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REVIEW

Evolving spectrum of diabetic nephropathy

Jonathan Kopel, Camilo Pena-Hernandez, Kenneth Nugent

ORCID number: Jonathan Josiah Kopel (0000-0001-5934-2695); Kenneth Nugent (0000-0003-2781-4816); Camilo Pena-Hernandez (0000-0002-5149-0930).

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Jonathan Kopel, Cell Biology and Biochemistry, Texas Tech University Health Sciences Center, Lubbock, TX 79416, United States

Camilo Pena-Hernandez, Department of Internal Medicine, Division of Nephrology, Lubbock, TX 79430, United States

Kenneth Nugent, Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX 79430, United States

Corresponding author: Jonathan Kopel, BSc, Research Scientist, MD-PhD Student, Cell Biology and Biochemistry, Texas Tech University Health Sciences Center, 3601 4th St, Lubbock, TX 79416, United States. jonathan.kopel@ttuhsc.edu
Telephone: +1-314-8058744
Fax: +1-806-7433143

Abstract

Diabetes remains an important health issue as more patients with chronic and uncontrolled diabetes develop diabetic nephropathy (DN), which classically presents with proteinuria followed by a progressive decrease in renal function. However, an increasing proportion of DN patients have a decline in kidney function and vascular complications without proteinuria, known as non-proteinuric DN (NP-DN). Despite the increased incidence of NP-DN, few clinical or experimental studies have thoroughly investigated the pathophysiological mechanisms and targeted treatment for this form of DN. In this review, we will examine the differences between conventional DN and NP-DN and consider potential pathophysiological mechanisms, diagnostic markers, and treatment for both DN and NP-DN. The investigation of the pathophysiology of NP-DN should provide additional insight into the cardiovascular factors influencing renal function and disease and provide novel treatments for the vascular complications seen in diabetic patients.

Key words: Diabetic nephropathy; Non-proteinuric diabetic nephropathy; Diabetes; Kidney vascular complications

Core tip: Diabetes remains an important health issue as more patients with chronic and uncontrolled diabetes develop diabetic nephropathy (DN). In recent years, an increasing proportion of DN patients have a decline in kidney function and vascular complications without proteinuria, known as non-proteinuric DN (NP-DN). This manuscript advances this discussion by examining the potential pathophysiological mechanisms, diagnostic markers, and treatments relevant to NP-DN. Furthermore, it illustrates the significance of

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INTRODUCTION: PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY

Diabetes remains an important health issue as an increasing number of patients with chronic and poorly controlled diabetes develop diabetic nephropathy (DN)[1-4]. The main risk factors associated with the development of DN include hypertension, poor glycemic control, smoking, and dyslipidemia[5]. Among several ethnicities, Native Americans have the highest incidence of DN followed by Asians, Hispanics,African-Americans, and Caucasians[6]. Several genetic polymorphisms are also associated with development of DN, including angiotensin type 2 receptor and angiotensin converting enzyme (ACE)[7-10]. In recent years, the number of patients seeking dialysis for kidney-related disorders has increased with the rise in DN[11]. Specifically, DN remains the leading cause of all excess mortality among type I and II diabetic patients with microalbuminuria, macroalbuminuria, or end-stage kidney disease[12,13]. Although kidney transplantation is an option, many DN patients have frequent post-operative complications associated with kidney transplant procedures, including cerebrovascular disease events and graft rejection[14,15]. As a result, clinical studies examining the pathophysiology and therapeutic interventions for DN remain an important public health concern for reducing DN-associated end-stage renal disease and mortality.

DN begins with glomerular hyperperfusion and renal hyperfiltration and then progresses to microalbuminuria and a lowered glomerular filtration rate (GFR). Current guidelines define DN using four main criteria: a decline in renal function, diabetic retinopathy, proteinuria, and a reduction in GFR[16]. Specifically, "Overt nephropathy is characterized by persistent proteinuria (> 500 mg/24 h) that usually precedes a fall in glomerular filtration rate (GFR) significant proteinuria has therefore long been regarded as the hallmark of DN"[17]. DN is diagnosed by urinalysis and confirmed, if necessary, by a kidney biopsy, and its progression is monitored through regular measurements of microalbuminuria, serum creatinine, and calculated GFR[1,18]. With advanced cases of DN, the kidney biopsy shows mesangial hypercellularity and expansion, thickening of the basement membranes, arteriolar hyalinosis, and interstitial fibrosis. In some cases, Kimmelstiel-Wilson lesion seen in DN kidney biopsies correlate with an increased risk of worsening renal function and retinopathy[19]. However, several studies have reported substantial variability in patients with DN that deviates from accepted guidelines, which has encouraged clinicians to incorporate routine biopsy of DN patients[20,21]. As a result, DN is now viewed as a spectrum of presentations with many authorities arguing for expanding the current pathological classification of DN to improve treatment strategies and outcomes[16,22,23].

Among the parameters used to identify DN patients, the presence of proteinuria represents an important prognostic factor reflecting damage to the glomerular filtration barrier[24]. However, several studies have described DN without significant proteinuria (> 500 mg/24 h) in over 50% of diabetic patients[25-32]. Among the 15773 Type 2 diabetic patients with varying severity of renal insufficiency examined in the Renal Insufficiency and Cardiovascular Events Italian Multicenter Study, 56.6% were normoalbuminuric, 30.8% were microalbuminuric (30 to 300 mg/24 h), and 12.6% were macroalbuminuric (> 300 mg/24 h)[33]. In some cases, the proteinuria vanishes with patients having normal albuminuria levels[34-36]. For example, a six-year longitudinal study conducted by the Joslin Clinic showed that 58 percent of the 386 patients who had microalbuminuria eventually had normal albuminuria levels[34].

Compared with patients with type II diabetes and DN, patients with type 1 diabetes and DN with normoalbuminuria had more of glomerular lesions, such as increased glomerular basement membrane thickness and more Kimmelstiel-Wilson nodules, and more frequent progression of DN[28]. As shown in Table 1, a new classification was created to characterize DN patients with a decline in kidney

function and vascular complications without proteinuria, known as non-proteinuric DN (NP-DN)[37,38]. Robles summarized these recent studies with this observation, "There have now been reports that in both type 1 and type 2 diabetes mellitus, a proportion of patients may have renal impairment without significant proteinuria or albuminuria, with a variable percentage of patients in these reports having advanced (stage 3–5) kidney disease. It could be interpreted as an accelerated kidney sclerosis due to the interaction of diabetes with other cardiovascular risk factors"[17]. Furthermore, a recent clinical study reported NP-DN is an increasing cause of chronic kidney disease globally[17]. At present, increasing age, repeated cardiovascular injury, such as hypertension, cardiovascular disease, and dyslipidemia, to the kidney, and an over-suppressed renal-angiotensin system have been proposed as potential mechanisms for NP-DN[17].

Despite the increased incidence of NP-DN, few clinical or experimental studies have thoroughly investigated the pathophysiological mechanisms and targeted treatment of NP-DN. As the nephrologist Jean Halimi summarized, "it is not clear why some patients develop the 'classical' deiabetic nephropathy with significant proteinuria, while others have impaired renal function associated with very low levels of proteinuria that sometimes persist as late as end-stage renal disease"[38]. Furthermore, a clinical review published by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative showed that "there is insufficient evidence to assume that interventions that prevent or reverse microalbuminuria will necessarily lead to improvement in clinical outcomes and conversely that failure to reduce microalbuminuria precludes a beneficial effect of treatment on diabetic kidney disease"[39]. In this review, we will discuss the differences between DN and NP-DN and consider potential pathophysiological mechanisms, diagnostic markers, and treatment for NP-DN.

POTENTIAL MECHANISMS OF NP-DN

Current research suggests that increased vascular resistance in renal interlobar arteries can damage glomerular and non-glomerular nephron structures and contribute to the onset and progression of NP-DN[37,40]. A recent study reported an elevation in arterial stiffness, measured using aortic and brachial-ankle pulse wave velocity, in NP-DN patients, which was strongly associated with increased atherosclerosis and cardiovascular morbidity and mortality and decreased renal function[40-47]. Thus, NP-DN patients likely have more atherosclerosis and increased vascular resistance which reduce glomerular function and damage glomerular-tubular structures.

Several studies examining NP-DN found elevated serum uric acid levels, which were strongly associated with the development of kidney disease[48-50]. Although an antioxidant in the blood, uric acid is also a potent pro-oxidant and damages mitochondria through the stimulation of NADPH oxidases[51]. Elevated uric acid levels could also damage vascular elements and induce endothelial dysfunction through various mechanisms, including activation of Toll-like receptor pathways[51,52]. Furthermore, uric acid induces renal inflammation, vascular smooth muscle cell proliferation, and activation of the renin-angiotensin system[53-56]. Prolonged elevation of uric acid levels in NP-DN patients can produce significant vascular changes that impair renal function leading to NP-DN[57]. Therefore, elevated uric acid levels in NP-DN patients can produce more vascular damage than in DN patients. In recent years, sodium-glucose 2 (SGLT2) inhibitors were shown to increas uric acid excretion through the proximal tubule transporter, SLC2A9 (GLUT9), which improved glycemia control, weight loss, and blood pressure control among DN patients[58-60]. Future clinical studies should include serial measurements of uric acid and uric excretion between DN and NP-DN patients prescribed SGLT2 inhibitors to investigate this mechanism.

Patients with NP-DN have elevated concentrations of serum tumor necrosis factor alpha (TNFα) and Fas-pathways[61]. TNFα is a key mediator of inflammation through the induction of chemokines, IFN-γ inducible protein-10, intercellular adhesion molecule-1, and vascular adhesion molecule-1, which increase glomerular vasoconstriction and albumin permeability[61]. Furthermore, TNFα is involved in the acute kidney injury, regulation of blood pressure, blood flow, and inflammation within the renal vasculature[62-64]. TNFα and Fas also have important roles in apoptosis[61]. The FasL-Fas system regulates renal cell apoptosis during immune and inflammatory responses through the activation of renal cell Fas receptors[65]. In addition, murine models that block the FasL-Fas system prevent renal and tubular cell injury during ischemia-reperfusion experiments[65]. Thus, increased levels of TNFα

Table 1 Pathophysiology of diabetic nephropathy and non-proteinuric diabetic nephropathy

Clinical parameter	Diabetic nephropathy	Non-proteinuric diabetic nephropathy
Proteinuria	Present	Absent
Regression of proteinuria	Present	Absent
Histology	Abnormal	Normal or abnormal
Glomerular filtration rate	Decreased	Decreased
Increased risk of chronic kidney disease	Present	Present

and Fas in NP-DN can alter renal vasculature and damage the kidney.

NP-DN patients also have elevated levels of osteoprotegerin and vascular endothelial growth factor (VEGF), which function in inflammation and angiogenesis, respectively[66]. Interestingly, VEGF levels are inversely related to proteinuria levels in DN patients[67]. In the presence of TGF-β, VEGF signaling leads to apoptosis and potentially cause glomerular vascular atrophy[68]. Elevated serum VEGF levels in murine models initiate a feedback inhibition of VEGF production by podocytes leading to glomerular injury[69]. In addition, osteoprotegrin is associated with chronic kidney disease in diabetic patients, leading to calcification of vascular tissue, glomerular damage, and proteinuria[70,71].

In summary, the pathogenesis of NP-DN appears to involve vascular and soluble elements circulating in the blood, as shown in Figure 1. Comparisons between DN and NP-DN patients should provide insight into the functions of these receptors and other inflammatory responses occurring within the kidney. Furthermore, additional studies investigating non-enzymatic glycation of proteins, metabolic stress, hypertension, N-terminal fragment of pro brain natriuretic peptide and glomerular vascular injury can provide additional insight into the pathogenesis of NP-DN[72]. This information may provide unique insights and possibilities for developing novel treatment for DN and NP-DN.

DIAGNOSTIC MARKERS FOR NP-DN

Given the recent identification of NP-DN, current guidelines should be expanded to include NP-DN and other forms of DN. Kidney biopsies are readily available and provide a detailed analysis of a patient's renal disease. However, complications, such as infection, bleeding, and other vascular injuries, limit its wider use by physicians[73]. Furthermore, kidney biopsies may not fully detect the vascular changes occurring in NP-DN and DN patients. As a result, the development of safer and accessible diagnostic markers is critical for improving early diagnosis and treatment of conventional DN and NP-DN patients.

Ultrasound technology is one alternative which has provided opportunities for diagnosing and monitoring the progression of DN. Unlike renal biopsies, ultrasound represents an inexpensive and non-invasive method for examining and grading the progression of DN and other related renal pathologies, such as renal cysts or stones[74]. Ultrasound technology can provide measurements on renal anatomy and function associated with DN, acute renal failure, and cirrhosis[75]. Recent studies using ultrasound have provided an additional method for evaluating renal function in DN patients at various stages of the disease[75-79]. Specifically, an increase in the Renal Resistive Index (RRI), which measures renal vascular resistance, has been shown to reliably detect and monitor the progression of DN and NP-DN[75,80,81]. For example, a study in diabetic patients showed that RRI values were elevated in diabetic patients without overt proteinuria or renal atherosclerosis[82]. Therefore, ultrasound sonography provides an effective method to screen, identify, and monitor hemodynamic and morphologic changes in DN patients[82]. Furthermore, diabetic patients identified as high risk for DN could qualify for preventative pharmacologic treatment, which might prevent the onset of DN before the appearance of proteinuria[83]. Recent reports with ultrasound technology and DN strongly suggest that this technology could be used to differentiate DN and NP-DN for diagnostic and screening purposes[82]. In addition, only a few studies have systematically compared the renal function, prognosis, and various blood and urine components in conventional DN and NP-DN patients. More studies examining changes in the levels of TNFα, TGF-β, endothelin, and other interleukins in the blood and urine of DN and NP-DN might provide additional diagnostic criteria and potential insight into the pathophysiological mechanisms of NP-DN. More analysis comparing both groups

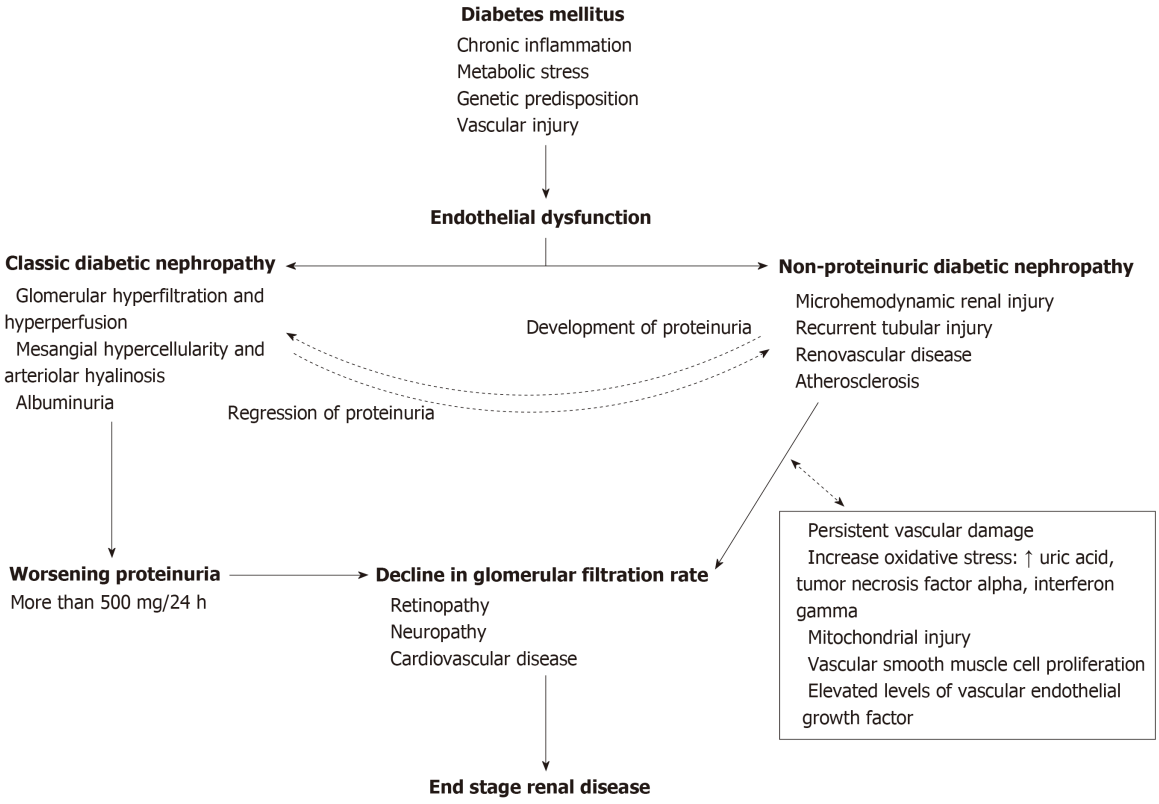

Figure 1 Pathophysiology of diabetic nephropathy and non-proteinuric diabetic nephropathy.

should help clarify distinct pathological and diagnostic criteria for DN and NP-DN.

