

ACHIEVING EFFECTIVE WEIGHT LOSS FOR TYPE 2 DIABETES MELLITUS CONTROL: FROM EVIDENCE TO PRACTICE

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ABSTRACT

Type 2 diabetes mellitus (T2DM) poses a significant public health concern in Singapore. It is well established that T2DM is strongly associated with obesity. In Singapore, the prevalence of obesity and overweight in adults has been increasing over the last two decades. By 2050, the prevalence of obesity in the nation is predicted to reach 15.9 percent, a rise from 4.3 percent in 1990. The total prevalence of T2DM is also projected to rise to 15 percent in 2050, which was 7.3 percent in 1990, in tandem with the rise in obesity prevalence. Moderate and sustained weight loss (5-10 percent) improves glycaemic control and cardiovascular risk factors in overweight or obese patients with T2DM. Disease-modifying effects in T2DM and improvement in long-term cardiovascular outcomes and mortality are associated with larger and sustained weight losses (>10 percent). In this article, we highlight the growing burden of T2DM and its complications in Singapore and the role of weight loss in T2DM control. This article aims to provide an overview of multidisciplinary/multipronged strategies (lifestyle interventions, patient-centred approach with preferential use of glucose-lowering medications of weight neutral/weight loss effect, consideration of pharmacotherapy for weight loss and metabolic surgery) to achieve effective weight loss for T2DM control.

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INTRODUCTION

Diabetes is a serious and highly prevalent public health concern globally. An estimated 537 million adults (aged: 20-79 years; one in ten) are currently living with diabetes globally and this figure is predicted to rise to over 780 million by 2045.¹ The International Diabetes Federation reported that diabetes or its complications was estimated to cause 67 million deaths and cost at least US\$966 billion in global health expenditure in 2021.¹ The Western Pacific region (which includes 38 countries, such as China, Thailand,

Malaysia, and Singapore) had the highest estimated number of deaths (2.3 million) due to diabetes.¹ Locally, one in three individuals is at a lifetime risk of developing diabetes.² In the absence of active lifestyle intervention, it is estimated that close to 1 million Singaporeans will have diabetes by the end of 2050.³ The Ministry of Health (MOH), Singapore, therefore, launched the “War on Diabetes” campaign in 2016, in response to the significant health and societal burden posed by diabetes.⁴

It is well-established that T2DM is strongly associated with obesity. In Asia, 56.1-69.2 percent of patients with T2DM are obese.⁵ The risk of T2DM increases with body mass index (BMI), with odd ratios ranging from 1.21 to 2.23 for each successively increasing BMI category in Asia.⁶ Data from the 2019/2020 Singapore National Population Health Survey showed that the prevalence of obesity was the highest among Malays (23.9 percent) followed by Indians (17.7 percent) and Chinese (7.4 percent), while the prevalence of diabetes followed a similar trend with Malays (14.4 percent), Indians (14.2 percent), and Chinese (8.2 percent).⁷ According to various local studies, the risk of developing T2DM increased with increasing BMI in all major ethnic groups,⁸⁻¹⁰ though there were also ethnic differences.^{11,12}

In the case of obesity, there are various pathological mechanisms resulting in insulin resistance and β -cell dysfunction that synergistically exacerbate the onset of T2DM.¹³ Hypertrophied adipose tissue in obesity is associated with elevated circulating free fatty acid (FFA), which causes insulin resistance¹⁴ and β -cell dysfunction.¹⁵ Visceral fat deposition, particularly in the liver and pancreas, plays an important role in diabetes pathogenesis. Hepatic fat worsens hepatic insulin resistance, while pancreatic fat affects insulin secretion and glucose tolerance.¹⁶ In addition, adipose tissue produces many pro-inflammatory adipokines (e.g., TNF- α , IL-6). The chronic pro-inflammatory state of obesity promotes insulin resistance.¹⁷

By 2050, the prevalence of obesity in the nation is predicted to reach 15.9 percent while the prevalence of overweight (≥ 25 kg/m²) is anticipated to reach close to 38.6 percent.^{18,19} The total prevalence of T2DM is also projected to rise to 15 percent by 2050, which was 7.3 percent in 1990, in tandem with the rise of obesity prevalence.¹⁹ As a result, one in two Singaporeans will be at risk of developing T2DM in their lifetime by 2050.¹⁹ Singapore has one of the most rapidly ageing populations in the world and the proportion of the population over 60 years of age is predicted to increase to 31.9 percent by 2050, which was 13.3 percent in 2010.¹⁹ If the trend continues, the annual incident cases of acute myocardial infarction (AMI), stroke, and end-stage renal disease (ESRD) amongst patients with diabetes is anticipated to increase by 50 percent by 2050, which represents a serious economic burden.²⁰

