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Medical Management of Diabesity: Do We Have Realistic Targets?

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Abstract
Purpose of Review The global prevalence of "diabesity"—diabetes related to obesity—is increasing steadily over the past few decades because of the obesity epidemic. Although bariatric surgery is an effective treatment option for patients with diabesity, its limited availability, invasiveness, relatively high costs and the potential for surgical and postsurgical complications restrict its widespread use. Therefore, medical management is the only option for a majority of patients with diabesity. Diabetes control with several anti-diabetic agents, including insulin, causes weight gain with probability of worsening diabesity. Rational use of anti-diabetic medications with weight loss potential in varying combinations may help to address this key issue for long-term management of diabesity. There is no consensus on such an approach from different professional bodies like American Diabetes Association, European Association for Study of Diabetes, or International Diabetes Federation. We attempt to discuss the key issues and realistic targets for diabesity management in this paper.
Recent Findings Rational use of anti-diabetic combinations can mitigate worsening of diabesity to some extent while managing patients.
Summary Retrospective studies showed that combination therapy with glucagon-like peptide-1 (GLP-1) receptor agonists and sodium glucose co-transporter 2 (SGLT-2) inhibitors, when administered along with other anti-diabetic medications, offer the best therapeutic benefit in the medical management of diabesity. Different combinations of other anti-diabetic drugs with minimum weight gain potential were also found useful. Because of insufficient evidence based on prospective randomised controlled trials (RCTs), future research should focus on evolving the appropriate rational drug combinations for the medical management of diabesity.

Keywords Diabesity · Anti-diabetic medication · Anti-diabetic drug combination · Anti-obesity agents · Management of diabesity

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Introduction

The obesity epidemic is hitting the global population with the force of an approaching tsunami that affected 13% of adults, with a disease prevalence of >600 million obese, and >1.9 billion overweight individuals (39%) worldwide in the year 2014 [1•]. Although a major proportion of this population reside in the developed countries, overweight and obesity are becoming serious healthcare challenges even in developing countries. Excess body weight is a risk factor for a multitude of diseases such as type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease, hypertension, heart failure, ischemic heart disease, stroke, obstructive sleep apnoea, cancers and osteoarthritis. Recent studies from the USA showed that 18% of 6–11-year olds and 21% of 12–19-year olds had BMI ≥ 95th percentile [2•], and paediatric obesity accounted for 45% of new onset T2DM [3]. "Diabesity" is the term used

to describe the pathophysiological interlink between T2DM and obesity/overweight.

Sims et al. first coined the term "diabesity" in early 1970s to describe the strong association between diabetes and obesity when they co-existed in an individual [4••]. Excess weight gain is associated with accumulation visceral fat that increases the insulin resistance and lead on to T2DM. Although there are many drugs available for successful management of T2DM, the medical management of obesity is always problematic to clinicians. Bariatric surgery is proven to be the best option for management of obesity that results in diabetes remission in a large proportion of patients [5•, 6•, 7] and therefore the most promising treatment modality for diabesity management. However, bariatric surgery is invasive, unacceptable to many patients, expensive, sometimes associated with long-term adverse health consequences, and often an underutilised treatment option for care of patients with diabesity. Until today, there are no formal guidelines from professional bodies such as American Diabetes Association (ADA), European Association for Study of Diabetes (EASD), International Diabetes Federation (IDF) or Diabetes UK (DUK) on optimal medical management of diabesity. Therefore, we discuss the medical management options for diabesity with an attempt to find the appropriate targets for these patients through this article.

Pathophysiology of Diabesity

There is a clear and well-established interlink between obesity, insulin resistance and T2DM [8••]. Positive energy balance as a consequence of overconsumption or underutilisation results in storage of energy substrates mainly as fat in the adipose tissues. Although this adiposity can be general, predominance in visceral tissues is observed in the later years of adult human life [9]. Visceral adiposity results in significantly higher metabolic risk for the development of T2DM compared with generalised obesity. Adipose tissue plays major roles in the pathophysiology of T2DM through a multitude of complex neurochemical, genetic, inflammatory and hormonal mechanisms.