POTENTIAL TARGETED THERAPIES FOR NP-DN

Uncontrolled hypertension produces hemodynamic stress that causes fibrinoid necrosis of small blood vessels leading to acute renal failure. The current pharmacological treatment for hypertensive disorders and glomerular vascular syndromes includes thiazide diuretics, beta blockers, ACE inhibitors, angiotensin II receptor blockers, calcium antagonists, and α_1 blockers. However, these anti-hypertensive drugs fail to prevent progressive declines in GFR and renal disease[84]. As a result, the development of new pharmaceutical regimens for managing DN and NP-DN are needed[85,86]. Several studies have found ACE-inhibitors lisinopril and enalapril and the angiotensin II receptor antagonist losartan were effective in treating patients with normoalbuminuric type II diabetes through reductions in albuminuria excretion, blood pressure, creatine clearance[87-89]. In recent years, pharmacological alternatives for DN, such as heparin and antibody therapy, have been proposed for treating glomerular vascular syndromes.

Heparin is a potent glycosaminoglycan and anticoagulant used to treat and prevent deep vein thrombosis, pulmonary embolism, and arterial thromboembolism. Patients with diabetes have abnormal metabolism and catabolism of glycosaminoglycans[90]. Diabetic mouse models treated with heparin sulfate and glycosaminoglycan had significant improvement in morphological and functional renal abnormalities[90]. Unlike antihypertensive drugs, heparin reduces proteinuria and improves GFR without interacting with the renin-angiotensin-aldosterone system[91]. Similarly, sulodexide, a heparin derivative, reduced proteinuria and improved renal function in murine models when given orally, intramuscularly, or intravenously[92,93]. Clinical trials with long-term low-dose sulodexide have reported reduced proteinuria and renoprotective properties in DN, chronic kidney disease, hypertensive nephropathy, and primary glomerulonephritis[93,94]. Thus, heparin could provide an effective additive for reducing proteinuria and GFR in conventional DN and NP-DN patients on conventional antihypertensive therapy.

Given the inflammatory activities associated with diabetes, some anti-inflammatory drugs, such as pentoxifylline, have been studied in the treatment of DN[95,96]. Pentoxifylline is a methylxanthine derivative and a non-specific phosphodiesterase

inhibitor of TNF-α. Several studies with pentoxifylline have shown a decrease or stabilization in the progression of DN with additional reno-protective effects, such as decreased C-reactive protein, TNF-α, and risk for long-term dialysis[97-100]. In addition, pentoxifylline attenuates the progression of glomerular crescents, sclerosis, mesangial expansion, and interstitial fibrosis seen in DN patients[101]. Patients with NP-DN have elevated levels of TNF-α and other cytokines and could respond to pentoxifylline with improvement in renal vasculature and glomerular structures. Additional studies investigating other anti-inflammatory drugs in DN and NP-DN patients would provide an alternative first-line treatment in conjunction with current anti-hypertensive therapy. Table 2 shows the summary of NP-DN literature.

In summary, inflammation remains a central factor involved in the onset and pathogenesis of diabetes and diabetes-related complications. With the increase in NP-DN cases, new treatment and diagnostic markers are needed to understand the pathogenesis of both DN and NP-DN. New therapies beyond current anti-hypertensive therapy regimens hold promise in providing an effective measure for the prevention and treatment of DN and NP-DN. More clinical studies are needed to examine the differences between DN and NP-DN in pathogenesis, diagnosis, and treatment. Specifically, additional studies examining the use of allopurinol to reduce uric acid levels among NP-DN patients would provide a readily accessible treatment for both clinicians and patients. Furthermore, studies examining RRI can yield additional anatomical and pathophysiological data distinguishing NP-DN and DN. Despite these challenges, investigation of the pathophysiology of NP-DN requires further analysis into the cardiovascular factors influencing renal function and disease and identify novel treatment for the vascular complications seen in diabetic patients.

Table 2 Summary of non-proteinuric diabetic nephropathy literature

Field	Summary of non-proteinuric diabetic nephropathy literature
Prevalence	57% of diabetic nephropathy patients
Pathogenesis	Vascular and soluble elements, such as uric acid, TNFα, and VEGF, affecting renal microhemodynamics
Diagnosis	(1) Increased renal resistive index; (2) Alterations in TNFα, TGF-β, endothelin, and other interleukins
Treatment	(1) Enalapril; (2) Losartan; (3) Heparin; (4) Pentoxifylline

TNFα: Tumor necrosis factor alpha; VEGF: Vascular endothelial growth factor; TGF: Transforming growth factor.

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MINIREVIEWS

Management of diabetic dyslipidemia: An update

Ishwarlal Jialal, Gurdeep Singh

ORCID number: Ishwarlal Jialal (0000-0001-9113-2604); Gurdeep Singh (0000-0001-6044-7419).

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Ishwarlal Jialal, California North-state University College of Medicine, VA Medical Center, Mather, CA 95757, United States

Gurdeep Singh, Lady of Lourdes Memorial Hospital, New York, NY 10041, United States

Corresponding author: Ishwarlal Jialal, MD, PhD, Professor, Assistant Dean, California North-state University College of Medicine, VA Medical Center, 9700 West Taron Drive, Elk Grove, Mather, CA 95757, United States. ishwarlal.jialal@cnsu.edu
Telephone: +1-530-7502859
Fax: +1-916-6867310

Abstract

Diabetic dyslipidemia is a cluster of lipoprotein abnormalities characterized by increased triglyceride level, decreased high-density lipoprotein-cholesterol levels and increase in small dense low-density lipoprotein (LDL) particles. It is extremely common in type 2 diabetes (T2DM) affecting around 70 % of patients. Diabetic is a significant risk factor for atherosclerotic cardiovascular disease (ASCVD) which is the most common cause of death in the United States and LDL-cholesterol is the number 1 predictor of ASCVD events in T2DM. The purpose of this review is to discuss the pathophysiology and treatment of diabetic dyslipidemia. In this review, we have discussed both non-pharmacological and pharmacological treatment modalities including major treatment trials which have impacted the cardiovascular outcomes in patients with diabetes. Statin therapy is the mainstay of treatment to reduce ASCVD by decreasing LDL-C by 30%-49% or at least 50% depending on risk level. Attractive adjunctive therapies include Ezetimibe which is more cost effective and PCSK9 inhibitors which display potent LDL-cholesterol lowering and ASCVD event reduction. For severe hypertriglyceridemia, to avert the risk of pancreatitis, both fish oil and fenofibrate in concert with diet is the best strategy.

Key words: Diabetes; Dyslipidemia; Statins; Atherosclerosis; Ezetimibe; PCSK9

Core tip: Atherosclerotic cardiovascular disease (ASCVD) is the major cause of mortality in diabetes. Low-density lipoprotein (LDL)-cholesterol lowering with statins reduce ASCVD and is the mainstay of therapy. Also, both ezetimibe and PCSK9 inhibitors are useful strategies when statins cannot be tolerated or the LDL-cholesterol goal is not achieved.

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INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is the commonest cause of death in the United States and western world[1]. It claims around 2300 lives in the United States every day[2]. Diabetes is a significant risk factor for ASCVD and it is the leading cause of mortality. Diabetic patients are 2-4 times more likely to die from ASCVD as compared to non-diabetic patients. The rapidly increasing burden of diabetes from 108 million in 1980 to 442 million in 2014 poses a significant threat globally[3].

Diabetes can cause microvascular complications (retinopathy, neuropathy, nephropathy) and macrovascular complications (ASCVD) manifesting as coronary artery disease, stroke and peripheral arterial disease)[4]. Dyslipidemia in diabetes is common and is characterized by hypertriglyceridemia (HTG) with decreased levels of high-density lipoprotein (HDL)-cholesterol. Whilst low-density lipoprotein (LDL)-cholesterol levels are usually not elevated there is a preponderance of small dense LDL particles which appear to be more atherogenic[5-6]. Furthermore, there is an increase in particle number as evidenced by increased apolipoprotein B levels and non-HDL-cholesterol levels[5-6].

The 2 major sequelae of diabetic dyslipidemia are premature ASCVD from the elevated apolipoprotein B carrying particles and pancreatitis with severe HTG > 1000 mg/dL.

PATHOPHYSIOLOGY

Dyslipidemia is very common in type 2 diabetes (T2DM) mellitus affecting around 72%-85% patients[7].

The exact mechanism of lipoprotein abnormalities in diabetes is not very well understood. Insulin resistance, rather than hyperglycemia, has been implicated in the pathogenesis of diabetic dyslipidemia because lipoprotein changes including an increase in triglycerides (TG), increase in VLDL particles, small dense LDL particles and a decrease in HDL level have been shown in patients with impaired fasting glucose and impaired glucose tolerance and T2DM[6-8].

Lipoprotein abnormalities in diabetes can be divided into quantitative and qualitative. Quantitative changes include an increased triglyceride level and decreased HDL-C level. Qualitative changes include an increase in small dense LDL particles and large very-LDL sub fraction (VLDL1) that predisposes to the formation of small dense LDL particles[7].

HTG occurs due to both increased production and decreased clearance, and it is the most common abnormality of diabetic dyslipidemia.

Insulin resistance causes increased production of VLDL. VLDL can be further divided into large VLDL1 (triglyceride-rich) and small, dense VLDL2.

Insulin resistance causes an increase in VLDL1 levels which worsens HTG[7,9].

In addition to increased secretion of VLDL, there is decreased clearance of VLDL due to decreased hepatic uptake and impaired activity of lipoprotein lipase[7,9,10].

HTG increases the activity of cholesterol ester transfer protein which leads to transfer of triglyceride to HDL and LDL from triglyceride-rich lipoprotein[11]. This causes an increase in the TG content of HDL and LDL.

Small dense LDL particles are more prone to post-secretory modifications such as glycation and oxidation and permeate the intima more easily where they are trapped by proteoglycans[6,7]. Thus whilst the LDL-cholesterol level is not overly increased there is an increase in the more atherogenic small dense LDL particles. In addition there is an increase in chylomicron and VLDL remnant particles in T2DM which are also atherogenic[7,12].

DIABETIC DYSLIPIDEMIA AND CARDIOVASCULAR DISEASE

Epidemiological studies have shown a correlation between increased TG level and cardiovascular disease (CVD), and recent studies have established a cause and effect relationship between TG rich lipoproteins and CVD *via* mutations in apolipoprotein C3[13,14].

The role of HDL in CVD is unclear. Studies have shown an inverse relationship between HDL and CVD[15]. However as will be discussed under therapy there is no benefit to raising HDL-cholesterol in T2DM with niacin therapy[16].

LDL-cholesterol has been the primary predictor of CVD. Multiple studies have shown a strong relationship between LDL and CVD. In diabetes, LDL concentration may or may not be increased, but there is an increase in the concentration of small dense LDL particles which are considered more atherogenic than large LDL particles[6,7,17]. Also, in the UKPDS study, Turner *et al*[18] showed that LDL-cholesterol was the number 1 predictor of ASCVD risk in T2DM following adjustment for both age and sex[18].

TREATMENT TARGETS BASED ON GUIDELINES

Treatment strategy has significantly changed over the last two decades, but LDL-cholesterol has remained the cornerstone of treatment.

In 2013 the American College of Cardiology (ACC)/American Heart Association (AHA) published guidelines for the management of cholesterol to reduce ASCVD. These guidelines recommended using high, moderate or low-intensity statins depending upon the 10-year CV risk score and presence or absence of ASCVD. These guidelines did not recommend specific cholesterol targets. The ACC/AHA recommended that any patient with diabetes mellitus type 1 or 2 aged 40-75 should be treated with moderate intensity statins with a goal reduction in LDL-C of 30%-49%. High-intensity statins were recommended if the 10- year CV risk score is ≥ 7.5% or if ASCVD was present with a target LDL-C reduction of > or equal to 50%[19].

In 2017 American Association of Clinical Endocrinologists guidelines categorized diabetic patients as high, very high and extreme risk patients for CVD. It recommended that patients with high risk [≥ 2 risk factors and 10 year risk 10%-20%, or chronic kidney disease (CKD) stage 3-4 with no other risk factors], very high risk [established acute coronary syndrome (ACS) or recent hospitalization for ACS, peripheral arterial disease, carotid, coronary artery disease, 10-year risk ≥ 20%, CKD stage 3-4 with 1 or more risk factors, heterozygous familial hypercholesterolemia], extremely high risk (progressive ASCVD, coronary artery disease with CKD stage 3-4, diabetes or heterozygous familial hypercholesterolemia, history of premature ASCVD in female with age < 65 or males with age < 55 years) should be treated for LDL targets of < 100, < 70 and < 55 mg/dL respectively[20].

The American Diabetes Association 2019 guidelines recommend that all diabetic patients with ASCVD or patients with a 10-year atherosclerotic cardiovascular risk > 20% should be treated with high-intensity statins (goal of 50% reduction in LDL-cholesterol) in addition to lifestyle modification[21]. Diabetic patients aged < 40 with additional atherosclerotic cardiovascular risk factors (LDL-C ≥ 100 mg/dL, hypertension, CKD, smoking, albuminuria and FH of premature ASCVD) , diabetic patients age 40-75 years without ASCVD or 10 year ASCVD risk < 20% and diabetic patients > 75 years old should be treated with moderate intensity statins with a goal of 30%-49% LDL-C reduction[21].

Most recently, the new ACC/AHA guidelines were published[22]. Diabetes was defined as a high risk condition for ASCVD. In addition they provided diabetes specific Risk Enhancers which included: Diabetes duration of >10 years in T2DM and >20 years duration for T1DM, Albuminuria > 30 mg/G creatinine, an estimated GFR < 60 mL/min /1.73m^2, retinopathy, neuropathy and an ankle-brachial index (ABI) < 0.9. In adults 40-75 years with diabetes regardless of 10-year risk initiate moderate intensity statin. In adults with diabetes with ASCVD or multiple ASCVD risk factors it is reasonable to prescribe high intensity statin to lower LDL-C by 50% or more. In adults > 75 years on a statin it is reasonable to continue statin therapy. In adults 40-75 years old with LDL-C between 70-189 mg/dL without ASCVD the 10-year risk should be assessed using the age and race based robust pooled cohort equation (PCE) which uses age, smoking, hypertension, serum cholesterol, HDL-C, and presence or absence of diabetes to compute the 10-year risk[22]. If the risk is 20% or higher, then therapy should aim for an LDL-C reduction of 50% or greater. In diabetics between 20-39 years of age it is reasonable to institute moderate intensity statin therapy if the following are present: T2DM with duration > or equal to 10 years, T1DM with duration > or equal to 20 years, albuminuria > 30 mg/G creatinine, e-GFR < 60 mL/min, retinopathy, neuropathy, ABI < 0.9[22].

Since the occurrence of a first ASCVD event in diabetic patients 40-75 years old is associated with increased morbidity and mortality compared to non-diabetic patients high intensity statin therapy is reasonable as they age (men > 50 and women > 60 years) or develop the risk modifiers including T2DM with duration > or equal to 10 years, T1DM with duration > or equal to 20 years, albuminuria > 30mg/G creatinine , e-GFR < 60 mL/min, retinopathy, neuropathy, ABI < 0.9[22]. Also, it is prudent to consider statin therapy in diabetic patients > 75 years taking into account side effects and co-morbidities and the life span of the patient.

THERAPEUTIC STRATEGIES

Diabetic dyslipidemia treatments can be divided into non-pharmacological and pharmacological. Non-pharmacological treatment includes medical nutrition therapy, weight loss, and physical activity.

Diabetic patients should increase the intake of plant stanols/sterols, viscous fiber (legumes, citrus, oats), n-3 fatty acids and decrease the intake of saturated and trans-fatty acids. American Diabetes Association recommends the Mediterranean diet or DASH (Dietary Approaches to Stop Hypertension) diet[21-23].

Tree nuts, peanuts, grains are a good source of unsaturated fat, and decrease cholesterol, blood pressure and risk of CVD and diabetes.

Consumption of a walnut-rich diet in a randomized study showed improvement of non-HDL cholesterol and apolipoprotein B[24]. An epidemiological association between nut consumption and decrease death due to CVD and overall mortality has been shown but randomized clinical trial data is still lacking[25].

Around a 5% reduction in body weight is associated with improvement in lipid profile, insulin resistance and glycemic control[26]. Weight loss decreases triglyceride level, raises HDL-C levels and can also improve blood pressure[27]. Even though weight loss was shown to improve multiple risk factors, such as hemoglobin A1C and blood pressure, the Look AHEAD study did not show improvement in the cardiovascular events (CVE) after long term weight loss with intensive lifestyle change[28], indicating the need for pharmacotherapy along with lifestyle modification to reduce ASCVD[23].

Pharmacological therapy includes statins, cholesterol absorption inhibitors, niacin, fibrates, bile acid sequestrants (BAS), PCSK9 inhibitors and omega-3 fatty acids[22]. The drugs that effectively and safely lower LDL-cholesterol are depicted in Table 1.

Statins

Statins inhibit 3-hydroxymethylglutaryl coenzyme A which is a rate-limiting step in the synthesis of cholesterol in the liver. Statins are used for primary and secondary prevention of CVD and stroke. Decreased cholesterol level in the liver leads to an upregulation of LDL receptors which leads to a decrease in plasma LDL cholesterol[29]. In addition to the decrease in LDL cholesterol, statins lower the level of TG and increase the level of HDL-cholesterol[30].

Statins also have pleiotropic effects and have been shown reduction of hsCRP and other markers of inflammation that help to stabilize plaque, improve endothelial function and decrease vascular inflammation and oxidative stress[30,31]. Statins are divided into high-intensity (atorvastatin 40-80 mg, rosuvastatin 20-40 mg) which can decrease LDL- C by approximately 50% or more; moderate-intensity (Atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40 mg, lovastatin 40 mg, Fluvastatin 80 mg, pitavastatin 2-4 mg) which can decrease LDL-C by approximately 30%-50% ; and low-intensity (Simvastatin 10mg, Pravastatin 10-20 mg, Lovastatin 20 mg, Fluvastatin 20-40 mg, Pitavastatin 1 mg) which decrease LDL-C by < 30%[19,22].

