Diabetes Improvement Following Bariatric and Metabolic Surgery

Rodolfo Lahsen, Marcos Berry and Patricio Lamoza
Clinica Las Condes, Chile

1. Introduction

Obesity rates are increasing worldwide. Free fatty acids derived from visceral adipose tissue impair insulin sensitivity and β-cell function (lipotoxicity), leading to the metabolic syndrome and type 2 diabetes.

Weight loss is the cornerstone for diabetes prevention and treatment, thus lifestyle and eventually pharmacological interventions that achieve significant weight loss are widely accepted. Nevertheless, long-term compliance to diet and exercise as well as safety and efficacy concerns regarding obesity drugs limit their benefits in real world. Moreover, weight gain is a common and undesirable side-effect of several oral antidiabetic drugs and insulins.

Bariatric surgery has demonstrated to be an effective and safe treatment option for type 2 diabetic patients who are severely obese, what is linked to weight loss and other mechanisms. Considering weight loss-independent mechanisms for diabetes improvement, investigators in several countries have started mostly metabolic than bariatric procedures for mildly obese or even overweight patients, focused on diabetes rather than obesity, and their early results have been encouraging.

1.1 Obesity and type 2 diabetes

Obesity is and its related metabolic disorders are increasing worldwide, especially in developing countries in western hemisphere (Ford & Mokdad, 2008). In most cases, an increase in body mass index (BMI) reflects an underlying increase in body fat that leads to diabetes, hypertension and dyslipidaemia (Bays, 2009), cardiovascular risk factors that are associated with increased mortality (Berrington et al, 2010).

Cardiometabolic risk increases not only with BMI, but waist circumference as well (National Institutes of Health [NIH], 1998). Waist circumference correlates tightly with visceral adipose tissue, and currently is a widely accepted assessment of the accumulation of intraabdominal or visceral adiposity (Despres et al, 2001).

Visceral adipose tissue is more likely to be related to insulin resistance than subcutaneous adipose tissue (Banerji et al, 1997, as cited in Zinman, 2006). Visceral obesity-derived cardiometabolic risk factors are frequently linked to insulin resistance and tend to cluster, what is clinically recognised as the metabolic syndrome (Alberti et al, 2009).
These factors follow a common and progressive course, so the prevalence of metabolic syndrome is 10 to 15% in normoglycaemic individuals, 44 to 64% in prediabetic, and 78 to 84% in type 2 diabetic patients (Isomaa et al, 2001). In other words, the more hyperglycaemic, the more dysmetabolic the individual will be.

Metabolic and ultimately cardiovascular complications of visceral obesity are summarised in Figure 1.

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![Visceral Adipose Tissue Diagram](image)

**Visceral Adipose Tissue**

- Free Fatty Acids and Cytokines
  - Liver
  - Muscle
  - Pancreas

- Non-Alcoholic Fatty Liver Disease
- Insulin Resistance
- β-cell Apoptosis

**GLUCO-TOXICITY**

- Prediabetes
- Metabolic Syndrome

**Cardiovascular Events and Mortality**

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**Fig. 1. Cardiometabolic risk derived from visceral obesity.**

Visceral adipose tissue shows a high lipolytic activity, releasing free fatty acids (FFAs) to portal and then systemic circulation (Wajchenberg, 2000). FFAs, as well as cytokines and tumor necrosis factor-α (TNF-α), both derived from visceral adipose tissue, impair insulin action at target cells in liver and muscle, causing a postbinding defect that blocks tyrosine kinase activity,1 uncoupling insulin signal transduction (Le Roith & Zick, 2001). Insulin resistance is a key factor for the development of non-alcoholic fatty liver disease (NAFLD), and atherogenic dyslipidaemia.

Insulin resistance is followed by pancreatic β-cell compensation and hyperinsulinaemia, due to fuel and neurohormonal signals derived from fat, liver, intestine, and brain (Prentki,
Hyperinsulinaemia stimulates sodium reabsorption at kidneys, as well as sympathetic nervous system activity, leading to vasoconstriction and enhanced cardiac output, increasing blood pressure (Reaven et al, 1996). In addition, hyperinsulinaemia exerts antilipolytic and lipogenic actions, thus maintaining and increasing visceral adipose tissue (Wajchenberg, 2000).

