

# Review of the Pharmacological interventions and Bariatric surgery for Diabetes

**Abbreviations:** T2DM: Type 2 diabetes; PBF: Percentage Body Fat; NEFA: Nonesterified Fatty Acid; SIGN: Scottish Intercollegiate Guidelines Network; ADA: American Diabetes Association; AGB: Adjustable Gastric Banding; SG: Sleeve Gastrectomy; RYGB: Roux-en-Y Gastric Bypass

## Introduction

The intrinsic association between obesity and Type 2 diabetes (T2DM) is well recognised, to the extent that the term Diabetes was coined by Dr Ethan Sims [1]. The definition of obesity according to the World Health Organization is “a condition in which percentage body fat (PBF) is increased to an extent in which health and well-being are impaired” [2], as is the case in T2DM where obesity compounds disease progression [3,4]. Obesity contributes to insulin resistance [5], and as such addressing obesity is a vital aspect in the management of T2DM [6]. Moderate and maintained weight loss has been demonstrated to be effective in lowering glycaemic levels in obese people with T2DM as well as reducing the need for oral hypoglycaemic medications [7]. T2DM guidelines recommend lifestyle interventions as first line management for obesity yet despite the evidence that lifestyle modifications can elicit 5-10% weight loss [8] and have clinically significant benefits in the management of T2DM many patients are unable to accomplish or sustain this in the long term [6]. This review will explore the evidence for pharmacological and surgical management for obesity in T2DM.

## Pathophysiology of Obesity in T2DM

Modulation of metabolism occurs with the release of nonesterified fatty acid (NEFA) as well as other substances, including pro-inflammatory substances, cytokines, leptin and glycerol from adipose tissue [5,9]. The release of NEFA is a major influence of insulin insensitivity and insulin resistance and may explain the connection between  $\beta$  cell dysfunction and insulin resistance [9]. Increased secretion of NEFA from adipose tissue is seen in obese individuals and T2DM. Development of insulin resistance commences with increased NEFA levels. However, with a reduction of NEFA plasma levels such as through the use an anti-lipolytic agent, homeostasis of glucose and peripheral insulin uptake are improved [5]. This demonstrates the importance of addressing obesity as part of the management plan to improve glycaemic control and reduce the myriad of obesity associated health complications.

Weight loss of 5-10% in obese people with T2DM can improve glycaemic control, cholesterol and blood pressure [8], and is recommended by the Scottish Intercollegiate Guidelines Network (SIGN) for obesity management [10]. These guidelines go further in recommending weight loss of 15-20% in people with a BMI >35 kg/m<sup>2</sup>. Anti-obesity drugs have been demonstrated to elicit a weight reduction of 7-10% over 2-4 years [11], which may address some of the adversities of Diabetes but yet falls short of

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the weight loss recommendations by SIGN [10]. This raises the question, Is anti-obesity medication effective as a stand-alone intervention and should other modalities be considered such as bariatric surgery? [12].

## Pharmacological Management of Obesity in T2DM

Pharmacological management of hyperglycaemia in T2DM is of paramount importance yet consideration should be given to those medications that are weight neutral or have potential to augment weight loss, see Table 1 for classes of anti-diabetic drugs in these categories and associated benefits and side effects. As the table demonstrates pharmacotherapy can have a significant clinical impact on weight loss and glycaemic control yet this has to be weighed against the adverse effects experienced by each individual. It must also be noted that lifestyle intervention (diet and physical activity) should be recommended as an essential along with the pharmacological management strategy [7].

A systematic review by Yanovski & Yanovski [13] reported that lifestyle intervention combined with either Orlistat, Phentermine/topiramate or Lorcaserin increases the prospect of patients to realise a >5% weight reduction in 12 months. However it must be recognised that the availability of these licensed drugs varies globally. The American Diabetes Association (ADA) and SIGN recommend ceasing anti-obesity medications at 3 months or earlier if any complications arise. If the weight reduction is <5% from baseline then consider alternate medications [7,10].

The timeframe used by clinical trials varies, however most report results at 12 months, whereas in the ‘real world’ setting these anti-obesity drugs should have been ceased at 3 months if following the ADA and SIGN recommendations [14,15]. Thus clinical trial data may often not be translatable to the ‘real world’ setting as recognised by Dunkley et al. [16]. It may be prudent to continue them if a trend of weight loss is recognised without adverse events for slightly longer (6-12 months) for pragmatic reasons.

Whilst some drugs are specifically licensed and targeted at weight loss there are also other classes of drugs that can elicit weight loss despite their primary usage or original design being for a different outcome. Table 2 highlights the efficacy of the most common drugs prescribed for weight loss as an adjunct therapy for T2DM.

A new treatment being explored is the use of Botulinum Toxin, the premise being that Botox injections into the stomach wall inhibit vagus nerve afferents thus interrupting the brain-gut axis communication pathway resulting in weight loss [17]. Phase two of clinical trial is currently being conducted to assess the efficacy and safety of Botulinum Toxin as a weight loss intervention; this may offer a new innovative treatment for obesity in T2DM.