Three main hypotheses have been proposed to explain the interplay between obesity and pathophysiological mechanisms resulting in diabesity [10]. (1) The "inflammation hypothesis" proposes causal links between pro-inflammatory cytokines such as interleukins, tumour necrosis factor-α and monocyte chemotactic protein-1 produced by excess adipose tissues and increased insulin resistance that lead on to T2DM. (2) The "lipid overflow hypothesis" says that lipid metabolites released from fatty tissues inhibit insulin signal transduction and induce insulin resistance. (3) The "adipokine hypothesis" suggests role of different hormonal and chemical substances secreted from adipose tissues, collectively termed as adipokines, induce inflammatory and metabolic cascades resulting in insulin resistance and T2DM.

These biochemical and hormonal mechanisms, along with abnormal genetic background and lifestyle factors, lead on to the complex molecular cascades that result in diabesity. Recent evidence also strongly support the genetic links between obesity and the role of central nervous system including those related to synaptic function, glutamate signalling, insulin secretion/action, energy metabolism, lipid biology and adipogenesis [11••].

Challenges in Diabesity Management

Considering the significant microvascular, macrovascular and metabolic risks posed by poor control of T2DM, optimal glycemic management becomes the first priority in patients with diabesity. However, many of the anti-diabetic pharmaceutical agents including insulin are associated with a risk of weight gain in patients with T2DM, thus theoretically worsen the diabesity. Therefore, balancing adequate glycemic control and diabesity risk becomes a priority for clinicians in choosing the anti-diabetic drug regimens. A multi-prong approach with setting up of immediate and long-term targets thus becomes mandatory in the successful management of diabesity.

Lifestyle Changes Change in lifestyle is the first step in management of T2DM as the disease has strong association with adverse lifestyles. Obesity is largely a consequence of imbalance between overconsumption and underutilisation of nutritional energy intake, and therefore, the first target in obesity and diabesity management should be intense lifestyle changes to break this state of disequilibrium.

Intense lifestyle intervention with regular physical activity and dietary modifications have been found to be helpful in prevention of T2DM in overweight or obese subjects in recent meta-analyses [12•, 13]. Furthermore, modest reductions in weight and glycated haemoglobin (HbA1c) levels were observed in the intervention group compared to normally treated cases indicating that intense lifestyle changes are useful in the management of diabesity [14, 15•]. For meaningful reductions of HbA1c, lipids and blood pressure, more than 5% weight loss should be targeted while managing diabesity with intense lifestyle changes [15•]. However, there is no clear evidence on the long-term and sustainable benefits of lifestyle interventions on diabesity management. Behavioural, psychological and environmental factors often influence the sustainability of such interventions. Although there are reports of significant improvements diabesity parameters with low carbohydrate/very low carbohydrate diets when combined with various medical interventions [16, 17], implementation of such dietary interventions for patients in a routine medical practice setting are challenging.

Insulin for Patients with Diabesity Because insulin is an anabolic hormone, insulin use is associated with weight gain

that usually has a linear relationship to the amount of insulin used. When glycemic control becomes the priority, the necessity for insulin treatment usually supersedes obesity management that may undermine the importance of addressing diabesity. In circumstances when immediate improvement in glycemic control is desirable such as symptomatic patients, pre-operative stabilization, patients with hyperglycemia and those with established diabetic complications which can deteriorate, insulin should be commenced.

However, clinicians should always consider the adverse long-term implications of diabesity and should devise optimal insulin regimes while treating obese T2DM cases. The intensity of insulin regimens has been found to be strongly associated with the degree of weight gain [18], and therefore, the clinicians' approach to diabesity management should balance the pros and cons of individual insulin regimes.