Nevertheless, while FFAs are one of the β-cell compensation signals, they can cause ultimately β-cell apoptosis, leading to prediabetic states and type 2 diabetes (Bell, 2003; Kasuga, 2006). Prediabetes (impaired fasting glucose and/or impaired glucose tolerance), in other words, slightly elevated plasma glucose levels, accelerates pancreatic failure through gluco-toxicity.

1.2 Weight loss in diabetes prevention and treatment

Weight loss is the cornerstone for diabetes prevention and treatment, thus lifestyle and eventually pharmacological interventions that achieve significant weight loss are widely accepted.

1.2.1 Lifestyle intervention in diabetes prevention

Modest weight loss, as part of a comprehensive intervention in lifestyle, has demonstrated significant reductions in the incidence of diabetes in high risk populations. In the Finnish Diabetes Prevention Study the intervention group showed a greater lose of weight when compared with a control group (weight reduction >5% in 43 versus 13% of the subjects, respectively), with a risk of type 2 diabetes reduced by 58% at 3.2 years (Tuomilehto et al, 2001). In the American Diabetes Prevention Program, the average weight loss in the lifestyle intervention group was 5.6 kg compared with 0.1 kg in the placebo group, with a risk of type 2 diabetes reduced by 58% at 2.8 years (Diabetes Prevention Program [DPP] Research Group, 2002). In the Indian Diabetes Prevention Programme, the lifestyle modification group reduced their risk of type 2 diabetes by 28.5% at 2.5 years compared with the control group, without loosing weight (Ramachandran et al, 2006).

1.2.2 Pharmacologic Interventions in diabetes prevention

Weight loss and antidiabetic drugs have been tested in the prevention of type 2 diabetes. Orlistat, a gastrointestinal lipase inhibitor used in the treatment of overweight and obesity, showed a 37.3% reduction in diabetes incidence at 4 years in obese subjects (Torgerson et al, 2004). Acarbose, an enteric α-glycosidase inhibitor used in the treatment of type 2 diabetes, reduced diabetes incidence by 25% at 3.3 years in subjects with impaired glucose tolerance (Chiasson et al, 2002). Another antidiabetic drug, metformin, which enhances insulin sensitivity at liver and muscle tissues, showed a 31% reduction in diabetes incidence at 2.8 years (DPP Research Group, 2002).

Two effective obesity drugs, rimonabant and sibutramine, have been recently withdrawn in several countries because long-term safety concerns.

1.2.3 Lifestyle intervention in diabetes treatment

One-year results of the ongoing Look-AHEAD clinical trial, which is intended to assess whether intensive lifestyle intervention decreases major cardiovascular events in type 2
diabetic subjects, showed a significant weight reduction with lifestyle intervention when compared with a control group (-8.6 vs. -0.7%, respectively). Diabetes control and other cardiovascular disease risk factors were also improved, with reduced medicine use (Pi-Sunyer et al, 2007).

Long-term compliance to diet and exercise could be a major issue in clinical practice. In addition, weight gain is a common and undesirable side-effect of several oral antidiabetic drugs and insulins (Turner et al, 1998; Kahn et al, 2006).

2. Diabetes improvement following weight loss surgery

Currently accepted indications for bariatric surgery are BMI $\geq 40 \text{ kg/m}^2$ or BMI $\geq 35 \text{ kg/m}^2$ when comorbidities are associated (NIH, 1998). Bariatric surgery has demonstrated significant weight reduction, and improvement on cardiometabolic risk factors such as type 2 diabetes mellitus, dyslipidaemia, and hypertension, in severely obese patients. Moreover, this procedures are associated with 29% decreased overall mortality at 15-year follow-up (Sjostrom et al, 2007). Because the improvement observed not only in excess weight reduction, but in cardiometabolic risk factors as well, these procedures have been recently recognised as “bariatric and metabolic”. Principal mechanisms leading to diabetes and metabolic improvement following bariatric and metabolic procedures are summarised in Table 1.

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>CLINICAL BENEFIT</th>
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<tr>
<td>Decreased Lipo-toxicity (weight loss)</td>
<td>Improved metabolic syndrome</td>
</tr>
<tr>
<td>Decreased ghrelin and increased PYY</td>
<td>Decreased appetite and increased satiety</td>
</tr>
<tr>
<td>Enhanced incretin effect</td>
<td>Improved diabetes control</td>
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</table>

Table 1. Main mechanisms for diabetes and metabolic improvement following surgery.

