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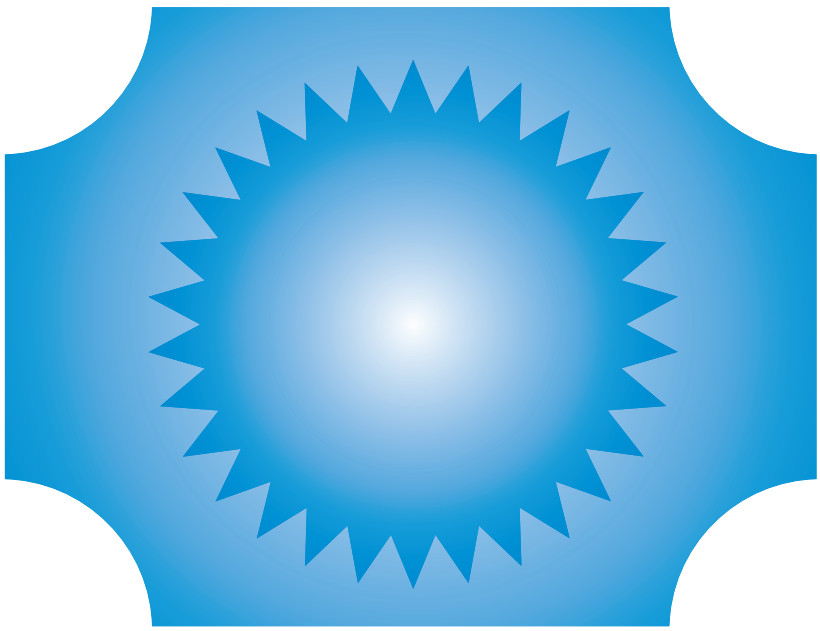
CIRUGÍA DIABETES IMC 24-34: ¿CÓMO Y POR QUÉ?

Coordinador:
Manuel Garciacaballero



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SUMMARY

DIABETES SURGERY BMI24-34: HOW AND WHY?

Coordinador: Manuel Garciacaballero

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Editorial

Diabetes surgery: minimum information on diabetic patients sample BMI 24-29 or BMI 30-34 for doing studies comparable

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In order to clarify the primary endpoint of our operations, when we use bariatric procedures for treating obesity, it is worldwide called Obesity Surgery. For identifying the bariatric surgery when it is primary used for treating Diabetes Mellitus (DM), I think we should call it Diabetes Surgery. In both cases we perform metabolic surgery.

DM is not a lineal and homogeneous disease. We have find patients with 37 years disease without metabolic syndrome (MS) nor diabetes complications, and other with only 5 years diagnosed disease already blind and 5 days/week dialysis. It could not be the same disease although we call always Diabetes Mellitus. Hence it is of maximum interest to be able to judge the effect of the different bariatric surgery procedures to have enough information on the diabetic patients included in the sample of the study.

Apart from C Peptidelevels and other parameters discussed in other chapter of this monographic issue, first distinction need to be, to differentiate between overweight patients (BMI 24-29) and already simple obese patients (BMI 30-34). Because simple obesity implies a preoperative excess weight of more than 20 kg and the consequences development of insulin resistance mechanism that could be the responsible of the type 2 diabetes mellitus. The elimination of this insulin resistance with the weight loss provoke by bariatric surgery, could already solve the problem without takes into account other mechanisms. While diabetic patients BMI < 30 that do not have so much excess weight and the consequent insulin resistance, it is more probable of having an important decrease of beta cells mass as responsible of their DM. So far, none of the studies or reviews that analyzed the results of bariatric surgery for treating DM in patients BMI < 35 does this distinction, considering both groups of patients equal for comparison.[1-4]

The second important source of error is the proportion of non insulindependent and insulindependent number of patients of the population sample included in the study. Patients that need insulin for controlling the levels of glycemia translate pancreas deterioration, decrease beta cell mass and consequently reduced possibility of stimulating it by surgical gastrointestinal changes. While those that need only oral antidiabetic drugs for controlling their DM means that their pancreatic beta cell mass still produces enough insulin for maintaining the glycemic control, what means that it still exists a beta cell mass stimulable by surgical gastrointestinal changes that could explain their results.

Information on years of evolution of the disease as well as of years in treatment with insulin, speak on the aggressiveness of DM and/or resistance of beta-cell and other tissues to deterioration and, similarly, the possibility of success of the surgical gastrointestinal changes. None of studies published so far supply this kind of information.

We can argue in the same direction on the exact information about the accompanied comorbidities, as part of the metabolic syndrome, that presented preoperatively the patients including in the study population sample, and the resolution rate after surgical gastrointestinal changes. Although in this regard we can find more information especially on the postoperative resolution rate.

Very limited data, if some, is given on the specific diabetes complications (cardiopathy, retinopathy, nephropathy, neuropathy, peripheral vasculopathy, severe hypoglycemia episodes, etc) and the postoperative effect of the surgical gastrointestinal changes. Also very important information due to the limitations that they provoke for the everyday life of the patients and the great advantage that bring the surgery. And for having an idea if gastrointestinal surgery could also have an effect in their resolution. Especially taken into account that the most important part of the high costs of DM management are related to the treatment of its complications.[5]

Anyway, in our personal experience we have found many surprises in the evolution of patients after gastrointestinal bypass surgery (since February 2008 when we operate our first patient specific to treat DM by One Anastomosis Gastric Bypass (BAGUA) for treating diabetes that makes preoperative prediction of surgical results for solving DM really challenging.

This point is one more reason for describing the patient population sample with a minimum of clinical

data to be able to compare the results of different gastrointestinal surgical procedures used. Important will be also to analyse and give information on those cases in which the preoperative prediction do not correlate with the expected postoperative results.

In my opinion standardization of the remission criteria have not sense if we do not standardize first, an enough and exact information on the diabetic patient sample. That is the main reason why some studies produce unexpected good results[6,7] and could also explain the wide variability using the same procedure.[8-16] We can have 0% or 100% DM resolution rate (no necessity of diabetes treatment, basal glycemia < 125 mg/dl, HbA1c < 6,5 or 7%) depending from the patients we included in a study. Obviously the results need to be related with the clinical characteristics of the patient, and this is not the case at present.

The other data we need for comparison are on immediate postoperative complications and medium and long term effects of gastrointestinal surgical changes related to the degree of gastrointestinal symptoms and nutritive state. In this sense we can also incorporate data on quality of life before and after surgery using the specific test developed and validated in different languages for bariatric procedures.[17,18]

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Current medical treatment of diabetes type 2 and long term morbidity: how to balance efficacy and safety?

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Abstract

Current medical treatment of type 2 diabetes mellitus (T2DM) requires special attention to different comorbidities that often are associated with hyperglycemia, such as overweight or obesity, dyslipidemia, hypertension, microvascular or macrovascular complications, etc. .. The control of these factors risk to health is as important as the glucose control in diabetes type 2, it is essential for the antidiabetes drugs consider these risk factors. The consensus statement published by the ADA/EASD and AACE emphasizes that the potential effects of antidiabetes medications on CV risk factors besides hyperglycemia (ie, overweight/obesity, hypertension, and dyslipidemia) should be considered in pharmacotherapy selection. Since T2DM is a progressive disease with worsening HbA1C values over time, monotherapy, even with different agents, will eventually fail to maintain the glycemic target. Because insulin resistance occurs in a variety of organs and tissues, many patients may achieve fasting glycemic control but develop postprandial hyperglycemia. Other issues include the risk for hypoglycaemia or weight gain with traditional glucose-lowering medications. The AACE/ACE algorithm for glycemic control is structured according to categories of HbA1C and suggests an HbA1C goal of ≤6.5%, although that may not be appropriate for all patients.42 The algorithm recommends monotherapy, dual therapy, or triple therapy based on initial HbA1C level of 6.5% to 7.5%, 7.6% to 9%, and >9% and reserves initiation of insulin therapy until treatment with oral or other injectable agents has failed. GLP-1 receptor agonists and DPP-4 inhibitors are novel options to improve glycemic control and reduce the incidence of weight gain. Combination therapy with newer and traditional agents improves glycemic control with a low incidence of hypoglycemia.

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Key words: *Diabetes type 2. Comorbidities. Antidiabetes medications.*

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TRATAMIENTO MÉDICO ACTUAL DE DIABETES TIPO 2 Y MORBILIDAD A LARGO PLAZO: ¿CÓMO EQUILIBRAR EFICACIA Y SEGURIDAD?

Resumen

El tratamiento médico actual de la diabetes mellitus tipo 2 (DMT2) requiere una especial atención a las distintas comorbilidades que a menudo aparecen asociados a la hiperglucemia, como por ejemplo el sobrepeso u obesidad, la dislipidemia, la hipertensión, las complicaciones microvasculares o macrovasculares, etc.. El control de estos factores de riesgo para la salud es tan importante como el control de la glucosa en la diabetes tipo 2, por lo que es fundamental que los medicamentos contra la diabetes tengan en cuenta estos factores de riesgo. La declaración de consenso publicado por la ADA (American Diabetes Association) / EASD (European Association for the Study of Diabetes) y la AACE (American Association of Clinical Endocrinologists) hace hincapié en que los efectos potenciales de los medicamentos antidiabéticos sobre los factores de riesgo cardiovascular, el sobrepeso/obesidad, hipertensión y dislipidemia, deben ser considerados en la selección del tratamiento farmacológico. Dado que la DM2 es una enfermedad progresiva con empeoramiento de los valores de HbA1c en el tiempo, la monoterapia, aunque sea con diferentes medicamentos antidiabéticos, a largo plazo será incapaz de mantener el objetivo glucémico. Debido a que la resistencia a la insulina se produce en una gran variedad de órganos y tejidos, muchos pacientes pueden conseguir el control glucémico en ayunas pero desarrollar hiperglucemia postprandial. Además, algunos fármacos llevan asociados riesgos adicionales como hipoglucemia o aumento de peso. La AACE/ACE han establecido un algoritmo para el control glucémico que se estructura de acuerdo a los niveles de HbA1C y sugiere un objetivo para los valores de HbA1C ≤ de 6,5%, a pesar de que puede no ser apropiado para todos los pacientes. El algoritmo recomienda monoterapia, terapia doble, o triple terapia basada en el nivel inicial de HbA1C de 6,5% a 7,5%, 7,6% a 9%, y > 9% y se reserva el inicio de la terapia con insulina hasta que el tratamiento con agentes orales u otros agentes inyectables no sea efectivo. Los agonistas del receptor de GLP-1 e inhibidores de la DPP-4 son nuevas opciones para mejorar el control glucémico y reducir la incidencia de aumento de peso. La terapia combinada con agentes nuevos y tradicionales mejora el control glucémico con una baja incidencia de hipoglucemia.

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Palabras clave: *Diabetes tipo 2. Comorbilidades. Fármacos antidiabéticos.*

Introduction

The latest reports from the International Diabetes Federation (IDF) reveal that currently 366 million people have diabetes, 4.6 million deaths are due to diabetes and millions of euros are spent on care for diabetes *(http://www.idf.org/global-diabetes-plan-2011-2021)*. Despite all efforts to control the disease, microvascular complications such as retinopathy, nephropathy and neuropathy are quite common and cardiovascular disease remains the leading cause of death in patients with type 2 diabetes mellitus (T2DM). Consequently, the treatment of diabetic comorbidities like obesity, hypertension, hyperlipidemia, subclinical inflammation and hypercoagulability assumes major importance and must be coordinated with good glycemic control for morbimortality reduction in type 2 diabetes mellitus.

Evaluating the magnitude of the problem

Complex pathophysiology and difficult management

Unlike what occurs in type 1 diabetes mellitus treatment based on the combination of insulin replacement, diet and exercise, T2DM is highly heterogenous, depending on the patient characteristics and the disease evolution stage. Treating type 2 diabetes patients ranges from the non-use of drugs (only dietary treatment and exercise) to the use of different types of drugs (oral or parenteral) or insulin, all alone or in some combinations.

There are some clinical clues, phenotypic changes and laboratory data that can help us to identify the main physiopathological mechanism underlying each specific patient in the clinical practice. These signs can help us to deem the disease evolution stage of each patient, in order to choose the most appropriate therapy. Weight status (obese or normal weight) is one of the most important determinants of therapy, since insulin resistance secondary to overweight is present in more than 80% of patients with T2DM. So that, most of diabetic patients will need an insulin sensitizer (metformin), besides diet and exercise, as the first line therapy approach. Time from diagnosis of T2DM is a very good predictor of residual insulin secretion; the longer the evolution, the lower the insulin reserve. When a patient is diagnosed of T2DM there is already a loss of beta cell mass and function between 30 to 70%. The combination of normal-low weight (suggesting minimal insulin resistance), long history of diabetes (more than 5 years) and high basal HbA1c values, is a very good indicator of advance beta cell loss and dysfunction and indicates that we should use not only an insulin sensitizer but a secretagogue from the beginning (dual therapy) or insulin, if the patient is symptomatic (poluric and losing weight).[1,2,3]

Accordingly with the ADA/EASD 2012 Position Statement on the Management of Hyperglycemia in T2DM[68] for most patients, initial treatment includes diet, physical activity, education and drug therapy with metfomin. If these measures are inadequate to get HbA1c bellow 7%, after 3-6 months, you should progress to combination therapy with 2 agents (Metformin plus either a sulphonylurea, GLP-1 analog, DPP4 inhibitor or pioglitazone). If necessary, during the following 3-6 months you can use a third drug or initiate basal insulin therapy in combination with oral agents. Finally, if you cant t get a good individualized metabolic control, you will need to use a complex multidose insulin approach.

Changes in treatment, based on the values of HbA1c should be early to prevent complications or delay its progression if they are already present.[4,5] Even with treatment, over 60% of patients do not achieve HbA1c normal (approx. 7%). Most should be treated with 2-3 drugs and insulin therapy schemes are increasingly more complex.[1,2,3]

Complications of type 2 diabetes

People with diabetes are at increased risk for multiple and complex complications related to macrovascular disease (coronary heart disease, stroke, and peripheral arterial disease) and microvascular disease (nephropathy, retinopathy, and neuropathy).[6,7] Diabetes complications begin early in the disease process and well before a clinical diagnosis. Patients who finally develop clinical diabetes have 2-4 times higher risk of cardiovascular disease, cardiac insufficiency and death, than those who did not develop diabetes.[8] It is well accepted that diabetic macrovascular disease is more related to coexistent insulin resistance, dyslipidemia, hypertension, hypercoagulability, endothelial dysfunction and subclinical inflammation, typical of T2DM, than due to hyperglycemia per se. One of the biggest challenges in the management of T2DM is to prevent the disease or to make an early diagnosis since by the time of its clinical appearance, patients already have some kind of dysfunction (e.g. diabetic retinopathy 20-30%, microalbuminuria 10-20%, Arterial hypertension > 50%, dyslipidemia > 66%, endothelial dysfunction 80-100%)[2] related to the complications mentioned above. Early treatment can delay the progression or reduce macrovascular and microvascular complications.[4]

How to Measure Glycemic Control?

Role of the HbA1c

Glycated haemoglobin (HbA1c) was initially identified as an "unusual" haemoglobin in patients with diabetes over 40 years ago.[69] After that discovery, numerous small studies were conducted correlating it to glucose measurements resulting in the idea that HbA1c could be used as an objective measure of glycaemic

control. The A1C-Derived Average Glucose (ADAG) study included 643 participants representing a range of A1C levels. It established a validated relationship between A1C and average glucose across a range of diabetes types and patient populations.[70] HbA1c was introduced into clinical use in the 1980s and has become a cornerstone of clinical practice.

HbA1c reflects average plasma glucose over the previous eight to 12 weeks.[71] It can be performed at any time of the day and does not require any special preparation such as fasting. These properties have made it the preferred test for assessing glycaemic control in people with diabetes. More recently, there has been substantial interest in using it as a diagnostic test for diabetes and as a screening test for persons at high risk of diabetes.[72]

A diabetic person with good glucose control as a HbA1c level that is close to or within the reference range Accordingly to for four of the major organizations involved in the control of diabetes, *American Diabetes Association (ADA), American College of Endocrinology (AACE/ACE), International Diabetes Federation (IDF) and European Association for the Study of Diabetes (EASD)* the use glycosylated hemoglobin (HbA1c) value is the best reducing risk indicator as it correlates with the appearance of micro and macrovascular complications in the long term and because it provides information on the control degree in the previous 2-4 months.

What is the Goal of HbA1c?

Lowering A1C to below or around 7% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes it is associated with long-term reduction in macrovascular disease. Therefore, a reasonable A1C goal for most adults is < 7%.

- The goal of HbA1c, according to the ADA, is ≤ 7%.[7] Failure to achieve this percentage should review and adjust the patient's treatment plan.
- The goal of EASD guidelines for HbA1c is < 6.5% for both type 1 diabetes and for type 2.[12]
- The goal of International Diabetes Federation (IDF) is < 6.5%,[13] a value that does not seem to perform better than goal of the ADA.[7]
- The goal of American College of Endocrinology is < 6.5%.

Providers might reasonably suggest more stringent A1C goals (such as,6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, long life expectancy, and no significant CVD.

Less stringent A1C goals (such as 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and extensive comorbid conditions and for those with longstanding diabetes in whom the general goal is difficult to attain despite self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.[7]

The benefits of early and tight glycemic control

Landmark clinical trials have established that glycemic control is critical for the prevention or delay of diabetic microvascular complications and may also help diminish macrovascular complications of the disease. The most important studies related to diabetes control like *Diabetes Control and Complications Trial (DCCT)*[9] and its follow-up observational study, the *Epidemiology of Diabetes Intervention and Complications (EDIC) study,*[15,20] *Multifactorial Intervention Steno-2 study,*[16] *United Kingdom Prospective Diabetes Study (UKPDS)*[10] and its follow up study,[73] *Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,*[17] *Action in Diabetes and Vascular Disease: Preterax and Diamicron modified release Controlled Evaluation (ADVANCE) study,*[18] and *Veterans Affairs Diabetes Trial (VADT)*, agree that an early and tight glycemic control of hyperglycemia can prevent microvascular complications.[19] Some of these studies have explored the issue of intensive blood glucose control in patients with diabetes type 2 and have also addressed whether other therapeutic options such as blood pressure reduction and/or lipid lowering can act in concert with improved glycemic control to reduce the incidence and progression of vascular complications particularly the macrovascular complications.

Studies like the *Diabetes Control and Complications Trial (DCCT)*[9] designed to evaluate the impact of an Intensive Insulin based approach to decrease HbA1c have shown that from values above 8% there is an proportional increase in micro and macrovascular complications.[9] Moreover, in the DCCT trial a reduction from HbA1C of 9% in the conventional treatment arm to 7.2% in the intensive treatment arm, decreased the relative risk for retinopathy (63%), nephropathy (54%), neuropathy (60%) and microalbuminuria. Studies such as the *United Kingdom Prospective Diabetes Study (UKPDS)*[10] demonstrated a direct relationship between the intensity of HbA1c reduction and the lowering in the risk of complications in T2DM patients. A reduction of HbA1c from 7.9% (Conventional Treatment Arm) to 7% (Intensive Treatment Arm) was translated into a 25 % reduction ($p = 0.0099$) in all microvascular complications, 22% reduction in the risk of any diabetes-related complication ($p = 0.029$), 6% decrease in total mortality ($p = 0.44$) and a 16% less incidence of Myocardial Infarction ($p = 0.052$) at the end of 8 years of active intervention.[10]

As mentioned above, there were no significant effects of blood glucose reduction on cardiovascular complications. Despite the observed effect of increased body weight with insulin and sulphonylureas, it is interesting to note that there was no increase in cardiovascular events in the intensive arm of UKPDS.

In the original UKPDS Trial patients whose body weight was more than 120% of their ideal weight could be randomised to an intensive glucose control policy with metformin instead of diet, sulphonylurea or insulin.[74] At the end of 8 years of active intervention, reductions in the risk of myocardial infarction of 39% (p = 0.01) and of death from any cause of 36% (p = 0.01) were observed.

The phenomenon of ongoing beneficial effects on diabetic complications after a period of improved glycemic control followed by a return to usual (often poorer) metabolic control was described as representing "metabolic memory" by the DCCT/EDIC investigators and as the "legacy effect" by the UKPDS investigators.[20,73] Following conclusion of original UKPDS Study, there was a post-trial monitoring to determine whether the improved microvascular outcomes observed during the active glucose control trial persisted and whether such therapy had a long-term effect on macrovascular outcomes.[73] Patients were asked to attend annual UKPDS clinics for 5 years, and all patients in years 6 to 10 were assessed through questionnaires but no attempts were made to maintain their previously assigned therapies. After 10 years of follow up (mean 18 years from initial aleatorization), the relative risk reduction in the sulfonylurea-insulin group was 9% for any diabetes-related endpoint (p = 0.04) and 24% for microvascular disease (p = 0.001) but most important, in the sulfonylurea-insulin group there were also achieved a reduction in relative risk for death related to diabetes (17%, P = 0.01), myocardial infarction (15%, P = 0.01), and death from any cause (13%, P = 0.007). In the Obese-Metformin treatment arm of UKPDS after 10 more years of follow up (for a total of 18 years), there was a drop in the risk for any diabetes-related endpoint to 21% (P = 0.01), diabetes-related death in 30% (P = 0.01), myocardial infarction in 33% (p = 0.005), microvascular disease in 16 % (p = 0.31) and death from any cause in 27% (p = 0.002).

"Metabolic memory" and "legacy effect" are terms used to describe the fact that an early and appropriate control of glucose levels has a great influence on the diabetes complications reduction and disease progression. Most patients with type 2 diabetes eventually require insulin to achieve glycemic targets. Early use of insulin therapy may help normalize blood sugar and HbA1C levels and thus improve the prognosis of the disease by preventing further vascular damage. For this purpose, the American Diabetes Association (ADA) established HbA1c values (depending on the group of patients) at which it is recommended initiation of appropriate therapy (according to their recommendations) to prevent an increase in vascular damage (table I).

Table I
Goals of glycemic control (HbA1c)

Standards of Medical Care in Diabetes 2009		
Goals of Glycemic Control (HbA1c)		
Prevention	*Hb1Ac*	*Recommendation*
Microvascular and Neuropathy: In general[1]	< 7%	A
Macrovascular: In general[2]	< 7%	B
Subgroup Strict Control[3,4]: Short duration of DM Hb1Ac low at the beginning, not CVD	6-6.5%	B
Subgroup Laxo Control[4]: Short life expectancy History of severe hypoglycaemia Advanced Microvascular Disease Long-term DM Atherosclerotic load	> 7%	C

[1] = DCCT, Stockholm Diabetes Study, UPPDG, Kumamoto.
[2] = DCCT CDIG UKPDS Follow-up.
[3] = Subgrupos de DDCT y UKPDS ADVANCE.
[4] = ACCORD, ADVANCE, VADI.
Nathan DM et al. *Diabetes Care* 2000; 12: 193.

Therapeutic management as a pathophysiological approach

The core pathophysiological defects in T2DM are marked by insulin resistance in the liver and skeletal muscle and, beta-cell failure in the pancreas. In addition to this "triumvirate," adipose tissue, the pancreatic alpha cell, the kidney, the brain, and the gastrointestinal (GI) tract play important roles in the development of glucose intolerance and hyperglycemia. The members of this "ominous octet" all have an interdependent role in the pathophysiology and the development of T2DM that represent targets for current and emerging therapies. These therapies include a range of antidiabetic drugs that are classified as:

Insulin secretagogues

– Sulfonylureas (glibenclamide, gliclazide, glipizide, glimepiride). The sulphonylureas act to enhance the sensitivity of the beta-cell to glucose and, when bound to the transmembrane sulphonylurea receptor (SUR-1), mediate the closing of the potassium-sensitive ATP channels on the cell membrane. Cellular efflux of potassium is reduced and membrane depolarisation takes place. Calcium influx is mediated by the opening of voltage-dependent Ca2+-channels that promote the release of pre-formed insulin granules which lie just adjacent to the plasma membrane. The net effect is increased responsiveness of beta cells to both glucose and non-glucose secretagogues (such as amino acids), resulting in more insulin being released

at all blood glucose concentrations. Thus, sulfonylureas are useful only in patients with some beta cell function.[75]

Insulin sensitizers

– Biguanides (metformin). Biguanides are generally considered the drugs of choice in obese type 2 diabetics. Metformin can be used in combination with any other class of oral antidiabetic drug or with insulin. The principal function of metformin is to reduce hepatic glucose production thtough a reduction in glyconeogenesis as well as glycogenolysis, and to improve peripheral insulin sensitivity, thus ameliorating hyperglycemia. So that, hepatic sensitivity to insulin is increased, thereby contributing to basal plasma glucose lowering effects. Skeletal muscle and adipocytes undergo up-regulation of the insulin-sensitive GLUT- 4 and GLUT-1 transporters to the cell membranes, thereby increasing glucose uptake and reducing postprandial glycemia.[21] Metformin has been shown to activate AMP activated protein kinase (AMPK). AMPK is a well-known serine/threonine kinase that functions as an intracellular energy sensor and has been implicated in the modulation of glucose and fatty acid metabolism.[76,77] Once activated, AMPK inhibit the expression of two key hepatic gluconeogenic genes, PEPCK and G6Pase, which, in turn, suppresses gluconeogenesis and lipogenesis while promoting both fatty acid oxidation and lipolysis.[21,76,77] Glucose metabolism in the splanchnic bed also increases. Further metabolic effects include suppression of fatty acid oxidation as well as triglyceride lowering.[21,22]

– Thiazolidinediones (pioglitazone, rosiglitazone). Thiazolidinediones (TZDs) mediate their function through binding to the PPAR-γ receptor that is expressed predominantly in adipocytes. It is expressed to a lesser extent in muscle and liver tissue. Binding of the PPAR receptor in turn mediates binding to the retinoic-X receptor (RXR-receptor). This heterodimer then binds to a nuclear response element which then switches on gene transcription. Many of the genes that are activated play a central role in carbohydrate and lipid metabolism. Interestingly, the thiazolidinediones also suppress the expression of TNF-α by adipocytes.[80]

Glycosidase inhibitors (Acarbose)

Acarbose, inhibit the activity of the glycosidase enzymes which are present in the brush border of enterocytes in the intestinal villi. Disaccharide and oligosaccharide cleavage is prevented with a net decrease in intestinal carbohydrate absorption. Overall, the α-glycosidase inhibitors reduce postprandial insulin concentrations through the attenuated rise in postprandial glucose levels.[81]

New drug modalities (Incretin based therapies)

Pharmacologic administration of GLP-1 is not practical because it is metabolized in minutes by the enzyme dipeptidylpeptidase-4 (DPP-4), but two strategies have been developed to take advantage of this hormone's beneficial properties. GLP-1 mimetics (Exenatide and Liraglutide) are protein derived injectable products, resistant to DPP4 action, that duplicate the effects of GLP-1 and demonstrate significant reductions in HbA1c in patients with type 2 diabetes. Also of interest as an incretin therapy is the use of DPP-4 inhibitors, which can be given orally and produce near-physiologic levels of GLP-1. These agents have been shown to have a prolonged inhibitory effect on DPP-4, enhancing half life of native GLP1 and GIP and stimulating insulin secretion in the presence of glucose and producing significant decreases in HbA1c. They have the added advantage of inducing moderate weight loss. Because they are peptide hormones, they have to be injected subcutaneously. There appears to be a significant frequency of nausea and vomiting with these agents, which for most patients is transient.

– Exenatide. The synthetic 39-amino acid peptide sequence overlaps with that of GLP-1, but has a longer half-life than native GLP-1. This incretin mimetic improves glycemic control mainly by stimulating glucose-dependent insulin secretion and suppressing postprandial glucagon secretion. It also delays gastric emptying, reduces food intake and facilitates weight loss.

– Liraglutide. Liraglutide has 97% homology with GLP-1 and resists DPP-IV degradation by FA acylation and albumin binding. Single-dose kinetic studies in DM2 subjects revealed a half-life of 13-14 hrs, allowing for single daily-dose administration, whereas native GLP-1 with a very short half-life of 1-3 min has limited clinical value. Liraglutide enhanced several β-cell function parameters and the enhancement was correlated with the improvement in glycemic control. The mechanisms of Liraglutide action, as expected, appear to be analogous to those exerted by endogenous incretins and others incretin mimetics like exenatide.

– DPP4 inhibitors (Vildagliptin, Sitagliptin, Saxagliptin, Linagliptin). Inhibition of dipeptidyl peptidase-IV stimulates the secretion of insulin in a glucose-dependent way, so minimising possible hypoglycemic side-effects. Inhibition of DDP-IV is dose-dependent. Recent data suggest restorative effects on pancreatic islet cells, thereby fuelling the hope that the DDP-IV inhibitors could potentially slow or reverse the course of beta-cell failure.[23,24] These drugs can be used as monotherapy in type 2 diabetes or in combination with metformin, SUs, TZDs or Insulin if the existing regimen no longer provides adequate glycaemic control. Sitagliptin, Saxagliptin and Linagliptin can be taken orally once daily and Vildagliptin must be taken twice daily. All have shown to reduce HbA1C levels by a

Table II
Oral Antidiabetic Agents (OAA) effect on T2DM pathophyisiologic defects

Parámeter	*SU*	*Glinides*	*Met*	*TZD*	*I-DPP-IV a-GLP1*
Insulin secretion	⇑	⇑			⇑
Insulin resistance			⇓	⇓	
Hepatic gluconeogenesis			⇓⇓	⇓	
Hypoglycemia risk	⇑⇑	⇑	⇓		⇓
Edema and ICC risk				⇑	
Weight change	⇑	⇑	⇓⇔	⇑	⇔⇓
Gastrointestinal effects			⇑		⇑
Use in renal insufficiency	⊘	⇔	⊘	⇔	⇑

SU = Sulphonylareas; TZD = Thiazolidinediones.

mean of 0.6-1%. Since the best predictor of hypoglycaemic effect of any drug is basal level of HbA1c, all DPP4-inhibitors can decrease HbA1c up to 3% if the A1C is high enough. Unlike the GLP-1 analogues, they have no effect on weight, but have the advantage of not being associated with the occurrence of nausea.

Algorithm for glycemic control according to HbA1c

The AACE/ACE algorithm for glycemic control is structured according to categories of HbA1C and suggests an HbA1C goal of ≤ 6.5%, although that may not be appropriate for all patients.[25] The algorithm recommends monotherapy, dual therapy, or triple therapy based on initial HbA1C level of 6.5% to 7.5%, 7.6% to 9%, and > 9%. Insulin therapy can be initiated as first-line treatment if the patient is symptomatic and A1C > 9% ("rescue insulin") or later on when treatment with oral or other injectable agents have failed.[26]

Initial treatment in T2DM with diet and physical activity is very common insufficient for blood glucose control, so that, at the time of diagnosis most patients will need pharmacological therapy with metformin or other drugs if the patient is metformin intolerant or has a contraindication for its use. After about 3 to 6 months without getting an acceptable metabolic control, a dual oral drug treatment must be established. The best predictor of the antidiabetic effect of any drug is basal hyperglycemia level and there is a difference in the potency and efficacy of distinct hypoglycaemic agents.[27] Therefore, insulin should always be considered when the patient has severe hyperglycemic symptoms, fasting glucose above 300 mg/dl or when he is ketotic. Frequently once achieved acceptable metabolic control with insulin and due to the resultant reduction of glucotoxicity and improvement in insulin sensitivity and secretory capacity, the use of insulin can be suspended and replaced with oral drugs. When initiating oral monotherapy treatment, up to 30% of patients respond inadequately. This phenomenon, known as "primary failure" and attributed initially only to sulphonylureas, has also been reported with other oral agents and is related to the degree of hyperglycemia and duration of diabetes.[28] In most cases, however, we can achieve an acceptable control that can last several years and thereafter there is a progressive metabolic control deterioration independently of the drug used. This phenomenon, known as "secondary failure" is due to a progressive loss of insulin secretion (Beta cell apoptosis) which is part of the natural evolution of T2DM, commonly genetically determined. It is estimated that up to 10% of patients/year fail to respond to monotherapy.[10,29,30,31,32] Most patients sooner or later, will need combination therapy with 2 or more drugs and finally with insulin since a heterogenous disease like diabetes mellitus, with multiple pathophysiologic dysfunctions, can t be addressed with one single drug that do not correct theses multiple deffcets (table II).

The justification for combination therapy is based not only to the high incidence of long term monotherapy failure, but in fact, supported by several studies; it is feasible to use the synergistic effect of different drugs action mechanisms.[5,33] A study has been shown that combination therapy with OAAs is more effective than intensified monotherapy.[34] In combination therapies, we must consider the use of new drugs based on the incretins (GLP-1 mimetics and DPP-IV inhibitors).

Among the defects that are involved in the pathophysiology of T2DM are abnormalities in the secretion of the incretin hormones GLP-1 and the glucose-dependent insulinotropic polypeptide (GIP).[35] GLP-1 and GIP are small peptides, having 30 and 42 amino acids and released by the enteroendocrine L cells located in the distal ileum and colon and by the K cells in the duodenum, and proximal jejunum respectively. Both rapidly stimulate the release of insulin only when blood glucose levels are elevated, thereby enhancing the glucose-sensing and insulin secretory capacity of the beta cells.[36] GLP-1 controls blood glucose via other actions besides stimulating glucose-dependent insulin release, and it is by inhibiting glucagon secretion and suppression of hepatic glucose output as well as by decreasing the rate of gastric emptying. On the other hand, GIP decreases gastric emptying to a much lesser degree and does not inhibit glucagon secretion.[36,37] GLP-1 also activates regions in the central nervous system important for control of satiety.[38] However, GLP-1 and GIP have also been shown in preclinical studies to exert significant cytoprotective and proliferative effects on the islets of Langerhans.[36,39,40] The incretin hormones elicit their actions through direct activation of distinct G protein-coupled receptors expressed on islet β-cells.[40] The short circulating half-life of bioactive intact GLP-1 and GIP initially limited enthusiasm for the potential use of incretin hormones in the treatment of diabetes. However, incretin analogs have been developed with significantly increased half-lives due to modification of the DPP-IV cleavage site and/or conjugation to large circulating proteins, such as albumin (i.e., liraglutide) or by inhibiting the DPP4 enzymes and prolonging endogenous GLP-1 and GIP. Nowadays, the majority of pharmacological efforts to develop incretin-based therapies are focused on GLP-1R agonist and DPP-IV inhibitors.