Trials have shown a reduction of CVE in diabetic patients with use of statins including the Heart Protection Study which reported a 22% reduction in CVE including ischemic stroke[32] and The Collaborative Atorvastatin Diabetes Study[33,34] which reported a 37% reduction in the primary end point of CVE also including ischemic stroke. Meta-analysis of 14 randomized clinical trials including over 18000 patients showed statin therapy reduced CVE by 21% and vascular mortality by 13% for every 39 mg/dL decrease in LDL-C during an average follow up of 4.3 years[34,35].

Statins can cause side effects but are well tolerated in general. Myalgia is the most common side effect, affecting 5%-10% patients[36]. Statin-induced necrotizing autoimmune myopathy and rhabdomyolysis are rare[36]. Risk factors for myopathy include age, female sex, low BMI, high risk medications such as azole antifungals, macrolides, protease inhibitors, cyclosporine, fibrates, nicotinic acid, renal disease, Asian descent, excess alcohol intake, trauma[19,22]. Statins can also cause new onset

Table 1 Summary of low-density lipoprotein-cholesterol lowering medications

Drug class	Mechanism of action	Clinical eficacy	Adverse reactions
Statins	Inhibition of HMG coenzyme A Reductase	Highly effective	Myalgia, myositis, rhabdomyolysis, elevation in liver enzymes, new onset diabetes
Ezetimibe	Decrease intestinal cholesterol absorption by binding to Niemann-Pick C1-like 1 protein	Moderately effective; Safe addition to statin therapy	Worsening of liver function, myopathy or rhabdomyolysis if added to statins; Nasopharyngitis, diarrhea, upper respiratory tract infection
PCSK9 inhibitors	Inhibition of Proprotein Convertase Subtilisin/Kexin Type 9	Very highly effective in combination with statin therapy	Injection site reaction including itching, swelling, erythema and pain
Bile acid sequestrants	Bind bile acids in the small intestine and prevent reabsorption	Moderately effective, safe addition to statin therapy, not desirable if triglycerides are > 300 mg/dL	Constipation, abdominal pain, bloating, drug malabsorption

HMG: Hydroxymethylglutaryl; PCSK9: Proprotein convertase subtilisin/kexin type 9.

diabetes; the exact underlying mechanism is not clear. The JUPITER (Justification for the use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial was the first trial to show an increased risk of diabetes. In this trial the risk of diabetes in the rosuvastatin group was increased by 0.6% compared to placebo group[37]. The risk is higher with higher doses and in patients with Metabolic syndrome, BMI > 30 and A1c > 6%[22]. The benefits of reducing CVE far outweigh the low risk for diabetes which can be prevented with diet and exercise.

Cholesterol absorption inhibitors (Ezetimibe)

Ezetimibe decreases cholesterol level by inhibiting intestinal absorption of cholesterol. It is used in combination with statins to achieve significant LDL-C reduction, or in patients who are not able to tolerate the required dose of statins.

In the IMPROVE-IT trial, 18144 patients with the ACS and LDL cholesterol between 50-125 mg/dL were randomized to simvastatin 40 mg with ezetimibe 10 mg or simvastatin 40 mg with placebo. During a median follow up of 6 years, patients who received simvastatin and ezetimibe had a significant reduction in LDL cholesterol compared to the simvastatin only group, 54 mg/dL *vs* 70 mg/dL respectively[38]. There was 6.4% reduction in the primary composite endpoint (myocardial infarction, cardiovascular death, coronary revascularization in 30 d, hospitalization for unstable angina, and stroke) demonstrating the additional benefit of adding ezetimibe to a statin[38]. More importantly in the patients with diabetes (27% of patients) there was a greater benefit on the primary end point with a 14% risk reduction. The combination of ezetimibe and simvastatin has been showed to decrease the risk of recurrent ischemic stroke when compared with simvastatin in patients with T2DM[39] underscoring the importance of ezetimibe in diabetic patients with CVD.

Fibrates

Fibrates include bezafibrate, gemfibrozil, ciprofibrate, and fenofibrate. Fibrates activate nuclear peroxisome proliferator-activated receptor alpha which causes a reduction in triglyceride level by stimulating lipoprotein lipase activity. Fibrates can decrease fasting plasma triglyceride level by 30%-50% and can also decrease postprandial lipemia by decreasing the synthesis of fatty acids. Fibrates increase HDL level by upregulation of apoA-1 and A-II[40]. Fibrates have also been shown to decrease small dense LDL level in some studies[41].

In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention trial, gemfibrozil compared to placebo resulted in a 31% reduction in TG, 4% reduction in cholesterol and a 6 % increase in HDL-cholesterol. Nonfatal myocardial infarction or death from coronary artery disease was decreased by 4.4%[42] in these patients with ASCVD and low HDL-cholesterol. However, these patients did not have a high-risk LDL-C and did not appear to receive statin therapy.

The Fenofibrate Intervention and Even Lowering in Diabetes (FIELD) study evaluated the effect of treatment with fenofibrate in reducing macrovascular and microvascular complications in 9795 patients with T2DM. After 5-year follow-up period, treatment with fenofibrate was associated with no significant reduction in the primary end point[43].

Also, in the ACCORD trial, a combination of simvastatin and fenofibrate in 5518 patients with T2DM, did not decrease the rate of nonfatal myocardial infarction, fatal

CVE or nonfatal stroke compared to simvastatin only group[44].

Fibrates are metabolized in the kidney and should be avoided or used with caution in patients with CKD. The combination of gemfibrozil and statin predisposes to a greater risk for myopathy as is essentially contra-indicated.

The major indication of fibrates is to reduce TG in patients with very high TG at risk for pancreatitis. This diabetic HTG has been reviewed by the principal author[45]. Briefly, in patients with severe HTG > 1000 mg/dL, secondary causes such as excess alcohol intake, drugs (steroids, oral estrogen, protease inhibitors *etc*.,) and kidney disease should be ruled out. In these patients in addition to good glycemic control and reduction in fat and total calories in the diet, fibrates and or fish oils 4 g/d therapy needs to be initiated to lower TG levels < 500 mg/dL to avert the risk of pancreatitis.

Niacin

Niacin is a very potent drug for increasing HDL-cholesterol levels. Niacin also lower TG and LDL-cholesterol. However, the combination of statin and niacin did not show any additional cardiovascular benefit when compared with statin alone.

The AIM- HIGH trial did not show any cardiovascular benefit after adding niacin in high-risk patients who were already receiving simvastatin and ezetimibe[16]. Heart Protection Study 2- Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) randomized 25673 patients with atherosclerotic vascular disease to receive niacin/laropiprant versus placebo. The treatment group did not show any cardiovascular benefit but there was a significant increase in new onset diabetes, bleeding and infections[46] No guidelines recommend niacin-statin combination therapy in patients with diabetes and patients with ASCVD since there is the potential for harm with no benefit.

Proprotein Convertase Subtilisin/Kexin Type 9 inhibitors

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK 9) inhibitors Alirocumab and Evolocumab are very potent drugs and can decrease LDL-C significantly when used as monotherapy or in combination with statins. PCSK9 inhibitors by binding PCSK9 prevents PCSK9 from binding LDL receptors and targeting them for intrahepatic lysosomal degradation. The leads to increased expression of LDL receptors causing a reduction in LDL-C level[47]. These are given as subcutaneous injections every 2-4 wk.

PCSK9 inhibitors are indicated in patients with ASCVD who are on maximum tolerated statin therapy with or without ezetimibe but have LDL-C ≥ 70 mg/dL or non-HDC ≥ 100mg/dL. They are also indicated in patients with LDL ≥ 190 mg/dL with underlying homozygous familial hypercholesterolemia or heterozygous familial hypercholesterolemia[47].

In 2015, ODYSSEY long term trial enrolled 2341 adults who were at high risk for CVE due to history of established coronary artery disease or had presence of Heterozygous Familial Hypercholesterolemia, or coronary risk equivalent states (ischemic stroke, peripheral arterial disease, moderate CKD with GFR 30-59 or diabetes mellitus with two additional risk factors). These subjects had LDL-C level ≥ 70 mg/dL despite being on maximum tolerated dose of statin and were randomized to receive alirocumab 150 mg or placebo. Alirocumab therapy decreased LDL-C from 122.8 mg/dL to 53 mg/dL at 48 mo[48].

In ODYSSEY outcomes trial, use of alirocumab was studied in patients who have had ACS. This was a randomized, multicenter, double blind, placebo control trial of 18924 patients who had an episode of ACS with in last 1-12 mo. These patients had an LDL-Cholesterol level of at least 70 mg/dL, an apolipoprotein B level of at least 80 mg/dL or a non-HDL cholesterol level of at least 100 mg/dL. These patients were already receiving maximum tolerated dose of statin or high intensity statin and were randomized to receive alirocumab 75 mg subcutaneously or placebo. After follow up 2.8 years there was a 15% reduction in the primary end point (composite of death from coronary heart disease, fatal or nonfatal ischemic stroke, nonfatal myocardial infarction or unstable angina requiring hospitalization), $P < 0.001$[49]. Diabetic patients comprised 29% of the cohort and appear to have accrued a benefit but this was not detailed.

OSLER-1 and OSLER-2 evaluated the PCSK9 inhibitor Evolocumab. 4465 patients were randomly assigned in a 2:1 ratio to receive Evolocumab with standard therapy or standard therapy alone. Evolocumab decreased LDL-C from a median of 120 mg/dL to 48 mg/dL (61% reduction) as compared to standard therapy alone[50].

PCSK9 inhibitors induce atheroma regression and decrease atheroma volume. In the Glagov randomized clinical trial, 968 patients were randomized to receive Evolocumab 420 mg subcutaneous injection monthly or placebo. Evolocumab decreased percent atheroma volume by 0.95% and total atheroma volume decreased by 5.8 mm[51].

In FOURIER trial 27564 patients with ASCVD and LDL level ≥ 70 mg/dL while

being on maximally tolerated statin were randomized to evolocumab subcutaneous injection (140 mg every 2 wk or 420 mg every mo) or placebo. At 48 wk, the mean percent reduction in LDL-C was 59% in the treatment group compared to placebo with an achieved LDL-C of 30mg/dL. There was a 15 % relative risk reduction in the primary end –point (composite of cardiovascular death, stroke, myocardial infarction, coronary revascularization and hospitalization from unstable angina), $P < 0.001$[52]. There was no increase in new onset diabetes. In a subsequent report in the 11031 diabetic patients they also showed a significant risk reduction in the above composite primary end point of 17%, $P = 0.0008$. There was no increase in new onset diabetes or any deleterious effect on glycaemia. However this was a study in diabetic patients with ASCVD so the role of PCSK9 inhibitors in primary prevention of ASCVD in diabetics remains unknown[53].

PCSK9 inhibitors are very expensive with the annual cost of > $14500[54] which is more than 100 times higher than generic statin and can be a significant economic burden even in developed countries. These drugs are well tolerated, but the patient can develop an injection site reaction.

BAS

Bile acids are the end product of cholesterol catabolism. Cholestyramine, colestipol, and colesevelam are commonly used BAS. These bind to bile acid in the intestinal lumen and decrease their enterohepatic circulation which leads to increased production of bile acid in the liver causing a decrease in cholesterol level.

Use of cholestyramine in men over the long term has been shown to decrease total cholesterol and LDL cholesterol level by 13.4% and 20.3% respectively and also to decrease coronary heart disease by 19% when compared to placebo[55]. Hence, they are a useful adjunct to statins in reducing LDL-C further. They are contra-indicated if TG levels are > 400 mg/dL since they can increase the risk of pancreatitis[45].

Multiple studies have shown improved glycemic control with colesevelam in T2DM and hence they have the benefit of reducing both LDL-C and HbA1C levels, however there is no data to support further reduction in CVE[56].

Omega-3 fatty acids

Omega-3 fatty acids are used as add on therapy to reduce triglyceride level. Omega-3 fatty acid formulations contain eicosapentaenoic acid (EPA) and docosahexaenoic acid.

Sub-analysis of the Japan EPA Lipid intervention trial showed that treatment with EPA of patients with impaired glucose metabolism and hypercholesterolemia resulted in a 22% reduction in coronary artery disease incidence compared to normoglycemic patients[57]. However, in the ORIGIN trial, the use of omega-3 fatty acids (1.0 g/d) did not show cardiovascular benefit compared to placebo in patients with impaired glucose tolerance, diabetes or impaired fasting glucose[58].

Recently, Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia (REDUCE-IT), double-blind, randomized multicenter, placebo control trial of 8179 patients with established CVD or diabetes and other risk factors was published. In this study, patients were already being treated with statins and had a fasting TG level of 135-499 mg/dL and LDL- cholesterol level between 41-100 mg/dL. They were randomized to receive either a total daily dose of 4 mg icosapent ethyl or placebo. The primary endpoint was a composite of cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, coronary revascularization or unstable angina with a median follow-up of 4.9 years. There was a 25 % reduction in the primary end point with icosapent ethyl versus placebo, $P < 0.001$[59]. Diabetics constituted around 58% of the patients and they appeared to accrue a similar benefit to non-diabetics. There was also a decrease in total mortality of 13% but an increase in hospitalizations for atrial fibrillation or flutter. However, before we can make any serious recommendations for diabetics, we need to see the publication in the diabetic sub-group but it could emerge as first line therapy for severe HTG and an adjunct to statins in patients with ASCVD and increased TG. Interestingly in the primary prevention cohort including diabetics there appears to be no significant benefit: Hazards Ratio of 0.88 (0.7-1.10).

CONCLUSION

Diabetic dyslipidemia is a prevalent condition and patients with diabetic dyslipidemia are at particularly high risk for ASCVD. For the majority of patients' statin therapy in concert with therapeutic life style changes remain first line. There are, however, many other lipid lowering medications available to treat individuals who do not attain LDL-C goals on statins such as ezetimibe and PCSK9 inhibitors.

EPA could also become another adjunctive therapy in diabetics with ASCVD.

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MINIREVIEWS

Novel pharmacological therapy in type 2 diabetes mellitus with established cardiovascular disease: Current evidence

Leonardo Pozo, Fatimah Bello, Andres Suarez, Francisco E Ochoa-Martinez, Yamely Mendez, Chelsea H Chang, Salim Surani

ORCID number: Leonardo Pozo (0000-0002-6352-1423); Fatimah Bello (0000-0002-5841-6987); Andres Suarez (0000-0002-2884-1755); Francisco E Ochoa-Martinez (0000-0001-5987-857X); Yamely Mendez (0000-0002-0863-6236); Chelsea H Chang (0000-0001-8309-5911); Salim Surani (0000-0001-7105-4266).

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Leonardo Pozo, Fatimah Bello, Andres Suarez, Chelsea H Chang, University of Texas Rio Grande Valley - Doctors Hospital at Renaissance Internal Medicine Residency Program, Edinburg, TX 78539, United States

Francisco E Ochoa-Martinez, Faculty of Medicine, Universidad Autonoma de Nuevo Leon, University Hospital "Dr. José Eleuterio González", Monterrey, NL 66455, Mexico

Yamely Mendez, Faculty of Medicine "Dr. Alberto Romo Caballero", Universidad Autonoma de Tamaulipas, Houston, TX 77058, United States

Salim Surani, Medical Critical Care Services, Christus Spohn Hospitals-Corpus Christi, Corpus Christi, TX 78404, United States

Corresponding author: Salim Surani, BSc, FACC, FACP, FCCP, MD, Professor, Medical Critical Care Services, Christus Spohn Hospitals-Corpus Christi, 701 Ayers street, Corpus Christi, TX 78404, United States. srsurani@hotmail.com
Telephone: +1-361-8857722
Fax: +1-361-8507563

Abstract

Cardiovascular diseases (CVDs) remain the leading cause of death in the world and in most developed countries. Patients with type 2 diabetes mellitus (T2DM) suffer from both microvascular and macrovascular diseases and therefore have higher rates of morbidity and mortality compared to those without T2DM. If current trends continue, the Center for Disease Control and Prevention estimates that 1 in 3 Americans will have T2DM by year 2050. As a consequence of the controversy surrounding rosiglitazone and the increasing prevalence of diabetes and CVDs, in 2008 the Food and Drug Administration (FDA) established new expectations for the evaluation of new antidiabetic agents, advising for pre and, in some cases, post-marketing data on major cardiovascular events. As a direct consequence, there has been a paradigm shift in new antidiabetic agents that has given birth to the recently published American Diabetes Association/European Association for the Study of Diabetes consensus statement recommending sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon like peptide-1 receptor agonists (GLP-1RA) in patients with T2DM and established CVD. As a result of over a decade of randomized placebo controlled cardiovascular outcome trials, the aforementioned drugs have received FDA approval for risk reduction of cardiovascular (CV) events in patients with T2DM and established CV disease. SGLT2i have been shown to have a stronger benefit in patients with congestive

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heart failure and diabetic kidney disease when compared to their GLP-1RA counterparts. These benefits are not withstanding additional considerations such as cost and the multiple FDA Black Box warnings. This topic is currently an emerging research area and this mini-review paper examines the role of these two novel classes of drugs in patients with T2DM with both confirmed, and at risk for, CVD.

