

Management of diabetes: Current concepts

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Abstract

The global prevalence of obesity is increasing rapidly with an exponential rise in incidence of type 2 diabetes mellitus in recent years. 'Diabetes', the term coined to show the strong interlink between obesity and diabetes, is the direct consequence of the obesity pandemic, and poses significant challenges in the management of the disease. Without addressing the clinical and mechanistic complications of obesity such as metabolic-associated fatty liver disease and obstructive sleep apnoea, a rational management algorithm for diabetes cannot be developed. Several classes of anti-diabetic medications including insulins, sulphonylureas, thiazolidinediones and meglitinides are associated with the risk of weight gain and may potentially worsen diabetes. Therefore, appropriate selection of antidiabetic drug regimen is crucial in the medical management of diabetes. The role of non-pharmacological measures such as dietary adjustments, exercise interventions and bariatric procedures should also be emphasised. Unfortunately, the importance of appropriate and optimal management of diabetes is often overlooked by medical professionals when achieving adequate glycemic control which results in inappropriate management of the disease and its complications. This review provides a narrative clinical update on the evidence behind the management of diabetes.

Key Words: Obesity; Diabetes; Metabolic-associated fatty liver disease; Antidiabetic medications; Glycemic control; Metabolic surgery

Core Tip: The worldwide prevalence of diabetes is increasing exponentially because of the global obesity pandemic in the past few decades. This is also expected to increase the prevalence of other associated chronic disorders such as hypertension, dyslipidemia, metabolic-associated fatty liver disease (MAFLD), obstructive sleep apnoea (OSA), and cardiovascular disease. Rational management of diabetes involves prompt control of diabetes while also optimally addressing other comorbidities such as obesity, hypertension, dyslipidemia, MAFLD, OSA and cardiovascular risk. Appropriate selection of the antidiabetic therapeutic agents and early planning of metabolic surgery when indicated are crucial to scientifically approach patients with diabetes. This evidence-based review addresses the key issues regarding management of diabetes.

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INTRODUCTION

Obesity has become a global pandemic over the past three decades because of the increase in prevalence of adverse lifestyle behaviours such as over-consumption of processed food and physical inactivity in the latter half of twentieth century. Consequently, a tsunami of more than fifty obesity-related problems has emerged which threatens human health and wellbeing on a global level. 800 million people around the world at present live with obesity, with an estimated health expenditure of one trillion United States dollars budgeted for managing obesity-related conditions in the year 2025[1]. There is also an expected increase in childhood obesity to 250 million by the year 2030. Unless there is a massive global action plan from health agencies and administrators to curtail the obesity pandemic, this is likely to continue to significantly impact individuals and healthcare systems.

The worst metabolic consequence of obesity is type 2 diabetes mellitus (T2DM), which substantially increases cardiovascular disease-related morbidity and mortality. Other obesity associated comorbidities such as dyslipidemia, hypertension, metabolic-associated fatty liver disease (MAFLD), obstructive sleep apnoea (OSA), heart failure, ischaemic heart disease, cancers and osteoarthritis further increase the morbidity, mortality, and health-related quality of life, especially when these patients additionally have T2DM. The term “diabetes” was coined by Sims *et al*[2] to describe the very strong pathophysiological link between diabetes and excess body weight in 1970s. Visceral adiposity, which leads to insulin resistance, is the putative mechanism in the development of diabetes. Therefore, an ideal treatment strategy for the disease should also include optimal management of obesity[3-5]. The real-world approach to the management of diabetes often ignores these crucial issues by simply focusing on glycaemic control. This manuscript provides an up-to-date overview of diabetes, in terms of pathophysiology and management. Particularly, we have reviewed and summarised newly published data from clinical trials that have shown the significant impact of glucagon-like peptide-1 (GLP-1) and sodium glucose cotransporter-2 (SGLT-2) inhibitors on diabetes. Therefore, we elaborate the conceptual, pathobiological, mechanistic, and therapeutic aspects of diabetes in this comprehensive review.

PATHOPHYSIOLOGY OF DIABESITY

The link between obesity and diabetes has been described in numerous studies to date. The key pathophysiological process is thought to be the development of insulin resistance, which, in turn, is associated with significant cardiovascular and metabolic morbidities, such as the development of T2DM [6]. Insulin resistance is described as inefficient glucose metabolism despite adequate insulin secretion [7]. In the presence of insulin resistance, a variety of insulin-sensitive tissues including the liver, skeletal muscle, as well as adipose tissue exhibit altered biochemical and cellular pathways[8].

There is a plethora of proposed pathophysiological processes for the development of diabetes in obesity. Perhaps the most described pathophysiological theory is that of chronic inflammation, with adipocytes shown to secrete a variety of pro-inflammatory substances including interleukin-6, tumor necrosis factor alpha and inflammatory cytokines, which, in turn, result in local and systemic inflammatory processes[9]. The resulting oxidative stress in adipocytes has been associated with lower adiponectin secretion, a protein that has been linked to improved glucose regulation and reduced

incidence of metabolic syndrome[10].

Another proposed mechanism is that of excess circulating lipid substrates, such as fatty acids, due to excessive consumption through a high fat diet, which also results in chronic inflammation and oxidative stress[11,12]. A long-term high fat diet may result in lipid deposition in tissues that would not normally be targeted by insulin. Triglyceride accumulation in the liver and skeletal muscle has also been shown to promote insulin resistance through impaired insulin signaling[13]. More recent literature describes the potential association between mitochondrial dysfunction, particularly in skeletal muscle, and diabetes. Mitochondrial dysfunction may be a consequence of pro-inflammatory stress and oxidation, affecting the organelle function leading to insulin resistance, at least in skeletal muscle tissues[14]. Further research is required to characterise the interplay between energy metabolism and the development of diabetes at mitochondrial level.

Recent publications highlight the impact of gut bacteria on obesity and insulin resistance. The gut microbiome has been shown to have a significant impact on nutrient metabolism. Individuals with reduced heterogeneity in their gut microbiome have been found to be at a greater risk of obesity and insulin resistance[15]. Linking to excess fat consumption, research suggests that excess lipid intake may result in bacterial production of short chain fatty acids, which in turn affect energy balance and metabolism[16,17] (Figure 1).