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It is reported that among patients with T2DM, one in four has poor control of their condition, which increases the risk for serious complications.²¹⁻²³ In 2010, the total economic burden (indirect and direct medical cost) of T2DM in Singapore among working-age adults was US\$787 million.²⁴ Due to the increase in the incidence of early-onset T2DM and ageing population, the cost burden is projected to increase to US\$1,867 million (2.4-fold increase) by 2050.²⁴ This growing burden will present Singapore with a wide range of challenges across the healthcare system. Lifestyle interventions emphasising building and maintaining positive health behaviours and weight management prevent and/or delay the development of T2DM and its complications.²⁵ This review discusses the role of weight loss and provides an overview of multidisciplinary/multipronged strategies to achieve and maintain weight loss in overweight or obese patients with T2DM.

ROLE OF WEIGHT LOSS FOR TYPE 2 DIABETES CONTROL

Weight management is key in both the prevention and management of T2DM. Multiple diabetes prevention studies indicate that intentional weight loss in patients at risk reduces the risk of incident T2DM.²⁶⁻²⁸ In patients with established T2DM, weight loss through surgical and nonsurgical methods may induce T2DM remission.^{29,30} In the DiRECT study, a primary care-led lifestyle intervention programme (12-20 weeks total dietary replacement followed by structured support for weight loss maintenance) aiming for 15 kg weight loss in an overweight or obese patient with T2DM with a duration of diabetes up to six years showed that the greater the weight reduction, the greater the odds of T2DM remission.^{29,30} For patients with overweight or obesity with T2DM, 5 percent weight loss is needed to achieve beneficial outcomes in glycaemic control, lipids, and blood pressure.³¹ Evidence showed that the clinical benefit of weight loss is progressive and a more intensive weight loss goal (15 percent) may be appropriate to maximise benefit depending on the individual patient profile, feasibility, and safety.^{32,33}

Cardiovascular events are a major cause of morbidity and mortality in patients with T2DM. Weight gain is associated with a higher hazard of cardiovascular disease (CVD) events and all-cause mortality in patients with T2DM vs those who had no change in weight.³⁴ However, lifestyle intervention studies, including the LookAHEAD study, targeting weight loss showed no effect on CVD events.³⁵ Nevertheless, there are still important benefits in weight reduction in patients with T2DM. Weight reduction of at least 5-10 percent is shown to improve diabetes control, CVD risk factors, physical and sexual function, and health-related quality of life (QoL), with larger weight loss with greater benefits.^{35,36} In the LookAHEAD study, approximately 50 percent of participants assigned to the intensive lifestyle group were able to maintain a weight loss of ≥ 5 percent at eight years, and they required fewer glucose-, blood pressure-, and lipid-lowering medications.³⁷

Even though lifestyle intervention does not show an effect on CVD outcome, a large meta-analysis showed that bariatric surgery was associated with substantially lower all-cause mortality rates than usual care, and the survival benefits are more pronounced for patients with diabetes than those without diabetes.³⁸ Weight loss is a matter of controversy for older T2DM adults (>65 years) due to concerns that weight loss could exacerbate loss of skeletal muscle mass and strength.³⁹ Celli A *et al* reported that combined weight loss (target goal: 10 percent decrease at the first year) and exercise therapy improved glycaemic control, physical function, and QoL in older adults (aged: 65-85 years) with T2DM.⁴⁰

STRATEGIES TO ACHIEVE EFFECTIVE WEIGHT LOSS FOR TYPE 2 DIABETES CONTROL

Nutrition, Physical Activity, and Health Behavioural Counselling

Lifestyle intervention is a cornerstone of optimal diabetes care (refer to **Table 1**). This includes: (i) medical nutrition therapy (MNT); (ii) physical activity; and (iii) health behaviour counselling.⁴¹⁻⁴³ The goal of MNT in patients with T2DM is to promote and support healthy eating patterns; improve overall health and specifically glycaemic, blood pressure, and cholesterol levels; achieve and maintain body weight goals; and delay or prevent complications of diabetes.⁴³ Due to the progressive nature of T2DM, when lifestyle intervention alone may not be adequate to maintain euglycemia over time, MNT continues to be important even after glucose-lowering medication is initiated. Any approach to MNT with meal planning should be individualised, considering the health status, current eating patterns, personal preferences, metabolic goals, and the ability of the individual to sustain the recommendation in the meal plan.⁴³ Weight loss can be attained with lifestyle intervention that focuses on nutritional changes, physical activity, and health behavioural counselling that achieve a 500-750 kcal/day energy deficit, which in most cases is around 1,200-1,500 kcal/day for women and 1,500-1,800 kcal/day for men (adjusted as per baseline body weight of individual).^{42,43}

