Surgical Options for Glycaemic Control in Type 1 Diabetes

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Abstract

In recent years, bariatric surgery, also referred to as metabolic surgery, has become the most successful treatment option in those with Type 2 diabetes and obesity. There are some similarities in the pathological pathways in Type 1 and Type 2 diabetes but the use of surgery in Type 1 diabetes remain unestablished and controversial. The treatment and management of Type 1 diabetes can be very challenging but recent advances in surgical interventions and technology has the potential to expand and optimise treatment options. This review discusses the current status of some surgical options available to people with Type 1 Diabetes. This includes, implantable continuous glucose monitoring systems, continuous intraperitoneal insulin infusion pumps, closed-loop insulin delivery systems (also known as the artificial pancreas system) utilising the latter two modalities of glucose monitoring and insulin delivery and bariatric or metabolic surgery. Whole pancreas and islet transplantation is beyond the scope of this review but has been discussed in brief.

Keywords: Type 1 Diabetes, Bariatric Surgery, Metabolic Surgery, Continuous Glucose Monitoring, Artificial Pancreas, Continuous Intraperitoneal Insulin Infusion.

Novelty Statement:
- Implantable devices such as continuous glucose monitoring systems, continuous intraperitoneal insulin infusion pumps and closed-loop insulin delivery systems show great promise in achieving glycaemic control for those with Type 1 Diabetes. Awareness that these therapeutic options exist, and their availability need to be raised.
- Bariatric or metabolic surgery has been shown to make tremendous improvements to the glycaemic status in people with Type 2 diabetes and obesity. These effects may potentially be translatable to those with Type 1 diabetes and obesity.

Introduction

The ultimate goals of diabetes management include optimisation of glycaemic control, minimising hypoglycaemia risk, prevention of diabetes-related complications and preserving quality of life (QoL). In recent years, a significant amount of focus and attention has been drawn towards the anti-diabetes effect of metabolic surgery in people with Type 2 diabetes and obesity. The beneficial effects include long term resolution of Type 2 diabetes and improvement of its associated co-morbidities. As a result, surgical intervention has been incorporated into many international Type 2 diabetes treatment guidelines(1).

Type 1 diabetes is classically defined as a disease of insulin deficiency as opposed to insulin insufficiency or resistance in Type 2 diabetes. The onset tends to be much earlier in life including childhood or adolescent years. Its precise mechanism is not entirely known but is thought to include both genetic and autoimmune factors. People with Type 1 diabetes rely on exogenous insulin replacement therapy for survival (2).

Diagnosis and differentiation between Type 1 and Type 2 diabetes can sometimes be challenging and the prevalence of Type 2 diabetes far outnumber those with Type 1 diabetes.
However, morbidity and mortality associated with Type 1 diabetes still remains high and management of the condition can be challenging for healthcare professionals and for individuals with Type 1 diabetes.

This review will explore and evaluate some of the potential surgical options for glycaemic control in those with Type 1 diabetes, including implantable continuous glucose sensors, continuous intraperitoneal infusion pumps, automated insulin delivery systems and metabolic surgery. As the role of surgery in Type 2 diabetes for those with and without obesity is established, the next logical question is whether these benefits can be extended to those with Type 1 diabetes? Do surgery and surgeons have a role in the management of Type 1 diabetes, particularly for those who are also obese. A detailed review of whole pancreas and islet transplantation is beyond the scope of this review but will be discussed in brief.

**Implantable Glucose Sensors**

Capillary finger-prick blood glucose testing remains the mainstay of self-monitoring of blood glucose (SMBG) amongst people with Type 1 diabetes and the National Institute of Clinical Excellence (NICE) recommend SMBG up to 7-10 times daily (3). There are several limitations to this method. Finger prick testing is non-dynamic and only gives a glucose value at a single point in time chosen by the individual. The direction of glucose trend, including impending hypo- and hyperglycaemia, cannot be detected unless testing takes places within small intervals of time. Barriers to finger-prick testing include impracticality of testing overnight whilst asleep, hesitancy to test in certain social settings (such as eating out and while at school/work) and the pain associated with it. Similarly, HbA1c is used as the gold standard in clinical practice to assess glycaemic control over an average period of approximately 3 months, but again does not give any information on daily fluctuations or variability of blood glucose.