MAJOR COMORBIDITIES TO BE ADDRESSED IN MANAGING DIABESITY

MAFLD

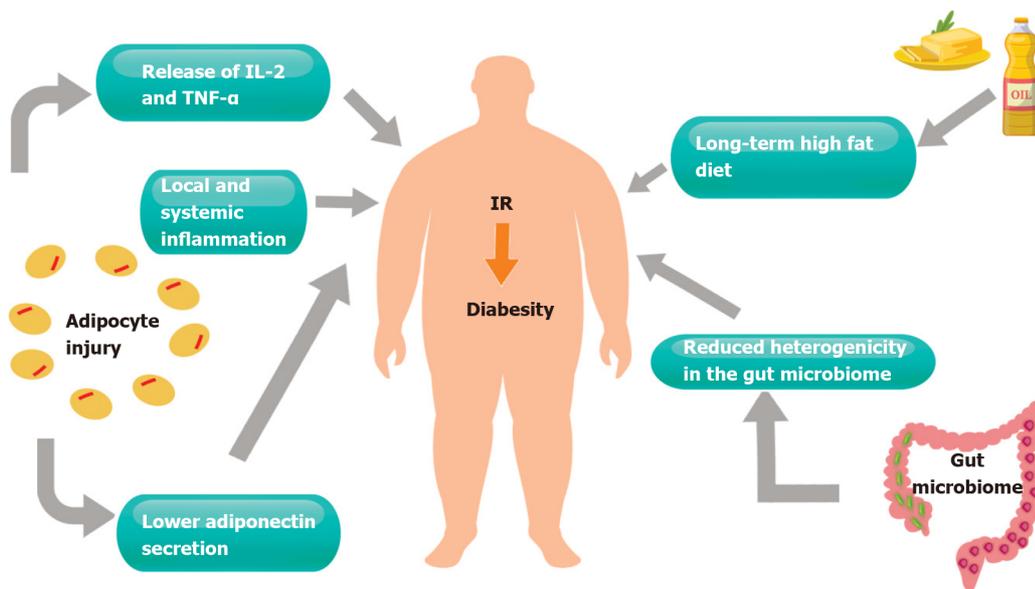
Metabolic dysfunction, and the inflammatory processes in obesity and T2DM, have been closely associated with non-alcoholic fatty liver disease. This has prompted the use of the new term, MAFLD, given the significant link between fatty liver disease and insulin resistance[18,19]. A variety of pathophysiological processes, as described in the previous section, result in excess adipose tissue accumulation in the liver. As a result, hepatic cellular damage, oxidative stress, and insulin resistance develop in such cases. A study investigating the presence of fatty liver disease *vs* simple hepatic steatosis in patients with T2DM or metabolic syndrome, revealed that almost all diabetic patients showed evidence of steatohepatitis on liver biopsy, without necessarily showing derangement in their liver function (98.6% of patients with T2DM *vs* 58.5% of patients with metabolic syndrome, $P < 0.0001$). This suggests that MAFLD may be one of the early end-organ complications of T2DM and metabolic syndrome, with early occult onset and progression without any clinical signs[20]. Hence early identification and management may have a significant impact on mortality and morbidity. MAFLD has also been directly associated with increased cardiovascular morbidity and both micro- and macrovascular complications in diabetic patients, further solidifying the need for early identification and management [21].

OSA and sleep disturbances

OSA involves partial or complete obstruction of the airway during sleep, which results in transient hypoxaemia, sleep restriction and reduction in intrathoracic pressures[22]. These have been linked to the activation of the hypothalamic pituitary adrenal axis resulting in excess stress hormone release and increased cardiovascular morbidity. OSA and hypoxia have also been linked to alterations in adipokine levels as well as oxidative stress. All, in turn, lead to the accumulation of excess adipose tissue and the development insulin resistance[23]. The reverse has also been reported, *i.e.*, OSA could be aggravated by T2DM and obesity[23,24]. One could argue that a patient with both conditions would be at risk of significant morbidity, with diabetes that would be challenging to control without optimising their sleep apnoea. Sleep apnoea and T2DM have both been associated with increased cardiovascular morbidity and mortality, hence a combination of the two may prove more detrimental[25]. Evidence suggests that the prolonged use of continuous positive airway pressure ventilation (CPAP), other than improving sleep quality and reducing hypoxaemia, may also improve glucose tolerance and insulin sensitivity in obese individuals[26-28]. A study of 40 T2DM patients treated with CPAP for 3 mo, assessed the effect of CPAP therapy on insulin resistance using hyperinsulinaemic euglycaemic clamp. Results revealed significant improvement in insulin sensitivity, as early as 2 d after commencing treatment with CPAP (5.75 ± 4.20 *vs* 6.79 ± 4.91 micromol/kg/min at 2 d; $P = 0.003$). The improvement persisted after 3 mo of CPAP therapy[28]. Hence, early identification and treatment of OSA in diabetes patients with CPAP may help to reduce cardiovascular complications and improve glycaemic control.

Dyslipidemia and cardiovascular risk

It has been proposed that diabetes significantly contributes to endothelial damage and heart failure, which are both exacerbated by dyslipidaemia. Through the mechanism of altered mitochondrial energy expenditure as previously described, diabetes may have a direct effect on mitochondrial function in cardiac muscle. This may result in inefficient energy production and expenditure, causing cardiac stress [29]. Additionally, it has been reported that patients with diabetes exhibit cardiac oxidative stress and poor utilisation of energy substrates, in turn causing dysfunction in cardiac muscle contraction[29,30].



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Figure 1 Pathophysiology of diabetes as evidenced by recent literature. IL-2: Interleukin-2; TNF- α : Tumor necrosis alpha; IR: Insulin resistance.

Increased consumption of fats, which results in increased circulatory fatty acids, may also contribute to cardiac steatosis which will also impair cardiac function. Studies using cardiac magnetic resonance (MR) spectroscopy have demonstrated cardiac steatosis, both in patients with diabetes, as well as in those with obesity[31]. Hence diabetes may have a direct link to structural alterations and stress of cardiac muscle, leading to heart failure. This is further supported by the Framingham study, which also demonstrated that an elevated glycated haemoglobin (HbA1c) level was associated with more severe heart failure[32].