It is important to note that the ability to sustain and maintain an eating plan that results in an energy deficit, irrespective of macronutrient composition or eating plan, is crucial for success.⁴⁴ It is recommended that overweight or obese patients with T2DM who have achieved weight loss should be offered long-term weight loss-maintenance strategies, which focus on ongoing monitoring of body weight, self-monitoring calorie intake, step count, nutrition assessment/counselling, health behavioural counselling, and encouraging participation in high levels of physical activity (200-300 min/week).⁴² On average, Singaporeans consume 12 teaspoons (or 60 g) of sugar daily derived from pre-packaged sugar-sweetened beverages (SSBs), higher than the recommendation of the Singapore Health Promotion Board (HPB), which is no more than 8-11 teaspoons per day.^{45,46} The consumption of SSBs in the general population

contributes to a significantly increased risk of T2DM, weight gain, heart disease, kidney disease, nonalcoholic liver disease, and tooth decay.⁴⁷ People are encouraged to replace SSBs with water as often as possible.

A structured, low-calorie meal plan, utilising high-protein foods and meal replacement products, when integrated with behavioural support and counselling, increases the pace and/or magnitude of initial weight loss and glycaemic improvements compared with best-practice care.⁴² A systematic review by Elia M *et al* highlighted that diabetes-specific nutrition formulas (DSNFs; with low glycaemic indices) delivered as a partial meal replacement as oral supplements were associated with improved glycaemic control as compared with standard formulas (high in carbohydrate, low in fat and fibre).⁴⁸ Results showed that DSNF significantly reduced the rise in postprandial blood

glucose and lowered peak blood glucose concentrations with no major effect on HDL-cholesterol, total cholesterol, or triglyceride concentrations.⁴⁸ Diabetes-specific nutrition formulas significantly improved morning postprandial glycaemic excursions in individuals who replaced their routine breakfast with DSNF.⁴⁹ Additionally, in individuals who replaced both breakfast and afternoon snacks, nocturnal glucose variability was improved.⁴⁹ These acute benefits have translated into meaningful reductions in long-term glycaemic control along with improvements in various cardiometabolic endpoints.⁵⁰ Evidence also suggests that individuals on structured meal plans with DSNFs experienced substantial reductions in body weight and improvement in health-related QoL.⁵¹ It has also proven to be a safe and effective method for increasing dietary compliance.⁵²

Table 1: Nutrition, physical activity, and health behavioural counselling for achieving effective weight loss in patients with type 2 diabetes mellitus.

Nutrition, physical activity, and behavioural counselling (to achieve and maintain ≥ 5 percent weight loss) are recommended for overweight or obese patients with T2DM.⁴² Larger, sustained weight losses (>10 percent) usually confer greater benefits, including disease-modifying effects and possible remission of T2DM, and may improve long-term cardiovascular outcomes and mortality.⁴²

Nutrition:

- Healthy eating is important for all individuals, regardless of body size, weight, or health status.
- Patients with T2DM should receive individualised MNT as needed to achieve treatment goals. Individualised meal planning should include optimisation of food choices to meet recommended dietary allowance for all micronutrients, providing adequate vitamins and minerals.⁴¹
- To support weight loss and improve HbA_{1c} and CVD risk factors in overweight or obese patients with T2DM, an individualised meal plan that results in an energy deficit in combination with enhanced physical activity is recommended.⁴¹⁻⁴³
- It is recommended to aim to achieve a 500-750 kcal/day energy deficit, which in most cases is around 1,200-1,500 kcal/day for women and 1,500-1,800 kcal/day for men (adjusted based on body weight) for overweight/obese patients with T2DM.⁴²
- Key factors to consider regardless of eating patterns and meal planning⁴³:
 - Emphasise non-starchy vegetables.
 - Minimise added sugars and refined grains.
 - Choose whole foods over highly processed foods to the extent possible.
 - Replace SSBs (including fruit juice) with water as much as possible.
- Meal replacement as part of lifestyle intervention reduces HbA_{1c}⁵³ and enhances weight loss in patients with T2DM.⁵⁴ It is a safe and effective method for increasing dietary compliance.