Metformin Although metformin is usually labelled as a weight-neutral agent in the management of T2DM, a previous review of multiple clinical trials showed modest reductions in body weight among metformin-treated patients compared with baseline or comparator drugs [19]. A recent meta-analysis also showed additional evidence for the weight loss benefit (mean weight loss, 1.1 kg) of metformin as an anti-diabetic agent [20••]. Metformin inhibits hepatic glucose production and gluconeogenesis, indirectly improves peripheral (muscle) tissue insulin sensitivity and exerts anorexiant effect in the users—all these effects benefit the diabesity management. Results of the Diabetes Prevention Program (DPP) clearly demonstrated that metformin treatment was associated with a 31% reduction of incident diabetes in high-risk patients with impaired glucose tolerance (IGT) [21, 22]. Metformin use is also associated with improvements in several health problems directly or indirectly linked with diabesity such as polycystic ovary syndrome (PCOS) [23, 24], gestational diabetes mellitus (GDM) [25, 26•], non-alcoholic fatty liver disease (NAFLD) [27•] and cancer [28, 29]. All these data suggest clear benefits of metformin in patients with diabesity.

Thiazolidinediones Medications of this class exert the anti-diabetic effect mainly through the insulin-sensitising effect. The main drug molecule of this group widely available for use presently is pioglitazone, after the controversy about increased risk of myocardial infarction with use of rosiglitazone in patients with T2DM. Although pioglitazone is useful as an add-on therapy with other anti-diabetic medications, the drug use is associated with weight gain in patients, and may theoretically worsen diabesity. Although a recent meta-analysis showed a mean weight gain of 2.6 kg with this drug [20••], the drug improves NAFLD [30], a consequence of metabolic syndrome and diabesity. However, pioglitazone use was found to be associated with increased risk of urinary bladder cancer in a recent large population-based study, although rosiglitazone did not show this tendency [31]. Use of thiazolidinediones were also found to be associated with increased risk of secondary osteoporosis [32].

Glucagon-Like Peptide-1 Receptor Agonists Glucagon-like peptide-1 (GLP-1) is an incretin hormone produced by the entero-endocrine cells in response to food intake that controls glucose metabolism and energy homeostasis through its effects on pancreatic islet cell hormone secretion, upper gastrointestinal motility and eating behaviour. GLP-1 analogues have been in the market for more than a decade for management of diabesity. Currently used drugs in this group include exenatide, liraglutide, lixisenatide, albiglutide and dulaglutide, though newer molecules continue to appear. Although the weight loss potential of individual molecules among GLP-1 agonists may vary, the average loss of weight associated with the most popular GLP-1 analogue drug liraglutide (1.2 mg daily) was reported to be 1.7 kg in a recent meta-analysis [20••]. However, there may be marked variability in the weight loss potential of GLP-1 agonists with much higher benefit in many patients.

Avoidance of initiation/increment of the dose of other anti-diabetic medications that may worsen diabesity management, especially insulin, are the main advantages of GLP-1 agonist use in many patients with diabesity. Multiple health benefits in terms of cardiovascular protection [33••], improvements in adverse lipid profile, NAFLD, nephropathy and pancreatic β-cell function, reduction of blood pressure and neuronal protection have been reported with GLP-1 agonist therapy [34, 35]. All these complications inherent to patients with diabesity should prompt clinicians to choose GLP-1 agonist therapy in cases where clinical situation is favourable. Concerns about the elevated risk of pancreatitis and cancer with the use of these drugs have been discredited by recent meta-analyses [36, 37, 38•]. High-dose liraglutide (3 mg daily) therapy has been found to be beneficial in medical management of obesity in patients without diabetes in a recent clinical trial [39•]. A mean weight reduction of 8.4 ± 7.3 kg has been reported in treated group compared with placebo, with 63.2% (vs. 27.1%) achieving >5%, 33.1% (vs. 10.6%) achieving >10% and 14.4% (vs. 3.5%) achieving >15% weight loss, respectively. Currently, this supra-maximal dose of liraglutide (usual maximal dose for diabetes management is 1.8 mg daily) treatment has approval from US Food and Drug Administration (FDA) and European Medicine Agency as an anti-obesity drug, although many countries including the UK have not yet given licence for the use. As obesity is the highest risk factor T2DM, benefit of this obesity treatment for prevention of diabesity should be a serious consideration for clinicians.

