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Diabetes Remission – The New Therapeutic Goal in Management of Type 2 Diabetes Mellitus

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Abstract

Type 2 Diabetes mellitus is a complex progressive metabolic disease with rising global prevalence. It was believed to be an inexorably progressive disease, despite optimum gluco - centric management with escalating pharmacotherapy and lifestyle modification. In recent years, the concept of diabetes remission has gained enormous public and professional interest. Type 2 diabetes mellitus is strongly linked to obesity and there is clinical evidence that substantial weight loss through weight loss interventions could make diabetes remission a reality. Diabetes remission can be achieved through metabolic bariatric surgery and intensive lifestyle interventions targeting weight loss. Novel pharmacotherapy, SGLT2 inhibitors and GLP1-RA have an important role in achieving weight loss in addition to glucose lowering effect. Even though diabetes remission is achievable in selected groups of individuals, maintenance of remission is the biggest challenge. It is the right time to embrace diabetes remission as a main therapeutic goal in diabetes management in order to face the increasing global burden.

Keywords: Diabetes remission, weight loss, metabolic bariatric surgery, low- calorie based weight management programme

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Introduction

Diabetes mellitus has become a global burden with increasing prevalence day by day. The IDF diabetes atlas (2021) reports that 10.5% of the adult population aged 20-79 has diabetes, and 1 in 8 adults will be having diabetes mellitus by 2045, which is an increase of 46% [1]. It is revealed that 3 in 4 adults with diabetes live in low and middle-income countries. The diabetes prevalence rates are alarming in Sri Lanka. The overall prevalence of diabetes was 27.6% in the urban population of Sri Lanka in 2018, which showed a significant rise in prevalence over the last decade [2], [3].

Type 2 diabetes mellitus is a complex heterogeneous chronic disease caused by multiple pathophysiological mechanisms [4]. It causes significant morbidity and mortality due to associated macrovascular and microvascular complications [5]. Obesity, resulting from an imbalance of energy intake and energy expenditure, is a major risk factor for the development of type 2 diabetes mellitus [6]. Recently published reports show that in 2022, 1 in 8 people in the world were living with obesity, and 16% of adults more than 18 years were obese [7].

Diabetes remission is defined in the consensus report 2021 by the Endocrine Society, the European Association of the Study of diabetes, Diabetes UK and the American Diabetes Association (ADA) as a return of HbA1C to < 48 mmol/mol (6.5%) that occurs spontaneously or following an intervention and persist for at least 3 months in the absence of usual glucose lowering pharmacotherapy [8]. Spontaneous diabetes remission is rare [9]. There is clinical evidence that diabetes remission can be achieved through metabolic bariatric surgery, pharmacotherapy, and intensive lifestyle interventions with low-calorie based weight management programmes [10]. Maintaining weight loss and changing the lifestyle is essential for the sustainability of diabetes remission, but it is a challenge due to barriers in the health sector, physician and patient levels.

Pathogenesis of diabetes remission

Diabetes is a slow onset disease that develops over many years due to insulin resistance and progressive decline in beta cell function [11]. According to the twin cycle hypothesis proposed by Prof Roy Taylor, type 2 diabetes is a result of excess liver fat resulting

When the maximum fat storage capacity is exceeded or fat storage in the adipocyte is impaired, the plasma triglyceride levels will increase and be diverted into the liver. Liver insulin resistance due to lipotoxicity will lead to elevated fasting insulin levels. High insulin levels will further stimulate lipogenesis and enforce the liver cycle. When there is excess fat accumulation in the liver, hepatic VLDL-TG is exported to the other tissues. The uptake and storage of fatty acids in the pancreas will initiate the pancreatic cycle. The prolonged exposure to lipotoxicity and glucotoxicity will lead to pancreatic beta cell dysfunction. During the early years, beta cells will overcome the stress by secreting more insulin, but when 50-60% of beta cells become dysfunctional, type 2 diabetes will result[13]. Substantial weight loss can reverse this process underlying type 2 diabetes. Weight loss causes a decrease in the intrahepatic fat content and the hepatic glucose production, leading to reversal of hepatic insulin resistance. Gradually with the continuation of calorie restriction, intrapancreatic fat content decreases. Following normalization of the liver fat and the pancreatic fat, the return of the non diabetic glucose state depends on the ability of the beta cell to recover [14].