Real-time continuous glucose monitoring (RT-CGM) technology first reached market almost two decades ago and accuracy and usability has improved since. The use of RT-CGM overcomes some of the barriers associated with SMBG and its uptake amongst people with Type 1 diabetes is increasing (4).

RT-CGM has been shown to improve overall glycaemic control (HbA1C) and reduce hypoglycaemia in people with Type 1 diabetes established on pump therapy and multiple daily injections of insulin with sub-optimal glycaemic control (5-9). RT-CGM also increases time spent in target glucose range and reduces severe hypoglycaemia (requiring third party assistance to treat) in Type 1 diabetes participants with impaired awareness of hypoglycaemia, compared with SMBG (10, 11) and reduces diabetes related distress (12). The use of CGM during pregnancy was shown to improve both glycaemic and neonatal outcomes (13). This included a lower incidence of large for gestational age, less neonatal ITU admissions and neonatal hypoglycaemia.

In the UK, the 2015 NICE criteria for RT-CGM in Type 1 diabetes include: >1 episode of severe hypoglycaemia/year; complete loss of awareness of hypoglycaemia; hypoglycaemia that is
causing problems with daily activities; extreme fear of hypoglycaemia; and HbA1c ≥9% (≥75mmol/mol) despite testing ≥10 times/day (3).

Most commercially available RT-CGM systems (Dexcom (San Diego, CA, USA) G5 and G6, Medtronic (Northridge, CA, USA) Guardian Connect Sensor 3 and Enlite, Medtrum (Shanghai, China) S7 Easy Sense) use enzyme-based subcutaneous needle type sensors that measure interstitial glucose every 5 minutes. This type of subcutaneous sensor can be inserted by the user and needs to be replaced every 7-10 days. All RT-CGM devices display an estimate of blood glucose, with alerts/alarms for hypo- and hyperglycaemia and real-time trends in glucose changes. Intermittent glucose monitoring (Abbott (Chicago, IL, USA) Freestyle Libre), also known as flash glucose monitoring, only displays glucose data including trends when the sensor is scanned with an NFC enabled reader or smartphone app (19). Details of the various subcutaneous needle-based sensors will not be discussed further in this review and the focus will be on implantable sensors.

At present, the only commercially available implantable subcutaneous glucose sensor for RT-CGM use is the Eversense system (manufactured by Senseonics, Maryland, USA) which was FDA-approved and CE marked in 2017. Eversense comprises of a small capsule (the sensor) that is implanted within the subcutaneous tissue of the lateral aspect of the upper arm. Contrary to the glucose oxidase enzyme technology used in the subcutaneous needle type sensors, the Eversense sensor utilises optical fluorescence technology and has a sensor life of 180 days (14). The sensor is surgically inserted under local anaesthetic using an aseptic technique, either by a trained surgeon or physician. Once the sensor is implanted a transmitter is worn externally over the sensor site. The transmitter communicates with the sensor and transmits interstitial glucose data wirelessly via Bluetooth to a receiver (a smartphone-base application) every 5 minutes. The system requires calibration with capillary blood glucose every 12 hours. The mean absolute relative difference (MARD) has been reported as 8.8% (15) suggesting better accuracy compared to the subcutaneous needle-based sensors which have a reported MARDs of 9.0 - 13.6% (16-18).

The main advantages of the implanted Eversense sensor compared to the needle-based subcutaneous sensors is the longer sensor life and better accuracy and the disadvantages include the invasive nature of sensor insertion requiring clinic attendance. Limitations of real-time subcutaneous sensor are the sensor lag due to differences between interstitial and blood glucose at any point in time, need for calibration and alarm fatigue. Only Dexcom G6 and the Freestyle Libre are calibration-free and licenced for non-adjunctive use for insulin dose-adjustment. Currently a MARD of under 10% is considered to be the level of accuracy required for safe use of CGM readings to make insulin dosing decisions (19). Intravenous glucose monitoring devices exist, but despite good accuracy, their use in day-to-day diabetes management are limited due to their invasiveness and potential risks.

As discussed, several barriers still exist and prevent CGM from reaching full potential. To address this, a joint statement from the European Association for the Study of Diabetes (EASD) and the American Diabetes Association Diabetes Technology Working Group (ADA) released in 2017 stated the following recommendations in order to try improve clinical and regulatory issues related to CGM (20):
• More systematic and structured premarketing evaluation GCM systems performance
• Greater investment in trial to provide evidence for CGM value and reliability for all patient groups
• Standardisation of CGM data reporting in clinical trials
• Improved consistency and accessibility to safety reports to regulatory authorities for market approval
• Increased communication and cooperation across stakeholder groups.

