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EDITORIAL

Long-term remission of type 2 diabetes—two roads to the elusive goal

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The remission of type 2 diabetes has always been and continues to be the "holy grail" of diabetes management. Considering the gradually progressive chronic nature of the disease and its attendant complications, both researchers as well as patients intensely hope to discover a means of achieving a sustainable, if not permanent, cure. The rising prevalence of diabetes has been linked to increase in obesity in the general population [1]. Although lean type 2 diabetes is increasingly recognized in several parts of the world, especially the Indian subcontinent, the contribution of obesity to the diabetes pandemic cannot be underestimated. In fact, WHO has lowered the cut-offs for defining obesity in certain susceptible populations [2]. In light of this understanding of obesity as an etiological factor, it is logical to pin hopes of diabetes remission on the control or reversal of obesity. The improvement in glycemic status with lifestyle interventions which target weight loss is already well known and forms an important component of the current standard of care for diabetes [3]. However, the reports of acute remission of diabetes after bariatric surgery lead to a revival of interest in this important topic [4].

Bariatric surgery and diabetes remission

Although initially approved only for morbid obesity, the observation of improved glycemic status of operated individuals with diabetes generated considerable interest in the role of this surgery in the management of diabetes. With the increasing number of surgeries performed, a substantial proportion of diabetic obese patients also underwent bariatric surgery. The data obtained from such patients revealed that diabetes improved in a high percentage of type 2 diabetes patients who underwent bariatric surgery [5]. In fact the indications of bariatric surgery were later expanded to obesity with difficult to control comorbidities including diabetes. Short-term follow-up reports showed that 60–90% of patients had remission of diabetes [6, 7]. However, the short-term remission depends upon factors such as age, glycated hemoglobin levels, duration of diabetes, and insulin/oral hypoglycemic agent use. The same factors may be expected to cause reappearance of diabetes post the initial remission, and hence, the durability of remission is a question of paramount importance. In this issue, Minhem et al. have tried to address this question by retrospectively reviewing the data of bariatric surgeries performed at their center in Lebanon. They report a promising 42.3% complete diabetes remission after a mean follow-up of around 5 years with an additional 20% showing a partial remission.

The existing literature on long-term remission from other parts of the world is equally promising. Long-term remission at 15 years was reported at close to 30% in one study [8]. Around 50% complete remission was reported at a median follow-up of 11 years in another study [9]. Around 40–60% remission (depending upon the surgical technique used) at 5 year follow-up was reported in RCT comparing bariatric surgery with conventional treatment. Minhem et al. show that the diabetes remission after bariatric surgery is not limited to Western populations and the benefits can be extended to other areas of the world. The variation in these studies may be attributed to the nature of surgical procedure and the patient factors affecting remission mentioned above. These issues notwithstanding, bariatric surgery does offer a ray of hope for the possible "cure" of diabetes for at least some, if not all patients.

The idea behind very low calorie diets—the less traveled road

An interesting observation regarding diabetes remission was that glycemic improvement appears immediately after

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bariatric surgery and achieves a peak much before clinically apparent weight loss has occurred [10]. This was surprising considering that obesity was believed to be a major driver of insulin resistance and diabetes. Several mechanisms have since been postulated to explain this glycemic improvement and the same have been demonstrated in experimental animals. These include increased GLP-1 secretion, reduction of "anti-incretins" secretion due to bypass of foregut, reduced glucose uptake in small intestine, bile acid absorption, FGF 19 levels, and gut microbiome [11, 12]. However, Lingvay et al. demonstrated a different phenomenon—changes in glycemic status that occur post-bariatric surgery can be observed prior to bariatric surgery in the same patients by exposing them to a diet regimen which usually followed post-surgery [13]. This paper concluded that the remission of diabetes may have very little relation to the actual surgery and anatomical changes it entails.

The statement that obesity causes insulin resistance and type 2 diabetes is a simplistic view of a metabolically complex pathogenesis. Insulin resistance is correlated more with central obesity rather than peripheral obesity—the use of waist hip ratio as a marker of metabolic syndrome reflects this observation. Further, it is understood that liver is a major source of insulin resistance and liver fat dictates the severity of insulin resistance [14]. Similarly an effect of pancreatic fat on beta cell function was also proposed. A major support to these findings came from the CounterPoint Study [15]. The study demonstrated that a 30% reduction in liver fat levels led to a normal fasting glucose in type 2 diabetes patients within a 7-day period. This reduction was achieved by utilizing a very low calorie diet (VLCD). Further, the insulin secretion also improved, albeit gradually—around 8 weeks later. The improvement in insulin secretion correlated with reduction in pancreatic fat. While this study provided a proof-of-concept that VLCD can be used to achieve diabetes remission, the durability of this response was circumspect. A mean weight loss of 15 kg was required to achieve normalization of both beta cell function as well as liver insulin resistance. Whether such a degree of weight loss can be sustained was doubtful. However, the Counterbalance study [16] proved that the weight loss can be sustained up to 6 months and the remission could be maintained up till significant weight regain did not occur. Subsequent to these two proof-of-concept studies, a large-scale trial named DiRect was launched. This trial randomized 306 obese type 2 diabetes mellitus patients in a primary care setting who were randomized to an intervention group who received VLCD for 3–5 months followed by reintroduction of food and a control group. Close to 50% of the subjects in the intervention arm managed to achieve a diabetes remission at the end of 12 months [17]. The 2-year follow-up of this trial was published recently which shows that 36% of patients have diabetes remission [18]. In the RCT published by Mollentze et al. in this edition, VLCD was able to induce diabetes remission at 6 months in one out of nine subjects and was well tolerated. This data shows that the impressive results of DiRECT study can be replicated elsewhere, although the remission rates may be lower.

The choice between two roads

The long-term sustainability of weight loss induced by VLCD has been questioned by several authors [19]. Even the existing data is up till 2 years only. One proposed reason refers to the increase in GLP-1 and PPY with fall in ghrelin noted after bariatric surgery while the reverse occurs after dieting—which may be a proxy for VLCD [20]. A comparison of available data suggests that the remission rates are much higher with bariatric surgery compared with VLCD.

It may be safe to therefore conclude that bariatric surgery is a superior modality in terms of diabetes remission rates. However, bariatric surgery apart from being a major invasive procedure is not without its share of problems. Adverse effects of bariatric surgery include dumping syndromes, malabsorption, vitamin deficiencies, and osteoporosis apart from direct surgical complications [21]. Further, not every patient with diabetes is likely to achieve remission—therefore, undergoing a surgery for the sole purpose of remission may not be a risk worth taking. Even among those who achieve a remission, failure to correct eating behavior after bariatric surgery does indeed lead to regain of the pre-surgery weight as well as reappearance of glycemic abnormalities.

In many such situations VLCD may be a viable alternative. Many patients would voluntarily opt for a nonsurgical alternative as a shot at remission instead of a major surgical intervention. The effects as well as adverse effects of VLCD would be easily reversed as compared with a permanent alteration in bowel anatomy. Further, those who are less likely to achieve a remission after bariatric surgery, as suggested by available scores such as DiaRem and Ad DiaRem [22], may try VLCD to achieve remission. Thus, VLCD may also help in selecting patients for bariatric surgery with a goal of diabetes remission.

Finally, in several resource limited settings such as Asia, the number of diabetes patients is huge and surgical treatments can be offered to only a small fraction of this population—in such settings VLCD can be a good interim as well as long-term option.

In the fight against type 2 diabetes, the elusive goal of remission is now a tangible one. With the two roads of bariatric surgery and VLCD at our disposal, a long-term solution for diabetes may be within reach.

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