Diabetes remission in metabolic bariatric surgery (MBS)

Metabolic bariatric surgery is a well-recognized effective therapeutic option for patients with obesity and type 2 diabetes mellitus [15]. There are several surgical methods used in bariatric surgery, such as Adjustable Gastric Band (AGB), Vertical Sleeve Gastrectomy (VSG), Roux-en-Y Gastric Bypass (RYGB), Biliopancreatic diversion(BPD), Biliopancreatic Diversion with a duodenal switch (BPD-DS) which have different efficacy rates. Weight loss and diabetes remission rates were highest in biliopancreatic diversion /duodenal switch, followed by gastric bypass, and least for banding

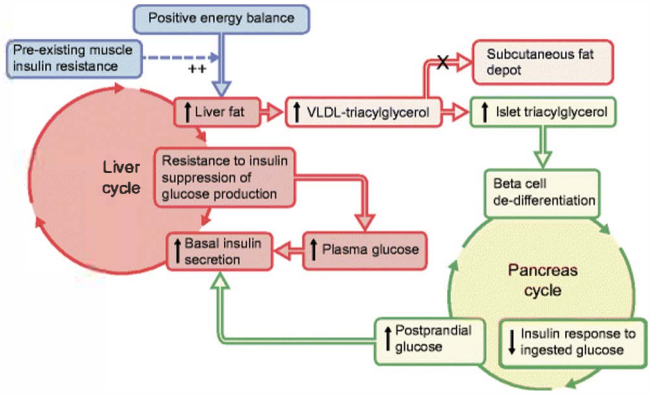

Figure 1 : Twin cycle hypothesis;
Imbalance in the energy intake and expenditure will result in fat accumulation in the liver. This process is stimulated by insulin, and individuals with pre-existing insulin resistance will accumulate liver fat more readily than others. As the liver insulin resistance develops, basal insulin secretion rate rises and fasting hyperglycaemia occurs. Excess lipids (TAG) produced in the liver will be exported and stored in organs like pancreas, initiating the pancreatic cycle. Eventually, the lipotoxicity and glucotoxicity will lead to beta cell dysfunction leading to the development of diabetes.
Adapted from - Roy, Taylor & Barnes, Alison. (2018). Translating aetiological insight into sustainable management of type 2 diabetes. Diabetologia. 61. 10.1007/s00125-017-4504-x

procedures [16]. Several mechanisms are suggested for remission of diabetes in MBS [17]. Reduced calorie intake, increased jejunal nutrient sensing, increased intestinal gluconeogenesis, increased GLP-1 secretion, increased glucose utilization in the roux limb, and deranged gut microbiota lead to altered gut physiology are the main proposed mechanisms. Alterations in the systemic factors such as reduced anti-incretin factors, increased GLP1, Peptide tyrosine tyrosine (PYY) and Oxyntomodulin (OXM), and increased bile acid pool lead to metabolic changes in the liver, pancreas and skeletal muscle. All these factors in combination, lead to improvement in pancreatic beta cell function with increased insulin release and sensitivity.

A Sri Lankan study was conducted in a tertiary care hospital to assess the short-term and long-term effects of MBS on diabetes reversal. Results of the study showed that 87.1% and 74.5% could achieve diabetes remission at 1 year and 5 years, respectively. It showed that age at the onset of diabetes, gender, preoperative weight and duration of diabetes had an impact on diabetes reversal, while preoperative BMI did not affect diabetes remission. The patients who underwent Roux-en-Y Gastric Bypass (RYGB) had a better diabetes reversal compared to Laparoscopic Sleeve Gastrectomy and Laparoscopic Mini- gastric Bypass surgery, which had similar outcomes[18]. The Alliance of Randomized Trials of Medicine versus Metabolic Surgery in Type 2 diabetes consortium assessed the durability and long-term effectiveness of metabolic surgery compared with medical and lifestyle management in patients with type 2 diabetes[19]. A total of 316 patients who were randomly assigned to STAMPEDE, TRIABETES, SLIMM-T2D, and CROSSROADS trials were enrolled in this study. After the three-year follow-up, a higher diabetes remission rate was achieved in the surgical participants (37.5%) than in medical/ lifestyle interventions (2.6%). Predictors of diabetes remission in MBS include younger age, better glycemic control, fewer glucose-lowering medications, no insulin treatment, and a greater degree of weight loss [20].