Key words: Type 2 diabetes mellitus; Glucagon-like-peptide 1 agonists; Sodium-glucose cotransporter-2 inhibitor; Cardiovascular disease; Major adverse cardiovascular event

Core tip: Cardiovascular diseases are of significant concern in patients with type 2 diabetes mellitus. Novel therapies offer a new opportunity for cardiovascular risk reduction and add complexity in terms of selecting antihyperglycemic treatment. These pharmacological therapies, however, also have additional considerations.

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INTRODUCTION

Cardiovascular disease (CVD) is the most important cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM), with approximately 20% of the individuals with this condition suffering from established atherosclerotic disease[1-4]. The cardiovascular (CV) risk seems to be driven largely by coexisting conditions in addition to the independent risk related to hyperglycemia[5].

Modern medicine uses a polypharmacy approach due to the nature of the disease. Lipid lowering agents have been studied for years and data supports their cardiovascular benefit in selected patient with and without T2DM[6]. Antithrombotic therapies for primary and secondary prevention are a topic of much debate in recent years, with data both supporting[7], and refuting[8] the idea of one-size-fits-all in patients with T2DM. Blood-pressure goals have also been a point of controversy, as demonstrated by Effects of Intensive Blood-pressure Control in T2DM trial [by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study group][9] and by the variation of goal blood pressures in major guidelines.

Intensive versus standard glycemic control has been a research question dating back to the 1990s with the United Kingdom Prospective Diabetes Study[10] with 3867 patients with T2DM and the Diabetes Control and Complications Trial[11] with 1441 patients with type 1 diabetes mellitus (T1DM). These trials demonstrated reduced microvascular endpoints but no difference in macrovascular endpoints with intensive glycemic control. Metformin use was associated with a reduction in DM-related complications and all-cause mortality. Fast-forward to 2008-09 and we have the large Action in Diabetes and Vascular Disease ADVANCE[12] trial with 11140 patients and the Veterans Affairs Diabetes Trial[13] with 1,791 patients, both showing intensive glycemic control having no impact on macrovascular outcomes in patients with T2DM.

Given the heterogeneity of diabetes, caution must be had in extrapolating results of one trial to a population with different baseline characteristics, whether that be the type of diabetes or the CVD risk. For example, the Epidemiology of Diabetes Interventions and Complications trial in 2005[14] showed that patients with T1DM had diminished rates of CVD with more stringent HbA1C targets. Then the same intervention of stringent HbA1C target resulted in the opposite outcome in those with T2DM in the large ACCORD trial in 2008[15] with 10251 patients, demonstrating increased mortality and no CV benefit.

With hypoglycemia identified as a driving factor for the increased rate of CV events and related mortality[16], our HbA1c targets became more liberal with many guidelines recommending HbA1c of 7%. As a result of the perceived need to avoid hypo-

glycemia, a new drug class, the dipeptidyl peptidase-4 inhibitors, became available in the United States in 2007. They have shown non-inferiority in atherosclerotic CVD, yet, saxagliptin in particular has shown a potential risk in congestive heart failure. For the purposes of this mini-review, this class will not be covered in detail as there are no studies showing superiority in preventing major cardiovascular events (MACE) (Table 1).

One provocative event was when Rosiglitazone had a post-marketing meta-analysis showing an increased risk of CV events in T2DM patients using this medication. With that debacle and the increasing prevalence of T2DM and CVDs, in 2008 the Food and Drug Administration (FDA) issued new mandates on MACE safety for new antidiabetic drugs. Studies had to be presented prior to approvals and these would be followed by post-marketing cardiovascular outcome trials (CVOTs). This decision has helped bring data that, otherwise, would not have been available.

The paradigm shift has been to have antihyperglycemic agents show, not only noninferiority, but superiority in reducing MACE. As a result of over a decade of randomized placebo controlled CVOT, drugs in two classes have received FDA approval for risk reduction of CV events in patients with T2DM and established CV disease; glucagon like peptide receptor agonists (GLP1RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i).

The decision for clinicians in selecting a second antihyperglycemic agent after metformin in T2DM has become significantly more complex with much more data to consider (Tables 2 and 3). We will review the pharmacology followed by the current evidence of cardiovascular, renal, blood pressure, weight and other effects of GLP1RAs and SGLT2is.

PHARMACOLOGY

Glucagon like peptide-1 receptor agonists (GLP-1RAs) have been available in the market since 2005, however it has taken over a decade to understand their effects. As an endogenous substance, its insulinotropic effect when associated with glucose-dependent insulinotropic polypeptide is very well established, giving rise to the incretin effect[17] (Figure 1), which is significantly reduced in T2DM. Moreover, the discovery of receptors in the periphery[18] sensitive to GLP1 have raised several questions regarding the reach in which our exogenous, man-made GLP-1RA can have a positive impact in the health of patients with T2DM[19] given their increased potency and half-life compared to endogenous GLP1.

SGLT2 inhibitors have been available in our armamentarium since 2012 and were first used unrelated to β-cell function and insulin sensitivity[20]. Originating from observations and studies made on patients with Familial Renal Glucosuria[21], the effects of inhibiting SGLT2 are still under thorough investigation given the presence of such molecules not only in the proximal tubule of the nephron, but also on the glomerular basement membrane and in the heart[22].

CURRENT EVIDENCE

Cardiovascular effects

Agents in both GLP-1RA and SGLT2i classes have obtained approval by the FDA for the indication of CV risk reduction in patients with T2DM and established CVD. Current data has proven that these agents can reduce the risk of MACE (CV death, nonfatal myocardial infarction and nonfatal stroke) with questions remaining on the ideal level of cardiovascular risk to benefit from GLP1RA. The CVOT design was intended to have both treatment groups maintain similar glycemic control, to minimize this confounder. In addition to this, SGLT2i have shown evidence of reduced hospitalization due to heart failure. New submissions to the FDA for both drug classes are in process.

The first GLP-1RA CVOT was the Evaluation of Lixisenatide in acute coronary syndrome trial[23] in 2015, studying the effects of lixisenatide in a high risk population with subjects that had an acute coronary syndrome in the 6 mo prior to the study with an average starting HbA1c of 7.7%, demonstrating noninferiority when compared to placebo but no superiority. One of the limitations of the trial was its short duration and the severity of the illness in this very high-risk population.

In 2016, GLP-1RA gained much more attention after the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)[24] trial demonstrated the superiority of liraglutide in the primary end point (PEP) when compared against placebo in subjects with T2DM and high risk for CV events. These

Table 1 Summary of dipeptidyl peptidase 4 cardiovascular outcome trials

Trial	NumberFollow up	CVD (baseline)	Characteristics (baseline)	Drug *vs* Placebo (%) PEP	Superiority
SAVOR-TIMI53 (Saxagliptin) 2013	*n* = 16492, 2.1 yr (median)	Pre-existing CV or high CV risk/multiple CV risk factors	65 y/o, DM duration: 10 yr; A1c: 8%; BMI: 31	7.3 *vs* 7.2	No
EXAMINE (Alogliptin) 2013	*n* = 5380, 1.5 yr (median)	Acute MI or HUA in previous 15 to 90 d	61 y/o, DM duration: 7 yr; A1c: 8%; BMI: 29	11.3 *vs* 11.8	No
TECOS (Sitagliptin) 2015	*n* = 14671, 3.1 yr (median)	Pre-existing CV disease (CAD, ischemic stroke, PAD)	65.5 y.o, DM duration: 11.6 yr; A1c: 7.2%; BMI: 30.2	11.4 *vs* 11.6 (4-point MACE)	No

Note, as a class dipeptidyl peptidase 4 inhibitor has no data for significant reduction in cardiovascular endpoints. The TECOS trial had a 4-point MACE, consisting of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke or hospitalization for unstable angina. DPP4: Dipeptidyl peptidase 4; CVOT: Cardiovascular outcome trial; CVD: Cardiovascular disease; PEP: Primary end point; BMI: Body mass index; HUA: Hospitalization due to unstable angina; MI: Myocardial infarctions; PAD: Peripheral artery disease; CAD: Coronary artery disease; MACE: Major cardiovascular events.

patients had a lower rate of CV death, nonfatal myocardial infarctions (MI) and nonfatal strokes (but no statistical difference with all strokes). Starting average HbA1c was 8.7%. The rate of hospitalization due to heart failure remained statistically nonsignificant.

Also, in 2016, the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6)[25] compared the once-weekly injection of semaglutide to placebo and had similar outcomes to liraglutide on a patient with a sizable prevalence of ischemic heart disease and hypertension (60% and 93% respectively). This was achieved with fewer patients and less years of follow-up (2 compared to 4 in the LEADER trial). The once-weekly injection of semaglutide was FDA approved in 2017 and in 2019 Novo Nordisk filed for FDA approval for a new CV indication based on the SUSTAIN-6 trial. Simultaneously they filed for FDA approval for oral semaglutide[26] which would be the first GLP1RA in a pill form and the pertaining CVOT PIONEER6 is discussed below.

Subsequently in 2016-2017, two CVOTs were published on another GLP1RA exenatide. The Exenatide Study of Cardiovascular Event Lowering Trial[27] confirmed noninferiority with once weekly subcutaneous injection of exenatide but lacking superiority when comparing to placebo. The study had the largest population in CVOT at the time with 14752 patients, from which 70% had a previous CV event, including coronary artery disease, ischemic cerebrovascular disease or peripheral artery disease. On average, the starting HbA1c was 8%. The main pitfall of the study was the inclusion of a sizable number of patients using SGLT2i in the placebo group. A phase 3 safety trial, FREEDOM-CVO[28], had more than 4,000 patients supplied with exenatide through a continuous implanted pump and announced non-inferiority in CV safety. The subcutaneous pump would potentially address the high rate of discontinuation with weekly exenatide, which was 43%.

Finally, in 2018, three more CVOTs with GLP-1RAs were announced and full results are yet to be reported. REWIND[29], investigating a weekly dulaglutide with an international scope, 46% women, and including T2DM with coexisting CVD or 2 or more CV risk factors. Only 36% of the 9901 patients had established CVD, yet at a median follow-up of 5 years, dulaglutide was still showing significantly reduced MACE. Next, Albiglutide was studied in the HARMONY[30] trial which was also international across 28 countries and enrolling 9463 participants but all had established CVD and it was superior to placebo in reducing MACE. Lastly, the PIONEER6[31] examined oral semaglutide in patients with T2DM with high risk of CV events and showed non-inferiority but not superiority in MACE. Secondary outcomes though showed statistically significant reduction in CV death and all-cause mortality in those 3183 patients.

SGLT2i also had its first CVOT published in 2015, Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME)[32]. They enrolled 7028 patients with recognized CVD or elevated CV risk with an average starting HbA1c of 8%, demonstrating superiority over placebo, similar to the PEP of the LEADER trial with an additional benefit for hospitalization for heart failure and diabetic nephropathy. Later, the Canagliflozin Cardiovascular Assessment Study (CANVAS)[33] and the Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with T2DM (CANVAS-R) trials had similar results by examining approximately 10000 patients with established CVD in a younger population.

Table 2 Summary of the results of the most important Randomized Controlled Trials prior to the new classes of antidiabetic medications

Study	Effects on microvascular complications	Effects on macrovascular complications	Effect on total mortality
DCCT[10] (1993), T1DM	Reduced retinopathy, nephropathy, neuropathy	No difference on major cardiovascular and peripheral vascular events	No difference
UKPDS[9] (1998)	Reduced microvascular endpoints	No difference on myocardial infarctions	No difference
ACCORD[14] (2008)	Reduced retinopathy, nephropathy, neuropathy	No difference on MACE	Increased mortality
ADVANCE[11] (2008)	Reduced nephropathy	No effect on MACE	No difference
VADT[12] (2009)	Reduced progression of albuminuria	No effects on major cardiovascular events	No difference

Note the lack of difference in macrovascular complications despite reduced microvascular complications, which is consistent among all studies. MACE: Major adverse cardiovascular events; DCCT: Diabetes Control and Complications Trial; T1DM: Type 1 diabetes mellitus; UKPDS: United Kingdom Prospective Diabetes Study; ACCORD: Action to Control Cardiovascular Risk in Diabetes; ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; VADT: Veterans Affairs Diabetes Trial.

However, the magnitude of the benefit with canagliflozin was smaller compared to other trials (only a third of 1%, meaning we would have to treat several hundred more patients to prevent a MACE). It also raised safety concerns by showing increased risk for lower limb amputations and fractures while also being consistent with previous CVOTs in regards of the increased risk for mycotic infections but no change in rates of Diabetic Ketoacidosis.

In 2019, the Dapagliflozin Effect on Cardiovascular Events trial (DECLARE – TIMI 58)[34] studied dapagliflozin for primary and secondary prevention in patients with T2DM and CVD or at high-risk for CVD and was the largest CVOT to date with 17160 patients. It showed noninferiority in MACE without superiority. A reduction in hospitalization for heart failure and all-cause mortality was established with robust reductions in the renal composite endpoints, suggesting a delay in the development and progression of renal disease.

Results have for the most part been consistent, as was demonstrated by Cheng *et al*[35], who analyzed a total of 12 double-blind randomized controlled trials, concluding that liraglutide, empagliflozin and canagliflozin to be superior in CV outcome in comparison to placebo in patients with T2DM and established or high-risk for CVD.

Renal effects

From the abundance of evidence, clinicians have already established that the intensification of glycemic control is the best approach to reduce microvascular complications. But when microvascular disease has already taken place, our options have remained limited, with our first line of defense consisting of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (ARB) in the case of nephropathy and blood pressure control, and symptomatic treatment for the case of neuropathy and retinopathy.

Most of the large RCTs involving either SGLT2i or GLP-1RA have demonstrated, to varying degrees, a reduction in microvascular endpoints and associated morbidity. This is especially relevant for patients with chronic kidney disease and albuminuria, who represent a vulnerable subset of patients who, until recently, lacked treatment options for both preventing the development of the disease and delayed the its progression when these two factors are already present.

SGLT2i have demonstrated effects in hyperglycemic states by enhancement of glycosuria and natriuresis[36]. These effects may have a renal protective role by indirectly lowering blood pressure by competitively blockading the SGLT2 receptors in the proximal convoluted tubules in the kidneys, thus preventing reabsorption of the filtered glucose and sodium, decreasing the overall effective intravascular volume in addition to the intended antihyperglycemic effect.

This is further exemplified by a new prospective analysis by Sugiyama *et al*[37]. In this study, dapagliflozin was used in patients with T2DM with ineffective glycemic control. Those patients who were treated with dapagliflozin had a significant decrease in urine albumin-to-creatinine ratio (UACR) and urine N-acetyl- β-glycosaminidase, a marker of kidney injury. We can speculate based on these findings that dapagliflozin might prevent the renal tubulointerstitial atrophy that is correlated with the development of chronic kidney disease (CKD) in patients with T2DM.

Patients with early and uncontrolled T2DM have an increased glomerular filtration

Table 3 Summary of glucagon-like-peptide-1 receptor agonists and sodium glucose cotransporter 2 inhibitors Randomized Controlled Trials

Trial	Number Follow up	CV disease (baseline)	Characteristics (baseline)	Drug *vs* Placebo (%) PEP	Superiority
ELIXA[22] (Lixisenatide) (2015)	*n* = 6068, 2.1 yr	Acute Coronary Events (previous 180 d)	Median age: 60; DM duration: 9.3 yr (median); A1c: 7.7%; BMI: 30.1	13.4 *vs* 13.2 (4-point MACE	No
LEADER[23] (Liraglutide) (2016)	*n* = 9340, 3.8 yr (median)	> 50 y/o + > 1 CV condition/CKD or Chronic HF or > 60 y/o > 1 risk factor for CVD	mean age: 64; DM duration: 12.8 yr (median); A1c: 8.7%; BMI: 32.5	13.0 *vs* 14.9	Yes
SUSTAIN-6[24] (Semaglutide) (2016)	*n* = 3297, 2.1 yr (median)	> 50 y/o + > 1 CV condition/CKD or Chronic HF or > 60 y/o > 1 CV condition	mean age: 65; DM duration: 13.9 yr (median); A1c: 8.7%; BMI: 30.1	6.6 *vs* 8.9	Yes
EXSCEL[26] (Exenatide) (2017)	*n* = 14752, 3.2 yr (median)	70% with previous CV events (CAD, ischemic cerebrovascular disease, or PAD)	mean age: 63; DM duration: 12 yr (median); A1c: 8.0%; BMI: 32	11.4 *vs* 12.2	No
REWIND (Dulaglutide) (2019)	?	?	?	?	?
EMPA-REG[31] (Empagliflozin) (2015)	*n* = 7020, 3.1 yr (median)	Established CV disease; high CV risk	mean age: 63; DM duration: > 10 yr 57%; 5-10 yr 25%; A1c: 8.07%; BMI: 30.6	10.5 *vs* 12.1	Yes
CANVAS[32] (Canagliflozin); ANVAS – R (Canagliflozin) (2017)	Total = 10142; CANVAS: *n* = 4330; CANVAS-R *n* = 5812; 3.6 yr (mean)	> 30 y/o at high CV risk (ASCVD) Or > 50 y/o > 2 CV risk factors	mean age: 63.3; DM duration: 13.5 yr (median); A1c: 8.2; %BMI: 32	9.8 *vs* 10.1	Yes
DECLARE[33] (Dapagliflozin) (2019)	*n* = 17160; 4.2 yr (median)	> 40 y/o established CVD or multiple risk factors	MEAN age: 64; DM duration: 11 yr (median); A1c: 8.3%; BMI: 32	8.8 *vs* 9.4	No

Not all the molecules currently available in the market have shown benefit for MACE. However, this can be explained by study design and/or random chance. More trials are needed to verify such findings. Note the CANVAS and CANVAS – R trials had to standardize their results to number of participants/1000 patient-yr. The results depicted in this table were converted to percentage. The REWIND trial results will become available on the ADA scientific meeting, 2019. The ELIXA trial had 4-point PEP that consisted in death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke or hospitalization for unstable angina. GLP-1 RA: Glucagon-like-peptide-1 receptor agonists; SGLT2i: Sodium glucose cotransporter 2 inhibitors; PEP: Primary end point; CV: Cardiovascular; MACE: Major cardiovascular events; CKD: Chronic kidney disease; CVD: Cardiovascular disease; HF: Heart failure; PAD: Peripheral artery disease; CAD: Coronary artery disease; ELIXA: Evaluation of Lixisenatide in acute coronary syndrome; LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; EXSCEL: Exenatide Study of Cardiovascular Event Lowering Trial; REWIND: Researching cardiovascular Events with a Weekly Incretin in Diabetes; EMPA-REG: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial; CANVAS: Canagliflozin Cardiovascular Assessment Study; CANVAS-R: A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with Type 2 Diabetes Mellitus; DECLARE: Dapagliflozin Effect on Cardiovascular Events trial.

rate (GFR). This exposes the proximal tubule to insulin and other growth factors, leading to hyperplasia and hypertrophy in the tubular cells with significant hyperfiltration[38]. In turn, hyperfiltration could be the leading cause of renal damage in people with T2DM. SGLT2i can reverse this hyperfiltration in certain patients by blocking the glucose reabsorption in the proximal tubule. A model of renal hyperfiltration developed with pharmacokinetics (PBPK) and pharmacodynamics (PD) by the Quantitative Systems Pharmacology Diabetes Platform have confirmed this hypothesis[39].