It is well accepted that the GLP-1R agonist liraglutide has more efficacy in lowering A1c than exenatide. In a head to head study liraglutide decreased A1c 0.3% more than exenatide with less nausea and with modest but more weight loss.[78] Single-dose studies of DPP-IV inhibitors, sitagliptin, saxagliptin, linagliptin and vildagliptin indicate that all compounds have similar clinical efficiency in reducing glucose excursion after oral glucose administration.[41,79] The use of these new drugs in monotherapy and combination therapy with metformin, sulphonylureas or TZDs, have shown at least not be inferior to the results obtained with the traditional antidiabetic drugs.

Balancing Efficacy *vs.* Safety of Oral Antodiabetic Agents (OAAs)

OAAs are by definition the starting point of pharmacologic treatment of T2DM. The modes of action of the five classes described are different, and offer an opportunity to "tailor treatment" addressing the likely pathogenetic mechanisms involved in this heterogeneous disease. "Failure" of one level of treatment should be monitored for at all times by appropriate checks on well being, fasting and post prandial blood glucose (self-monitoring), HbA1c, safety issues like weight, hypoglycaemia, edema and G-I tolerance (nausea, diarrhea, flatulence.

Cardiovascular safety of OAAs

Probably, the most important safety aspect is long term cardiovascular effects. A "safe OAAs" at least, should not increase CV risk. On the long term, insulin in Type 1 DM (DCCT / EDIC Trial);[20] sulphonylureas (UKPDS-FU Study, ADVANCE, VADT Trial),[18,19,73] metformin (UKPDS Obese-Metformin Arm),[74] and insulin in T2DM[73] have demonstrated CV safety in the treatment of hyperglycemia.

Hypoglycemia as a limiting factor in the treatment of T2DM

Glucose counterregulatory mechanisms have generally been found to be intact early in the course of type 2 diabetes.[51,52] However, as also noted above, iatrogenic Hypoglycemia becomes progressively more limiting to glycemic control over time,[47,53] and the frequencies of severe iatrogenic hypoglycemia have been reported to be similar in type 2 and type 1 diabetes matched for duration of insulin therapy.[54] Given progressive insulin deficiency in type 2 diabetes,[47] these findings indicate that iatrogenic hypoglycemia becomes a progressively more frequent clinical problem as patients approach the insulin-deficient end of the spectrum of type 2 diabetes.

In T2DM treatment, incidence of hypoglycemia is very difficult to predict due to the extreme heterogeneity of these patients, age, diabetes duration, renal function, treatment modality but what quite certain is that with sulphonylureas, meglitinides and insulin use, there is an increased risk.

In UK Hypoglycaemia Sludy Group trial,[55] about 7% of people with type 2 diabetes who were followed for an average of 8 yeras, had experienced at least one episode of severe hypoglycaemia in the first 2-3 years of insulin therapy, a proportion similar to those treated with sulfonylurea.[56] A retrospective study has reported 15% severe hypoglycemic episodes in type 2 insulin treated patients directly related to the duration of insulin use > 5 years.[57] People with type 2 diabetes constitute a disparate group, the ability of each patient to secrete glucagon in response to hypoglycaemia being related to the degree of insulin deficiency.[58] Glucagon secretion was almost absent in type 2 diabetic patients who exhibit total insulin-deficiency. By contrast, glucagon secretion is intact in OAAs-treated patient and in type 2 diabetic patients who have

recently started insulin. These patients do not experience hypoglycaemia more frequently than patients taking SU at similar HbA1c levels.[10] In a retrospective cohort of Medicaid patients, recent hospital discharge was the strongest predictor of subsequent hypoglycaemia in SU or insulin treated patients aged ≥ 65 years.[59] In the Fremantle Diabetes Study severe hypoglycaemia frequency was studied in older patients with cognitive impairment.[60] Hypoglycaemia requiring health services assistance was three times higher in patients with cognitive impairment or dementia. These patients were older, 76 4.6 years, 27.5% treated with insulin + OAD and 45% by SU, 46.4% having an HbA1c ≤ 7%. Dementia was present in 9.3% and cognitive impairment without dementia in 19.9%. Summarising, many studies support that the risk factors for hypoglycaemia with the treatment of T2DM patients are: older age, duration of diabetes, decreased food intake, unhealthy lifestyle habits, depression, cognitive dysfunction, dementia, fragile low weight patients, exercise, alcohol use, renal impairment, and use of secretagogues (sualphnylueas, meglitinides) and insulin.[61,68]

Other potential adverse effects of OAAs

– Sulphonylureas (SUs): Hypoglycemia is the most troublesome side-effect. It is very important to keep in mind that since all sulphonylureas are highly bound to plasma proteins, they can potentially interact with other protein-bound drugs. Displacement from plasma proteins because of drug interactions has been implicated as a cause of severe SU-induced hypoglycaemia. This adverse effect is more likely in the presence of impaired renal function and in the underweight elderly patient. Use of the sulphonylurea types that bind the SUR-2 A and B receptors (glibenclamide, glipizide, glimepiride) should be avoided in high-risk patients suspected of having significant coronary artery disease CAD.[43,44] Another side-effects that have been described include, weight gain (1-4 kg over 6 months), skin reactions, acute porphyria and, rarely, hyponatraemia.[45,46] There have been reports in the literature of glimepiride-induced acute cholestatic hepatitis.[47]

– Thiazolidinediones (TZDs): The main negative effect related to use of TZD is the fluid retention. Which includes several potential mechanisms such as increased vascular permeability, decreased urinary sodium excretion, increased sympathetic tone and altered interstitial ion transport? It has also been postulated that TZDs may actually unmask previously undiagnosed cardiac dysfunction owing to their effects on salt and water retention.[48] The use of TZDs in patients with New York Heart Association (NYHA) class III or IV heart failure is not recommended in view of the side-effects of fluid retention and weight gain. There are studies showing an increased risk of bone fractures in women.[49] The TZD effect on bone appears to be an inhibition of osteoblast differentiation, with a resultant negative effect on cortical bone formation without a change in bone resorption.

– Biguanides: Side-effects of these drugs can include lactic acidosis. Metformin increases lactate production in the splanchnic bed and portal venous system due to a reduction in the activity of pyruvate dehydrogenase enzyme, thereby shifting the metabolism towards the anaerobic spectrum. However, the incidence of metformin induced lactic acidosis is rare, with only 0.03 cases per 1,000 patient-years reported in the literature. Abdominal discomfort and diarrhoea are the most frequent side-effects. Vitamin B12 deficiency owing to decreased GUT absorption can occur.[50] Its gastrointestinal side effects are made worse usually by too large a dose initially, and increasing doses too quickly.

– Glucosidase inhibitors: Exist a high rate of gastrointestinal intolerance to these drugs, perhaps related to prescribing too large a dose initially, not taking it with appropriate meals and increasing the dose too quickly. Side-effects include flatulence, abdominal discomfort and diarrhoea, but tolerance of the side-effects quickly develops. Hypoglycaemia can occur only if used in conjunction with a sulphonylureas, meglitinides or insulin.

Selection criteria for hypoglycemics drugs

The management of patients with type 2 diabetes has been given a firm evidence base in recent years through the results of randomised clinical trials, notably the UKPDS. An improved understanding of the pathogenesis and natural history of this complex metabolic disorder has facilitated the application of new therapeutic agents. Attainment and maintenance of near-normal glycemic control, while minimising the risk of iatrogenic hypoglycaemia, is a central long-term objective of therapy; however, this is often difficult to achieve in practice. Many outcomes besides HbA1c are important when evaluating and comparing oral diabetes medications, such as blood pressure control, weight and lipid changes, adverse events, quality of life, micro and macrovascular disease, and mortality. It is critical to evaluate adverse events, since these affect adherence as well as morbidity and mortality. Additionally, certain diabetes medications may be less safe for patients with certain comorbid conditions.

Evidence based medicine (EBM) shows that most diabetes medications reduced HbA1c levels to a similar degree. Metformin, TZDs, GLP-1 mimetics and SPU are more effective than other medications (acarbose, meglitinides, DPP4-i) as monotherapy as well as when used in combination.[68] Metformin has a beneficial trend in body weight, blood pressure and plasma lipid levels. It was difficult to draw conclusions about the comparative effectiveness of type 2 diabetes medications on all-cause and cardiovascular mortality,

cardiovascular and cerebrovascular morbidity, and microvascular outcomes because of low-quality of the trials or because of insufficient evidence. EBM shows that the risk for hypoglycemia with sulfonylureas exceeds the that of metformin or thiazolidinediones and that the combination of metformin plus sulfonylureas is associated with 6 times more risk for hypoglycemia than the combination of metformin plus thiazolidinediones. Moderate-quality evidence shows that the risk for hypoglycemia with metformin and thiazolidinediones is similar. Metformin is associated with an increased risk for gastrointestinal side effects. Thiazolidinediones are associated with an increased risk for heart failure, and both rosiglitazone and pioglitazone are contraindicated in patients with serious heart failure.[62,63]

Surgical Approach of T2DM

Today, the most common surgical procedures are performed laparoscopically and include adjustable gastric band (LAGB), sleeve gastrectomy (LSG), Roux-en-Y gastric bypass (RYGB), One Anastomosis Gastric By-pass (BAGUA) and biliopancreatic diversion (BPD). BPD often includes duodenal switch (BPD/DS) and sleeve gastrectomy. RYGB, BAGUA and BPD show the best long-term results in terms of fat loss[64,65] and diabetes resolution.[66] Whereas LAGB and LSG exert their effects through mechanical gastric volume and food intake reduction, RYGB and BPD (with sleeve gastrectomy) combine this effect with malabsorption of nutrients by means of bypassing a substantial part of the small intestine. In addition, the intestinal reconfiguration results in a rapid improvement of diabetes within days in most patients, which cannot be entirely ascribed to energy restriction or fat loss.

Bariatric surgery has been demonstrated to have an extremely beneficial effect on T2DM. There are at least two distinct mechanisms for this effect. In the early postoperative period following operations involving gastrointestinal bypass (RYGB biliopancreatic diversion with/without duodenal switch) and probably sleeve gastrectomy, there is an increase in the incretin response, which leads to augmentation of insulin secretion from beta cell mass. This effect is independent of weight loss. In later follow-up, progressive weight loss from any bariatric procedure leads to improved peripheral insulin sensitivity.

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Metabolic surgery: who and when? Is there a good answer?

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Abstract

Currently there is little doubt that the body mass index (BMI) is not an appropriate tool to grant access to metabolic surgery, especially in type 2 diabetics (T2D).

Several studies are pointing towards other parameters that should go along with BMI in the treatment decision tree in non morbidly obese diabetics.

Insulin resistance, fat distribution among others are considered good tools to predict favorable outcomes in medically non controlled diabetics if sent to surgery.

The bottom line in good T2D control is to decrease cardiovascular mortality. Using adequate tools to screen patients to the appropriate surgical treatment may favor patients that are not under control after lifestyle changes and best medical treatment, thus decreasing longterm cardiovascular mortality secondary to type 2 diabetes.

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Key words: *Metabolic surgery. Selection criteria. BMI. Insulin resistance. Fat distribution.*

CIRUGÍA METABÓLICA: ¿QUIÉN Y CUÁNDO? ¿EXISTE UNA BUENA RESPUESTA?

Resumen

En la actualidad, existe poca duda de que el índice de masa corporal (IMC) no es una herramienta apropiada para garantizar el acceso a la cirugía metabólica, especialmente en los diabéticos tipo 2 (DT2).

Diversos estudios apuntan a que otros parámetros deberían considerarse junto con el IMC en el árbol de decisión terapéutica de los diabéticos sin obesidad mórbida. La resistencia a la insulina y la distribución de la grasa, entre otros, se consideran buenas herramientas para predecir unos resultados favorables en pacientes diabéticos no controlados médicamente si se les deriva para cirugía.

La idea de base en la DT2 bien controlada es disminuir la mortalidad cardiovascular. Utilizando las herramientas adecuadas para cribar a los pacientes para el tratamiento quirúrgico apropiado puede favorecer a los pacientes que no se controlan después de los cambios en el estilo de vida y el mejor tratamiento médico, disminuyendo así la mortalidad cardiovascular a largo plazo secundaria a la diabetes tipo 2.

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Palabras clave: *Cirugía metabólica. Criterios selección. IMC. Resistencia insulina. Distribución grasa.*

Introduction

Currently, there is little doubt that the body mass index (BMI) is not an appropriate tool to grant access to bariatric and or metabolic surgery, especially in type 2 diabetics (T2D). And it is of little argument that it is not even a good tool for choosing the best therapeutical option for a diabetic patient, medical or surgical. BMI alone does not reflect the degree or distribution of adiposity; it discriminates unfairly on the basis of gender, race, age, fitness, and body fat composition.[1]

But, if BMI alone should not be the only tool for the adequate patient's screening for their best treatment, what should we pursue as ancillary tools for the best therapy for diabetic patients?

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How to identify candidates?

It is clear that T2D is a primary medical disease, but it is a very expensive one, as it consumes around 11% of the US healthcare budget.[2] This devastating disease has a 10-year mortality of 51%, it is responsible for 68% of fatal cardiovascular events and stroke, it is a major cause of limb's amputation and the main cause of blindness and new cases of renal failure.[2] Finally, the overall risk of dying among people with diabetes is at least double the risk of their peers without diabetes.

The continuing morbidity and mortality in persons with diabetes is a sign that the answer as to the best management for type 2 diabetes in terms of maxi-

mizing metabolic control is still elusive. Given this scenario, the option of bariatric/metabolic intervention needs to be considered in appropriately selected individuals.

A recent report by Lopez-Jimenez et al, from the Mayo Clinic, showed that regardless of BMI, visceral fat is the worst predictor for cardiovascular events and death, and it is clearly associated to the insulin resistance syndrome.[3]

There are 2 kinds of obese individuals, the malignant and the benign phenotype.[4] Stefan et al., described at the same BMI there are some conditions that augment the metabolic risk. They defined that at any given amount of total body fat, metabolically benign obese was not accompanied by insulin resistance and early atherosclerosis. Ectopic fat in the liver rather than visceral fat may be more determinant for insulin resistance, thus defining metabolically malignant obesity.

What parameters should be used with BMI?

Wajchenberg in 2002[5] demonstrated visceral adipose tissue imaged by computed tomography (CT) or magnetic resonance imaging (MRI) is associated with the metabolic syndrome features, being morphologically and functionally different from subcutaneous adipose tissue (SAT). By pooling all data, correlation analysis indicated that VAT contributes more to insulin resistance (HOMAIR) than SAT does.

Stefan again, in 2011[6] highlighted the importance of non-alcoholic fat liver disease (NAFLD). It is the emerging observation that NAFLD without any liver-specific consequences is often already strongly associated with metabolic alterations, most importantly with insulin resistance, which plays an important role in the pathophysiology of dyslipidemia, type 2 diabetes, and cardiovascular disease. Fabbrini in 2010[7] stressed as well the importance of NAFLD and insulin resistance. Interesting was the correlation of the ectopic liver fat accumulation with HOMA IR, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and magnetic resonance. There was little correlation with ultrasound.

Stern in 2005[8] suggests how to identify patients with insulin resistance based on routine clinical measures. Insulin resistance was defined based on BMI, HOMA IR, family history and triglycerides. Insulin resistance patients were identified if BMI was over 28.7 *or* BMI > 27 with a positive family history *or* HOMA IR over 4.6 or BMI higher than 27 *plus* HOMA IR greater than 3.6. And if BMI followed the same criteria above, but family history was negative, insulin resistance (metabolic malignant profile) would be diagnosed if triglycerides levels were over 216 mg/dl. Those parameters are relatively easy and quick to achieve.

Besides ectopic liver and musculoskeletal fat distribution and the clinical parameters described above, some studies revealed interesting markers for metabolic syndrome severity and cardiovascular mortality.

$$BAI = \frac{Hip}{Height^{1.5}} - 18$$

$$BAI = \frac{Hip}{Height\sqrt{Height}} - 18$$

Fig. 1.—BAI - body adiposity index.

Fasting insulin levels were predictors of the severity of metabolic syndrome.[4]

In a recent study about bariatric surgery and long-term cardiovascular events,[9] baseline insulin level was the strongest predictor of cardiovascular events. Surprisingly in this study, BMI levels did not predict any cardiovascular events after 20 years follow up. And in the same BMI range, there was a direct relation between the carothideal intima thickness and atherosclerosis. Seeking for other alternatives than BMI to spot the severity of metabolic syndrome, a mathematical model was developed based on the hip and height, the body adiposity index (BAI)[10] (fig. 1). BAI is strongly associated body fat mass regardless of BMI.

The BAI correlate with the percentage of body fat mass, body mass composition measured by Dual-energy X-ray absorptiometry (DXA), and predicts the severity of the metabolic syndrome components.

Other parameters

Fasting C peptide over 1 ng/dl and qualitative response after a mixed meal challenge may reflect the β cell function and should be tested before any therapeutical option is offered.[11] Waist circumference[2] and adiponectin levels (higher in insulin sensitive patients) are good tools to be eventually used in new perspectives in the treatment of T2D patients.

Conclusions and future directions

It is clear that BMI alone is not a good tool to screen candidates that can benefit from the good outcomes after metabolic/bariatric surgery.[12] Visceral fat, mainly ectopic hepatic fat play a major role in the determination of metabolically malignant obesity. Baseline fasting insulin levels are the mostly important isolated factor that predicts cardiovascular events and mortality. Worldwide healthcare policy makers are urged to reevaluate the older BMI centered criteria.

Randomized controlled trials (RCTs) are important to determine the adequate role of gastrointestinal surgery and T2D control. Recently, 2 RCTs were published[13,14] that showed the superiority of surgery when compared to medical treatment.

But we need to move forward. RCTs are needed to prove real “hard points” benefits of surgery over

Table I

Summary of other tools that may help for the indication of metabolic surgery

– High fasting insulin level	– Positive family history
– Thicker carotideal intima media	– 4 to 5x higher levels of AST/ALT
– High HOMA IR	– High BAI (hip circumference)
– Lipid profile (high triglycerides)	– Large waist circumference

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; BAI: Body aposity index.

medical treatment, such as micro vascular disease control. Other than this, RCTs should focus on the best timing for surgery (the sooner the better?), selecting the appropriate candidates and finding if there is any place for surgery as the first line of treatment for T2D. It is unquestionable that metabolic surgery has definitively its role for the treatment of diabetes and/or metabolic syndrome.

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Management of patients with type 2 diabetes before and after bariatric surgery: evolution and microvascular complications

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Abstract

Bariatric surgery is increasingly seen as a treatment option for patient with type 2 diabetes (T2DM) and severe complex obesity (SCO). There is however no consensus on how to manage this cohort preoperatively and postoperatively. Patients with T2DM having cardiac surgery benefit from glycaemic optimisation prior to surgery. National Health Service Diabetes in the United Kingdom recommends that glucose is optimised prior to all elective surgery. However, bariatric surgery such as gastric bypass (RYGB) is distinct from general surgery. Glycaemic control improves immediately after RYGB and thus all T2DM patients need a review of their glucose lowering medications postoperatively. Preoperatively most bariatric centres use a low calorie diet (LCD) which improved glycaemic control and may predisposed patients using insulin or sulphonylureas to risks of hypoglycaemia. There are no protocols and consensus among bariatric centres on how best to manage patients with T2DM preoperatively and postoperatively. Moreover patients with difficult to control T2DM are at risk of microvascular complications of diabetes. So far, there is little evidence on the impact of bariatric surgery on diabetes nephropathy, retinopathy and neuropathy.

In conclusion, bariatric surgery improves glycaemic control; however, there are limited studies, and no guidelines on how to manage patients with T2DM pre and postoperatively. Given the increasing proportion of T2DM patients referred for bariatric surgery, there is a need to review current practice on how to manage these patients in the short term and long term with a specific focus on improving end organ damage such as retinopathy, neuropathy and nephropathy.

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Key words: *Diabetes. Obesity. Bariatric surgery. Microvascular complications.*

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MANEJO DE PACIENTES CON DIABETES TIPO 2 ANTES Y DESPUÉS DE LA CIRUGÍA BARIÁTRICA: EVOLUCIÓN Y COMPLICACIONES MICROVASCULARES

Resumen

La cirugía bariátrica se considera cada vez más como una opción de tratamiento para los pacientes con diabetes tipo 2 (DM2) y obesidad severa compleja (SCO). Sin embargo, no hay consenso sobre cómo manejar este grupo de pacientes ni preoperatoria ni postoperatoriamente. Los pacientes con diabetes tipo 2 se benefician de los conocimientos procedentes de la cirugía cardiaca en la optimización de la glucemia antes de la cirugía. Por otra parte, el Servicio Nacional de Salud para la diabetes del Reino Unido recomienda que la glucosa haya sido optimizada antes de toda cirugía electiva. Sin embargo, la cirugía bariátrica como el bypass gástrico (BPG) es diferente de la cirugía general. El control glucémico del paciente intervenido mejora inmediatamente después de la cirugía (BGYR) y por lo tanto, todos los pacientes con DM2 necesita una revisión de sus medicamentos para el control de la glucosa durante el postoperatorio. Antes de la operación, la mayoría de los centros bariátricos utilizan una dieta baja en calorías (LCD) que mejora el control glucémico y si algunos de estos pacientes continúan usando sus fármacos antidiabéticos como insulina o sulfonilureas existe un alto riesgo de hipoglucemia. Hasta el momento no existen protocolos y no hay consenso entre los centros bariátricos sobre la mejor manera de tratar a los pacientes con diabetes tipo 2 antes de la cirugía y durante el postoperatorio. Además los pacientes con difícil control de la DMT2 se encuentran en riesgo de padecer complicaciones microvasculares debidas a la diabetes. Hasta el momento, hay pocas evidencias acerca del impacto de la cirugía bariátrica sobre la nefropatía diabética, retinopatía y neuropatía. En conclusión, la cirugía bariátrica mejora el control glucémico, sin embargo, hay pocos estudios, y no hay directrices sobre la manera de tratar a los pacientes con diabetes tipo 2 antes y después de la operación. Dado el creciente número de pacientes con DM2 que se someten a cirugía bariátrica, hay una necesidad de revisar las prácticas actuales sobre la forma de tratar a estos pacientes tanto a corto como a largo plazo con un enfoque específico en la mejora de daños tales como retinopatía, neuropatía y nefropatía.

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Palabras clave: *Diabetes. Obesidad. Cirugía bariátrica. Complicaciones microvasculares.*

Introduction: the obesity epidemic

The exponential rise in obesity is predicted to increase the prevalence of Type 2 diabetes mellitus (T2DM) by 50%.[1] The total number of people with T2DM is projected to rise from 171 million in 2000 to 366 million in 2030.[2] Meantime, management of T2DM has also evolved, though at a much slower pace. Conventional medical treatment of T2DM such as use of sulphonylureas and insulin inevitably leads to weight gain which exacerbates insulin resistance, hence, the management of obese T2DM patients has been challenging. The newer drugs such as glucagon-like peptide 1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors have a better weight profile. Increasingly, weight loss surgery has also been seen as a treatment for patients with T2DM and severe and complex obesity (SCO) defined as a body mass index above 35 kg/m² with life or limb threatening co-morbidities.[3] The International Diabetes Federation's (IDF) position statement in 2011 recommend bariatric surgery to be included in future algorithms for treatment of complex obese T2DM.[4]

Obesity surgery and diabetes

Obesity surgery originated as a form of gastrointestinal surgery, which was first performed in 1954. The jejuno-intestinal bypass strived for weight loss by circumventing the middle section of the small intestine.[5] Over time, this has evolved and today the three commonest weight loss surgeries are laparoscopic Roux-en Y gastric bypass (RYGB), adjustable gastric banding (AGB) and vertical sleeve gastrectomy (VSG). Gastric bypass involved division of the stomach into a small pouch which is drained by a proximal jejunum.[6] Food bypasses the gastric remnant and duodenum as a result. Gastric banding consists of the placement of a percutaneous adjustable band just distal to the gastro-oesophageal junction.[7] Sleeve gastrectomy involves stapling the stomach along its length to convert it into a tube, reducing its capacity down to 20% "sleeve" and removal of a large region of the stomach following the major curve.[8] All of these have also been termed as metabolic or diabetes surgery due to their effects in improving glycaemic control.[6,9,10] A randomised controlled trial of 60 patients with SCO and T2DM showed that bariatric surgery (gastric bypass or biliopancreatic diversion) achieved better diabetes remission (75% and 95% respectively) when compared to best medical therapy.[11] Despite its superior effect on diabetes remission, biliopancreatic diversion is not commonly performed[12] as in inexperienced hands it causes significant malabsorption and nutritional deficiencies. A meta-analysis by Buchwald (2009) showed that diabetes resolution was achieved in 80.3% of those undergoing RYGB.[6] It is important to note that the definitions used for remission of T2DM in all the above studies varied significantly. There was a lack of guidance on definition of remission of diabetes until the release of American Diabetes Association (ADA) guideline on "How do we define cure of diabetes" in November 2009. Since then, complete remission of diabetes has been defined as a return to normal glucose values (HbA1c < 6%, fasting glucose < 5.6 mmol/L) for at least one year after bariatric surgery without glucose lowering medication.[13] Pournaras et al. evaluated the proportion of patients achieving complete remission of T2DM using the stringent ADA guideline and found that of the 209 patients that had various types of bariatric surgery for their diabetes, only 34.4 % achieved complete remission of diabetes. The remission rate for gastric bypass was significantly lower with the new definition than with the previously used definition (40.6% *versus* 57.5 %; $P = 0.003$).[14] Schauer et al also found remission rate of 42%in their randomized controlled trial comparing gastric bypass and best medical treatment.[3] This new ADA definition therefore has therapeutic implication as more patients will have to remain on diabetes surveillance programs as well as on diabetes medication rather than the current practice of discontinuing treatment early.

The UK National Bariatric Surgery Registry showed that of 3,817 gastric bypasses performed in 2010, 27.5% of patients had T2DM.[15] This percentage is expected to rise, but there is no consensus in how to manage these patients preoperative, perioperative or postoperatively.

General surgery and diabetes outcome

Patients with T2DM are associated with a two to four fold increase in cardiovascular disease including hypertension, coronary artery disease and stroke.[1,16] The majority of people with T2DM planned for surgery are likely to have one or more cardiovascular risk factors and a significant number will have microvascular disease (retinopathy, nephropathy or neuropathy). These patients are at high risk of perioperative complications and even mortality.[1] The perioperative mortality rate is reported to be up to 50% higher than that of the non-diabetic population.[1,17] Diabetes patients are more at risk of poor wound healing, respiratory infection, myocardial infarction, admission to intensive care, and increased length of stay in hospital.[1,18,19] Perioperative poor glycaemic control has significant impact on postoperative infection.[17] The UK's National Health Service's department of Diabetes (NHS Diabetes) published: "Management of adults with diabetes undergoing surgery and elective procedures: improving standards" in April 2011. They recommended that all patients with diabetes undergoing elective surgery should have their glycaemic control optimised preoperatively.[1] However, this recommendation was made based on the majority of evidence on morbidity and

mortality of T2DM patients undergoing surgery, which were from the setting of cardiac surgery and to a lesser extent non-cardiac surgery. There was no specific evidence for bariatric surgery.

Bariatric surgery and diabetes outcome

There is no data on whether preoperative glycaemic control could influence the outcome of bariatric surgery and remission of diabetes. In non-bariatric surgery (orthopaedics, spinal, vascular, colorectal), elevated HbA1c preoperative has been associated with increased hospital length of stay (LOS) and worsen postoperative outcome.[20-24] There is also a belief amongst clinicians that optimised glycaemic control before surgery would aid wound healing and reduce immediate postoperative complications.

However, bariatric surgery such as RYGB should be distinguished from general surgery because of its immediate beneficial effect on glycaemic control postoperatively. The rapid glycaemic improvement appears independent of weight loss.[25] Moreover, these patients often followed low calorie diets preoperatively[26,27] which lead to improvement in glycaemia immediately before surgery. General surgery does not alter glycaemic control postoperatively; neither does it require patients to follow low calorie diet preoperatively. The question thus arises whether bariatric patients should follow a distinct pathway from the general surgical population and should we manage their diabetes differently? Would the preoperative, perioperative and postoperative glucose management impact on improvement and remission of diabetes?

A retrospective study reviewed 468 patients scheduled for bariatric surgery and grouped them into three categories based on HbA1c preoperatively. Poor preoperative glycaemic control was associated with worse glucose control postoperatively, as well as less weight loss and fewer cases of complete remissions of their T2DM at 18 months. An elevated postoperative glucose was independently associated with wound infection ($p = 0.008$), and acute renal impairment ($p = 0.04$).[28]

Remission of diabetes

Although remission of diabetes after gastric bypass surgery is well recognised, there is a paucity of data on when remission occurs, how to manage diabetes in patients that are not in immediate postoperative remission, and how to optimise patients going into remission of diabetes. Scopinaro et al showed that giving a low dose of long acting insulin analogue therapy for the first few weeks after biliopancreatic diversion improves the number of patients achieving remission.[29] Another cohort study in patients with type 2 diabetes requiring insulin suggested that after gastric bypass surgery tight glycaemic control (fasting blood glucose < 6.5 mmol/L for 1-2 week after surgery) can improve the remission rate of T2DM after one year.[30] It is possible that the pancreas undergoes a period of regeneration within the early postoperative period, and a healthy glucose environment is beneficial for cell function not only in the short, but in the long term. This may be analogous to islet cell "rest" immediately post islet transplant in type 1 diabetes, where exogenous insulin is given to avoid glucotoxicity.[31,32]

Complications of diabetes

Management of diabetes is not confined to glycaemic control only. Diabetes is characterised by micro- and macrovascular complications which could lead to significant morbidity and mortality.[33-35] United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that early intensive glycaemic control reduced the risk of developing microvascular complications in patients with T2DM.[36] The UKPDS follow up study further demonstrated that early intensive glycaemic control has long term beneficial effects on both micro and macrovascular complications.[37] However, there are some uncertainties around rapid intensive glycaemic management as the Diabetes Control and Complications Trial (DCCT) reported a paradoxical deterioration in microvascular complications such as retinopathy and neuropathy after rapid glucose lowering in Type 1 diabetes.[38,39] The safety and effectiveness of intensive glycaemia were also questioned by recent trials.[40-42] Hence, the question remains whether diabetes surgery alter the course of diabetes complications? Would the rapid improvement in glycaemic control cause more harm to retinopathy, as seen in pregnancy?[43] It is therefore important to assess the influence of bariatric surgery on the progression of diabetes complications.

Macrovascular complications such as cardiovascular disease were reduced following bariatric surgery[44] with improvements in coronary heart disease (CHD).[45] Similar results were also reported in the Swedish Obesity Subject (SOS) study and by Adam et al.[46,47] The SOS study is a prospective controlled cohort study comparing bariatric surgery to medical treatment for long-term mortality. The study compared 2,010 subjects who underwent bariatric surgery with 2,037 subjects receiving conventional treatment for their weight. Both groups were matched to 18 variables including gender, age, weight, height, waist circumference and blood pressure. The study found that the adjusted hazard ratio was 0.71 in the surgery group ($p = 0.01$) as compared with the control group.[48] Surgery was associated with a reduced number of cardiovascular death compared to the control group (28 *vs* 49 events, adjusted HR 0.47, $p = 0.02$).[46] The only group that had a cardiovascular benefit from surgery was those with baseline plasma insulin above the median of 17 IU/L. The microvascular complications in another case-controlled study with 10-years' follow-up comparing bil-

iopancreatic diversion versus those associated with conventional therapy on microalbuminuria, and glomerular filtration rate (GFR) in 50 newly diagnosed T2DM showed all surgical treated subjects recovered from microalbuminuria; whereas there was progression of microalbuminuria in non-operated subjects.[45] Metabolic complications such as hypertension, hyperlipidaemia, and obstructive sleep apnoea were all improved following bariatric surgery.[49] However, there had been case report of worsened diabetes neuropathy after RYGB;[38,50] and retinopathy[51] had been noted to deteriorate after very rapid improvement of glycaemic control. One year data after RYGB does however suggest that neither retinopathy nor microalbuminuria deteriorates, with the latter possibly showing some improvement.[52]

Role of pre-operative low calorie diet

Low calorie diet (800-1,200 kcal/day) and very low calorie diet (≤ 800 kcal/day) lead to rapid weight loss and improvement in T2DM.[53] It has also been shown to place type 2 diabetes in remission.[54] The diet has been used preoperatively in many bariatric centres to induce acute weight loss before surgery. The duration of preoperative diet varied between 2 to 6 weeks depending on practices. Low calorie diet(LCD) has shown to reduce visceral fat, liver volume and intrahepatic fat.[55] Reduction in liver size may have safety implication, as it facilitates the use of laparoscopic approach in obesity surgery.[55]

Despite the wide use of preoperative diet, Vargas et al. (2011) found a lack of evidence to supports its benefits as most of these studies were retrospective and could be underpowered.[26] Van Nieuwenhove et al. carried out a prospective, randomised multicentre study which randomised 273 patients to preoperative LCD or control before laparoscopic RYGB. The study reported no differences in mean operating time, estimated blood loss and intraoperative complications. However, the 30 days postop complications were lower in the LCD group.[27]

The use of LCD in patients with T2DM improves glycaemic control, and in some patients, may predispose them to the risk of hypoglycaemia especially if insulin doses were not reduced. Thus far, there is no published data on management of glucose during the perioperative period whilst on LCD or immediately after surgery. Some bariatric units may discontinue insulin treatment while others reduce the dose; some units may even discontinue all glucose lowering agents.