Dipeptidyl Peptidase-4 Inhibitors Mechanism of action of dipeptidyl peptidase-4 (DPP-4) inhibitors are similar that of GLP-1 analogues. These drugs inhibit the rapid metabolism of

endogenously secreted GLP-1 in the gut by DPP-4 enzyme and prolong the ultra-short duration of action of incretin hormones. Currently available molecules in this class of drugs include sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, teneligliptin and anagliptin, although newer agents are emerging in the global pharmaceutical market. A reduction in HbA1c level by 0.5–1.0% has been reported without the risk of weight gain with DPP-4 inhibitors [34]. This property should encourage clinicians to use the drug class for management of diabesity in patients without contraindications. Significantly better response in HbA1c reduction and pancreatic β-cell function has been observed in Asians compared with Caucasian patients treated with these medications [40]. This observation is especially noteworthy because diabesity is well known to be worse among Asians compared with Caucasians having comparable BMIs. Although the cardiovascular safety of various DPP-4 inhibitors has been well tested in recent clinical trials and observational studies with some promising results [41•, 42, 43], these medications were found to increase the hospitalisation rates in patients with established heart failure [44••]. Heart failure being a common association in cases with diabesity, DPP-4 inhibitors should be used with caution in obese diabetics.

Sodium Glucose Co-transporter 2 Inhibitors In a healthy adult, kidney glomeruli filter approximately 180 g of glucose/day, the most of which is reabsorbed from the tubules by sodium glucose co-transporter 2 (SGLT-2), the major co-transporter of renal glucose re-absorption. Therefore, SGLT-2 inhibition results excretion of a significant proportion of the glucose entering the kidney tubules by filtration, with an insulin-independent glucose lowering mechanism compared with most other anti-diabetic medications. Currently available SGLT-2 inhibitors are dapagliflozin, canagliflozin and empagliflozin. Although these drugs can be used alone for diabetes management, usual use is as add-on therapy with other anti-diabetic medications.

SGLT-2 inhibitors were associated with HbA1c reduction of 0.66% (95% CI, 0.73% to 0.58%), body weight loss of 1.8 kg (95% CI, 3.50 to 0.11 kg; $p < 0.05$) and a systolic blood pressure drop of 4.45 mmHg (95% CI, 5.73 to 3.18 mmHg; $p < 0.05$) compared with placebo in a meta-analysis [45••], all positive effects in managing patients with diabesity. Comparative reductions in body weight, HbA1c levels and blood pressure were reported in other more recent meta-analyses also with SGLT-2 inhibitors [46, 47]. Reduction of cardiovascular mortality and improvement of renal outcomes are the other promising benefits reported recently with these novel class of drugs that would be very useful in management of patients with diabesity [48••, 49]. Increased risk of urinary tract infections and genital fungal infections are the main side effects encountered that may lead on to discontinuation of these medications [45–49].

Sulphonylureas Sulphonylureas are less often used by most diabetolgists for T2DM because of the weight gain potential and risk of hypoglycaemia. Different agents in clinical use are gliclazide, glimepiride, glipizide and glybenclamide, with reported average weight gain of 1.8–2.6 kg in a recent meta-analysis [20••]. This group of drugs may be used as a single agent in exceptional circumstances (especially when other medications are contra-indicated) or as an add-on therapy with other anti-diabetic medications [50•]. However, the chance of worsening diabesity with this approach should be taken into account before commencing in obese T2DM cases.

Other Anti-obesity Medications Several anti-obesity medications were marketed in recent years by the pharmaceutical industry with claims of significant benefits for obese patients. Few of them were withdrawn later because of serious adverse effects. When combined with lifestyle interventions, few of these drugs such as phentermine/topiramate-extended release (ER), orlistat and lorcaserin were shown to cause meaningful weight loss of ≥5% at the end of 1 year [51]. Lorcaserin is a selective serotonin agonist that decreases food intake, while phentermine/topiramate-ER combination suppresses appetite and enhances satiety. Both these agents received FDA approval in recent years and were shown to be beneficial in obese patients with co-morbidities including diabesity [51, 52]. With lifestyle interventions, use of orlistat was associated with significant weight loss and improvement of diabetes in obese patients [53]. A reported overall mean weight reduction of 4.25 kg (95% CI, 4.5 to 3.9 kg; $p < 0.001$) when used in appropriate clinical setting makes this drug a promising agent in diabesity management.

