMENTS								
COMMENTS								

Fig. 7: Sample of **annotated glucose record** (UMA Endocrine Diabetes Care and Education Center, Athens, Ohio) for listing capillary blood glucose results in relationship to meals with commentary explaining aberrant values [38].

offspring many years into the future [55]. Glycemic targets for pregnancy have been defined by the American Diabetes Association [56] and the American College of Obstetrics and Gynecology [57] with separate reference to females with gestational diabetes and to those with preexisting diabetes mellitus. The Endocrine Society has succinctly, and appropriately, defined consistent targets for all pregnant females with diabetes mellitus [54]. Recent evidence from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study found that there is a continuous linear relationship between maternal glucose levels and fetal hyperinsulinism, as reflected by C-peptide levels in cord blood [58].

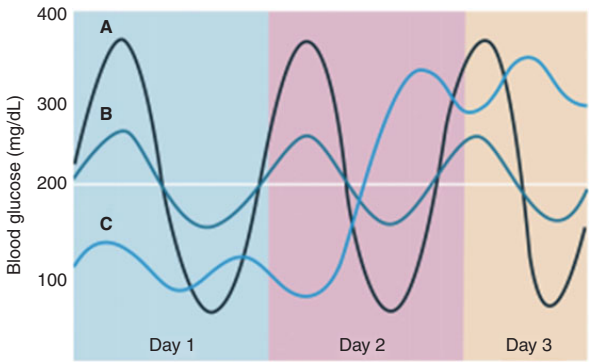

Fig. 8: Glycemic variability in three hypothetical patients who have the same mean blood glucose concentration. Patient B has relatively small variations during the day and on different days; this patient should have little difficulty in lowering daily mean blood glucose concentrations without inducing hypoglycemia. In comparison, patient A has marked blood glucose variations on the same day and patient C has marked blood glucose variations on different days, making control more difficult [43].

Glycemic Targets in Pregnancy

- Preprandial≤95mg/dL(5.3 mmol/L) and either
- One-hour postmeal ≤140 mg/dL (7.8 mmol/L) or
- Two-hour postmeal ≤120 mg/dL (6.7 mmol/L)

Fig. 9: Glycemic Targets in Pregnancy [54].

Goals for the elderly, the terminally ill, those with unpredictable meal preferences, must be considered carefully and are frequently liberalized in the interest of avoiding hypoglycemia (Fig. 10).

Children and juveniles also represent special groups that require sensitive implementation of behavior modification to slowly achieve desired levels of glycemic control without undermining self-confidence and contributing to the perception of an anomalous existence.

Baseline HbA1c appears to be a decisive factor in determining final glycemic control in Type 2 diabetes, with patients at higher levels being less likely to achieve target HbA1c < 7% [59, 60]. Other studies have suggested that patients with baseline HbA1c > 9% were less likely to maintain HbA1c at target levels achieved, compared to those with baseline HbA1c < 7.9% [61]. These results should not be interpreted with pessimism but should be viewed as reflecting beta cell reserve, and should serve as a guide for intensification of intervention involving both counseling for behavior modification and combination therapy, including insulin. Realistic self-monitored blood glucose targets should be defined to assist patients in achieving individualized HbA1c goals [62].

Key to the comprehension of the importance of "glycemic targets" and "glycemic control," irrespective of the cacophony generated in the clinical trials literature, is the fundamental axiom that the regulation of biological functions involves rhythms.

These rhythms relate to metabolic processes in prokaryotes [63] and eukaryotes alike and apply to the function of all cells. Increasing complexity in cellular association characteristic

of higher-order organisms demands harmony of a multitude of oscillations in order to ensure optimal function, which we identify as "health." The smooth interrelationship of cellular pacemakers receives vital cues from the environment with its circadian cycle, as documented in the new fields of Chronobiology and Chronotherapeutics [64, 65]. The subtle oscillations of glucose in this paradigm relate to those of other substrates, e.g., free fatty acids [66] and protein [67], hormones, and the nervous system in a seamless pattern of "entrainment." Derangement in the glycemic profile generates profound perturbations in rhythms throughout the body, damaging tissues and interfering with restorative functions. The glycemic targets proposed by professional societies and described in this chapter represent an effort to introduce acceptable limits for glucose fluctuations in the fasting and fed states. They are the product of consensus based on the best available data, with the understanding that the swings in the profile considered adequate in providing a stable fuel supply for the central nervous system and peripheral tissues and in limiting tissue damage are still a far cry from the harmonious rhythm created by the message of the healthy beta cell interacting with fully functional receptors throughout the body. Our challenge is to study the patient's profile and its relationship to the environment and to select and employ medications and

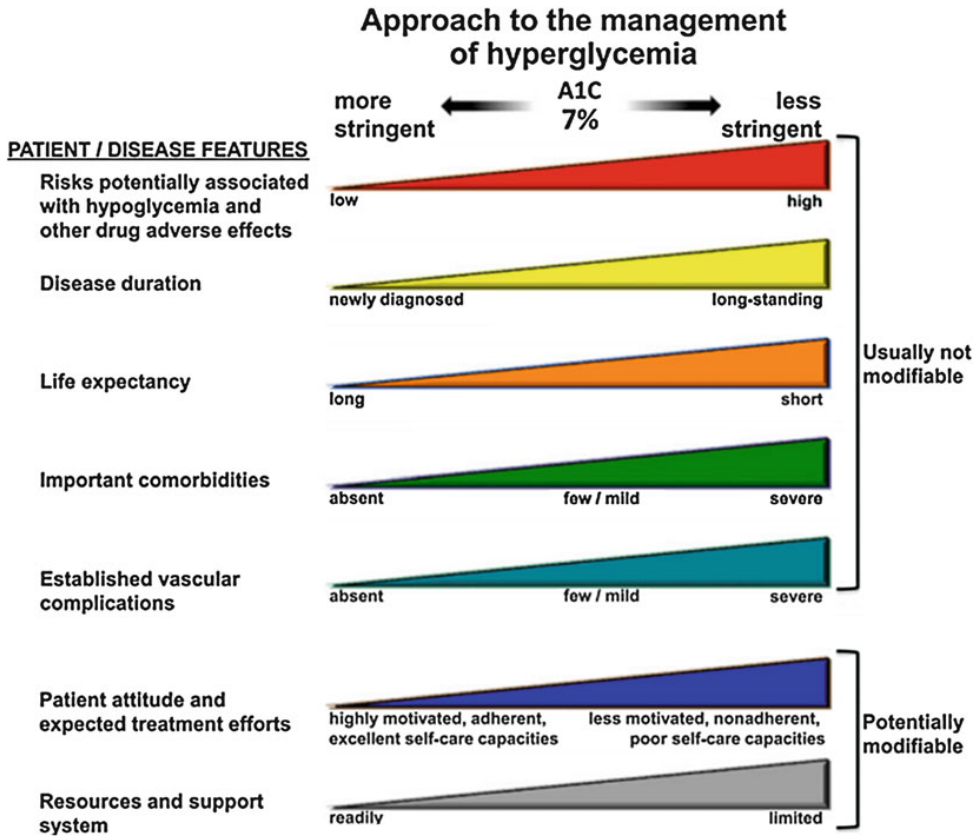

Fig. 10: Hyperglycemia management goals vary according to patient and disease features listed (*left*) [42].

resources judiciously, in targeted fashion, and appropriately timed. Restoration of harmonious rhythm is the reward for the patient and the physician alike.

Summary

In the era of combination therapy, introduced in the 1990s [68, 69], and popularized in this decade with the introduction of many new classes of diabetes medications, both oral and injectable, the importance of the maxim "primum non nocere" acquires special significance. The value of achieving near normal glycemia in diabetes management is irrefutable, but a quote from Sir William Osler most accurately epitomizes our current therapy guidelines: "Ask not what disease the person has, but rather what person the disease has."

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4

Screening, Diagnosis, and Management of Gestational Diabetes

Lisa E. Moore

Fast Facts

- The best method of screening for gestational diabetes mellitus (GDM) is controversial.
- Diagnosis of type 2 diabetes during pregnancy is controversial.
- The American Diabetes Association (ADA), the International Association of Diabetes in Pregnancy Study Group (IADPSG), and the American College of Obstetricians and Gynecologist (ACOG) have each proposed different methods of diagnosis and screening.
- Depending on the method used, up to 25% of pregnancies in the United States are affected by GDM.

Introduction

Gestational diabetes mellitus (GDM) is glucose intolerance with onset or first recognition during pregnancy. This definition, though standard, is suitable only for categorization. During pregnancy, patients may have undiagnosed type 2 or, rarely, type 1 diabetes. They would still fall under the designation of GDM. This is problematic because the complications for both the mother and the fetus differ between GDM and preexisting diabetes. The definition does have the advantage of allowing a uniform approach to detection and classification of diabetes during pregnancy.