Management of hypertension post-surgery

The Copenhagen study showed that for each 10% increase in BMI, there was a 2-6 mm Hg raise in systolic pressure, and a 1-3 mmHg raise in diastolic blood pressure.[56] There was a significant correlation between mass of visceral adiposity and the level of blood pressure.[56] Consequently, patients with hypertension and diabetes are more at risk of developing end stage renal failure. A study looking at Austrian dialysis transplant registry showed that of the 50,000 patients, cardiovascular mortality was significantly higher for BMI 30-35 kg/m^2, compared to less than 30 kg/m^2.[56]

Aetiology of obesity related hypertensions are multifactorial. Hyperlipidaemia, activation of sympathetic nervous centre and renin-angiotensin activities have all been suggested as possible causes. Studies had shown that weight loss could improve hypertension.[57] A meta-analysis by Buchwald (2004) showed that hypertension resolved in 61.7% of total populations with hypertension following bariatric surgery; and it improved or resolved in 78.5% of the population.[49] Sarkhosh et al. reviewed 32 studies of laparoscopic sleeve gastrectomy and concluded that hypertension resolved in 58% of patients, and improved or resolved in 75% of patients at one year follow up. Each one percent reduction in body weight decreased systolic blood pressure by 1 mmHg, and diastolic blood pressure by 2 mmHg.[57] The SOS study showed that at 2 years, 34% of the surgical group recovered from hypertension, as compared to 21% of control group, but at 10 years only 19% of surgical group recovered from hypertension, as compared to 11 % of the control.[58]

Bariatric surgery has a positive effect on hypertension; however, its effect in the long term is less clear. Blood pressures therefore need to be monitored and antihypertensives titrated accordingly. Thus far, there is no study looking at management of changes in blood pressure after weight loss surgery. In diabetes patients, medications such as angiotensin converting enzyme inhibitor (ACE inhibitor) maybe initiated for renal protective effect rather than blood pressure lowering effect. Therefore physicians and surgeons need to be mindful when titrating blood pressure medication. As the SOS study illustrated, blood pressure might progress with time, and therefore one has to be vigilant in monitoring of these patients.

Management of hyperlipidaemia post surgery

Obesity and hyperlipidaemia are associated with higher cardiovascular risk as the Framingham Heart Study showed there was an increase in cardiovascular disease in overweight men and women.[59] Angina and myocardial infarctions are more common in overweight individuals. There are correlations between lipids concentration and development of coronary heart disease.[59] The most commonly encountered dyslipidaemia in obese individuals are a cluster of interrelated plasma lipid and lipoprotein abnormality including hypertriglyceridemia, low high-density lipoprotein cholesterol(HDL-C), raised small-density lipoprotein cholesterol (LDL-C).[60]

Meta-analysis of weight loss through diet showed a significant reduced total cholesterol(TC), LDL-C, very

low-density lipoprotein cholesterol (VLDL-C), and triglyceridaemia.[61] A retrospective observational study of 114 patients undertaking RYGB shared similar results. TC improved from 211.2 ± 3.8 mg/dL to 172.3 ± 5.5 mg/dL, $p < 0.001$ at 18 months; LDL-C reduced from 131.7 ± 3.3 mg/dL to 96.6 ± 4.0 mg/dL, $p < 0.001$; triglycerides reduced from 132.3 ± 5.3 mg/dL to 69.7 ± 3.7 mg/dL, $p < 0.001$; HDL-C increased from 52.9 ± 1.2 mg/dL to 63.1 ± 2.7 mg/dL, $p < 0.001$. There was significant association between changes in lipid profile and weight loss.[60] In another non randomised prospective cohort study assessing lipid profile of 102 patients undertaking VSG and RYGB, weight loss and reduction of triglycerides were similar between both procedures at one year. RYGB group has significant reduction in LDL-C (125.9 ± 29.3 to 100.3 ± 26.4 mg/dl, $p < 0.001$), as compared to VSG group (118.6 ± 30.7 to 114.6 ± 33.5 mg/dl, $p = 0.220$). However, VSG group showed significant increase in HDL-C of 15.4 ± 13.1 mg/dl compared to RYGB group (9.4 ± 14.0 mg/dl, $p = 0.032$).[62]

The concern is always that while patients are in a negative energy balance dyslipidaemia will improve, but may return to previous set points when patients become weight stable and there are limited studies with long term follow up. Gleysteen reported changes in lipid profiles for 2 cohorts of patients after RYGB and were followed up for different length of time.[59] The 1980-1981 cohort (N = 33) were followed up for up to 5-7 years; while 1985-1986 cohort (N = 23) were followed up for 1 year. Both cohorts showed significant increase in mean HDL-C at 1 year and 5-7 years. Both cohorts also showed significant reduction in the TC: HDL-C ratio at follow up. In the 1980-1981 cohort, significant weight reduction was noted at 1 year, but there was a mean weight regain of 11% at 5-7 year. Despite these, the changes in lipid profiles were maintained. The magnitude in weight loss does not correspond to changes in lipid profiles.[59] SOS study which compared 2,010 bariatric surgery patients with controls showed that the rate of recovery from hypercholesterolaemia did not differ significantly between surgical and control groups at 2 years and 10 years follow up. Rate of recovery from hypertriglyceridaemia and HDL-C were more frequent in the surgical group. In the surgical group, triglycerides improved by 27.2% at 2 years, the effect reduced to 16.3% at 10 years follow up; whereas HDL-C increased by 22 % at 2 years and 24% at 10 years.[58] Data on the long term follow up of lipids post bariatric surgery are limited. There is thus no logical reason why patients should stop treatment for dyslipidaemia or those who had discontinued lipid lowering treatment not to be monitored yearly and lipid lowering medication restarted as per usual protocol.

Conclusion

Diabetes is a disease which involves multiple systems. Management of T2DM has long term implications on macrovascular complications such as coronary heart disease and microvascular complications (retinopathy, nephropathy, neuropathy) and should not be limited to glucose management alone. A holistic approach to patients care is needed. Blood pressure and lipid control, as well as management of diabetes eye, kidney and nerve disease should not be overlooked. Glucose control improved following bariatric procedures such as gastric bypass surgery, but very little effort has focused on the long term cardiovascular risk and progression of microvascular complications.

Currently, there are no recognised guidelines in managing glycaemic control before and after bariatric surgery. More specifically, the effect of tight or more relaxed glucose control and the adjustment of insulin in the perioperative and early postoperative period could impact on long term outcomes in diabetes remission, mortality and diabetic microvascular and macrovascular complications. Whether patients would benefit from glycaemic optimisation before bariatric operations in order to decrease mortality and perioperative morbidity has not yet been determined. Each bariatric procedure has different effect on insulin secretion and insulin resistance and may also have differential effects on macrovascular and microvascular complications. The lessons learned from diabetes management in cardiac surgery necessitates us to evaluate management strategies in patients with T2DM scheduled for bariatric surgery especially as more patients are encouraged to consider surgery as a treatment for T2DM.

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Diabetes surgery in type 2 BMI 24-29 *vs* IMC 30-34 diabetic patients: is there differences among restrictive, malabsorptive and gastric bypass procedures?

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Abstract

Diabetes mellitus (DM) is a public health problem with a prevalence of 345 million people worldwide that it may double by the year 2030 and have a high costs and mortality. Gastrointestinal surgery is accepted as a form of treatment that was already suggested for obese in 1987 by Pories, confirmed for obese patients by the meta-analysis of Buchwald and the direct comparison of gastric bypass with medical treatment in the study of Schauer that demonstrate a 4 fold greater resolution rate of DM with surgery. Improvement occurs immediately after surgery, before the patients lose weight in with BMI > 35; but there is doubt if the existent evidence is enough to extrapolate these results to patients with BMI < 35 and especially with BMI < 30, in spite that four reviews in patients with this BMI and DM2 demonstrated the same results when stomach, duodenum and part of jejunum is bypassed as happen gastric bypass (better results with this of one anastomosis than of two anastomosis, Roux-en-Y) BPD. For patients with a BMI between 30 and 35 restrictive techniques: LAGB and SGL are good but not better than the mixed: RYGB, BAGUA, or SG-DJB with remission from 60 to 100%, minor in the derivative: BPD and above on the IID with a 81% of remission. There are no differences in the metabolic control in comparison to the obese, It is progressively better with DJB, SDS, IID and BAGUA especially in patients who do not require insulin, have less time with disease, have normal C peptide levels, and not so much relation with the initial BMI that is only important to decide the degree of restriction. Although several mechanisms has been suggesed for explaining these results such as caloric intake, hormonal changes, bypass of the anterior or early stimulation of posterior intestine, fundectomy, intestinal gluconeogenesis and others, new ones will appear in the near future.

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Key words: *Diabetes surgery BMI 24-34. Restrictives bariatric procedures. Malabsorptives bariatric procedures.*

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CIRUGÍA EN PACIENTES CON DIABETES TIPO 2 IMC 24-29 VS IMC 30-34: ¿EXISTEN DIFERENCIAS ENTRE LOS PROCEDIMIENTOS RESTRICTIVOS, MALABSORTIVOS Y BYPASS GÁSTRICO?

Resumen

La diabetes mellitus (DM) es un problema de salud pública, con una prevalencia de 345 millones de personas, que puede duplicarse para el año 2030 y con importante repercusión en costes y mortalidad. La cirugía gastrointestinal es aceptada como una forma de tratamiento sugerida en obesos desde 1987 por Pories, y confirmada por el meta-análisis de Buchwald y la comparación directa del bypass gástrico con el mejor tratamiento médico en el estudio de Schauer que pone de manifiesto un índice de remisión 4 veces mayor con la cirugía. La mejoría ocurre inmediatamente después de la cirugía, antes de la pérdida de peso en pacientes con IMC > 35; pero hay duda si la evidencia existente es suficiente para extrapolar estos resultados a pacientes con IMC < 35 y especialmente con IMC < 30, a pesar de existir cuatro revisiones en pacientes con este IMC y DM2 que demuestran los mismos resultados que en obesos cuando se puentea estómago, duodeno y parte del yeyuno como pasa en el bypass gástrico y la DBP. Para pacientes con IMC entre 30 y 35 las técnicas restrictivas: BGAL Y GVL son buenas pero no superiores a las mixtas: BGYR, BAGUA o GV-BDY con remisión desde 60 a 100%, menor en las derivativas: DBP y mayor en la IID con un 81% de remisión. En pacientes con sobrepeso no existen diferencias en el control metabólico respecto a los obesos. Es progresivamente mejor con DBP, CDC, IID y BAGUA sobre todo en pacientes que no requieren insulina, tienen menos tiempo con la enfermedad o con un nivel de peptido C normal, factores determinantes y no así el IMC inicial que sólo influye en el volumen de restricción. Aunque se han sugerido distintos mecanismos para explicar los resultados como ingesta calórica, hormonales, teoría del intestino anterior o posterior, fundectomía , neoglucogénesis intestinal y otros, aparecerán más en un futuro no lejano.

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Palabras clave: *Cirugía diabetes IMC 24-34. Procedimientos bariáticos restrictivos. Procedimientos bariátricos malabsortivos.*

Introduction

Diabetes Mellitus (DM) is at present an important health problem and gastrointestinal surgery is every time a more accepted solution as was hypothesized some years ago.[1] However, the great number of patients suffering DM make impossible to operate all of them and we need to choose those that can obtain the best benefit from the gastrointestinal changes perform by surgery for solving DM.

World Health Organization (WHO) advise that there are 346 millions people affected by Diabetes mellitus Type 2 and this number could be duplicated for the 2030 if we do not take special care to prevent it.[2] This illness is the responsible for 5% of all deaths over the world and we need to emphasized that there are a lot of cases undiagnosed and it could reach 4 to 6% (USA vs Spain) and this is the reason why we need to use the diagnosis criteria as ADA mention (126 mg/dl in fasting glycemia,…),[3] also use the HbA1c as the best marker to follow up the evolution of the disease because it is a good expression of the illness control and we know HbA1c is an oxidative product of glucose metabolism and could be deleterious above 7% because below this level the endothelium has the same evolution as the normal subjects.[4,5]

For obese patients the surgical criteria are clear and unanimous accepted.

Since 1987 when Pories started to publish their papers about the diabetes mellitus evolution in obese patients after the Greenville gastric bypass, where he mentioned that it could be possible that arrangements in the gastrointestinal tract as gastric bypass were the responsible of the improvement of the disease,[6-8] a lot of studies have appeared that try to clarify that question. The positive effect of bariatric procedures (mostly gastric bypass) has been confirmed by meta-analysis,[9] which demonstrated the superiority of the biliopancreatic diversion procedures as gastric bypass and BPD without or with duodenal switch over the restrictive procedures. And also direct randomized studies comparing gastric bypass and sleeve gastrectomy versus the best medical treatment,[10] demonstrating in this case the superiority of gastric bypass over sleeve gastrectomy (42% *vs* 37% of the patients with glycated hemoglobin < 6% 12 months after surgery), as well as the superiority of both over intensive medical treatment (only 12% of the patients with glycated hemoglobin < 6%).

However, so far, there is not the same certainty for extrapolating the results obtained in morbid obese to patients with BMI < 35. Although all the experience on the resolution of DM type 2 by bariatric surgery reported until now demonstrate that the effect is seen immediately after surgery, before weight loss happen and, hence, not direct related with the preoperative weight of the patient.[11,12]

The general idea is that obese patients could have more benefit from bariatric surgery based on the assumption: more obesity come to more insulin resistance than beta cell mass deficit and, hence, more possibility of diabetes resolution by the weight loss produce by bariatric surgery. While less obesity would speak on more beta cell deficit than insulin resistance and less possibility of resolution by bariatric surgery. But these pathophysiological deductions need to be confirmed by the evidence, especially if we consider our ignorance on the mechanisms responsible of the results we obtain by gastrointestinal surgery in BMI < 35 diabetic patients.

The other uncertainty in relation with the surgical treatment of DM in patients BMI < 35 is, which gastrointestinal surgical changes could have more and/or better effect on the diabetes resolution.

We analyze separately patients with BMI30-34 and those with BMI below 30, emphasizing the postoperative change of some variables as HbA1c, Fasting Glycemia, Dyslipidemias, its relation with the bariatric surgery procedures used, as well as the limitations of the data supplied in the studies.

Results of bariatric surgery use primary for treating diabetes in patients BMI 30-34

It has been published four reviews[13-16] on the role of bariatric-metabolic surgery in the treatment of type 2 diabetes with BMI < 35. All four reviews included the same studies. The difference is that the first one included only 13 of them,[15] the second 14,[13] 16 studies and 343 patients the third[14] and the last published in 2012 included 29 studies with 1,209 patients.[16] As in the case of obese diabetic patients, overall the percentage of resolution of DM is superior for the procedures that bypass most of the stomach, duodenum and part of the jejunum than for the restrictive procedures.[14,16] But in this case the better results are obtained for gastric bypasses of one anastomosis (One Anastomosis Gastric Bypass —BAGUA— and Mini Gastric Bypass —MGB—) over Roux-en-Y Gastric Bypass and pure malabsorptive procedures.[14,16]

Restrictive procedures

The first paper that reported the results on the effect of a bariatric restrictive procedure to treat Metabolic Syndrome was O'Brien[17] using lap-band in 2006. Before that, Angrisani in 2004[18] and Parikh in 2006[19] published their series using lap-band but they only mentioned patients with lost weight and those who have DM2 (4 and 8 respectively). O'Brien et al.[17] compared the results obtained through an adjustable gastric band surgery versus medical treatment based on a very-low-calorie diet, use of drugs (Orlistat®), and a supervised program of change of habits and behavior as well as physical activity in 80 patients with a 24-month follow-up.

While this is not a specific study on type 2 diabetes, 37.5% of patients had a diagnosis of metabolic syn-

drome (MS) according to the ATP III criteria,[20] which is closely linked to disorders in the glucose metabolism. The results of this serie reflected that MS persisted in only 2.7% of patients after surgical treatment, while it persisted in 24% of patients undergoing medical treatment. Regarding excess weight loss, it was of 87.2% in the group that underwent the surgical procedure *vs.* 21.8% in the group subject to medical treatment ($p < 0.001$).[17]

Then in 2009 Sultan et al.[21] do the same, publishing their results but again he did not inform about DM2. He just mentioned the number of patients with the disease. One year later Lee[22] published that SGL could improve FPG and HbA1c (240,1 to 132,9 and 10.1 to 7,1 respectively) and the changes are loss weight related.

Mixed procedures

Analyzing the studies reporting results with mixed procedures we observe that since 2006 when Cohen published his first paper[23] until 2008 with Lee,[24] we do not find anyone. After that appeared eight new studies in USA, Latin América, Asia and Europe (De María, Shah, Huang, Lee, Boza, DeSa, Navarrete and Garcia-caballero)[23-32] presenting similar results in BMI and weight loss, FPG and HbA1c.

In 2006, Cohen et al published their experience with Roux-en-Y Gastric Bypass in type 2 diabetes patients with class I obesity.[23] This is a prospective study with 37 patients and average follow-up of 20 months in which all patients were treated before operation by oral anti-diabetic drugs without insulin. The patients were also hypertensive and dyslipidemic. After the procedure, there was 100% remission of diabetes (fasting glucose values normal without medical treatment, and glycosylated hemoglobin [HbA1c] < 6%) and 36 patients showed remission of all related co-morbidities. There was no morbidity and no patient had an excessive weight loss.

According to data obtained from the American Society for Metabolic and Bariatric Surgery through its Centers of Excellence program, between 2007 and 2009, there were 235 patients reported with a BMI < 35 who underwent metabolic surgery to treat type 2 diabetes in the United States,[25] ninety two percent of procedures were made by laparoscopic approach. Hundred nine patients underwent a laparoscopic Roux-en-Y gastric bypass (RYGB). From that year on, new studies with more or less similar results, with similar BMI and weight loss as well as glycemia and HbA1c control came out in Asia,[26-28] Latin America[29-31] and Europe.[32] In all these studies, patients reach an almost normal BMI and remission of diabetes goes from 60%[24,27] up to 100%.[23,26] Navarrete et al have a similar experience in 15 patients with type 2 DM and BMI30-35 who underwent a RYGB, with a gastric pouch of about 50 ml, a biliopancreatic limb of 50 cm and an alimentary limb of 100 cm who reached a BMI 24.2, blood glucose of 85.35 mg/dl and HbA1c 5.53% with remission of the disease in 93% of the subjects.[31] García Caballero et al. reporting on 60 patients,[32] 35 of whom were BMI 30-34 (11 non insulin dependent and 24 insulin dependent) and 25 BMI 24-29 (9 non insulin dependent and 16 insulin dependent) find a mean resolution (postoperative HbA1c < 7% + resolution DM+MS without any treatment) rate of 67%. But when they analyzed separately non insulin dependent patients found a 100% resolution rate while in insulin dependent patients there were 50% resolution, 22,5% improvement needed only with oral anti-diabetic drugs and 27,5% move from 3-4 rapid insulin and 1 or 2 delayed insulin injections/day to only one of very reduced dose of delayed insulin/ day. These data demonstrated the importance of given precise information on the preoperative diabetes situation of the patients to be able to evaluate the effect of the different gastrointestinal surgical changes in diabetes resolution or improvement as was already discussed in the editorial of this monographic issue. They do not find difference in the results between patients related with the preoperative BMI 30-34 and BMI 24-29.[32]

It seems, then, that in the last two years, sufficient clinical evidence of the benefits and low risk of the laparoscopic gastric bypass has emerged in the management and treatment of DM, regardless of the approximated size of the gastric pouch: 15 ml (29), 30 ml[27,32] or 50 ml[30,31] or the length of the intestinal limbs: bilio-pancreatic 50 cm,[26] 100 cm,[29] or 100-150 cm in one anastomosis[32] and mini gastric bypass;[24] or alimentary 100 cm or 150 cm.[26,29-31] But not only RYGB or One Anastomosis[33] and Mini[34] Gastric Bypass have these mechanisms. also a new technique was proposed by Alamo et al.[35] doing a Sleeve Gastrectomy with a distal Jejunal Bypass preserving the duodenal absorption and 200 cm common channel. They reported 81,6% complete remission.

Malabsorptive procedures

In 1998 Noya et al published the first serie of 10 patients with type 2 diabetes, and class I obesity (mean BMI 33,2) who underwent a biliopancreatic diversion with gastric preservation. They observed normal blood glucose values and a mild weight loss in nine patients within the first postoperative weeks.[36] In 2007 Scopinaro et al published a retrospective analysis with 7 patients with type 2 diabetes and BMI < 35 who had undergone a biliopancreatic diversion. Although this was a small serie had a follow-up of 13 years, making it the only one reporting long-term results up to this date. Diabetes was controlled by 28.5% and improved by 100% without medical treatment, and no patient had undesirable weight loss.[37] Recently the same group published the results of a prospective controlled study comparing the effects of BPD in type 2 diabetic patients overweight or with mild obesity and they showed an improvement of HbA1c and FSG in com-

parison with the control group one and 2-years after surgery, confirming the superiority of BPD to standard medical care.[38] They also conclude that it exists a significant difference between the BMI ranges 25-30 and 30-35 in BPD effect on glycemic control, and thus in the biological severity of the disease, giving additional information on the related consequences.[38]

The ileal interposition

First performed by De Paula,[39] Ileal Interposition with sleeve gastrectomy comprises of a gastric sleeve with inter-positioning of a segment of ileum in to jejunum. The operation can be performed in two ways: with or without diversion of the duodenum. In the non-diverted version the ileal segment is interposed in to the proximal jejunum (termed Jejuno-Ileal Interposition JII). Therefore there is absolute no malabsorption. In the diverted version, the duodenum is diverted from 2-3 cm distal to the pylorus and the ileal segment is interposed in between the distal part of the sleeve and proximal jejunum, thereby bypassing the duodenum and the proximal jejunum (termed Duodeno-Ileal Interposition DII).

De Paula et al have a lot of experience with interesting results,[40] better with DII than with JII. In his first paper with 39 patients BMI below 35 (mean BMI = 30.1, range, 23.4-34.9), using the two laparoscopic procedures described above with mean operative time of 185 min, mortality rate 2.6%, and an adequate glycemic control in 86.9%.[40] In 2010 they published a randomized controlled trial including 38 patients BMI below 30 (JII 27 *vs* DII 29,9) comparing both operations, with better results for DII: remission rate was 81.3% DII *vs* 35.3% JII and HbA1c 5,39% DII *vs* 6,31% JII and they concluded that both operations were safe and effective for controlling type 2 DM in a nonobese (BMI 21-34) population.[41]

Experience with bariatric surgery for treating diabetes in patients BMI < 30

That is from the beginning the most controversial group based on the pathophysiological deductions mentioned above: less insulin resistance, more beta cell mass deficit and less possibility to be influenced by the surgical changes in the gastrointestinal tract. That is reason why the first results on bariatric surgery for treating diabetes published by the first author of this review were in this group of patients.[42] It was no reason to believe that the effect on DM resolution of surgical gastrointestinal changes in patients BMI < 35 could differ from those in patients BMI < 30. The difference between both are some kilograms but both are obese (morbid or simple obesity) and part of the type 2 diabetes is due to the insulin resistance linked to the lack of capacity of adipose tissue to store more fat and the consequent high amount of circulating fatty acids. [43,44] Even in diabetic patients with BMI < 30 the fat distribution (more visceral than subcutaneous as it seen at surgery) can condition the progression of insulin resistance to develop type 2 diabetes[45] and could explain the parallel postoperative evolution of DM in morbid obese (BMI > 35), simple obese (BMI 30-34) and non obese (BMI < 30) diabetic patients after bariatric surgery with the intention of solving their diabetes mellitus.[32,42,46] As well as that the results are in all cases more related to years of evolution of DM, non insulin treatment, years of insulin treatment and preoperative Peptide C levels, than to preoperative BMI.[42]

The same results were also reported by all the few clinical experimental studies included DM patients below BMI 30 existing in the literature.[47-55]

Initially, only the concepts of intestinal modifications of the RYGB were used[56-61] as well as performing a Duodenojejunal Bypass (DJB), preserving the stomach and the pyloric mechanism without adding an element of restriction.[47-52] As described by De Meester, the Duodenal Switch[62] was used for the first time for the treatment of recurrent gastroesophageal reflux disease, and despite good metabolic outcomes without significant weight loss,[47,48] the emergence of problems in gastric emptying probably due to the increase of GLP-1[63] and the need to restrict intake to contribute to the improvement of diabetes,[26,63] lead to incorporate a Vertical Gastrectomy as in the Classic Duodenal Switch.[64-73] Navarrete et al decided to call it Short Duodenal Switch (SDS)[53] showing good results in 11 patients operated by laparoscopy with a Vertical Gastrectomy with a 60 Fr boogie, a biliopancreatic limb of 50 cm and an alimentary limb of 100 cm, with remission in 60% of patients and control in the rest of operated subjects, which is a little lower than the Classic Duodenal Switch[64-73] and the Gastric Bypass.[23-32] This difference could be due to the maintenance of part of the gastric antrum in the sleeve gastrectomy in comparison with the complete bypass of it obtained with the gastric bypasses procedures. García Caballero et al. using BAGUA with a gastric pouch bigger than in obese and excluding only 100 cm jejunum distal to Treitz ligament in 13 patients mean preoperative BMI 27, reported 77% DM2 remission (77% insulindependent patients, 3 of them with Peptide C zero) with mean postoperative HbA1c 6.6% and mean SFG 100 mg/dl.[42] And Kim et al. in Korea reported in 2011 a prospective serie (mean preoperative BMI 27,2) with 70% DM2 remission and mean HbA1c 6.7% using MGB with a gastric pouch of 150-180 ml.[54]

These results are also comparable with De Paula findings despite the patients baseline condition were not so severe: younger (mean age 51 years and 63 in Garcíacaballero serie), 44% using insulin *vs* 77%[42] and shorter DM evolution (more than eleven years *vs* 16 years in Garcíacaballero serie) could have 95% well controlled without medication and HBA1c < 7% and 65% remission after two years of follow-up.[55] The patients reach a postoperative BMI near 21 as García-

caballero serie with BAGUA and had quite similar metabolic results 65%[55] *vs* 77% DM remission.[42]

So we have different gastrointestinal procedures to treat DM patients BMI < 30: BGYR,[23] BAGUA,[42] MGB,[24,55] DJB without Gastrectomy,[47-53] BDJ with SG or SDS,[53] ileal interposition JII or DII type[39-41] and BPD[38] and we do not fully know all the mechanisms involved in the control of carbohydrates metabolism after these surgical procedures? However, the results of the published series including low BMI DM patients[14,16] have been very consistent in terms of their effectiveness and low morbidity, with rates of improvement, control and remission totally superior to those obtained by conventional medical therapy.[10,74]

Different surgical gastrointestinal changes and their influence in the possible mechanisms for controlling carbohydrates metabolism

Among other aspects, the dietary restriction, imposed by most of these bariatric surgical procedures, is one of those mechanisms since it is well known that the mere decrease of caloric intake improves diabetes.[26,63] But biliopancreatic diversion procedures as gastric bypass, exclude the duodenum and jejunum from the alimentary circuit, but not restrictive techniques, can abolish type 2 diabetes within days of surgery, even before any significant weight loss has occurred. This means that calorie restriction alone cannot entirely account for this effect.

The complex hormonal changes that occur when altering the small intestine anatomy are undoubtedly one of the most studied findings of these and other surgeries.[75-82] After a gastric bypass, a biliopancreatic derivation or a duodenal-jejunal bypass, and before the patients lose weight significantly, there is an increase in the values of certain incretins (mainly GLP-1 and PYY), which translates into a better glucose homeostasis.[57,59-61] These results were reproduced more accurately in the experimental studies of Rubino[1,59,83] (theory of the upper intestine) and De Paula[39-41,55] (theory of the lower intestine).

It is important to highlight that the changes of intestinal anatomy to bypass the upper part of the gastrointestinal tract seems to improve 2 or 3 times the mass and function of the pancreatic beta cell.[61,84]

These effects suggest that the intestine is itself involved in the immediate regulation of carbohydrate homoeostasis throughout an increase in insulin sensitivity, disappearance of hypertriglyceridaemia and decrease in levels of circulating fatty acids, disappearance of the mechanisms of lipotoxicity in the liver and skeletal muscle, changes in the activity of digestive vagal afferents and changes in intestinal flora, all of them mechanisms that need to be studied in greater detail.[81]

Procedures that involve the resection of the gastric fundus like the vertical gastrectomy, cause a significant decrease in the levels of ghrelin, creating better conditions for the control of glycemia, as has been reported in experimental studies by Li et al.[85] and by Peterli et al.[86] in diabetic obese patients. Recently Chronaiou et al have observed that adding a fundectomy to the BGYR produce a high elevation of the GLP1 and PYY hormone effect to the decrease of ghrelin, achieving a persistence of this phenomenon is attributable to the decline of this hormone.[87]

The group of Mithieux (see also his chapter in this issue) recently published a study in experimental models, which suggest the existence of a sensitive hepatoportal pathway which might explain part of the beneficial effects on the control of glycemia after these procedures.[88,89]

So it exits a physiological basis, although nascent, that begins to unveil the physiology of metabolic surgery, specifically that related to the treatment of type 2 diabetes.

Final remarks

The results of the series published in patients with a BMI < 35 allows us to affirm that gastrointestinal surgical procedures are effective also in this group of patients, and that while these are short-term studies of 1 and 2 years of follow-up, the outcome is comparable to that observed in patients with severe obesity, so it is reasonable that long-term behavior will be also similar.

Although recurrence of diabetes has been reported after 3 years in some patients who had experienced remission after a gastric bypass[90,91] the possibility of delaying the occurrence of serious diabetic complications by 5 or 10 years represents a breakthrough for patients and society.

A special mention and consideration in our Western countries should be done about non-obese patients with type 2 diabetes like Scopinaro[38] and other authors[39,47,53,91] very well pointed out. Apparently, the metabolic response in these subjects is different since the improvement in glycemic control is not as good as in obese subjects BMI > 30, so this is not the only element to be considered.[1] Other factors like anti-GAD antibodies, C-peptide,[1,47,92] time of progression of the disease,[92-94] age[1,27] and some others already outlined in the introduction of this issue as minimum necessary information from the patients, should be taken into consideration as well as probably many other factors unknown to us in the light of current knowledge.

From all existing bariatric procedures, the laparoscopic gastric bypass and the gastric band are the most proven. The first being the most effective but with higher morbidity. Major complications are rare and mortality is rather exceptional, so it can be considered a safe surgery in these regards.[14,16]

Also, patients do not lose excessive weight so nutritional complications are not relevant.

The performance of the Duodeno-Jejunal Bypass should be considered in the management of patients

with a BMI < 30[53] because of its excellent results,[33,45,46] especially since the volume of restriction of the vertical gastrectomy is greater[94] in selected patients, always aware that it is a more complex surgery and a more expensive one with longer hospital stay and greater morbidity.[53,64-66] A tailored BAGUA could be also a good alternative in the management of this patients with lower risk and costs and even superior results.[42]

It is important to note that weight loss achieved by RYGB with a gastric pouch of 50 ml in patients with a BMI30-34 compared with the duodenojejunal bypass SG 160 ml associated with the equal length of limbs (biliopancreatic limb 50 ml and alimentary limb100 ml) in patients with BMI < 30, is statistically significant.[31,53] Therefore it is recommendable to associate less restriction to lower BMI[53,42,54] and again can also be considered the possibility of a BAGUA[42] or a minigastric bypass.[54] The ileal interposition although had good metabolic results,[95] seems more complex to perform and more expensive.

Based on the analyzed results, gastrointestinal surgery for type 2 diabetic patients with a BMI 24-34 is an alternative that should be part of the therapeutic options, especially in patients that conventional medical treatment is unable to provide adequate control of the disease.

Not all meta-analysis studies are suitable, for which it is recommended that they meet criteria so that their results have the desired impact.[97] Conducting controlled studies with greater samples and long-term follow-up becomes essential, in order to establish whether the surgical option may be routinely recommended. And reaching a consensus among the different medical and surgical specialties in order to provide the best therapy against one of the most devastating diseases today.