**Continuous Intraperitoneal Insulin Infusion**

Continuous intraperitoneal insulin infusion (CIPII) is viewed by some as a valuable alternative to continuous subcutaneous insulin infusion (CSII). At the moment it is still largely only used in cases where there are challenges with the use of CSII. Intraperitoneal insulin is absorbed into the portal system via the visceral peritoneum capillaries. Compared to subcutaneous delivery, insulin is first presented to the liver, promoting hepatic uptake and subsequently reducing the level of insulin within the peripheral circulation. There are several positive effects related to this, including an improved glucose and glucagon response to variable glucose levels and exercise. The effects of intraperitoneal insulin are also faster and supports better stability of glucose levels (21, 22).

There are two types of CIPII delivery systems. One is an entirely implanted programmable pump (Medtronic older MiniMed implantable pump) and the second is an external pump with a percutaneous catheter connected (Roche Accu-Chek Diaport System). Implantable pumps have a significantly higher associated cost due to the need for follow up visits. There is a need to refill the insulin reservoir with frequent device removal and replacement at the end of the battery life. The entirely implantable MiniMed pump in now no longer available but the manufacturer still provides consumables for those already using the pump in Europe but not in the USA. However, the emergence of the newer percutaneous access ports systems such as the Diaport system has refreshed interest in intraperitoneal insulin technology.

Listed in table 1 are some indications and contraindications to CIPII (21)

**[TABLE 1]**

Current published data show promising results. A Dutch clinical trial of 23 participants demonstrated that the use of CIPII can improve quality of life and lead to greater patient satisfaction. The same cohort was followed up 6 years later, glycaemic control was found to be stable. When compared to subcutaneous insulin therapy, there were also less hypoglycaemic episodes (23). A separate study (n= 60) by the European Diaport study group showed that CIPII reduced hypoglycaemic episodes, increased QoL without weight gain (24). A subsequent French systematic review published in 2014 evaluated 15 publications echoed this and more importantly also concluded that CIPII was effective at HbA1c level reduction and hypoglycaemic episodes (25). The benefits of CIPII are listed in table 2 below.

**[TABLE 2]**
As with any device, there are also associated complications (26). For both types of devices, the most common complication is catheter obstruction. Other potential issues include pump dysfunction, port site or device associated infection and pain.

In the USA FDA approval is no longer sought by companies due to issues during the infancy for this technology. Thus, in the USA individuals with Type 1 diabetes no longer have access to this treatment option unless they travel abroad. Globally awareness of this treatment option is low and only a few centres have the expertise to implant and manage CIPII. It is estimated that globally only 400 patients in total receive CIPII treatment with only 50 new individuals considered annually (27). In the UK, the first Diaport device was only implanted in 2015 (28).

Current data is promising for CIPII. More long-term high-quality data is certainly required regarding, effectiveness, long term complications and its metabolic effects. Although the number of individuals who may benefit are relatively low, this cohort is also one with extremely challenging insulin and glucose dynamics on alternative existing regimens of insulin therapy. For those where CSII is unsuccessful due to a variety of reasons, CIPII provides a potential alternative option to subcutaneous insulin which may improve both glycaemic control and quality of life.

**Closed-loop Insulin Delivery Systems**

The emergence of subcutaneous CGM has enabled the development of portable artificial pancreas (AP) systems, also referred to as closed-loop insulin delivery system. An AP system comprises of a glucose sensor, a control algorithm that calculates the required insulin dose based dynamic glucose changes and an insulin pump for insulin delivery. AP systems have been shown to improve glycaemic control and reduce hypoglycaemia over short durations within supervised clinic environments and over longer unsupervised time periods at home (29-31). AP systems in development utilise either a single-hormone (insulin only) or bihormonal (e.g. insulin and glucagon) and are either fully automated or semi-automated (hybrid) systems that require announcement of certain events such as meals and exercise. The first commercially available hybrid closed-loop system (the MiniMed 670G pump, Medtronic, Northridge, CA, USA) gained FDA-approval in 2016 and CE mark in 2018 for use in Type 1 diabetes (32).

