Review Article

Predictors for type 2 diabetes mellitus remission after metabolic/bariatric surgery

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Abstract: Type 2 diabetes mellitus (T2DM), fueled by an obesity epidemic, have emerged as a major health problem worldwide. Metabolic surgery, derived from bariatric surgery, is now proposed for the treatment of obese T2DM patients. Several randomized trials aimed at T2DM treatment have been performed and universally showed that metabolic surgery is more effective than medical treatment in glycemic control. However, not every T2DM patient benefit from metabolic surgery. An article review disclosed that pre-operative β-cell function, and its surrogates, including duration of diabetes and C-peptide, was the most important predictor of T2DM remission. Other factors were insulin use, HbA1c level, BMI, age, type of operation and miscellaneous ones. Some scoring systems, such as "ABCD" in the Diabetes surgery score (age, BMI, C-peptide and duration of T2DM), may help evaluate effectiveness of T2DM remission after surgery. In conclusion, metabolic surgery is a novel treatment option for obese T2DM patients but not all the patients are indicated. Pre-operative β-cell function (including duration of diabetes and C-peptide) are important predictor of the success of metabolic surgery. A scoring system is helpful for counseling patients and referring physicians, and may help to guide their expectations.

Keywords: Type 2 diabetes; metabolic surgery; predictor; remission

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Introduction

Type 2 diabetes mellitus (T2DM), booster by obesity epidemic, poses a major threat to health and represents an economic burden worldwide now (1). Bariatric/metabolic surgery is becoming a potential cure for T2DM in an unexpected way. Strong evidences have shown that this kind of surgery provides significant and durable weight loss and remission of associated T2DM in morbidly obese patients (2-4). A 78.1% complete remission (so-called "cure") rate of T2DM was reported by Buchwald *et al.* in a meta-analysis study (2). Meijer *et al.* reported a similar 62–83% of T2DM remission rate at a 2- to 4-year follow-up in a systemic review (3). Pories *et al.* than reported a long-term T2DM remission rate of 82.9% at a 10- to 14-year follow-up in a case series. However, these studies were aimed at obesity treatment in morbid obese patients and using relatively loose criteria for T2DM remission. On the other hand, bariatric/metabolic surgery, sometimes irreversible, may cause considerable short- and long-term risks or co-morbidities (5). Therefore, for patients with T2DM, to achieve the most benefit from bariatric/metabolic surgery, strict and cautious preoperative evaluations are required. Optimal outcomes for the surgical treatment of T2DM depend on the way that distinguish patients suitable for surgery from patients not likely to respond well to surgery. Understanding the criteria for the latter group is critical in

patients counseling and referring physicians and help guide their expectations with regard to the outcomes of various weight-relate disease. Although weight loss plays a key role in diabetes remission, other pre-operative predictors for diabetes remission are also important and should be considered in counseling patients for surgery. There were some review articles but lack an adequate number of relevant articles for review, resulting in controversial or inconsistent conclusions (5,6). In this review, we will focus on reported pre-operative predictors and predicting system for T2DM remission after metabolic surgery.

β-cell preserve

Because β cell is progressively deteriorating in the natural course of T2DM, the most important predicting factor for the success of metabolic surgery is related to the β-cell preserve and function of the T2DM patients. However, at present there is no good way to direct evaluate the beta cell mass or function of insulin secretion. There are several surrogates of β-cell function, such as C-peptide, duration and some challenge tests. We will discuss in the following.

C-peptide

C-peptide is a connecting peptide to insulin and was secreted at the same time when insulin was secreted. Although insulin levels have a similar indication as C-peptide levels, directly measuring insulin levels may be difficult because of the hepatic clearance or in patients receiving insulin therapy. Therefore, C-peptide becomes a surrogate of insulin and represents the capacity of insulin secretion, and can be used as an important predictor of patients who may benefit from bariatric surgery. As β cells are progressively destroyed in late stage T2DM, C-peptide levels may progressively decrease to very low levels in late stage patients. Therefore, levels of C-peptide levels reflect the pancreas preservation of T2DM patients. Measuring C-peptide levels help us to understand the β-cell preserve of T2DM patients. Although some controversies remained (7), many studies reported that fasting C-peptide is an important predictor of T2DM remission because C-peptide may represent the residual β-cell function of T2DM patients (8-19). Lee found that elevated C-peptide is very important in predicting the success of T2DM remission after LSG in low BMI patients for the first time (8). C-peptide was found to be linear correlated with the BMI and measurement of C-peptide is indicated in low BMI T2DM patients before considering metabolic surgery for the treatment of T2DM (9). High C-peptide levels equate to a good reserve of beta-cell function with sufficient mass, especially in the low BMI and Asian groups. Elevated C-peptide levels usually implicated the existence of insulin resistance and a compensated secretion of insulin by well-preserved pancreatic β-cell. Therefore, a greater C-peptide level usually associates with a higher T2DM remission rate after metabolic surgery (8,10). Some studies found that stimulated C-peptide level or total secretion amount of C-peptide (measured by area under curve during glucose tolerate test) was also predictor of T2DM remission (20,21).