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Obesity and metabolic surgery in type 1 diabetes mellitus

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Abstract

Background: **Obesity surgery is an effective method for treating obesity and diabetes mellitus type 2. This type of diabetes can be completely resolved in 78.1% of diabetic patients and can be improved or resolved in 86.6% of diabetic patients. But little is known about bariatric surgery in type 1 diabetes mellitus.**

Methods: **We report of 6 female obese patients with diabetes mellitus type 1 who had bariatric surgery. Two of them underwent Roux-en Y gastric bypass (RNYGB), one of them had sleeve gastrectomy and the remaining three had biliopancreatic diversion with duodenal-switch (BPD-DS).**

Results: **Our results showed a remarkable weight reduction as well as an improvement in their blood glucose control and the insulin requirement in the follow-up years after surgery. Pre-surgery the BMI of our 6 patients ranged between 37.3-46.0 kg/m² and improved to 25.8-29.0 kg/m² one year after surgery. HbA1c decreased from 6.7-9.8% pre-surgery to 5.7-8.5% after one year post-surgery. The total amount of daily insulin requirement was reduced from 62-150 IU/day pre-surgery to 15-54 IU/day after one year.**

Conclusion: **The results are impressive and show an improvement in insulin sensitivity following obesity surgery. However, an optimal blood glucose control still remains very important in the therapy of diabetes mellitus type 1 to avoid long-term-complications.**

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Key words: *Type 1 diabetes. Diabetes. Obesity surgery.*

OBESIDAD Y CIRUGÍA METABÓLICA EN LA DIABETES MELLITUS TIPO 1

Resumen

Introducción: **La cirugía de la obesidad es un método eficaz para el tratamiento de la obesidad y la diabetes mellitus tipo 2. Este tipo de diabetes puede se resuelve por completo en el 78,1% de los pacientes diabéticos y mejora en el 86,6% de los pacientes diabéticos. Sin embargo, poco se sabe acerca de la cirugía bariátrica en la diabetes mellitus tipo 1.**

Métodos: **Presentamos 6 pacientes mujeres obesas con diabetes mellitus tipo 1 que se sometieron a cirugía bariátrica. Dos de ellas fueron sometidas a un bypass gástrico en-Y-Roux (BPGYR), una se le realizó una gastrectomía en manga y a las tres restantes una derivación biliopancreática con-switch duodenal (DBP-SD).**

Resultados: **Nuestros resultados mostraron una reducción de peso notable, así como una mejora en el control de la glucosa en sangre y el requerimiento de insulina en los años de seguimiento después de la cirugía. El IMC prequirúrgico de las 6 pacientes osciló entre 37,3-46,0 kg/m² y mejoró a 25,8-29,0 kg/m² un año después de la cirugía. La HbA1c disminuyó de 6,7-9,8% antes de la cirugía a 5,7-8,5% un año después de la cirugía. El requerimiento diario de insulina se redujo de 62-150 UI/día antes de la cirugía a 15-54 UI /día al cabo de un año.**

Conclusión: **Los resultados son impresionantes y muestran una mejora en la sensibilidad a la insulina tras una cirugía de la obesidad. No obstante, un control óptimo de la glucosa de sangre sigue siendo muy importante en la terapia de la diabetes mellitus tipo 1 para evitar complicaciones a largo plazo.**

(Nutr Hosp 2013; 28 (Supl. 2):31-34)

Palabras clave: *Diabetes tipo 1. Diabetes. Cirugía de la obesidad.*

Introduction

The prevalence of obesity and type 2 diabetes mellitus is increasing worldwide. In 2011 the prevalence of diabetes was 8.5% (= 366 million people with diabetes), this number is expected to reach 8.9% (= 552 million people with diabetes).[4]

Obesity surgery is an effective method for treating obesity and diabetes mellitus type 2. This type of diabetes can be completely resolved in 78.1% of diabetic patients and can be improved or resolved in 86.6% of diabetic patients. Weight loss and diabetes resolution is dependent on the type of surgery performed. After gastric banding there was a resolution of type 2 diabetes in 48% of patients, after gastric

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Table I
Sachsenhausen Hospital, Frankfurt; St. Josef Krankenhaus, Monheim, own data, 2011

	Patient A RNYGB 05/2011	*Patient B Sleeve 02/2010*	*Patient C RNYGB 07/2009*	*Patient D BPD-DS 02/2009*	*Patient E BPD-DS 01/2007*	*Patient F BPD-DS 02/2006*
Age at surgery	33	38	50	43	42	52
Diabetes duration at surgery	18	19	21	8 (LADA)	12	25
Therapy	CSII	CSII	ICT	ICT	ICT	CSII
Oral antiddiabetics prior surgery	No	Yes	Yes	Yes	Yes, initial	No

bypass in 84% of patients and after biliopancreatic diversion in 98% of patients.[1]

But little is known about bariatric surgery in type 1 diabetes mellitus. Only 6 cases of bariatric surgery and type 1 diabetes mellitus have been described in the last years by Czupryniak et al in 2004 and 2010 respectively by Mendez et al. in 2010.[2,3,5]

Methods

We report of 6 female obese patients with diabetes mellitus type 1 who had bariatric surgery.

Patient A and C underwent Roux-en Y gastric bypass (RNYGB). Patient A with RNYGB was 33 years old, had had diabetes for a period of 18 years and was treated with CSII (continuous subcutaneous insulin infusion system). The other one with RNYGB, Patient C was 50 years old, with a diabetes duration of 21 years at surgery. She controlled her diabetes with intensive insulin therapy (ICT) and metformin.

Patient B had sleeve gastrectomy. At surgery she was 38 years old, had had diabetes since 19 years and controlled her diabetes with CSII and metformin.

Patient D, E and F underwent biliopancreatic diversion with duodenal-switch (BPD-DS). At surgery they were 43, 42 and 52 years old and had had diabetes since 8, 12 and 25 years respectively. Patient D and E were also treated with intensive insulin therapy and metformin. Patient F controlled her diabetes with CSII (table I).

Results

Our results showed for all patients a remarkable weight reduction as well as an improvement in their blood glucose control and the insulin requirement in the follow-up year after surgery. Pre-surgery the BMI of our 6 patients ranged between 37.3-43.0 kg/m^2 and improved to 25.3-29.0 kg/m^2 one year after surgery. HbA1c decreased from 6.7-9.8% pre-surgery to 5.7-8.5% after one year post-surgery. The insulin requirement (units per kg body weight) was reduced from 0.72-1.13 IU/kg pre-surgery to 0.14-0.62 IU/kg after one year. The total amount of daily insulin requirement was reduced from 62-150 IU/day pre-surgery to 15-54 IU/day one year post-surgery. Only few data we have for Patient C because she discontinued follow-up.

In Patient A we observed the blood glucose values and the insulin requirements during her stay in our hospital. The evening before surgery we started this control with the CGMS (Continuous subcutaneous glucose monitoring system). We observed an improvement of insulin sensitivity directy after surgery – the same effect which is described after gastric bypass surgery in type 2 diabetes mellitus (table II).

Discussion

Several studies show that obesity surgery is an effective method for treating obesity and type 2 diabetes

Table II
Patient A development of insulin requirements the first days after surgery

Patient A with CSII	*Amount of insulin during stay in hospital*
1st day	50% of basal rate (basal rate = 24.2 IU)
2nd day – surgery in the morning	During surgery CSII was stopped
3rd day	40% of basal rate (11 am CSII was started again)
4th day	30-40% basal rate
5th day	40 % basal rate
6th day	During the night 40%, during the morning 30% due to more physical activity, in the afternoon 50%

mellitus although we do not clearly understand the mechanisms leading to resolution of type 2 diabetes mellitus after obesity surgery.

But we know little about obesity surgery in type 1 diabetes mellitus. As far as we know only 6 cases have been described in the literature till now.

In 2004 Czupryniak et al reported the first time about bariatric surgery in type 1 diabetes mellitus. They observed 2 female patients at the age of 23 and 28 who underwent gastric bypass. In both cases a reduction of the BMI (pre-surgery 38.8/46.3 kg/m^2 and one year post-surgery 26.6/30.1 kg/m^2) and an improvement of insulin sensitivity could be described. The daily insulin requirement could be reduced from 68/120 IU prior surgery to 45/70IU one year after surgery.

In 2010 Czupryniak et al. described a third case. A 19 year old man underwent RNYGB with a BMI of 41.5 kg/m^2 and a daily insulin dose of 96 IU. Five years after surgery his BMI decreased to 30.4 kg/m^2 and the daily insulin requirement to 30 IU.

Mendez et al reported in the year 2010 of 3 female patients with type 1 diabetes mellitus who had gastric bypass surgery. The pre-surgery BMI was 40.6-53.3 kg/m^2 and the daily insulin dose ranged between 52.2-180 IU. One year post-surgery the authors could observer a remarkable improvement not only of body-weight but also of insulin sensitivity. The BMI was

Table III

Overview – results after obesity surgery. Sachsenhausen Hospital, Frankfurt; St. Josef Krankenhaus, Monheim, own data, 2011

Type 1 diabetes mellitus overview						
Patient	*A*	*B*	*C*	*D*	*E*	*F*
Type of surgery	*RNYGB 05/2011*	*Sleeve 02/2010*	*RNYGB 07/2009*	*BPD-DS 02/2009*	*BPD-DS 01/2007*	*BPD-DS 01/2006*
BMI (kg/m^2)						
Presurgery	43.9	37.3	38.3	43	46	42
4 weeks post-surgery	38.0	33.3	35			
3 months post-sugery		29.4		34.4	40.9	34.1
6 months post-surgery	29.7	26.3	29.3	29.2	34.5	31.8
1 year post-surgergy		25.3		29	28.4	28.6
2 years post-surgery					26.4	
3 years post-surgery					27.1	
4 years post-surgery						28
HbA1c (in %)						
Presurgery	6.7	7.4	8.6	9.8	8.7	7.9
4 weeks post-surgery		6.5				
3 months post-sugery	6.9	6.6		8.1	7.3	7.6
6 months post-surgery	6.6	6.5	8.3	9.4	6.4	7.9
1 year post-surgergy		7.2		6.4	5.7	8.5
2 years post-surgery					6.7	
3 years post-surgery					6.9	
4 years post-surgery						7.9
Total amount of insulin per day (IU)						
Presurgery	62.2	88.6		110	150	110
4 weeks post-surgery	21.7	45.5				
3 months post-sugery		62.5		18	37	40
6 months post-surgery	25.0	46.0		18	54	35
1 year post-surgergy		48.0		15	54	30
2 years post-surgery				12	52	
3 years post-surgery					65	
4 years post-surgery						48
Amount of insulin (units per kg)						
Presurgery	0.54	0.72		1.13	0.93	1.2
4 weeks post-surgery	0.22	0.41				
3 months post-sugery		0.65		0.18	0.3	0.37
6 months post-surgery	0.32	0.53		0.18	0.51	0.35
1 year post-surgergy		0.58		0.14	0.62	0.32
2 years post-surgery					0.65	
3 years post-surgery					0.79	
4 years post-surgery						0.53

reduced to 26.7-30.8 kg/m^2 and the daily amount of insulin was 25.6-48.2 IU.

We found the same results. Due to obesity we observed an impressive weight reduction in every patient. The BMI prior surgery ranged between 37.3-46.0 kg/m^2. One year after surgery our patients reduced their weight to a BMI from 25.3-29.0 kg/m^2.

The results regarding insulin sensitivity are remarkable too. We saw an improvement in insulin sensitivity not only due to the weight reduction but also in the first days after surgery. This effect is already described for patients with type 2 diabetes mellitus in the days directly after surgery.

In our 6 patients the total amount of daily insulin requirement could be reduced from 62-150 IU prior surgery to 15-54 IU/day one year after surgery.

But as we could observe a decrease in BMI does not automatically lead to a good glycemic control. The HbA1c prior surgery ranged between 6.7-9.8%. One year after surgery we found an HbA1c from 5.7-8.5%. An optimal blood glucose control and a regular consultation with the diabetologist remains very important in the therapy of diabetes mellitus type 1 to avoid long-term complications due to diabetes.

Conclusion

Obesity surgery is an effective method for weight reduction and treatment of co-morbidities not only for type 2 diabetes mellitus but also for obese type 1 diabetes mellitus patients.

But patients with type 1 diabetes need to have an optimal glycemic control to prevent long-term complications due to diabetes. This remains a challenge for all.

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Improvement of C peptide zero BMI 24-34 diabetic patients after tailored one anastomosis gastric bypass (BAGUA)

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Abstract

Background: **Although bariatric surgery proved to be a very effective method in the treatment of patients in whose pancreas still produce insulin (type 2 diabetes), the accompanied metabolic syndrome and their diabetes complications, there is no information on the effect of this type of surgery in BMI24-34 patients when pancreas do not produce insulin at all (type 1, LADA and long term evolution type 2 diabetes among others).**

Patients and methods: **We report preliminary data of a serie of 11 patients all with a C-peptide values below 0.0 ng/ml. They were followed for 6 to 60 months (mean 19 months) after surgery. We studied the changes in glycemic control, evolution of the metabolic syndrome and diabetes complications after one anastomosis gastric bypass (BAGUA).**

Results: **All values relative to glycemic control were improved HbA1c (from 8.9 ± 0.6 to 6.7 ± 0.2%), FPG (Fasting Plasma Glucose) [from 222.36 ± 16.87 to 94 ± 5 (mg/dl)] as well as the daily insulin requirement of rapid (from 40.6 ± 12.8 to 0 (U/d) and long-lasting insulin (from 41.27 ± 7.3 U/day to 15.2 ± 3.3 U/day). It resolved 100% of the metabolic syndrome diseases as well as severe hypoglycaemia episodes present before surgery and improved some serious complications from diabetes like retinopathy, nephropathy, neuropathy, peripheral vasculopathy and cardiopathy.**

Conclusions: **Tailored one anastomosis gastric bypass in BMI 24-34 C peptide zero diabetic patients eliminated the use of rapid insulin, reduced to only one injection per day long-lasting insulin and improved the glycemic control. After surgery disappear metabolic syndrome and severe hypoglycaemia episodes and improves significantly retinopathy, neuropathy, nephropathy, peripheral vasculopathy and cardiopathy.**

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Key words: *T1DN. LADA. One anastomosis gastric bypass. C-peptide. Metabolic syndrome. Micro-and macro-vascular diabetes complications.*

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MEJORÍA DE PACIENTES DIABÉTICOS PÉPTIDO C CERO IMC 24-34 TRAS BYPASS GÁSTRICO UNA ANASTOMOSIS (BAGUA) TALLADO

Resumen

Introducción: **Aunque la cirugía bariátrica ha demostrado ser un método muy eficaz en el tratamiento de pacientes diabéticos cuyo páncreas aún es capaz de producir insulina (diabetes tipo 2), así como del síndrome metabólico y las complicaciones relacionadas con la diabetes, no hay información sobre el efecto de este tipo de cirugía en pacientes IMC 24-34 cuando el páncreas no produce insulina en absoluto (tipo 1, tipo LADA y diabetes tipo 2 de larga evolución, entre otros).**

Métodos: **Presentamos datos preliminares de una serie de 11 pacientes todos con valores de Péptido C < 0,0 ng/ml. El seguimiento postoperatorio varia de 6 y 60 meses (media 19 meses). Estudiamos los cambios en el control de la glucemia, evolución del síndrome metabólico y complicaciones relacionadas con la diabetes tras bypass de una anastomosis (BAGUA).**

Resultados: **Mejoraron todos los valores relativos al control glucémico HbA1c (de 8,9 ± 0,6 a 6,7 ± 0,2%), FPG (Glucosa Plasmática Ayunas) (de 222,36 ± 16,87 a 94 ± 5 (mg/dl)) así como el requerimiento diario de insulina, tanto de insulina rápida (de 40,6 ± 12,8 a 0 U/día) como de insulina retardada (41,27 ± 7,3 U/día a 15,2 ± 3,3 U/día). Se resolvieron el 100% de las comorbilidades estudiadas y se mejoraron algunas complicaciones graves derivadas de la diabetes como retinopatía o nefropatía.**

Conclusiones: **El bypass gástrico de una anastomosis adaptado a pacientes diabéticos IMC24-34 con péptido C cero elimina el uso de insulina de acción rápida, reduce a una sola inyección diaria la insulina retardada y mejora el control glucémico. Tras la cirugía desaparecen el síndrome metabólico y los episodios severos de hipoglucemia, y mejora significativamente la retinopatía, neuropatía, nefropatía, vasculopatía periférica y cardiopatía.**

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Palabras clave: *DMT1. LADA. BAGUA. Péptido-C. Comorbilidades.*

Introduction

Intensive glucose control did not succeed in showing mortality or cardiovascular benefits as demonstrated two recent meta-analysis,[1,2] but doubles the occurrence of hypoglycemia severe enough to warrant intervention,[3] does not improve quality of life[1,2] and is associated with "dead-in-bed" syndrome[4] and 3.4-fold increased risk of death.[5]

Morbidity and mortality in type 1 diabetic patients derive mainly from advanced microvascular, neuropathic, and macrovascular complications, with the major clinical impact beginning 15-20 years after the onset of diabetes.[6-9] The problem is that normally type 1 diabetes appear in these patients during the first years of life.

Metabolic Surgery offers hope and the possibility of a treatment for patients suffering from DM who are always at risk of developing the diabetes life threatening complications. The treatment of those complications can be very difficult to endure for patients and a new treatment that would minimize this, is eagerly awaited by these patients. Therefore, surgery for them is not just a way of treating their illness it might prevent or ameliorate the present treatments and their side effects, or treatment that they have to endure with consequent impacts on their daily quality of life.

However, the possibility of curing DM with surgery is limited. There are doubts as to its action mechanism, perioperative risk, possible side effects and long-term effectiveness, among other limitations. Diabetes patients are permanently looking for new advances that can help them to improve their quality of life and prevent the development of diabetes complications. When bariatric surgery was discovered as a viable alternative able to get a complete reversion of diabetes, many patients (including those with diabetes mellitus type 1 and C-peptide < 0.0 ng/ml) consulted the possibility of using this option to improve their current situation and prevent the future.

At this moment, the experience accumulated in type 1 diabetes (C Peptide 0,0 ng/ml) refer to only a few cases and in obese patients operated by bariatric procedures to solve their obesity, although, the surgery has demonstrated to solve or improve diabetes control and its complications.[10-12] The results of these few studies describe the remarked effect of surgery on insulin sensitivity, not only due to weight loss, but also on the first days after the operation. The same effect that has also been described by many authors in patients with type 2 DM in obese[13,14] as also in non obese patients.[15-17]

On the other hand the effect of bariatric procedures, especially gastric bypass, on metabolic syndrome and the evolution of diabetic complications (retinopathy, neuropathy, cardiopathy and peripheral vascular disease) seems to be more related to an extra effects of gastric by-pass (which pathophysilogical mechanisms are unknown so far) that to the direct effect on diabetes.

A final question of IMC24-34 C Peptide zero diabetic patients that ask to be operated by gastric bypass for improving their health after we explained them that so far there is no evidence for supporting the surgery in their case was: in case the gastric bypass do not do anything on my diabetes, what are the consequences for my health?. And the answer is that apart for the operatory risk (morbi-mortality near to 0-0,16%- for obese and easier surgery in normal weight patients), long term negative consequences are really minimal as has been proven over decades performing this type of surgery,[18] while every day appear more evidence of the positive effects,[19,20] independent of the BMI.[21]

All these arguments: low risk surgery, desperate health situation and long term expectations of the patients (especially those that started type 1 DM in childhood[22] and the possibility of a very positive effect that could improve their every day quality of life and prevent future devastating diabetes complications, and the decisive support of the patients in spite of the lack of direct evidence, prompted us to initiate this study.

We hypothesise that tailored BAGUA is able to improve glycaemic control, metabolic syndrome, severe hypoglycaemia and other diabetes complications in patients with C-peptide < 0.0 ng/ml without direct relationship with the weight loss.

To attempt to demonstrate this hypothesis, we performed the following studies in patients undergo tailored BAGUA: 1. To study the changes in blood glucose levels and glycosylated haemoglobin after laparoscopic tailored BAGUA. 2. To evaluate the needs of antidiabetic treatment after laparoscopic tailored BAGUA. 3. To assess the changes in weight and body mass composition after tailored BAGUA. 4. To study the changes in diet, exercise and daily quality of life. 5. To evaluate the evolution of the metabolic syndrome as well as diabetes complications present before surgery.

Patients and methods

Patients

We report a preliminary experience in 11 diabetes mellitus patients with C-peptide levels < 0.0 ng/ml who underwent tailored BAGUA. Seven of the patients had a BMI 24-29 and 4 patients BMI 30-34. Sixty four percent were male and 36% female with an age ranging from 17 to 76 years. Five of them suffered from type 1 DM with demonstrated positive antibodies, four were LADA and two long term evolution type 2 DM. They were followed for a mean period of 19 months (ranged between 6 to 60 months) after surgery. A complete description of the characteristics of the patients population is summarized in tables I and II.

Variables of the study

All patients completed a structured interview to obtain the following data: sex, age, weight, height, medical history, drug use, and prevalent diseases. In the same way it was recorded their dietary habits and

Table I
Patients characteristics

	Sex	Age	H (m)	W (kg)	BMI	Follow up (months)	DM type	DM2 evol (years)	Oral antidiab.	Insulin		Glucose (mg/dl)	C-pept (ng/ml)	HBA1C (%)
										Rapid insulin	Delayed insulin			
NA	M	76	1,75	71	24	24	T2	37	No	21	26	211	< 0.01	8.80
EG	M	17	1,74	74	24	11	T1	6	No	19	46	189	< 0.01	7.00
AM	F	55	1,53	62	26	16	LADA	26	No	0	52	160	< 0.01	6.00
MS	F	53	1,64	72	27	13	T1	27	No	24	40	200	< 0.01	8.90
BL	F	40	1,62	72	27	6	T1	34	Sí (2)	21	30	206	< 0.01	10.20
MJG	F	60	1,60	73	28	10	T2	6	No	40	21	188	< 0.01	10.10
AS	M	65	1,75	88	29	24	LADA	11	No	24	24	218	< 0.01	8.60
AR	M	46	1,71	91	31	16	LADA	16	No	90	60	243	< 0.01	9.60
RM	M	42	1,74	98	32	6	T1	30	No	28	20	261	< 0.01	6.60
JC	M	35	1,74	102	34	24	T1	29	No	30	45	200	< 0.01	8.7
AB	M	38	1,85	118	34	60	LADA	5	Sí (2)	150	100	370	< 0.01	13.1

H: Height; W: Weight.

Table II
Comorbidities and diabetes complications

Patients	Comorbidities and complications	Treatment	Uric acid (mg/dL)	Liver. Profile	(ALT-GOT and ALT-GPT) (U/L)
NA	Arterial hypertension, permanent atrial fibrillation, nonproliferative diabetic retinopathy	Sintrom, Coaprovel, Simvastatina 20	6.8		
EG	No	No	2.1		
AM	Hypercholesterolemia	Galaxdar 50 (1-0-1), Crestor 5 (0-0-1), Disnal (1-0-0)	2.4		
MS	Hypercholesterolemia	No	5.3		
BL	Periphery vasculopathy, cerebral ictus	Adiro 100, Daflon	3.0		
MJG	Arterial hypertension, neuropathy, diabetic retinopathy	Aprovel 150, Neurotin 600, Omeprazol 20	4.1		
AS	Arterial hypertension, hypercholesterolemia	Prevencor 40, Aprovel 150, Omeprazol 20 mg	6.8	Altered	↑ALT-GOT 40 U/L ↑ALT-GPT 48 U/L
AR	Hypertriglyceridemia, retinopathy	Adiro 100, Lopid 900	↑ (7.9)	Altered	ALT-GOT 26 U/L ↑ALT-GPT 43 U/L
RM	Arterial hypertension, diabetic retinopathy, with repeatedly photocoagulation, diabetic nephropathy	Angiodrox 300 (1-0-0), Parapres 32 (1-0-0), Adiro 300, Alopurinol 100, Torasemida 10, Carduran neo 4, Pantoprazol	↑ (7.7)		
JC	Arterial hypertension	Aprovel 150, Adiro 100	4.5		
AB	Arterial hypertension, Hypercholesterolemia, Hypertriglyceridemia	Prevencor 40, Aprovel 150, Lopid 600, Daflon, Anapril	↑ (8.0)	Altered	↑ ALT-GOT 42 U/L ↑ ALT-GPT 48 U/L

physical activity. Body composition was determined by bioimpedance (TANITA(R) is effected by placing feet of the patient over the electrodes. It transmits the patient an electric current type alternate, of 800 LA and at a frequency of 50 MHz. It is accepted that the body conducts electricity through the lean tissue and fat is not conductive. Mathematically it can be calculated the proportion and the amount of lean body mass and fat mass from weight and height and body impedance. The variation of the hydration status modifies the results by affect the conductivity, being an error factor.

Blood samples were extracted from peripheral vessels by vein puncture after fasting for 12 hours. From this sample is determined the concentrations of glucose by visible ultraviolet spectrophotometry and the glycosylated hemoglobin by high performance liquid chromatography (HPLC). The normal values of our laboratory are: Fasting Plasmatic Glucose from 65

to 105 mg/dl and glycosylated hemoglobin of 4.3 to 6.1% (23-43 mmol/mol).

C-Peptide (human proinsulin connecting peptide) is a polypeptide of 3,600 Da and 31-amino-acid that is synthesized in pancreatic islets β-cells. It is an excision product of insulin biosynthesis and serving to link and stabilize the A- and B-chains of the insulin molecule, thus enabling correct folding and interchain disulfide bond formation. Proinsulin is divided enzymatically to insulin and C-peptide, which is stored in the pancreas and is secreted in equimolar amounts.That makes it a useful marker of insulin release because, unlike insulin, C-peptide is not extracted by the liver, but goes entirely to the bloodstream. Another C-peptide advantage is that its determination is not affected by insulin autoantibodies presence, which are frequently in patients treated with insulin. Beta-cell function, measured as C-peptide, is well recognised in autoimmune diabetes both through its correlation with endogenous insulin secretion and in relation to complications.[22,23] Also in non-autoimmune diabetes, interest in Beta-cell function has recently risen considerably.[24,25] The levels of C-peptide were determinate by immunological methods. Normal values are 0.8 to 4 ng/ml.

Furthermore we take 10 ml more samples for obtaining serum samples that are stored -80º C for future research purposes. These extractions are repeated 1 and 3 months for comparing the changes obtaining by diabetes surgery. We analyzed variables of lipid, cholesterol, HDL-cholesterol and triglycerides by visible ultraviolet spectrophotometry (LDL-cholesterol was obtained by the Friedewald formula). Normal levels in our laboratories are: Cholesterol from 130 to 220 mg/dl, HDL-cholesterol greater than 35 mg/dl, LDL-Cholesterol below 150 mg/dl and triglycerides between 45 and 185 mg/dl in men and between 40 and 160 mg/dl for women. Similarly, follow-up of the antidiabetic treatment and metabolic syndrome comorbidities, as well as the weight, body composition, eating habits, physical activity, DM complications (retinopathy, nephropathy, cardiopathy, neuropathy and peripheral vasculopathy).

Quality of life was determined by the validated spanish version Moorhead-Ardelt II questionnaire[26] through successive postoperative interviews. The questionnaire have six questions scored from 1 to 10 points each. Good quality of life accounts from 42 to 60 points, medium 19-41 and bad 1-18.

Preoperative evaluation

All patients were subjected to a preoperative study following the indications of the Clinical Practice Guideline (CPG) of the European Association for endoscopic surgery (EAES).[27] This study consists of an analytical of blood in which we studied the following parameters: complete blood count with differential leukocyte, blood type, glucose, urea, Na, Cl, K, Ca, clotting time and prothrombin activity, total cholesterol, HDL, triglycerides, alkaline phosphatase, AST, ALT, GGT and bilirubin, plasma cortisol, thyroid hormones: TSH, T3 and T4, total protein and proteinogramme, serum iron, B12 vitamin and antibodies anti-Helicobacter Pylori.

In addition there was a radiologic study, with abdominal ultrasound, Rx A-P and lateral chest and oesophagus-gastro-intestinal transit; cardiologic exploration with electrocardiogram (ECG) and stress and/or coronary ischemia tests (if applicable); functional respiratory tests and endoscope study (only in selected cases).

Before making the final decision we indicate the patients to contact with other type 1 DM patients already operated by BAGUA to treat their diabetes, for comment on self expectations and how was for the other the already operated patients. And so obtain information on what they could expect. Last question of the new patients to those already operated was if they will do surgery again, and unanimous answer was: yes.

Surgical procedure

All patients take only liquid diet during five days previous to surgery and received antibiotic and antithrombotic prophylaxis before surgery. The laparoscopic gastric bypass of single anastomosis (BAGUA)[28] consists of the construction of a gastric pouch from the gastroesophageal junction to the end of the minor gastric curvature at the lower level of cisura angularis. The stapler line of the gastric pouch is fixed in approximately 12 cm to an intestinal loop (first layer of the anti-reflux mechanism) and anastomosed to it in a latero-lateral position excluding from the feeding course a length proportional to the BMI and distal to the Treitz ligament. Finally the anti-reflux mechanism is completed fixing the afferent loop to the gastric remnant and the efferent loop to the antrum. Both, the size of the gastric pouch and the length of bowel excluded depend on the BMI of the patient. In this group of patients the gastric pouch was always double as the size for obese patients and we excluded only 100 cm jejunum distal to the Treitz ligament for patients BMI 24-29, 120 cm BMI 30-32 and 150 cm BMI 33-34. We left systematically drainage during the 48 hours hospital stay.

Immediate postoperative care

First 24 hours patients received analgesics, antibiotics, low molecular weight heparin, procinetic, omeprazol and fluid-therapy. Patients are stimulated to start walking 8 hours after surgery. After the first 24 hours we retired all treatment except fluid-therapy and omeprazol. Around 48 hours after surgery we perform a gastro-graphic radiological test to check the gastro-intestinal anastomosis. If it is correct we start liquid diet and discharge patient home with only oral omeprazol and sucralphate. First week patient continues with liquid diet, second and third weeks every food pure and then start normal diet again.

Table III
Weight and body composition after BAGUA

Patient	*Sex*	*Age*	*Heigth (m)*	*Follow up (months)*	*Weight (BB) (kg)*	*Weight (AB) (kg)*	*BMI (BB)*	*BMI (AB)*	*Fat mass (BB) (%)*	*Fat mass (AB) (%)*
NA	M	76	1.75	24	71	53	24	20	27	18
EG	M	17	1.74	11	74	60	24	21	14,5	6,3
AM	F	55	1.53	16	62	51	26	21	15	7
MS	F	53	1.64	13	72	54	27	20	24	10
BL	F	40	1.62	6	72	60	27	23	27	16
MJG	F	60	1.60	10	73	54	28	21	50	14
AS	M	65	1.75	24	88	60	29	20	21	12,5
AR	M	46	1.71	16	91	70	31	24	25	17
RM	M	42	1.74	6	98	72	32	23	35	18
JC	M	35	1.74	24	102	71	34	23	48	17
AB	M	38	1.85	60	113	80	34	23	55	20

BB: Before BAGUA; AB: After BAGUA.

Adjustment of the preoperative medical treatment

The diabetic treatment is adjusted according to the necessities that the patients had during the five days liquids diet that we indicated routinely as preparation for surgery. Patients with C Peptide < 0,0 ng/ml, starting with reduced dose of long-lasting insulin (1 to 10 iu) allowing during the first days a plasma glucose levels until 200 mg/dl and adjusting the dose progressively until as near as possible of normal values. This adjustment is done by phone contact as frequent as the patients need.

We indicated always the total abandon of antihypertension, anti-uricemic and antilypemic drugs, and exceptionally patients need taken treatment again and, if so, just some doses. Regarding anti-thrombotic medication when patient have stent implant or previous vascular accident, we reduced dose and/or drug classes according with the internist of the group (Dr. Miralles). We leave the control other diseases or diabetic complications, especially, retinopathy, nephropathy and cardiopathy to the correspondent specialities.

Follow up

The data were collected prospectively according with a previously fixed protocol. This protocol included a baseline evaluation preoperatively that studied parameters related to the evaluation of the disease, comorbidities, diabetic complications, weight and body composition. Similarly we took a sample of blood for the analysis of biochemical variables. After surgery by BAGUA (the procedure explained before) and the protocol outlined (diets, drugs) follow up was performed in biochemical variables. Mean follow-up study was 17 months. Routinely we continue seeing the patients at 1, 3, 6, 12, 18 and 24 months and then yearly. In these patients a phone contact is open 24 hours if necessary.

Statistical analysis

The qualitative variables will be described through frequencies and percentages. Quantitative variables were analyzed by Student's T-test in the case of the variables with normal distribution. In all analyzes shall be deemed to be statistically significant p values less than 0.05. Analyzes carried out with the statistical package SPSS (version 15.0 for Windows, SPSS, Chicago, IL) and Excel 2007.

Results

Changes in body weight and body composition

All results obtained in relation to weight, BMI, and body fat, were as expected after a bariatric surgery intervention. We measured in all cases a reduction in both weight and the amount of body fat mass (table III and fig. 1). We obtained the largest decreases in those patients who had a higher BMI (table III). However, despite the initial difference in the patients weight on the study, all stabilized around a mean BMI of 21.6 ± 2.5 kg/m^2. Three patients were not happy with the weight loss during the first postoperative year (NA, AM, MJG):" they wanted some kilos more".

Fat mass values obtained by bioimpedance were reduced in all cases. These changes were statistically significant (P < 0.001). They decreased from a mean value of 31.0 ± 4.2% (before surgery) to 14.9 ± 1.3% (after surgery). In addition there is a positive correlation between the decrease in these values and those obtained for triglycerides with a bilateral significance of 0.012 and a correlation coefficient of 0.526.

Quality of Life assessment by Moorehead-Ardelt II Questionnaire (MA-II)

- Al patients were in the range good (42 to 60 points) after evaluation by MAII at six months

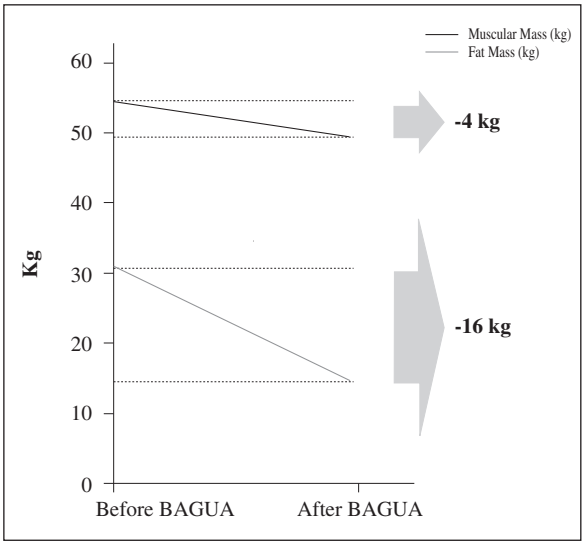

Fig. 1.—Evolution of Fat Mass and Muscular Mass after BAGUA.

from surgery. Although patients had a mean preoperative score of 47, corresponding to a good quality of life (except two patients in medium range), after surgery it improve until 52 (table IV).