Most of the AP systems in development, including the Medtronic 670G, use a subcutaneous glucose sensor and CSII. In this review we focus our attention on closed-loop insulin systems using CIPII.

An alternative closed-loop insulin delivery system designed to overcome the challenges associated with the pharmacokinetics of insulin delivered in the interstitial space and the subcutaneous sensors, as well as the constraints of wearing an external device, was attempted by Renard et al. in 2006 (n=4) with an implantable system based on intraperitoneal insulin delivery, a proportional integral derivative (PID) controller and a venous glucose sensor (33). The concept was optimistic, and although the results were similar to the subcutaneous- subcutaneous closed-loop trials conducted at the same time, the
disadvantages associated with the intravenous sensors, such as significant time-lag, level of invasiveness and the need for annual replacements, prevented its use in subsequent trials.

In 2010 the same study group conducted another 2-day semi-automatic (pre-meal boluses of insulin given) closed-loop trial in 8 participants using a simpler system with a subcutaneous sensor, intraperitoneal insulin delivery and a PID algorithm which showed that a higher percentage of time was spent in the study glucose target (4.4-6.6mmol/L) during closed-loop vs. open-loop (39.1% vs. 27.7%, p=0.05) and 76.5% of the time blood glucose was between 4.4-10mmol/L in closed-loop vs. 63.7% in open-loop (intraperitoneal insulin) (34). More recently, a non-randomized 24-hour sequential AP study (n=10) comparing a subcutaneous AP system (using a fast-acting insulin analogue) versus an intraperitoneal AP system (using regular insulin via the Diaport system) using a model predictive control algorithm was conducted. Percentage time spent within the primary endpoint glucose target range (80 to 140 mg/dL) was significantly higher for intraperitoneal delivery than for subcutaneous delivery: 39.8 ± 7.6 vs 25.6 ± 13.1 (P = 0.03)(35). The first AP system integrating the Eversense implantable subcutaneous glucose sensor will be evaluated as part of the International Diabetes Closed Loop (IDCL) trial, but outcome data have not yet been published.

Larger and longer term studies evaluating implantable AP systems are required and are underway, but technological advancements may soon set a new breakthrough in the ‘artificial pancreas’ treatment of Type 1 diabetes (36). There are still limitations with AP systems that need to be addressed but with improving pump, sensor and artificial intelligence technology people with Type 1 diabetes will hopefully soon have access to a range of automated artificial pancreas systems to aid self-management of their condition.

**Metabolic Surgery in Type 1 Diabetes**

Originally intended for weight loss, metabolic surgery has now been proven to lead to significant Type 2 diabetes resolution and improvement in diabetes and obesity related co-morbidities(37, 38). Globally, 98.8% of operations are performed laparoscopically(39) and were traditionally classified either as restrictive, malabsorptive or a combination of the two. These are listed in table 3.

**[TABLE 3]**

The two most common operations currently performed in the United Kingdom are the Sleeve Gastrectomy (see Figure 1) and Roux-En-Y Gastric Bypass (see Figure 2) (40). Although the classifications suggest a restrictive and malabsorptive action, the effects of surgery extend beyond this. One description is the BRAVE effects (41) which include Bile flow alteration, Reduction of gastric size, Anatomical gut rearrangement and altered flow of nutrients, Vagal manipulation and Enteric gut hormone modulation. This collectively contributes to the anti-diabetic post-operative effects.

**[FIGURE 1]**

Figure 1. Sleeve Gastrectomy

**[FIGURE 2]**

Figure 2. Roux-En-Y Gastric Bypass
Table 4 illustrates and summarises some of the most recently published long term clinical trials for comparing metabolic surgery to best medical therapy for Type 2 diabetes remission.

[TABLE 4]

The precise underlying mechanisms are yet to be fully established but there are both weight dependent and weight independent factors. There is now growing evidence to suggest that surgery in some people with Type 1 diabetes also has health benefits. It is important to highlight that those with obesity on top of the symptoms and sequelae unique to Type 1 diabetes are postulated to be the potential benefactors.

Data is currently limited and there are no randomised controlled trials published to date investigating bariatric and metabolic surgery for Type 1 diabetes participants specifically but several recently published systematic reviews and meta-analyses demonstrate promising results and potential in this cohort (42, 43). It is important to note that these cohorts all have Type 1 diabetes and obesity. There is currently very little published literature with results in those with Type 1 diabetes alone.