The evidence evaluating renal benefits of SGLT2i until recently, was limited by the fact that there has been no RCT trial where the primary outcome is renal with SGLT2i (recently, this has changed, see below). A meta-analysis of the CVOTs of SGLT2i in patients with T2DM including 34322 patients performed by Zelniker *et al*[40] in *Lancet* 2019 concluded that SGLT2i decreased the risk of progression of renal failure by 45% with lesser reductions in progression of renal disease in patients with more severe kidney disease at baseline.

Another 2019 systematic review of 27 studies totaling 7363 participants with T2DM and CKD[41] found SGLT2is demonstrated a nonsignificant decline in estimated glomerular filtration rate (eGFR) slope, though a significantly reduced risk of the composite renal outcome. A retrospective analysis made by Kobayashi *et al*[42], defined the renal effects of SGLT2i in Japanese patients with T2DM with CKD. Results were

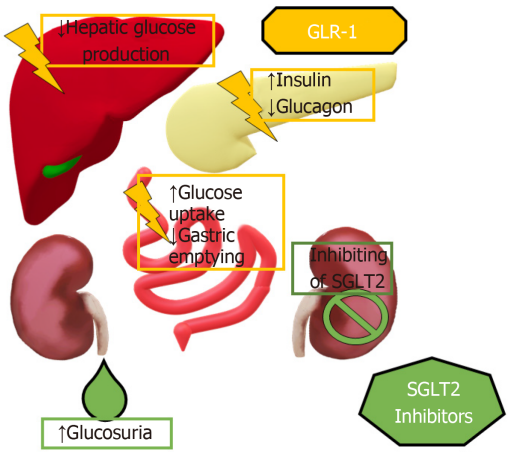

Figure 1 Mechanism of action of the sodium glucose cotransporter 2 inhibitors and the glucagon-like-peptide-1 receptor agonists. Glucagon-like-peptide-1 receptor agonists slows gastric emptying, suppresses glucagon secretion while also stimulating insulin secretion by inhibiting and stimulating, respectively, Alfa and Beta cells in the pancreas. This in turn inhibits hepatic gluconeogenesis with subsequent increase in glucose uptake in the skeletal muscles, diminishing hyperglycemia. Sodium glucose cotransporter 2 inhibitors reduce glucose reabsorption in the proximal convoluted tubule, inherently enhancing glucosuria. This created a global hypovolemic and hypocaloric state, which diminishes hyperglycemia. SGLT2: Sodium glucose cotransporter 2; GLP-1: Glucagon-like-peptide-1.

statistically significant for reduction in the UACR. GLP-1 RA have also demonstrated a certain degree of renal protection. Liraglutide and semaglutide have shown to decrease albuminuria while also halting the worsening of the eGFR[43].

GLP-1 acts directly in the kidney by inhibiting the NH3-dependent sodium reabsorption in the proximal tubule. The renal outcomes were a secondary outcome assessed in the LEADER trial[23], showing a delay in new onset macroalbuminuria with a reduction of 26% in patients with liraglutide and a notable decrease in UACR[44].

Due to lacking studies with primary renal outcomes, no GLP1RAs or SGLT2s have FDA approval for indication of renal benefits with T2DM. The recently published Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial[45], whose data was published recently, might be a game changer. It is been almost 18 years since the advent of renin-angiotensin-aldosterone system blockers, the last advancement in the area. The study randomly assigned patients to receive canagliflozin or placebo on top of renin-angiotensin-aldosterone-system (RAAS) blocker therapy, observing an impressive 30% relative risk reduction in the primary endpoint consisting of end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death that seems to be independent of the glucose lowering properties due to the minimal A1c difference at the end of the study (0.1%). This concept will be tested in the ongoing trials for dapagliflozin and empagliflozin (Dapa-CKD and EMPA-KIDNEY trials respectively) which have a sizable portion of participants without diabetes.

Additionally, it is also important to remember renal dosing requirements. SGLT2i require, in general, an eGFR greater than 45. For now, dulaglutide and liraglutide remain as the only novel medications that can be used in moderate to severe CKD given the evidence provided by the Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7) trial[46] and the LEADER trial.

Blood pressure effects

Both SGLT2is and GLP1RA have shown reduction in blood pressure, independent from their hypoglycemic mechanisms[47]. In Tikkanen's[48] study of patients with T2DM and hypertension, at week 12 the mean difference versus placebo in mean 24-h systolic blood pressure was -3.44 mmHg and -4.16 mmHg with 10 mg and 25 mg of empagliflozin, respectively. Blood pressure can be reduced also in patients with nocturnal hypertension, as demonstrated in the SGLT-2i and ARB Combination Therapy in Patients with T2DM and Nocturnal Hypertension (SACRA) study, conducted in Japan. The reduction in nighttime systolic blood pressure (SBP) with the use of empagliflozin was associated with daytime reductions in SBP and 24-h SBP[49].

The activation of the RAAS increases the SGLT2 mRNA expression in the proximal renal tubular epithelial cells with subsequent sodium intake. This causes an expansion

in the intravascular volume that leads to hypertension[50]. Although the inhibition of SGLT2 will activate the RAAS, it is suggested to combine the SGLT2i with any RAAS blockers to suppress RAAS and thus prevent hypertension[51].

Within GLP1RAs, exenatide and liraglutide have displayed a reduction in the systolic and diastolic blood pressure from 1 to 5 mmHg in comparison with other antidiabetic medications, like insulin, glimepiride, metformin, or placebo[52]. Co-initiating the GLP1RA exenatide and the SGLT2i dapagliflozin compared to either agent alone, the DURATION-8[53] trial showed the combination lowered the systolic blood pressure 4.1 mmHg, which was greater than either agent alone. Similar to renal outcomes, blood pressure has been a secondary outcome yet a beneficial one in alleviating some burden of hypertension with an antidiabetic agent[54].

Weight effects

Increasing BMI can lead to the development of T2DM and poses a greater risk of CVD and all-cause mortality. Weight loss in patients with T2DM is critical in the improvement of hyperglycemia and cardiovascular comorbidities like hypertension and hyperlipidemia[55].

Currently, the American Diabetes Association and the European Association for the Study of Diabetes have made an emphasis in the importance of lifestyle modifications, diet and exercise in patients with T2DM. Unfortunately, many of our antihyperglycemic agents are associated with weight gain including thiazolidinediones, sulfonylureas and insulin. Though modest at 1-3kg weight loss[56], this has made the SGLT2i and the GLP-1RAs benefits in weight loss even more exciting.

In the DURATION-6[57] trial, extended-release exenatide demonstrated an average weight loss of about 2.87 kg, and liraglutide[58] has shown to reduce 4 to 6 kg of weight loss. The SCALE[59] trial evidenced an 8.4 kg weight loss compared to a placebo group of 2.8 kg when treating patients without T2DM with a high-dose of 3.0 mg injected liraglutide as an adjunct to diet and exercise. One must keep in mind the CVOT trials were mostly the 1.8 mg dosing and the applicability of these results to the 3.0 mg dose is unknown.

Moreover, in 2017, semaglutide[23] was associated with significant weight loss, which has shown to be superior to liraglutide in its dose for treatment for T2DM. Even though semaglutide not been approved for pharmacological weight loss therapy, it opens the possibility for one more GLP-1 RA being used as an anti-obesity drug that would prevent cardiovascular events in patients with T2DM. SGLT2i are associated with a more modest reduction of body weight, with dapagliflozin showing a mean 1.63 kg reduction compared with placebo. The DURATION-8[52] clinical trial confirmed that a combination of dapagliflozin and exenatide, plus metformin as a background therapy, resulted in a secondary outcome of weight loss of 3.4 kg, which was greater than either drug alone. Nevertheless, the trend is that GLP1RAs offer more weight loss compared to SGLT2i, which is a relief compared to the classes that are associated with weight gain such as insulin and sulfonylureas.

While these medications are helpful in weight management, it is important to keep in mind this does not triumph over comprehensive lifestyles changes with aerobic exercise and dietary changes. Also, equally important, weight loss using GLP-1 RA should be monitored at least every 3 mo from the starting of the treatment due to side effects[60].

Additional considerations

Several concerns exist with both GLP-1RAs and SGLT2is which must be weighed against the benefits detailed above. Like with any agent, discussion of risks and benefits when starting treatment is recommended. GLP-1RAs most common adverse effect is gastrointestinal with nausea, vomiting and diarrhea[61]. Commonly, nausea tends to wane over time. Patients should be informed about this as well as the possibility of injection site reactions when beginning therapy. An increased rate of acute and/or chronic pancreatitis has been established with the available RCTs, but there is no firm evidence pointing towards causality[62]. Preclinical data from studies done in rodents[63] raised the possibility of a medication induced carcinogenesis, specifically medullary thyroid cancer (MTC), however, these effects may be irrelevant in humans[64]. Nevertheless, a Black Box warning remains with GLP1RAs and risk of thyroid c-cell tumors, including a contraindication in patients with personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2.

SGLT2is most common adverse effect is genitourinary. There is a fivefold increased risk of genital fungal infections with SGLT2i, including an FDA warning about rare occurrences of Fournier's gangrene[65]. Multiple RCTs show increased risk of bacterial urinary tract infection versus placebo, which can prove to be a challenge when considering treatment[66]. No clinical trial has examined special circumstances (indwelling bladder catheterization, benign prostatic hypertrophy, chronic

obstruction or ureteral reflux) but caution under these circumstances is advised. Given the inherent diuretic effect, patients who are prone to volume depletion (use of loop diuretics, the elderly) are at increased risk of complications, including hypotension[67].

The FDA[68] has issued a warning regarding SGLT2i users being more prone to DKA, secondary to the intrinsic shift in the metabolism of glucose to fat oxidation with the promotion of hyperglucagonemia and ketosis[69]. Canagliflozin has been associated with an increased risk for fractures[70] and lower-limb amputations[32], including a Black Box warning for the amputation risk. There is need for further research on whether these side effects are a class effect or unique to canagliflozin.

One of the most controversial topics is the cost-effectiveness and the prohibitive out-of-pocket costs of both drug classes. Studies with reliable results on the long-term economic burden are scarce. The number needed to treat on both classes is in the hundreds based on the CVOTs from which the indication for cardiovascular prevention was approved by the FDA. GLP-1RAs demonstrated CV benefit after several years of median follow up, compared to SGLT2is, specifically empagliflozin, which demonstrated a divergence in survival curve for MACE at 3 mo in the EMPA-REG study. Some of the drugs that had a statistically significant benefit in the PEP for cardiovascular outcome had a very small percentage of benefit over placebo (*i.e.*, canagliflozin with 0.3% benefit over placebo). Side effects like lower-limb amputations, DKA and pancreatitis can be economically damaging and add several thousand dollars to the already high economic burden.

CONCLUSION

In summary, given the current data, both GLP-1 RA and SGLT2i have, to varying degrees, a benefit in renal and cardiovascular protection independent of their glucose-lowering potential in patients with T2DM and high risk of CVD. Additionally, they have more modest benefits in blood pressure and weight control. The low risk for hypoglycemia is appealing.

When starting therapy, the cost-effectiveness is a concern shared by clinicians and patients. The number needed to treat to prevent MACE in both drug classes are in the hundreds and the economic burden is in the thousands to millions per patient per year. Considering the benefits in each study were observed after several years of follow up, the out-of-pocket expense could be prohibitively high.

Both common and rare adverse effects are also a consideration. SGLT2i carry an increased risk for mycotic urinary tract infections, dehydration and DKA. Canagliflozin additionally has the concerns of bone fractures and lower-limb amputations. GLP-1RAs have been associated with both acute and chronic pancreatitis, as well as a common side effect of nausea. The evidence for pancreatitis is debatable and weak since it is not supported by trials or a meta-analysis. Reports of increased MTC risk in rodents has the resultant black box warning of thyroid c-cell tumors. Specific trials designed to take a closer look at these effects will be necessary in the future to prepare a better risk-benefit assessment. The economic burden needs to be added to the equation.

As more studies concerning different agents on the same class of drugs are added to the already existing data, the question on whether each new finding is a class affect or a molecule-based outcome will be determined. With the current evidence at our disposal, we cannot guarantee that GLP-1 RAs all have the same benefits and what the ideal patient population is to maximize those benefits. SGLT2is, on the other hand, seem to offer a more homogenous effect with certain differences that can be attributed to each individual study to a certain extent, but more research is necessary.

As clinicians, we are moving a step forward in T2DM management. Now, patients can be offered antihyperglycemic agents that will treat micro and macrovascular complications while also treating independent risk factors, maintaining an acceptable level of antihyperglycemic effect with a low risk for hypoglycemic events.

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ORIGINAL ARTICLE

Observational Study

Association of hypoglycaemia in screening oral glucose tolerance test in pregnancy with low birth weight fetus

Ananth U Nayak, Arun M A Vijay, Radha Indusekhar, Sushuma Kalidindi, Venkata M Katreddy, Lakshminarayanan Varadhan

ORCID number: Ananth U Nayak (0000-0002-1286-0812); Arun M A Vijay (0000-0003-1127-2725); Radha Indusekhar (000-0002-2808-5240); Sushuma Kalidindi (0000-0001-9901-7600); Mahesh V Katreddy (0000-0001-7538-7826); Lakshminarayanan Varadhan (0000-0003-1976-8071).

Author contributions: Nayak AU and Katreddy VM contributed to study conception and design and writing of article; Nayak AU contributed to data acquisition, data analysis and interpretation, and writing of article; all authors contributed to editing, reviewing and final approval of article.

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Informed consent statement: The use of relevant patient database was approved for undertaking this audit locally. There was no active patient intervention in this study and written patient consent was not needed as per the audit requirements.

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Ananth U Nayak, Arun M A Vijay, Radha Indusekhar, Sushuma Kalidindi, Venkata M Katreddy, Lakshminarayanan Varadhan, Combined Antenatal Diabetes Clinic, University Hospital of North Midlands NHS Trust, Stoke on Trent ST4 6QG, Staffordshire, United Kingdom

Corresponding author: Ananth U Nayak, FRCP, MBBS, MRCP, Consultant Physician and RCP Tutor, Combined Antenatal Diabetes Clinic, University Hospital of North Midlands NHS Trust, Newcastle Road, Stoke on Trent ST4 6QG, Staffordshire, United Kingdom.
ananth.nayak@nhs.net
Telephone: +44–1782–679997
Fax: +44–8436–365428

Abstract

BACKGROUND

Gestational diabetes mellitus (GDM) is a common metabolic derangement in pregnant women. In the women identified to be at high risk of GDM, a 75 g oral glucose tolerance test (OGTT) at 24-28 wk gestation is the recommended screening test in the United Kingdom as per National Institute for Health and Care Excellence (NICE). Hypoglycaemia following the glucose load is often encountered and the implication of this finding for the pregnancy, fetus and clinical care is unclear.

AIM

To determine the prevalence of hypoglycaemia at any time during the screening OGTT and explore its association with birth weight.

METHODS

All deliveries between 2009 and 2013 at the local maternity unit of the University hospital were reviewed. Of the total number of 24,154 women without pre-existing diabetes, those who had an OGTT for GDM screening based on NICE recommended risk stratification, who had a singleton delivery and had complete clinical and demographic data for analysis, were included for this study (n = 3537). Blood samples for fasting plasma glucose (FPG), 2-hour plasma glucose (2-h PG) and HbA_{1c} had been obtained. Birth weight was categorised as low (≤ 2500 g), normal or Macrosomia (≥ 4500 g) and blood glucose ≤ 3.5 mmol/L was used to define hypoglycaemia. Binary logistic regression was used to determine the association of various independent factors with dichotomized variables; the differences between frequencies/proportions by χ^2 test and comparison between group means was by one-way ANOVA.