Why Should We Screen for GDM

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study was conducted at 15 centers in 9 countries. Data was collected and analyzed for 23,316 women who underwent a 75 g OGTT between 24 and 32 weeks. The study found a strong continuous association with maternal blood

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Table 1: Diagnostic values after a 100 g OGTT.

	O'Sullivan whole blood values	Values modified to use plasma (NDDG)	Carpenter and Coustan modification
Fasting		105	95
1 h	165	190	180
2 h	143	165	155
3 h	127	145	140

glucose levels lower than the level considered consistent with diabetes and poor maternal, fetal, and neonatal outcomes [1, 2].

Diabetes during the pregnancy increases the risk of preeclampsia, of macrosomia, and of neonatal hypoglycemia, hypocalcemia and respiratory distress [3, 4].

GDM increases the risk of type 2 diabetes. It has been projected that 50% of women with GDM will develop type 2 diabetes within 30 years of the index pregnancy. Hispanic women with a diagnosis of GDM have a 60% chance of developing type 2 diabetes within 5 years unless lifestyle modification is undertaken [4].

The concept of the "fetal origin of adult disease" or in utero programming indicates that the offspring of diabetic mothers are at increased risk of childhood obesity, metabolic syndrome, and type 2 diabetes [5, 6].

Identification of women with GDM represents an opportunity to disrupt the process of evolving glucose intolerance in the patient and in her children.

Screening/Diagnosis of GDM

The two-step screening process currently endorsed by ACOG was based on work by O'Sullivan and Mahan, who created cutoffs for diagnosing GDM based on a 100 g glucose load [7]. Interestingly these values were retrospectively validated based on their ability to predict future development of diabetes and were not related to fetal outcomes. In 1973 the same group introduced the 50 g load as a screening test and reported that a cutoff of 130 mg/dL was 79% sensitive and 87% specific for GDM. The values of the original O'Sullivan glucose tolerance test are still used today though they were modified in 1979 by the National Diabetes Data Group (NDDG) to adjust for the use of plasma instead of whole blood. Carpenter and Coustan used a more specific method of quantifying blood glucose and recommended using lower values as cutoffs [3].

Table 1 shows the original O'Sullivan values and the NDDG and Carpenter and Coustan values. Either NDDG or Carpenter and Coustan values can be used for the diagnosis of GDM. They are both endorsed by ACOG.

In 2010, the American Diabetes Association (ADA) working with the IADSP made the following recommendations for the diagnosis of GDM [8]:

- A fasting plasma glucose (FPG) > 126 mg/dL or a random blood glucose > 200 mg/dL is diagnostic of diabetes, and no glucose challenge is required.
- Either one-step testing using the 75 g 2 h oral glucose tolerance test (OGTT) or the two-step approach currently used in the United States can be used to diagnose GDM.

In 2013, the World Health Organization (WHO) gave guidelines for the diagnosis of overt diabetes during pregnancy and for the diagnosis of GDM [9].

To diagnose overt diabetes in pregnancy, one or more of the following criteria must be met:

Fasting plasma glucose ≥ 126 mg/dL

Two hour plasma glucose ≥ 200 mg/dL after a 75 g glucose load

A random plasma glucose ≥ 200 mg/dL in the presence of symptoms of diabetes

WHO additionally recommended that GDM should be diagnosed at any time in pregnancy if one or more of the following criteria are met:

- Fasting plasma glucose of 92–125 mg/dL (note 126 mg/dL is indicative of preexisting diabetes)
- One hour plasma glucose ≥ 180 mg/dL after a 75 g load
- Two hour plasma glucose between 153 and 199 mg/dL after a 75 g glucose load

These values were adopted from the IADPSG consensus panel [10] and are endorsed by the American Diabetes Association (ADA). They were chosen based on the odds ratio of 1.75 for adverse neonatal events such as macrosomia, elevated C-peptide levels, and percent body fat >90th percentile.

Currently in the United States, the American College of Obstetricians and Gynecologists (ACOG) has not adopted one-step testing. It is worth pointing out that the lack of a worldwide consensus on the diagnosis of diabetes in pregnancy significantly limits the ability to define the worldwide prevalence of GDM and makes comparisons between studies that use different difficult criteria.

Conclusions of the 2013 NIH consensus on diagnosing gestation diabetes were that two-step testing identified 5–6% of the population as having GDM. The use of the 75 g 1 h test would increase the prevalence of GDM to 15–20%. It is not known whether these additional women would actually benefit from treatment. They concluded that there was not sufficient evidence to support adoption of the one-step testing [11].

In 2014 the United States Preventive Services Task Force (USPSTF) endorsed both two-step and one-step testing [12].

Who to Screen for GDM

Universal vs targeted screening.

Universal: every pregnant woman without known preexisting diabetes is screened.

Targeted: screen only those women with risk factors. Risk factors for GDM are shown in Table 2.

Due to the possible complications of undiagnosed gestational diabetes, universal screening is recommended.

Table 2: Risk factors for GDM.

Two or more are considered high risk for GDM
Advanced maternal age
Obesity
Ethnicity (highest to lowest—Native American, Asian, Hispanic, African American, non-Hispanic White)
GDM in previous pregnancy
Previous macrosomic infant
Previous unexplained fetal death
Previous polyhydramnios
Polycystic ovarian syndrome
Metabolic syndrome
First degree relative with type 2 diabetes

When to Screen for GDM

Screening is traditionally done between 24 and 28 weeks. Insulin resistance increases during the second trimester due to placental hormones and other physiologic adaptations of pregnancy [13].

Patients with a previous history of GDM, a body mass index ≥ 30, and known impaired glucose tolerance or members of high-risk ethnic groups should be screened at the first prenatal visit [2, 4]. The test should be repeated at 24–28 weeks if initially negative.

For women who fail the 1 h but pass the 3 h at 28 weeks, an additional 11% will fail the 3 h if repeated in 4–6 weeks. A repeat 3 h test should be considered for ultrasound-proven fetal growth >85%.

How to Screen for GDM

Screening for GDM can be performed by either one-step testing or two-step testing. If you fall under the umbrella of ACOG, the current recommendation is for two-step testing. The ADA supports one-step testing and the USPSTF endorses both.

Two-Step Testing

Step 1. Screening for GDM: Step 1 identifies women who may have GDM and should be given the diagnostic 3 h test. Step 1 consists of a 50 g oral glucose load. The patient does not have to be fasting. Technically it should be done after 3–5 days of a high-carbohydrate diet. Suggested cutoffs range from 130 to 140 mg/dL. A cutoff of 130 mg/dL or 135 mg/dL identifies more patients and should be used in populations with a high rate of diabetes.

Patients who meet or exceed the cutoff for step 1 then go to step 2.

Step 2: Diagnosis of GDM: Step 2 consists of a 100 g oral glucose load. Blood sugar is checked prior to receiving the glucose and at 1, 2, and 3 hours after the glucose load. The patient must be fasting. Table 1 shows the NDDG and Carpenter and Coustan values. Two or more values that meet or exceed the cutoffs are diagnostic of GDM. Table 3 provides an overview of the different criteria for diagnosing GDM worldwide.

One-Step Testing

The patient should be fasting. The fasting blood glucose is measured, and a 75 g oral glucose load is given. Blood glucose is then checked at 1 and 2 h. One abnormal value makes the diagnosis of GDM. Recommended cutoffs are fasting ≥ 92 mg/dL, 1 h ≥ 180 mg/dL, and 2 h ≥ 153 mg/dL.

Management

Patients with gestational diabetes should check their blood glucose four times each day: fasting and either 1 or 2 h after each meal.

Glycemic goals are fasting <95 mg/dL, 2 h postprandial < 120 mg/dL, or 1 h postprandial < 140 mg/dL.

Failure to meet these glycemic goals with appropriate diet and exercise requires the addition of medication. If 20% of all values or 20% of the values for a specific testing period (i.e., fasting or postprandial breakfast, lunch, or dinner) are above the glycemic goals for a consecutive 2 weeks, medication should be started.

Example 1: A patient checks blood glucose four times a day, and over a 7 day period, three of her fastings are high. She returns in 1 week and two of her fastings are high. This meets the rule that 20% of her values during a specific testing period (i.e., fasting) are abnormal for 2 consecutive weeks.

