

Reversibility of diabetes mellitus: Narrative review of the evidence

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Author contributions: Ang GY contributed to the manuscript.

Conflict-of-interest statement: No potential conflicts of interest.

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Manuscript source: Invited manuscript

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Received: March 26, 2018

Peer-review started: March 27, 2018

First decision: April 13, 2018

Revised: April 19, 2018

Accepted: May 31, 2018

Article in press: May 31, 2018

Published online: July 15, 2018

Abstract

The global disease burden of diabetes mellitus is high. It is well-established that prediabetes is reversible but it is unclear whether diabetes is reversible once it has been diagnosed. The objective of this narrative review is to review the evidence of reversibility of diabetes me-

llitus and stimulate interest in prolonged remission as a treatment target. The current evidence for bariatric surgery is stronger than intensive medical management and the evidence is stronger for type 2 diabetes patients compared with type 1 diabetes patients. It is also unclear whether non obese diabetes patients would benefit from such interventions and the duration of diabetes before diabetes become irreversible. Further research is needed in this area especially with regards to the subgroup of diabetes patient who will benefit from these interventions and the long term safety and efficacy remains unknown especially with intensive medical management.

Key words: Diabetes; Reversibility; Remission; Bariatric surgery; Obesity

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Core tip: Diabetes mellitus is potentially reversible especially with bariatric surgery. Intensive medical management is promising but the evidence is weaker. The subgroup that is likely to go into prolonged remission is those with insulin resistance, short duration of diabetes and obesity. Further research is needed to identify those that can go into remission and how to use intensive medical management to achieve this.

Ang GY. Reversibility of diabetes mellitus: Narrative review of the evidence. *World J Diabetes* 2018; 9(7): 127-131 Available from: URL: <http://www.wjgnet.com/1948-9358/full/v9/i7/127.htm> DOI: <http://dx.doi.org/10.4239/wjd.v9.i7.127>

INTRODUCTION

The number of adults with diabetes in the world has increased from 108 million in 1980 to 422 million in 2014 due to rise in prevalence, population growth and

ageing^[1]. Diabetes Mellitus has been projected to become the 7th leading causes of death in 2030^[2]. It has been estimated that the direct medical costs of diabetes to the world is more than United States \$827 million^[2]. It is well-established that prediabetes is reversible^[3-7], but it is unclear whether diabetes is reversible once it has been diagnosed.

Type 2 diabetes mellitus is potentially reversible^[8]. A better term to use would be remission which is defined to be achieving glucose level below the diabetic range in the absence of active pharmacologic or surgical therapy^[9]. It can further be divided into partial or complete and if complete remission lasts for more than 5 years, it would be considered as prolonged remission^[9]. In community settings, in the absence of bariatric surgery, the 7-year cumulative incidence of partial, complete or prolonged remission was found to be 1.47% (1.40%-1.54%), 0.14% (0.12%-0.16%) and 0.007% (0.003%-0.020%)^[10] which is very low.

In this narrative review, the evidence of reversibility of diabetes mellitus will be reviewed in light of new studies recently published. This can help stimulate interest in prolonged remission as a treatment target for patients with established diabetes.

BARIATRIC SURGERY

There are several systematic reviews on the impact of bariatric surgery on diabetes mellitus^[11-13] and some have distinguished between type 1 diabetes^[14-16] and type 2 diabetes^[17-20] (Table 1). The percentage of diabetes remission after bariatric surgery is estimated to be 76.8%^[12] to 92%^[11]. However, the exact physiological and molecular mechanisms behind diabetes remission after bariatric surgery remains incompletely understood^[21,22]. (Figure 1) There are several reviews that looked at the role of bariatric surgery in managing diabetes mellitus^[23-26] and the mechanism behind reversibility of type 2 diabetes mellitus^[27,28]. All agree that diabetes remission can be an important outcome to look at after bariatric surgery and there are many risk prediction models which can predict diabetes remission^[29].

Besides diabetes remission, bariatric surgery may also reduce inflammation^[30,31], improve renal function^[31], reduce cardiovascular risk^[32] and reduce microvascular and macrovascular complications^[33]. The impact of bariatric surgery on all these remains incompletely understood.

Even if the evidence is strong for remission of diabetes after bariatric surgery, it is unlikely to be advocated at the population level due to the high cost and lack of surgeons well trained to perform bariatric surgeries. Furthermore, the indication for bariatric surgery is currently for patients with a body mass index above 35 kg/m² or between 30 and 35 kg/m² with inadequate glycemic control despite optimal medical treatment^[34]. This would not benefit diabetes patients who are non-obese (body mass index < 30 kg/m²) and the remission

rate has been shown to be much lower in non-obese diabetes patients^[18].

