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EDITORIAL

Bariatric surgery: a metabolic solution or a paradigm for novel treatment options?

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The prevalence of obesity has increased substantially, afflicting approximately 10% of the world's population.[1] Obesity has important negative physical, psychosocial and economic consequences.

In general, quality of life in morbid obesity is decreased, which is well demonstrated by the findings that patients seeking weight loss surgery are on average willing to accept a 13% risk of death to achieve their most desired health or weight state. Social stigma or public distress, and the interference of role functioning due to physical limitations, are reported to be the major determinants of their lower quality of life.[2] Worldwide, a large number of patients undergo bariatric surgery to mitigate obesity-related complications. Metabolic surgery, as bariatric surgery is also called, has indeed been demonstrated to significantly improve or resolve cardiometabolic complications of obesity, such as type 2 diabetes (T2D), hypertension, and dyslipidaemia, as well as sleep apnoea and psychological disturbances.[3] With respect to T2D, a recent meta-analysis showed that the overall T2DM remission rate in the first 12-24 months after surgery is 63.5%.[4]

An intriguing aspect of bariatric surgery is that it greatly improves glycaemic control, often within days after surgery, and out of proportion to postoperative weight loss.[5] Therefore, in the clinical practice of bariatric surgery for patients with insulin-dependent T2D, the dosages of insulin used should be reduced to prevent postoperative hypoglycaemia. Cruijsen *et al.* show in their study in this issue of the Netherlands Journal of Medicine that an insulin dose reduction of 75% may be safe, as shown by the observations that no hypoglycaemic events occurred in the early postoperative phase, and 26% of all glucose measurements on the day of surgery and only 4% of the measurements one week after discharge were above 15 mmol/l.[6] This type of studies are valuable to provide practical tools to physicians involved in bariatric care. At present not all underlying mechanisms of the fast T2D remission have been revealed. However, elucidation of these mechanisms is of paramount importance, since they may yield improvement of surgical techniques or novel noninvasive anti-diabetic treatment strategies.

In this context, it has been shown that vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB) induce changes in the regulation of intestinal hormones leading to decreased appetite and increased satiation.[5] Remission of T2D occurs more frequently after VSG and RYBG than after laparoscopic adjustable gastric banding (LAGB). After all these types of surgical procedures, hepatic insulin sensitivity increases rapidly, and in a later phase insulin sensitivity also increases in the peripheral tissues. In addition, VSG and RYBG are also associated with improved beta cell function and an exaggerated postprandial secretion of glucagon-like peptide 1, which is attributed to the altered transit of nutrients. The vagal pathway is also suggested to be involved in the neurohumoral regulatory pathways controlling post-bariatric glucose homeostasis and appetite. Although the exact mechanisms are not yet clear, it has recently been suggested that alterations in the gut microbiota, as well as changes in bile acid concentrations, may contribute to post-bariatric improved glucose and lipid metabolism.[5]

For these reasons, metabolic surgery to treat T2D, rather than targeting obesity per se, is receiving growing attention. At present, on average, it is the most effective treatment for these conditions.[7] It should be noted, however, that the potential benefits have to weighed against the still problematic short-term and long-term risks of surgery. These risks consist of complications (17%), reoperation (7%), and death (0.31% after 30 days).[7] In the long term, nutritional complications frequently occur, which can be attributed to several causes: preoperative malnutrition, decreased food intake and inadequate nutrient supplementation. The last-mentioned can be due to poor compliance or insufficient types of supplements, malabsorption, or inadequate professional nutritional support by long-term follow-up.[8] Standard multivitamin supplementation is often not sufficient to prevent nutritional deficiencies after RYGB. It was shown that two

years after RYGB, 98% of the patients required at least one specific supplement (e.g. calcium, vitamin D, vitamin B-12, iron) in addition to the multivitamin supplementation.[8] Also, deficiencies of other nutrients such as copper and zinc can lead to adverse consequences such as poor immunity, anaemia, hair loss, and neuromuscular dysfunctioning.[9]

The effects of bariatric surgery beyond decreasing BMI and improving T2D are expected to be stabilisation or improvement of cardiovascular, renal, retinal, peripheral nervous, reproductive and hepatic end-organ damage. However, most of these outcomes have not yet been studied with randomised controlled clinical trials comparing bariatric surgery with non-surgical interventions.[10] These trials are needed to better evaluate whether the risks of surgery outweigh the significant benefits for end-organ outcomes. This is in particular important considering also the risk of weight recidivism post-bariatric surgery.