Rationalising Drug Combination Regimens

Combination therapy is usually necessary in most patients with diabesity and rationalising the drug regime can be a challenge to clinicians while addressing the issue. Most patients with T2DM need multiple anti-diabetic drugs for optimal glycemic control. As discussed in the previous sections, some of these medications including insulin have weight gain potential that should be a consideration in devising the anti-diabetic regime.

Metformin is the first-line drug for T2DM unless there is a contraindication (such as kidney or liver disease) or intolerance (mostly due to GI side effects). When control is inadequate with metformin alone, second-line drugs should be added that should be ideal with a weight loss potential or weight neutral for avoidance of worsening diabesity. A choice of the combination regimen depends on the baseline diabetes control and the patient preference. In a patient with poorly controlled diabetes, combining insulin with metformin should be the first choice for initial management because glucose toxicity (at pancreatic and target tissues of insulin action)

inherent to poor control is associated with a relative inefficiency of other anti-diabetic drugs in managing diabetes [54•, 55].

Metformin and Insulin When hyperglycemia is persistent with very poor glycemic control, addition of insulin to the anti-diabetic regime should be the first approach to control it, as insulin helps rapid improvement of glucose toxicity. Rapid achievement of normoglycemia with the treatment improves glucose toxicity and the related tissue damage [56–58]. In general, when HbA1c level is above 9%, insulin is always better than the other anti-diabetic agents for optimal glycemic control, because the HbA1c reduction achievable with each of the other agents is ≤1%, although fall in HbA1c levels may be higher in some patients with very high baseline levels. Adding a basal insulin is the usual initial approach to bring down elevated HbA1c levels that can be further modified if target glycemic control is not achieved [50•].

Although addition of insulin to metformin was associated with better glycemic control compared with other anti-diabetic agents in a meta-analysis, weight gain and hypoglycaemia were the major drawbacks of addition of insulin [59]. Weight gain ranging from 1.8 to 3.0 kg was reported in another meta-analysis [60]. In a large placebo-controlled clinical trial of combination therapy of insulin and metformin, insulin when combined with metformin was associated with significantly less weight gain compared to insulin and placebo (1.6 vs. 4.2 kg) [61]. Insulin dose required for control of hyperglycemia was also significantly less in the metformin arm (1.04 vs. 1.36 IU/kg), clearly indicating the advantage of this combination in patients with diabesity and poor glycemic control.

Metformin and Sulphonylure Addition of sulphonylureas to metformin worsens diabesity as weight gain is a disadvantage of such a regimen. However, this group of drugs are economic and effective in controlling hyperglycemia when used as an add-on therapy in many cases. Improvement of HbA1c and achievement of glycemic targets were observed in a significant proportion of patients on this combination regime, especially when started early in the course of T2DM [62, 63]. Increased risk of hypoglycaemia, nervous system side effects and reduction of high-density lipoprotein levels were the other disadvantages of combination regime. Although reported gastrointestinal side effects related to combination therapy was lower [63], the metformin dose used in combination regimes in randomised trials were lower than conventional dose of the drug when used as monotherapy [64••]. However, metformin monotherapy was associated with better weight loss potential when compared with the combination regime (mean difference, −2.3 kg (95% CI, −3.0 to −1.6 kg; $p < 0.05$)) [64], an important consideration in diabesity management.