PANCREAS TRANSPLANTATION AND ISLET CELL TRANSPLANTATION

A recent review found that there is a need for multicenter randomized trials in pancreas transplantation to define clearly the efficacy, risks, and long term benefits due to lack of high quality evidence^[35]. The indications for pancreas transplantation alone are in patients with severe metabolic complications, incapacitating problems with exogenous insulin therapy and failure of insulin based management to prevent acute complication^[35]. It would not be to induce diabetes into remission. A systematic review on islet cell transplantation for type 1 diabetes mellitus has also concluded that there is low to very low quality evidence for all outcomes of interest such as remission of diabetes^[36].

The next question to ask is whether pancreas transplantation is able to reverse complications of diabetes such as diabetic nephropathy. A recent study has demonstrated that diabetic nephropathy may be reversible after pancreas transplantation^[37] that is contrary to current thinking. Further research is needed to look at whether it is possible to reverse diabetes and/or its complications after pancreas or islet cell transplantation.

INTENSIVE MEDICAL MANAGEMENT

There are relatively fewer studies on non-surgical remission of diabetes mellitus. A randomized controlled trial found that 40.7% of patients with type 2 diabetes for less than 3 years had complete or partial remission at 12 mo^[38]. A cluster-randomized trial found that primary care-led weight management achieved a remission rate of 46% at 12 mo in patients with type 2 diabetes for less than 6 years^[39]. A retrospective observational study of obese patients with type 2 diabetes found that 4.6 % achieved partial or complete diabetes remission after a 12-wk intensive program for diabetes weight management^[40]. These studies did not look at the long term effectiveness of such intervention of the remission of type 2 diabetes mellitus and whether the same effect could be seen in patients with type 1 diabetes, non-obese diabetes patients or those with longer duration of type 2 diabetes.

Further research is needed to evaluate the long term effectiveness and safety of intensive medical management before recommending this but the results seem promising.

CLUSTERS OF DIABETES MELLITUS

A recent study has identified 5 replicable clusters of adult-onset diabetes with different disease progression and risk of diabetes complications^[41]. The 5 clusters are

Table 1 Bariatric surgery systematic reviews

Ref.	Type of diabetes	No. of studies included	Remission percentage (95%CI)
Chang <i>et al</i> ^[11] , 2014	Not specified	164 (37 randomized clinical trials and 127 observational studies)	Randomized clinical trials: 92% (85%-97%) Observational studies: 86% (79%-92%)
Buchwald <i>et al</i> ^[12] , 2004	Not specified	136	76.8% (70.7%-82.9%)
Gloy <i>et al</i> ^[13] , 2013	Not specified	11	59.90%
Ashrafian <i>et al</i> ^[14] , 2015	Type 1 diabetes mellitus	27	Weighted mean decrease in insulin requirement: 44.5 units 78.1% (73.8%-82.3%)
Chow <i>et al</i> ^[15] , 2016	Type 1 diabetes mellitus	13	Weighted mean total daily insulin requirement decreased from 98 +/- 26 IU/d to 42 +/- 11 IU/d
Mahawar <i>et al</i> ^[16] , 2016	Type 1 diabetes mellitus	15	Not reported
Buchwald <i>et al</i> ^[17] , 2009	Type 2 diabetes mellitus	621	76.2% insulin free
Baskota <i>et al</i> ^[18] , 2015	Type 2 diabetes mellitus	10	61.8% medication free
Goh <i>et al</i> ^[19] , 2017	Type 2 diabetes mellitus	24	Remission rate Duodenal-jejunal bypass: 20%-40% Duodenal-jejunal bypass with sleeve gastrectomy: 79%-93% Duodenal-jejunal bypass sleeve: 62.5%-100%
Yan <i>et al</i> ^[20]	Type 2 diabetes mellitus	6	Ileal interposition with sleeve gastrectomy: 47%-95.7% Type 2 diabetes mellitus remission rate for roux-en-y gastric bypass <i>vs</i> medical treatment: OR: 76.4 (95%CI: 20.7-281.7)