Example 2: A patient checks blood glucose four times a day, and over a 7 day period, her abnormal values are 5/7 fasting abnormal, 3/7 breakfast abnormal, 3/7 lunch abnormal, and 1/7 dinner abnormal. Her food diary was reviewed, and she was counseled about carbohydrate intake and advised to have 30 min of exercise each day. She returns in 1 week. She has reduced her carbohydrates and is walking 15–30 min a day. Her abnormal values for the 7 day period are 3/7 fasting abnormal, 3/7 breakfast abnormal, 1/7 lunch abnormal, and 2/7 dinner abnormal. Greater than 20% of her values for 2 consecutive weeks have been abnormal, and she is a candidate for medication.

This may seem very quick, and there is a tendency to wait another week or two to see what happens. Consider that 2 weeks is equivalent to 5% of the baby's total in utero life. Four weeks is 10% of the baby's total in utero life. The longer that medication is delayed the greater the length of time that the baby is exposed to high blood glucose.

Table 3: Diagnostic criteria for GDM.

Committee	Guidelines			Comments
ACOG [15]	Two step testing at 24–28 weeks			1 h cutoff of 130 mg/dl identifies more people but some will be normal
	Step 1: 50 g load test in 1 h			140 mg/dl identifies fewer people but they are more likely to have glucose intolerance
	Nonfasting			For the 3 h, Coustan values identify 50% more patients
	Cutoff (130–140)			
	Step 2: 100 g load			
	Test fasting 1,2,3 h limits are			
		Coustan	NDDG	
	Fasting	95	105	
	1 h	180	190	
	2 h	155	165	
	3 h	140	140	
	ADA			
	2 abnormals make the dx			
IADP SG 2010 [10]	1 step 75 g 2 h OGTT			Using IADP guidelines ~18% of US women will have dx of GDM
	Fasting < 92 mg/dl			IADPSG also supports a dx of overt diabetes for a fasting ≥126 mg/dl
	1 h < 180 mg/dl			
	2 h < 153 mg/dl			
	1 abnormal makes the dx			
ADA 2016 [16]	Supports either one-step or two-step testing			ACOG recommends 130–135 mg/dl in high prevalence populations
	One-step testing			Either carpenter and Coustan values or the NDDG values can be used
	75 g-OGTT			
	F ≥ 92 mg/dl			
	1 h ≥ 180 mg/dl			
	2 h ≥ 153 mg/dl			
	Two step testing			
	(1) 50 g glucose load			
	1 h ≥ 140—Go to step 2			
	(2) 100 g OGTT			
		C/C	NDDG	
	F	≥95 mg/dl	105 mg/dl	
	1 h	≥180 mg/dl	190 mg/dl	
	2 h	≥155 mg/dl	165 mg/dl	
	3 h	≥140 mg/dl	145 mg/dl	

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NICE 2015	2-h 75 g OGTT	www.Nice.Org.uk/guidance/ng3
	In women with risk factors	To convert mmol/l to mg/dl multiply by 18
	If GDM in previous pregnancy	
	Offer test at first visit and repeat at 24–28 weeks if necessary	
	If fasting ≥ 5.6 mmol/l (100 mg/dl)	
	OR	
	2-h ≥ 7.8 mmol/l	
	140 mg/dl	
USPSTF 2014 [12]	Either 1-step or 2-step testing may be used	

ACOG American College of Obstetricians and Gynecologists, *IADP* International Association of Diabetes in Pregnancy, *ADA* American Diabetes Association, *NICE* National Institute for Health and Care Excellence (UK), *USPSTF* United States Preventive Service Task Force

Is There a Difference in Checking Preprandial or Postprandial?

Many endocrinologists recommend preprandial testing for nonpregnant patients. This allows bolus insulin to correct for any elevated blood glucose prior to the meal and to compensate for the carbohydrates in the planned meal. However it does not tell if the amount of insulin was correct or whether there is continued postprandial hyperglycemia. After a meal, blood glucose peaks in approximately 1 h and returns to preprandial levels in 2–3 h. If blood glucose is tested postprandial, it doesn't matter what the preprandial level was because if the postprandial level meets goal, then the amount of insulin or other medications taken was correct. More importantly elevated postprandial blood glucose is associated with the development of fetal macrosomia [3].

Medication

When 20% of values fail to meet goals, medication should be started. Insulin is considered the gold standard for treatment of diabetes and has traditionally been the first-line agent for treatment of hyperglycemia in pregnancy not managed with diet and exercise. In actual practice oral agents are usually the first-line agent rather than insulin. The use of oral agents has been associated with enhanced compliance due to both ease of use, no need to measure insulin into a syringe, and patient comfort, no need to inject medication [14].

Once patients are on medication, either insulin or an oral agent, they should receive monthly growth scans, and antennal testing should be initiated at 32 weeks.

Delivery should be considered at 38 weeks for patients with suboptimal glucose control on medication.

Summary

Universal screening for GDM is recommended due to the epidemic of obesity and diabetes worldwide. GDM can be diagnosed using either the two-step method or the one-step method. The two-step method consists of an initial screen with a 50 g glucose load followed by a diagnostic 100 g 3 h test.

The one-step method is a 75 g oral glucose load with blood glucose measures at fasting and 1 and 2 hours after administration.

Once diagnosed, patients should check blood glucose four times each day. Medication should be initiated when diet and exercise fail to control hyperglycemia.

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5

Diabetes and Metabolic Syndrome: Improved Control May Reduce Stone Risk

Kathleen M. Zatavekas, Kristina L. Penniston

Introduction

Diabetes mellitus and obesity are associated with kidney stones. Diet and lifestyle play a role in diabetes and obesity, both of which are sequelae of or associated with metabolic syndrome. Diet and lifestyle also play a role in the epidemiology of some kidney stones. Weight gain, increased body mass index (BMI, kg in body weight divided by height in meters squared), and diabetes were found to be associated with the incidence of stone disease in the Nurses' Health Studies I and II and in the Health Professionals Follow-up Study [1]. Since these studies, there has been data to confirm increased stone risk with the metabolic syndrome [2].

What Is the Metabolic Syndrome?

Metabolic syndrome is a constellation of concurrent factors that raise the risk for cardiovascular disease and other health problems. It is "metabolic" in that it involves aberrations in biochemical processes involved in normal physiological homeostasis. It is a "syndrome" in that it is not singularly typified by any one feature. There are many definitions of the metabolic syndrome, including by groups such as the National Cholesterol Education Program Third Adult Treatment Panel, the World Health Association, the American Heart Association, and the European Group for the Study of Insulin Resistance (Table 1). Definitions by these groups agree that the presence of

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Table 1: Required and additional non-required criteria for diagnosing metabolic syndrome from national and international organizations.

	IDF[a]	AHA/NHLBI[b]	AACE[a]	NCEP[b]ATPIII	EGIR[a]	WHO[a]
Required criteria						
Insulin resistance (or fasting insulin) in top 25% or type 2 diabetes mellitus					x	x
Glucose >100 mg/dL or 2 h glucose ≥140 mg/dL						x
High risk for insulin resistance or BMI >25 or waist ≥102 cm (men) or ≥88 cm (women)			x			
Ethnic-based waist, European, ≥94 cm (men) or ≥80 cm (women); Asian, ≥90 cm (men) or ≥80 cm (women)	x					
Non-required criteria, at least 2 or 3 :						
Glucose, ≥100 mg/dL[c]	x	x	x	x	x	
2 h glucose, ≥140 mg/dL			x			
HDL, <40 mg/dL					x	
HDL, ≤35 mg/dL (men) or ≤40 mg/dL (women)						x
HDL, <40 mg/dL (men) or <50 mg/dL (women)	x	x	x	x		
Triglycerides, ≥150 mg/dL	x	x	x	x	x	x
Obesity, waist ≥102 cm (men or ≥88 cm (women)		x		x		
Obesity, waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30						x
Obesity, waist/hip ratio ≥94 cm (men) or ≥80 cm (women) or BMI ≥30					x	
Hypertension, ≥130/85 mmHg	x	x	x	x		
Hypertension, ≥140/90 mmHg					x	x
Microalbuminuria, ≤20 mcg/min or albumin/creatinine ratio ≥30 µg/mg						x

Criteria shown are from the recommendations of the International Diabetes Federation (2006); American Heart Association and National Heart, Lung, Blood Institute (2005); American Association of Clinical Endocrinology (2003); National Cholesterol Education Program Adult Treatment Panel III (2001); European Group for the study of Insulin Resistance (1999); and World Health Organization (1999)

[a]Requires 2 of the non-required criteria

[b]Requires 3 of the non-required criteria

[c]In 2003, the American Diabetes Association changed the criteria for impaired fasting glucose tolerance from 110 to 100 mg/dL. Some organizations set the criteria for elevated fasting glucose at 110 mg/dL. But because these were developed prior to the change, the table reflects only the more stringent definition

hypertension, dyslipidemia, and insulin resistance is critical for the diagnosis of metabolic syndrome. The International Diabetes Federation (IDF) has acknowledged a need for a universal diagnostic means to define the metabolic syndrome. The IDF definition differs from other definitions by including waist circumference with ethnicity threshold values as a means to identify central obesity plus two or more of the aforementioned core components. Of note, according to this definition, waist circumference need not be measured to identify the presence of central obesity if BMI is >30 [3, 4]. Some organizations are calling for the renaming of metabolic syndrome to insulin resistance syndrome [5].