Hypertension and coronary artery disease

The association between diabetes, obesity and macrovascular disease has been well established through the years[33,34]. Burke *et al*[34] demonstrated that obese individuals without metabolic complications had a significantly higher coronary calcium score when compared to non-obese patients (17% increase in risk of higher coronary artery calcium scores). This suggests that obesity alone, even without the presence of diabetes, would result in increased coronary artery disease risk. Kronmal *et al*[35] investigated the association between coronary artery calcium progression and a multitude of risk factors which included T2DM in 5756 individuals. Results demonstrated that T2DM, particularly of longer duration, was associated with progression of coronary artery calcium. This suggests that patients with diabetes are at significantly increased risk of myocardial events[35]. Therefore, in the diabetes epidemic, it would be of paramount importance that the patient's cardiovascular risk is stratified and addressed early on, in order to prevent significant cardiovascular events, perhaps with coronary artery calcium assessment. Recent advances in cardiac imaging modalities, including cardiac MR and computed tomography coronary angiography, may allow for early identification and management of coronary artery disease in diabetes patients as shown in recent trials[29,36].

Diabetes-related chronic kidney disease

It has been suggested that the development of diabetes-related kidney disease may be mediated through insulin resistance. Insulin is essential for normal glomerular function and podocyte biology, and dysfunctional insulin signaling has been shown to dysregulate vascular endothelial growth factor A signaling pathway and affects glucose transport[37]. Studies demonstrated podocyte damage, glomerulosclerosis, and albuminuria occur in patients with insulin resistance[38]. In more recent years, studies have also suggested that proximal tubule cells have a role in nutrient regulation in the kidney. Excessive amounts of glucose, fatty acids, and amino acids present in the proximal tubule due to obesity or diabetes, will cause dysregulation in the relevant pathways normally protecting kidney, and consequently result in tubular injury, fibrosis, and inflammation[37-39]. Therefore, medications such as SGLT-2 inhibitors may help to prevent the presence of excessive nutrients in proximal tubule cells, due to induction of glycosuria, and therefore help to minimise tubular damage through this mechanism[40].

MANAGEMENT OF DIABESITY - LIFESTYLE MEASURES

Dietary modifications

As mentioned earlier, T2DM and obesity are inter-linked and share common pathophysiological mechanisms of disease origin, especially adverse lifestyle behaviours. Hence, the first step in the management of diabetes, prior to medical intervention would be to attempt weight loss *via* lifestyle modifications such as changes in diet and exercise. Multiple studies have shown that weight loss can induce remission of T2DM. It has been suggested that weight loss of 15 kg can induce remission of T2DM in around 70% of individuals[41,42]. Achieving weight loss through dietary restriction can be difficult and challenging, and ultimately, it aims to reverse the mechanisms induced by nutrient overconsumption. Therefore, setting realistic stepwise targets may aid patients in achieving sustained weight loss. Smaller degrees of weight loss such as 5 kg have been shown to decrease fasting blood glucose and improve the insulin sensing ability of adipose, skeletal muscle and liver tissues. Stepwise incremental weight loss has been shown to result in a gradual improvement in HbA1c[43].

Larger randomised controlled trials have been conducted in this field, such as the look-AHEAD trial, which demonstrated that remission of diabetes correlated with the degree of weight loss and was inversely correlated with the duration of T2DM[44]. A similar primary care study in the United Kingdom, DiRECT, randomised patients in a control group (standard diabetes care) or a structured weight management program. The weight management program group showed greater weight loss [10 kg *vs* 1 kg, adjusted difference -8.8 kg, 95% confidence interval (CI): -10.3 to -7.3; $P < 0.0001$], greater incidence of diabetes remission (46% *vs* 4%, odds ratio = 19.7, 95%CI: 7.8 to 49.8; $P < 0.0001$), with the degree of weight loss correlating to the improvement in diabetes management[45]. However, large scale trials mainly involved short-term high intensity weight loss programmes. We could argue that a long-term, permanent change in diet would be desired to achieve sustainable benefits in our patient cohort. Ajala *et al*[40] has reviewed the beneficial effects of possible dietary modifications in overweight patients with diabetes. Their study demonstrated that a lower carbohydrate, lower glycaemic index, Mediterranean style diet and high protein diet led to significant improvement in glycaemic control [HbA1c change of -0.12% ($P = 0.04$), -0.14% ($P = 0.008$), -0.47% ($P < 0.00001$), and -0.28% ($P < 0.00001$), respectively][46]. Mediterranean and high protein diets have also been shown to reduce cardiovascular risk in diabetes patients and should be considered[46,47]. More recent research (Ozsoy *et al*[48], 2022) investigated the possibility of modulating gut microbiota through diet, hence altering neurotransmitter pathways of satiety and insulin sensitivity. It was suggested that perhaps the Mediterranean diet would be successful in achieving a varied balance in the gut microbiome.

Physical activity

Regular physical activity, regardless of the associated weight loss, has been shown to improve HbA1c and insulin sensitivity. Exercise comes with a variety of benefits including reduction in visceral adipose tissue, improvement in lipids and blood pressure and hence a reduction in the cardiometabolic risk[49, 50]. Effects seem to be proportional to energy expenditure, *i.e.*, total calories burnt, rather than the type of exercise itself[50,51]. Therefore, exercise programmes should be personalised and tailored to patient preference and co-morbidities. Despite the improvement in biochemical parameters, exercise alone does not seem to lead to the remission of diabetes[49-52], therefore a combined diet and exercise programme is recommended in order to achieve the best possible outcome. Results from the Malmö study further support this, where patients on a combined diet and exercise modification programme demonstrated long-term sustainable benefits, with half the T2DM patients in remission at 5 years. Improvement in glycaemic control was proportional to the degree of weight loss ($r = 0.19$, $P < 0.02$) and also to change in fitness levels ($r = 0.22$, $P < 0.02$)[53].

