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Exploring Remission Options for Patients with Type 2 Diabetes

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ABSTRACT

Type 2 diabetes (T2DM) is a chronic health condition caused by several genetic and/or environmental factors. T2DM does not have an immediate cure; this requires strategies to manage symptoms and slowly start remission. This review paper dives into treatment options for T2DM such as lifestyle intervention, prescription medication, and bariatric surgery. The focus will be on exploring their effectiveness in patients with T2DM as well as examining any potential side effects. This paper highlights the importance of treatment plans that take into account the nature of T2DM. After exploring three options, our results suggest that the different options correspond to different stages of the disease: lifestyle intervention is best for the early stages, medication is best for the middle stage, and bariatric surgery is one of the last options given by physicians.

Introduction

Type 2 diabetes (T2DM) is a chronic health condition caused by several genetic and/or environmental factors (Artasensi et al., 2020). The impact of diabetes is significant, with more than 422 million adults affected, and is expected to increase to 693 million by 2045 (Artasensi et al., 2020). T2DM was initially thought to be caused by insulin resistance in adults which could progressively worsen to complete resistance, however, reduced β-cell function is the key problem in T2DM (Artasensi et al., 2020). It is common for obese patients to develop T2DM due to low adiponectin levels and a leptin-resistance state. This dysfunction leads to insulin resistance, which has consequences primarily on adipose, muscular, and hepatic tissues. In this situation, there is an increased production and secretion in the circulation of fatty free acid (FFA) which are also responsible for the insulin-resistance (Figure 1).

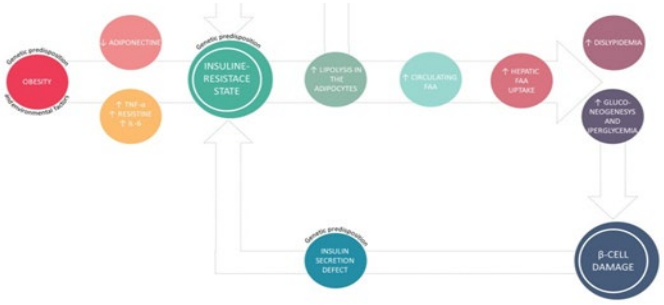

Figure 1. Pathophysiology of Type 2 Diabetes (*Type 2 Diabetes Mellitus: A Review of Multi-Target Drugs,* 2020)

There are several other risk factors associated with T2DM such as genetic influences, poor physical fitness, and environmental influences. Genetics plays a crucial role in the development of diabetes. The most common forms of T2DM are polygenetic, meaning there are changes in multiple genes (Artasensi et al., 2020). A sedentary lifestyle

increases the risk of T2DM as physical activity helps to control body weight and lower glucose levels (Artasensi et al., 2020). The increase in T2DM is related to the gut microbiota and the advances that lead to microbiome dysbiosis, which induces metabolomic and signaling pathways related to insulin resistance (Artasensi et al., 2020). Treatment for T2DM is challenging and researchers are actively studying aspects of the disease to identify targets for therapy and develop effective strategies, for managing diabetes. This review will provide an overview and critical analysis of the most common treatments for T2DM, physical activity and diet control, prescription drugs, and bariatric surgery.

Lifestyle Intervention

One of the most common ways to treat T2DM is lifestyle intervention by increasing physical activity. Multiple types of physical activity improve health and glycemic management, resulting in improved insulin sensitivity (Kanaley et al., 2022). Regular exercise can increase insulin secretion to regulate glycolipid metabolism and meet daily physical activity needs (Yang et al., 2019). A survey in China found that glucose metabolism, fat metabolism, blood pressure, and BMI were significantly improved after regular exercise in T2DM patients; this led to a decline in diabetes-related complications (Yang et al., 2019). Many different types of exercise training have specific effects on patients with T2DM. Short-term aerobic exercise improves whole-body insulin action through gains in peripheral insulin sensitivity (Kanaley et al., 2022). Conversely, resistance training increases lean skeletal muscle mass and reduces A1C levels (Kanaley et al., 2022). One study discovered that resistance training increases maximal oxygen consumption (VO2MAX) (Nery et al., 2017). Individuals with T2DM have been shown to have 20% lower VO2MAX levels (Leite et al., 2009). Yoga may improve A1C, blood lipids, and body composition in adults with T2D (Innes & Selfe, 2016); whereas, tai chi may improve glycemic management, balance, neuropathic symptoms, and some dimensions of quality of life (Ahn & Song, 2012).