Urolithiasis and Diabetes Mellitus

Diabetes mellitus is one of the major manifestations of the metabolic syndrome. Diabetes mellitus type 2 (also known as type 2 diabetes) is a chronic metabolic disorder that develops over time and is characterized by hyperglycemia, insulin resistance, and relative insulin insufficiency [1]. The link between kidney stone disease and diabetes is complex and is associated with both uric acid stones and calcium oxalate stones [6]. Uric acid stones are more commonly seen in patients with diabetes. The rate of uric acid stones in patients with diabetes is around 30–40% compared to a rate of 5–10% in the general population [7]. Risk factors for uric stone formation are hyperuricosuria, acidic urine, and low urine volume. Risk factors for calcium oxalate stone formation are low urine volume, high urinary excretion of calcium and/or oxalate, and low urinary excretion of magnesium and/or citrate. These conditions may occur as a result of idiopathic, genetic, and/or lifestyle causes. In the presence of insulin resistance and obesity – common sequelae in patients with diabetes – there is increased uric acid excretion [8]. Also, when ammoniagenesis is impaired, which is common in diabetes, urinary pH is reduced, favoring the formation of uric acid stones. Notably, obesity – with or without diabetes – is linked to increased renal excretion of calcium and uric acid as well as urine acidity, all of which increase the risk of both uric acid and calcium oxalate stone formation [7, 9].

Nutritional Management of Diabetes

Medical nutrition therapy (MNT) is recommended for people with type 1 and type 2 diabetes as part of their overall medical treatment plan [10]. Individualized MNT is provided by a registered dietitian nutritionist (RDN) who is knowledgeable in diabetes. For adults with diabetes, the aim of MNT is to emphasize eating a variety of nutrient-dense foods, in appropriate serving sizes, so that patients may realize and sustain favorable body weight goals, achieve good glycemic control, meet lipid and blood pressure goals, and postpone or avert diabetes and its complications. These goals require individualization as patients are quite heterogeneous with respect to their expression of the above.

Energy balance and distribution of macronutrients For adults with type 2 diabetes who are overweight or obese, reducing energy intake while retaining a healthy and nutrient-adequate eating

pattern is recommended. Even a moderate amount of weight loss may improve glycemia, blood pressure, and blood lipids, especially among those in the early stage of the diabetic disease process. To achieve a reasonable amount of weight loss, MNT, physical activity, and/or behavior change is encouraged [11]. As evidence suggests there is not a single dietary plan that is appropriate for all people with diabetes, the distribution of dietary macronutrients as well as micronutrients should be based on an individualized assessment of food preferences, eating patterns, and metabolic goals [12]. The Dietary Reference Intakes (DRIs) [13] – which include recommended dietary allowances (RDAs), adequate intakes (AIs), estimated safe and adequate daily dietary intakes (ESADDIs), and tolerable upper intake levels (ULs) – provide a general framework from which to individualize each patient's nutritional goals. According to the DRIs, the acceptable macronutrient distribution range for adults is 45–65% of total energy needs from carbohydrates, 10–35% from protein, and 20–35% from fat. Note that the wide ranges for each of these macronutrients include those that are recommended for patients with diabetes, underscoring the need for individualized dietary recommendations.

Carbohydrate/dietary fiber Both quantity and type of carbohydrate influence blood glucose levels. The total amount of carbohydrate eaten is the primary predictor of glycemic response. Monitoring carbohydrate amounts is thus a useful strategy for improving postprandial glucose control. Carbohydrates from fruits, whole grains, legumes, vegetables, and dairy are recommended. Other sources of carbohydrates, such as those with added sodium, sugar, and fats, are not recommended or, if consumed, recommended in lower amounts [10, 12]. Common lore suggests that patients with diabetes should limit their intake of carbohydrates. Indeed, many patients erroneously believe they should eliminate fruits and/or starchy vegetables from their diets. But without adequate carbohydrate intake, protein is used for energy as opposed to being used to synthesize new proteins critical for maintaining homeostasis and immune function. Thus, complete avoidance of these foods may compromise the nutritional quality of the diet and overall health. Instead of eliminating, strategies for good glucose control include the distribution of carbohydrates throughout the day, consuming carbohydrate-rich foods with meals, and avoiding concentrated carbohydrate doses. A variety of methods for diabetes meal planning are presented to patients by RDNs or diabetes educators and include the plate method, carbohydrate counting, and glycemic index [13]. Fiber, which can reduce the impact of food-derived glucose on blood glucose, is recommended in the same amounts as for the general population. Fiber is nondigestible and therefore provides little to no energy. Patients with diabetes should aim for about 25 (adult women) and 38 (adult men) grams of fiber daily. This amounts to approximately 14 g of fiber/1,000 kcals/day [14].

Protein The amount of protein intake required to optimize glycemic control among those with diabetes is controversial, but all experts agree that protein intake goals should be individualized within the DRI ranges [14]. People with diabetes, including those with diabetic kidney disease, should not reduce their dietary protein intake unless it is specifically advised; doing so could alter glycemic control and negatively impact kidney function, cardiovascular risk, and bone status [15]. Meats of all kinds, fish, poultry, cheeses, and lower-fat dairy foods, eggs, and some

plant-based foods are all good sources of high biological value protein and should be encouraged in moderation.

Fat Fats are grouped into unsaturated (monounsaturated and polyunsaturated) and saturated fats. Trans fats, a special type of fat created during certain food processing techniques, have negative health effects similar to saturated fat. The amount of dietary saturated fat, cholesterol, and trans fats recommended for people with diabetes is the same as that for the general population [10]. The 2015 Dietary Guidelines for Americans recommendations include limiting saturated fats to <10% of calories and limiting trans fats as much as possible [16]. As evidence is lacking for an "ideal" amount of total fat intake for those with diabetes, the goal should be individualized, again within the range suggested in the DRIs. Because fat provides more than twice the energy per gram than either carbohydrates or protein, patients with diabetes who need to lose or maintain weight are encouraged to moderate and/or lower their fat intake [10]. Foods richer in unsaturated fats are overall more encouraged than foods richer in saturated or trans fats.

Integrating Dietary Recommendations for Diabetes and Kidney Stone Prevention

Patients with diabetes are typically advised dietary recommendations that reduce the risk of hyperglycemia as well as those that reduce their risk for cardiovascular disease. RDNs can be instrumental in helping patients with both diabetes and kidney stones integrate dietary recommendations for both conditions. Below, the most common dietary aspects of kidney stone prevention are addressed with respect to whether or not they conflict with dietary recommendations to manage diabetes.

Fluid intake No conflict with dietary recommendations for managing diabetes. Patients with diabetes and a risk for urinary stones should drink as much as possible from a variety of beverages to induce the output of at least 2 L of urine. Concentrated fruit juices and sugary beverages should be limited, however, as these may result in a relatively quick spike in blood glucose.

Calcium intake No conflict with dietary recommendations for managing diabetes . Patients with diabetes and a risk for urinary stones should consume calcium at the levels recommended in the DRIs, which are specific for age and gender [14]. Food and beverage sources are preferred over calcium supplements as the risk for excessive calcium intake is higher in those who supplement. Patients at particular risk for calcium oxalate stones, with or without evidence of hyperoxaluria, may be recommended to distribute their calcium intake at meals to maintain suitable control of dietary oxalate absorption as calcium binds oxalate in the gastrointestinal tract and reduces its absorption. An ideal scenario might be to include about 300 mg of calcium with each of three meals daily, providing 900 mg of calcium. Some yogurts provide around this amount of calcium per serving. Calcium-fortified nondairy milks typically provide this amount in six fluid ounces vs. dairy milk, which requires 8 oz to obtain 300 mg of calcium. Kefir and some other calcium-fortified

products may also provide around 300 mg of calcium per serving. The additional 300–600 mg of calcium required per the DRIs, depending on age and gender, is easily obtained without supplementation from other food and beverage sources in a balanced diet.