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RESULTS

Amongst the study cohort (3537 deliveries), 96 (2.7%) women had babies with LBW (< 2500 g). Women who delivered a LBW baby had significantly lower FPG (4.3 ± 0.6 mmol/L, $P = 0.001$). The proportion of women who had a 2-h PG ≤ 3.5 mmol/L in the LBW cohort was significantly higher compared to the cohorts with normal and macrosomic babies (8.3% *vs* 2.8% *vs* 4.2%; $P = 0.007$). The factors which predicted LBW were FPG, Asian ethnicity and 2-h PG ≤ 3.5 mmol/L, whereas maternal age, 2-h PG ≥ 7.8 mmol/L and HbA_{1c} were not significant predictors.

CONCLUSION

A low FPG and 2-h PG ≤ 3.5 mmol/L on 75-gram OGTT are significantly associated with low birth weight in women identified as high risk for GDM. Women of ethnic backgrounds (Asians) appear to be more susceptible to this increased risk and may serve as a separate cohort in whom we should offer more intensive follow up and screening for complications. Cost implications and resources for follow up would need to be looked at in further detail to support these findings.

Key words: Hypoglycemia; Glucose tolerance test; Low birth weight; Pregnancy

Core tip: Hypoglycaemia following a glucose load in a oral glucose tolerance test is often encountered whilst screening for Gestational diabetes mellitus in pregnant women categorized as high risk and our study with a large cohort, confirms an association between hypoglycaemia and low birth weight (LBW) delivery. In addition to this, our study also finds that Asian ethnicity confers a risk for LBW babies.

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INTRODUCTION

It is estimated that 700000 women give birth in England and Wales each year and 5% of these are complicated by diabetes mellitus. Gestational diabetes mellitus (GDM) accounts for the vast majority of this cohort (87.5%)[1]. A 2-h 75 g oral glucose tolerance test (OGTT) is undertaken at 24-28 wk gestation in women at high risk as a screening test for GDM, in line with National Institute for Health and Care Excellence (NICE) recommendations[1]. Women diagnosed with GDM based on this test have specialist antenatal intervention during pregnancy with improved maternal and neonatal outcomes[2].

A small proportion of women experience hypoglycaemia during the screening OGTT in pregnancy, which on a routine basis is not considered abnormal, and does not usually have an impact on antenatal care. This is despite such women being deemed "high risk" based on initial NICE risk stratification to necessitate an OGTT in the first place. Maternal hypoglycaemia during pregnancy in women with pre-existing diabetes mellitus is associated with intrauterine growth retardation and pre-eclampsia[3,4]. Low maternal glucose might hinder growth-promoting aspects of the fetus' environment, a mechanism that is not clearly understood, that could potentially explain the lower birth weight fetus in women with hypoglycemia during pregnancy. Low levels of human placental lactogen has been linked to intra uterine growth retardation and other suggested mechanism include a reduced insulin level in fetus of a mother with low blood sugar levels[4]. It is unclear if hypoglycemia during a screening OGTT in high risk women is associated with adverse perinatal outcomes with some studies potentially suggesting such an association[3-8]. Maternal hypoglycaemia during a glucose challenge test has been linked to intra uterine growth retardation and low birth weight (LBW) as early as 1970's[5,6] and a number of

subsequent studies have shown similar link[7-9], however, a study by Weissman *et al*[10] showed no increase in small for gestational age infants in this group.

We aimed to determine the prevalence of hypoglycaemia on OGTT (both fasting and 2-h PG) in women screened for GDM at 24-28 wk gestation in our hospital and explore the association between maternal hypoglycaemia during OGTT screening and birth weight.

MATERIALS AND METHODS

Patient selection

We reviewed all deliveries in the maternity unit of our University hospital over a consecutive 4-year period between years 2009 and 2013, identifying 24154 women without pre-existing diabetes mellitus. Utilising the risk stratification recommended by National Institute of Clinical Excellence (2008), 7207 women were categorized as at "high risk" for GDM, who were then offered an OGTT at 24-28 wk as part of GDM screening. HbA_{1c} estimation is undertaken simultaneously with all OGTTs as per the local trust guidelines[11]. Laboratory data that was obtained from the clinical biochemistry department was thereafter linked to the clinical information that was taken from the electronic patient records in the obstetric registry on the dataset.

Those women with singleton pregnancy delivered on or after 37-wk gestation were identified (n = 6716) for the purpose of this study to avoid the impact of the preterm deliveries on birth weight during analysis. No other selection criteria were used however complete demographic and clinical data was available in 3537 women and these women formed the cohort used for analysis.

Categorisation by birth weight and glycaemic parameters

Birth weight definitions: LBW: ≤ 2500 g[12]; Normal birth weight: 2501- 4499 g; Macrosomia: ≥ 4500 g[13].

Glycaemic parameters: A fasting plasma glucose (FPG) ≥ 5.6 mmol/L and/or a 2 h plasma glucose (2-h PG) post 75 g glucose load ≥ 7.8 mmol/L in the OGTT were the cut offs used to diagnose GDM. Blood glucose value ≤ 3.5 mmol/L was classed as hypoglycaemia. Based on the 2-h PG, the cohort was categorised into "low" 2-h PG (≤ 3.5 mmol/L), "normal" 2-h PG (3.6-7.7 mmol/L) and "high" 2-h PG (≥ 7.8 mmol/L).

Analytical methods

OGTT was performed after a minimum of 8-h overnight fast as per standard protocol. A blood sample for FPG was obtained each participant was given a glucose drink (75 g of D-dextrose powder dissolved in 200 mL of water). Samples for FPG and 2-h PG were obtained by taking 2 mL of venous blood in tubes containing sodium fluoride. A sample for HbA_{1c} estimation was obtained along with the sample for FPG. HbA_{1c} was measured using high performance liquid chromatography on a Tosoh G7 analyser (Tosoh Bioscience Ltd., Worcestershire, United Kingdom). The performance scores in the United Kingdom National External Quality Assurance Scheme were: A scores < 100 and B scores < 2%. The between-batch coefficient of variation was 1.8% and 1.4% for an HbA_{1c} of 5.7% and 9.5% respectively.

The International Federation of Clinical Chemistry (IFCC) units for HbA_{1c} levels were introduced in the United Kingdom since 1st June 2009. Locally, the IFCC reference system was adopted and the dual reporting of HbA_{1c} with IFCC units and the corresponding calculated Diabetes Control and Complications Trial value was available during the period and utilised for the analysis of data among the participants.

Statistical analysis

Data were analysed using SPSS version 21 (SPSS Inc., Chicago, IL). Data are presented as mean ± SD unless otherwise stated. All statistical tests were considered significant at $P < 0.05$. Comparison between multiple group means was by one-way ANOVA and the differences between frequency/proportions by Chi-square test. Binary logistic regression analysis was undertaken to determine the association of independent factors with dichotomised variable (birth weight).

RESULTS

The demographic details and the glycaemic parameters of the cohort (n = 3537) of women are shown in Table 1. The proportions of women with LBW and macrosomic

babies were each 2.7%, and remaining 94.6% had babies with normal birth weight. In-total 130 women (3.7%) had hypoglycaemia (blood glucose ≤ 3.5 mmol/L) on the OGTT, majority on the 2-h PG value (n = 107 (3.0%)).

Women who delivered LBW fetus had a significantly lower FPG compared to women delivering babies with normal birth weight or macrosomic babies (Table 1). The mean 2-h PG was similar in the three cohorts by birth weight, however the proportion with 2-h PG ≤ 3.5 mmol/L in the LBW cohort was significantly higher compared to the other two cohorts (8.3% *vs* 2.8% *vs* 4.2%; P = 0.007).

On binary logistic regression independent predictors of LBW were FPG (OR = 0.52, 95%CI: 0.32-0.86; P = 0.010, B = minus 0.654), Asian ethnic origin (OR = 2.36, 95%CI: 1.45-3.84; P = 0.001) and 2-h PG ≤ 3.5 mmol/L (OR = 2.52, 95%CI: 1.11-5.72; P = 0.028). Maternal age, 2-h PG ≥ 7.8 mmol/L and HbA_{1c} were not significant predictors of LBW.

Comparing the "low" *vs* "normal" *vs* "high" 2-h PG cohorts (Table 2), women in "low" 2-h PG cohort, compared to "normal" and "high", were younger (27.2 ± 5.8 *vs* 28.4 ± 5.7 and 30.6 ± 5.5 years, P < 0.001), with more Caucasians (86% *vs* 82% and 73%, P < 0.001). Birth weight (mean ± SD) for "low", "normal" and "high" 2-h PG cohorts were 3357 ± 591 *vs* 3480 ± 515 *vs* 3349 ± 459 g, being significantly lower in "low" cohort compared to "normal" (mean difference in weight = -122.9 g, Std. error 50.33 g; P = 0.015), but comparable to the "high" 2-h PG cohort. "Low" 2-h PG cohort had a significantly higher proportion of LBW compared to those with "normal" and "high" 2-h PG (7.5% *vs* 2.6% *vs* 2.5%; χ^2 =13.9, P = 0.008). The still-birth rates were similar in the three cohorts of 2-h PG.

DISCUSSION

Our study on a large cohort of pregnant women at high risk of GDM, delivered at 37 wk gestation or later, demonstrates that low FPG and/or 2-h PG ≤ 3.5 mmol/L on OGTT at 24-28 wk gestation, both independently predict LBW baby. This supports the previous smaller studies that found a relation between maternal hypoglycaemia during OGTT and LBW[7-9]. Melamed *et al*[12] have calculated that a threshold of 88.5 mg/Dl (4.9 mmol/L) following 100 g glucose challenge will predict a birth-weight < 10th percentile. In a recent study[13] on women who had postprandial hypoglycaemia on OGTT comparing with GDM and normoglycaemic groups, when subsequently monitored with self-monitoring of blood glucose, nearly half of them had elevated FPG readings above 5.1 mmol/L on at least 2 occasions in the 1-wk period were in the GDM range when using the Australian Diabetes in Pregnancy Society criteria. However, the study did not find any differences in the pregnancy outcomes amongst the groups studied or enough evidence to recommend use of self-blood glucose monitoring in this cohort[13].

Women who had babies with a LBW were more likely to have blood glucose of ≤ 3.5 mmol/L compared to those who had babies with normal birth weight or macrosomia. This highlights the importance of not dismissing this important finding in a pregnant woman with a low blood glucose value detected on OGTT.

This study also highlights the importance of ethnicity when assessing risk, as we have found that the women of Asian ethnicity were at a greater risk of delivering a baby of LBW babies (29%). A study of pregnant women in India showed a higher incidence of LBW in those with fasting hypoglycaemia and this increased risk was found across different nutritional and pre-eclamptic statuses[14]. Therefore, women of Asian ethnicity may be a sub-group who require more closer follow-up.

In our analysis maternal age did not appear to a be a factor associated with LBW, contrary to the previous study[15] which found that the women with hypoglycaemia were younger and had lower pre-pregnancy body mass index (BMI). Maternal BMI is associated with increase in insulin resistance predominantly in the skeletal muscle and adipose tissue potentially increasing risk of impaired glycaemia on OGTT and risk GDM.

The findings of our study may have implications in terms of obstetric follow up and further investigations for growth and assessment of those mothers identified with low blood glucose values on their OGTT. This would hold particularly true for those women of Asian descent and this group should have lower threshold to investigate fetal growth and optimize neonatal outcomes. The findings of our study and the fact that these women are considered "high risk" as per NICE criteria for needing the OGTT screening, this cohort of "high risk" women with hypoglycaemia may need appropriate intensive antenatal care with fetal growth monitoring, rather than being discharged due to the fact that OGTT does not suggest GDM.

One of the limitation of this study is that body mass index was not available and

Table 1 Demographics and glycaemic parameters for the cohort categorised by birth weight

	Birth Weight			
	< 2500 g (LBW) (*n* = 96)	2500-4500 g (normal BW) (*n* = 3346)	> 4500 g (macrosomia) (*n* = 95)	
Maternal age (yr)	28.6 ± 5.6	28.7 ± 5.6	29.0 ± 5.4	*P* = 0.85
Proportion Asians	29%	15%	1%	*P* = 0.001
FPG (mmol/L)	4.3 ± 0.6	4.5 ± 0.6	4.7 ± 0.5	*P* = 0.001
2-h PG (mmol/L)	5.5 ± 1.9	5.8 ± 1.6	5.8 ± 1.3	*P* = 0.26
Proportion with 2-h PG ≤ 3.5 mmol/L	8.3%	2.8%	4.2%	*P* = 0.007
HbA_{1c} IFCC (mmol/mol)	34.5 ± 3.4	34.3 ± 4.3	34.3 ± 0.4	*P* = 0.92

LBW: Low birth weight; FPG: Fasting plasma glucose; 2-h PG: 2 h plasma glucose on the oral glucose tolerance test.

could potentially impact on the association we report. Shinohara *et al*[16] studied the pre-pregnancy BMI in the context of hypoglycaemia in OGTT and found that the hypoglycaemia was significantly associated with small for gestational age babies among underweight women(BMI < 18.5 kg/m^2).

In conclusion, low FPG and/or 2-h blood glucose ≤ 3.5 mmol/L on 75-g OGTT is significantly associated with LBW in women identified as high-risk for GDM. Women of ethnic backgrounds (Asian) appear to be more susceptible to this increased risk and may serve as a separate cohort in whom we should offer more intensive follow up and screening for complications may need to be offered. Cost implications and resources for follow up would need to be looked at in further detail to support these findings.

Table 2 Demographics and clinical parameters for the cohorts categorised by 2-h plasma glucose

	2-h PG category (mmol/L)			
	Low (≤ 3.5) *n* = 107	Normal (3.6-7.7) *n* = 3066	High (≥ 7.8) *n* = 364	
Maternal age (yr)	27.2 ± 5.8	28.4 ± 5.7	30.6 ± 5.5	$P < 0.001$
Proportion caucasians (%)	86	82	73	$P < 0.001$
Birth weight in grams	3357 ± 591	3480 ± 515	3349 ± 459	[1]$P < 0.001$
Proportion with LBW (%)	7.5%	2.6%	2.5%	$P = 0.008$

[1]Overall $P < 0.001$; on *post hoc* tests there was a significant difference only between the "low" 2-h PG cohort compared to "normal" 2-h PG (mean ± SE = 122.9 ± 50.3 g, $P = 0.015$). There was no difference in the birth weight between "low" 2-h PG and "high" 2-h PG cohorts. LBW: Low birth weight; 2-h PG: 2 h plasma glucose on the oral glucose tolerance test.

ARTICLE HIGHLIGHTS

Research background

Screening for gestational diabetes in high risk women during pregnancy is undertaken with oral glucose tolerance test (OGTT). This paper is an observational study auditing the prevalence of significant hypoglycaemia on the screening OGTT during pregnancy and exploring its impact on the birth weight, if any association with low birth weight (LBW). Currently those women identified as with hypoglycaemia on OGTT do not have any additional antenatal monitoring. Any association of such hypoglycaemia noted on the screening OGTT with LBW might help in targeting antenatal care in such women towards improving pregnancy outcomes.

Research motivation

The results of our study support allocation of resources for antenatal monitoring of women noted to have hypoglycaemia, especially the Asian ethnic cohort who appeared to be at higher risk of having babies with low birth-weight.

Research objectives

This study was undertaken to determine the prevalence of hypoglycaemia on the OGTT during screening for gestation diabetes in high risk women and explore any association with fetal birth weight.

Research methods

We audited data on all woman deemed high risk and had the screening OGTT during pregnancy identifying 3537 women who met the criteria and had the required complete data for analysis. Having defined hypoglycaemia (blood glucose ≤ 3.5 mmol/L) and categorizing birth weight as low (≤ 2500 g), normal (2500 to 4499 g) or Macrosomia (≥ 4500 g) we analysed the prevalence of hypoglycaemia on the OGTT screening and its association with birth weight using ANOVA to compare group means and logistic regression analysis to assess the factors independently predicting the low birth-weight.

Research results

In this audit on 3537 women deemed high risk as per NICE criteria and who had the OGTT screening, the proportion who has hypoglycaemia was 3.7%, majority of the hypoglycaemia being on the 2-h plasma glucose (2-h PG) value. 2.7% women had babies with LBW and this cohort had significantly lower fasting glucose (4.3 ± 0.6 mmol/L, $P = 0.001$) and a higher proportion of this cohort had 2-h PG ≤ 3.5 mmol/L compared to the cohorts with normal and macrosomic babies (8.3% *vs* 2.8% *vs* 4.2%; $P = 0.007$). The factors which predicted LBW were fasting plasma glucose, Asian ethnicity and 2-h PG ≤ 3.5 mmol/L. Maternal age, 2-h PG ≥ 7.8 mmol/L and HbA_{1c} were not significant predictors of LBW.

Research conclusions

We observed the prevalence of hypoglycaemia in the screening OGTT during pregnancy to be about 3.7%. Such hypoglycaemia appears to be independently associated with risk of fetal LBW, and Asian ethnic origin being another risk factor for fetal low birth.