One meta-analysis published in 2015 found 26 retrospective non-randomised studies. This produced a combined dataset of 142 participants with Type 1 diabetes who underwent bariatric surgery (42). Post-operatively, pooled analysis of all the studies found that there was a significant weighted mean decrease in HbA1c of 0.79%. There was also a significant reduction in insulin requirement of 0.3 (95%CI 0.172-0.443) units/kilogram/day and a mean BMI reduction of 12.9kg/m². Although fewer studies reported other metabolic measures, systolic & diastolic blood pressure, triglyceride and LDL levels were also shown to decrease. Concurrently HDL levels increased.

A separate meta-analysis included 9 studies which totalled to 78 participants (43). This meta-analysis reported a minimal change in HbA1c but a significant reduction in insulin requirements and BMI.

The third and final meta-analysis (44) included 86 participants in total from 13 studies. Consistent with other studies, there was a significant reduction of HbA1c from 8.46±0.78% to 8.13±0.86%. Mean total daily insulin requirement was reduced from 98(±26) units to 42(±11) units. A BMI reduction of 12 kg/m² was found.

The above studies have a degree of overlap, but current evidence seems to suggest that people with Type 1 diabetes benefit from a significant reduction in weight and insulin requirements. Glycaemic control also seems to improve but not significantly and importantly not to the <7% (<53mmol/mol) level where control is deemed adequate.

A further literature search found 4 more recent studies not included in the meta-analyses above showing similar beneficial effects of metabolic surgery in Type 1 diabetes cohorts. This is summarised in table 5.

[TABLE 5]
Correlation of weight loss and insulin requirement is interesting and challenges the theory that Type 1 diabetes is a condition of purely insulin deficiency. Particularly in those with Type 1 diabetes and concomitant obesity, there may be a degree of overlap between insulin insufficiency and insulin resistance. Improvements in post-operative insulin requirements may be due to improvement in insulin sensitivity, similar to those seen in Type 2 diabetes participants. Individuals with latent autoimmune diabetes in adults (LADA) are another subgroup that challenges the overlap of insulin insufficiency and resistance.

The spectrum of disease may also explain why it is sometimes difficult to differentiate between the two. Current use of laboratory tests including C peptide levels, islet cell antibodies along with clinical correlation can still be extremely challenging (45).

As we further understand diabetes, the classical Type 1/Type 2 diabetes classification is further challenged. Type 1 and Type 2 diabetes may belong to different ends of a spectrum driven by an underlying insulin disorder or perhaps a whole new classification may be required (46).

In the obese Type 1 diabetes cohort, even if glycaemic control is not drastically improved compared to Type 2 diabetes cohort, the improvement in cardiac, metabolic and obesity associated risk factors such as blood pressure and circulating triglycerides may also be beneficial in the long run and is worth further investigation (47, 48).

When considering operative intervention, thought needs to be given to the post-operative glucose absorption dynamics as fluctuations in Type 1 diabetes are much more of a problem compared to Type 2 diabetes. Patients who undergo Roux-en-Y Gastric bypass will have more rapid rises and troughs in blood glucose levels compared to Sleeve Gastrectomy (49). Sleeve Gastrectomy may be more appropriate in Type 1 diabetes due to the more predictable and stable nature of carbohydrate absorption (44, 49). Safety of those undergoing surgery is also another important point that has to be considered. None of the collective studies describe any major complications of note, but the studies were not designed to look at potential complications. Prospective studies and clinical trials are required to further investigate and address this issue.

Type 1 diabetes is a complex multi system disease process and any person who undergoes bariatric surgery is at risk of potential complications (50). Any surgical intervention should be discussed, thoroughly evaluated and managed on a case by case basis by a joint bariatric and diabetes multidisciplinary team.

From an academic point of view, metabolic surgery presents a unique opportunity to further understand the underlying mechanisms of the diabetes spectrum. By studying the effects post operatively, we may gain a different perspective. Through better understanding of underlying pathways, we may subsequently be able to tailor or find new treatment targets to help people with Type 1 diabetes achieve better outcomes.
Pancreas and Islet cell transplantation

The first successful pancreatic transplant was performed in 1966(51). Standardisation of surgical technique and the progressive introduction of induction T cell depleting agents and immunosuppressive agents has led to lower rejection rates and improved graft survival rates in the modern day(52).