Low sodium No conflict with dietary recommendations for managing diabetes. Patients at risk for calcium-containing stones are usually advised to limit sodium chloride (salt) intake because of its ability to raise urinary calcium excretion. Patients with diabetes are usually similarly advised due to their higher risk of cardiovascular disease. Patients with hypertension – a common additional feature of metabolic syndrome – are especially advised a lower salt intake. Thus, a lower salt intake is, with little difficulty, integrated in the dietary plan for diabetes and for reducing the risk of calcium-containing kidney stones whose primary etiology is hypercalciuria. Note that while reducing sodium intake may not be a top priority for the stone former without hypercalciuria or, for example, whose risk is not for calcium stones, it is still appropriate for the patient with diabetes to lower his/her sodium intake.

Fruits and vegetables No conflict with dietary recommendations for managing diabetes. However, two common challenges exist. A higher intake of fruits and vegetables is one way to enhance urinary citrate excretion, especially when including those with a higher concentration of bicarbonate precursors (organic acids) [17]. Patients with diabetes are sometimes frustrated with recommendations to increase their fruit and vegetable intake for stone prevention as fruits and starchy vegetables are ample sources of carbohydrates. Some patients perceive a conflict. Even though it is a misconception that fruit intake should be eliminated by people with diabetes, data show that some patients believe this [18]. In fact, fruits contain many compounds that are beneficial for health, including promoting a higher urinary citrate excretion. As discussed earlier, people with diabetes may safely eat fruits as long as they (a) eat them most frequently in their whole vs. juiced forms and (b) consume them with meals that also provide protein, fat, and fiber, all of which may blunt the effect of the carbohydrates from fruit on glycemic response.

The other challenge is when patients at risk for calcium oxalate stones, with or without hyperoxaluria, are commonly told – usually in the form of general recommendations – to reduce or eliminate high-oxalate foods, many of which are fruits and vegetables. All patients with diabetes should include vegetables and fruits in their meal planning strategies to meet fruit/vegetable intake recommendations. As fruits and vegetables appear variably on lists of purportedly high-oxalate foods, confusion and frustration about which fruits and vegetables can be eaten by patients with both diabetes and a risk for calcium oxalate stones are common. In truth, most vegetables and other plant foods contain some oxalate; eliminating oxalate completely from the diet is not only impossible but inadvisable for health reasons. It is also unnecessary. When patients consume adequate calcium (as described earlier), they can usually safely consume most all fruits or vegetables regardless of whether they contain any oxalate. Individualized nutrition assessment and intervention in the form of MNT is usually necessary to identify those patients who may benefit from a more restricted list of acceptable fruits and vegetables, but even this usually requires only moderated or lower intakes of the highest-oxalate fruits and vegetables.

Protein intake No conflict with dietary recommendations for managing diabetes. But challenges may exist. Patients with diabetes are frequently advised by diabetes educators to consume dietary protein sources along with carbohydrate-rich foods as a means to blunt the effect on blood glucose [15] and to use protein-rich foods vs. carbohydrate-rich foods as snacks between meals. Examples of such foods are largely animal derived (e.g., eggs, lean meats, cheeses, and other dairy). Conversely, patients at risk for uric acid stones (when higher uric acid production is a target of nutrition therapy) or calcium-containing stones (when hypercalciuria is a target of nutrition therapy) may be advised to moderate or reduce their intake of "flesh foods" (e.g., meats, poultry, fish, game, fowl) due to their potential as uric acid precursors or as contributors to higher dietary acid load and concomitant calciuria. While the consumption of these protein-rich foods by patients with uric acid or calcium stone risk might seem contraindicated, it need not be. It is not usually necessary to become totally vegetarian to reduce urinary uric acid excretion and the risk for uric acid stones. Uric acid synthesis and metabolism is complex and is not always significantly affected by diet. In fact, in one recent study, individuals who consumed a vegan diet had higher serum uric acid concentrations than meat eaters and non-vegan vegetarians [19]. Another study confirmed that a balanced omnivorous diet could significantly reduce urinary uric acid excretion in those who changed from a Western-type diet [20]. Moreover, the intake of foods with a higher potential renal acid load can be offset by an ample intake of foods with an alkaline load [21]. Thus there is room for a moderate intake, individually assessed and implemented, of foods from animal tissue by patients with both diabetes and a risk for uric acid and/or calcium stones. This allows for their use as lower-carbohydrate foods in diabetes meal planning.

What about high-protein nuts and seeds? Many patients with diabetes are encouraged to use these low-carbohydrate foods as snacks for their ability to help in maintaining appropriate blood glucose control while also providing heart-healthy nutritional benefits [22]. On the other hand, nuts and seeds are commonly limited in calcium oxalate stone prevention due to their relatively high oxalate content. But depending on the severity of the patient's hyperoxaluria (if present) and/or on the etiology of his/her hyperoxaluria, a dietary oxalate restriction that allows the use of nuts or seeds in diabetes meal planning could be devised. Especially when consumed with a simultaneous source of calcium, nuts and seeds may be enjoyed in moderation without perturbing urinary oxalate excretion [23]. Moreover, some patients who form calcium oxalate stones have other reasons for their stone formation (e.g., low urine citrate, high urine calcium, low urine volume) and do not benefit from attention to or restriction of their dietary oxalate intake. Attention in this instance to the primary risk factors is warranted. A referral to or consultation with a RDN could help in defining the protein needs of patients with both diabetes and a need for stone prevention.

Fat intake No conflict with dietary recommendations for managing diabetes. As noted earlier, patients with diabetes are typically advised to consume a low-fat diet. This has no conflict with general stone prevention recommendations and may actually complement dietary recommendations, especially for patients with malabsorption and/or a tendency for higher urinary oxalate excretion. When excessive dietary fat is consumed, it binds with calcium in the gastrointestinal tract, reducing the availability of calcium to bind dietary oxalate. Thus, a low-fat intake may be

useful for stone prevention, especially in those prone to higher urinary oxalate excretion. A lower-fat intake is also useful for anyone working to reduce stone recurrence risk by losing weight. As fat provides more than twice the energy of carbohydrates and proteins (9 vs. 4 kcals per gram), its restriction can be a useful and efficient tool abetting weight loss.

Summary

Dietary regimens to manage diabetes and prevent future kidney stone formation and/or growth are not contradictory, but their integration may be challenging. This presents an ideal opportunity to engage an RDN to individualize and integrate dietary recommendations that address both disorders and to suggest strategies for implementation. In some cases, a re-prioritization of dietary recommendations that reduce stone risk within existing diabetes meal planning recommendations may be all that is needed. In other cases, additional recommendations to those used in diabetes meal planning may be required. Patients should be advised that there is no inherent contradiction in managing diabetes while also preventing kidney stones and provided education and resources needed to implement appropriate dietary changes. Indeed, emerging evidence [24, 25] suggests that poor glycemic control may be an independent risk factor for kidney stones. As diabetes incidence increases and coalesces with urolithiasis, future nutritional studies that provide data to better understand how to reduce patients' risk factors for diabetes complications and stone recurrence are warranted.

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6

Diabetes Management in Older Adults With Chronic Kidney Disease

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Abstract

Older adults often live with chronic disease including diabetes and its complications. In this review, we examine the complexity and heterogeneity of older adults with diabetes and chronic kidney disease, explore the nuances in their diabetes-related monitoring, and discuss their best diabetes management. Although there remains an overall lack of studies in older adults with diabetes and chronic kidney disease, recent reports have highlighted their vulnerabilities. These individuals face an increased risk of cognitive impairment and dementia, frailty, dysglycemia, polypharmacy, declining kidney function, and acute kidney injury. Their diabetes management should focus upon safer antihyperglycemic medications, close monitoring, and care individualization. Older adults with diabetes and chronic kidney disease are a complex population who requires careful diabetes management and monitoring. Research efforts might focus on improving the care and outcomes of these patients.

Keywords: Diabetes, Older adults, Chronic kidney disease, Antihyperglycemic medications, Frailty, Hypoglycemia, Comorbidity

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Introduction

With enhancements in medicine and improved survival, our population is aging [1]. The number of people over the age of 60 is expected to double by 2050 [1], and with the high prevalence of hypertension and obesity, not surprisingly, many of these individuals will live chronic, non-communicable disease, including diabetes and its complications [2].

Chronic kidney disease (CKD), typically defined by an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, albuminuria, or both (for a minimum of 3 months) [3], affects 25–40% of patients with diabetes [4]. Older adults who live with both diabetes and CKD are a complex, heterogenous population that requires careful diabetes management. In this review, we illustrate their complexities, highlight their need for special monitoring, review the antihyperglycemic medications that are most efficacious and safe in this population, and provide suggestions for their best management.

The Complexity of Older Adults With Diabetes and CKD

Cognitive Impairment

Metabolism and physiological function changes as we age, and older adults frequently live with co-morbidity. This is particularly true for older adults with diabetes and CKD. In addition to living with diabetes and its complications [5], these individuals remain at increased risk of geriatric syndromes including falls, chronic pain, depression, functional, and cognitive decline [6].