Remission of T2DM is entirely possible through a change in diet. In 2008 the twin cycle hypothesis postulated that there were cycles of fat accumulation in the liver and pancreas that led to the development of type 2 diabetes over at least a decade (fig 2). The hypothesis was developed from knowledge of the relationship between liver fat and control of the flow of glucose into the blood as well as observation that normal insulin secretion returned after weight loss in (Taylor et al., 2021). It predicted that major calorie restriction would lead to a rapid fall in liver fat, and decrease to normal levels of glucose production by the liver. T2DM is strongly related to weight gain and the accumulation of fat in the liver and pancreas (Lean et al., 2018). A study was conducted in which participants with T2DM were asked to follow the Counterweight-Plus management program. A total diet replacement using a low-energy diet plan with 825-833 kcal/ day for 3 months was used for weight loss; all oral drugs were discontinued (Lean et al., 2018). The outcomes were a reduction in weight of 15kg or more, low A1C levels, and a remission of diabetes (Lean et al., 2018). An additional study tested a 600 kcal/ day diet with patients of T2DM. After one week, liver fat decreased by 30% and insulin sensitivity stabilized (Taylor, 2013). Decreasing liver fat content improves insulin suppression of glucose production and fasting plasma glucose (Taylor, 2013). A third study tested the effects of a low-fat, high-carbohydrate, high-fiber diet on glycemic levels in persons with T2DM. After 9 years of the diet, 8% of participants achieved FPG levels of less than 7.8 mmol and 9% achieved HbA_{1c} levels under 7% (Turner et al., 2005). However, diabetes control deteriorated such that after 3 years approximately 50% of patients could attain this goal, and by 9 years this declined to approximately 25% (Turner et al., 2005). This suggests that the majority of patients need multiple therapies to attain these glycemic target levels in the longer term (Turner et al., 2005).

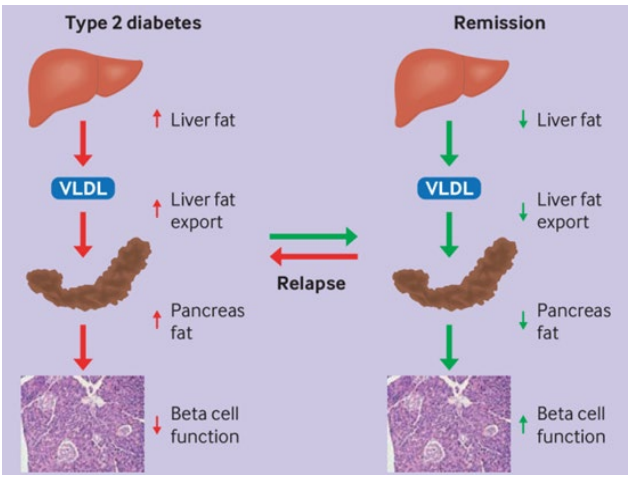

Figure 2. Type 2 diabetes develops as long-term intake of excess food energy leads to accumulation of liver fat. (*Nutritional Basis of Type 2 Diabetes Remission,* 2021)

The type of diet also affects the prevalence of T2DM. Approximately 7.6% of nonvegetarians are diagnosed with T2DM, while a significantly less amount is diagnosed in vegan individuals (2.2%) (Pollakova et al., 2021). Studies have found that consuming fruits, vegetables, legumes, bread, rusk, and pasta reduced the risk of 10-year T2DM by 40% (Pollakova et al., 2021). Individuals with the highest decile of PDI- the Plant-based Diet Index in which more plant foods correspond to a higher score- reduced T2DM risk by approximately 20% (Pollakova et al., 2021). Five other observational studies show a significant reduction in HbA_{1c} levels after a vegan diet (Pollakova et al., 2021). Additionally, a vegan diet has shown antihyperglycemic effects (Pollakova et al., 2021). However, it is advised that clinical trials be conducted to evaluate the quality of carbohydrates and nutrients in vegan diets; larger studies are needed to confirm the effectiveness and safety of vegan diets on patients with T2DM (Pollakova et al., 2021). Such monitoring can be done using new technologies such as the FreeStyle Libre to monitor glucose levels in patients with T2DM (Daly & Hovorka, 2021). Some studies have tested to see if continuous monitoring brought down HbA_{1c} levels in participants, however, results only saw great improvement combined with personalized feedback from physicians and a healthy diet (Lee et al., 2022).