Research perspectives

This study on a large cohort of high risk women may improve awareness amongst clinicians about the potential impact of hypoglycaemia on birth weight and potentially help in considering assessment of fetal weight with serial growth scans as a part of antenatal care towards improving pregnancy outcomes. Future studies incorporating other risk factors associated with the fetal birth weight and studies looking at resource implications to implement the required fetal growth monitoring for such at-risk women with hypoglycaemia would be recommended.

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META-ANALYSIS

Association between sarcopenic obesity and higher risk of type 2 diabetes in adults: A systematic review and meta-analysis

Dima Khadra, Leila Itani, Hana Tannir, Dima Kreidieh, Dana El Masri, Marwan El Ghoch

ORCID number: Dima Khadra (0000-0002-4711-6540); Leila Itani (0000-0003-3166-4945); Hana Tannir (0000-0002-3420-1965); Dima Kreidieh (0000-0001-5797-0460); Dana El Masri (0000-0001-9939-8116); Marwan El Ghoch (0000-0003-4277-4752).

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Dima Khadra, Leila Itani, Hana Tannir, Dima Kreidieh, Dana El Masri, Marwan El Ghoch, Department of Nutrition and Dietetics, Faculty of Health Sciences, Beirut Arab University, Beirut 11072809, Lebanon

Corresponding author: Marwan El Ghoch, MD, Academic Research, Chairman, Full Professor, Professor, Head of Department, Department of Nutrition and Dietetics, Faculty of Health Sciences, Beirut Arab University, PO Box 11-5020 Riad El Solh, Beirut 11072809, Lebanon. m.ghoch@bau.edu.lb
Telephone: +961-1-300110

Abstract

BACKGROUND

The coexistence of sarcopenia and obesity is referred to as sarcopenic obesity (SO) and it has been hypothesized that the two components of SO may synergistically increase their negative effects. However, many uncertainties still surround this condition especially with regard to its potential negative effects on health outcomes.

AIM

To conduct a systematic review to determine the prevalence of sarcopenia among adults with overweight and obesity and to investigate whether SO was associated with a higher risk of type 2 diabetes (T2D).

METHODS

This study was conducted in adherence with the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines. Literature searches, study selection, methodology development and quality appraisal were performed independently by two authors and the data were collated by means of meta-analysis and narrative synthesis.

RESULTS

Of the 606 articles retrieved, 11 studies that comprised a total of 60118 adults with overweight and obesity of both genders met the inclusion criteria and were reviewed, revealing two main findings. First, the overall prevalence of sarcopenia is 43% in females and 42% in males who are with overweight and obesity. Secondly, the presence of SO increases the risk of T2D by 38% with respect to those without SO (OR = 1.38, 95%CI: 1.27-1.50).

CONCLUSION

A high prevalence of sarcopenia has been found among adults with overweight and obesity regardless of their gender and this condition seems to be associated

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with a higher risk of T2D. Clinician should be aware of this scenario in their clinical practice for the better management of both obesity and T2D.

Key words: Obesity; Overweight; Sarcopenia; Type 2 diabetes; Reduced lean body mass

Core tip: The coexistence of sarcopenia and obesity is referred to a phenotype termed sarcopenic obesity, defined as the increase in body fat deposition, and the reduction in lean mass and muscle strength. Since many uncertainties still surround this condition, especially with regard to its potential negative effects on health outcomes, we conducted this systematic review and found a high prevalence of sarcopenia among adults with obesity. Moreover, this condition seems to be associated with a higher risk of type 2 diabetes (T2D). Clinicians should be aware of this scenario in their clinical practice for better management of obesity and T2D.

Citation: Khadra D, Itani L, Tannir H, Kreidieh D, El Masri D, El Ghoch M. Association between sarcopenic obesity and higher risk of type 2 diabetes in adults: A systematic review and meta-analysis. *World J Diabetes* 2019; 10(5): 311-323
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INTRODUCTION

A condition that occurs because of the coexistence of sarcopenia and obesity has been termed sarcopenic obesity (SO)[1-7]. Many uncertainties still surround this phenomenon with regard to its definition and its potential negative effects on health outcomes, especially those related to obesity, namely the so-called cardio-metabolic diseases[8,9] such as type 2 diabetes (T2D), cardiovascular diseases, dyslipidaemia and metabolic syndrome[5,6,10-13]. In fact, it has been hypothesized that the two components of SO may synergistically increase their negative effects on health, however this is still a matter of debate[14-16].

Several studies have been conducted with a specific focus on determining the association between SO and T2D, however data regarding the contention that individuals with SO are likely to have poorer glycaemic profiles (*i.e.*, hyperglycaemia, high HbA1c, insulin resistance, *etc.*,) are still contradictory and require further clarification[11,17-23]. Moreover, to the best of our knowledge no systematic review posing this issue as a primary outcome has yet been conducted in order to provide an unbiased interpretation of the evidence published to date. In light of these considerations, we set out to systematically review the published literature with the aim of determining the prevalence of sarcopenia among adults with overweight and obesity and to investigate whether SO was associated with higher risk of T2D, in accordance with the PICO process[24-26] as detailed below: P – population: Individuals in the overweight or obese categories, however they were defined [*i.e.*, body mass index (BMI), body fat percentage, waist circumference, *etc.*,][27]; I – seeking treatment (*i.e.*, weight-loss or any other treatment if recruited from a clinical setting), otherwise non-treated if subjects were recruited from the general population; C – comparison: Comparison between individuals with sarcopenia and those without SO and with the healthy control group (when available); O – outcome: (i) Prevalence of SO however it was defined in the studies' Methods section (*i.e.*, low muscle mass, low muscle strength, low physical performance, increased visceral adiposity, increased waist circumference *etc.*,) and assessed [*i.e.*, bioelectric impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), handgrip, *etc.*,] among the entire obesity groups in the two genders; (ii) The prevalence of T2D however it was defined in the studies' Methods section (*i.e.*, fasting plasma glucose and glycated hemoglobin A1c, oral glucose tolerance test *etc.*,) in the SO and non-SO groups.

MATERIALS AND METHODS

The review conformed to the Preferred Reporting Items for Systematic Review and

Meta-Analyses guidelines[28-30] and was registered in the PROSPERO Registry, No. CRD42018111931[31].

Inclusion and exclusion criteria

All studies that evaluated SO and T2D in adults were included, provided that they met the following criteria: (i) Studies written in English; (ii) Original research with a cross sectional or longitudinal design; and (iii) Prospective or retrospective observational (analytical or descriptive), experimental or quasi-experimental controlled or non-controlled studies, documenting clearly the prevalence of SO, as well as the association or relationship between SO and T2D. No reviews or non-original articles (*i.e.*, case reports, editorials, "Letters to the Editor" and book chapters) were included.

Information source and search strategy

The literature search was designed and performed independently in duplicate by two authors, namely the principal (DK) and the senior investigator (ME). The PubMed and Science direct databases[32] were systematically screened using the MeSH terms and a manual search was carried out to retrieve other articles that had not been identified via the initial search strategy. Publication date was not considered an exclusion criterion for the purposes of this review.

Study selection

Two independent authors (DK and ME) screened the articles for their methodology and suitability for inclusion. The quality appraisal was conducted according to the Newcastle-Ottawa Scale (NOS), which relies on a 9-star system whereby scores of 0-3, 4-6 and 7-9 are considered poor, moderate and good quality, respectively[33]. Consensus discussion was used to resolve disagreements between reviewers.

Data collection process and data items

The title and abstract of each paper were initially assessed by two independent authors (DK and ME) for language suitability and subject matter relevance, the selected studies were then assessed in terms of their suitability for inclusion and the quality of the methodology. The studies that passed both rounds of screening are presented in Table 1.

Data synthesis

The 11 studies that met the inclusion criteria have been presented as a narrative synthesis. In addition, a meta-analysis was conducted on the included studies using Med Calc. software[34]. The Mantel Haenszel fixed and random effect models were used to estimate the overall effect size and 95%CI. The pooled estimate and 95%CI of the prevalence of SO among males and females in the included studies was estimated similarly.

RESULTS

The initial search retrieved 606 papers. After the first round of screening, 366 papers were excluded for: (i) Languages other than English; (ii) Non-human studies; and (iii) Dealing with obesity without sarcopenia, or the latter without the former. The second round of screening excluded 229 articles due to: (i) Inappropriate paper type, not original research articles (*i.e.*, clinical reviews, Letters to the Editor, chapters in a book and case reports); (ii) Descriptions of SO, but not health-related outcomes; and (iii) An unclear definition of SO or identification of individuals with this condition. Accordingly, following the screening process, 11 articles were included in the systematic review and underwent narrative synthesis and meta-analysis (Figure 1). The NOS checklist proved that the studies were of a high quality (n = 11) (mean score = 7.36 points) (Table 2).

Narrative synthesis

In 2012, Sénéchal *et al*[35] conducted a cross-sectional evaluation in which the authors assessed dynapenic obesity, defined as low leg muscle strength combined with abdominal obesity, in 1963 individuals with abdominal obesity. Of these patients, 566 had dynapenic obesity (data per gender is not available). Regardless of gender the mean age and mean BMI in the dynapenic obesity and non-dynapenic obesity groups were 65.4 ± 9.9 years and 29.9 ± 4.6 kg/m^2 and 65.5 ± 9.6 years and 30.8 ± 4.5 kg/m^2 respectively. Furthermore, 130 of the 566 individuals with dynapenic obesity had T2D compared to 196 of the 1397 individuals in the non-dynapenic obesity group.

One year later, Lu *et al*[18] completed a cross sectional study in which they assessed

Table 1 Studies included in the systematic review

Study	Design	Definition of SO	Body composition	Gender	Sample	Mean age	Mean BMI	Prevalence Sarcopenic Obesity	Prevalence of Diabetes
Sénéchal *et al*[35], 2012	Cross sectional	Dynapenic obesity, defined as low leg muscle strength, combined with abdominal obesity	Kin- Com dynamometer	M-F	T = 1963	Non DO: 65.5 ± 9.6; DO: 65.4 ± 9.9	Non DO: 30.8 ± 4.5; DO: 29.9 ± 4.6	DO: *n* = 566/1963 (Did not distinguish in gender)	T2D: Non DO: *n* = 196; DO: *n* = 130
Lu *et al*[18], 2013	Cross sectional	Defined by combination of total skeletal muscle mass/wt. (100) and BMI ≥ 25 kg/m^2	BIA	M-F	T = 180; M = 60; F = 120	Non SO: 69.9 ± 7.3; SO: 61.1 ± 9.9	Non SO: 26.8 ± 1.6; SO: 27.8 ± 2.6	*n* = 35/60 in males; *n* = 80/120 in females	T2D: Non SO: *n* = 12/65; SO: *n* = 17/115
Poggiogalle *et al*[36], 2015	Cross sectional	Defined by ASMM/h^2 or ASMM/wt. < 2SD of sex specific mean combined with assessment of FM and FFM	DXA	M-F	T = 727; M = 141; F = 586	46.49 ± 13.73; 46.99 ± 13.76	38.85 ± 5.88; 38.84 ± 5.79	SO: *n* = 68/141 in males; *n* = 350/586 in females	Pre-diabetes or T2D: Non-SO: *n* = 69; SO: *n* = 155
Ma *et al*[37], 2016	Retrospective; Cross sectional	SO: BMI > 30 kg/m^2 and 24 h- UC < median	Sex-specific 24-h urinary creatinine excretion	M-F	T = 310; M = 144; F = 166	71.8 ± 7.6	34.1 ± 4.0	SO: *n* = 44/144 in males; *n* = 52/166 in females	T2D: Non SO: *n* = 51; SO: *n* = 40
Xiao *et al*[38], 2017	Retrospective	FMI/FFMI ratio > 95 percentile of sex, BMI and ethnicity specific population-representative references	BIA	M-F	T = 144; M = 45; F = 99	Non SO: 56.6 ± 12.7; SO: 54.6 ± 10.1	Non SO: 44.0 ± 7.6; SO: 49.1 ± 8.3	SO: 73/144 in total; (Did not distinguish in gender)	T2D: Non SO: *n* = 36/71; SO: *n* = 34/71
Kang *et al*[39], 2017	Cross sectional	ASM/Wt < 1 SD the mean of the reference group, and BMI ≥ 25 kg/m^2	DXA	F	T = 1555	Non SO: 61.05 ± 0.44; SO: 62.91 ± 0.44	Non SO: 26.80 ± 0.07; SO: 27.93 ± 0.11	SO: *n* = 855/1555 (All females)	T2D: Non SO: *n* = 105/700; SO: *n* = 165/855
Aubertin-Leheudre *et al*[40], 2017	Cross sectional	Dynapenic obesity, defined as low handgrip strength (≤ 19.9 in females; ≤ 31.9 in males), combined with BMI ≥ 30 kg/m^2	Jamar Handheld Dynamometer	M-F	T = 670; M = 213; F = 457	Non SO: 76.3 ± 4.7; SO: 78.0 ± 4.6	Non SO: 35.6 ± 4.8; SO: 34.9 ± 4.8	SO: *n* = 77/213 in males; *n* = 179/457 in females	T2D: Non SO: *n* = 133/414; SO: *n* = 81/256
Park *et al*[41], 2018	Cross sectional	SO defined by combination of SMI < 2 SD and WC ≥ 90 cm for men and ≥ 85 cm women	BIA	M-F	T = 53818; M = 38820; F = 14998	Non SO: 40.5 ± 9.2; SO: 40.0 ± 11.3	Non SO: 26.9 ± 2.2; SO: 30.7 ± 3.4	*n* = 6513; M = 3341; F = 3172	T2D; Non-SO: *n* = 2176; SO: *n* = 391
Kreidieh *et al*[42], 2018	Cross sectional	ALM/BMI < 0.512	BIA	F	T = 154	33.26 ± 14.65	31.42 ± 4.94	*n* = 31	T2D: Non SO: *n* = 3/123; SO: *n* = 4/31

Khazem *et al*[43], 2018	Cross sectional	ALM/BMI < 0.789, (ALM/Wt.) × 100% < 25.72, and (ALM/Wt.) × 100% < 29.60	BIA	M	T = 72	32.79 ± 13.65	33.69 ± 5.85	23.9%-69.4%	T2D: Non SO: *n* = 1/22; SO: *n* = 3/50
Scott *et al*[46], 2018	Cross sectional (includes a longitudinal part)	ALM/height < 7.26 kg/m^2 combined with handgrip strength < 30 kg and/or low gait speed ≤ 0.8 m/s. Obesity was defined as body fat percentage ≥ 30%	DXA Handgrip strength Gait speed	M	T = 525	Non SO: 75.9 ± 4.7; SO: 80.3 ± 6.5	Non SO: 30.7 ± 3.4; SO: 27.2 ± 2.3	*n* = 80	High fasting glucose or diabetes medications: Non SO: *n* = 177/445; SO: *n* = 29/80

SO: Sarcopenic obesity; DO: Dynapenic obesity; BMI: Body mass index; M: Male; F: Female; BIA: Bioelectric impedance analysis; T2D: Type 2 diabetes; DXA: Dual-energy X-ray absorptiometry.

SO defined as the coexistence of obesity (BMI ≥ 25 kg/m^2) and sarcopenia based on the skeletal muscle index estimated by BIA. A sample of 180 individuals with obesity (60 males and 120 females) was recruited. Of the 60 males included in the sample 35 had SO compared to 80 of the 120 females. Regardless of gender the mean age and BMI in the SO group were 61.1 ± 9.9 years and 27.8 ± 2.6 kg/m^2, and 69.9 ± 7.3 years and 26.8 ± 1.6 kg/m^2 in the non-SO group. Moreover, 12 of the 65 patients in the SO group had T2D compared to 17 of the 115 patients in the non-SO group.

In early 2016, Poggiogalle *et al*[36] conducted a cross sectional study in which the authors assessed SO using DXA, with SO defined as the coexistence of obesity (BMI ≥ 30 kg/m^2) and sarcopenia (ASMM: height^2 < 6.54 and < 4.82 kg/m^2 for males and females respectively) or (ASMM: weight < 0.2827 and < 0.2347 for males and females respectively). This study enrolled a sample of 727 individuals with obesity (141 males and 586 females), with mean ages of 45.63 ± 13.53 and 45.76 ± 13.58 years, and mean BMIs of 37.56 ± 5.99 and 37.80 ± 5.77 kg/m^2 respectively for each gender. Of the 141 male patients 68 had SO, while 350 of the 586 females had the condition. In addition, 155 of the 418 patients had pre-diabetes or T2D in the SO group compared to 70 of the 309 patients in the non-SO group.

In the same year, Ma *et al*[37] performed a cross-sectional evaluation on SO defined by BMI and sex-specific 24-h urinary creatinine excretion, in 310 patients (166 females and 144 males) with obesity (BMI ≥ 30 kg/m^2). Fifty-four of the 144 males and 52 of the 166 females had SO. The mean BMI and age of the SO group were 34.1 ± 4.0 kg/m^2 and 71.8 ± 7.6 years, while they were 34.9 ± 4.4 kg/m^2 and 67.8 ± 6.8 years in the non-SO group, respectively. Furthermore, 40 of the 106 patients had T2D in the SO group in comparison to 51 of the 204 patients in the non-SO group.