2.1 Decreased lipo-toxicity

Diabetes remission, defined as fasting plasma glucose $<126 \text{ mg/dL} (7.0 \text{ mmol/L})$ without hypoglycaemic therapy, occurs in 72 and 36% at two and ten years respectively in surgical patients, compared with 21 and 13% in conventionally treated subjects. On the other hand, diabetes incidence in non-diabetics is 1 and 8% at two and ten years respectively in the surgical group compared with 8 and 24% in the control group (Sjostrom et al, 2004, as cited in Dixon et al, 2011).

Undoubtedly, such metabolic benefit is closely related to weight loss because a marked reduction in FFA-derived lipo-toxicity. Lipo-toxicity impairs insulin action at target tissues and increases pancreatic $\beta$-cell apoptosis. One randomised controlled trial that compared laparoscopic adjustable gastric banding (LAGB), a pure restrictive technique, versus comprehensive medical therapy for obese type 2 diabetic individuals showed a significant 5.5-fold higher remission at two years in the surgical group (Dixon et al, 2008). In this regard, procedures that achieve weight loss and decrease lipo-toxicity should be viewed as “metabolic”.

2.2 Weight loss-independent mechanisms for diabetes control

Bypass or malabsortive procedures appear to result in greater metabolic benefit than restrictive ones, and a common observation is that diabetes remission is achieved within
days to weeks of undergoing surgery, before significant weight loss has occurred (Pories et al, 1995). These facts lead to conclude that additional and, at some extent, weight loss-independent mechanisms are involved. These mechanisms, thus more metabolic than bariatric, could be summarised as reduced caloric intake and enhanced incretin effect (Lahsen & Berry, 2010).

2.2.1 Reduced caloric intake
Gastrointestinal hormones and peptides involved in the regulation of energy homeostasis may be modified following bariatric surgery. Roux-en-Y Gastric Bypass (RYGB) and Sleeve Gastrectomy (SG) increase peptide YY (PYY) (Morinigo et al, 2006) and reduce ghrelin levels (Cummings et al, 2002, Karamanakos et al, 2008). PYY is an appetite suppressant peptide secreted by distal ileum and colon, whereas ghrelin is an orexigenic hormone secreted by gastric fundus. Thus, post surgery changes in gut-derived hormones result in decreased appetite and increased satiety, which enhance patients’ compliance to lifestyle intervention guidance.

2.2.2 Incretin effect
Food intake is followed by the release of several intestinal peptides, some of which increase insulin levels. The increase in insulin secretion is higher after oral or enteral glucose ingestion when compared to intravenous administration, what is called the incretin effect. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinoensive peptide (GIP) are the two most studied peptides, being GLP-1 probably the most important in terms of carbohydrate homeostasis. GLP-1 secretion from L-cells at the ileum rises after a meal and enhances insulin biosynthesis and release by pancreatic β-cells, decreases glucagon release by pancreatic α-cells, improves glucose uptake and glycogen synthesis in liver and peripheral tissues, slows gastric emptying, and decreases appetite and increases satiety at central nervous system. GIP is released from K-cells in duodenum, and stimulates post-meal insulin secretion and promotes β-cell mass expansion (Drucker, 2003). Type 2 diabetes is associated with a reduced or lost incretin effect that contributes with impaired insulin secretion (Toft-Nielsen et al, 2001). Bariatric surgery, especially RYGB, significantly enhances GLP-1 levels and activity in severely obese subjects with or without diabetes (Laferrere et al, 2007).

3. Metabolic surgery in non-severely obese type 2 diabetics
Theoretically, it could be plausible the design of surgical techniques focused mainly on weight loss, caloric intake, or incretin effect, depending on patients’ individual needs and careful clinical judgment.

3.1 Duodenal-Jejunal bypass and the Hindgut and Foregut hypothesis
Experimental studies were performed in non-obese diabetic rats, who underwent duodenal-jejunal bypass (DJB), a stomach-preserving RYGB that excludes proximal intestine, or gastrojejunostomy (GJ), which creates a shortcut for ingested nutrients without bypassing intestine (Rubino et al, 2006). No differences in body weight, food intake, or nutrient absorption were observed between surgical groups, however DJB-treated rats improved
their oral glucose tolerance. When GJ rats were reoperated to exclude proximal intestine a marked improvement in oral glucose tolerance was observed and, conversely, restoration of duodenal passage in DJB rats impaired oral glucose tolerance. In this study, Rubino demonstrated that bypassing proximal intestine directly ameliorates diabetes by weight loss-independent mechanisms.