Another potential strategy is food prescription to promote healthier eating habits; additionally, portion control and fasting are strategies for weight loss, with reports of loss of up to 13% (Taylor et al., 2021). Intermittent fasting has become popular, reaching approximately 25% lower intake of food energy (Taylor et al., 2021). Weight loss is directly related to the remission of T2DM because it improves glycemia, blood pressure, and lipids, preventing complications (Forouhi et al., 2018). Researchers recommend promoting weight loss by reducing energy intake (Forouhi et al., 2018). However, there have been dietary shifts in low and middle-income countries leading to increased fat intake, decreased intake of coarse cereals, pulses, fruits, and vegetables, and increased intake of caloric beverages, suggesting that there may be an increase in T2D in these countries if proper education isn't provided to the populations (Forouhi et al., 2018).

Additionally, it has been found that gut microbiota is involved in obesity, one of the major characteristics of people with T2DM (Zhu et al., 2022). The gut microbiota composition can affect the human body's ability to acquire nutrients and regulate energy usage (Geng et al., 2022). However, calorie restriction can improve gut microbiota and lead to remissions of T2DM in 80% of patients with obesity and T2DM (Wu et al., 2023).

Prescription Medication

If lifestyle changes do not yield adequate improvement, then drug treatment should be initiated (or intensified) and managed based on the HbA1c (Pfeiffer & Klein, 2014). Researchers recommend an HbA1c range of 6.5% to 7.5% (Pfeiffer & Klein, 2014). If the HbA1c target is not reached after 3-6 months of basal therapy (lifestyle intervention), then medications should be administered (Fig 3). The first choice is metformin; however, if it is not tolerated then other forms of drugs are given (Fig 3). The guidelines for the pharmacological management of diabetes provided by the American Diabetes Association suggest that metformin be prescribed as the initial intervention for T2DM patients (Borse et al., 2021). Treatments such as human insulin and glibenclamide have demonstrated efficacy in clinical trials (Fig 3). However, if the target is still not reached after 3-6 months of monotherapy, insulin is given alone or as a 2-drug combination (Fig 3). Individuals are given three options to choose from: metformin and insulin which has had high-quality trials but may lead to hypoglycemia and weight gain, metformin and glibenclamide which can be taken orally but has occasionally led to high cardiovascular mortality, hypoglycemia and weight gain, or, lastly, metformin and a DPP-4 inhibitor which doesn't show weight gain or hypoglycemia but studies have indicated possibly elevated risks of pancreatitis and pancreatic tumors (Fig 3). If after 3-6 months the HbA1c target is not reached, then the fourth step is to intensify the insulin types (Fig 3). Preprandial short-acting insulin, conventional insulin therapy, and intensified insulin therapy are some of the ways T2DM can be treated in this step (Fig 3). However, all these medications should be combined with exercise and diet restriction (Pfeiffer & Klein, 2014).