In 2017, Xiao *et al*[38] performed a retrospective study on the prevalence of SO and its association with health outcomes in patients seeking weight loss treatment in a bariatric surgery setting. Body composition analysis was conducted by means of BIA and SO was defined by a fat mass:fat-free mass index (FMI: FFMI) ratio greater than the 95th percentile of sex, BMI and ethnicity-specific population-representative references. A sample of 144 adults with obesity (99 females and 45 males) were enrolled, with a mean age of 55.6 ± 11.5 years and a mean BMI of 46.6 ± 8.4 kg/m^2. Of the 144 patients included in the sample 73 had SO (data per gender is not available). The mean age and BMI of the individuals with obesity only were 56.6 ± 12.7 years and 44.0 ± 7.6 kg/m^2, compared to 54.6 ± 10.1 years and 49.1 ± 8.3 kg/m^2 in those with SO. Furthermore, 34 of the 73 patients had T2D in the SO group in comparison to 36 of the 71 patients in the non-SO group.

In 2017, Kang *et al*[39] conducted a large cross-sectional study to assess the association between SO and metabolic syndrome in postmenopausal women. SO was defined by the co-existence of sarcopenia (ASM/weight < 1 standard deviation below the mean of the reference group) and a BMI cut-off point for obesity which referred to a score of of 25 kg/m^2 on the basis of the Asia-Pacific obesity criterion. The study included 1555 females with obesity, of whom 855 had SO, with a mean age of 62.91 ± 0.44 years and a mean BMI of 27.93 ± 0.11 kg/m^2. On the other hand, 700 did not have SO and had a mean age of 61.05 ± 0.44 years and a mean BMI of 26.80 ± 0.07 kg/m^2. In

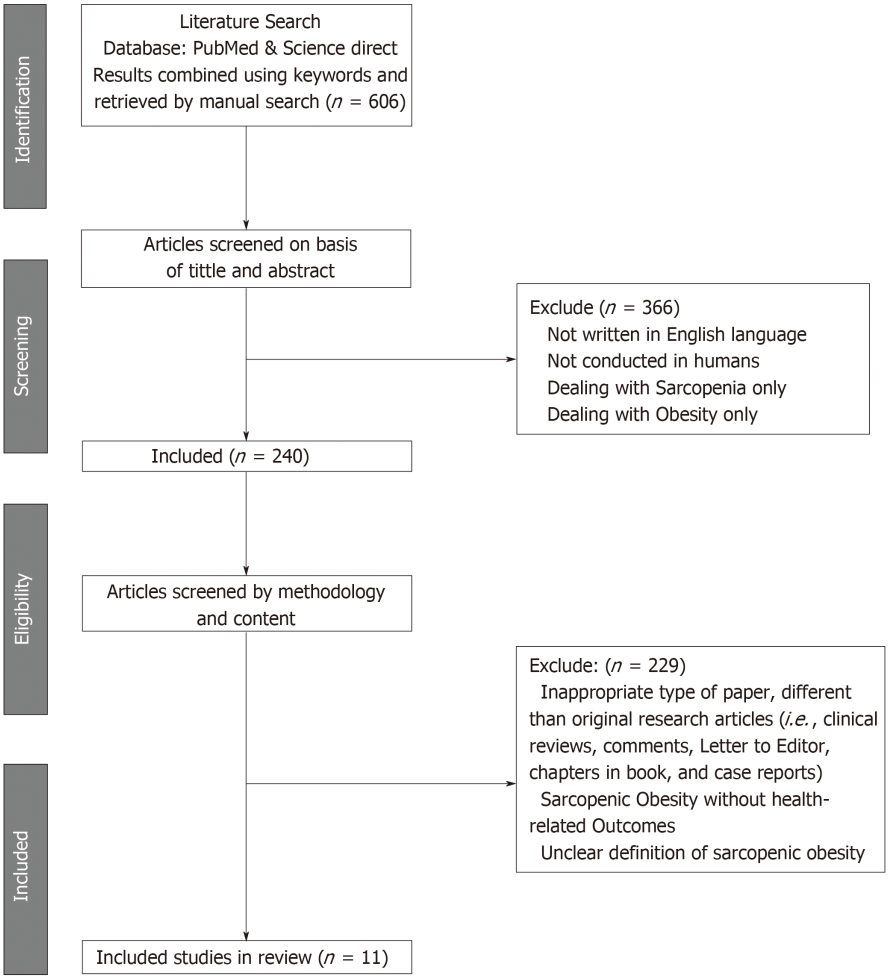

Figure 1 The flowchart summarizing the study selection procedure.

addition, 165 of the 855 patients had T2D in the SO group while 105 of the 700 patients in the non-SO group had T2D.

In the same year, a cross-sectional study by Aubertin-Leheudre *et al*[40] aimed to examine the association between dynapenic obesity and metabolic risk factors in older adults (age ≥ 70 years). Dynapenic obesity was defined as low handgrip strength (u 19.9 in females; ≤ 31.9 in males) combined with a BMI of ≥ 30 kg/m^2. The study included 670 participants with obesity (213 males and 457 females), of whom 256 had dynapenic obesity, with a mean age of 78.0 ± 4.6 years and a mean BMI of 34.9 ± 4.8 kg/m^2, and 414 did not have dynapenic obesity, with a mean age of 76.3 ± 4.7 years and a mean BMI of 35.6 ± 4.8 kg/m^2. Furthermore, 81 of the 256 individuals in the dynapenic obesity group had T2D while 133 of 414 individuals in the non-dynapenic obesity group had T2D.

In 2018, Park *et al*[41] conducted a large cross sectional study in two sites, which included a total of 53818 adults with overweight and obesity of both genders (38820 males and 14998 females), of whom 6513 had SO defined as below two standard deviations of the mean of the skeletal muscle mass index for young adults assessed by BIA and a waist circumference of ≥ 90 cm for men and ≥ 85 cm for women. The mean age and BMI of the individuals with obesity only were 40.5 ± 9.2 years and 26.9 ± 2.2 kg/m^2 compared to those with SO who had a mean age of 40.0 ± 11.3 years and a mean BMI of 30.7 ± 3.4 kg/m^2. Moreover, 391 of the 6513 patients had T2D in the SO group compared to 2176 of the 47305 patients in the non-SO group.

In 2018, Kreidieh *et al*[42] conducted a cross sectional controlled study in which body composition measurements were conducted by BIA using a definition that in addition to appendicular lean mass (ALM) also involved BMI, and patients were considered affected by SO if ALM:BMI < 0.512. The study included 154 females with overweight and obesity with a mean age of 33.26 ± 14.65 years and a mean BMI of 31.42 ± 4.94 kg/m^2. Of the 154 female patients 31 had SO. Moreover, four of the 31 patients had T2D in the SO group compared to three of the 123 patients in the non-SO group.

In 2018, Khazem *el al*[43] performed a cross-sectional controlled study on 72 adult

Table 2 Quality assessment of the included studies

Author	Sénéchal *et al*[35], 2012	Lu *et al*[18], 2013	Poggiogalle *et al*[36], 2016	Ma *et al*[37], 2016	Xiao *et al*[38], 2017	Kang *et al*[39], 2017	Aubertin-Leheudre *et al*[40], 2017	Park *et al*[41], 2018	Scott *et al*[46], 2018	Kreidieh *et al*[42], 2018	Khazem *et al*[43], 2018
Selection											
Represents cases with independent validation	1	1	1	1	1	1	1	1	1	1	1
Cases are consecutive or obviously representative	1	1	1	1	1	1	1	1	1	1	1
Controls from the community	1	1	1	1	1	1	1	1	1	1	1
Controls have no history of sarcopenic obesity	1	1	1	1	1	1	1	1	1	1	1
Comparability											
Controls are comparable for the most important factors	1	1	1	1	1	1	1	1	1	1	1
Control for any additional factor	0	0	1	0	0	1	0	1	0	0	0
Ascertainment of exposure											
Secured record or structured interview where blind to /control status	1	1	1	1	0	1	1	1	1	1	1
Same method of ascertainment for cases and controls	1	1	1	1	1	1	1	1	1	1	1
Cases and controls have completed follow up	0	0	0	1	0	0	0	0	1	0	0
Total score	7	7	8	8	6	8	7	8	8	7	7

Newcastle-Ottawa Scale (NOS) for longitudinal and cross-sectional studies. Yes = 1, No (not reported, not available) = 0; Studies with scores of 0-3, 4-6, 7-9 were considered as low, moderate and high quality, respectively.

males with overweight and obesity with a mean age of 32.79 ± 13.65 years and a mean BMI of 33.69 ± 5.84 kg/m^2. In this study the authors used three different definitions proposed by Batsis *et al*[44], Levine and Crimmins[21], and Oh *et al*[45] based on ALM:BMI

and (ALM: weight) × 100% to define SO. Body composition was assessed by BIA. Based on each formula the prevalence of SO varied between 23.9% and 69.4%. However, based on the definition that was revealed to be more useful from the clinical perspective, 50 of the 72 patients had a reduced lean body mass with a prevalence of 69.4%. Moreover, three of the 50 patients had T2D in the SO group in comparison to one of the 22 patients in the non-SO group.

Finally, in 2018 Scott *et al*[46] conducted a large sampled study that aimed to investigate the cross-sectional association between SO and components of metabolic syndrome in community-dwelling older men. SO was defined by the co-existence of sarcopenia as ALM/height < 7.26 kg/m^2 combined with handgrip strength < 30 kg and/or low gait speed ≤ 0.8 m/s, while obesity was defined as a body fat percentage of o 30%. The study included 525 males with obesity, of whom 80 had SO, with a mean age of 80.3 ± 6.5 years and mean BMI of 27.2 ± 2.3 kg/m^2 and 445 did not have SO, with a mean age of 75.9 ± 4.7 years and mean BMI of 30.7 ± 3.4 kg/m^2. Furthermore, 29 of the 80 individuals in the SO group had T2D in comparison to 177 of the 445 individuals in the non-SO group.

Meta-analysis

The meta-analysis estimated the overall prevalence of SO among males and females. With high heterogeneity among the included studies, a random effect model was considered for the estimation of the overall prevalence of SO. The forest plots in Figures 2 and 3 show that SO affected 43% (95%CI: 28-59) of females and 42% (95%CI: 31-53) of males. In addition, the overall odds ratios of T2D in patients with SO as compared to those without SO are presented in Figure 4. The fixed effect weighted pooled odds for T2D in patients with SO indicated an increased risk of T2D of approximately 38% compared to those without SO (OR: 1.38, 95%CI: 1.27-1.50). The heterogeneity analysis revealed moderate variability (I^2 = 60%).

DISCUSSION

This systematic review aimed to provide benchmark data on the prevalence of sarcopenia in individuals with overweight and obesity and to assess any potential association between SO and T2D in this population. The major finding is that sarcopenia seems to affect approximately 40%-45% of individuals with overweight and obesity of both genders, and the co-existence of both conditions, namely sarcopenia and excess weight/obesity increases the risk of T2D by nearly 38% when compared with those who had excess weight or obesity alone. The underlying mechanism behind this association is still unclear, however it seems that there is a bi-directional interaction between obesity, chronic inflammation, insulin resistance and sarcopenia[19]. In fact, the chronic inflammation plays an important role in the pathogenesis of T2D. For this reason we speculate that coexistence of both obesity and sarcopenia under the so-called phenotype "SO", may have a synergistic effect with chronic inflammation being a common "denominator" seen in both conditions, which seems to exacerbate further glucose metabolism impairment (*i.e.*, insulin resistance, pre-diabetes and T2D)[19].

The clinical implication of this review's findings is the awareness of the high prevalence of sarcopenia in the overweight/obese population that should be raised among clinicians and patients. Secondly, these results reveal the importance of screening for SO in individuals affected by excess weight and obesity, since this condition also seems to be strongly associated with T2D.

This systematic review has certain strengths. To the best of our knowledge this is the first systematic review to assess the overall prevalence of SO in males and females with overweight and obesity. In fact, the studies that have been conducted on this topic reported varying levels of prevalence that ranged between 0 and 100%, depending on the applied definition of SO[47,48]. Higher prevalence tends to be reported in studies that accounted for body mass (*i.e.*, BMI), whereas a lower prevalence is reported in those that did not[43,49]. A low prevalence may also be explained by the use of definitions that have primarily been developed from studies in older cohorts and these may not be applicable to younger adults[47].

However, this systematic review also has certain limitations. Foremost, our results need to be interpreted with caution with regard to the association between SO and the prevalence of T2D, since the cross-sectional design of the studies (*i.e.*, non cohort), included in our systematic review indicates only simple associations between SO and T2D at best and does not provide solid information regarding any causal relationships between the two conditions[50,51]. In other words, these studies lack evidence to determine if SO may lead to the onset or deterioration of T2D, since very few studies

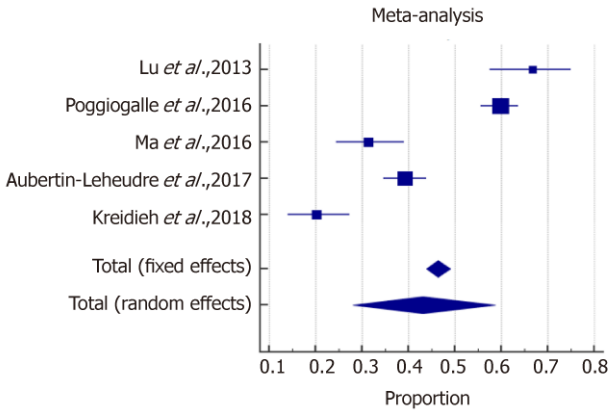

Figure 2 Forest plot for the pooled estimate of proportion of females with sarcopenic obesity.

have longitudinally investigated the "real" effects of SO on health[52]. These shortcomings in the current research indicate the need to design longitudinal studies to clarify the real effect of SO on the onset and progression of T2D.

In conclusion, a high prevalence of sarcopenia has been found among adults with overweight and obesity regardless of their gender, and this condition seems to be associated with a higher risk of T2D. Clinicians should be aware of this scenario in their clinical practice for better management of both obesity and T2D.

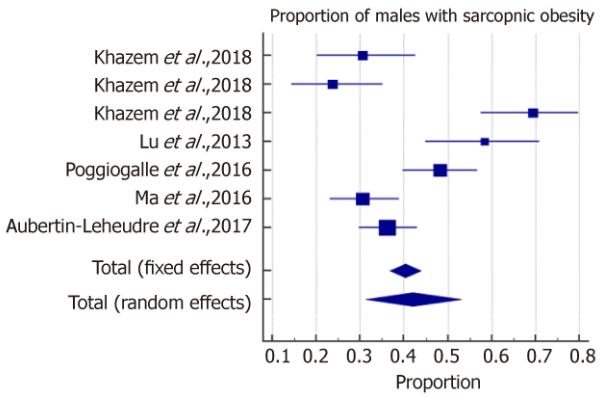

Figure 3 Forest plot for the pooled estimate of proportion of males with sarcopenic obesity.

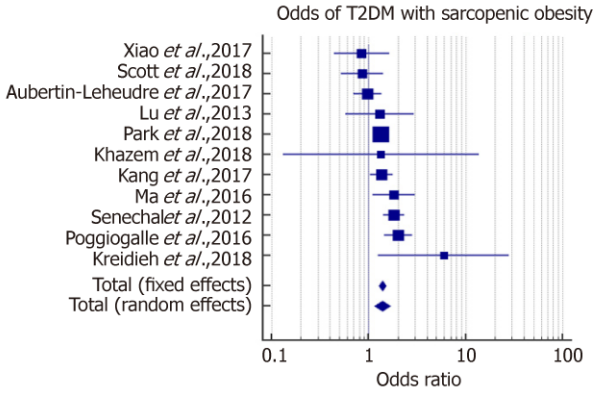

Figure 4 Forest plot for the pooled estimate of the odds of type 2 diabetes with sarcopenic obesity.

ARTICLE HIGHLIGHTS

Research background

The coexistence of sarcopenia and obesity has been termed as sarcopenic obesity (SO). Several studies have been conducted in order to determine any potential association between SO phenotype and type 2 diabetes (T2D). However, the available data are still contradictory and require further clarification.

Research motivation

To our knowledge no systematic review on the primary outcome related to the association between SO and T2D has been conducted yet to provide an unbiased interpretation of the evidence published to date.

Research objectives

We set out to systematically review the published literature with the aim of determining the prevalence of sarcopenia among adults with overweight and obesity and to investigate whether SO was associated with higher risk of T2D.

Research methods

The review conformed to the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines, and data were collated by means of narrative synthesis and meta-analysis.

Research results

The prevalence of SO in adult with overweight and obesity is 43% in females and 42% in males, and the presence of this condition increases the risk of T2D by 38% with respect to those without SO.

Research conclusions

A high prevalence of sarcopenia has been found among adults with overweight and obesity regardless of their gender, and this condition seems to be associated with a higher risk of T2D. The clinical implication of our findings is to raise awareness of the high prevalence of this phenotype in the overweight/obese population, and the importance of screening for SO in

individuals affected by excess weight, since this condition seems to be strongly associated with T2D. However, our results need to be interpreted with caution with regard to the association between SO and the prevalence of T2D, since the cross-sectional design of the studies included in our systematic review indicates only associations between the two conditions and that does not provide information regard the causal relationships.

Research perspectives

The current research indicates the need to design longitudinal studies to clarify the real effect of SO on the onset and progression of T2D. In other words, the available studies lack in evidence to determine if SO may lead to the onset or deterioration of T2D, since very few studies have longitudinally investigated the "real" effects of SO on health.

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