Physical Activity and Health Behavioural Counselling:

- Patients with diabetes should perform aerobic and resistance exercise regularly.²⁵
- Moderate-to-vigorous aerobic activity bouts should ideally last for at least 10 minutes, with the goal of ~ 30 minutes/day or more (at least 150 mins/week), with no more than two days to elapse between exercise sessions as this has been shown to improve insulin sensitivity.⁵⁵
- Two to three sessions/week of resistance exercise of any intensity on non-consecutive days is encouraged to improve strength, balance, and the ability to engage in activities of daily living.⁵⁶

- For those who achieve weight loss goals, long-term (≥ 1 year) weight maintenance strategies and counselling are recommended.⁴² These include regular assessment and counselling focusing on nutrition changes, encouraging physical activity, ongoing monitoring of body weight (weekly or more frequently), and self-monitoring of calorie intake and step counts to achieve a 500-750 kcal/day energy deficit.⁴²
- It is advised to decrease the amount of time spent on daily sedentary behaviours (e.g., working at a computer, watching TV). Prolonged sitting should be interrupted every 30 minutes.
- Healthcare providers should provide follow-up sessions consistent with repetition and relevance to support the development of self-efficacy and intrinsic motivation to facilitate positive health behaviour change.

T2DM: Type 2 diabetes mellitus

MNT: Medical nutrition therapy

SSBs: Sugar-sweetened beverages

HbA_{1c}: Glycated haemoglobin

CVD: Cardiovascular disease

PHARMACOTHERAPY AND SURGICAL MANAGEMENT OF WEIGHT LOSS IN TYPE 2 DIABETES MELLITUS

Glucose-Lowering Medications and Medications for Comorbid Conditions

Patients with T2DM may initially be treated with lifestyle modification unless they are symptomatic or severely hyperglycaemic, in which case pharmacological therapy should be initiated together with lifestyle intervention.⁴¹ A patient-centred approach is recommended when considering glucose-lowering medication for patients with T2DM taking into consideration the efficacy and key patient factors⁵⁷:

- Important comorbidities, such as atherosclerotic cardiovascular disease (ASCVD) and indicators of high ASCVD risk, chronic kidney disease (CKD), and heart failure
- Hypoglycaemia risk
- Effects on body weight
- Side effects
- Cost
- Patient preferences

Specifically, for overweight or obese patients with T2DM, metformin should be started at the time T2DM is diagnosed (unless there are contraindications) in combination with lifestyle modifications.⁵⁷

Additional and/or alternative agents may be considered in special circumstances and/or considering the medication's effect on weight and glycaemic goals.⁵⁷ Medications associated with varying degrees of weight loss include metformin, α -glucosidase inhibitors, sodium-glucose co-transporter 2 (SGLT-2) inhibitor, and glucagon-like peptide (GLP-1) receptor agonists.⁴² Dipeptidyl peptidase 4 (DPP-4) inhibitors are weight neutral. In contrast, insulin secretagogues (sulphonylureas), thiazolidinedione, and insulin are often associated with weight gain; hence, the use of these medications should be carefully considered.⁴²

Pharmacotherapy for Weight Loss in Overweight/Obese Patients with T2DM

Pharmacotherapy for weight loss can be considered as an adjunct to lifestyle intervention to decrease weight and improve metabolic and/or health parameters when lifestyle intervention alone has been ineffective, insufficient, or without sustained benefit.⁵⁸ It can be used for patients with BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² with obesity-related comorbidities.⁵⁸ Increasing data show that pharmacotherapy may be used to maintain weight loss that has been achieved by lifestyle interventions and to prevent weight regain.⁵⁸ The mechanism of action, adverse side effects, and safety and tolerability of each medication must be considered in the context of each patient's comorbidities and existing medications.⁵⁸ Pharmacotherapy that can be used in conjunction with lifestyle intervention for weight loss and improvement in glycaemic control are subcutaneous (SC) liraglutide 3 mg daily, naltrexone/bupropion combination, orlistat, and phentermine, all of which are currently approved by Health Science Authority Singapore (HSA) for short- (6-12 months) and long-term (>12 months) use for weight management locally.^{18,58} Metabolic surgery (bariatric surgery) may be considered in Asian patients with T2DM with BMI ≥ 37.5 kg/m² or 32.5 kg/m² and obesity-related comorbidities, who do not achieve durable weight loss and improvement in metabolic goals with nonsurgical methods.⁴² Substantial evidence demonstrates that metabolic surgery can promote significant and durable weight loss and achieve superior glycaemic control and reduction in cardiovascular risk in overweight or obese patients with T2DM compared to nonsurgical methods.⁵⁹ Data also showed that a great proportion of patients with T2DM who underwent metabolic surgery attained diabetes remission after 1-5 years.⁶⁰ **Table 2** lists key recommendations on achieving weight loss through choice of appropriate pharmacotherapy and metabolic surgery in patients with T2DM.