At some extent, two theories are born. The “hindgut hypothesis”, is explained by the rapid nutrient delivery to distal intestine that enhance the secretion of GLP-1, PYY, and oxyntomodulin, which are involved in the reduction of food intake and gastrointestinal motility, and improvement in glucose homeostasis. The second theory, the “foregut hypothesis” or duodenal exclusion, clearly demonstrates that duodenum and proximal jejunum bypass of nutrients plays a major role in diabetes resolution.

3.2 Rationale for metabolic surgery in diabetic patients with BMI <35 kg/m²

The American Diabetes Association established for first time in 2009 that bariatric procedures should be considered for diabetic adults with BMI ≥35 kg/m² when diabetes is poor controlled with lifestyle and pharmacologic therapy. American Diabetes Association does not recommend surgery in patients with BMI <35 kg/m² outside a research protocol (American Diabetes Association, 2009). Nevertheless, and as observed in landmark diabetes clinical trials, most type 2 diabetic individuals are overweight or mildly obese, with a BMI close to 30 kg/m², below the cut-off for eligibility in current guidelines, disregarding the presence of a visceral pattern of obesity (LaHsen & Berry, 2010). Precisely, type 2 diabetic individuals having the metabolic syndrome have a very high risk of cardiovascular complications (Isomaa et al, 2001). Table 2 summarises the criteria followed by the authors to consider bariatric and metabolic surgery in type 2 diabetic subjects.

<table>
<thead>
<tr>
<th>BODY MASS INDEX (kg/m²)</th>
<th>OBSERVATIONS</th>
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<tbody>
<tr>
<td>≥ 35</td>
<td>Consider surgery</td>
</tr>
<tr>
<td>&lt; 35</td>
<td>Consider surgery when metabolic syndrome is present</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Consider surgery only as part of a Clinical Research Protocol</td>
</tr>
</tbody>
</table>

Table 2. Selection criteria for bariatric and metabolic surgery in type 2 diabetes.

In recent years, several groups performing both established and novel surgical procedures in type 2 subjects with BMI <35 kg/m² have shown encouraging metabolic results. It must be noted that these procedures should be performed as part of a clinical research protocol with local ethical approval.

3.3 Clinical results of metabolic surgery

Our group started a clinical research protocol assessing DJB in early 2008, and 19 non-obese (BMI <30 kg/m²) type 2 diabetic patients underwent surgery by late 2010. Our preliminary metabolic results are encouraging, however surgical technique modifications have been done due to concerns regarding gastroparesis, a previously reported surgery-derived adverse effect on gastric emptying. This issue was handled performing a non-restrictive SG, turning DJB into a modified duodenal switch, a well known procedure with proven benefits on glucose metabolism. The authors have seen better results, less morbidity (no
gastroparesis) and a better metabolic control with diabetes remission in near 75% of the cases, what was presented at the XIV Latin American Diabetes Association Congress held in Santiago, Chile, in November 2010 (Table 3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-Surgery</th>
<th>Post-Surgery</th>
<th>P*</th>
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<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>27.7</td>
<td>25.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL (mmol/L)</td>
<td>163 (9.1)</td>
<td>131 (7.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.3</td>
<td>6.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with HbA1c &lt;7%, %</td>
<td>26.3</td>
<td>73.60</td>
<td>0.05**</td>
</tr>
<tr>
<td>Pharmacologic treatment (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Oral monotherapy</td>
<td>2</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Oral combination therapy</td>
<td>15</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* T test; ** Fisher test.

Table 3. Clinical results of Modified Duodenal-Jejunal Bypass in 19 non-obese type 2 diabetic patients.

But, Why to perform “the most aggressive” surgery in non-obese patients? What about their weight loss? To answer the first question it must be considered the almost pure hormonal effect that is achieved in this subset of patients, where weight loss is not the “common factor” observed in restrictive and malabsorptive bariatric procedures. Answering the second question requires considering that obese patients with different degree of severity who undergo the same surgery lose almost the same excess weight proportion, what can be explained as an “accommodation” of the caloric intake to the metabolism “real requirements”. Our patients, with BMI between 25 and 30 kg/m², experienced a moderated lose of weight during the first 12 weeks after surgery, recovering later their inicial weight or maintaining BMI close to 25 kg/m², with no excessive weight loss. This fact was also noted by Scopinaro, who performed a novel surgical procedure in type 2 diabetic individuals with BMI <35 kg/m², achieving metabolic control and moderated weight loss (Scopinaro et al, 2007).