The risk of dementia in diabetes and CKD is gaining increasing attention. Diabetes (type 1 or 2) is a well-recognized risk factor for the development of mild cognitive impairment (MCI) and dementia, especially vascular and Alzheimer's dementia [7]. People with type 2 diabetes develop dementia on average 2.5 years earlier than those without diabetes [8], an effect which is intensified in those who have MCI [8].

Proposed mechanisms linking diabetes with MCI or dementia, include vascular damage, abnormalities in glucose, insulin and amyloid metabolism, hypertension, and increased body mass index [7, 8]. A longer duration of diabetes (≥ 5 years) has also been associated with a 40–60% increased risk of dementia [7]. Hypoglycemia is an additional risk factor for dementia in patients with diabetes [7], and interestingly, a hemoglobin A1c (HbA1c) $>7.0\%$ in patients with MCI has also been associated with an increased risk of conversion to dementia [9].

In older adults, CKD and end-stage kidney disease (ESKD) have also been independently linked with cognitive impairment. In addition to their underlying vascular disease [10], it is has been proposed that uremic toxins might have a direct effect on cerebral structure and function in these patients [11]. The risk of cognitive decline increases as kidney function declines [12, 13], but unfortunately, cognition does not seem to improve with dialysis [14]. CKD might also accelerate the rate of cognitive decline in patients with diabetes through processes of anemia, inflammation, or oxidative stress [15].

A synergistic relationship between diabetes and CKD on cognition in older adults has also recently been postulated. In one cross-sectional study of 1358 older adults (mean age 68.6 years), diabetes and kidney disease (eGFR < 60 ml/min/1.73 m^2) had an interactive effect on cognitive impairment as measured by the Mini-Mental State Examination (relative excess risk due to interaction of 2.74) [15]. Compared with individuals who had no diabetes or kidney disease, patients with both conditions faced a multi-adjusted odds ratio of 4.23 (95% CI, 2.10–8.49) for cognitive impairment. Mechanisms common to both diabetes and CKD, such as inflammation, peripheral vascular disease, and cardiovascular disease might explain these findings [15].

Whatever the mechanism linking diabetes and CKD with dementia, its development in older adults brings major challenges, particularly in their self-management and safety [6]. A recent systematic review explored the relationship between cognitive impairment and self-care in diabetes [16] and found that those with cognitive impairment (particularly those with deficits in learning, memory, and executive function) had significant impairment in all self-care domains. They had difficulties in problem-solving, understanding their disease, and action-taking. They faced an increased risk of hospitalization, but also had lower clinic attendance, and diabetes-related screening (eye examinations, HbA1c, and low-density lipoprotein [LDL] cholesterol measurement).

Sarcopenia and Frailty

Traditional micro- and macro-vascular complications of diabetes appear to account for only half of diabetes-related disability in older adults. Sarcopenia and frailty are increasingly being considered as a third category of diabetes-related complications [17••, 18].

From the age of 30 years, there is a progressive decline in muscle mass which accelerates with time [19]. Sarcopenia, a component of the frailty construct, relates to this loss of muscle mass. Definitions of sarcopenia vary and include either gender-specific cutoffs for grip strength and appendicular lean muscle mass or loss of muscle mass with associated reduced strength and/or low physical performance [18]. Frailty is a multi-dimensional condition characterized by low physiologic reserve which leads to an increased vulnerability to physiologic and environmental stressors, when compared to others of the same age [20–22]. There is no consensus definition of frailty: it comprises both physical and psychosocial components, including reduced lean muscle mass and sarcopenia, functional impairment, cognitive impairment, mental health, and social issues [23]. Frailty is also associated with an increased risk of adverse health outcomes, such as falls, fractures, hospitalization, dependency, disability, institutionalization, and lower health-related quality of life [18, 23].

Older adults with diabetes and CKD are at increased risk of sarcopenia and frailty. In early diabetes, poor glycemic control, oxidative stress, and inflammation have been postulated to play a role in the development of sarcopenia, whereas in the later stages of diabetes, complications including peripheral neuropathy play more of a role [18]. Insulin resistance, even in patients without diabetes, has also been linked with protein energy wasting and sarcopenia in those with CKD. [24] Vitamin D deficiency is also a well-recognized risk factor for frailty and is especially apparent in patients with diabetes and CKD (those with diabetes at increased risk of low 25-hydroxyvitamin D; 1,25 dihydroxyvitamin D production can be low in CKD) [23]. Additional

risk factors for frailty might include chronic disease and multimorbidity [18, 23, 25], altered body composition including increased fat mass and reductions in muscle mass and function, malnutrition, and inflammation [26].

The prevalence of frailty has been found to increase across the CKD stages, with up to 70% of dialysis patients considered frail [6]. This effect appears independent of diabetes, cardiovascular disease, and CRP level [26]. Among patients with CKD, the frailty phenotype is associated with an increased risk of early dialysis therapy or death [26].

Dysglycemia

In addition to their risk of cognitive decline, dementia, sarcopenia, and frailty, older adults with diabetes and CKD are at risk of both hyperglycemia and hypoglycemia. Even without underlying diabetes, an eGFR< 60 ml/min/1.73m^2 has been linked with insulin resistance and reductions in insulin secretion [27]. Postulated contributing factors include vitamin D deficiency and secondary hyperparathyroidism [28, 29], reduction in GFR, acid-base homeostasis, physical activity, body composition/adiposity, and medication use [27]. If using peritoneal dialysis, patients can have higher blood sugars secondary to higher dialysate glucose [30].

The risk of hypoglycemia is also substantial in older adults with CKD, with and without diabetes. In a population-based cohort study of older adults from 2002 to 2010 (mean age 75 years), we examined the 3-year incidence of hypoglycemia across the stages of kidney disease [31]. In patients who used antihyperglycemic medications, the risk of hypoglycemia increased from 82 (95% CI, 71–94) encounters per 10,000 person-years in those with an eGFR ≥ 90 ml/min/1.73 m^2 to 785 (95% CI, 689–894) encounters per 10,000 person-years in those receiving dialysis. This graded relationship was also apparent in those who did not use antihyperglycemic medications and where kidney function was defined using a combination of eGFR and albuminuria [31].

The reasons for hypoglycemia in older adults with diabetes and CKD can be manifold. Many antihyperglycemic medications are cleared by the kidneys, putting patients with CKD at increased risk of drug-induced hypoglycemia [32, 33]. Muscle wasting and dysfunction might also contribute to reduced insulin clearance [27]. Patients with CKD and diabetes also have more medical comorbidities (including autonomic neuropathy) which might increase their susceptibility to hypoglycemia [34, 35]. Additionally, they often have longer-standing diabetes which is a known risk factor for hypoglycemia [35]. Dementia, MCI, poor meal planning, and insulin product mix-ups have also been implicated [36–38]. In patients with CKD without diabetes, hypoglycemia might be related to malnutrition with lower glycogen stores [39] and reduced renal gluconeogenesis [40, 41].

Compounding their hypoglycemia risk is that older adults with diabetes often experience impaired awareness of hypoglycemia. In a study of patients with type 2 diabetes, those age ≥ 65 years had a different awareness and response to hypoglycemia than younger individuals (age 39–64 years). They also had a less pronounced increase in autonomic and neuroglycopenic symptoms at the end of hypoglycemic plateaus [42]. The study did not specifically evaluate if these effects were independent of beta blocker use.

Over recent years, hospitalizations for hypoglycemia have surpassed the number for hyperglycemia, especially in those ≥ 75 years. In a study of US Medicare beneficiaries from 1999 to 2011, hospitalization rates for hypoglycemia were nearly two-fold higher in those ≥ 75 years compared with those 65–74 years [38]. Hypoglycemia can have significant consequences for patients including cardiac disturbances, neurological complications, impaired quality of life, and even death [43]. Prevention is thus key in the older adult population.

Polypharmacy

With their many medical conditions, older adults with CKD and diabetes are at increased risk of polypharmacy. In a study of 685 nursing home residents, 53.3% reported using five to nine medications (defined as polypharmacy), and 16.4% had evidence of excessive polypharmacy (ten or more medications). An eGFR < 60 ml/min/1.73 m^2 was associated with polypharmacy in multivariable analysis [44]. Unfortunately, polypharmacy has been linked with adverse drug reactions [45], especially in those with CKD.

Heterogeneity

It is important to emphasize that older adults with diabetes are a heterogenous population. Although many live with functional impairment, comorbidities, polypharmacy, and have frequent hypoglycemia, others do not. Older adults can have new-onset type 2 diabetes after their diagnosis of CKD, if their kidney disease is due to non-diabetic glomerular syndromes (which are more common in older adults) [46]. Older adults with type 1 diabetes also now survive into older age [47]. Thus, age does not always equate with patient complexity.