Metformin and GLP-1 Receptor Agonists A recent network meta-analysis showed that GLP-1 receptor agonists when combined with metformin resulted in average weight loss of 1.15–2.26 kg with an improvement HbA1c level in significant proportion of individuals [65]. Another meta-analysis comparing addition of GLP-1 receptor agonists vs. insulin to metformin-treated T2DM cases demonstrated an achievement of target HbA1c by 31.7% of treated patients (31.1% with premixed insulin) with a weight loss of −5.27 kg (95% CI, −6.17 to −4.36 kg; $p < 0.05$) compared with premixed insulin [66]. Addition of GLP-1 receptor agonists to metformin resulted in an HbA1c reduction of 0.82% (95% CI, 1.05%–0.59%; $p < 0.05$) that was comparable with addition of basal insulin in another meta-analysis [60]. Improvement of adverse lipid profile inherent to metabolic syndrome compared with many other noninsulin anti-diabetic agents was another advantage of addition of GLP-1 receptor agonists to metformin for control of T2 DM [67]. All these results should be very encouraging to clinicians in managing diabesity. However, the tolerability of combination regime because of gastrointestinal side effects and in patients with renal impairment can be issues in some patients.

Metformin and DPP-4 Inhibitors Being weight neutral with different mechanisms of action, a combination of these two agents would appear rational in terms of diabesity management. In a recent study examining effect of adding sitagliptin or sulphonylurea to metformin for elderly patients with T2DM, comparable glycemic control without risk of hypoglycaemia in the sitagliptin arm was observed [68]. Significant body weight loss also was observed in sitagliptin group in this study, favouring this combination regime in patients with diabesity. However, the efficacy of DPP-4 inhibitors in glycemic control seems to diminish with time [69].

Metformin and SGLT-2 Inhibitors Although the experience with this combination regime is limited, preliminary results are very encouraging in terms of glycemic control, weight loss and improvement of blood pressure, with slightly elevated risk of genital tract fungal infections and urinary infections [70, 71, 72•]. Reductions in HbA1c of 0.66%, fasting glucose of 1.49 mmol/L and body weight of 2.09–2.66%, and improvement of β-cell function in terms of homeostasis model assessment (HOMA2-%B) of 15.59% have been reported in a recent meta-analysis of canagliflozin–metformin combination therapy with mild increase in incidence of genital tract mycosis and polyuria (increased urine frequency) in the treated group [71]. Therefore, combination therapy with metformin and SGLT-2 inhibitors should be encouraging to clinicians managing diabesity.

Metformin and Thiazolidinediones Although this combination may be effective in glycemic control, weight gain may be a major concern in diabesity management [71]. However, this combination regimen may be a good choice in patients with

NAFLD, an important consequence of diabesity [27, 73, 74•]. A significant proportion of patients with NAFLD progresses to end-stage liver disease, and the combination regimen may retard progression of the disease especially when combined with lifestyle changes targeting weight loss.

Other Dual-Agent Therapy in Metformin Intolerance/Contraindications A variety of different drug combinations such as sulphonylurea–thiazolidinediones, sulphonylurea–GLP-1 agonists, sulphonylurea–DPP-4, sulphonylurea–SGLT-2, DPP-4–thiazolidinediones and DPP-4–SGLT-2, along with varying combinations of one of these agents with insulin may be used for management of T2DM. However, weight neutrality/potential for least weight gain should be the first consideration in choosing the regime in patients with diabesity.

Multidrug Combination Therapy Patients with diabesity often need multiple anti-diabetic drug combination for optimal glycemic control. Combination regimens with least potential for weight gain should be chosen by the clinician considering the long-term implications of diabesity. However, reluctance from patients on commencement of injectable drugs such as GLP-1 receptor agonists may pose hindrance to clinician in tailoring optimal diabesity regimens. Combination of oral medications with weight loss potential such as metformin, DPP-4 inhibitor and SGLT-2 inhibitor would be an ideal choice in such circumstances [72•, 74•]. In a recent meta-analysis, addition of other anti-diabetic agents to the conventional and popular old regime of metformin and sulphonylurea demonstrated significant improvements in HbA1c with all the agents, although addition of SGLT-2 inhibitors only showed a weight loss of 1.43–2.07 kg [75•]. Addition of thiazolidinediones, insulin glargine and sitagliptin to the above regime resulted in weight gain (1.48–3.62 kg) compared with placebo/control in this study. Another more recent meta-analysis showed that addition of either a SGLT-2 inhibitor or GLP-1 receptor agonist resulted in weight loss of 1.71 and 1.14 kg, respectively, and reduction in systolic blood pressure of 3.73 and 2.90 mmHg, respectively, with improvements in glycemic control in a failing regime of metformin–sulphonylurea [76].