**Table 1:** Weight loss with Anti-diabetic drugs.

Drug Class & Medication	Potential Effect on Weight	Reduction in A1c	Side Effects	Reference
Biguanide (Metformin)	2-3kg weight loss	1.5-2%	Lactic acidosis, gastrointestinal	[8]
Sodium-glucose co transporter 2 inhibitors (SGLT2)(Empagliflozin, Canagliflozin, Dapagliflozin)	2-3kg weight loss	0.6-0.9%	Urinary tract infection, genital mycotic infection, increase in potassium, creatinine and low density lipoproteins cholesterol	[8]
Glucagon-like peptide 1 agonists (Exenatide, Liraglutide, Dulaglutide)	2.87-3.84kg weight loss	0.9-1%	Medullary thyroid cancer, acute pancreatitis, gastrointestinal	[8,14]
Amylin analogues (Pramlintide)	2.57kg weight loss	0.3-0.4%	Gastrointestinal	[8]

**Table 2:** Pharmaceuticals for weight loss.

Drug	Mechanism of Action	Side Effects	Weight Loss	Proportion of Subjects Achieving >5% Weight Loss
Lipase inhibitor (Orlistat)	Inhibits pancreatic and gastric lipase thus reducing absorption of energy dense fat [4]	Gastrointestinal side effects such as: fatty faecal incontinence, steatorrhea, urgency of bowel movements	2.6-3.7kg weight loss [4]. 3% weight loss [13]	35-73% [13]
Selective Serotonin receptor agonist (Lorcaserin)	Selective stimulation of 5HT2C which regulates appetite and promotes satiety [6]	Fatigue, dizziness, nausea and headaches [13]	3% weight loss [13], 2014) 3kg [7]	37-47% [13]
Sympathomimetic amine anorectic/antiepileptic combination Phentermine	Targets hypothalamus to stimulate adrenal glands to release noradrenaline which regulates appetite and promotes satiety [6]	Insomnia, irritability [13]	9% weight loss [13]	67-70% [13]
plus				
Toprimate	Antiepileptic drug works on multiple cellular levels- unknown how this reduces weight [6]			
Opioid antagonist/aminoketone antidepressant combination (Naltrexone /bupropion)	Influences the hypothalamic melanocortin system and food cravings and moods through the brain reward systems (Billes et al. 2014)	Constipation, nausea, vomiting [7]	2-4.1kg [7]	36-57% [7]
Acylated human glucagon-like peptide 1 receptor agonist (Liraglutide)	Acts on peripheral and central nervous pathways responsible for appetite, activates metabolism through hindbrain and hypothalamus [3]	Hypoglycaemia, headaches, diarrhoea [7]	5.8-5.9kg [7]	51-73% [7]

## Surgical Intervention for Obesity in T2DM

Bariatric surgery is also called gastrointestinal surgery for obesity. Surgery changes the digestive process which elicits weight loss through reduction of nutrient absorption and thus lessens calorie intake [18]. The most common types of bariatric

surgery are Adjustable Gastric Banding (AGB), Sleeve Gastrectomy (SG) and Roux-en-Y Gastric Bypass (RYGB). RYGB is currently considered the gold standard of weight loss surgery [18]. The mechanism of weight loss and differences in outcomes of these procedures can be seen in Table 3.

**Table 3:** Common Bariatric surgery procedures.

Type of Surgery	Adjustable Gastric Banding	Sleeve Gastrectomy	Roux-en-Y Gastric Bypass (RYGB)
Mechanism for weight loss	Restricts food intake [26,10]	Restricts food intake	Restricts food intake
		Suppression of hunger through changes to hormones [10]	Suppression of hunger through changes to hormones
			Reduces absorption of nutrient and delays digestion [26,10]
Procedure	A band is placed around the upper stomach to create a small pouch, this can be adjusted through increasing or decreasing fluid in the band [10]	Surgical removal of the outer part of the stomach and reshaping of the stomach to a sleeve shape occurs. This reduces the volume to approximately 100-150mL (from 2L) [10]	The procedure causes food to bypass the stomach directly to a gastric pouch with a volume of approximately 15mL then proceeds to the jejunum [10]
Follow up required	1 month post-surgery Minimum every 3 months for first year until adequate clinical weight loss achieved Thereafter minimum of annually Repeated band adjustments as required [32]	1 month post-surgery Minimum every 3 months for the first year [32].	1 month post-surgery Minimum every 3 months for the first year. Minimum every 6 months for second year Annually thereafter [32]
Remission of type 2 diabetes	20% [12]	62.5% [12]	52% [12]
Weight loss	Median 37% excess weight loss 1 year post-surgery. Median 3 years post-surgery 40% patients maintained>50% excess weight loss [31]	Median 56% excess weight loss 1 year post-surgery Median 3 years post-surgery 46% patients maintained>50% excess weight loss [31]	Median 66.5% excess weight loss 1 year post-surgery Median 3 years post-surgery 65% patients maintained>50% excess weight loss [31]
Complications	Meta-analysis of RCTs indicates complication rates of 13% [30]	Meta-analysis of RCTs indicates complication rates of 13% [30]	Meta-analysis of RCTs indicates complication rates of 21% [30]