Special Monitoring

Increased attention has been paid to the need for special diabetes-related monitoring in older adults with diabetes (i.e., monitoring of kidney function and glycemic control).

Impact of Aging on Measures of Kidney Function

The measurement of kidney function (filtration and secretion) can be challenging in older adults. GFR is typically used to provide a measure of functioning nephrons, and in clinical practice, it is estimated using the clearance of the endogenous marker, creatinine [48]. Formulae including the Cockcroft–Gault, [49] the Modification of Diet in Renal Disease, [50] and the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) [51] are validated creatinine-based formulae to estimate kidney function. These estimating equations were, however, not specifically developed in older adults [52].

Additionally, there are limitations to using creatinine to estimate GFR in older patients. Creatinine production is dependent upon muscle mass, and in older adults, the production of creatinine can be heterogeneous [52]. Patients can also have variable creatinine secretion

(e.g., those with nephrotic syndrome) [53]. Thus, despite having a normal creatinine, older adults can have "concealed renal failure" with a declining GFR [54].

Recently, new eGFR formulas have been proposed which use cystatin C and creatinine as endogenous markers. Although more validation studies are needed, these equations (e.g., Berlin Initiative Study 2 Equation) seem to yield smaller biases in renal function measurement than creatinine-based formulae [52]. Such equations are, however, not routinely available.

Although the best measures of kidney function in older patients remain controversial, all equations seem to provide similar estimates when GFR is < 30 ml/min/1.73 m^2, which is a frequent cutoff to guide drug dosing [55]. It might be reasonable then to use any equation to guide antihyperglycemic medication dosing [56]. If there is need to accurately quantify kidney function (e.g., in cases where highly toxic drugs or kidney transplantation are being considered), one might perform a nuclear measurement of GFR (i.e., renal scan). Although 24 urine creatinine collections can also be considered in these situations [57], there remains the possibility of inaccurate collections especially in older adults.

Trajectory of Kidney Function Among Older Adults

Due to fibrosis, tubular atrophy, obliterated arterioles, vascular resistance, and defective autoregulation, GFR and tubular secretion decline naturally with time in older individuals [58]. In a study of 4380 patients (mean age 72 years), 6% had an annual decline of eGFR > 3 ml/min per 1.73 m^2 when using creatinine-based equations, and 25% had an annual decline of eGFR > 3 ml/min/1.73 m^2 when cystatin C–based equations were used [59]. It is also known that older adults with diabetes and CKD face an increased risk of acute kidney injury (AKI) [2], which might be due to comorbid disease such as prostatic hypertrophy or congestive heart failure [2] or the use of nephrotoxic medications [2, 58].

Glycemic Control

In addition to monitoring their kidney function, special attention needs to be paid to glycemic monitoring in older adults with CKD. Where HbA1c is suggested for monitoring in most healthy individuals, this test is affected by reduced red cell survival, use of erythropoietin, hemoglobin modifications, and mechanical destruction of blood cells [60, 61]. These conditions are often present in CKD, and the correlation between HbA1c and fasting glucose weakens with lower kidney function [61].

The use of glycated albumin and fructosamine as alternative measures of glycemic control in patients with CKD has been suggested, but these measures may be equally flawed [62]. Their usefulness depends upon normal serum albumin levels, which are rarely observed in patients with CKD as they often have altered plasma protein turnover. Moreover, glycated albumin and fructosamine are affected by many physiological conditions and may fail to serve as stable markers [63].

In the absence of consistent and sufficient data to show superiority of their use over HbA1c as markers for glycemic control, it would be reasonable to continue using HbA1c or capillary blood glucose to monitor glycemic control in this population.

Challenges in Diabetes Management

Antihyperglycemic Agents

A cornerstone of diabetes management is the administration of antihyperglycemic drugs. Over the last several years, the armamentarium of drugs available to treat patients with diabetes has grown. Unfortunately, however, therapeutic choices can be limited in older adults, especially in those with CKD.

Metformin

Due to its low cost, neutral effect on weight, low risk of hypoglycemia, and effectiveness in lowering blood glucose, metformin is currently the recommended first-line therapy for the management of diabetes [64]. However, in older adults, particularly in those with CKD, metformin has been reported to increase the risk of lactic acidosis and gastrointestinal (GI) side effects [65]. In those with CKD, it is suggested that metformin can be used without dose reduction to an eGFR > 45 mL/min/1.73 m^2 but that a reduction to 1000 mg daily be used in patients with eGFR 30–44 mL/min/1.73 m^2 [65]. Although recommendations vary, metformin is not advised in those with a serum creatinine ≥ 1.5 mg/dL in men or ≥ 1.4 mg/dL in women, when eGFR is < 30 mL/min, or in those over the age of 80 with reduced kidney function [65].

Sulfonylureas

Sulfonylureas are effective agents for lowering blood glucose and are often used in combination with other glucose-lowering agents, including metformin. Hypoglycemia can, however, occur with these drugs, and this effect appears most pronounced in older adults with CKD due to reduced renal clearance of these agents and their metabolites [66]. Chlorpropamide and glyburide/glibenclamide should be avoided in the elderly because of their high hypoglycemia risk [67]. Glipizide, gliclazide, and glimepiride are safer options because their clearance and half-life are not heavily affected by renal function [68]. It is currently suggested that these agents still be used with caution in those with eGFR < 60 mL/min/1.73 m^2 [69, 70].

TZDs

Thiazolidinediones do not cause hypoglycemia as monotherapy and have durable effects on glycemic control. However, they are associated with weight gain, fluid retention, edema, congestive heart failure, and bladder cancer [65], and in older women in particular, an increased risk of fragility fracture has been described [71, 72]. As such, these agents should not be used in patients with New York Heart Association (NYHA) class III or IV heart failure or in older adults with osteoporosis. Bone density should be monitored when these agents are prescribed in patients with osteopenia. Rosiglitazone and pioglitazone are both metabolized by the liver; therefore, dose

adjustment is not needed in patients with CKD [63]. Nonetheless, the risk of fluid retention makes the use of these drugs limited in older patients with CKD.

Meglitinides

Meglitinides have rapid onset time and short half-life, and when taken before meals, they can control postprandial hyperglycemia [65, 73•, 74]. Compared with sulphonylureas, they are associated with a lower risk of hypoglycemia [65]. While nateglinide is contraindicated in patients with an eGFR < 60 mL/min/1.73 m^2 [73•], repaglinide can be used without dose adjustment [75]. Among patients with CKD treated with repaglinide, a clearance as low as 20 mL/min was not associated with hypoglycemia [76]. Meglitinides, however, are costly and require frequent dosing, which may limit their use in the elderly population.

Incretins

Incretins (glucagon-like peptide-1 [GLP-1] receptor agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors) have garnered more attention in recent years, with large clinical trials providing evidence on the efficacy and safety of these agents.

GLP-1 Receptor Agonists Although there is evidence of the efficacy and safety of GLP-1 receptor agonists (exenatide, liraglutide, dulaglutide, lixesenatide, and albiglutide), there have been no studies specifically conducted in older adults with diabetes and CKD. However, there is no reason to believe that there would be major differences in the efficacy and safety profiles between older and young patients [77]. GLP-1 receptor agonists carry a low risk of hypoglycemia and can encourage weight loss, but they are costly and need to be delivered by injection. GI upset is common, which may not be tolerable in older patients. Impaired kidney function reduces the clearance of exenatide, and its use should be avoided in patients with an eGFR < 30 mL/min [78]. Although guideline recommendations vary, no dose adjustments are needed for liraglutide, dulaglutide, lixesenatide, or albiglutide in CKD patients, but caution is advised in the advanced stages given a lack of data in this population [67, 73•].

DPP-4 Inhibitors DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, and alogliptin) reduce blood glucose by decreasing glucagon secretion and blocking the breakdown of GLP-1, an incretin hormone [70, 71]. These drugs then stimulate insulin secretion in a glucose-dependent fashion and reduce gastric emptying [78, 79].

DPP-4 inhibitors are associated with a low risk of hypoglycemia and are weight neutral. Several clinical trials have shown the efficacy, safety, and tolerability of these agents in older adults with CKD [80–82]. All DPP-4 inhibitors except linagliptin are excreted via the kidneys to some extent. As such, these agents require dose adjustment according to eGFR [83]. Older adults prescribed DPP-4 inhibitors, including sitagliptin, do not appear to be at an increased risk of pancreatitis compared with those prescribed other antihyperglycemic medications [84].