Diabetes Severity Markers by Diabetes Type and Evolution

- *HbA1c:* A general improvement was observed in all study groups undergoing BAGUA (fig. 2) regardless of diabetes type. The mean value of HbA1c in patients with T1DM decreased from 8.3 ± 0.6% to 6.7 ± 0.4%, in patients with LADA of 9.3 ± 1.5% to 6.5 ± 0.2 % and in patient with T2DM decreased from 9.4 ± 0.6 to 7.2 ± 0.7%. None statistically significant differences between groups were found (P 0.05).

Table IV
Quality of life evolution measured by Moorehead-Ardelt (MA-II) questionnaire

Patients	*MA-II score*	
	Before surgery	*After surgery*
NA	46	48
EG	54	57
AM	49	51
MS	46	57
BL	47	52
MJG	48	50
AR	50	52
AS	48	55
RM	41	44
JC	41	55
AB	51	53
Mean score	47	52

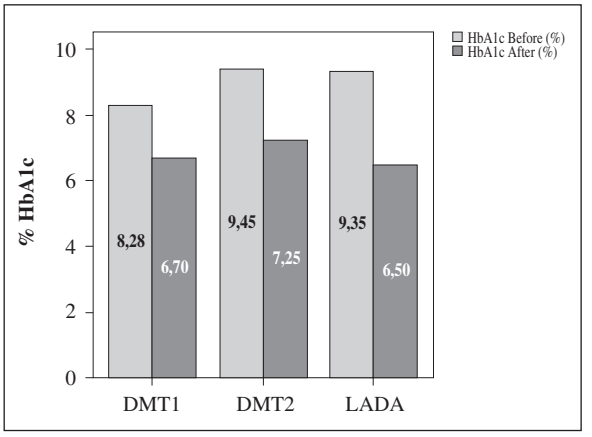

Fig. 2.—HbA1c diferences between T1DM, LADA and T2DM before and after BAGUA.

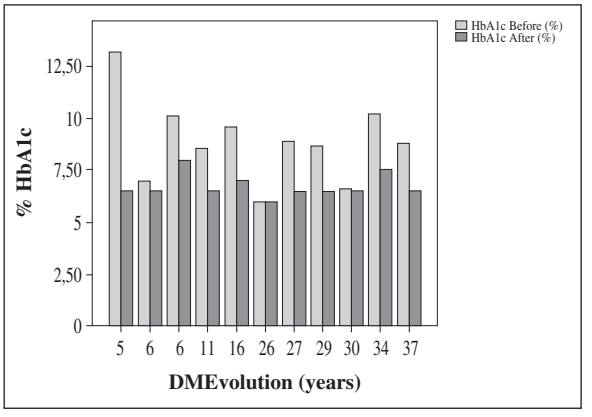

Fig. 3.—HbA1c diferences between patients before and after BAGUA.

Glycosylated hemoglobin values decreased in all studied cases (fig. 3) without relation to years of DM evolution. In general, the mean preoperative HbA1c was 8.9 ± 0.6% and decreased to 6.7 ± 0.2% for a mean follow-up period of 19 months. This decrease was statistically significant (P = 0.003).

- *FPG (Fasting plasmatic glucose):* Glucose levels decreased in the 3 patients classes (fig. 4), showing a FPG values of 211.20 ± 12.7 (mg/dl) before BAGUA and 93 ± 5 (mg/dl) after in DMT1 patients. In LADA patients the decrease was higher, 247.75 ± 44.3 (mg/dl) before the operation and 100 ± 11 (mg/dl) after. Finally, in T2DM patients the decrease was from 199.5 ± 11.5 (mg/dl) to 84 ± 14.5 (mg/dl).
  All patients in the study showed a decrease in FPG levels after surgery (fig. 5). Although this decrease was not related to the years of diabetes evolution. The values that were observed in the overall mean FPG levels before (222.36 ± 16.8 mg/dl) and after BAGUA (94 ± 5 mg/dl). This change is statistically significant (P = 0.00).
- *Insulin:* daily insulin patients requirement decreased in the 3 type of diabetes after the BAGUA (fig. 6). In

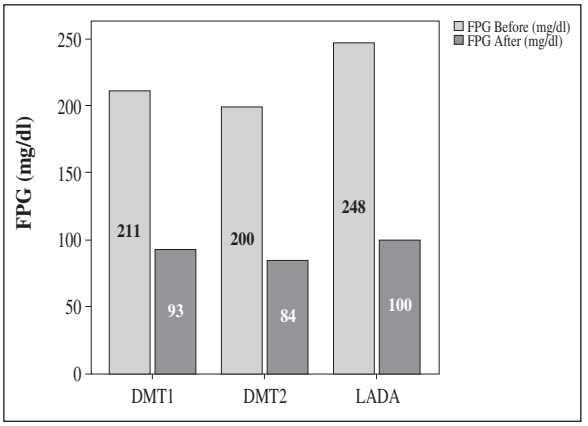

Fig. 4.—FPG (mg/dl) diferences between T1DM, LADA and T2DM before and after BAGUA.

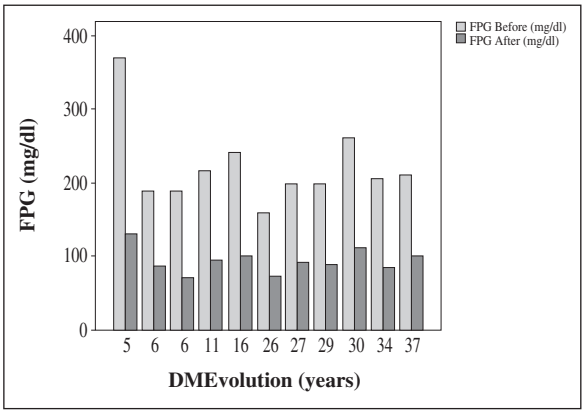

Fig. 5.—FPG (mg/dl) diferences between patients before and after BAGUA.

T1DM patients the daily amount rapid insulin needed, decreased from 24.4 ± 2 to 0 and long lasting insulin requirement decreased from 36.2 ± 5 to 13.4 ± 3. In LADA patients, rapid insulin requirements were reduced from 66 ± 33.8 (U/Day) to 0 (U/Day). Daily long lasting insulin units required by these patients decreased from 56.5 ± 17.6 to 18.58 ± 8.7. Patients with T2DM also decreased their rapid insulin needs from 30.5 ± 9.5 to 0 (U/Day) and long lasting insulin from 23.5 ± 2.5 to 13 ± 3 (U/Day). No statistically significant differences were found between the three diabetes types.

The required insulin units per day decreased in 11 patients after the BAGUA. This decrease was observed in both rapid insulin and long lasting insulin units (table V). Overall mean daily rapid insulin units needed before surgery was 40.6 ± 12.8 (U/day) and decreased to 0 (U/day) after surgery (fig. 9). This decrease was statistically significant (P = 0.01). Was also statistically significant (P = 0.00) the decrease in and long lasting insulin amount required by patients 41.3 ± 7.3 (U/day) at 15.3 ± 3.3 (U/day) (fig. 7).

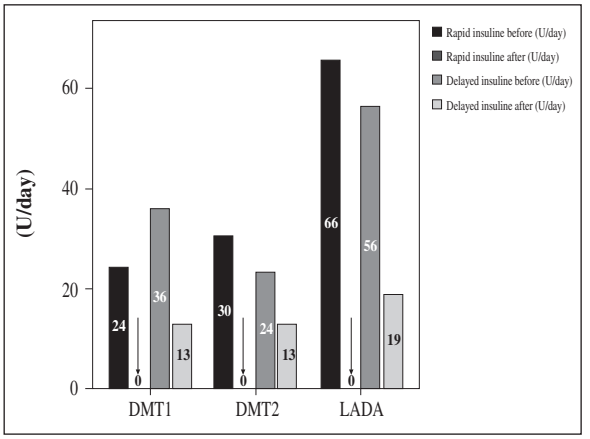

Fig. 6.—Rapid insulin and delayed insulin requirements before and after BAGUA.

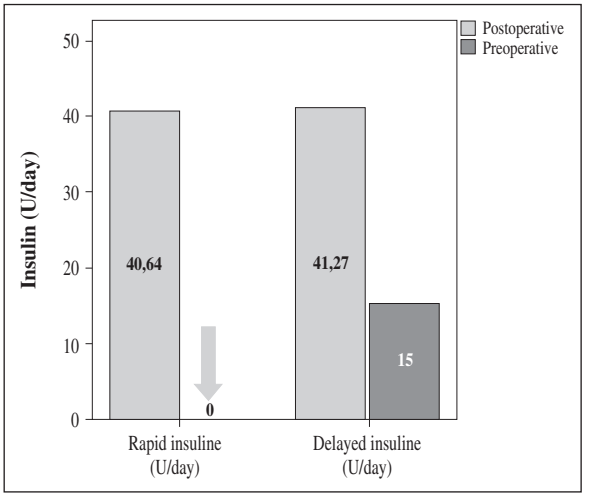

Fig. 7.—Rapid insulin and delayed insulin requirements before and after BAGUA.

Metabolic changes

We measured a general decrease in all the parameters of the lipid metabolism.

- *Triglycerides*: all study subjects had a decrease in triglyceride levels (fig. 8) and this decrease was even more pronounced in patients with hypertriglyceridemia (patients AR and AB). In these patients the decrease in triglyceride levels were 186 to 120 mg/dl in patient AR and from 198 to 97 mg/dl in the patient AB, both returning to normal values. Overall there was a decrease of 87.9 ± 17.21 mg/dl to 69.18 ± 8.1 mg/dl which was not statistically significant (P = 0.13). There is a positive correlation between the decrease in triglyceride levels and decreased body fat mass, with a two-sided significance of 0.012 and a correlation coefficient of 0.526.
- *Cholesterol, HDL-cholesterol y LDL-cholesterol:* Total cholesterol values decreased from harmful to normal in patients with hypercholesterolemia (patient MS from 231 to 165 mg/dl and patient AB from 241 to 162 mg/dl) (fig. 9). In all other

Table V
Insulin requirements before and after BAGUA

Patient	BMI	DM type	Oral antidiabetic		Rapid insulin (U/d)		Delayed insulin (U/d)	
			(BB)*	(AB)**	(BB)	(AB)	(BB)	(AB)
NA	24	T2	No	No	21	0	26	10
EG	24	T1	No	No	19	0	46	16
AM	26	LADA	No	No	0	0	52	32
MS	27	T1	No	No	24	0	40	4
BL	27	T1	Yes (2)	No	21	0	30	15
MJG	28	T2	No	No	40	0	21	16
AS	29	LADA	No	No	24	0	14	8
AR	31	LADA	No	No	90	0	60	35
RM	32	T1	No	No	28	0	20	10
JC	34	T1	No	No	30	0	45	2
AB	34	LADA	Yes (2)	Yes (1)	150	0	100	0

*BB = Before BAGUA; **AB = After BAGUA.

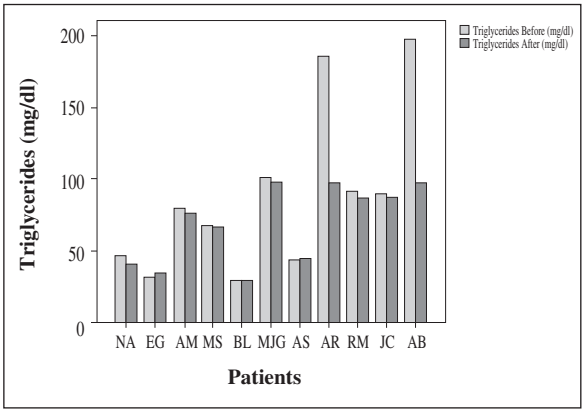

Fig. 8.—Triglycerides (mg/dl) diferences between patients before and after BAGUA.

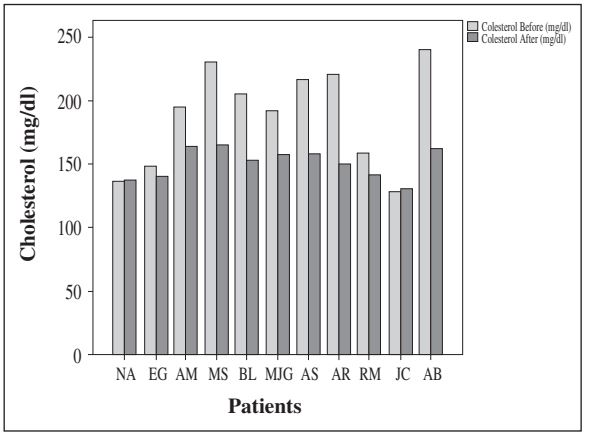

Fig. 9.—Cholesterol (mg/dl) diferences between patients before and after BAGUA.

patients also a decrease was observed in total cholesterol levels but less marked. The general mean values decreased from 187 ± 12.16 to 150.81 ± 3.47 mg/dl (fig. 10). This decrease was statistically significant (P = 0.01). This decrease in total cholesterol correlated with LDL-cholesterol levels, with a Pearson correlation ratio of 0.9 and a two-sided significance of 0.00. Patient AB (only with LDL-cholesterol above normal) recovered normal values 161-100 mg/dl (fig. 10). Overall, there was a statistical significant change (P > 0.014) in the levels of LDL-cholesterol, which decreased from 108.72 ± 9.77 to 91.18 ± 4.51 mg/dl (fig. 10). The levels of HDL-cholesterol had not significant variations.

- *Evolution of comorbidities:* 8 of the patients presented one or more comorbidities before surgery (table VI). Dyslipidemia appeared in 2 patients; both of them used lipid-lowering drugs. Six patients were hypertensive and were treated by antihypertensive drugs. In 3 patients were detected harmful levels of cholesterol (HCO) requiring the use of medications. Uric acid high levels were observed in 3 patients and other 3 had an altered levels of GOT and GPT.

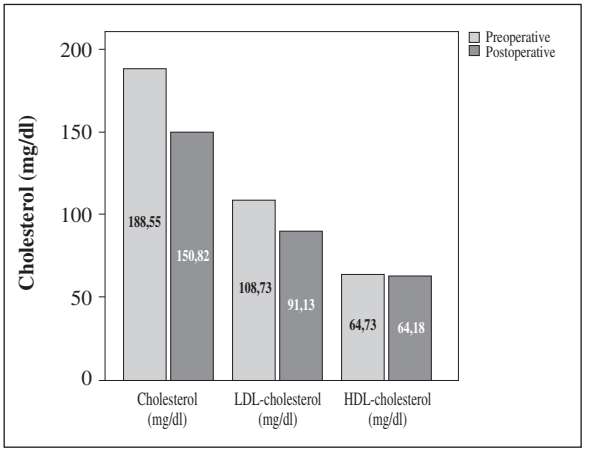

Fig. 10.—Cholesterol total, LDL-cholesterol and HDL-cholesterol (mg/dl) differences before and after BAGUA.

During the follow-up time, the resolution of comorbidities occurs in all patients undergoing BAGUA regardless of the evolution of DM.

- *Complications:* four patients in the study presented diabetes complications such as heart disease, retinopathy, nephropathy or peripheral vasculopathy

Table VI
Evolution of comorbilities after BAGUA

Patients	MS		AHT		HCO		HTG		Uric acid (mg/dL)		Liver profile (ALT-GOT and ALT-GPT) (U/L)	
	(BB)*	(AB)**	(BB)	(AB)	(BB)	(AB)	(BB)	(AB)	(BB)	(AB)	(BB)	(AB)
NA			Yes	Resolved								
EG												
AM					Yes	Resolved						
MS					Yes	Resolved						
BL												
MJG			Yes	Resolved								
AR							Yes	Resolved	↑ (7.9)	(5.9)	Altered (ALT-GOT 26 U/L) ↑ ALT-GPT 43 U/L	Resolved
AS	Yes	Resolved	Yes	Resolved	Yes	Resolved					Altered ↑ ALT-GOT 40 U/L ↑ ALT-GPT 48 U/L	Resolved
RM			Yes	Resolved					↑ (7.7)	(5.2)		
JC			Yes	Resolved								
AB	Yes	Resolved	Yes	Resolved	Yes	Resolved	Yes	Resolved	↑ (8.0)	(6.7)	Altered ↑ ALT-GOT 42 U/L ↑ ALT-GPT 48 U/L	Resolved

MS: Metabolic syndrome; AHT: Arterial hyperten yeson; HCO: Hyper cholesterolemia; HTG: Hyper triglyceridemia.

(table VII). Retinopathy evolution was stopped according subsequent exams and nephropathy and vasculopathy were improved. Heart diseases also experiment an improvement reducing the necessary medication to a minimum. All patients suffered medium to severe hypoglycaemic crisis before BAGUA. After the BAGUA and during the monitoring time, these episodes disappeared 100% in all the patients.

Discussion

The treatment of type 1 diabetes is really challenging and many sophisticated alternatives are being suggested.[30] The present conventional treatment implies very high costs[31] and life threatening side effects.[5]

Conventional medical treatment try to avoid or delayed the development of diabetes micro- and macro-vascular complications that shorten the years of life of the patient. However the intensification of the treatment produce by itself new side effects that also increase the morbidity and mortality of the patients[5,32] creating a difficult vicious circle.

But the treatment of diabetes have changed in the last years just by chance.[33] Surgical changes in the gastrointestinal tract have demonstrated to be able to resolve or improve DM and the other metabolic disturbances present in many patients with only one therapeutic intervention.[13-17] We do not know until now the exact mechanisms by which the effect is produced, but the good news for diabetic patients is that the effect is there.[34] The effectiveness of surgery happen not only when the pancreas have still a normal function and the failure is due to an increased insulin resistance as is the case in simply of morbid obese patients, but also in patients insulin dependent in which the insulin production by the pancreas have already failed. The majority of the patients of our serie (putting together type 2 and those with C Peptide zero) were insulin dependent (67%)[34] and in all of them tailored BAGUA had a positive effect on the glycemic control, coming to no necessity of treatment at all, or changing from insulin to oral antidiabetic drugs, or from great amount of insulin in several doses per day to only one injection per day of small amount.

This experience although small (only sixty five patients until now BMI 24-34 type 2 and type 1 DM) have produced very regular and repetitive results. Showing good correlations between the preoperative state of the pancreas (given by the values of fasten C Peptide) and the answer to surgery. This answer is not lineal and homogeneous. There is not a direct correlation between preoperative C Peptide levels and rapidity and intensity of the answer: resolution of DM without necessity of medication from surgery or transition period. And sometimes patients with lower C Peptide levels answered better than other with higher levels.

The years of disease have even worse correlation. There are patients with 20 years evolution and still in treatment with only oral anti-diabetic drugs, while other with only few years (less than ten) already need great amount of insulin and have developed severe micro- and macro-vascular complications.

The years of treatment with insulin translate, at least initially, time from the failure of pancreas for producing

Table VII
Diabetes complications before and after BAGUA

Patient	*Cardiopathy*		*Retinopathy*		*Nephropathy*		*Neuropathy*		*Peripheral vasculopathy*		*Hypoglycemia*	
	BB	*AB*	*BB*	*AB*	*BB*	*AB*	*BB*	*AB*	*BB*	*AB*	*BB*	*AB*
NA	Yes	Improve	Yes	Stopped	No	No	No	No	No	No	Yes	No
EG	No	No	No	No	No	No	No	No	No	No	Yes	No
AM	No	No	No	No	No	No	No	No	No	No	Yes	No
MS	No	No	No	No	No	No	No	No	No	No	Yes	No
BL	No	No	No	No	No	No	No	No	Yes	Improve	Yes	No
MJG	No	No	No	No	No	No	Yes	Resolved	No	No	Yes	No
AS	No	No	No	No	No	No	No	No	No	No	Yes	No
AR	No	No	Yes	Stopped	Yes	Improve	No	No	No	No	Yes	No
RM	No	No	Yes	Stopped	Yes	Improve	No	No	No	No	Yes	No
JC	No	No	No	No	No	No	No	No	No	No	Yes	No
AB	No	No	No	No	No	No	No	No	No	No	Yes	No

*BB = Before BAGUA; **AB = After BAGUA.

enough insulin. However, the evaluation of this data need to take into account the idea of the family doctor or endocrinologist responsible of the patient, to indicate a more or less intensive glycemic control. Or also the attention that the patient pay to his/her illness. Again we find great variability in the correlation of this parameter with the postoperative evolution of the patient.

In summary, from 60 first patients evaluated with a follow-up longer than 6 months,[34] we find a 100% resolution (no treatment and HbA1c < 7%) in patients that only need oral anti-diabetic drugs preoperatively (n = 20,nine BMI 24-29 mean C Peptide 2,4 ng/ml and eleven BMI 30-34 mean C Peptide 3,5 ng/ml). From the 40 insulin dependent patients, the resolution rate was 50% (n = 20, five BMI 24-29 mean C Peptide 1,8 ng/ml and fifteen BMI 30-34 mean C Peptide 2,3 ng/ml). There were other 20 insulin dependent patients that only improve DM after surgery. Nine abandon insulin and needed only oral anti-diabetic drugs (n = 9, four BMI 24-29 mean C Peptide 1,02 ng/ml and five BMI 30-34 mean C Peptide 2,0 ng/ml). And 11 come from 3-4 injections of rapid and long lasting insulin per day to only one injection of long lasting insulin. Nine of these patients had C Peptide 0,0 ng/ml and are included in the sample analysed in this paper and other two patients had a C Peptide level of 0,88 and 1,17 ng/ml but continue needing one daily injection of long lasting insulin.

In our sample of 26 obese patients treated by BAGUA[35] we found a similar postoperative evolution of the patients. Some of them needed oral anti-diabetics drugs to control glycemia and one obese patient (female) with type 1 diabetes reduced from four to one injection the insulin and improving the control of the nephropathy she suffered.

The lessons learned from this experience in type 2 DM and one obese patient with type 1 DM, and the 6 obese patients with type 1DM described in the literature,[10-12] shows the same improvement after gastric bypass.

So, it seems to be three different situations in diabetes surgery: 1) Patients in treatment before operation with only oral anti-diabetics drugs that normally have variable period of DM evolution and an increased (depending of the degree of insulin resistance) or normal C Peptide level and presumably a healthy (still enough beta cell mass) but over stimulated pancreas that will cure DM after surgery; 2) Others patients already in treatment before operation with insulin, that normally have variable but longer period of DM evolution as well as variable period of insulin treatment and an increased (depending of the insulin resistance degree), normal or decreased C Peptide level and presumably damaged pancreas (limited beta cell mass) that can cure, need only oral anti-diabetic drugs or, rarely, one injection of minimal amount of long lasting insulin for controlling DM after surgery; and 3) Patients with no pancreas function at all, independent of the autoimmune or long lasting pancreas over load mechanism, also with variable period of DM evolution (although normally longer than in the previous described situations) and insulin treatment (that will depend of the genetic resistance of the different tissues and organs) that will need one injection of different amounts of long lasting insulin for controlling DM.

That means, from the point of view of the effect of diabetes surgery, type 1 diabetes have a different mechanism of damaging the pancreas function, that start earlier and that come sooner to total pancreas destruction. While LADA[36] and type 2 diabetes provoke this destruction more slowly. But by both mechanisms the pancreas can come to a total destruction.

Thus could be explained why the effect of type 1 and type 2 DM on the body is similar,[37] developing the same damage of the pancreas and organ complications[31,32,37-39] and, hence, there is no logical reason to think that surgery will not have the same effect in type 1 as in type 2 diabetes based only in the different pancreas destruction mechanism.

The present paradigm in diabetes surgery is to operate only type 2 DM, and only those patients that could solve DM 100%. But, sometimes improvement is of central

importance for the DM evolution and life expectancy of the patient. The Wisconsin Epidemiologic Study of Diabetic Retinopathy and a semi-Markov model predict a mortality of 51% at 10 years, prevalences of stroke and myocardial infarction of 18% and 19%, of nonproliferative diabetic retinopathy, proliferative retinopathy, and macular edema of 45, 16, and 18%, respectively. Microalbuminuria, proteinuria, and end-stage renal disease were predicted to be 19, 39, and 3%, respectively. Clinical neuropathy and amputation 52 and 5%, respectively, at 10 years. Over 10 years, average undiscounted total direct medical costs were estimated to be 53,000 US dolars per person.[40] We think it is worth to examine the role of gastrointestinal surgery, which already have proved to ameliorate type 2 DM, for improving this disaster and costly evolution of patients with C Peptide zero, that means no pancreas function at all.

This simple and logical a priori appreciation, that type 1 diabetes will have a positive answer to gastric bypass, has been confirmed by the results of the present study. There was a positive effect on glycemic control and metabolic syndrome resolution without major complications and no mortality, similar to that obtained previously in type 2 DM operated by BAGUA.[17,34] There was not excessive weight loss or long term digestive side effects as was also observed in type 2 DM BMI 24-34 patients.[17,34,41] And the quality of life of the patients improved.

It is very interesting from the point of view of the mechanisms by which the gastrointestinal changes induced by the gastric bypass act on diabetes resolution even without any internal insulin production (as happen in all these patients).

However, the heterogeneous evolution of DM described above could be understand if we look into the complex mechanisms of glucose metabolism very nice explained in other papers of this issue. A fail in one or more of the many steps of this complex process, could conditioned different degrees and intensity of malfunction. After gastric bypass surgery it seems to be two different pathways for controlling glucose metabolism: one of them is pancreas depending; and the other is pancreas independent and is related to the derivation of food to the distal intestine and the consequent release of glucose into the portal blood. Which induce a brain response that enhanced the suppression of hepatic glucose production by insulin.[42] These changes demonstrated in animals and humans[43-45] could also explained the postive effect of surgery in absence of pancreas function.

So, could be explained that these patients do not need rapid insulin after surgery. And that they could control the glycaemia levels with only one injection per day of 4 to 10 fold less long lasting insulin.

But other questions are open as: what is the mechanism by which improve the evolution of the clinically established complications as cardiopathy, retinopathy, nephropathy, peripheral vasculopathy, neuropathy and sexual impotence after BAGUA? Is only a consequence of the better diabetes control, reduced use of insulin, or are specific gastric bypass effects? What is the role of the degree of organ damage in the improvement of clinically established diabetes complications in the postsurgical amelioration and what are the mechanisms by which this amelioration developed?

In summary, what these results pointed out is that the gastrointestinal tract play a central role in the regulation of glucose metabolism (as is also reported in other papers of this monographic issue) and that this effect is independent of pancreas function.

The present results, that should be confirmed by other similar experiences, could suppose an important help in the difficult management of type 1 and other type of diabetes in which pancreas has been destroyed.

Conclusions

One anastomosis gastric bypass (BAGUA) appears to be a real alternative for treating patients without any pancreas function (C-peptide < 0.0 ng/ml). Improving glycemic control, resolving the metabolic syndrome, and improving the serious complications of the disease such as cardiopathy, retinopathy, nephropathy, peripheral vasculopathy, neuropathy and sexual impotence. However, further studies are needed with larger series and longer follow-up periods in order to make a real assessment of the effect of this type of surgery on these patients.

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Morbidity and mortality of diabetes with surgery

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Abstract

The prevalence of Type 2 diabetes mellitus (T2DM) has increased; as a result the number of patients with T2DM undergoing surgical procedures has also increased. This population is at high risk of macrovascular (cardiovascular disease, peripheral vascular disease) or microvascular (retinopathy, nephropathy or neuropathy) complications, both increasing their perioperative morbidity and mortality. Diabetes patients are more at risk of poor wound healing, respiratory infection, myocardial infarction, admission to intensive care, and increased hospital length of stay. This leads to increased inpatient costs. The outcome of perioperative glycaemia management remains a significant clinical problem without a universally accepted solution.

The majority of evidence on morbidity and mortality of T2DM patients undergoing surgery comes from the setting of cardiac surgery; there was less evidence on non-cardiac surgery and bariatric surgery. Bariatric surgery is increasingly performed in patients with severe obesity complicated by T2DM, but is distinguished from general surgery as it immediately improves the glucose homeostasis postoperatively. The improvements in glycaemia are thought to be independent of weight loss and this requires different postoperative management. Patients usually have to follow specific preoperative diets which lead to improvement in glycaemia immediately before surgery.

Here we review the available data on the mortality and morbidity of patients with T2DM who underwent elective surgery (cardiac, non-cardiac and bariatric surgery) and the current knowledge of the impact that preoperative, intraoperative and postoperative glycaemic management has on operative outcomes.

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Key words: *Mortality. Morbidity. Perioperative management. Bariatric surgery.*

MORBI-MORTALIDAD EN PACIENTES DIABÉTICOS TIPO 2 TRAS CIRUGÍA ELECTIVA

Resumen

La prevalencia de la diabetes mellitus tipo 2 (DM2) ha incrementado en los últimos años, y como resultado, el número de pacientes con DM2 sometidos a procedimientos quirúrgicos también ha aumentado. Esta población posee un alto riesgo de complicaciones macrovasculares (enfermedad cardiovascular, enfermedad vascular periférica) o microvasculares (retinopatía, nefropatía o neuropatía), ambos incrementan tanto la mortalidad como la morbilidad perioperatoria de estos pacientes. Los pacientes con diabetes tienen un mayor riesgo de una mala cicatrización de las heridas, infección respiratoria, infarto de miocardio, ingreso en la UCI y mayor duración de la estancia hospitalaria. Todo esto incrementa los costes de tratamiento de este tipo de pacientes. El control de la glucemia perioperatoria sigue siendo un importante problema clínico sin una solución universalmente aceptada.

La mayoría de los conocimientos sobre la morbilidad y mortalidad de los pacientes con DM2 sometidos a cirugía proviene de la de la cirugía cardíaca, y algunos, aunque menos, de la cirugía no cardiaca y cirugía bariátrica. La cirugía bariátrica se realiza cada vez más en pacientes con obesidad mórbida complicado con diabetes tipo 2, y se diferencia de la cirugía general en que inmediatamente mejora la homeostasis de la glucosa tras la operación. Las mejoras en el control de la glucemia parecen ser independientes de la pérdida de peso y esto requiere un manejo postoperatorio diferente. Los pacientes por lo general tienen que seguir dietas específicas preoperatorias que conducen a la mejora de la glucemia inmediatamente antes de la cirugía.

En este artículos revisamos los datos disponibles sobre la mortalidad y la morbilidad de los pacientes con diabetes tipo 2 sometidos a cirugía (cirugía cardíaca, no cardíaco y bariátrica) y el conocimiento actual de los efectos preoperatorios, intraoperatorios y postoperatorios que el control de la glucemia tiene sobre los resultados operatorios.

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Palabras clave: *Mortalidad. Morbilidad. Control perioperatorio. Cirugía bariátrica.*

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Introduction

Type 2 diabetes mellitus (T2DM) is a very common metabolic disorder. More specifically, the prevalence of T2DM for all age-groups worldwide was estimated to be 2.8% in 2000 and to increase to 4.4% in 2030.[1] In developed countries, over the next decade, the exponential rise in obesity is predicted to increase the prevalence of T2DM.[2] This will have major implications for health services, with particular impact on inpatient care. A recent audit has shown that the prevalence of T2DM in the United Kingdom inpatient population now ranges from 10-28%, and this figure is certain to rise in the future.[3] T2DM related comorbidities increase the need for surgical and other operative procedures.[4-6]

T2DM is associated with a two to four fold increase in cardiovascular disease including hypertension, coronary artery disease and stroke.[7] The majority of people with T2DM planned for surgery are likely to have one or more cardiovascular risk factors and a significant number will have microvascular disease (retinopathy, nephropathy or neuropathy). As a result, patients with T2DM are at high risk of perioperarative complications and even mortality.[8-10] The effect of preoperative, intraoperative and postoperative diabetes management and the effect of perioperative hyperglycaemia and hypoglycaemia in the short-term and long-term operative outcomes remains a significant clinical problem without a universally accepted solution.[2]

In this review, we summarize the knowledge regarding the mortality and morbidity in patients with T2DM who underwent elective surgery in three major surgical categories: cardiac surgery, non-cardiac surgery and bariatric surgery. The stronger body of evidence regarding T2DM and perioperative glucose management comes from the setting of cardiac surgery.[11-15] We have less evidence for the non- cardiac surgeries or specifically bariatric surgeries which are a separate category as they immediately improve glucose homeostasis postoperatively. The improvements in glycaemia after bariatric surgeries are often thought to be independent of weight loss and this should require different postoperative management regimens. Moreover, patients who come for bariatric procedures have often followed low calories diets preoperatively,[16,17] this can lead to improvement in glycaemic control.