Indications for bariatric surgery are people with a BMI of 40 kg/m<sup>2</sup> or greater, or those with a BMI of 35 kg/m<sup>2</sup> or greater with co morbidities, such as T2DM (NICE, 2014). The NICE guidelines [19] advice that people diagnosed with T2DM in the past 10 years should receive expedited referrals without the need of having tried lifestyle management interventions first, due to improvements in quality of life and reduced risk of mortality that bariatric surgery can offer. Explored the effects of bariatric surgery during different stages of T2DM progression [20]. The results demonstrated that bariatric surgery during early onset of T2DM elicited highest rates of T2DM remission and reduced micro and macrovascular complications, whereas bariatric surgery on people with T2DM with existing micro or macrovascular complications produced no improvements in life expectancy or regression of microvascular complications [20]. Bariatric surgery is considered the most

sustainable and effective management for obesity (class III) [21]. Several studies purport that weight loss through bariatric surgery is cost-effective compared to nonsurgical management [22,23,11].

Following RYGB surgery NEFA levels initially increase with fat deployment through rapid weight loss, levels of NEFA normalise as weight loss plateaus Dirksen et al. [24]. SG and RYGB affect pancreatic  $\beta$  cell function, NEFA levels and insulin sensitivity thus enhancing glucose metabolism Thomas et al. [25].

A meta-analysis by Buchwald et al. [26] demonstrated remission of T2DM of 57% for gastric banding and 80% for gastric bypass. These results correlate with a large scale trial of bariatric surgery in Sweden (the SOS project) that showed 72% remission of T2DM post-surgery at 2 years [11]. This evidence supports the use of bariatric surgery for management of obesity in T2DM.

### Comparison of Interventions

A systematic review and meta-analysis by Müller Stich et al. [27] determined that surgical management for obese individuals with T2DM was more effective in lowering glycated haemoglobin A1c, improving glycaemic control and had higher rates of T2DM remission than medical management in nonseverely obese individuals in the short term (12-36 months). A systematic review and meta-analysis of the long term (3 years) effectiveness of bariatric surgery compared to non-surgical intervention established that bariatric surgery was superior in eliciting: weight loss, remission of diabetes, larger reductions

in glycated haemoglobin A1c, and decreased systolic pressure [28]. Furthermore a 5 year controlled trial also confirmed the superiority of surgical intervention over medical management for obesity in T2DM, espousing that over 80% of individuals whom underwent bariatric surgery maintained a glycated haemoglobin A1c of <7% with no or few antidiabetic medications Mingrone et al. [29]. Table 4 demonstrates further associated benefits and complications of bariatric surgery and a comparison of lifestyle with pharmaceutical intervention versus bariatric surgery; the evidence confirms that surgical intervention is superior to pharmaceutical intervention for obesity in T2DM [30-32].

**Table 4:** Bariatric surgery clinical trials.

Study	Weight Loss	Complications	Benefits
Swedish Obesity Subjects trial (SOS) [11]	Mean weight loss below baseline: 1-2 years RYGB 32±8% Gastric banding 20±10%	Over first 3 months: 0.25% deaths in intervention group compared to 0.1% in control group One or more nonfatal complication in 14.5% of bariatric intervention group; 2.9% of these patients required reoperation.	30% risk reduction in mortality after 13 years. 72% remission in T2DM after 2 years Long-term reduced macrovascular complications post-surgery Patient reported reductions in sleep apnoea from 23% pre-surgery to 8% 2 years post-surgery Increased physical activity at 2 and 10 year follow-up Improved quality of life at 10 year follow-up
	After 10 years RYGB 25±11% Gastric banding 14±14%		
	15 years RYGB 27±12% Gastric banding 13±14%		
The Diabetes Surgery Study [15]. Comparison of efficacy of RYGB versus intensive lifestyle with pharmacotherapy	26.1% loss of initial body weight with RYGB	50% and 55% more RYGB participants suffered serious adverse events and non-serious adverse events respectively compared to participants from the lifestyle pharmacotherapy group.	75% of RYGB participants achieved A1c<7% compared to 32% in the lifestyle pharmacotherapy group
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### Conclusion

Diabetes detrimentally affects quality of life, life expectancy and places significant demands on healthcare resources. If T2DM and obesity cannot be prevented then efficacious and cost effective

management and interventions must be implemented. There is a significant clinical evidence to suggest that pharmaceutical and surgical interventions can be effective for combating obesity in T2DM and thus improving glycaemic control and reducing related co-morbidities. The large scale clinical trials of both surgical and

pharmaceutical interventions need to be replicable in the real world and, as of yet, despite the promising results within trials many pharmaceutical interventions fall short. However meta-analysis of surgical interventions has shown long term success in maintaining weight loss and remission of T2DM. The feasibility of health systems to offer bariatric surgery to all those in need is a huge question and more effective pharmacological interventions should be sought through research and development. Nevertheless, optimum diet and active lifestyle should be promoted to prevent obesity in the first instance as an preventive strategy.

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