DRUG THERAPY

Metformin

Metformin is one of the first-line medications for the management of T2DM and is known for its good safety profile and low cost. Metformin works by inhibiting hepatic gluconeogenesis, improving insulin sensitivity in skeletal muscle and reduction of appetite, although its mechanism of action is not yet fully understood[54,55]. It is one of the antidiabetic medications recommended globally as first-line therapy for T2DM[56]. Previous studies have demonstrated significant weight loss benefits, ranging between 0.6 to 2.9 kg[5]. Wu *et al*[57] has proposed that, in addition to the known mechanisms of action of metformin, this medication may also positively affect the composition of the gut microbiome and may potentially lead to improved glucose metabolism in the gut, resulting in weight loss. Day *et al*[58] has suggested that metformin also increases the expression of growth differentiating factor 15 (GDF-15), which results in appetite suppression and weight loss. However, more *in vivo* studies are required to further investigate this association. Multiple health benefits have been demonstrated with metformin use, which include reversibility of hepatic steatosis and a lipid lowering effect. It has been suggested

that these are indirect effects of weight loss associated with metformin, rather than a direct effect on hepatic lipid metabolism and storage[59]. A recent review by Lv *et al*[60] looking into the clinical benefits of metformin, demonstrated significant benefits in a variety of health issues including chronic kidney disease, cardiovascular disease and several cancers by preventing growth and metastasis of tumor cells and the effect on the gut microbiome[60-62].

Insulin

Insulin therapy is recommended in patients with significantly elevated HbA1c, where the aim is rapid and effective optimisation of glycaemic control. This may be the case in patients with significant diabetic complications or patients requiring urgent surgical procedures[5]. However, insulin therapy has been associated with significant weight gain, especially when compared to other hypoglycaemic agents. Weight gain ranging between 1.56-5.75 kg has been reported with insulin use, which may make clinicians reluctant to prescribe it in overweight/obese diabetic patients[63]. It has been previously demonstrated that the dose as well as the type of insulin may influence the degree of weight gain in diabetic patients. Greater doses of insulin have been associated with greater weight gain[64]. Basal insulin has been shown to have a lesser effect on weight than pre-mixed insulin[65]. Freemantle *et al*[66] suggested that the use of glargine insulin resulted in significantly less weight change when compared to pre-mixed insulin. Results when using glargine were comparable with detemir, degludec, and neutral protamine Hagedorn insulin. Therefore, careful consideration, with joint decision making between patients and specialists, is recommended when prescribing insulin in patients with diabetes, to minimise the risk of weight gain while achieving the benefits of rapid optimisation of glycaemic control.

Sulphonylureas

Sulphonylureas are generally not recommended in patients with obesity, due to significant risk of hypoglycaemia, weight gain, reduced efficacy, and the need for careful dose titration in patients with renal disease[67]. Hypoglycaemia risk has been reported to vary between sulphonylurea agents, with gliclazide having the lowest reported incidence among this class of medications[68]. Usually prescribed in combination with other agents, sulphonylureas have been reported to result in weight gain of approximately 2.01-2.3 kg[63,69]. Therefore, sulphonylureas appear to pose significant risk of hypoglycaemia, as well as weight gain, and poorer outcomes in patients with diabetes. Furthermore, recent large randomised controlled trials did not show any significant change in cardiovascular risk, in patients treated with sulphonylureas *vs* other oral antihyperglycaemic agents such as pioglitazone or linagliptin [70-72].

Thiazolidinediones

Thiazolidinediones are the only oral antihyperglycaemic agents that specifically target and improve the phenomenon of insulin resistance. Through the activation of the peroxisome proliferator-activated receptor gamma system, they increase glucose utilisation, decrease hepatic steatosis, and decrease circulating free fatty acids[73]. These oral agents, despite having a low risk of hypoglycaemia, and relatively favourable efficacy in HbA1c reduction, have been also associated with significant weight gain between 2.3-4.25 kg[63]. Weight gain in patients on this class of medication is not entirely attributed to the deposition of adipose tissue, as patients may experience fluid retention as a side effect of thiazolidinedione use, which also leads to apparent weight gain[74]. A recent review (Lebovitz *et al* [73]) summarised the different trials looking into the effects of pioglitazone and rosiglitazone on cardiovascular risk. It has been suggested that both medications have been superior to sulphonylureas, with pioglitazone showing a more favourable efficacy and safety profile.

Hesitation to prescribe these agents has also risen from previously reported risk of bladder malignancy, osteoporosis, and heart failure. More recent literature (Lewis *et al*[75]) suggests that these risks may not be as grave as previously thought. Recent retrospective follow-up studies of patients diagnosed with bladder cancer, did not find a significant association between pioglitazone use and the development of bladder malignancy[75,76]. However, the literature relating to thiazolidinedione use and fracture risk confirms increased risk of fractures in female patients, regardless of menopausal status. The TOSCA-IT study did not find a significantly increased risk of fractures when comparing patients on pioglitazone *vs* sulphonylurea therapy[70]. Although it has been proven that thiazolidinediones increase the incidence of heart failure, there is no causal link to progression, severity, or death from heart failure in such patients[73]. Therefore, overall data may suggest superiority of this class of medication over sulphonylureas in patients diabetes especially when they have co-existing MAFLD.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) agents are considered as “weight neutral” agents, with minimal effect on overall body weight[63]. This class of medications works by inhibiting the breakdown of GLP-1 and glucose dependent insulinotropic peptide (GIP) in the gut, maximising the duration of action of these incretin hormones[5]. They have been reported to positively impact HbA1c control, with about an overall 0.75% reduction when prescribed alongside other antihyperglycaemics[77]. This class of medications is not generally used as monotherapy, rather than in combination with other oral

antihyperglycaemic agents. The addition of DPP-4 inhibitors to metformin therapy, showed favourable weight outcomes when compared to the addition of sulfonylureas or thiazolidinedione in recent trials [78]. However, caution needs to be exercised when prescribing this class of medications to patients with cardiovascular disease, as the use of DPP-4 inhibitors has been shown to increase the incidence of hospitalisation from heart failure. Saxagliptin, vildagliptin and alogliptin have all been associated with an increased incidence of hospitalisation for heart failure in diabetic patients[79]. It is thought that clinical deterioration is evident shortly after treatment is initiated, and this requires careful titration and clinical monitoring.