Mortality and morbidity after cardiac surgery in patients with T2DM

Long term mortality

A prospective study of 9,125 survivors of isolated coronary artery bypass graft (CABG) surgery found that cardiac-specific survival at 5 and 10 years was lower in patients who required insulin compared to patients who only needed oral medications for T2DM and patients without diabetes.[18] The need for insulin, chronic kidney disease, peripheral vascular disease, and a low ejection fraction were all independent risk factors for late cardiac death.[18] Another study, of 1025 patients (45 with diabetes) who underwent CABG and were followed up for a mean of 7.4 years, showed that long-term mortality was increased in patients with T2DM despite similar early mortality.[9] Furthermore, 3,707 patients who were investigated over a 12 year period after isolated CABG included 250 patients on diet or oral therapies for T2DM and 162 T2DM patients on insulin. The survival and the cardiac event-free curves revealed no difference between the groups with T2DM. However, there was a significant difference between both groups with T2DM and patients without diabetes.[8] Finally, Marcheix et al in a retrospective study with 1,000 patients (722 without and 278 with T2DM) reports that after off-pump coronary artery bypass graft (OPCABG) the ten-year survival and the free survival of major adverse cardiac events was decreased significantly in the group with T2DM.[10]

Early mortality (30-days mortality)

The data regarding the early mortality after CABG show conflicting results.[8-10] Risum et al and Marcheix et al have reported that the early mortality was not significantly higher when comparing patients with and without T2DM.[9,10] On the other hand, Salomon et al found that the perioperative mortality after CABG was greater in patients with T2DM compared to patients without diabetes.[8]

Morbidity

Cardiac surgery in patients with T2DM is associated with longer hospital stay, higher health care resource utilization, and greater perioperative morbidity than in subjects without T2DM.[4-6,11] The higher morbidity in patients with T2DM is related in part to the heightened incidence of comorbid conditions including coronary heart disease, hypertension, and renal insufficiency, as well as the adverse effects of hyper- and hypoglycaemia in clinical outcome.[4,8,19,20] More specifically, patients with T2DM have worse outcomes after percutaneous coronary intervention than patients without T2DM.[20] A recent study which compared patients with T2DM to patients without T2DM, after implantation of drug-eluting stents or bare metal stents, found that the 2-year risk of myocardial infarction was 6.9% greater in the T2DM patients.[20] Moreover, the 2-year risk of target lesion revascularization was significantly higher for patients with T2DM. Thus 2 years after drug-eluting stent or bare metal stent implantation, patients with T2DM had a greater risk of myocardial infarction and death.[20]

As regards to coronary artery bypass graft (CABG), patients with T2DM had a higher incidence of postoperative death (3.9% *versus* 1.6%) and stroke (2.9%

versus 1.4%), but not Q wave myocardial infarction (1.8% *versus* 2.9%) compared to patients without T2DM (19). They also had lower survival (5 years, 78% *versus* 88%; 10 years, 50% *versus* 71%) and lower freedom from percutaneous transluminal coronary angioplasty (5 years, 95% *versus* 96%; 10 years, 83% *versus* 86%). In the same study, the authors reported that patients with T2DM and patients without T2DM had similar freedom from myocardial infarction events (5-years, 92% versus 92%; 10-years, 80% *versus* 84%) and similar freedom from additional coronary artery bypass grafting (5-years, 98% *versus* 99%; 10-years, 90% *versus* 91%) (19).

Salomon et al. reports that the extent of diffuse coronary disease as judged angiographically and at CABG was significantly greater in patients with T2DM as compared to those without.[8] No difference was noted in the incidence of localized coronary disease between the groups and the average number of grafts was greater in patients with T2DM. The incidences of sternotomy complications, renal insufficiency and total hospital length of stay were significantly greater in the group with T2DM when compared to those without.[8] Moreover, this study indicates that patients with T2DM have quantitatively and qualitatively more coronary artery disease than non- diabetes patients and therefore higher perioperative morbidity and mortality, and a lower long-term survival rate when compared to patients without T2DM.[8] In contrast, a recent study reports that T2DM patients had no increased risk of perioperative myocardial infarction, or of low-output syndrome necessitating intraortic balloon pumping, and no excess incidence of late non-fatal myocardial infarction or late chronic heart failure after CABG compared to patients without diabetes.[9]

Finally, a comparison between patients with T2DM on oral medications or diet and those requiring insulin showed that the mean number of complications per patient was higher in patients who needed insulin.[21] The major differences in perioperative complication rates were found in the need for prolonged (> 24 hours) ventilation, occurrence of respiratory or renal insufficiency, and mediastinitis. The mean length of stay in the intensive care unit and for total hospitalization were longer in patients with T2DM treated with insulin compared to diet/oral medications (4.3 ± 2.8 days *versus* 2.8 ± 2.7 days and 11.1 ± 2.2 days *versus* 7.2 ± 2.4 group, respectively).[21] Moreover, overall late cardiac and non-cardiac complication rates were significantly higher in patients with T2DM needing insulin compared to those on oral medications and diet.

Impact of perioperative glycaemic control on mortality and morbidity after cardiac operations

Evidence from observational studies suggests that in surgical patients, with and without T2DM, improvement in glycemic control positively affects morbidity and mortality postoperatively.[22,23] After cardiac surgery, a retrospective study which analysed 8,727 adults found that inadequate postoperative blood glucose control was a predictor of in-hospital mortality and morbidity.[24] Randomised controlled trials for patients with T2DM undergoing CABG have investigated the effect of tight glycemic control compared to conservative glucose management on perioperative outcomes. Patients were prospectively randomised to tight glycemic control (serum glucose 125 to 200 mg/dL) with a modified glucose-insulin- potassium (GIK) solution or standard therapy (serum glucose < 250 mg/dl). Patients with tight control had a significant lower incidence of atrial fibrillation (16.6% *versus* 42%), a shorter postoperative length of stay, a significant survival advantage over the initial 2 years after surgery, significant decreased episodes of recurrent ischemia (5% *versus* 19%) and they developed fewer recurrent wound infections (1% *versus* 10%).[14] Another randomised controlled trial evaluated if aggressive glycaemic control (90-120 mg/dL) would result in more optimal clinical outcomes and less morbidity than moderate glycemic control (120-180 mg/dL) using continuous intravenous insulin solutions in patients with T2DM undergoing CABG surgery. The results showed that patients with aggressive control had a lower mean glucose at the end of 18 hours of insulin infusion, higher incidence of hypoglycemic events, but there were no differences in the incidence of major adverse events between the groups.[15]

Impact of preoperative glucose control on mortality and morbidity after cardiac surgery

Increased haemoglobin A1c (HbA1c) and inadequate preoperative glycaemic control could be a predictor of adverse outcomes after CABG.[25,26] A study on 3,555 consecutive patients who underwent CABG reported that an elevated HbA1c level predicted the in-hospital mortality after CABG.[25] More specifically, an HbA1c greater than 8.6% was associated with a 4-fold increase in mortality and for each unit increase in HbA1c, there was a significantly increased risk of myocardial infarction and deep sternal wound infection.[25] Moreover, renal failure, cerebrovascular accident, and deep sternal wound infection occurred more commonly in patients with elevated HbA1c. Preoperative HbA1c levels in patients with T2DM were not predictive of long-term outcomes after OPCABG as shown in 306 patients that had undergone OPCABG and were divided in 3 groups according to their preoperative HbA1c.[27]

Mortality and morbidity after non-cardiac surgery in patients with T2DM

Long term mortality

A retrospective study of 179 patients with T2DM undergoing non cardiac surgery (plastic, abdominal,

orthopaedic, ophthalmic, gynaecology, urological), reported a postoperative mortality of 24% at 10 months after surgery, with one third of the fatalities occurring during the first 30 days. Established ischaemic heart disease before the operation was associated with a postoperative mortality of 44%, which was significantly higher compared to patients with T2DM, but without pre-existing cardiovascular disease.[28] Another study of patients undergoing non-cardiac surgery with 7-year follow–up showed mortality was higher in patients with T2DM as compared to those without, 37.2% *vs* 15% ($p < 0.00001$). Cardiovascular disease was the main causes of death in the T2DM population, 56.8% *vs* 18.6% ($p < 0.0001$). Therefore in non-cardiac surgery, patients with T2DM also appear to have a higher mortality rate as compared to the non-diabetes group.[29]

Short term mortality

A study that compared 274 patients with T2DM and 282 non diabetes patients having non-cardiac surgery (abdominal, gynaecological, orthopaedic, otolaryngological, thoracic, vascular, urology) showed significantly higher short term mortality (≤ 21 days) in the diabetes group, 3.5% *vs* 0% ($p < 0.05$).[29] A study in non-cardiac surgery (general surgery, neurosurgery, surgical oncology, orthopaedic, vascular, thoracic, urology, otolaryngology except tonsillectomy, gynaecology) comparing 2,469 non-diabetes and 643 patients with T2DM, showed a 30-day mortality of 2.3% (72 of 3,112 patients). The diabetes group showed a trend towards higher mortality as compared to non-diabetes patients, 3.1% *vs* 2.1% ($p = 0.11$).[4] The multivariate analysis, suggested that the risk of death increased in proportion to perioperative glucose level, but this was only significant in those not known to have T2DM.

Morbidity after non-cardiac surgery

Perioperative hyperglycaemia is associated with increased length of stay (LOS) and postoperative pneumonia.[4] Patients with T2DM compared to non diabetes had a significantly higher rate of complications including pneumonia (12.1 *vs.* 5.4%), wound and skin infections (5 *vs.* 2.3%), systemic blood infection (3.6 *vs.* 1.1%), urinary tract infections (4.5 *vs.* 1.4%), acute myocardial infarction (2.6 *vs.* 1.2%), and acute renal failure (9.6 *vs.* 4.8%). In addition, patients with T2DM had significantly higher LOS in the hospital and significantly higher ICU LOS compared to non-diabetes subjects (8.8-10.6 days *vs.* 7-10.8 days and 2.3-6.2 days *vs.* 1.8-6.5 days respectively).[4] A retrospective study of 183 patients with T2DM who underwent colorectal resection showed that 28 (15%) patients developed surgical site infections postop. Hyperglycaemia, use of drains, and the use of prophylactic antibiotics for more than 24 hours were associated with surgical site infections.[30]

Mortality and morbidity in patients with T2DM after bariatric surgery

Mortality

Bariatric surgery is effective in improving weight loss and glycaemic control in patients with T2DM and severe & complex obesity. The Swedish Obesity Subject (SOS) Study, a prospective, controlled cohort study comparing bariatric surgery to medical treatment for long-term mortality found that the adjusted hazard ratio was 0.71 in the surgery group ($p = 0.01$) as compared with the control group.[31] McDonald et al. had also reported that mortality in patients with T2DM who underwent gastric bypass surgery was 9% compared to 28% of diabetes control group at 9 years follow up.[32] The most common cause of death was myocardial infarction. The recently published SOS data on bariatric surgery and long term cardiovascular events showed that surgery was associated with a reduced number of cardiovascular death compared to control group (28 *vs* 49 events, adjusted HR 0.47, $p = 0.02$).[33] The benefit of surgical treatment was significantly associated with a raised baseline plasma insulin above the median of 17 IU/L, with greater relative treatment benefit in subjects with higher insulin (p for interaction < 0.001).

These are also supported by Adams et al. which showed that patients with T2DM who undergo bariatric surgery have a 92% relative risk reduction compared to the matched control group at a mean follow up of 7.1 years.[34] The acute improvement in glycaemic control and other metabolic co-morbidities together with the significant weight loss after gastric bypass may play a significant role in the decreased mortality after bariatric surgery.

Morbidity

Perioperative complications

A prospective study aimed to assess outcome of laporoscopic Roux-en Y gastric bypass on T2DM reported that of the 191 subjects, there were 8.4% early major complications, most commonly due to pneumonia and gastrojejunal leaks. There were also 29 early minor complications including gastrojejunal leaks without peritonitis, and wound infections. Approximately 5.2% of patients presented with late major complications due to small bowel obstruction and deep vein thrombosis, and 9.9% of patients reported late minor complications most commonly prolonged emesis and marginal ulcers. The overall major complication rate was 13.6%, and minor compli-

cations rate was 24.9%.[35] These had not been compared to the non-diabetes cohort. However, an earlier study by Schauer that looked at outcomes after LRYGB in 275 patients, of which 22% had T2DM, showed early major complications of 3.3%, which is lower than the diabetes cohort. However, the study showed 27% of the cohort had early minor complications, and 47% of the cohort had late complications and side effects. These raised complication rate coincided with the introduction of laparoscopic approach to RYGB, and may be explained by the relative inexperience of surgeons at that time. The LABS study reported that of the 2,975 subjects who undertook LRYGB, the composite end point of death, venous thromboembolism, reintervention, or failure to be discharged by 30 days after surgery was 4.8%.

Complications of diabetes

Macrovascular complications such as cardiovascular disease were reduced following bariatric surgery[32] with improvements in coronary heart disease (CHD).[36] Similar results were reported in the SOS study and by Adam et al.[33,34] The microvascular complications in a case-controlled study with 10-years' follow-up comparing biliopancreatic diversion versus those associated with conventional therapy on renal microvascular outcome (macro- and microalbuminuria, and glomerular filtration rate/GFR) on 50 newly diagnosed T2DM showed all surgical treated subjects recovered from microalbuminuria, whereas there was progression of renal microalbuminuria in non-operated subjects.[36] Metabolic complications such as hypertension, hyperlipidaemia, and obstructive sleep apnoea were all improved following bariatric surgery.[37] However, there had been case report of worsen diabetes neuropathy;[38,39] and retinopathy[40] following LRYGB and improved glycaemic control. The safety and effectiveness of intensive glycaemia were also questioned by recent surgical trials.[41-43]

Impact of pre and postoperative glycaemic control on outcome of bariatric surgery

Elevated HbA1c has been associated with increased hospital LOS and worsen postoperative outcome in non-bariatric surgery patients.[44] However, there is no data on whether preoperative glycaemic control could influence the outcome of bariatric surgery and remission of diabetes, especially as many units use a 2 week pre-operative very low calorie diet which will improve glycaemic control substantially. A retrospective study reviewed 468 patients scheduled for bariatric surgery and grouped them into three categories based on HbA1c preoperatively. Poor preoperative glycaemic control was associated with less weight loss and fewer cases of complete remissions of their T2DM at 18 months. An elevated postoperative glucose was independently associated with wound infection (p= 0.008), and acute renal failure (p = 0.04)[44]. A cohort study in patients with type 2 diabetes requiring insulin suggested that after gastric bypass surgery tight glycaemic control (fasting blood glucose < 6.5 mmol/L for 1-2 week after surgery) can improve the remission rate of T2DM after 1 year.[45]

Conclusion

Diabetes management preoperatively, and in the early postoperative period after non- cardiac surgery, and bariatric surgery are not protocol driven. More specifically, the effect of tight or more relaxed glucose control and the adjustment of insulin in the perioperative and early postoperative period could have a result on the long term outcomes in diabetes remission, mortality and diabetic microvascular and macrovascular complications. Whether patients would benefit from glycaemic optimisation before non-cardiac operations in order to decrease mortality and perioperative morbidity has not yet been determined. Each bariatric procedure has different effect on insulin secretion and insulin resistance, and may therefore also have differential effects on macrovascular and microvascular complications. The lessons learned from diabetes management in cardiac surgery necessitates us to evaluate management strategies in patients with T2DM scheduled for bariatric surgery especially as more patients are encouraged to consider surgery as a treatment for T2DM.

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Diabetic retinopathy

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Abstract

This paper describes the importance of diabetic retinopathy in the loss of visual function. We exposed the most important risk factors, such as diabetes duration, poor metabolic control, pregnancy, puberty, hypertension, poor control of blood lipids, renal disease, and sleep apnea syndrome. We describe the pathogenesis of the disease, small retinal vessel microangiopathies which produce extravasation, edema and ischemia phenomena. We put special emphasis on the vascular endothelial growth factor (VEGF) and its pathogenic importance.

They are also described the main clinical symptoms as microaneurysms, intraretinal hemorrhages, hard and soft exudates, intraretinal microvascular abnormalities (IRMA), venous disorders, formation of new vessels and diabetic macular edema (the latter being the most common cause of vision loss).

Finally we describe the latest diagnostic techniques and eye treatment, with special emphasis on obesity surgery importance as more important preventive factor to eliminate the predisposing and precipitating disease symptoms.

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Key words: *Diabetic retinopathy. Metabolic surgery. VEGF.*

RETINOPATIA DIABETICA

Resumen

En el presente trabajo se describe la importancia de la retinopatía diabética en la pérdida de función visual. Así como de los factores de riesgo más importantes, como la duración de la diabetes (tiempo de evolución), mal control metabólico, embarazo, pubertad, hipertensión arterial, mal control de lípidos en sangre, nefropatía, y síndrome de apnea del sueño. La patogenia de la enfermedad, como microangiopatías de pequeños vasos retinianos que produce extravasación, edema y fenómenos de isquemia. Se hace especial énfasis en el vascular endotelial Growth factor (VEGF) y su importancia patogénica.

También se describen los síntomas clínicos principales como microaneurismas, hemorragias intra retinianas, exudados duros y blandos, anormalidades microvasculares intraretinianas (AMIR), arrosaramiento venoso así como edema macular diabético (siendo esta última la más frecuente causa de pérdida de visión) y la formación de neovasos.

Finalmente se describen las técnicas más actuales de diagnóstico y tratamiento, haciendo especial énfasis en la importancia de la cirugía de la obesidad como factor preventivo más importante para eliminar los síntomas predisponentes y desencadenantes de la enfermedad.

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Palabras clave: *Retinopatía diabética. Cirugía metabólica. VEGF.*

Introduction

Diabetic retinopathy is a retinal vasculitis caused by complications of diabetes mellitus. Oftalmological changes that may occur are neovascularization and macular edema, the latter being the most frequent alteration. The incidence of diabetic retinopathy has increased very significantly to become the leading cause of visual impairment and blindness in adults over 20 years in industrialized countries.

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Risk factors

Duration of diabetes

This is the most important factor. In type 1 diabetes with less than two years of evolution the incidence is 2% while diabetes with fifteen or more years of evolution, it reaches 98%. In type 2 diabetes treated with or without insulin, the incidence with 5 years of evolution

is 20% while with 15 years of evolution it reaches 80%. This apparent increased incidence of type 2 diabetes is due to the lack of an early diagnosis in asymptomatic patients. Diabetic retinopathy is very uncommon before puberty and rarely occurs 5 years before the beginning of diabetes.

Poor metabolic control

An early good glycemic control can prevent or delay the development of diabetic retinopathy. High levels of glycated hemoglobin is associated with a higher risk of severity.

Pregnancy

It is occasionally associated with rapid progression of diabetic retinopathy.

Puberty

The risk of diabetic retinopathy before puberty regardless of the duration of diabetes is very low and after age 13 increases the frequency and severity. Hormonal changes may be responsible for this.

High blood pressure

It has been one of the most researched systemic factors, known to be directly related to retinopathy although it is unclear whether hypertension is due to nephropathy and in this case, both would be diabetic complications.

Lipids

The relationship between high levels of lipids and retinopathy seems to be proved. High cholesterol levels are associated with elevated hard exudates levels. The severity of retinopathy is associated with high triglyceride levels.

Nefhropathy

In multicentric studies the coincidence of nephropathy and diabetic retinopathy in both type 1 and type 2 diabetes was observed. Diabetic retinopathy may be the most common microvascular complication of diabetes, preceding nephropathy.

Sleep apnea syndrome

In diabetic patients suffering from this syndrome, diabetic retinopathy and macular edema can get worse.

Optimal control of all these risk factors can help to improve eye health of patients with diabetes.

Pathogenesis

Diabetic retinopathy is a microangiopathy affecting small retinal vessels, arterioles, capillaries and venules. The vascular lesion is the basis of the complications that are seen in the retina. Endothelial damage appears to be the leading cause of these lesions. This together with microvascular complications produce the clinical presentation of diabetic retinopathy.

How can maintained hyperglycemia linked to predisposing factors produce endothelial damage, consequent obstructive phenomena and extravasation of diabetic retinopathy?

Biochemical changes (increased sorbitol and glucose metabolism final products) hematologic changes (hypercoagulability), anatomical changes (thickening of the basal menbrane and pericyte loss) physiological changes (reduced blood supply) and blood-retinal barrier breakdown.

Consequences

Increased permeability of vessels losing plasma proteins and lipids leading to retinal edema and hard exudates. Phenomena of microthrombosis with retinal microinfarcts that produce Cotton wool spots (soft exudates) synonymous with hypoxia and ischemia. Hypoxia produces an effect for releasing angiogenic factors and new vessel formation in retina and iris (rubeosis iridis) The extravasated liquid produces edema especially in macular area.

In these circumstances vascular endothelial grow factor (VEGF) is synthesized in several retinal cells (not only endothelium) and in case of hypoxia it increases 30 times its production. This is important because of two mechanisms:

- It stimulates neovessels formation.
- It stimulates vascular permeability and edema. In consequence, all retinal cells (vessels, glia and neurons) become altered and lead to visual deficits.

Clinical presentation

Nonproliferative diabetic retinopathy

It is characterized by the appearance of:

a) *Microaneurysms.* The earliest sign is the appearance of red spots. These are saccular dilations due to hyperpermeability. They can decrease, disappear and reappear in other locations. Microaneurysms are a sign of severity and progression of the disease.

b) *Intraretinal hemorrhages.* Are due to blood extravasation and can be deep or superficial (flame-shaped). It can disappear and reappear. It indicates severity.

c) *Hard exudates.* These are deposits of lipids with a predilection for the macular region. In ophthalmoscopy are seen as small white to yellow deposits. It indicates severe cystoid macular edema.

d) *Soft exudates or cotton wool spots.* These are the result of arteriolar occlusion and microinfarcts, seen as dark areas in angiography. It increases with disease progression.

e) *Intraretinal microvascular abnormalities (IRMA).* These are large areas of non-perfusion and ischemia indicating severity and disease progression.

f) *Rosary-like abnormality of retinal veins.* It is the most important vascular change. It is characterized by irregular, segmented beading of the retinal veins. It indicates a high probability of progression to proliferative diabetic retinopathy.

Proliferative diabetic retinopathy

a) *Neovessels.* It appears as a response to ischemia -in optical disk or periphery and in AGF it shows intense fluorescence.

b) *Fibrous proliferation.*

c) *Preretinal or subhyaloid Bleeding.*

d) *Recurrent hemovitreous.*

e) *Fractional retinal detachment.*

f) *Late stages.* Rubeosis iridis, neovascular glaucoma and phthisis bulbi.

g) *Macular edema.* It is the most frequent cause of vision loss in diabetes. It is due to the output of plasma components that produce a macular thickness and this fluid can not be compensated by the saturated external blood-retinal barrier.

Diagnosis

1. Clinical diagnosis oftalmoscopy.
2. Angiography.
3. Optical Coherence Tomography (OCT).

Treatment

1. *Medical.* Good glycemic control, avoid risk factors, control of hypertension, hyperlipidemia and obesity. Kidney function control. Prevent sleep apnea syndrome as well as a good glycemic control in pregnancy.

2. *Laser fotocoagulation.* It is one of the most important advances in Ophthalmology. Argon laser is used to burn tissue and replace it by a glial scar (which consumes little oxygen) Capillaries disappear and neovascular proliferative factors are eliminated. It is usually done in all retinal extensiom (panphotocoagulation).

How do we treat proliferative changes in the macula? Using intravitreal treatments.

a) Antiangiogenic drugs or antiVEFG, Ranibizumab (Lucentis), Bevacuzumab (avastin) compassionate use.

b) Intravitreal corticoids (for macular edema) Ozurdex. It is an intravitreal implant of dexamethasone prolonged release (3 months) with low impact of intraocular pressure. Triamcinolone

c) Surgery: Vitrectomy.

Conclusions

Diabetic retinopathy is a complication of diabetes mellitus. There are 5-year latency between symptom onset and diagnosis which should serve to treat all the predisposing factors, where bariatric surgery plays an important role in preventing progression.

Retinal hypoxia-ischemia is the key factor in the evolution of the disease. It requires a good control of the underlying disease.

Angiography plays a very important role regarding both diagnosis and treatment.

It is mandatory to treat neovascularization and areas of ischemia with argon laser photocoagulation. Anti-VEGF treatment plays a relevant role in the treatment of diabetic retinopathy.

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Diabetic nephropathy: changes after diabetes surgery?

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Abstract

Introduction: **Obesity, as a central piece inside metabolic syndrome, is associated with early chronic kidney disease (CKD). In addition, several observational, cross sectional, and longitudinal studies have demonstrated that obesity is as an independent risk factor for the onset, aggravated course, and poor outcomes of CKD including diabetic nephropathy. This implies that when obesity is reversed, many CKD risk factors and CKD itself could be favorably influenced. So all measures aimed at weight loss are recommended to minimize risks from obesity-related conditions and generate improvements in the metabolic profile. Recent evidence shows that bariatric surgery (BS) can revert or improve proteinuria and CKD in morbidly obese patients.**

Objectives and methods: **The present review is aimed to provide the evidence regarding the beneficial effects of weight loss after BS in different stages of CKD including kidney transplant recipients, with an special focus on the beneficial effect in reducing or improving proteinuria and renal failure. Furthermore, this updated systematic review of the literature analyzes potential adverse effects that BS could induce not only on renal function but also on morbidity and mortality risk in perioperative and postoperative period.**

Conclusions: **Results from the different case reports, meta analysis as well as systematic review of clinical trials show that obesity treatment by way of lifestyle changes, pharmacotherapies and BS can reduce proteinuria and help to prevent loss of renal function. Also BS may reduce complications, and allow obese patients with end-stage renal disease to undergo kidney transplantation with good results.**

(Nutr Hosp 2013; 28 (Supl. 2):57-65)

Key words: *Obesity. Chronic kidney disease. Microalbuminuria. Proteinuria. Weight loss.*

NEFROPATÍA DIABÉTICA: ¿CAMBIA TRAS LA CIRUGÍA DE DIABETES?

Resumen

Introducción: **La obesidad, como pieza clave dentro del síndrome metabólico, está asociada con el enfermedad renal crónica (ERC) temprana. Además, varios estudios observacionales, de corte transversal y longitudinal han demostrado que la obesidad es un factor de riesgo independiente para la aparición, progresión y empobrecimiento del pronóstico de la ERC incluida la nefropatía diabética. Esto implica que cuando se revierte la obesidad, mejora mucho de los factores de riesgo de ERC y la propia ERC. Por lo tanto, todas las medidas encaminadas a la pérdida de peso permitiría minimizar los riesgos asociados a la obesidad y mejorar el perfil metabólico. La evidencia actual ha demostrado que la cirugía bariátrica (CB) puede revertir o mejorar la proteinuria y la ERC en pacientes con obesidad mórbida.**

Objetivos y métodos: **Esta revisión tiene como objetivo proporcionar evidencia sobre los efectos beneficiosos de la pérdida de peso tras la CB en los diferentes estadios de la ERC incluido los receptores de trasplante renal, especialmente los efectos beneficiosos en la reducción o mejora de la proteinuria y de la insuficiencia renal. Además, esta revisión sistemática actualizada de la literatura analiza los efectos adversos potenciales que podría producir la CB no solo sobre la función renal, sino también sobre la morbimortalidad en el período peri y postoperatorio.**

Conclusiones: **Los resultados de los diferentes casos clínicos, metaanálisis, así como, revisiones sistemáticas de los ensayos clínicos demuestran que el tratamiento de la obesidad mediantes cambios en el estilo de vida, tratamiento farmacológico y CB pueden reducir la proteinuria y prevenir la pérdida de la función renal. Asimismo, la CB minimiza las complicaciones, y permite a los pacientes obesos con ERC avanzada recibir un trasplante renal con buenos resultados.**

(Nutr Hosp 2013; 28 (Supl. 2):57-65)

Palabras clave: *Obesidad. Enfermedad renal crónica. Microalbuminuria. Proteinuria. Pérdida de peso.*

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Introduction

The epidemic of obesity and type 2 diabetes (T2DM) is on the rise worldwide at an alarming rate. The International Diabetes Federation estimates that in 2003, 194 million people had diabetes, and that by 2025, 333 million people will have this disease.[1,2] This epidemic is taking place in both developed and developing nations. In the U.S. alone, at least 16 million people have T2DM, with 1 million more being diagnosed annually. Obesity is also increasing at alarming rates. In the U.S., the majority diagnosed with T2DM are overweight, of which 50% are obese (i.e., body mass index (BMI) > 30 kg/m^2) and 9% are morbidly obese (BMI > 40 kg/m^2).[3] Evidence from several studies indicates that obesity and weight gain are associated with an increased risk of diabetes and that intentional weight loss reduces of developing diabetes.[2,4,5] Each year, an estimated 3.000.000 US adults die of causes related to obesity, and diabetes is the sixth leading cause of death. Correspondingly, both obesity and diabetes generate immense health care costs.[4] A substantial portion of the health costs attributed to obesity is related to T2DM. Also T2DM and its complications have substantial socioeconomic impact on the patients, their family and society. It is an inexorably progressive disease, leading to deterioration in multiple organs and systems, and the most common cause of adult blindness, limb amputations, and renal failure in Western communities, as well as the leading independent risk factor for coronary artery disease.[3]

Prevention of diabetes and obesity, through effective public health initiatives to modify the population's dietary habits and lifestyle should be of highest priority.[3] Lifestyle modifications including behavioral therapy, diet, and exercise aimed at weight loss are recommended to minimize risks from obesity-related conditions and generate improvements in the metabolic profile and quality of life.[5] Unfortunately, dietary and pharmacological therapies are relatively ineffective in achieving or maintaining adequate weight loss in the long term, especially for morbidly obese patients. However, recent evidence shows that bariatric surgery (BS) can revert T2DM in morbidly obese patients.[6]

BS was first reported by Pories et al., in 1992.[7] A systematic review and meta-analysis of the English literature reported complete resolution of T2DM (difined as discontinuation of all diabetes-related medications and blood glucose levels withing the normal range) in 78.1% of cases. This percentage increased to 86.6% if patients reporting improvement of glycemic control were included. Diabetes resolution occurred concurrently in patients who experienced and average weight loss of 38.5 kg (55.9% of the excess weight).[1] Although randomized, comparative clinical trials have not yet been carried out, the available data suggests that the clinical benefits of BS far outweigh the risks of complications, in morbidly obese individuals. However, the surgical mortality is 0.15%-0.35%, and there are considerable rates of early and late complications.[5] Although all types of BS procedures improve T2DM by promoting weight loss, gastric bypass surgery and duodenal exclusion technique provides improvement in hyperglycemia and other metabolic abnormalities with the lowest rate of postoperative complications. It therefore seems the safest surgical option. The improvement in glycemic control occurs in patients with BMI both above and below 35 kg/m^2. The mechanism behind the correction of T2DM, though not fully understood, seems to be largely related to changes in anatomy, gastrointestinal hormone secretion, and various metabolic factors. Resolution of T2DM is associated with shorter duration of T2DM, dietary or oral antidiabetic agent therapy, major loss of weight after surgery and diversionary procedure.[8,9]

Obesity as an important risk factor f or Chronic Kidney Disease (CKD)

Various cross-sectional and cohort studies have consistently evidenced epidemiological associations between obesity, metabolic syndrome components (defined as the presence of 3 of the following 5 traits: abdominal obesity, impaired fasting glucose, hypertension (HTN), hypertriglyceridemia, and a reduced HDL cholesterol), and early CKD, understood as presence of albuminuria and/or a decreased glomerular filtration rate (GFR; < 60 ml/min/1.73 m^2).[10] Obesity is an important CKD risk factor. This implies that when obesity is reversed, many CKD risk factors are favorably influenced. Obesity ca exacerbate other causes of CKD and has been associated with an acceleration of immunoglobulin A glomerulopathy (IgA nephropathy) as well as greater rate of kidney functional decline and proteinuria after unilateral nephrectomy when compared with subjects with a normal BMI level. Other obesity-related conditions such as dyslipidemia, hyperinsulinemia, HTN, DM, and other associated inflammatory states facilitate the progression of CKD. These obesity-related conditions are interdependent, and exacerbate kidney damage to a greater extent than what they would individually. Individuals with both HTN and DM have a 5- to 6-fold greater risk of developing end-stage renal disease (ESRD) compared with people with only HTN and no DM.[5] Hsu et al., analyzed 2.691 community-based patient population the presence of DM, hemoglobin A_{1c}, and serum cholesterol were significantly associated with increased risk for kidney impairment and thus associated with the development of CKD.[11] Furthermore, obesity appears to independently increase CKD risk and progression in the setting of diabetes.[12]

Diabetic nephropathy (DN) is the leading cause of ESRD and accounts for over 40% of new cases each year in the United States. Untreated DN is associated

with the fastest rate of progression in CKD with a yearly loss of GFR of 10 ml/min.[5] The Multifactorial intervention and Cardiovascular Disease in Patients with T2DM Trial showed that intensive therapies directed at dyslipidemia, hyperglycemia, HTN, and microalbuminuria (MA) resulted in secondary prevention of cardiovascular disease (CVD) and a 50% risk reduction for onset of DN.[13]

MA, defined as an excretion rate of 30 to 300 mg per 24 hours, is the first manifestation of DN and is associated with risk of progression to ESRD and increasing risk of premature death. It is also recognized as an early independent risk factor for insulin resistance, DM, HTN and CVD-related morbidity and mortality. Reversal of early-onset glomerular changes and regression in CIKD with associated complications has been shown in numerous lifestyle and intensive glycemic control studies.[5] A positive correlation between urinary albumin excretion and body weight has been evidenced in both non-diabetic and diabetic overweight individuals. The effect of obesity on proteinuria is not bimodal, but a continuum that is directly related to increasing BMI.[14] Obesity-induced MA has been found to precede histologic changes in the glomerulus and is hypothesized to be a result of increased intraglomerular pressure. In a retrospective analysis of the database of a population study on the impact of MA on renal and cardiovascular risk, found that the prevalence of MA in men increased from 9.5% in those with normal BMI (< 25) to 18.3% in those who were overweight, and to 29.3% in those who were obese, in women, the respective percentages were 6.6%, 9.2%, and 16.0%.[15] On the other hand, a decrease in urinary protein excretion is associated with metabolic improvement and decreased cardiovascular risks.[16] Accordingly, a 50% decrease in urinary protein excretion is associated with 18% decrease in cardiovascular risks.[17] Therefore, reducing proteinuria is used as a surrogate outcome for evaluating CKD treatment.