In Type 1 diabetes, whole pancreas transplantation or islet transplantation may be considered, as an alternative therapeutic option to intensive insulin therapy, in selected individuals. Although transplantation can potentially achieve insulin independence, there are still significant risks associated with surgery and immunosuppression. Whole pancreas and islet transplantation is therefore at present restricted to those already requiring immunosuppression for kidney transplantation or those with unawareness of hypoglycaemia experiencing episodes of life-threatening severe hypoglycaemia.

Individuals with Type 1 diabetes considered for pancreas or islet transplantation broadly fall into three categories: 1) Simultaneous Pancreas Kidney (SPK) or simultaneous islet kidney transplants are performed in those with chronic kidney disease (calculated glomerular filtration rate of less than equal to 20ml/min); 2) Pancreas or islet after kidney transplants are performed in those with a previous kidney transplant and have maintained satisfactory renal function. Those considered for islet after kidney must also have a history of severe hypoglycaemia or a HbA1c >53mmol/mol, 3) Pancreas Transplant Alone (PTA) or islet alone are performed in those with normal or near-normal renal function and disabling hypoglycaemia (evidenced by episodes of severe hypoglycaemia and significant impaired awareness of hypoglycaemia) (53). PTA when compared to SPK transplants have a higher rate of technical graft loss(52). PTA remains controversial as although recipients report an improved quality of life, improved patient survival is yet to be demonstrated. PTA is also an independent risk factor for developing renal failure in those who would other have normal or near normal renal function(54). This explains why there are a relatively lower number of PTAs performed.

The latest UK annual report on pancreas and islet transplantation (55) showed graft survival rates (mean 95% confidence interval)) of 89 (86-91) % and 79 (75-82) %, at one- and five-years after simultaneous pancreas and kidney transplant, respectively. Graft survival for pancreas only transplants are 88 (77-94) % and 52 (42-61) % at one and five years, respectively. The one year graft survival of a routine islet transplant is 84 (73-91) %. For those recipients with a functioning graft at one-year post-transplant, the five-year graft survival is 60 (42-74) % for those recipients who receive an additional priority islet graft and 44 (24-62) % for those who do not. Balancing the potential risks and benefits of pancreas and islet transplantation requires a comprehensive clinical evaluation in a specialist transplant unit.

Conclusion

Management of Type 1 diabetes, despite best efforts by the person with Type 1 diabetes and their health care professional, can be challenging and frustrating. However, the surgical and
technological advances detailed in this review provide a whole new world of possibilities in treatment pathways. Implantable continuous glucose sensors, continuous intraperitoneal insulin infusion pumps, closed-loop insulin delivery systems and metabolic surgery all show good promise. Each approach comes with its own advantages and disadvantages. Any diabetes management strategy involving surgical intervention should ideally be discussed in a joint diabetes multidisciplinary team setting. The best treatment approach will depend on the individual’s specific indications. There is no doubt that more long-term clinical studies are required for all surgical interventions listed but awareness that these options exist, and their availability need to be raised.

References


Surgical Options for Glycaemic Control in Type 1 Diabetes


**TABLE 1**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Severe hypoglycaemia with subcutaneous insulin therapy</td>
<td>• High serum insulin anti-body levels</td>
</tr>
<tr>
<td>• Hypoglycaemia unawareness</td>
<td>• Poor therapy compliance</td>
</tr>
<tr>
<td>• Subcutaneous insulin resistance</td>
<td>• Poorly controlled psychiatric conditions</td>
</tr>
<tr>
<td>• Suboptimal glycaemic control, both long term or with marked fluctuations</td>
<td>• Gastrointestinal conditions (i.e. colonic disease, adhesions)</td>
</tr>
<tr>
<td>• High insulin requirements in marked insulin resistance</td>
<td>• Those who were unsuitable of external pump use in subcutaneous therapy</td>
</tr>
<tr>
<td>• Injection site insulin associated lipohypertrophy with subcutaneous insulin not controlled by site rotation</td>
<td></td>
</tr>
<tr>
<td>• Skin conditions preventing subcutaneous insulin administration</td>
<td></td>
</tr>
</tbody>
</table>