Duration of T2DM

The importance of disease duration as predictor of T2DM was first reported by Pories *et al.* in his historical landmark article (4). Since then, many studies consistently confirmed that disease duration is an important predictor and the most commonly reported predictor of T2DM remission (10,12,13,17-19,22-40). Duration has also been confirmed by a multivariate analysis to be the only pre-operative predictor of T2DM remission after adjustable banding in a randomized trial (23). In sleeve gastrectomy patients, Rosenthal *et al.* found that the T2DM remission rate become very low once the patient's T2DM duration greater than 5 years (25). Lee *et al.* also reported that the duration of T2DM was the most important predictor of success after metabolic using a decision tree analysis (28). Arteburn *et al.* in a big cohort study of 4,434 gastric bypass patients identified that longer diabetes duration is a significant predictor of complete remission and relapse (35). Because T2DM is a disease with progressive decrease of both of β-cell mass and function, the duration of disease usually can reflect the residual β-cell preserve. The long duration of T2DM indicates a smaller chance of T2DM remission. The cut-off point was calculated in some articles as 1.6, 2, 4, 5, 8 and 10 years. Therefore, earlier surgical intervention, equates to better outcomes, should be encouraged. Although some may argue that disease duration is subjective and estimated, this study shows the importance of disease duration in predicting the success of metabolic surgery. Therefore, earlier intervention is not only important to increase the rate of T2DM remission but can also prevent the development of T2DM (41).

Pre-operative β-cell function

Although C-peptide levels may partially reflect residual

β-cell function, fasting levels of C-peptide have some limitations, such as their suppression in hyperglycemic status. Thus, the interpretation of low C-peptide levels must be made with caution (7). Various preoperative assessments of beta-cell function, including glucose sensitivity β-cell glucose sensitivity (BCGS) (42,43), lower insulin sensitivity (ISR) (44), glucagon like peptide-1 (GLP-1) response (45), area under the curve (AUC) of glucose, insulinogenic index derived from a standard meal test (IGIstm), acute insulin response to glucose (AIRg), disposition index derived from an intravenous glucose tolerance test (DIfsivgtt) (46), disproportion index (DI) (47), HOMA-%B (48), ISSI (49) and so on, have been proven to be useful in evaluating the degree of the beta-cell function reserve and predicting T2DM remission rates. However, these studies are too complex for routine clinical practice. C-peptide and duration are simple and good surrogates of β-cell preserve and should be adopted in pre-operative evaluation of T2DM patients for metabolic surgery.

Disease severity of T2DM

Good glycemic control is the principle goal of diabetes treatment. The severity of T2DM is interpreted by glycemic control represented by hemoglobin A1c (HbA1c) or using insulin therapy.

Pre-operative HbA1c or fasting glucose

HbA1c generally reflects the range of glucose fluctuation in the past two weeks and may indicate the severity of T2DM. Greater HbA1c levels indicate high blood glucose levels which usually result from poor higher insulin resistance or lower β-cell function. Many studies reported that lower HbA1c levels (HbA1c cut-off point was <7–8%) equate to a higher T2DM remission rate after surgery (24,26,30,34,35,37,50-52). High HbA1c correlates to a poorer baseline and lower probability of remission. However, many studies also found HbA1c is not a independent predictor when duration and C-peptide are consider because newly diagnosed T2DM patients might present with very high HbA1c but will response to surgery well. In addition, very T2DM patients with high HbA1c should not be denied for the metabolic surgery because high HbA1c means very high risk of diabetic related complication and those are the best to benefit from metabolic surgery (53). In some studies without HbA1c data, fasting glucose level was shown to be an independent predictor of T2DM remission (34,50).