The hemodynamic effects of overweight on kidney function and albuminuria are magnified in the presence of HTN, which itself is a clinical complication of obesity. A similar amplifier effect of obesity has been reported in overweight diabetics. In a cross-sectional study analyzing risk factors for MA among African Americans with recently diagnosed T2DM, the urinary albumin to creatinina ratio was independently associated with BMI in 23.4%.[18] Moreover, another study has evidenced that even moderate weight loss can reduce proteinuria by 30% in overweight diabetics.[19] There is, therefore, strong evidence that weight reduction, achieved by BS or dietary caloric restriction, decreases proteinuria in obese individuals, with and without T2DM.[20,21] Additional long-term studies are needed to evaluate the durability of the beneficial effects of weight loss on kidney function and whether this is translated into an improvement in outcomes, such as slowing the development of ESRD. Weight loss will not only improve glycemic control but will also reduce the risk of CVD through beneficial effects on blood pressure, dyslipidemia, and serum markers of inflammation.[22] The weight loss global should be both achievable and maintainable; the National Kidney Foundation (NKF) recommends a target BMI of 18.5-24.9 (i.e., within the normal range) for patients with diabetes and CKD.[23] Weight management programs should comprise lifestyle measures (dietary restriction and increased physical activity) and anti-obesity medications if needed, coupled with appropriate support and counseling.[22] However, this target is un realistic for most overweight or obese patients with T2DM and is rarely achieved BS offers major improvement or complete remission of DM even independently of weight loss.[7]

Benefits of bariatric surgery on renal function

Bariatric Surgery in patients with normal renal function

BS has been associated with significant improvement in all parameters of renal function. Interestingly, the impact of BS on renal function occurs in patients both with and without established chronic renal impairment, as shown in table I. Serra et al., studied albuminuria levels before and after BS in 70 extremely obese patients with normal renal function. The patients has higher albuminuria levels (14.8 *vs.* 6.5 mg/24 h) than the control group with normal body weight.[24] These levels decreased significantly to 12.8 mg/24 h, 12 months after BS (Roux-en Y gastric bypass, RYGB), after a drastic reduction in body weight (mean BMI reduction from 53.3 to 33.6 kg/m^2). Navarro-Díaz et al., (25) followed up this group a further 12 months following surgery (2 years follow-up) and evidenced a further decrease in albuminuria (14.20 *vs.* 12.55 mg/24 h; p = 0.006). Other renal parameters (urea, creatinina, creatinina clearance, and proteinuria) were not significantly different from the 12 month follow-up stage.

Agrawal et al., analyzed 94 obese patients who underwent RYGB. At baseline, 32 patients had T2Dm, 37 had metabolic syndrome, and 25 had obesity alone. At 12 months, there was improvement in lipid profiles and reductions in body weight, blood pressure, glycated hemoglobin levels, and in total cholesterol levels. At 12 months there was a significant decrease in urinary albumin to creatinine ratio (ACR) in the diabetic and metabolic syndrome groups, whilst the reduction was not significant in obese patients with obesity alone.[26] The prevalence of Ma (ACR ≥ 30 mg/g) after surgery was reduced only in the diabetic group (35.7% to 7.1%, p = 0.008). These studies suggest that improvement in renal parameters may be associated with improvement in diabetic status, but also that patients with diabetes and the metabolic syndrome may benefit most (from the renal perspective) by undergoing BS.

Table I

Studies of Bariatric Surgery reporting on patients with microalbuminuria, proteinuria and Chronic Kidney Disease

Study (reference)	*Population*	*Etiology ESRD*	*Type of surgery*	*Follos-up (weeks)*	*ABMI (kg/m²)*	*ΔGFR (ml/min)*	*ΔPU (g/24 h)*	*ΔMAU (mg/24 h)*	*ΔCr (µmol/L)*
Micralbuminuria									
Serra[24] 70	–	RYGB	52	-20	-13	-0.03	-2.0	–	
Navarro-Díaz[25]	61	–	RYGB	54	-21	-21.5	-0.03	-1.7	-7
Agrawal[26]	94	–	RYGB	52	–	–	–	-14	–
Saliba[27] 35	T2DM (N = 19)	52	-15	-23	–	–	-1		
Gross proteinuria/CKD									
Chagnac[28]	8	–	VBG	52	-16	-35	–	–	–
Alexander[29]	9	MG (N = 2), FSGS (N = 5), DN (N = 2)	RYGB	161	-15.7	–	–	–	–
Izzedine[30]	1	DN	LRYGB	116	–	–	-6.2	–	-21
Cuda[31]	1	FSGS (DM)	LRYGB	56	-16	–	-0.9	–	–
Fowler[32]	1	FSGS	LRYGB	60	-25	–	-0.2	–	–
Agnani[33]	1	FSGS	N/S	34	-14	–	–	–	-27
Soto[34]	1	IgAN	LRYGB	230	–	–	–	–	-398
Tafti[35]	1	Vascular	LRYGB	40	-15	–	–	–	-194
Alexander[36]	19	NS / (DM = 7)	LRYGB	15	-18.4	–	–	–	–
MacLaughilin[37]	9	FSGS(N = 2); PKD (N = 1); ND (N = 1); HTN (N = 3); IgAN (N = 1); PP (N = 1)	LSG	52	-9.5	No	–	–	–

RYGB: Roux-en-Y gastric bypass; LRYGB: Laparoscopic Roux-en-Y gastric bypass; RRYGB: Robotic Roux-en-Y gastric bypass; VBG: Vertical-banded gastroplasty; N/S: Not specified; AGB: Adjustable gastric band; LSG: Laparoscopic sleeve gastrectomy; BMI: Body mass index; GFR: Glomerular filtration rate; PU: Proteinuria; MAU: Microalbuminuria; Cr: Serum creatinine; CrCl: Creatinine clearance; T2DM: Type 2 diabetes; MG: Membranous glomerulonephritis; FSGS: Focal segmental glomerulosclerosis; DN: Diabetic nephropathy; HTN: Hypertension; IgAN: IgA nephropathy; PP: Porhyria.

Having evidenced the benefit of RYGB in improving obesity-related hyperfiltration, Saliba et al., further investigated the effects of the bariatric procedure on tubular defects using urinary Cystatin C to urinary creatinina ratio. They confirmed that GFR is improved by RYGB; however, tubular damage was only reversed in non-diabetic obese patients.[27] This may imply that the pathogenesis of renal disease in diabetics with excess weight may be a different from non-diabetic obese patients.

To evaluate the effect of restrictive BS on BMI and glycemic control, Chagnac et al.[28] studied renal glomerular function in eight subjects with severe obesity (BMI 48.0 ± 2.4) before and after vertical banded gastroplasty (at 12-17 months follow-up). None of the patients had history of renal disease, and all had normal urea and creatinina values and negative proteinuria on dipstick testing. Nine healthy subjects served as controls. GFR and renal plasma flow (RPF) were determined by measuring inulin and r-aminohippuric acid (PAH) clearance. In the morbidly obese group, mean BMI fell from 48 to 32 kg/m^2 after bariatric surgery. Interestingly, GFR decreased from 145 to 110 ml(min and RPF from 803 to 698 ml/min. This finding of an apparent worsening in renal function (decreasing GFR) may represent an evolving injury. However, it could also demonstrate a reduction in the hyperfiltration which is the hallmark of obesity-related renal damage.

Bariatric Surgery n patients with chronic kidney disease

To the extent of our knowledge, there are only a few case reports and series of BS performed on CKD patients (table I).

Alexander et al., monitored renal function pre- and post open gastric bypass in 45 morbidly obese non-transplant patients with CKD. Nine of these patients have resolution, improvement, or stabilization of their renal function after the procedure. Underlying renal disease in these nine patients were: primary focal segmental glomerulosclerosis (FSGS) (N = 5), glomerulonephritis (GN) (N = 2), and DN (N = 2). One of the patients with GN had complete remission of renal disease at 9 years follow-up. Two of the FSGS patients on dialysis were able to discontinue dialysis for 27 and 7 months. The remaining patients had stable renal function with a follow up for 2-5 years. There were no post-operative complications.[29] Larger series of patients are needed to confirm these results. This series is very small and with the patients all suffering from different renal disorders it is difficult to draw firm conclusions, but the reversal of these diseases appears significant.

Proteinuria is an important and well-studied indicator of renal dysfunction and a number of case reports show an improvement in proteinuria after BS (table I). Izzedine et al.[30] report a 25 kg weight reduction in an obese diabetic patient after RYGB and a reduction of proteinuria by 99% (6.3 g/24 h pre- *vs.* 0.07 g/24 h post-procedure). A further weight loss led to normalization of creatinine level. Cuda et al.[31] also describe the effect of BS on a patient with CKD requiring multiple medications with significant proteinuria (1.15 g/24 h). Following laparoscopic RYGB, her weight was reduced 46 kg to a post-procedure BMI of 20.2. Her proteinuria declined to 0.27 g/24 h and she was able to stop all her medications. The impact of BS in an adolescent with chronic renal failure was evaluated by Fowler et al.[32] The 17 year-old girl underwent laparoscopic RYGB, which reduced her BMI from 56.8 to 35.9 kg/m^2. Initially, her proteinuria was in the nephrotic range, but it normalized after BS, requiring no pharmacological therapy.

Surgical treatment of morbid obesity was also reported to stabilize creatinine during and 8-months period after gastric bypass in a 43-year-old man with chronic renal failure (creatinine 380 μmol/L before bypass and 353 μmol/L at 8 months after gastric bypass).[33] Soto et al.[34] reported a patient with IgA nephropathy and a creatinine of 539 μmol/Lat the moment of surgery. He required dialysis during the immediate post-operation, the serum creatinine had decreased to 141 μmol/L. Tafti et al.[35] report the impact of robotic gastric bypass on a patient on dialysis with ischemic chronic kidney impairment following type a aortic dissection. As an institutionally required bridge to renal transplantation, the patient underwent BS, which led to decrease in BMI from 52.5 to 37.6 kg/m^2. His creatinine fell from 362 μmol/L pre-operative to 168 μmol/L at 9 months following surgery and he was able to discontinue dialysis.

Obesity and Dialysis

Contrary to the evidence that obesity promotes the onset and, progression of CKD patients, obesity in dialysis patients appears to provide them a survival advantage ("reverse epidemiology").[38] This disparity may be due to the fact the patients on dialysis have an inherent survival advantage in comparision to the patients that have died before reaching ESRD and renal function replacement. The fact that the first report that describe this finding compared survival data with different follow-up in dialysis and non-dialysis patients (10 years for non-dialysis, and 4 years in dialyzed patients). Another reason for an advantage of obesity in dialyzed patients could be that higher BMI patients had better nutrition status. However, this survival advantage in obese patients is not found in all studies. Several studies have reported worse outcomes in dialysis patients who were overweight or obese.[14,39] Kaizu et al.[40] observed an increased mortality among a chronic hemodialysis (HD) population at the extremes of BMI levels producing a "U"-shaped mortality curve.

Obesity and Transplant

The apparently beneficial effect of obesity in dialysis patients has not been found to apply to transplant patients. The most extensive study on this topic was presented by Meier-Kreische et al.[41] who analyzed data from the United States Renal Data System (USRDS) database between 1988 and 1997 involving 51,927 adult transplant recipients. The relative risk ratio for graft loss was approximately 1.4 in patients with a BMI > 36 kg/m^2 compared with those with normal BMI. Similar risk ratios were found for death censored graft loss (not including patients who died with functioning grafts; RR = 1.45 for BMI > 36 kg/m^2), death with a functioning graft (RR = 1.36), and for cardiovascular-related complications (RR = 1.4). The best overall results were found in patients with a BMI of 22-24 kg/m^2. Cacciola et al., compared patients with BMI 30-34.9 to patients with BMI 35 or greater who underwent renal transplant (RT). The patients survival at 5 years for the lower BMI group was 95% and for the higher BMI group it was 79%. Graft survival at 5 years was 94.5% for the lower BMI group and 63% for the higher BMI group.[39]

Bariatric surgery as a bridge to renal transplantation

It is well documented that obese patients have a higher incidence of wound complications and delayed graft function when they receive transplants.[43] As a result of the increased incidence of surgical complications and death from CVD, most transplant center will not transplant patient with a BMI > 35 kg/ m^2. Therefore, one of the major reasons for performing BS in morbidly obese dialysis patients may be to improve their comorbidities and prepare them for transplantation. Table II shows BS studies reporting BS on CKD before and after receiving RT. Takata et al.[47] report results after laparoscopic RYGB in seven ESRD patients without perioperative complications of death. After an average 15 months follow-up, mean excess body weight loss was of 61% and all patients were accepted for transplant. Reviewing the USRDS (2001-2004), Modanlou et al.[48] identified 29 BS operations performed on patients on transplantation waitlist, and 72 BS performed on patients waiting to be enrolled in the transplant list. Comparison to published clinical

Table II

Studies of Bariatric Surgery reporting on patients after renal transplant or before renal transplant

Study reference	*Population*	*Type of surgery*	*Follow-up (weeks)*	*ΔBMI (kg/m^2)*	*Comments*
Alexander[36]	8 aRT	LRYGB	260	-16.9	DM (N = 2)
	3 (bRT)	LRYGB	260	-9.7	DM (N =1)
Rex[42]	1 (aRT)	VBG	24	-55	HTN
Marterre[43]	3 (aRT)	RYGB	36	–	DM resolution. Cyclosporin requirement increased 33% (p = NS)
Weiss[44]	1 (aRT)	AGB	80	-24.7	GNC
Newcombe[45]	3 (bRT)	AGB	85.2	-10.8	DM (N = 2)
Buch[46]	1(bRT); 1(aRT)	RYGB	12/1	–	DN (N = 1); HTN (N = 1)
Takata[47]	7 (bRT)	LRYGB	7	-15	DN (N = 3); HTN (N = 1); PKD (N = 1); SEL + DM (N = 1)
Modanlou[48]	87 (aRT)	RYBG (N = 65); VBG (N = 31)	–	-4.7	DN (N = 11); HTN (N = 13); GNC (N = 14); Other (N = 63); DM (N = 30)
	101 (bRT)	RYBG (N = 50); VBG (N = 16); BPD (N = 1)	–	-7	DN (N = 31); HTN (N = 12); GNC (N = 20); Other (N = 24); DM (N = 35)
Koshy[49]	3 (bRT)	AGB	60	-5.7	DN (N = 2); FSGS (N = 1)
Szomstein[50]	5 (aRT)	LRYGB (N = 4)/Gastrectomy (N = 1)	24	-20.3	PKD (N = 1); GNC (N = 1); ND (N = 3)

RYGB: Roux-en-Y gastric bypass; LRYGB: Laparoscopic Roux-en-Y gastric bypass; VBG: Vertical-banded gastroplasty; N/S: Not specified; AGB: Adjustable gastric band; BMI: Body mass index; BPD: Biliopancreatic diversión; DM: Diabetes; DN: Diabetic nephropathy; HTN: Hypertension; PKD: Polycystic disease; SEL: Systemic erythematous lupus; GNC: Chronic glomerulonephritis; FSGS: Focal and segmental glomerulosclerosis; bRT: Before renal transplant; aRT: After renal transplant.

trials of BS in populations without kidney disease indicates similar weight los (approximately 60%) but higher post-BS mortality (3.5%) in this USRDS sample. Twenty of the 29 BS cases performed on patients on list proceeded to transplantation, with a median waiting time of 17 months. It is unlikely they would have been transplanted without their bariatric surgery. The remaining nine patients had not received at transplant by the end of follow-up.

Concerns exist regarding BS and the resultanting malabsorpsortion, that can affect the pharmacodynamics of immunosuppressive medications, especially with RYGB. Szomstein et al.[50] however reported no need for increasing levels of cyclosporine in their series, whilst Alexander et al.[36] reported a modest increase in dosage for some patients following RYGB, indicating that extra vigilance may be required in immunosuppresive therapy in post-BS RT recipients.

In addition, there are concerns about providing highly technical BS in patients who have received a RT. Nevertheless, both Szomstein et al.[50] and Alexander et al.[36] report the safety of performing Bs on RT recipients with neither group's patients suffering from anastomotic leak, hernia or graft loss. These reports indicate that the provision of RYGB in RT recipients is both safe and efficacious.

Risks of bariatric surgery on renal function

Acute Kidney Injury (AKI)

The development of post-operative AKI is a well-recognized and highly concerning complication of BS. The use of general anesthesia can induce a reduction in renal blood flow in about 50% of patients, which can further exacerbate advanced CKD and promote delayed clearance of medications and anesthesia. The perioperative period is a time of increased stress originating from fluid and hemodynamic shifts that can lead to AKI. This is of special concern if there is some degree of underlying CKD.

In CKD patients, obesity is associated with higher perioperative death rates. Approximately 1.2% of patients undergoing general surgery develop AKI,[51] but this can be as high as 7% in the DM population. Acute perioperative kidney failure is associated with an increased risk for acute mortality of 40% to 90%. A prospective study of 109 patients with a baseline GFR of 82 ml/kg/min that underwent BS, found that the rate of AKI (defined as a rise in serum creatinine more than 25% above baseline or 0.5 mg/dl) was 6.4%. The majority of these cases had primary cardiopulmonary complication such as myocardial infarction, stroke, heart failure, or venous thromboembolism. The risks of AKI in patients with more advanced CKD undergoing BS are unknown.[5]

Risk factors for the development of kidney injury included increased weight several medical co-morbidities, and the concurrent administration of nephrotoxic medications such as non-steroidal anti-inflammatory agents and angiotensin converting enzyme inhibitors. Both rhabdomyolysis and nephrolithiasis are noted to be common factors in post-bariatric surgery AKI.[39]

Rhabdomyolysis

Although rhabdomyolysis in BS has been described as a rare complication in some case series, it was diagnosed in 22-77.3% in one report.[52] A major risk factor for the development of rhabdomyolysis is the length of operative time. The presence of medical co-morbidities is a further risk factor for the development of rhabdomyolysis following BS, as were HTN and DM.[39]

Nephrolitiasis and oxalate nephropathy

Obesity itself appears to be a risk factor for stone formation. Early cross-sectional studies evidenced that the prevalence of nephrolithiasis was related to BMI. Furthermore, larger body size is associated with higher urinary urate and oxalate excretion, which may further promote calcium-oxalate stone formation.[39] Other important potential precipitating factors were decreased urinary volume and decreased urinary citrate. There is general agreement in the literature that hyperoxaluria is a characteristic feature of post-bariatric renal stones and is associated with a reduction in both urinary citrate concentration and urine volume.[53]

In an attempt to investigate a possible difference between malabsorptive and restrictive bariatric procedures, a group of 18 patients undergoing restrictive obesity surgery [sleeve gastrectomy (n = 4) and gastric banding (n = 14)] had urinary metabolites measured over a 2-months period. The group was compared to controls 8n = 168 =, adults with kidney stones (n = 1,303) and RYGB patients (n = 54). There was no significantly increased risk for kidney stone formation when compared to a control cohort of both stone- and non-stone forming subjects. Furthermore, over a period of 2 months, the urinary oxalate excretion of the restrictive group was significantly less than that of the RYGB cohort (n = 54), suggesting that restrictive techniques of BS may be less lithogenic than malabsorptive methods.[54]

The lithogenicity of BS (in particular RYGB) is thought to be multifactorial. Lipid malabsorption due to the reduction of the gastric and small bowel capacity enhances the saponification of calcium in the gut, which limits the amount of available calcium to bind oxalate in the colon. In addition, as the absorption of bile salts is reduced, their concentration in the colon is larger and contributes to enhance the colonic mucosa's permeability to oxalate. This further leads to increased oxalate absorption and subsequent renal excretion. Studies have also suggested that oxalate processing

bacteria in the gut may play a role. Colonization with *Oxalabacter formigenes* has been shown to be associated with lower urinary oxalate secretion whereas antibiotic-associated decolonization can increase these levels.[53]

The treatment of nephrolithiasis in patients with bariatric surgery is standard and comprises removal of the stones and prevention of recurrence. Recent guidelines suggest that prophylactic dietary modification is the current best strategy. A low oxalate diet in combination with calcium supplements (as oxalate binding agents) has been shown, to be effective in protecting post-RYGB patients with enteric hyperoxaluria from developing nephrolithiasis. Additionally, administration of oral calcium is recommended because calcium forms a complex with free oxalate and limits its absorption.[53]

Oxalate nephropathy is a complication of BS that is frequently under-reported. It is characterized by tubular deposition of calcium oxalate crystals, which can lead to AKI and CKD. The main risk factor for calcium oxalate deposition is hyperoxaluria; however, the presence of fluid depletion and previous renal insufficiency markedly increase the risk of renal failure. The prognosis of oxalate nephropathy after RYGB is poor and leads to ESRD in the majority of patients. Nasr et al., reported 11 patients who developed oxalate nephropathy after RYGB. Eight patients were morbidly obese, three patients were intervended due to gastric adenocarcinoma. Their conclusion was that oxalate nephropathy is an under-recognized complication of RYGB, and patients, with pre-existing renal disease may be at higher risk of developing it.[55] There are no guidelines for the management of oxalate nephropathy after RYGB. Of note, renal biopsy should be considered in people whose renal function deteriorates after RYGB.[53] Whether the reversal of bypass surgery leads to improvement in renal function is controversial and needs to be clarified with further research.

Conclusions

Since obesity is a major risk factor in the natural history of CKD and CVD risk, it is understandable that sustained and substantial reductions in body fat reduces the risk for both CKD and CVD. There is evidence that BS resolvers or significantly improves DM, even immediately after surgery, and other risk factors such as HTN and dyslipidemia in obese patients. However, these benefits must be weighed against the risk of acute or chronic kidney failure in the postoperative period and the risk of nephrolithiasis in the longer term.

The literature is still scarcer in relation to the effect of BS on longer-term renal function. In patients with normal kidney function assessed by GFR, the majority of the studies have been undertaken using RYGB and indicate that the greatest improvement in renal parameters can be seen in patients with diabetes and metabolic syndrome as opposed to simple morbid obesity.

There is little information on patients with established kidney disease undergoing BS either before or after RT. However, these studies do indicate an important effect of RYGB in this "at-risk" population. Prospective studies are needed to evaluate the effect of the diverse types of BS on renal function in obese CKD patients.

Evidence shows that BS has potential to improve outcomes in chronic renal impairment. BS may enable obese patients with ESRD to be eligible for a renal transplantation, and in itself my slow down CKD progression. However, more data is required to compare obese patients who do and do not undergo BS and examine dialysis requirements, transplant-related outcomes, and overall survival. Future research will address how the timing of BS may affect transplant-related outcomes.

Whereas diabetes is strongly associated with increased morbidity and mortality following BS, the benefits of bariatric operations in morbidly obese diabetic patients can hardly be overlooked. Consequently, conventional bariatric procedures are increasingly being used worldwide to treat T2DM in association with obesity, and among less obese or merely overweight patients.

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Quality of life of diabetic patients with medical or surgical treatment

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Abstract

Introduction: **In general, most of the studies agree in that the quality of life (QoL) of patients with diabetes is worse than that of the general population. Furthermore, these same studies have also described very positive effects on quality of life after bariatric surgery. The aim of this study was to analyze whether the impact on quality of life of diabetic patients after being submitted to bariatric surgery is the one supposed to be.**

Methods: **We prospectively analyzed our data on 524 diabetic patients submitted to bariatric surgery between 2001 and 2005. All the patients filled up three QoL questionnaires before the surgery and at 1, 3, 6, and 12 months after the surgery. The answers were gathered from an annual database. All patients were submitted to adjustable gastric band surgery, Y-Roux gastric bypass, or BPD-Scopinaro.**

Results: **We obtained complete data on 89 patients that were included into the study. One year after the surgery, the QoL had significantly improved independent of disease remission and weight loss. Diabetes got improved in all the cases. The improvement on the quality of life was higher in the patients with total remission of the disease than in those only improving their health status, although it was lower than that of those patients without diabetes before the surgery.**

Conclusions: **After a literature review and with our own prospective data, we may conclude that the benefits obtained by diabetic patients from bariatric surgery are mainly due to improvement of their diabetes, irrespective of their initial BMI and the BMI decrease after the intervention. Further studies are needed to investigate the results of the QoL test in diabetics with low BMI after bariatric surgery and in the long run.**

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Key words: *Quality of life. Diabetes. Bariatric surgery. Metabolic surgery.*

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CALIDAD DE VIDA DE PACIENTES DIABÉTICOS; TRATAMIENTO MÉDICO *VS* CIRUGÍA

Resumen

Introducción: **En general, la mayoría de los estudios coinciden en que la calidad de vida de las personas con diabetes es peor que la calidad de vida de la población general (QoL). Además, estos mismos estudios también han descrito efectos muy positivos sobre la calidad de vida tras cirugía bariátrica. El objetivo de este estudio fue analizar si el impacto sobre la calidad de vida de los pacientes diabéticos después de ser sometidos a cirugía bariátrica según el test (QoL) es el que se supone debería ser.**

Métodos: **Analizamos nuestra colección de datos prospectivos de 524 pacientes diabéticos que se sometieron a cirugía bariátrica entre 2001 y 2005. Todos los pacientes realizaron 3 cuestionarios de calidad de vida antes de la cirugía y después de 1, 3, 6 y 12 meses. Las respuestas se recogieron en una base de datos anual. Todos los pacientes se sometieron a una intervención de banda gástrica ajustable, Bypass Gástrico en-Y-Roux o BPD-Scopinaro.**

Resultados: **En total se obtuvieron los datos completos de 89 pacientes que fueron incluidos en el estudio. 1 año después de la cirugía, la calidad de vida mejoró de manera significativa e independientemente de la remisión de la enfermedad y de la pérdida de peso. La diabetes mejoró en todos los casos. La mejora en la calidad de vida fue superior en los pacientes con remisión de la enfermedad que en los que únicamente mejoraron su estado, pero inferior que en los pacientes que no tenían diabetes antes de la operación.**

Conclusiones: **Tras el análisis de la literatura y de nuestros propios datos prospectivos, podemos concluir que los beneficios que obtienen los pacientes diabéticos tras la cirugía bariátrica son debidos principalmente a la mejora de su diabetes, independientemente del IMC inicial y de la disminución del IMC tras la intervención. Se necesitan más estudios para investigar los resultados del test QoL en diabéticos con bajo índice de masa corporal tras la cirugía bariátrica y a largo plazo.**

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Palabras clave: *Calidad de vida. Diabetes. Cirugía bariátrica. Cirugía metabólica.*

Background

Unlike the clinical outcome (mortality, morbidity) typically measured in clinical trials, Health related Quality of Life (HRQOL) reflects the impact of medical procedures from the perspective of the patient, and thus provides a more holistic picture of procedures impact and recovery. Perception of patients HRQOL and its influencing factors will assist in developing strategies to improve HRQOL for diabetic patients with medical or surgical treatments.[1,2,3]

As bariatric surgery is no longer only considered as a surgery only for the obese patient,[4] but a metabolic procedure,[5,6,7] quality of life became most important and measurements should be shifted to metabolic issues, too. The comparison of medically treated patients with surgical procedures on diabetic patients is of special interest related to changes in HRQOL.

Health related quality of life in diabetic patients

More than 180 million people worldwide have diabetes mellitus, and the number of diabetes patients is estimated to double by 2030.[8] The increasing trend of diabetes has been reported for both, type 1 diabetes (T1D)[9,10,11] and type 2 diabetes (T2D) populations.[12,13,14]

Diabetes has detrimental effects on health outcomes including quality of life (QoL).[14] Studies have shown significant negative associations between the disease state, health related quality of life (HRQOL) and its prognosis.[15,16,17]

Further understanding of the determinants of HRQOL among individuals with diabetes could potentially help to tailor and to target interventional strategies for the benefit of this population group.

Medical and lifestyle determinants of HRQL and life satisfaction in adults with type 2 diabetes have been investigated in many studies[15,19] and showed a multidimensional construct. Many factors with high impact on QOL were shown to be significantly associated with life satisfaction and HRQL in adults with T2D and T1D as well as in Adolescents[20-26] and will be more differentiated in this article.

Measurement of Health Related Quality of Life (HRQL)

The two broad approaches to health-related quality of life measurement have emerged-generic and disease specific.

The generic approach involves the use of measures applicable across health and illness groups. The most widely used generic measure of quality of life in studies of people with diabetes is the Medical Outcomes Study (MOS) Short-Form General Health Survey[29,30] in its several forms (SF-36, SF-20, SF-12).

The Rand Quality of Well-Being Self- Administered (QWB-SA) survey[31] is similar to the SF-36 in its aim to comprehensively assess health-related well-being or quality of life. It contains scales designed to measure acute and chronic emotional and physical symptoms, mobility, and physical activity. Other instruments used at least occasionally to assess general health status in people with diabetes include the Sickness Impact Profile[32] and the Nottingham Health Profile.[33]

Generic measures like the SF-36 are most useful for comparing quality of life in people with different diseases and the quality of life in people who have no diseases with the quality of life in people who have a disease.

Such measures can be used to assess cost-effectiveness and cost benefits across various interventions and illnesses.

Many generic measures of emotional status have been employed in studies which include people with diabetes. These include the Well-Being Questionnaire,[34] the Proile of Mood States,[35] the Symptom Checklist (SCL-90R),[36] the Mini-Mental Status Exam,[37] the Kellner Symptom Questionnaire,[38] and the Affect Balance Scale.[39] Depression in people with diabetes has been studied using the following scales: the Beck Depression Inventory,[40] the Zung Self-Rating Depression Scale,[41,42] and the Center for Epidemiological Studies Depression Scale.[43] Anxiety in people with diabetes has been studied using the following scales: the Beck Anxiety Inventory,[44] and the Zung Self-Rating Anxiety Scale.[45] Both depression and anxiety in people with diabetes have been studied using the Hospital Anxiety and Depression Scale.[46]

The most widely used diabetes-specific quality of life measure is the Diabetes Quality of Life (DQOL) measure,[47] developed for use in the Diabetes Control and Complications Trial (DCCT). The DQOL was designed to measure diabetes-specific quality of life. It contains scales to assess five separate areas: satisfaction with treatment; impact of treatment; worry about the future effects of diabetes; worry about social and vocational issues; and overall well-being. The last scale was derived from national surveys of quality of well-being and can be used to compare people with diabetes and a wide variety of other populations. The Satisfaction and Impact scales seem to be broad gauges of diabetes-related quality of life, whereas the Worry scales address concerns more specific to patient perceptions of diabetes-related emotional distress. Since the DQOL was introduced, a number of other comprehensive diabetes-specific quality of life measures have been developed. The Diabetes-39 instrument[48] was developed for use with people who have either Type 1 or Type 2 diabetes ± whether managed with insulin, oral agents or diet alone.

The Problem Areas in Diabetes (PAID) survey [49] is a relatively new measure of psychosocial adjustment specific to diabetes. The PAID contains items measuring burden of illness, satisfaction with treat-

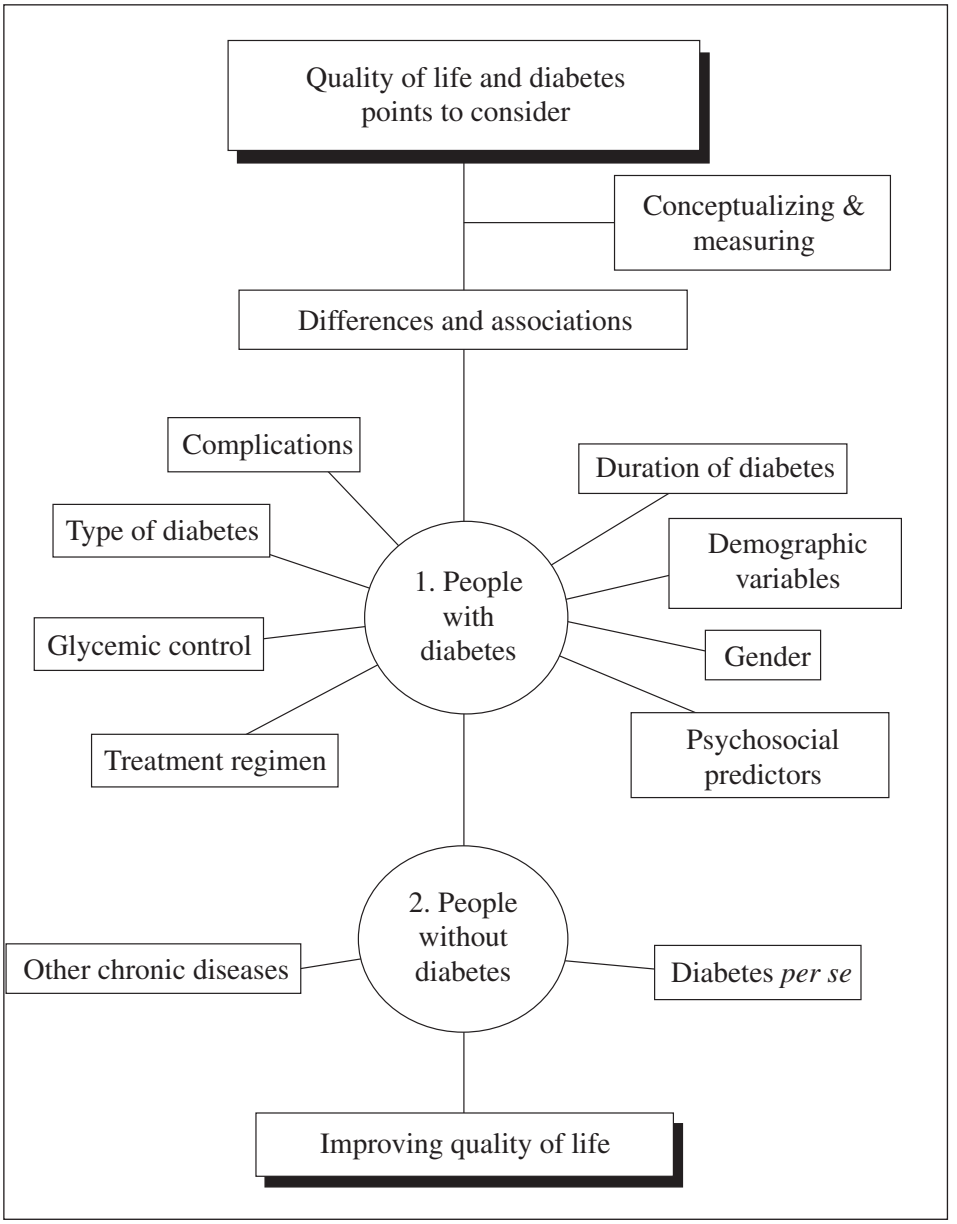

Fig. 1.—Rubin et al., 1999 in Diabetes Metab Res Rev; 15: 205-218: Main Impacts on QoL in diabetic patients.

ment, impact of treatment, and worries about the future effects of diabetes. The authors designed the PAID, which may be used with patients who have either Type 1 or Type 2 diabetes, to tap the breadth of emotional responses to diabetes. Lewis and colleagues[50] developed an instrument, the Diabetes Treatment Satisfaction Questionnaire (DTSQ), designed to measure only diabetes treatment satisfaction.