GLP-1 receptor agonists

GLP-1 receptor agonists work by the stimulation of insulin secretion and suppression of glucagon production. Furthermore, they modulate receptors in the gut to delay gastric emptying, as well as neurons involved in appetite regulation. These mechanisms lead to reduced appetite and improved feeling of satiety, hence contributing to weight loss[63]. Current preparations include subcutaneous injections and oral tablets. Injections vary in frequency, from daily (exenatide, lixisenatide, and liraglutide) to once weekly (exenatide-extended release, dulaglutide, albiglutide, and semaglutide). A recently approved oral form of semaglutide is also licensed for use, which has shown comparable effects to the subcutaneous semaglutide preparation[80].

There have been multiple research trials with significant data, surrounding the use of GLP-1 inhibitors in diabetes, as well as obesity alone, in the recent years, as summarised in Table 1. Data has shown an association with significant weight loss, ranging between 1.14-6.9 kg, and an improvement in HbA1c between 1%-2%[63]. High dose liraglutide has been approved for use in the management of obesity. Semaglutide, has also recently been shown to be beneficial in the management obese non-diabetic patients. A recent study (Wilding *et al*[81]) showed that the use of 2.4 mg semaglutide alongside lifestyle intervention, resulted in sustainable weight loss after 68 wk (-14.9% for semaglutide *vs* -2.4% for placebo). However, a significant percentage of patients in the semaglutide group had to discontinue therapy due to side effects (4.5% for semaglutide *vs* 0.8% for placebo). Research has also demonstrated that the improvement in glycaemic control achieved by GLP-1 agonists was comparable to that of insulin[82]. Therefore, GLP-1 agonists should be the first-line injectable therapy for consideration in diabetes patients, with remarkable benefits on body weight while also resulting in improved glycaemic control.

Additionally, GLP-1 agonists have been shown to have significant systemic benefits, including reduction in cardiovascular risk in high-risk patients[83], and reduction in urinary albumin excretion. The 2019 REWIND trial investigated the effect of dulaglutide on renal outcomes, and reported improved morbidity, particularly a reduction in the incidence of new macroalbuminuria, and slower renal function decline[84]. Another trial conducted by Mann *et al*[85], comparing liraglutide with placebo, showed reduced rates of development of renal disease (hazard ratio = 0.78; 95%CI: 0.67 to 0.92; $P = 0.003$), particularly macroalbuminuria (hazard ratio = 0.74; 95%CI: 0.60 to 0.91; $P = 0.004$).

Figure 2 shows the mechanisms of actions of GLP-1 agonists in improving diabetes. A concern with the use of GLP-1 agonists is the high rates of discontinuation by patients, often due to pronounced gastrointestinal side effects of nausea, diarrhoea or vomiting which are commonly reported. Mostly, these are self-limiting presentations that resolve with time[80]. Furthermore, the use of GLP-1 agonists was previously thought to be associated with pancreatitis, and the development of certain types of cancer, such as pancreatic and thyroid cancer[86]. However, a meta-analysis by Abd El Aziz *et al*[87] argues that there is no significant risk of developing pancreatitis or malignancy secondary to GLP-1 agonist therapy. It is also thought that GLP-1 agonists are expected to cause a modest rise in lipase and amylase, which occasionally led to the misdiagnosis of pancreatitis in the previously reported data.

SGLT-2 inhibitors

Use of SGLT-2 inhibitors have been an important area of research in the last few years in many clinical trials, with great developments and changes in diabetes, cardiovascular and renal guidelines recently (Table 2). Their main mechanism of action is the reduction of glucose reabsorption in the renal tubules, resulting in increased glucose excretion in the urine[88]. They have been associated with a reduction in HbA1c of about 0.69% and a weight loss between 0.9-2.5 kg[63]. Weight loss is thought to occur due to caloric deficit from impaired glucose reabsorption from the kidney. Studies have shown improvement in waist circumference, central obesity, and visceral adiposity, all of which are features of diabetes as well as metabolic syndrome[89].

There has been extensive research into the role of SGLT-2 inhibitors in improving diabetes, cardiovascular and renal morbidity. A recent meta-analysis by Giugliano *et al*[90] revealed a reduction in hospitalisation or death from heart failure by 23%, with significantly reduced risk in every trial included. Results were comparable in patients with and without diabetes, indicating that SGLT-2 inhibitors have significant cardiovascular benefits in both groups of patients. Therefore, significant cardiovascular risk may be observed in diabetes patients.

Another meta-analysis of 8 trials, demonstrated the benefits on renal mortality and morbidity through the use of SGLT-2 inhibitors, with an overall reduced risk by 35%[91]. Data was strongest for canagliflozin, with significantly positive results in every trial[90,91]. The EMPEROR-R trial further

Table 1 The benefits of different glucagon-like peptide-1 agonist molecules in the management of diabetes based on recent landmark clinical trials[103]

Drug molecule	Mean weight reduction in kg (95%CI)	Mean % HbA1c reduction (95%CI)	Follow-up period (yr)
Exenatide (weekly)	-1.27 (-1.4 to -1.13)	-0.53 (-0.57 to -0.50)	3.2
Liraglutide	-2.3 (-2.5 to -2.0)	-0.40 (-0.45 to -0.34)	3.8
Lixisenatide	-0.7 (-0.9 to -0.5)	-0.27 (-0.31 to -0.22)	2.1
Albiglutide	-0.83 (-1.06 to -0.60)	-0.52 (-0.58 to -0.45)	1.5
Dulaglutide	-1.46 (-1.67 to -1.25)	-0.61 (-0.65 to -0.58)	5.4
Semaglutide	-2.87 (-3.47 to -2.28) for 0.5 mg -4.5 (-4.94 to -3.75) for 1 mg	-0.66 (-0.80 to -0.52) for 0.5 mg -1.05 (-1.19 to -0.91) for 1 mg	2.0

HbA1C: Haemoglobin; CI: Confidence interval.