Table 2: Choice of appropriate pharmacotherapy options and metabolic surgery for achieving weight loss in patients with type 2 diabetes mellitus.

Pharmacotherapy:

- Consider the effects of glucose-lowering medications on weight⁴²:
 - Weight loss: metformin, SGLT-2 inhibitors, GLP-1 receptor agonists, α -glucosidase inhibitors
 - Weight neutral: DPP-4 inhibitors
 - Weight gain: sulfonylureas, thiazolidinediones, and insulin
- Review the medication list and consider minimising the use of medications that are associated with weight gain or the use of alternative options that have the least tendency of promoting weight gain for comorbid conditions.
- Pharmacotherapy for weight loss can be used as an adjunct to lifestyle intervention (nutrition, physical activity, and behavioural counselling) if lifestyle intervention alone has been ineffective, insufficient, or without sustained benefit. It can be used for patients with T2DM with BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² with obesity-related comorbidities.⁵⁸
- Liraglutide 3 mg daily, naltrexone/bupropion combination, orlistat, and phentermine are currently approved by Health Science Authority Singapore for short- and long-term use for weight management in Singapore.^{18,58}

Metabolic Surgery:

Consider metabolic surgery for Asian patients with T2DM of BMI above 37.5 kg/m², or above 32.5 kg/m² with obesity-related comorbidity, who do not achieve durable weight loss and improvement in metabolic goals with non-surgical methods.⁴²

T2DM: Type 2 diabetes mellitus
DPP-4: Dipeptidyl peptidase-4

SGLT-2: Sodium-glucose cotransporter-2
GLP-1: Glucagon-like peptide 1

BMI: Body mass index

CONCLUSION

Type 2 diabetes mellitus poses a significant public health concern in Singapore. Obesity is strongly associated with the development of T2DM. A multidisciplinary/multipronged approach should be utilised to achieve and maintain weight loss in overweight or obese patients with T2DM. Lifestyle intervention is a cornerstone for the management of T2DM and obesity. Lifestyle interventions that contribute to 500-750 kcal/day energy deficit are recommended to aid in weight loss in overweight or obese patients with T2DM. Individualised MNT, which promotes long-term adherence to reduced-calorie diets, use of meal replacements with DSNFs, regular assessment and counselling focusing on nutrition changes, and encourages physical activity, ongoing monitoring of body weight (weekly or more frequently), and self-monitoring of calorie intake and step counts should be integrated as a part of strategies to achieve and maintain weight loss. When choosing glucose-lowering medications for overweight or obese patients with T2DM, it is important to consider the medication's effect on weight. Healthcare providers should consider minimising the use of weight-promoting medications or the use of alternative options with the least tendency to promote weight gain for comorbid conditions whenever possible. Pharmacotherapy for weight loss and metabolic surgery can be considered in a selected group of overweight or obese patients with T2DM who do not achieve durable weight loss and improvement in metabolic goals.

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LEARNING POINTS

- **In overweight or obese patients with T2DM, modest (5–10 percent) and sustained weight loss is associated with clinically meaningful improvements in glycaemic control, cardiovascular risk factors, cardiovascular outcome, quality of life, and reduced need for glucose-lowering medications, with a greater amount of weight loss conferring greater benefits.**
- **To support weight loss and improve HbA_{1c} and CVD risk factors in overweight or obese patients with T2DM, an individualised meal plan that results in an energy deficit of 500–750 kcal/day in combination with enhanced physical activity is recommended.**
- **Lifestyle interventions, which include individualised low-calorie medical nutrition therapy with the use of meal replacements, coupled with regular periodical assessment and counselling on positive health behaviour, can synergistically promote clinically meaningful and sustained weight loss in patients with T2DM.**
- **When choosing glucose-lowering medications, the medication's effect on weight should be considered in addition to its efficacy and key patient factors.**