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Long-Term Outcomes of Bariatric Surgery on Type Diabetes Remission

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ABSTRACT

While the effectiveness of bariatric surgery in achieving diabetic remission in people with moderate to severe obesity is well established, the decision between surgical and non-surgical treatment for patients with mild obesity remains unresolved. In order to achieve diabetic remission, we want to assess the effects of surgical and nonsurgical treatment for patients with a BMI of less than 35kg/m². All of the obese and prediabetic individuals who were monitored at our tertiary centre and had BS are being evaluated in this retrospective observational analysis. Regardless of A1c, patients on antidiabetic medications were deemed to have diabetes. After applying the previously indicated exclusion criteria, all 689 patients with prediabetes were included in this study, with the exception of those with BS who had no A1c during the first year of follow-up or who had undergone gastric band surgery. Bariatric surgery is superior to non-surgical treatment for achieving diabetes remission in 7 included trials with 544 participants [OR 25.06, 95%CL 9.58-65.54]. Significant decreases in HbA1c [MD -1.44, 95%CL (-1.84)-(-1.04)] and FPG [MD -2.61, 95%CL (-3.20)-(-2.20)] were more likely to occur after bariatric surgery. The BMI may decrease after bariatric surgery [MD -3.14, 95%CL (-4.41)-(-1.88)], which is especially noticeable in Asians. In conclusion Bariatric surgery is more likely than nonsurgical treatment to result in diabetes remission and improved blood glucose control in people with type 2 diabetes whose BMI is less than 35kg/m².

INTRODUCTION

According to data released by the International Diabetes Federation (IDF), the global prevalence of diabetes among people aged 20-79 is estimated at 10.5% (536.6 million people) in 2021 and is expected to rise to 12.2% (783.2 million) by 2045^[1]. T2DM has high incidence rate, morbidity and mortality, causing a heavy burden on individual families and society. The 2021 ADA consensus statement updated the recommended definition of diabetes remission: HbA1c <6.5% for at least 3 months after suspending hypoglycemic drug^[2]. If there are factors that affect the accuracy of HbA1c detection, the surrogate indicator can be used: the average HbA1c <6.5% estimated by continuous blood glucose monitor or fasting blood glucose <7.0mmol/L^[3]. Diabetes requires long-term treatment with antidiabetic medications, which is essential to prevent acute complications and reduce the risk of long-term complications. However in recent years, this statement is gradually changing with the continuous accumulation of evidence-based medicine^[4]. When patients reach diabetes remission, they can free from hypoglycemia medications for some time and delay disease progression. Little is known regarding the effect of bariatric surgery (BS) on the remission of prediabetes. BS is a highly effective treatment for obesity, which is associated with a significant cardiometabolic improvement and has been proven to reduce cardiovascular risk both in patients with diabetes and prediabetes^[5]. There is firm evidence regarding diabetes remission after BS and glucose metabolism improvement^[6,7]. Our group has previously studied predictors of diabetes remission after BS and concluded that patients' age, preoperative glycated haemoglobin (A1c) and preoperative beta cell are useful for predicting diabetes remission^[8]. In addition, Moriconi D. *et al.*, showed that short T2D duration and good glycaemic control before BS were associated with longlasting diabetes remission^[9]. This is in accordance with data from Panunzi^[10]. However, data regarding prediabetes remission after BS is scarce, besides being biologically plausible. We believe that this is an important gap in knowledge, considering the possible benefit of bariatric surgery in prediabetes.

According to NIH (National Institutes of Health) standard, type 2 diabetes patients who BMI above 35kg/m² are eligible for bariatric surgery. However this standard was formulated 20 years ago and have not updated and now the mortality and complications of surgery have been reduced compared with 20 years ago^[11,12]. Indication for bariatric surgery in patients with BMI <35kg/m² is controversial and no guidelines currently recommend bariatric surgery for non-obese patients. Therefore, it is necessary to study diabetes patients with BMI <35kg/m². Current nonsurgical treatments for patients with BMI <35

kg/m² are often ineffective in achieving significant long-term weight loss and diabetes remission. There is new evidence to support that the mild obese diabetic patients who suffered bariatric surgery are more able to reach diabetes remission than those who had non-surgical therapy^[13]. This article aims to evaluate the diabetes remission, weight loss and blood glucose control of patients with BMI <35kg/m² who had bariatric surgery and other nonsurgical treatments and provide clues whether to have bariatric surgery for patients who BMI do not meet the surgical criteria.