Rationale for GLP-1 and SGLT-2 Combination in Diabesity Management The theoretical advantage of weight loss potential with these two agents forms the scientific rationale for combining them for diabesity management although there is insufficient data on this combination regime. Two recent retrospective cohort studies showed promising results of this combination especially when used with conventional anti-diabetic agents [77, 78••]. Saroka et al. reported significant reductions in HbA1c and body weight by 0.39% and 4.6 kg, respectively, when canagliflozin was added to GLP-1 receptor agonist-containing anti-diabetic regimens, and Deol et al. reported improvements in these parameters (1.05% and 3.07 kg, respectively) when SGLT-2 inhibitors were added to similar regimens. Significant reduction of insulin doses (6.8 units) at 3–6 months follow-up was another very promising outcome of one of these short-term observational studies with further reductions in insulin doses, body weight and BMI (12 units, 8.31 kg and 2.65 kg/M^2, respectively) and improvement of HbA1c (1.13%) in a smaller sub-group who had a second follow-up at 9–12 months [78••]. This interesting clinical observation warrants further evaluation through long-term randomised controlled clinical trials for development of such treatment strategies in diabesity management.

One of the major clinical trial showed that the efficacy of SGLT-2 inhibitors in glycemic control gradually wean off with time [48••]. Increased glucagon production by pancreas may be one of the mechanisms for this phenomenon [79••]. GLP-1 receptor agonists suppress islet cell glucagon production and reduce the hepatic glucose output [80]. Therefore, a combination of these two classes of medications may result in drug synergism by counteracting the adverse metabolic consequences of each other, enhancing the efficiency in glycemic control. Moreover, both drug classes help weight loss, and thereby, the diabesity management. Additional benefits in terms of cardiovascular and renal protection were reported recently [33••, 34, 35, 48••, 49], which should encourage clinicians for rationalising the diabesity management with this new regime.

Table 1 shows the weight loss and HbA1c reduction potential of individual medications and drug combinations.

Glycemic and BMI Targets

Targets for glycemic control for patients with diabesity should be individualised taking into consideration the age, disease comorbidities, professional background, acceptability of drug regimens and long-term outcome goals. Glycemic targets need not be different from that for any patient with T2DM. Until today, there are no promising drug regimens that help patients to attain marked reduction of obesity, and the currently available drugs/regimens confer only modest weight loss benefit as discussed above. Therefore, the major long-term goal for patients should be the avoidance of weight gain that worsens diabesity. Although difficult, the goal may be achievable through a multi-prong approach by encouraging the patients to adopt healthy lifestyles and adhere to medication regimens, and a close follow-up with the clinicians who should revise the drug regimens as and when necessary with the latest scientific evidence.

What to Do When Targets Are Not Achieved?

Even with multidrug regimens, glycemic control can be an issue in many patients with diabesity. If the glycemic targets are not achieved, the clinician should always revisit the existing management plan/patient compliance and revise the

Table 1 Drugs and drug combinations used for medical management of diabesity with the effects on mean/average HbA1c reduction and weight loss from baseline

Drug molecule/combination	HbA1c reduction (95% CI)	Weight loss (95% CI)
Metformin	1.1% (1.19–1.01)	1.1 kg (0.31–1.83)
GLP-1 agonists	1.0% (0.5–1.5)	1.73 kg (2.4–1.06)
DPP-4 inhibitors	0.5–1.0%	Weight neutral
SGLT-2 inhibitors	0.66% (0.73–0.58)	1.8 kg (3.50–1.10)
Metformin + GLP-1 agonist	0.82% (1.05–0.59)	1.6 kg (2.12–1.08)
Metformin + DPP-4 inhibitors	0.64% (0.71–0.57)	0.21 kg (−0.1–0.53)
Metformin + SGLT-2 inhibitors	0.72% (0.85–0.59)	2.15 kg (2.63–1.67)
GLP-1 agonists + SGLT-2 inhibitors	0.39–1.05%	3.07–4.6 kg