Table 2 The beneficial effects of different sodium glucose cotransporter-2 inhibitors in the management of diabetes based on recent landmark clinical trials[104-108]

Ref.	Drug molecule	Mean weight reduction in kg (SE/95%CI)	Mean % haemoglobin reduction (95%CI)	Follow-up
Neal <i>et al</i> [104], 2017 (CANVAS)	Canagliflozin	-1.60 (-1.70 to -1.51)	-0.58 (-0.61 to -0.56)	3.5 yr
Wiviott <i>et al</i> [105], 2019 (DECLARE)	Dapagliflozin	-1.80 (-2.00 to -1.70)	-0.42 (-0.45 to -0.40)	4.2 yr
Häring <i>et al</i> [106], 2014 (EMPA-REG)	Empagliflozin	-1.63 (-2.11 to -1.5) for 10 mg -2.01 (-2.49 to -1.53) for 25 mg	-0.57 (-0.70 to -0.43) for 10 mg -0.64 (-0.77 to -0.50) for 25 mg	24 wk
Rosenstock <i>et al</i> [107], 2018 (VERTIS-MET)	Ertugliflozin	-3.00 (-3.30 to -2.70) for 5 mg -2.90 (-3.20 to -2.60) for 15 mg	-0.70 (-0.90 to -0.50) for 5 mg -0.90 (-1.00 to -0.70) for 15 mg	24 wk
Dagogo-Jack <i>et al</i> [108], 2018 (VERTIS-SITA)	Ertugliflozin	-2.0 (-2.7 to -1.4) for 5 mg -1.7 (-2.4 to -1.1) for 10 mg	-0.70 (-0.90 to -0.50) for 5 mg -0.80 (-0.90 to -0.60) for 10 mg	26 wk

HbA1C: Haemoglobin; CI: Confidence interval.

demonstrated that empagliflozin improved renal outcomes in patients with reduced ejection fraction or other types of heart failure[92].

The main risks associated with the use of SGLT-2 inhibitors include increased incidence of urinary tract infections and genital thrush, due to glycosuria, as well as euglycaemic ketoacidosis. However, significant benefits have been reported in obesity, renal and cardiovascular health, making this class of medication one of the most important in the management of diabetes and obesity, whether they are in co-existence or not. Patient counselling will help to identify and manage side effects promptly and efficiently (Figure 3).

Amylin analogues

Amylin is a pancreatic hormone secreted in response to the presence of nutrients in the gut. It modulates calcitonin and amylin receptors, and thereby regulates energy utilisation as well as body weight. This is achieved through the enhancement of satiety and delay in gastric emptying. Treatment with amylin analogues is not currently licensed in England but licensed and used abroad. It involves mealtime injections, similar to insulin[93]. Pramlintide, a type of amylin analogue has been associated with a reduction in HbA1c and also a weight loss of 1.5-2.5 kg[63]. Several studies have shown a significant reduction in body weight, with or without the presence of diabetes. However, most of these trials are pre-clinical and further research is needed to further evaluate the beneficial effects and safety profile of amylin analogues in day-to-day clinical practice[93].

Other anti-obesity drugs

In recent years, diabetic medications have been used more and more in the management of obesity. As discussed above, metformin, GLP-1 analogues and SGLT-2 inhibitors show significant weight loss effects. Amylin analogues, although not globally licensed, also demonstrate a beneficial weight loss

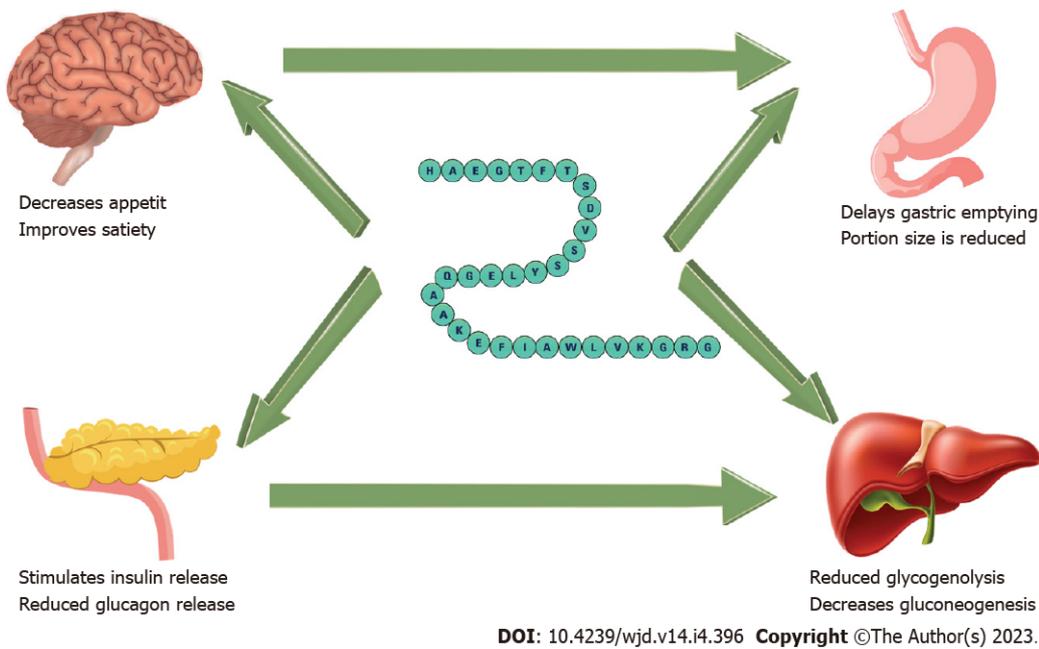


Figure 2 The mechanisms of actions of glucagon-like insulinotropic peptide-1 agonists in improving diabetes.