MATERIALS AND METHODS

This is a retrospective observational study evaluating all the patients with obesity and prediabetes who had BS and were followed in our tertiary centre. Patients taking antidiabetic drugs were considered to have diabetes regardless of A1c. Patients with BS who had no A1c during the first year of follow-up or who had had gastric band surgery were not included in the analysis, but all other patients with prediabetes, 689 patients in all were included in this research after the aforementioned exclusion criteria were applied. Categorical variables are defined as proportions (percentages), while continuous variables are defined as mean \pm standard deviation or median (25th to 75th percentiles). We conducted both unadjusted and adjusted logistic regression analysis with the primary outcome being the remission of prediabetes. Sex, age, baseline A1c, type of surgery and weight loss were all included in the modified model. The model was constructed using biological plausibility and existing information of risk variables and confounders. To evaluate the relationships between our predetermined factors (sex, age and kind of surgery) and prediabetes remission, we conducted subgroup analysis. Stata software, version 14.1 (StataCorp), was used for statistical analyses.

RESULTS AND DISCUSSIONS

(Table 1) shows the demographic and clinical characteristics of the included population (n=689). The population had a mean age of 46.3 \pm 11.2 years-old, body mass index of 44.7 \pm 6.6kg/m² and median A1c of 6.8 [6.7, 7.2] %. The majority of patients (68.2%) underwent gastric bypass (GB) surgery. Supplementary (Table 1) shows loss of follow-up per year (31.7%, 44.8% and 64.2% respectively for 2nd, 3rd and 4th years).

(Table 2) show our subgroup analysis regarding remission of pre-diabetes according to the type of surgery. There are no differences between patients which underwent GB surgery and gastric sleeve (GS) surgery in the 1st and 2nd years post BS. Patients who had GS had a higher odds ratio for prediabetes remission in the 3rd year of follow-up both in adjusted and

Table 1: Clinical and Demographic Characteristics of the Population Included (n=689)

Age, years	46.3±11.2
Feminine sex, n (%)	571 (82.8)
Weight, kg	116.6±20.1
Body Mass Index, kg/m ²	44.7±6.6
Waist circumference, cm	124.8±14.1
Hip circumference, cm	132.6±12.3
Dyslipidaemia, n (%)	309 (44.8)
Hypertension, n (%)	443 (64.2)
Glycated haemoglobin, %	6.8±[6.7, 7.2]
Type of surgery	
Gastric bypass, n (%)	470 (68.2)
Gastric sleeve, n (%)	219 (31.7)

Table 2: Remission of Pre Diabetes According to the Type of Surgery (4 Years of Follow Up)

	Unadjusted analysis		Adjusted analysis ^a	
	OR	95% CI	OR	95% CI
Year 1	2.01	0.68-2.55	0.79	0.46-2.33
Year 2	0.98	0.65-2.56	2.53	0.87-3.74
Year 3	2.74	2.07-3.85	3.01	2.12-4.60
Year 4	2.28	0.77-3.18	2.61	0.86-4.00

Table 3: Remission of Pre Diabetes According to Sex (4 Years of Follow Up)

	Unadjusted analysis		Adjusted analysis ^a	
	OR	95% CI	OR	95% CI
Year 1	0.52	0.27-0.96	0.47	0.20-2.07
Year 2	0.99	0.55-2.78	2.04	0.49-2.02
Year 3	0.29	0.12-0.69	0.50	0.20-2.31
Year 4	0.59	0.24-2.48	0.50	0.18-2.40

Table 4: Remission of Pre Diabetes According to Age Terciles (4 Years of Follow up, 1st Arteriole as Comparer)

	Unadjusted analysis				Adjusted analysis ^a			
	2nd tercile		3rd tercile		2nd tercile		3rd tercile	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Year 1	0.77	0.41-2.42	0.70	0.38-2.28	0.88	0.46-2.69	0.91	0.48-2.72
Year 2	0.79	0.41-2.48	0.56	0.31-2.03	0.90	0.46-2.75	0.73	0.37-2.39
Year 3	0.87	0.45-2.66	0.42	0.23-0.76	0.96	0.49-2.89	0.42	0.22-0.81
Year 4	0.55	0.28-2.9	0.51	0.36-0.997	0.76	0.36-2.60	0.63	0.30-2.30

non-adjusted analysis. No differences were seen in the 4th year of follow-up. (Table 3) refer to remission of pre-diabetes according to sex. Female patients present a lower odds ratio for prediabetes remission in the 1st and 3rd years of follow-up, only in the non-adjusted analysis. (Table 4) concern the remission of pre-diabetes according to age terciles (1st tercile, 19-38 years-old, 2nd tercile 39-48 years-old, 3rd tercile 49-67 years-old). Older patients (3rd tercile compared to 1st tercile) have a lower odds ratio for pre-diabetes remission through-out follow-up in the non-adjusted analysis from 3rd year of follow-up onwards, this is significant only for the 3rd year in the adjusted analysis.