Pre-operative Insulin use

Insulin usage is the second most reported preoperative predictor. Many studies reported that patients who did not receive insulin therapy are more likely to have T2DM remission after surgery than the patients who underwent insulin treatment after surgery (24,27,29,30,34,35,50,52,54-56). Insulin was usually prescribed when the residual β-cell reserve could not provide enough insulin for glycemic control. In another words, insulin usage implied a more severe disease stage, thus decreasing the DM remission rate. However, some of the studies which reported use of insulin is an independent predictor didn't have the information of duration of T2DM (50,52,54,56). Because the longer the disease, the higher of the rate of insulin usage, insulin usage might not be a important predictor if duration was analyzed at the same time. Other important confounding factors of insulin usage are regional guideline, drug license, local practice and the compliance of patients (57). For example, UK had a higher rate of insulin usage than in the USA (23.3% *vs.* 8.1%) (58,59). In another randomized trial of surgical versus medical treatment of diabetes patients, more than 70% of the USA patients used insulin, while only 30% of Taiwanese patients used insulin (20). This study found that insulin usage is not a predictor of T2DM remission in the low BMI and Asian groups.

General physical status

Many general physical statuses had been reported to be independent predictors. These factors included age, sex, BMI, waist and some miscellaneous factors.

Age

Some studies found that young age predict a higher T2DM remission rate than old age (4,9,18,27,31,52,56,60-62). Age not only represents the general reserve of physiological function but also β-cell preserve. Increase of the age implied the decline of β-cell mass and functional reserve. It was found that each additional 12 years of age reduced 20% the chance of T2DM remission by metabolic surgery (62). Although young-onset T2DM patients had a worse glycemic control than adult-onset, young-onset patients had a better T2DM remission rates after metabolic surgery (63). Therefore, metabolic surgery is highly recommended not only in the early stage of T2DM but also in young-onset

T2DM patients.

Pre-operative BMI (body mass index)

The predictive power of morbid obesity (BMI >35 Kg/m^2) on T2DM remission after surgery is controversial. Lee *et al.* was the first to found that T2DM remission rate was lower in low BMI patients than in high BMI patients (64). Hayes *et al.* reported five independent predictors including BMI (50), whereas Mingrone *et al.* found negative results with BMI (65). Both studies had similar pre-operative mean baseline BMIs of 48 Kg/m^2. Other studies support the role of BMI (10,18,31-33,61) where others didn't (9,11,30,33,36,66). However, super-morbid obesity (BMI >50 Kg/m^2) was found to be a negative predictor of T2DM remission (34), possibly as a result of the correlation between super obesity and severe insulin resistance or destroyed β-cells. Although BMI as a preoperative factor remains controversial, high BMI usually associated with greater weight loss and may provide a greater effect on T2DM remission. In randomized trials, the reported T2DM remission rate was progressively lower with decreasing of BMI (16,40,65,67). The T2DM remission rate after Roux-en-Y gastric bypass was 80% in a study with mean BMI of 48 Kg/m^2 (65) and 50% in a study with mean BMI of 36 Kg/m^2 (67), and less than 30% in those with a mean BMI <30 Kg/m^2 (16,40,67). Other studies of patients with BMIs < 35 Kg/m^2 also reported that BMI was an independent predictor (12,18,31,36). Therefore, the T2DM remission rate is probably higher in patients with BMIs >35 but <50 Kg/m^2 than in patients with BMIs <35 Kg/m^2. Although BMI as a predictor of T2DM remission after metabolic surgery remained controversial, it was important in evaluating the low BMI or Asian groups.

Waist

Data on waist is controversy, one study found waist is an independent predictor of T2DM remission after metabolic surgery (13) but another study found that waist is a negatively predict (54). One study found that visceral-to-subcutaneous fat ratio is an important predictor of T2DM remission (51). Cohen *et al.* found that reduction of 7% waist is the only predictor of T2DM remission after gastric bypass (68).

Sex

One study found that female was a favor predictor of T2DM remission (62) but controversy existed (56). Another study found that male was a negative predictor of T2DM remission (61).

Miscellaneous factors

Some miscellaneous factors reported to be predictors of T2DM remission after metabolic surgery was listed below.

Oral medication

One study found that oral medication (usage of sulfaurea) was a predictor of T2DM remission and put this factor into a predictive score, DiaRem score (52).

Meal stimulated GLP-1 response

Two studies found that strong response of meal stimulated GLP-1 response was a predictor of T2DM remission after surgery (43,45).

sRAGE

One study reported that soluble RAGE is a predictor of T2DM remission after surgery (69).