3.4 Novel metabolic procedures

Clinical researchers worldwide are performing novel surgical and endoscopic procedures and assessing their metabolic and surgical long-term efficacy and safety.

3.4.1 Sleeve gastrectomy

While SG is considered a pure restrictive technique, it is noteworthy that weight loss-mediated decrease in lipo-toxicity is metabolic per se, and SG reduces ghrelin, increases
peptide YY, and increases GLP-1 (Peterli et al, 2009), so SG must be viewed as metabolic surgery as well. We have assessed clinical and metabolic results in obese patients with easily controlled or recently diagnosed diabetes, which underwent SG with promising results: remission of the disease, no medication longer required, and very low morbidity rates.

3.4.2 EndobARRIER®

One of the non invasive metabolic procedures currently under investigation is the “EndobARRIER®”, a polypropylene sleeve endoscopically installed, anchored to the pylorus, that extends until the first portion of the jejunum. Its mechanism of action is the isolation of the food from the pancreatic enzymes and bile. This device has to be removed at 12 month, while an acceptable glycaemic control has been observed, and early results in obese patients also shows a moderated weight loss.

4. Current and future indications for metabolic surgery

Current obesity guidelines consider surgery when type 2 diabetes is associated with BMI $\geq 35$ kg/m$^2$, however diabetes guidelines have incorporated surgical options very recently. In 2009 the American Diabetes Association established that bariatric surgery should be considered for diabetic adults with BMI $\geq 35$ kg/ m$^2$ if metabolic control is difficult to achieve with lifestyle and pharmacological therapy. In March 2011 the International Diabetes Federation released a position paper which considers with some restrictions bariatric surgery for type 2 diabetic patients with BMI $\geq 30$ kg/m$^2$, and historically, for first time includes bariatric surgery in a diabetes treatment algorithm.

Probably future guidelines will consider not only BMI but also waist circumference and other elements of the metabolic syndrome as well as the presence and extent of diabetic chronic complications, patients’ preference and quality of life.

5. Conclusions

Bariatric surgery has demonstrated to be an effective and safe therapy for obesity in subjects with BMI $\geq 40$ kg/m$^2$, and in type 2 diabetic patients with BMI $\geq 35$ kg/m$^2$.

The major factor involved in metabolic improvement after surgery is weight loss, which decreases lipo-toxicity. Any procedure that achieves weight loss must be recognised as metabolic.

There are weight loss-independent mechanisms for metabolic improvement that can be summarised as decreased appetite and increased satiety, due to post surgical changes in ghrelin and PYY, and enhanced $\beta$-cell function, due to an increased incretin effect.

Novel surgical techniques have been developed in recent years, aimed to correct dysmetabolism through weight loss-independent mechanisms in type 2 diabetic patients who are mildly obese or even overweight, with promissory early results.

Nowadays, these procedures have been part of clinical investigation protocols approved by each local ethics committee.

Future indications for metabolic procedures will consider other factors than BMI.
6. References

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Pi-Sunyer, X.; Blackburn, G.; Brancati, FL.; Bray, GA.; Bright, R.; Clark, JM.; Curtis, JM.; Espeland, MA.; Foreyt, JP.; Graves, K.; Haffner, SM.; Harrison, B.; Hill, JO.; Horton, ES.; Jakicic, J.; Jeffery, RW.; Johnson, KC.; Kahn, S.; Kelley, DE.; Kitabchi, AE.; Knowler, WC.; Lewis, CE.; Maschak-Carey, BJ.; Montgomery, B.; Nathan, DM.; Patricio, J.; Peters, A.; Redmon, B.; Reeves, RS.; Ryan, DH.; Safford, M.; Van Dorsten, B.; Wadden, TA.; Wagenknecht, L.; Wesche-Thobaben, J.; Wing, RR., & Yanovski, SZ., for the Look-AHEAD Research Group. (2007) Reduction in Weight


Bariatric surgery has gained importance in the last 20 years because of the high prevalence of global obesity, and the vast understating of the physiological and pathological aspects of obesity and associated metabolic syndromes. This book has been written by a number of highly outstanding authors and pioneering bariatric surgeons from all over the world. The intended audience for this book includes all medical professionals involved in caring for bariatric patients. The chapters cover the choice of operation, preoperative preparation including psychological aspect, postoperative care and management of complication. It also extends to concept and result of metabolic surgery and scarless bariatric surgery.

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