Our findings indicate a high rate of prediabetes remission following bariatric surgery, which is particularly noteworthy for younger, male and GS surgery patients. These findings contribute to closing the information gap about how bariatric surgery affects prediabetes. In the first year following BS, we report an 82% remission rate of prediabetes, in the second, third and fourth years following BS, the corresponding remission rates are 73%, 66% and 58%. Furthermore, our findings indicate that in the second, third and fourth years following BS, 3%, 6% and 5% of

patients, respectively, developed diabetes. Despite the paucity of precise data about the remission of prediabetes following BS, there is evidence that BS significantly improves fasting plasma glucose levels over the long term in a population with a wide range of ethnic backgrounds^[6]. Dicker *et al.* sought to determine the rate of conversion from prediabetes to diabetes in patients with prediabetes during a 5-year follow-up following BS and they found that the conversion rate was 10.1%^[14]. A number of factors, including the many populations examined and the variations in the follow-up duration, could account for the discrepancy between this convergence rate and ours. With regard to the subgroup analyses, our results show that patients who underwent GS surgery are more prone to prediabetes remission, comparing to patients who underwent GB in the 3rd year of follow up. We believe that the lack of significant results at 4th year is due to the missing data. Although there is a clear gap in knowledge in this regard, there are data comparing the two procedures considering overt T2D remission. However, results are quite controversial. Some authors argue that both surgical procedures are associated with a similar diabetes remission rate^[15,16] while others show that GB is a better option comparing to GS^[17-19].

GB has long been regarded as the gold-standard procedure in surgical treatment of obesity and its related comorbidities. However, GS is being more frequently performed due to its easier and potentially safer technique^[20]. There are few studies comparing the two regarding the outcomes and our study contributes to the missing information. Peteril *et al.* report no significant difference between the two procedures concerning excess BMI loss at 5 years of follow-up after BS^[20].

The results of the BMI analysis were not all the same. We attempted to identify the factors that are important sources of heterogeneity using the subgroup analysis method. For subgroup analysis, we created several subgroups, including various baseline, diabetes duration and race., however, the source of heterogeneity was still not identified. In order to identify the cause of heterogeneity, we also employed the trim-and-fill technique. When we removed the Wenhuan F's study, heterogeneity I² is 41%. We compared all the study that we included, finding the decrease of BMI in bariatric group in this study was lower than other studies. It may be due to the higher baseline mean BMI or shorter follow up month, which leads to lower decrease of BMI. That may be the reason for the heterogeneity of BMI^[21]. Bruno G's study also the source of heterogeneity in outcome of BMI. It can be explained that the baseline BMI is far lower in this study and his baseline BMI is 26.3kg/m² (control group) and 26.1kg/m² (surgical group). Therefore, the weight loss effect is not obvious in both control group and surgical group, resulting in the heterogeneity. Bruno G's study supposed that the effect of glucose metabolism is a direct consequence of metabolism rather than a secondary effect of weight loss. However, more possibilities need to be supported by more research^[22]. In the analysis of HbA1c and FPG heterogeneity also exists in the results and heterogeneity comes from Bruno G's study. when Bruno's study is removed, heterogeneity I² is 34% (outcome of HbA1c) and 0% (outcome of FPG). Both HbA1c and FPG reflect blood glucose control, indicating that compared with other studies, the blood glucose control in this study was slightly poor. However, after 12 months of follow-up, patients still had significantly decrease of blood glucose and HbA1c than before and after the surgery glucose homeostasis was improved and diabetes resistance was reduced. It is important to recognize that this study has inherent limitations. First of all, because this is a longitudinal retrospective study, particular bias is more likely to occur. For example, prediabetes was classified only using A1c because we lack fasting glucose data. Additionally, we have a significant amount of missing data because follow-up was lost starting in the third year following BS. This could cause selection bias to impact our findings and

could help to explain why certain results fall short of statistical significance. Furthermore, even while we think our model of adjustment takes into account the most pertinent confounders, there are still those that we might not have considered. The significance of our findings and the sheer quantity of participants from this frequently disregarded group, however, more than make up for these drawbacks and pave the way for future research in this field. In addition to estimating the likelihood of remission based on age, sex and the kind of surgery, our data can assist doctors in counselling patients with prediabetes about the high chance of remission following BS.

CONCLUSION

Bariatric surgery is more likely than nonsurgical treatment to result in diabetes remission and improved blood glucose control in people with type 2 diabetes whose BMI is less than 35kg/m². Remission of prediabetes appears to be particularly important in younger, male and GS-affected patients. These findings contribute to closing the information gap about how bariatric surgery affects glucose metabolic disorders.

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