**Other Considerations**

• Severe liver impairment
• On immunosuppression
• Other intraperitoneal therapies (Chemotherapy/Peritoneal dialysis)

TABLE 2

Benefits of CPII
• Decrease of HbA1c
• Lower incidences of hypoglycaemia & hyperglycaemia
• Less glucose level variability
• Improved Quality of Life

TABLE 3

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Traditional Classification</th>
</tr>
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<tbody>
<tr>
<td>Laparoscopic Adjustable Gastric Band</td>
<td>Restrictive</td>
</tr>
<tr>
<td>Laparoscopic Sleeve Gastrectomy</td>
<td>Restrictive</td>
</tr>
<tr>
<td>Laparoscopic Roux-En-Y Gastric Bypass</td>
<td>Combination</td>
</tr>
<tr>
<td>Biliary Pancreatic Diversion with Duodenal Switch</td>
<td>Combination</td>
</tr>
<tr>
<td>Mini / One Anastomosis Gastric Bypass.</td>
<td>Combination</td>
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</table>

Table 3. The most common Metabolic Procedures and Traditional Classifications

TABLE 4

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Treatment Groups</th>
<th>No of Subject</th>
<th>Time (months)</th>
<th>Type 2 Diabetes Remission Rates</th>
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</thead>
<tbody>
<tr>
<td>Schauer et al (37)</td>
<td>2017</td>
<td>RYGB vs SG vs MT</td>
<td>50/50/50</td>
<td>60</td>
<td>29% (RYGB) vs 23% (SG) vs 5% (MT)</td>
</tr>
<tr>
<td>Purnell et al (56)</td>
<td>2016</td>
<td>RTGB vs LAGB</td>
<td>466/140</td>
<td>36</td>
<td>68% (RYGB) vs 30% (LAGB)</td>
</tr>
<tr>
<td>Ikramuddin et al (57)</td>
<td>2016</td>
<td>MT &amp; RYGB vs MT</td>
<td>60/60</td>
<td>36</td>
<td>19% (MT &amp; RYGB) vs 0% (MT)</td>
</tr>
<tr>
<td>Mingrone et al (38)</td>
<td>2015</td>
<td>BPD vs RYGB vs MT</td>
<td>20/20/20</td>
<td>60</td>
<td>63% (BPD) vs 37% (RYGB) vs 0% (MT)</td>
</tr>
</tbody>
</table>

Table 4. Published Clinical Trials with Type 2 diabetes remission rates. MT = Medical Therapy RYGB = Roux en Y gastric bypass SG = Sleeve Gastrectomy LAGB = Laparoscopic adjustable gastric band BPD = Bilipancreatic diversion

TABLE 5

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No of Subjects</th>
<th>Hba1c (%)</th>
<th>Insulin Requirement (units/kg/day)</th>
<th>Insulin Requirement (units)</th>
<th>BMI (kg/m²)</th>
<th>Follow up (months)</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Pre-Op</td>
<td>Post Op</td>
<td>Pre-Op</td>
<td>Post Op</td>
<td></td>
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<tr>
<td>Vilarrasa et al.(58)</td>
<td>2017</td>
<td>32</td>
<td>8.5±1.3</td>
<td>7.9±1.4</td>
<td>0.8±0.3</td>
<td>0.5±0.2</td>
<td>92±40</td>
</tr>
<tr>
<td>Al Sabah et al. (59)</td>
<td>2017</td>
<td>10</td>
<td>8.6±1.2</td>
<td>8.3±1.4</td>
<td>0.7±0.3</td>
<td>0.5±0.3</td>
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<tr>
<td>Rottenstreich et al. (60)</td>
<td>2016</td>
<td>13</td>
<td>8.4±1.5</td>
<td>7.6±0.8</td>
<td>0.8±0.3</td>
<td>0.4 (0.3-0.5)</td>
<td>84±40</td>
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<tr>
<td>Faucher et al. (61)</td>
<td>2016</td>
<td>13</td>
<td>8.3</td>
<td>(7.8-9.0)</td>
<td>7.6 (C.I. NA)</td>
<td>0.8 (0.7-1.0)</td>
<td>40.6</td>
</tr>
</tbody>
</table>

Table 5. Recent Published studies found outside of the discussed systematic reviews demonstrating the effects of metabolic surgery on Hba1c, Insulin Requirement and BMI in Type 1 Diabetes cohorts.