SGLT-2 Inhibitors

Sodium-glucose cotransporter 2 inhibitors reduce glucose uptake from the kidney, and their antihyperglycemic action depends on urinary glucose excretion. As such, their glycemic-lowering potential is reduced in patients with CKD [83].

Only a few randomized trials have examined the efficacy or safety of canagliflozin and dapagliflozin in older adults (mean age of 67–69 years) with diabetes and CKD [85, 86]. As anticipated, these studies showed that the glycemic-lowering potential of SGLT-2 inhibitors was reduced in older adults, particularly in those with impaired kidney function [87]. Studies were limited to patients who were relatively healthy, without any serious comorbid conditions or cognitive impairment.

In addition to lowering blood sugar and inducing weight loss by promoting a negative calorie balance, reduction of blood pressure has been reported due to osmotic diuresis [85]. For this reason, SGLT-2 inhibitors may be beneficial in older patients with uncontrolled hypertension, but they should not be used in those with hypotension.

It is currently suggested that canagliflozin should not be used in patients with an eGFR < 45 mL/min/1.73 m^2, and dapagliflozin is not recommended for patients with an eGFR < 60 mL/min/1.73 m^2 [87]. No more than 100 mg once daily of canagliflozin should be used in patients with eGFR 45–59 mL/min/1.73 m^2 [73•]. While the hypoglycemia risk of these agents is low in middle-aged patients, the incidence of hypoglycemia is increased in older adults, particularly among those with later stages of CKD [85–89]. These agents are also expensive with a 30-day supply estimated to cost $350–400 US dollars. As such, older adults on fixed incomes may have difficulty affording these therapies [83].

Insulin

With age comes progressive β-cell function decline, making insulin therapy often necessary in older adults. However, as it is cleared by the kidneys, an initial insulin dosage reduction of 25% is sometimes recommended in patients with eGFR 10–50 mL/min to reduce the risk of hypoglycemia [75]. When long-acting insulin such as glargine or detemir are used, dose reductions of 50% have also been suggested [75]. These long-acting basal insulin analogues might be preferred given they appear to have a lower hypoglycemia risk than NPH or regular insulin, [90] although studies are duly lacking in those with CKD. If needed for post-prandial control, rapid-acting insulin administration after a meal in those with CKD may be beneficial [73•].

Comorbidities, poor physical function, and cognitive impairment can make safe insulin administration difficult. More complicated insulin regimens can increase the odds of dosing error and the risk of hypoglycemia, especially in older patients with cognitive impairment. Between 2007 and 2011 in the USA, there were 97,648 hospital encounters for insulin-related hypoglycemia and errors [38]. Compared with those aged 65–79 and 45–64 years, patients over the age of 80 had higher rates of emergency department visits (34.9 per 1000 insulin-treated patients with diabetes). Almost 2/3 of patients had severe hypoglycemia. [38]

Glycemic Targets

A summary of guideline recommendations for glycemic targets in older adults is included in Table 1.

Some suggest that it is not unreasonable for healthy older patients who have normal life expectancy to aim for the same glycemic targets as younger adults (HbA1c <7%). In older patients with only a few comorbidities and a reasonable life expectancy, < 7.5% is a reasonable goal. There is growing recognition that intensive glycemic control in older frail patients with diabetes has limited benefit and probably causes harm and as such, a target HbA1c of < 8.0% has been suggested. In the severely frail, functional outcomes appear best over 2 years when patients have an HbA1c > 8.0%, and as such, as target of < 8.5% has been proposed in this population [17••].

It is, however, important to prevent severe hyperglycemia in older adults. Hyperglycemia can lead to polyuria, polydipsia and nocturia, visual impairment, dehydration, and can predispose patients to urinary tract infections, candidiasis, and cardiovascular events [17••]. Screening and treatment of potential microvascular complications should also not be disregarded in this age group.

Table 1: Guideline recommendations for HbA1c targets for older adults with diabetes.

American Diabetes Association [91]		**Diabetes Canada [92]**		**International Diabetes Federation [93]**	
Healthy: few existing chronic illnesses, intact cognitive, and functional status	< 7.5%	Functionally independent	≤ 7.0%	Functionally independent	7.0–7.5%
Complex/intermediate: multiple coexisting chronic illnesses or ≥ 2 instrumental ADL impairments or mid-to-moderate cognitive impairment	< 8.0%	Functionally dependent	7.1–8.0%	Functionally dependent	7.0–8.0%
Very complex/poor health: long-term care or end-stage chronic illnesses or moderate-to-severe cognitive impairment or ≥ 2 ADL dependencies	< 8.5%	Frail and/or presence of dementia	7.1–8.5%	Functionally dependent with frailty	< 8.5%
		End of life	A1c measurements not recommended. Avoid hypoglycemia and symptomatic hyperglycemia	Functionally dependent with dementia	< 8.5%
				End of life	Avoid symptomatic hyperglycemia

ADL activities of daily living

Discussion

Older adults with diabetes are a complex, heterogenous population. Health care professionals who manage these patients should play close attention to their comorbidities and functional status, practice safe and cautious prescribing, individualize their glycemic targets, closely monitor them, involve other care professionals in their management, and provide them with patient-centered care.

Awareness of Comorbidities and Functional Status

Care professionals who treat older adults with diabetes and CKD should be fully aware of their comorbidities and functional status. During their clinical assessments, providers might periodically screen for cognitive dysfunction and depression or involve geriatric teams to help with this screening [94]. Frailty is a recognized complication of diabetes and reduced kidney function but is often not assessed in older adults with diabetes. There are multiple frailty measures available, many of which require minimal training for accurate use [17••].

Attention should also be paid to the risk of nutritional deficiency in older adults [94]. Good nutrition with vitamin D and protein intake (especially the amino acid leucine) has been associated with improvements in muscle mass and function [18]. Physical rehabilitation and multi-component exercise programs incorporating balance exercises, gait re-training, and strength, power, and resistance training have the potential to reverse frailty deficits [18]. Vision and hearing should be screened, and attention should be paid to health literacy and self-management skills [94, 95].

Practice Safe, Cautious Prescribing

Before prescribing new medications, the medication lists of older adults with CKD should be reviewed. Where patients are at increased risk of polypharmacy, their need for prescribed therapies might be re-evaluated, and medications should be reconciled [94]. Providers might also look for nephrotoxic medications and use drug interaction checkers when reviewing their medication lists.

We also suggest that when prescribing antihyperglycemic medications, regimens should be made simple. Prescribers might choose the lowest effective dose of medications, ensure that patients know how to take their drugs [96], and ensure that they can distinguish between therapies to avoid product mix-ups [38]. Although older adults with CKD are frequently excluded from clinical drug studies, it would be reasonable to choose antihyperglycemic medications with a strong benefit to risk ratio for these patients. As they are at increased risk of drug-associated hypoglycemia, it would be important to choose agents with a lower hypoglycemia risk. It is also necessary to consider the cost of antihyperglycemic medications given older adults are frequently on fixed incomes or have limited drug benefits.

Individualization of Glycemic Targets

Glycemic targets should be based upon the individual patient. Given the heterogeneity of older adults with diabetes, there are no age specific recommendations for glycemic control. Targets should depend upon their function, life expectancy, and risk of hypoglycemia [97]. In older adults, it also remains important to identify overtreatment and to de-intensify and de-prescribe to minimize harm [98]. Unfortunately, the overtreatment of older adults remains an issue. In a study of patients >70 years with type 2 diabetes prescribed sulphonylureas or insulin in the UK [98], almost 1/3 had an HbA1c < 7%. Those with CKD or dementia were over treated just as commonly as those without these conditions.

Monitor Closely

While HbA1c measurement might be useful to evaluate glycemic trends, attention to capillary and venous blood glucose is important in older adults with diabetes and CKD. The kidney function of these individuals might also be monitored more frequently, given the risk of declining function and AKI.

Involve Family, Healthcare Team

Given their complexity, care professionals might involve multidisciplinary care teams in the management of older adults with diabetes and CKD. Geriatricians can bring expertise in managing multi-morbidity, de-prescribing, falls risk reduction, and rehabilitation [17••]. In older adults, multidisciplinary teams (i.e., geriatricians, diabetes nurse educators, registered dietitians) can improve glycemic control and self-care behaviors when compared with usual diabetes care [99].

Conclusion

Older adults with diabetes and CKD are a complex, vulnerable population. We suggest a patient-centered, individualized approach to their best management. Where the number of patients living with these conditions will continue to increase, more efforts might be taken to understand their outcomes and the ideal therapies and targets to use in this population.

Compliance with Ethical Standards

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Niamh O'Regan and Jinnie J. Rhee declare that they have no conflict of interest.

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