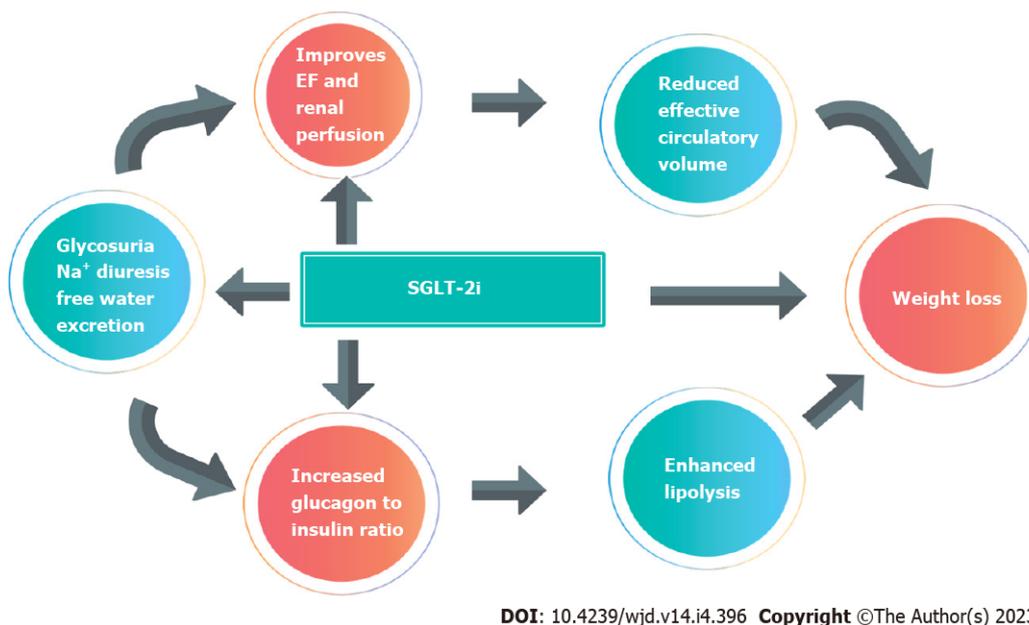


Figure 3 Mechanisms of actions of sodium glucose cotransporter-2 inhibitors in improving diabetes and their potential effects on organ protection such as kidney and heart. EF: Ejection fraction; SGLT-2i: Sodium glucose cotransporter-2 inhibitor.

effect. The recent literature mentions the discovery of GLP/GIP/glucagon receptor poly-agonists, with affinity to more than one receptor[94]. While most medications in this category are still in the experimental phase, a GLP1/GIP poly-agonist, Tirzepatide, demonstrated to have significant effects on weight loss in a recent phase 3 trial. This is a medication administered *via* weekly subcutaneous injection. This medication has recently been licensed for use in obese patients with T2DM[95].

Current developments in anti-obesity drugs seem to target leptin, ghrelin, GDF-15 pathways. Leptin sensitizers show promising results in patients with genetic obesity, although there is no significant weight reduction in obese patients without genetic cause, such as most diabetes patients[94]. Combination therapy with amylin analogues (pramlintide) has shown greater effects in weight reduction in obese rats (12.7%, $P < 0.01$)[96]. Hence the role of leptin sensitizers in managing diabetes is currently very limited and requires further investigation. Melanocortin 4 receptors (MC4R), stimulated by leptin to regulate energy expenditure, are other potential targets of novel anti-obesity medications. MC4R agonists, particularly setmelanotide, were licensed in the treatment of genetic obesity, but again,

their effect on polygenic obesity is not clear at this stage[94]. Treatments involving ghrelin modulation, a hormone that stimulates appetite, adipose tissue deposition and insulin secretion, are still under trials with no significant benefits demonstrated so far[94]. GDF-15 has been linked to metabolic disease, cardiovascular disease, and cancer. As mentioned earlier, metformin modulation of GDF-15 levels is a proposed mechanism of weight loss[58]. Exogenous administration of GDF15 has been shown to reduce body weight, however evidence comes from animal studies, therefore further research is required in this area[94].

BARIATRIC PROCEDURES

Bariatric endoscopy

Endoscopic bariatric surgery is a rapidly developing intervention that has revolutionised bariatric surgery. Endoscopic methods target the stomach, and through a variety of techniques aim to restrict gastric capacity, emptying or food absorption[97,98]. Intra-gastric balloon treatment (IGB) is the most widely used device since its introduction in 1982. IGB is generally recommended for patients with a body mass index (BMI) between 35-40 kg/m², or as an interim measure, with an aim for more definitive bariatric surgery, in patients with BMI > 40 kg/m². Studies have shown a BMI reduction of 5.7 kg/m² and improvement in diabetes and cardiovascular parameters with IGB[99]. Further techniques have been developed more recently, such as endoscopic sleeve surgery, where the capacity of the stomach is reduced. In this procedure, sutures are applied along the gastric wall, with the help of endoscopic equipment. Studies showed a 18% total body weight loss at 24 mo, with relatively low adverse effect profile[100].

Metabolic surgery

Bariatric surgery continues to be the most effective mode of definitive treatment for marked weight loss and diabetes. A recent review by Roth *et al*[101] reviewed the current literature around weight loss and the side effect profile depending on the type of metabolic surgery. Duodenal switch was associated with the most weight loss, of 70%-80% at 2 years, and resolution of obesity and diabetes related comorbidities. Roux-en-Y bypass and sleeve gastrectomy showed similar reduction in BMI, ranging between 60%-70%, with studies failing to demonstrate superiority of one over the other. Lower rates of diabetes remission were observed in insulin dependent diabetics following bariatric surgery compared to patients on oral agents, with rates of 16% *vs* 56% at 12 years. In terms of cardiovascular disease, metabolic surgery was shown to improve 5-year survival from coronary artery disease, in diabetic patients who are insulin treated[101]. Robotic assisted surgery is becoming increasingly more prominent, with data so far showing similar outcomes in robotic and laparoscopic bariatric procedures [102].

FUTURE CONSIDERATIONS

The last few years have seen significant developments in the management of obesity and diabetes. Numerous trials revealed the benefits of SGLT-2 inhibitors and GLP-1 agonists in both achieving good glycaemic control as well as weight loss as summarised earlier. Ongoing research and developments in anti-obesity pharmacopeia show promising results, with anti-obesity medication targeting various hormones involved in the pathophysiological process of appetite, satiety, and adipose tissue deposition. This area of research is still in its infancy, with most trials still in the early stages. Studies in human subjects are yet to be developed. Modulation of leptin and ghrelin shows promising results in animal studies and shall be a future topic of research. The new concept of the gut microbiome and its effects on energy expenditure and metabolism is another area where further research is required, in order to further understand its contribution to obesity. With rapidly evolving technology, it is expected that less invasive endoscopic and robotic bariatric techniques will soon be developed for bariatric surgery. An algorithm for management of diabetes is shown in [Figure 4](#).