Diabetes remission with pharmacotherapy

Achieving type 2 diabetes remission using glucose-lowering agents is controversial because the definition of diabetes remission includes withdrawing all anti-diabetic treatment. The glucose - and weight-lowering properties of new antidiabetic drugs are being used in clinical practice. Therapeutic regimens based on insulin treatments have been investigated with regard to diabetes remission [21]. These studies have been conducted in newly diagnosed type 2 diabetes patients treated with continuous subcutaneous insulin infusions for 2- 3 weeks duration [22]. These studies showed that beta cell function can be improved through reversal of glucotoxicity. Evidence shows that diabetes remission induced by short-term intensive insulin therapy can last up to 1 year even [23]. SGLT2 inhibitors (SGLT2i) interfere with glucose reabsorption at the renal tubules and cause glycosuria, which leads to calorie and weight loss. SGLT2i are used in combination with other drugs to achieve diabetes remission [24]. An

open-label randomized controlled trial in which 24.7% went into remission in the intervention group treated with insulin glargine, metformin and dapagliflozin compared to the control, which was 16.9% though it was statistically not significant [25]. GLP1-RA is an incretin hormone that inhibits glucagon production, increases insulin secretion, delays gastric emptying, increases satiety, and reduces hunger. Liraglutide, a GLP1-RA, is used at a dose of 1.8mg daily for diabetes mellitus management and 3mg daily for chronic weight management. There are studies that have demonstrated that Liraglutide is associated with weight loss and reduction in HbA1C[26]. Use of Semaglutide, a GLP1-RA, has had promising results in weight management in adults with obesity[27]. A phase 3 double-blinded randomized control trial showed that the use of 2.4 mg of subcutaneous Semaglutide once a week resulted in an estimated change in mean body weight of 9·6% compared to 3·4% with placebo. 45.6% of patients treated with Semaglutide 2.4mg achieved a more than 10% of body weight reduction after 68 weeks, and 67.5% achieved a HbA1C of less than 6.5%. Tirzepatide , a dual agonist of GLP1 and GIP, has more of an effect on weight reduction. Tirzepatide showed diabetes remission rates ranging from 66% to 81% after 52 weeks, dependent on the treatment dose [28], [29]. Orlistat, a gastrointestinal lipase inhibitor, improves glycemic profile, reduces visceral fat, improves hepatic and peripheral resistance, and increases secretion of GIP and GLP-1. Meta-analysis 2005 showed that 120 mg of Orlistat three times a day resulted in an average weight loss of 3.9% after 12 weeks, compared to 1.44% in the placebo group [30]. Lorcaserin, a selective serotonin 2C receptor agonist, is associated with a significant reduction in HbA1C and reduced weight [31], [32].

Low - calorie based weight management programmes

Nutritional intervention and exercise promotion are the most crucial aspects of reducing weight and achieving diabetes remission. There are several studies done worldwide that have promising results for weight loss through a low-calorie diet, together with increased physical activity that leads to diabetes remission. Look AHEAD study was a landmark study published in 2012, in which the participants were randomized to the intervention group that received a low-calorie diet (1200-1800 Kcal/d) and physical activity (175 minutes a week with moderate exercise) and the control group received conventional diabetes management [34]. In the intervention group, diabetes remission rates at 1st, 2nd and 4th years were 11.5%, 10%, and 7.3%, respectively. DiRECT study, an open-label, cluster-randomized, controlled trial was conducted at primary care practices in the UK with 149 participants per each control group and intervention group [35]. The control group received best-practice care according to guidelines. The intervention group was subjected to a total diet replacement (TDR) with an 825–853 kcal per day formula diet for 12–20 weeks, stepped food reintroduction for 2–8 weeks, and then structured support for weight-loss maintenance. At the end of the first, second, and fourth year 46%, 35.6%, and 13% were in diabetes remission. The study showed that the more weight loss there is, the higher the diabetes remission rates are. The strongest predictors of diabetes remission were greater weight loss, and being on fewer prescribed antidiabetes medications at baseline while disease duration, fasting insulin and C-peptide did not impact the likelihood of remission [36]. Sustainability of diabetes remission and higher weight losses over time was observed in men. Following the DiRECT study, similar studies targeted different ethnic populations worldwide. DIADEM-I was an open-labelled parallel grouped randomized control study done in primary care and community settings in Qatar [37]. The trial compared the effects of intensive lifestyle intervention with usual medical care on weight loss and glycaemic outcomes in individuals with type 2 diabetes from the Middle East and North Africa region. The participants in the control group received usual diabetes care according to the clinical guidelines. The intervention group received an intensive lifestyle intervention comprising a total diet

Table 1: Studies investigating the efficacy on anti-obesity drugs in type 2 diabetes mellitus