The data for drug combination regimens are those with additional improvement in these parameters after commencement of the treatment

Abbreviations: *HbA1c* glycated haemoglobin, *95% CI* 95% confidence interval, *GLP-1* glucagon-like peptide-1, *DPP-4* dipeptidyl peptidase-4, *SGLT-2* sodium glucose co-transporter 2

plan as and when necessary. A thorough modification of management plan and repeated discussions about the importance of compliance (when adherence is an issue) may sometimes help in attaining the targets. Although bariatric procedures were not planned previously for various reasons, a discussion/re-discussion of the benefits should be done where appropriate. Finally, modification of the targets as per the clinical situation, balancing the risks and benefits, by the clinician and the patient should be done in some cases realistically.

Algorithm for Diabesity Management

As mentioned above, the algorithm for diabesity management should be individualised by the clinician and patient. A broad evidence-based algorithm for glycemic management in diabesity is shown in Fig. 1. Multidisciplinary and multipronged approach involving changes in diet, lifestyle and pharmacotherapy should be devised by the healthcare professionals for a rational and scientific algorithm design for patients with diabesity, taking the age, co-morbidities, social and cultural aspects of individual cases into consideration.

Conclusions

Diabesity has emerged as a major public health issue in the past few decades because of the global obesity epidemic. The pathophysiology of diabesity is complex that involves multiple neuro-chemical, genetic, inflammatory and hormonal mechanisms. Although bariatric surgery is a very promising treatment option for the successful management of diabesity, limited availability, high costs, invasiveness of the procedure and chances of immediate and long-term complications, make this choice unacceptable to many patients.

There are no clear guidelines from different professional bodies on the optimal medical management of diabesity. Rational combinations of different anti-diabetic drugs discussed in this paper help the clinician to choose the appropriate regimens for the management of diabesity. Immediate and long-term treatment goals should be devised liaising with the patient and consideration of the clinical scenario for individualised action plans. Patients should be followed up closely with appropriate revision/modification of the treatment regime to achieve the targets. Prompt and regular update

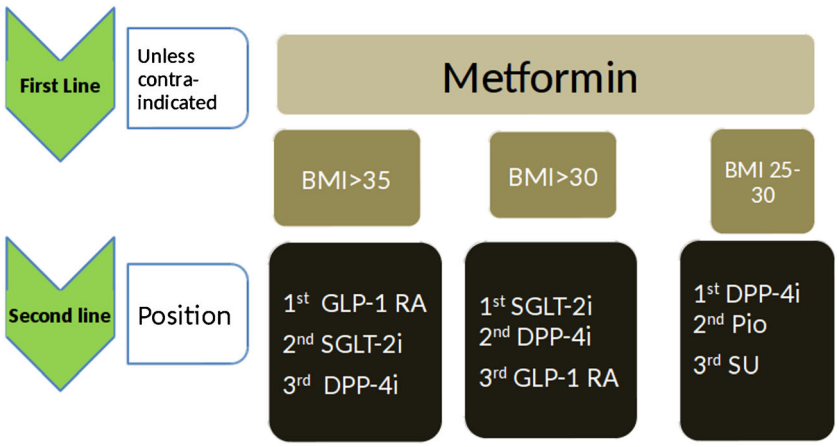

Fig. 1 Algorithm for glycemic management in patients with diabesity. Abbreviations: *GLP-1RA* glucagon-like peptide-1 receptor agonist, *SGLT-2i* sodium glucose co-transporter 2 inhibitor, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *Pio* pioglitazone, *SU* sulphonyurea

of scientific evidence should also help clinicians to devise optimal management strategies for this alarming global epidemic.

Compliance with Ethics Standard

Conflict of Interest Joseph M. Pappachan declares that he has no conflict of interest. Ananth K. Viswanath received lecture fees from MSD, NovoNordisk, Takeda, Eli Lilly and Jansen and sponsorship from NovoNordisk, Takeda, Novartis and Jansen to attend international conferences.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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