PREDICTORS OF SUCCESSFUL POST-BARIATRIC WEIGHT LOSS

It has been extensively demonstrated that bariatric surgery is highly effective as a weight loss treatment for a large number of patients.[7] With non-surgical weight loss programs the problem is often to maintain the lost weight in the long term. New insights into the well-known yo-yo effect after dietary restriction have recently been obtained. This was demonstrated by a study by Sumithran *et al.* showing that one year after a ten-week very-low-energy diet, the levels of circulating mediators of appetite that stimulate weight regain do not revert to baseline values.[11] This biological drive towards weight regain may also exhibit similarities with a subgroup of post-bariatric patients who experience weight regain. The rate of post-bariatric weight regain is reported to range from 5-39% with a mean of 21%.[12] The causes can be categorised as patient-related or operation specific. The reported major patient-related determinants are loss of dietary control with grazing behaviours (consumption of smaller amounts of food over extended periods of time) and poor diet quality, physical inactivity and uncontrolled mental disorders, e.g. binge eating, depression, alcoholism or psychiatric diagnosis.[13] Importantly, endocrine and metabolic imbalances have been reported to be associated with weight regain, such as increased plasma ghrelin levels, low peptide YY and altered glucose regulation, as shown by glucose tolerance testing with reactive hypoglycaemia at 1-2 hours after the glucose load.[14] These alterations also seem to be related to increased hunger and maladaptive eating behaviour. The major surgery-related determinants of weight regain are stomal dilation and pouch length and type of surgery with more weight regain after adjustable gastric band procedures.[13]

In the ideal world we would be able to exactly predict in advance which patients will benefit from bariatric surgery and which patients will achieve a long-term weight loss. This, of course, also applies to other anti-obesity treatments such as lifestyle interventions with diet and exercise, cognitive behavioural therapy, EndoBarrier, vagal blocking or medical therapy. Unfortunately, at present this is not the case. However, some first attempts have been made with respect to metabolic surgery outcomes. The non-surgical baseline predictors for unsuccessful weight loss or T2D remission which have been identified are: impulsive behavioural traits,[15] older age, more severe and longer duration of T2D and lower C-peptide levels,[16] higher preoperative BMI and personality disorders.[17] Greater post-bariatric benefit was reported for patients with higher educational status, Caucasian or Hispanic ethnicity, non-shift-work working patterns, female gender and social support, as well as increased levels of preoperative physical activity and an absence of binge eating behaviour.[18,19]

Most of the studies investigating predictive factors of post-bariatric weight loss comprise a relatively short follow-up, while studies with long-term follow-up are scarce. Importantly, the majority of these studies do not take into account potentially relevant other biological factors, such as genetic factors, resting energy expenditure or endocrine factors (e.g. appetite and metabolism regulating hormones). Holistic pre-treatment phenotyping of obese patients is of great importance, not only to detect underlying diseases, but also to determine which type of patients are the good responders in the long term. Considering the invasive procedures and lifelong follow-up to treat the long-term complications, which is all accompanied by high costs, it is essential to be able to predict which patients will benefit. Studies addressing all these various contributing factors to obesity simultaneously are urgently needed. This can lead to a way of personalised medicine and improve efficacy of all types of anti-obesity treatments.

Thus, bariatric surgery is indeed a solution for obesity-related metabolic disturbances for many, but not all, severely obese patients. In addition, the effects of metabolic surgery yield important new insights into the regulation of body weight and metabolism and may therefore also lead towards novel non-surgical treatment options.

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