CONCLUSION

With the obesity epidemic, diabetes, and the evident link between the two, the diabetes, is a widely recognised emerging public health issue. Understanding the pathophysiological mechanisms involved in the interplay between diabetes and obesity is paramount, both for primary as well as secondary care physicians, in order to guide the clinical management of such patients. Our paper offers a summary of the current concepts in the pathophysiology and management of diabetes. The emerging theories around the impact of the gut microbiome on diabetes and obesity are still in their infancy but show promising results so far. The potential role of metformin in modulating the gut microbiome is an area

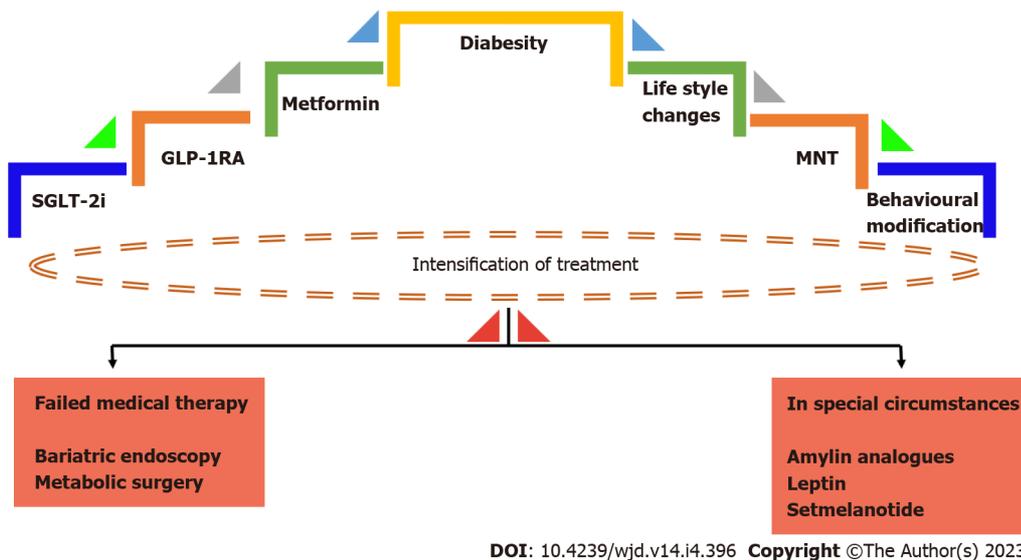


Figure 4 An evidence-based management algorithm for the management of diabetes. GLP-1RA: Glucagon-like insulinotropic peptide; MNT: Medical nutrition therapy; SGLT-2i: Sodium glucose cotransporter-2 inhibitor.

that requires further investigation. Future research and better understanding of the involvement of gut bacteria in energy expenditure and the development of diabetes may guide the development of modulatory treatments and reduce risk in affected individuals.

Diabetes is associated with a host of complications, including MAFLD. Our review of literature suggests that the majority of patients with T2DM exhibit hepatic steatosis in the initial stages of their diabetes, without derangement of liver function. Occult liver disease may be difficult to diagnose unless liver biopsy is carried out, and understandably this would not be indicated as a baseline investigation in all obese diabetic patients. Clinicians should be mindful of the likelihood of MAFLD in obese diabetics, and offer management to improve weight and glycaemic control, which will in turn aid to reduce the long-term consequences of hepatic steatosis. Early identification and management of OSA is also important, as intervention in the form of CPAP has been shown to improve insulin resistance. Therefore, early diagnosis and management of OSA may aid glycaemic control, whereas missing this diagnosis may make glycaemic management more challenging, leading to further complications. Additionally, monitoring for cardiovascular disease, potentially with coronary artery calcium score, as well as early cardiology referral where indicated, would be important in order to address and minimize cardiovascular mortality and morbidity.

Lifestyle modification remains paramount, but it is important to set realistic achievable targets which are agreed between the patient and the multi-disciplinary team. From our review, we could infer that exercise alone is not expected to result in significant improvement in diabetic control, unless accompanied by weight loss. On reviewing the recent literature, the common theme appears to be that a Mediterranean diet may be beneficial in achieving weight loss and better glycaemic control in diabetes patients. The Mediterranean diet has been shown to have a greater impact on overall HbA1c when compared to low carbohydrate, high protein, and low fat dietary modifications. When combined with exercise, dietary modification appears to be more effective, with a significant chance of inducing T2DM remission if the patient is motivated and adheres to the interventions offered.

Rapid advances in pharmacotherapy have revealed the dual action of medications such as GLP-1 agonists and SGLT-2 inhibitors in improving diabetes and achieving weight loss. The most recent relevant trials as summarised in our review show promising results, with improvement in both weight and HbA1c with these agents. GLP-1 agonists and SGLT-2 inhibitors are expected to play a pivotal role in the management of diabetes in the coming years, with an increasing number of patients being prescribed these medications.

Newly proposed mechanisms of action of metformin to improve weight and glycaemic control have been published, and these include a potential effect on the gut microbiome, and an association with increased GDF15 levels. Further research is required to confirm these modulatory effects, but metformin remains one of the first line medications for the treatment of diabetes. Rapid advances in technology show a promising future for bariatric surgery, which can be very effective in achieving weight loss and reversing diabetes. Therefore, an early referral to weight management services for patients that fulfil the relevant criteria, and timely intervention could lead to early resolution of the disease.

FOOTNOTES

Author contributions: Michaelidou M substantially contributed to literature search, interpretation of relevant literature, article drafting, and revision; Pappachan JM conceived the idea, contributed to the interpretation of relevant literature, and revision of the paper; Jeeyavudeen MS contributed to the conception and design of the article, literature search and revision of the article created the figures; and all authors have read and approved the final version of the manuscript.

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