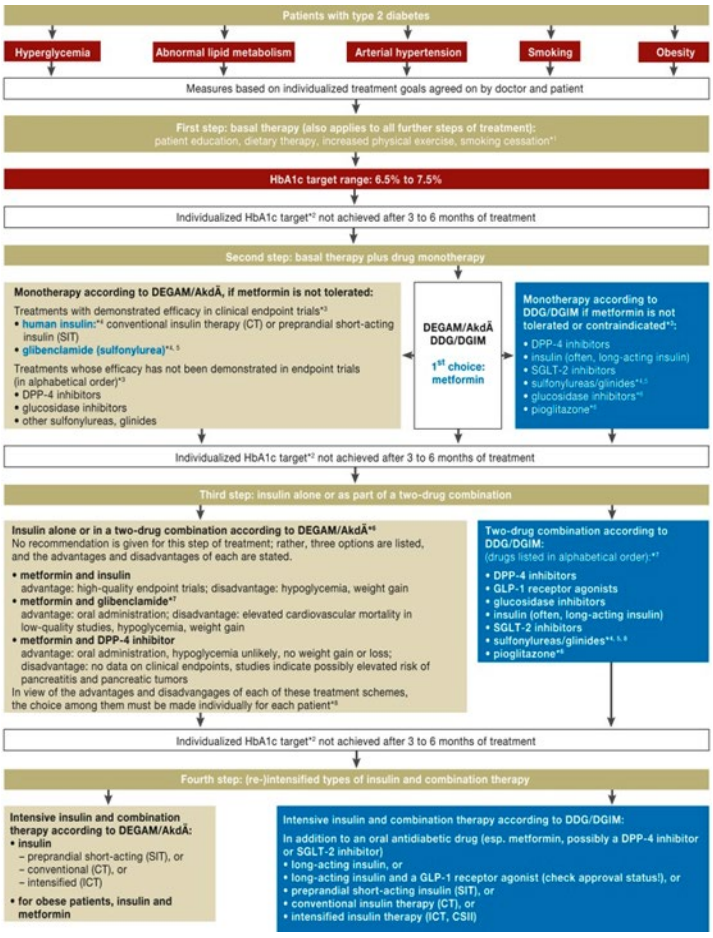

Figure 3. Treatment algorithm for type 2 diabetes (*The Treatment of Type 2 Diabetes,* 2014)

Bariatric Surgery

Bariatric surgery is another alternative treatment for T2DM. Bariatric surgery is a potential treatment for obesity because it causes substantial weight reduction (Shah et al., 2016). One study documenting obese adults treated with bariatric surgery found a 25% reduction in body weight and a 30% reduction in mortality over twenty years (Shah et al., 2016). For participants with type 2 diabetes at baseline, the remission rate at 15 years for those who did not undergo surgery was 6.5%; for those who did undergo surgery, remission was seen at 30% (Shah et al., 2016). The risk of developing microvascular complications of diabetes in the surgical group was approximately one-half of that observed in the control group that did not have surgery (Shah et al., 2016). Although there has also been a slow and steady recurrence of diabetes in some surgical patients who initially experience remission, the rates of diabetes do not approach the high levels they were once at (Shah et al., 2016).

For adults, the 2011 International Diabetes Federation statement recommends that weight-loss surgery should be prioritized for patients with type 2 diabetes who have a BMI >40 kg/m2 (Shah et al., 2016). Another study tested the effectiveness of bariatric surgery for T2DM patients and found a benefit from the procedure. In the study, 61 participants with obesity and T2DM were randomized to either bariatric surgical treatments (Roux-en-Y gastric bypass [RYGB] or laparoscopic adjustable gastric banding [LAGB]) or an intensive lifestyle weight loss intervention (LWLI) program for 1 year (Courcoulas et al., 2020). Lower-level lifestyle weight loss interventions (LIS) were then delivered for 4 years (Courcoulas et al., 2020). After 5 years those in the RYGB group had the largest percentage of individuals (56%) not requiring any medications for T2DM compared with those in the LAGB (45%) and LWLI (0%) groups (Courcoulas et al., 2020).

Conclusion

Over 422 million adults are affected with Type 2 Diabetes Mellitus and this is expected to increase to 693 million by 2045 (Artasensi et al., 2020). The three forms of treatment this article covered are lifestyle intervention, prescription medication, and bariatric surgery. The treatment options required are different for every individual (Pfeiffer & Klein, 2014). For example, most individuals with pre-diabetes or who are in the early stages of T2DM are recommended to undergo basal therapy, through exercising and controlling the diet (Pfeiffer & Klein, 2014). However, if HbA1c levels continue to rise, then prescription medication, such as metformin, may be administered combined with lifestyle intervention (Pfeiffer & Klein, 2014). If these options continue to be unsuccessful, then bariatric surgery may be advised to lose weight and improve A1c levels (Shah et al., 2016). It is important to recognize that these treatments have their limitations and cannot cure or prevent T2DM entirely. This underscores the need for research and exploration into therapies related to Type 2 Diabetes Mellitus.

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