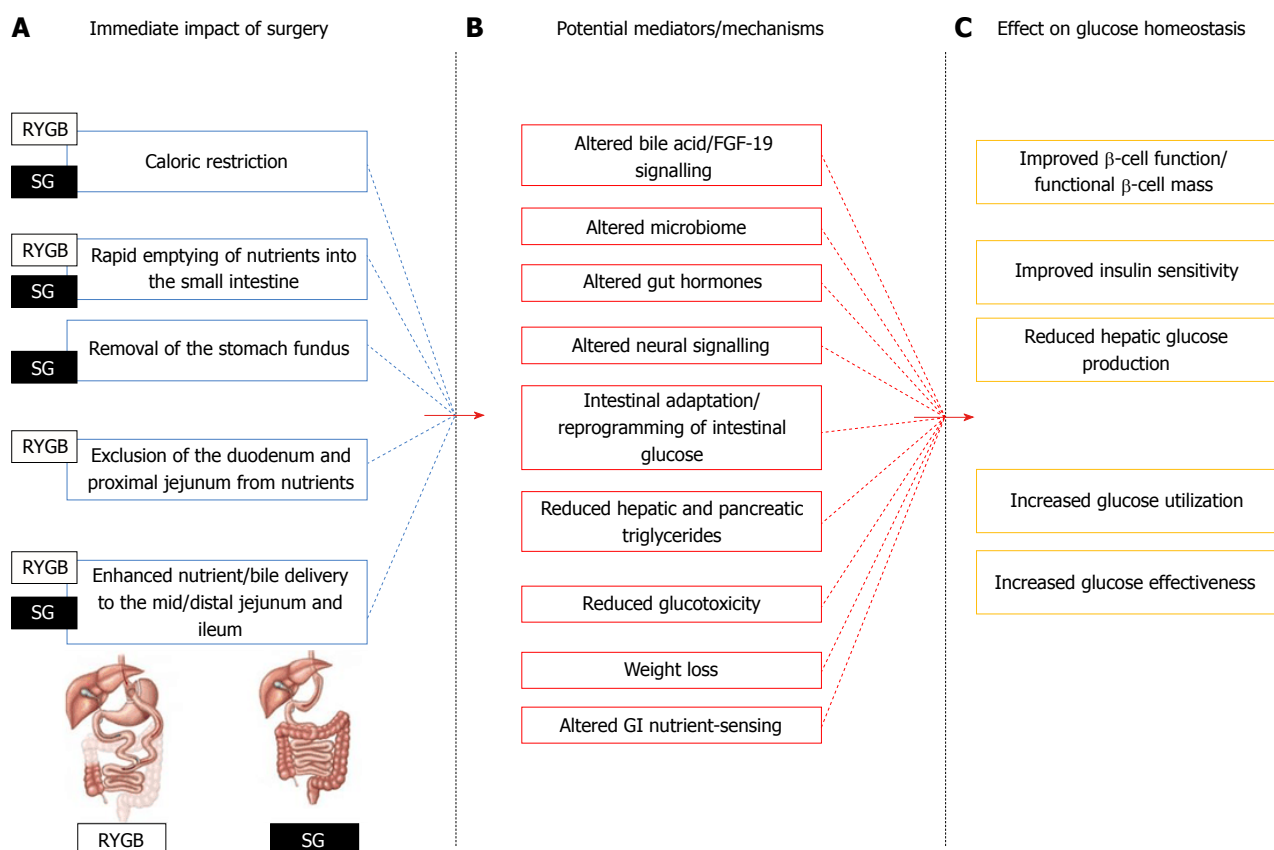


Figure 1 Potential mechanisms contributing to improved glycaemia after roux-en-Y gastric bypass and vertical sleeve gastrectomy. A: Immediate effects of improved glycaemia after roux-en-Y gastric bypass and vertical sleeve gastrectomy due to anatomical changes; B: Potential mediators/mechanisms involved. Cross talk occurs among these factors; C: Effects on glucose homeostasis^[21]; RYGB: Roux-en-Y gastric bypass; SG: Sleeve gastrectomy.

severe autoimmune diabetes (SAID), severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild obesity-related diabetes (MOD) and mild age-related diabetes (MARD)^[41](Table 2).

Of the 5, it would be interesting to see which are

more likely to go into prolonged remission with either bariatric surgery or intensive medical intervention so that clinicians can better define their treatment end-goals and treat accordingly. Based on insulin resistance, it would likely be SIRD, MOD and MARD that could go

Table 2 Subgroups of adult-onset diabetes

Subgroups	Body-mass index	Metabolic control	Insulin deficiency/resistance
Severe autoimmune diabetes	Relatively low	Poor	Insulin deficiency
Severe insulin-deficient diabetes	Relatively low	Poor	Insulin deficiency
Severe insulin-resistant diabetes	High	Fair	Insulin resistance
Mild obesity-related diabetes	High	Fair	Insulin resistance
Mild age-related diabetes	Relatively low	Fair	Insulin resistance

into prolonged remission.

Researchers may want to collect baseline data on glutamate decarboxylase antibodies, age at diagnosis, body mass index, glycated haemoglobin, and homeostatic model assessment 2 estimates of β -cell function and insulin resistance in future studies.

CONCLUSION

Diabetes Mellitus especially type 2 diabetes can go into prolonged remission *via* bariatric surgery or intensive medical therapy. The current evidence for bariatric surgery is stronger than intensive medical management but intensive medical management is likely to have a greater impact in type 2 diabetes management. More research is needed to understand the mechanism behind prolonged remission and to identify the group of diabetes patients that will benefit the most from such interventions.

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P- Reviewer: Cheungpasitporn W, Pecoraro V **S- Editor:** Cui LJ

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