Drug	Route and dose	Weight loss %	HbA1C<6.5%in drug vs. placebo group
GLP-1 RA			
Liraglutide[26]	Subcutaneous 3mg once daily	6.0% in 56 weeks	6.0% in 56 weeks
Semaglutide[27]	Subcutaneous 2.4mg once weekly	6.2% in 68 weeks	6.2% in 68 weeks
GLP-1 and GIP analogue			
Tirzepatide [29]	Subcutaneous 5mg, 10mg, 15mg once weekly	-7.0 kg in the 5 mg group, -7.8 kg in the 10 mg group, -9.5 kg in the 15 mg group in 40 weeks	-1.87% in the 5 mg group, -1.89% in the 10 mg group, -2.07% in the 15 mg group, compared with 0.04% in the placebo group
Gastrointestinal lipase inhibitor			
Orlistat[33]	Oral 120mg three times per day	10% in 26 weeks	Not mentioned
Selective Serotonin 2C receptor agonist			
Lorcaserin [31]	Oral 10 mg once or twice daily	2.6 kg diabetic and 2.8 kg in prediabetic patients in 52 weeks	33.9% vs. 8%

replacement phase with low-energy diet replacement products followed by gradual food reintroduction combined with physical activity support and a weight-loss maintenance phase involving structured lifestyle support. In the intervention group, 21% of participants achieved more than 15% weight loss within 1 year compared with 1% of participants in the control group. Diabetes remission occurred in 61% of participants in the intervention group compared with 12% of those in the control group. STANDby trial was done in the UK targeting the South Asian population to assess whether weight loss with total diet replacement with 850 kcal per day formula diet for 3 - 5 months led to type 2 diabetes remission as in other ethnic populations [38]. In the STANDby trial, 43% achieved type 2 diabetes remission, and 35% lost over 10kg of body weight which was comparable with white cohorts. DiRECT - Aus study assessed whether diabetes remission of type 2 diabetes could be achieved with low-energy total diet replacement in an Australian primary care setting. 56% of the participants achieved type 2 diabetes remission at the end of 12 months [39].

Moderate-intensity exercise improves outcomes related to diabetes in addition to physical and mental health improvement [40]. Aerobic, anaerobic, and endurance studies lead to an immediate improvement in glycemic control. The 6-year Malmo feasible study showed a significant reduction in glucose and insulin response to the oral glucose tolerance test that 54% of the participants achieved diabetes remission after 5 year follow-up with increased physical activity [41].

Challenges and the long term benefits of diabetes remission

Even though there is enough positive clinical evidence for achieving diabetes remission, sustainability remains a challenge. The remission rates of the Look Ahead study declined as 11.5%, 10%, 7% at the end of year 1, 2, and 4. The DiRECT three-year extension study has revealed that only nearly a quarter of participants in remission from type 2 diabetes at 2 years in the original study remained in remission at five years. The remission rates dropped from 45.6% to 35.6% during the first year of extension, and still 50% of participants required relapse management [42].

The currently available evidence suggests that diabetes remission is a possibility, but there is doubt about whether remission could prevent long-term microvascular and macrovascular complications. Metabolic memory has a long-term influence on the development of microvascular and macrovascular complications. Diabetes remission achieved in the early years after the diagnosis would lower the risk of complications. It is important to note that continuous monitoring and surveillance for complications is essential even after diabetes remission is achieved. MBS has been shown to be associated with high rates of remission and fewer microvascular and macrovascular complications in the long term [43]. A long-term follow-up of a Swedish Obese Subjects study showed that bariatric surgery was associated with more frequent diabetes remission and fewer complications than usual care [44]. Look AHEAD study compared the effect of a 12-year intensive lifestyle intervention with that of diabetes support and education on cardiovascular disease and other long-term health conditions [45]. Participants with diabetes remission had a 33% lower rate of CKD and a 40% lower rate of CVD. Since diabetes is a chronic progressive disease, it significantly affects one's quality of life. Diabetes remission and quality of life were assessed in the DiRECT study, and it was significantly improved in the intervention group [46]. Type 2 diabetes imposes a significant economic burden on healthcare systems. The DiRECT study assessed the within-trial and lifetime cost-effectiveness of the weight management programme, which achieved 46% remissions of type 2 diabetes at 1 year. The DiRECT intervention was predicted to be both more effective and cost-saving in adults with type 2 diabetes compared with standard care when compared to the quality-adjusted life years (QALY) saved [47].

Diabetes remission according to the definition requires withdrawal of all antidiabetic medications. New antidiabetic drugs like GLP1-RA and SGLT2i are now being used in management of diabetic patients. There is clinical evidence that SGLT2i could reduce the risk of MACE, hospitalizations due to heart failure, and progression of kidney disease regardless of diabetes status [48]. There are studies on GLP1-RA on favorable cardio renal outcomes in patients with type 2 diabetes mellitus [49]. Considering these facts, the decision to withhold all anti-diabetic drugs that have proven cardio-renal benefits has to be subjected to further discussions.

Conclusion

Type 2 diabetes is now recognised as a potentially reversible condition with the possibility of long-term remission. Metabolic bariatric surgery and weight management programs have been effective in achieving diabetes remission. Diabetes remission improves quality of life and has a positive impact on long-term treatment outcomes, but more clinical evidence is needed.

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