Rapid response to low calories diet (LCD)

One study reported that a rapid response to LCD is a predictor of success of metabolic surgery (66).

Robust incretin response

One study found that a robust incretin response was a predictor of success of metabolic surgery on T2DM treatment (49).

Weight loss

Since obesity is the most important risk for the development of T2DM, body weight reduction of course is important for T2DM remission. Many studies reported weight loss was important predictor of T2DM remission after surgery (12,22,30,39,55,60,62). A review article showed that decrease of HbA1c was linear correlated with weight loss even in BMI <35 Kg/m^2 T2DM patients (70). One study found that weight loss was the most important predictor for success of metabolic surgery in patients with BMI

Table 1 Predictors in different scoring system for T2DM remission of metabolic surgery

Predictors	ABCD score (18)	DiaRem score (52)	Estimate (29)	Statistic (19)	Simple L (50)	Logistic M (39)	Predictive E (11)
T2DM Duration	★		★			★	★
C-peptide	★			★			★
Insulin usage		★	★	★	★		
HbA1c		★			★		
BMI	★					★	
Age	★	★					
Oral drug (sulfaurea)		★					
Sex				★			
Fasting sugar				★		★	
Weight loss				★			★
Op type						★	

T2DM, type 2 diabetes mellitus; Op, operation; L, logistic; M, model; E, equation.

<30 Kg/m^2 (71). Because weight loss itself can't be predicted before surgery but might be predicted by procedure, the role of weight loss as a pre-operative predictor was usually replaced by operation type.

Operative type

Gastric bypass procedure was found to have a higher T2DM remission rates than various restrictive procedures, such as laparoscopic adjustable gastric banding or laparoscopic sleeve gastrectomy (13,32,33,65,67,72-74). The superiority of different bypass procedures can be attributed to a greater weight loss rather than different anatomical changes and physiologic mechanisms (BPD > RYGB/MGB > SG > ABG) (70). However, recent studies found that duodenum exclusion plays an important role on T2D treatment (75-77). Duodenum jejunal bypass (DJB) tube was a concept pioneered by Rubino for the treatment of T2DM in animal model (78). A recent developed new device, duodenum jejuna sleeve tube or liner, was demonstrated having a similar glycemic control effect in human (79). Therefore, metabolic surgery with duodenum exclusion is more favor than other procedure for the treatment of T2DM (40,67,76).

Scoring system

If we can select T2DM patients who are best suited for metabolic surgery and exclude those who are predicted to have poor results, we shall have optimal outcomes for metabolic surgery. This requires an understanding of the predictor of T2DM remission after surgery and designing specific scoring system to counsel patients and referring physicians. Several scoring systems had been proposed (11,18,19,29,50,52). *Table 1* showed the consisted components of different scoring systems. A model for predicting the resolution of type 2 diabetes in severely obese subjects following Roux-en Y gastric bypass surgery was first proposed by Hayes *et al.* (50). Another statistical model to predict type 2 diabetes remission after bariatric surgery was then designed by Ramos-Levi *et al.* (19). Dixon *et al.* using a simple score of duration, BMI and C-peptide can predict a 92% success rate of remission (11). Recently, a "Diabetes Surgical Score (ABCD score)" included age, BMI, c-peptide and duration of disease using prospectively collected data was proposed by Lee *et al.* (13). Still *et al.* proposed another probability score, DiaRem score, using age, use of insulin, HbA1c and type of anti-diabetic medication (52). The DiaRem score has been validated in different area but was found to be limited in high score patients (80,81). The ABCD score has a better differentiate power than DiaRem score, especially in patients with high DiaRem score (82,83). The ABCD score, system has also been validated in different population (84-87). One study demonstrated that ABCD score is the only important predictor of durable T2DM remission after metabolic surgery other than weight loss (88). Therefore, this ABCD score is recommended to identify the best candidates for metabolic surgery.

Conclusions

Bariatric/metabolic surgery significantly improves glycemic control in T2DM patients and may result in complete remission of T2DM in some patients. This review suggests that some pre-operative factors may be useful in clinical application. The most important factor is the pre-operative beta-cell preserve, represented by duration of disease and C-peptide level, which highlights the importance of early surgical intervention to treat T2DM. A simplified diabetes surgery scoring system, ABCD score, has been developed. This score system can help the physician in clinical practice. The endocrinologist may use this system to set the priority for referring T2DM patients for metabolic surgery. The surgeon can use this system to counsel the patients for outcome and choice of surgical procedure.

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