Quality of life and impact factors in conservative treatment of diabetes

Rubin et al described in 1999[15] in a systematic literature review the main impacts on QOL in diabetics patients (fig. 1). The main concerns will be displayed in the following.

Type of diabetes

Despite aetiological differences between T1D and T2D,[51-53] differences in levels of HRQL and QoL as well as their determinants between the two diabetes types have not been thoroughly investigated in adults with diabetes. Jacobson and colleagues[47] compared HRQL scores between 240 adults with T1D or T2D, and identified higher HRQL in T2D after adjusting for demographic factors (i.e., age, marital status and education), diabetes complications, and diabetes duration.

They used the SF-36 and the DQOL to assess quality of life and found that Type 2 patients not taking insulin reported higher quality of life that type 2 patients taking insulin. Type 2 patients on insulin still experienced better HRQOL that Type 1 patients.

Another study compared levels of three HRQL measures in adults (T1D, N = 236; T2D, N = 889) and found no differences in EQ-5D and QoL-DN scores between the two samples, but a higher global health profile (SF-36) score in the T2D group.[54] Interestingly, in two studies on children and adolescents with diabetes, HRQL was lower among T2D individuals compared to those with T1D.[55,56]

That age seems to be a strong variable in the outcomes of HRQL was also shown in the Alberta Longitudinal Exercise and Diabetes Research Advancement (ALEXANDRA) study in 2011[14,19] With the exception of age, the determinants of HRQL appear to be similar between T1D and T2D adults, suggesting that both diabetes groups may benefit from achieving generic approaches in targeting optimal control of glycemic level and comorbidities as well as promoting healthy lifestyle.[14]

In fact, some researchers have found few meaningful differences between those with each type of diabetes in functional status or well-being.[57,58]

Based on the limited available data, it is probably fair to say that while quality of life or some of its components may differ as a function of diabetes type, these differences are probably the result of other factors, such as treatment regimen or age, which are associated with diabetes type.

Treatment regimen

Results of research on the association between treatment regimen and quality of life in people with diabetes are mixed, with some indication that increasing treatment intensity in patients with Type 2 diabetes from diet and exercise alone, to oral medications, to insulin, is associated with worsening quality of life.[15,47,59-64]

Presence of diabetes-related complications

The research addressing this question is consistent in finding that the presence of complications, particularly the presence of two or more complications, is associated with worsened quality of life both in studies with generic or diabetes-specific measures.[28,47,57,60,65-78]

Main complications identified in these studies were presence of neuropathy, cardiovascular disease,[68,69,70] nephropathy,[28] gastroparesis.[71] Diabetic retinopathy,[72,73] erectile dysfunction.[74-78]

Glycemic control

The past few years have brought a burgeoning of research on the relationship between glycemic control and quality of life in people with diabetes, and a number of these studies suggest that a relationship does exist, especially when quality of life is assessed by diabetes-specific measures rather than generic ones. Studies employing generic measures such as the SF-36, SF-20 often reported null findings.[67,69,72,79,80,81,82] Only one study which used the SF-36 to assess quality of life found significant associations between HbA1c and some SF-36 scales in some sub-populations:[68] Klein et al found that SF-36 general health and overall self-rated health scores were associated with HbA1c levels for younger onset subjects only (i.e. diagnosed before 30 years and taking insulin).Wikblad and colleagues[83] reported that scores on the Swedish Quality of Life Scale (SWEDQUAL) were lowest for those with the highest HbA1c levels (8.1%), highest for those with HbA1c levels 7.1 ± 8.0%, and intermediate for those with the lowest HbA1c levels (7.0%).

This data suggests that there may be a curvilinear relationship between HbA1c level and health-related quality of life, perhaps as a result of decrements in quality of life associated with more complex treatment regimens or increased incidence of hypoglycemia.

Studies using disease-specific questionnaires[66,84,85,86] support this suggestion, whereas studies using generic instruments (esp. SF-36) cannot show any relationship.[80] This issue might be due to the fact that generic questionnaires may not adaequatly address to the important issues of the diabetic patients-this effect could be shown by Tief et al in 1998.[66]

A few studies have found no significant relationship between HbA1c levels and diabetes- specific measures of quality of life,[59,64] but the HbA1c levels of the participants in these studies were quite low, averaging about 7.0%, so the restricted range of glycemia may have contributed to the null finding.

Some studies have found significant associations between quality of life and measures of glycemia other than HbA1c. Lower fructosamine levels were associated with higher DQOL treatment satisfaction scores[62] and lower fasting plasma glucose levels were associated with lower levels of fatigue as measured by the Profile of Mood States.[58]

Overall, the majority of studies suggest that better glycemic control is associated with better quality of life.

This association is stronger for measures of diabetes-specific quality of life and generic measures of emotional distress than for generic measures of quality of life.[15]

Gender

A number of researchers have reported that quality of life is better among diabetic men than among diabetic women. This is consistent with reported gender differences in health-related quality of life in the general population.[87-92] Rubin et al. published in 1998[93] that men were more satisfied with their diabetes treatment regimen, and missed less work and fewer leisure activities as a result of their diabetes, than women did. Peyrot et al found[65] that treatment satisfac-

tion was higher and diabetes burden lower in men than in women, and[57] that men were significantly less likely to report symptoms of depression or anxiety consistent with the presence of a clinical disorder than women. Others have found that men with diabetes report less disease impact,[62,94] more treatment satisfaction,[59,64,94] and higher scores on all SF-20 scales[61] than women. These findings, suggesting that diabetic men have an advantage over diabetic women in health-related quality of life, reinforce the need to control for gender in future investigations of quality of life in diabetes.

Demographic variables

While Peyrot et al.[57] have found no meaningful pattern of association between age and quality of life, others[61,68] who assess aspects of functioning more likely to be affected by age suggest there is an association between age and specific aspects of well-being, as also suggested in the different results comparing type 2 and type 1 diabetes between adults and adolescents

Significant associations have also been demonstrated between socioeconomic status (measured by income or educational level) and quality of life in the general population and in diabetic patients.[57,61]

Few have studied the relationship between race or ethnicity and quality of life in people with diabetes, in which no difference was to be found.[57,61]

Marital status appears to be related to quality of life in the general population,[95,96] and Payrot et al.[57] found that study subjects who were not married were significantly more likely than those who were married to report symptoms of depression consistent with the presence of a diagnosis of clinical depression. Jacobson and colleagues[28] reported a pattern of relationships between marital status and quality of life (as measured by the SF-36 and DQOL), which indicated that separated or divorced individuals experienced worse quality of life than those who were single or married. A study of people with Type 2 diabetes conducted in Norway found that those living alone reported lower levels of physical functioning and psychosocial well-being than those who lived with others.[97]

Psychosocial predictors

There are studies which have suggested that health-related quality of life in people with diabetes may be affected by psychosocial factors such as health beliefs, social support, coping strategies and personality traits.[28,98-101] but the literature does not give clear answers on that very multidimensional and subjective question.

Differences in people with and without diabetes

In general, most studies report that quality of life among people with diabetes is worse than quality of life in the general population.

Ware and colleagues published data based on responses to the 1990 National Health Survey of Functional Status,[30,102,103,104] which included a sample of 541 people with Type 2 diabetes. They found that those with diabetes reported lower quality of life than the general population on the scales of SF-36 assessing physical functioning, role functioning and general health perception, but differences were not significant on SF-36 scales measuring social functioning and mental health. Other studies comparing diabetics versus control groups found similar results.[85,105-111] Nevertheless all studies could show that differences were not seen on all scales of the psychometric instruments, which reinforces the point that certain disease and demographic characteristics may powerfully affect quality of life in people with diabetes, while diabetes per se may not.[15]

Diabetes and other chronic conditions

Rubin et al. investigated this issue in 1999[15] in en extensive literature review. They concluded that because most studies do not generate estimates for subsamples of diabetic subjects who vary by disease or demographic characteristics which are strongly associated with quality of life, it is not possible to conclude that quality of life differences are due to diabetes per se rather than some other characteristic associated with diabetes. Nor is it possible to conclude which subgroups of diabetes patients have better or worse quality of life than non-diabetic comparison groups.

Impact of bariatric surgery on diabetes

Weight gain and obesity are driving the global epidemic of type-2 diabetes through metabolic and inflammatory pathways. Insulin resistance and impaired pancreatic beta-cell function, are the two important factors that are directly responsible for the development of this disease in susceptible populations. Lifestyle methods and modest weight loss are powerful in preventing and managing type-2 diabetes, but sustaining substantial weight loss is problematic. Bariatric surgery provides exceptional sustained weight loss and remission of type-2 diabetes in 50-85% of subjects, especially if treated early before irreparable beta-cell damage has occurred. In addition, there is substantial evidence that bariatric surgery provides additional comorbidity and quality-of-life improvements and reduces mortality in patients with type-2 diabetes. An association between the extent of weight loss and remission of type-2 diabetes has been shown.[112] Diversionary bariatric procedures such as gastric bypass and biliopancreatic diversion induce a rapid non-weight-loss-associated improvement in glycemic control.

Several mechanisms have been proposed for this exciting and novel effect that may provide key insights

into the pathogenesis of type-2 diabetes. A range of novel surgical, endoluminal procedures/devices, and pharmacologic therapies are likely to evolve when we better understand how bariatric surgery enables long-term changes in energy balance and non-weight-related metabolic improvements. Bariatric surgery should be considered for adults with BMI > or = 35 kg/m^2 and type-2 diabetes, especially if the diabetes is difficult to control with lifestyle and pharmacologic therapy. Although all bariatric procedures produce exceptional results in the management of type-2 diabetes, the choice of procedure requires a careful risk-benefit analysis for the individual patient.[113]

There is currently a global pandemic of obesity and obesity-engendered comorbidities; in particular, certain major chronic metabolic diseases (eg, type 2 diabetes) which markedly reduce life expectancy and quality of life and that metabolic/bariatric surgery is a highly successful therapeutic option for obesity and diabetes.[114,115,116]

Ikramuddin found in his cost-effectiveness that bariatric surgery is not cost-effective over shorter time horizons, or if the negative quality-of-life impact of increased body mass index is ignored.[116] Depending on the surgical procedure the effects are different. In the latest analyses by Inabenet 23,106 patients were investigated regarding the resolution of diabetes. The 12-month remission rate of diabetes was least for gastric banding (28%) compared with the other procedures (RYGB 62%, sleeve gastrectomy 52%, BPD/DS 74%).[123]

Quality of life after bariatric surgery

Various studies have shown that quality of life is improving after bariatric surgery in relation to weight reduction and improvement of comorbidities.[117-122] Comparative studies between diabetics and non-diabetics are still missing, but various studies have shown that diabetes is rapidly improving with bariatric surgery and therefore improvement in Quality of Life is to be expected.

Quality of life in diabetic patients after bariatric surgery

In our own data we have been using prospective data from a group of total 524 patients which underwent bariatric surgery in between 2001 and 2005.

The data were collected in an ongoing prospective longitudinal survey executed in a single center in Germany. All patients underwent standardized presurgical evaluation and all procedures were performed laparoscopically. Evaluation took place 1 day prior to surgery, after 1, 3, 6, 9, and 12 months, and then at yearly intervals. 3 standardized surgical procedures were evaluated:Adjustable Gastric banding, Roux-en-Y gastric bypass, and BPD-Scopinaro.

Table I
Measurement instrument for HRQL-overview

Generic questionnaires	Medical Outcomes Study (MOS) SF-36, SF-20, SF-12
	Rand Quality of Well-Being Self-Administered survey (QWB-SA)
	Sickness Impact Profile
	Nottingham Health Profile
Diabetes-Specific questionnaires	Diabetes Quality of Life (DQOL) measure
	Diabetes-39 instrument
	Problem Areas in Diabetes (PAID) Survey
	Diabetes Treatment Satisfaction Questionnaire (DTSQ)

Sociodemographic (sex and age) and clinical data (current weight, height, metabolic, pulmonary, cardiovascular, or other comorbidities) were evaluated with the 16-item Non-Quality of Life (NQoL) scale of the Bariatric Quality of Life Score (BQL) index. Therefore group splitting according to comorbidities could be done. For comparative purposes, we administered 4 questionnaires to all patients: the BQL, the Short Form 12 (SF-12v2; short form of the MOS), the Gastrointestinal Quality of Life Index (GIQLI) and the Bariatric Reporting and Outcome System (BAROS). The old version of the BAROS with the 5-point Likert scale MA-I-QoL questionnaire was used, since the study was started in 2001 and the new version was not available at that time. The BQL consists of a NQoL subscale, which detects comorbidities, side-effects, and medication intake, and a QoL subscale including 14 items with a 5- point Likert scale ranging from 0-5 points.[117]

Mean age was 38.35 years (SD-10.02), the mean BMI was 45.15 kg/m^2 (SD-7.92), and 80.9% of the patients were female. According to the chi-value of 2.61, there was no preference for any type of surgery by the gender of the patients.

We defined 3 groups:

1) Non-diabetic patients (patients, who indicated 0 at the non-QoL-scale of the BQL preoperatively).
2) Diabetic patients with remission of diabetes (patients, who indicated 1 at the non-QoL-scale of the BQL preoperatively and indicated 0 at 6 and 12 months).

Table II
Patient characteristics according to surgery tipe

Type of surgery	*n*	*%*
Gastric Banding	100	19,1
Gastric Bypass	355	67,7
BPD	69	13,2
Total	524	100

Table III
Characteristics of the subgroups

Subgroup	*n*	*%*
No-preop. diabetes	435	83
Diabetes in remission	44	8,4
Diabetes improved	45	8,6
Total	524	100

3) Diabetic patients with improvement of diabetes (patients, who indicated 1 at the non-QoL-scale of the BQL preoperatively and indicated 1 at 6 and 12 months, but did loose either their insulin or their or medication at one of the measurement points).

The lack of the study was that HbA1c levels were not conducted and that the assessment was sole done via the questionnaire. Furthermore no differentiation was made between Diabetes Mellitus Type 1 and Type 2. The retrospective control of this data is currently in process of work.

The data regarding type of surgery are displayed in table I.

As far as the majority of diabetes patients were in the bypass group, there was no differentiation made between the different types of surgery regarding the impact on diabetes, because the separate analysis would not create helpful results. The data regarding the subgroups are displayed in table II. Interestingly all patients with diabetes showed at least an improvement in diabetes after bariatric surgery.

All data were included with had full data (BQL score, SF-12 score, BAROS) available at all Measurement Times at 0,6 and 12 months of surgery. In total data from 286 patients could be included into the evaluation.

As far as that with the BAROS no pre-op data assessment is possible, we defined month 1 as first measurement point.

The Development of BMI is displayed in table III for the different subgroups. All groups had a significant weight loss achieved, there was no significant difference in BMI loss between the groups (fig. 1), so that the sole weight loss cannot be the explanation for the differences measured in Quality of Life in between the groups.

Regarding the evaluation of the Quality of Life in the diabetic patients we evaluated the applicated 3 questionnaires according to the assigned groups and we did find with the BQL significant differences within the groups, especially between patients with remission and non-diabetics. (fig. 2). These results did not show significant correlation to the BMI loss, which emphasizes the fact that the sole BMI loss is not the course for the changes in QoL.

We could show, that obese patients seeking for surgery with Diabetes have a worse quality of life than non-diabetics, but that their quality of life improves with the resolution up to the level of non-diabetics. Moreover we could find a difference between patients in which the diabetes improved and the patients with remission, as far as their levels improve with time and

Table IV
BMI Development within the subgroups

Subgroup	*BMI pre-op*	*BMI at 6 months*	*BMI at 12 months*
No pre-op Diabetes (n = 180)	45,44 ± 7,8	36,36 ± 6,55	32,51 ± 6,01
Diabetes in remission (n = 26)	47,79 ± 6,0	38,20 ± 5,75	34,21 ± 6,06
Diabetes improved (n = 7)	47,3 ± 7,28	38,29 ± 5,76	35,46 ± 5,59
Total (n = 213)	45,79 ± 7,6	36,64 ± 6,45	32,81 ± 6,02

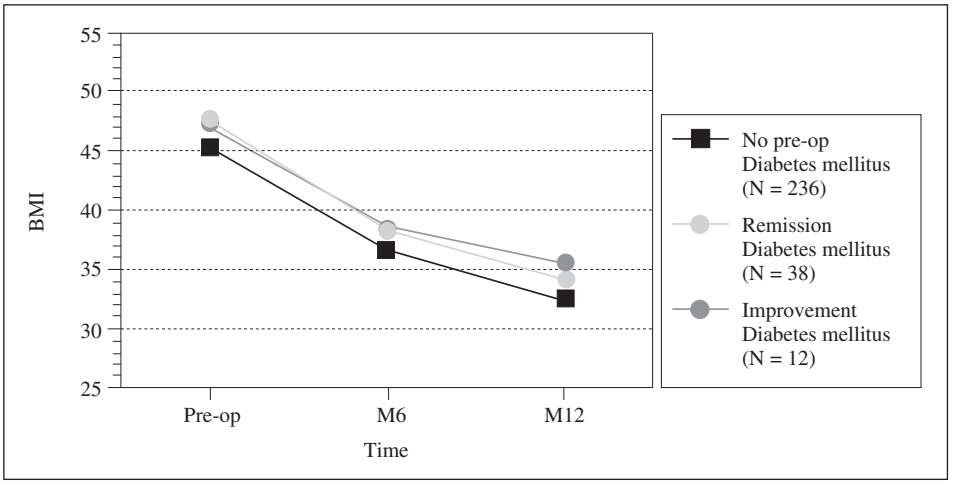

Fig. 2.—BMI loss within the subgroups.

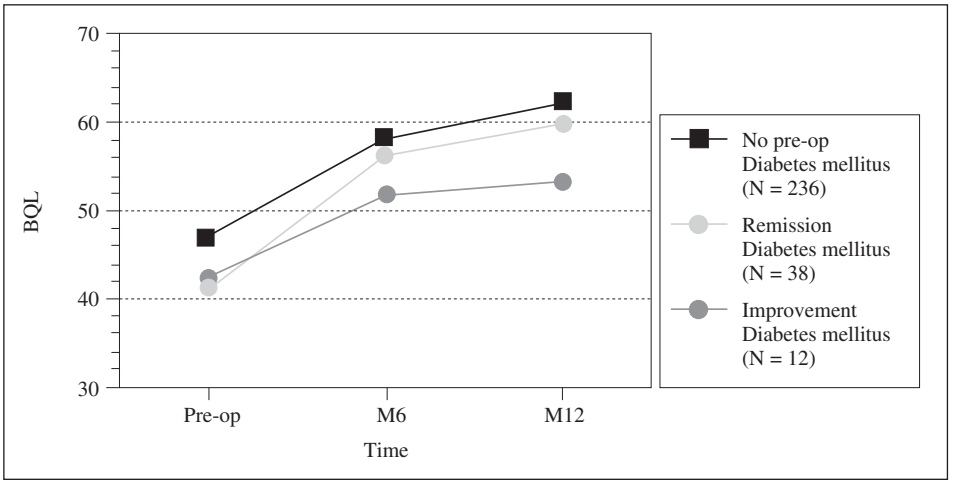

Fig. 3.—Quality of life with time after bariatric surgery (BQL).

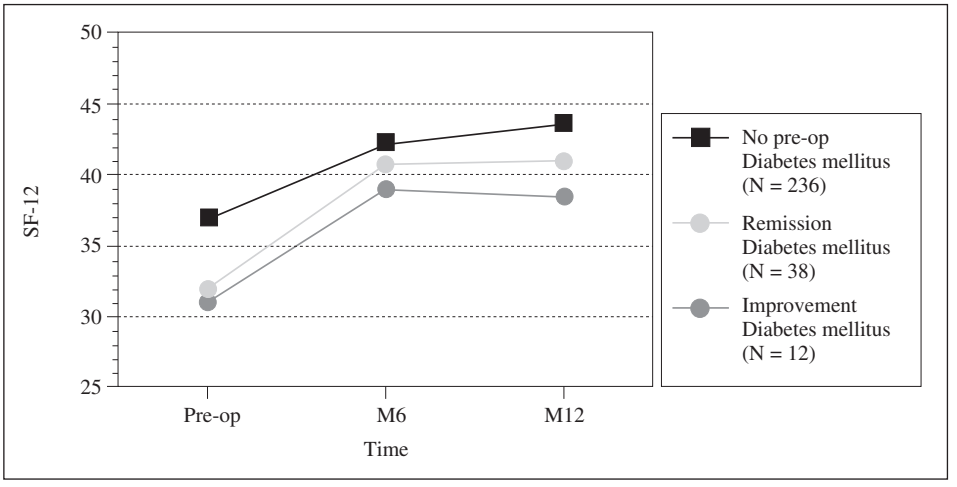

Fig. 4.—Quality of life with time after bariatric surgery (SF-12).

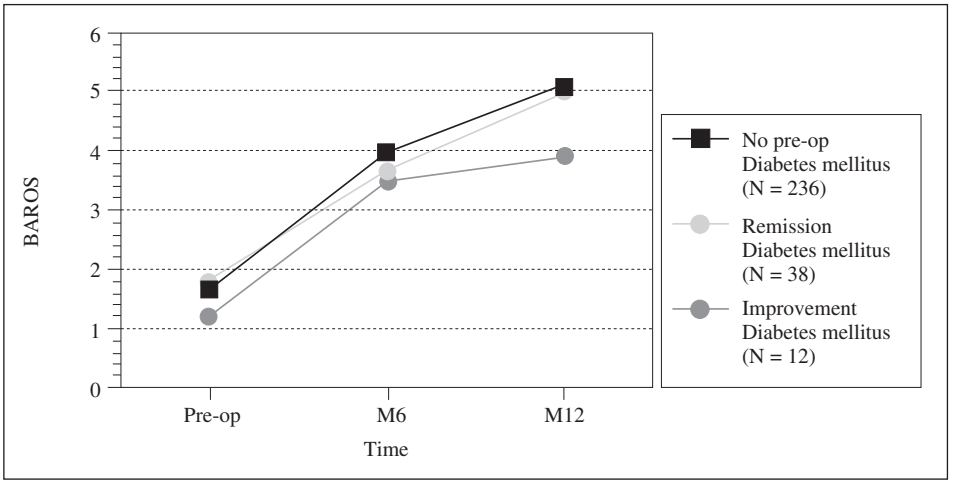

Fig. 5.—Quality of life with time after bariatric surgery (BAROS).

weight loss, but they can not adapt to the level of non-diabetics. These findings are similar to what the experiences from the conservative diabetes treatment have shown, despite the fact that in conservative strategies the remission can not be achieved. Therefore it can be stated that with bariatric surgery obese diabetics profit even more from the surgery than non-diabetics. Regarding these finding it can probably expected that even non-obese diabetics might profit from bariatric surgery regarding their qulity of life. Moreover these

results show, that the BQL is able to measure differences also for this specific issue.

Interestingly we could measure similar results with the MOS Short Form 12 (SF-12), but as expected from the above listed literature from the conservative diabetes treatment investigations the changes are not that strong. With these small numbers no significance could be shown between these groups, but it underlines the results of the BQL. Here again the differences between generic and disease-specific can be detected.

The most interesting result was the data of the applicated BAROS (Bariatric Analysing and Reporting Outcome System) together with the MA-II questionnaire. Even slight differences similar to the results of the BQL and the SF-12 could be seen, but there could be no significance shown. This is probably due to the fact that the weight loss (measured in EWL in %) is part of the final result and gives to much impact on the outcome and therefore the BAROS is not able to detect the differences between the diabetics and non-diabetics.

Conclusions

Can quality of life in people with diabetes be improved?

Several studies describe medical interventions designed to improve health status in people with diabetes, and report assessments of impact on quality of life. Some of these studies implied that patients who had a decrease in HbA1c of 1% were associated with substantial decrements in quality of life, while decreases of the same magnitude showed smaller, but clinically relevant, improvements in quality of life.

Thus, it appears that health-related quality of life in people with diabetes can be improved by certain medical interventions and by educational and counseling interventions designed to enhance coping skills. However, it generally is difficult to know what aspect of the intervention is producing the change in quality of life because all relevant factors were not measured and incorporated into the analysis.

The improvement of glycemic control in diabetics is the leading pattern with regard to the improvement of Quality of Life in patients with diabetes type 1 and 2.[15] Differences between these 2 groups could only be estimated with regard to age. In patients with surgical treatment (various procedures), of the metabolic syndrome quality of life can be improved in all diabetic patients in relation to their glycemic control and their weight loss. It seems that surgery has a stronger impact on the stabilization of the glycemic control in patients with either diabetes type 2 or type 1 than the medical treatments. The effect on the improvement of Quality of Life is more pronounced, when obesity is a coexisting entity. More comparative randomized controlled studies are mandatory to verify this encouraging perspective.

What can be concluded from the actual study?

From the literature it is evident that Quality of life is worse in the diabetic patient. We could show that diabetic patients with obesity have a worsened quality of life compared to obese non-diabetics, as far as no differentiation was made between Diabetes Type 1 and Type 2. QoL improves more in the diabetes patient with remission and/or improvement compared to the non-diabetic group. The better improvement in the diabetic patient is correlated to BMI loss, but the BMI loss does not explain the differences to the non-diabetes group. The BQL as a specific instrument is able to show these differences.

Further investigation needs to be done, regarding the inpact and change of HbA1c levels and the resolution of co-related comorbidities (hypertension etc.)

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Pathophysiology of diabetes mellitus type 2: beyond the duo "insulin resistance-secretion deficit"

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Abstract

T2DM involves at least two primary pathogenic mechanisms: (a) a progressive decline in pancreatic islet cell function resulting in reduced insulin secretion and (b) peripheral insulin resistance resulting in a decrease in the metabolic responses to insulin. This dynamic interaction between insulin secretion and insulin resistance is essential to the maintenance of normal glucose tolerance (NGT). The transition from the normal control of glucose metabolism to type 2 diabetes mellitus occurs through the intermediate states of altered metabolism that worsen over time. The first state of the disease is known as prediabetes, and consists of a set of metabolic disorder characterized by a great hyperglycemia, enough to increase of retinopathies, nephropathies and neuropathies incidence.

If we advance in the T2DM temporal sequence we found a remarkable change in the pancreatic cells population that form the Langerhans islets, mainly caused by amylin fibers accumulation over these cells from polypeptide hormone called amyloid polypeptide or IAPP. The IAPP hypersecretion and amylin fibers deposition attached to the endoplasmic reticulum stress caused by excessive workload due to biosynthesis overproduction of insulin and IAPP result in β-cell apoptosis. In addition to these alterations, we must also consider the changes observed in incretins profiles like GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide 1) directly related to glucose homeostasis maintenance. Risk factors that predispose to a healthy individual to develop T2DM are several, but the most important is the obesity. The body mass index (BMI) has been used in numerous epidemiological studies as a powerful indicator of T2DM risk. Lipotoxicity caused by circulating free fatty acids increased, changes in lipoprotein profiles, body fat distribution and glucotoxicity caused by cells over-stimulation are other risk factors to consider in T2DM developing.

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Key words: *Diabetes. Insulin resistance. Glucose.*

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FISIOPATOLOGÍA DE LA DIABETES MELLITUS TIPO 2: MÁS ALLÁ DEL DÚO "RESISTENCIA INSULINA - DÉFICIT DE SECRECIÓN"

Resumen

El desarrollo de la DMT2 está provocado principalmente por dos mecanismos patogénicos: (a) un progresivo deterioro de la función de las células de los islotes pancreáticos que provoca una disminución de la síntesis de insulina y (b) una resistencia de los tejidos periféricos a la insulina que da como resultado un descenso de la respuesta metabólica a la insulina. Esta interacción entre la secreción y resistencia a la insulina es esencial para el mantenimiento de una tolerancia normal de la glucosa. El desarrollo de la diabetes mellitus tipo 2 puede describirse como una serie de alteraciones celulares y metabólicas que afectan y deterioran la homeostasis de la glucosa. La transición desde el control normal del metabolismo de la glucosa a la diabetes mellitus tipo 2 se produce a través de estados intermedios alterados de dicho metabolismo que empeoran con el tiempo. El primer estado de la enfermedad se conoce como prediabetes, y consiste en un conjunto de desordenes metabólicos caracterizados por una gran hiperglucemia, suficiente para incrementar la incidencia de retinopatías, nefropatías y neuropatías.

Cuando avanzamos en la secuencia temporal de la DMT2 encontramos una notable alteración en la población de células del páncreas que componen los islotes de Langerhans, provocada principalmente por la acumulación sobre estas células de fibras de amilina procedentes de la hormona polipeptídica llamada polipéptido amiloide de los islotes o IAPP. Esta hipersecreción de IAPP y deposición de fibras de amilina junto al estrés del retículo endoplásmico provocado por el exceso de carga de trabajo debido a la sobreproducción en la biosíntesis de insulina e IAPP dan como resultado la apoptosis de las células β. A todas estas alteraciones debemos sumar las observadas en los perfiles de incretinas como GIP (glucose-dependent insulinotropic polypeptide) y GLP-1 (glucagon-like peptide 1) relacionados directamente con el mantenimiento de la homeostasis de la glucosa. Los factores de riesgo que predisponen a una persona sana a desarrollar la DMT2 son varios, pero sobresale por encima de todos la obesidad. El índice de masa corporal (IMC) ha sido utilizado en numerosos estudios epidemiológicos como un potente indicador del riesgo de padecer DMT2. La lipotoxicidad causada por el aumento de ácidos grasos libres circulantes, el cambio en los perfiles de las lipoproteínas, la distribución de la grasa corporal y la glucotoxicidad provocada por la sobre-estimulación de las células son otros de los factores de riesgo a tener en cuenta en el desarrollo de la DMT2.

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Palabras clave: *Diabetes. Resistencia a la insulina. Glucosa.*

Background

Type 2 Diabetes mellitus (T2DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia, which results from resistance to insulin actions on peripheral tissues as well as inadequate secretion of insulin[1] and an impaired suppression of glucagon secretion in response to ingested glucose. Thus, T2DM involves at least two primary pathogenic mechanisms: (a) a progressive decline in pancreatic islet cell function resulting in reduced insulin secretion and inadequate suppression of glucagon secretion[3,4] and (b) peripheral insulin resistance resulting in a decrease in the metabolic responses to insulin.[1] It is widely recognized that both insulin secretion and insulin resistance are important elements in the pathogenesis of type 2 diabetes. Subjects with insulin resistance require more insulin to promote glucose uptake by peripheral tissues, and genetically predisposed individuals may lack the necessary β-cell secretory capacity. The resulting insulin deficiency disrupts the regulation of glucose production in the liver and is a clue element in the pathogenesis of glucose intolerance.[5] In populations with a high prevalence of T2DM (eg. obese individuals), insulin resistance is well established long before the development of any impairment in glucose homeostasis, particularly in subjects with abdominal or ectopic (liver, muscle) fat accumulation. However, as long as the beta cell is able to secrete sufficient amounts of insulin to offset the severity of insulin resistance, glucose tolerance remains normal. This dynamic interaction between insulin secretion and insulin resistance is essential to the maintenance of normal glucose tolerance (NGT) and interruption of this crosstalk between the beta cell and peripheral tissues results in the progressive deterioration of glucose homeostasis.

The pathogenic mechanisms in T2DM involve not only insulin, but also glucagon, and it is the interplay between these two processes the key component in the understanding of the pathophysiology of T2DM. The prevalence of T2DM, its specific complications and the presence of other diseases that often accompany T2DM make this disease one of today's main social and public health problems.

Development of T2DM

Our knowledge about the time sequence, in which all cellular and metabolic alterations are developed during different disease stages are still insufficient. Which are the cellular and metabolic events chain and what are the main risk factors that cause the transition from a normal glucose homeostasis to DMT2 are questions to be answered in the near future.

Following glucose ingestion, the balance between endogenous glucose production and tissue glucose uptake is disrupted. The increase in plasma glucose concentration stimulates insulin release from the pancreatic beta cells, and the resultant hyperinsulinemia and hyperglycemia serves to stimulate glucose uptake by splanchnic (liver and gut) and peripheral (primarily muscle) tissues and to suppress endogenous glucose production by the liver.[6,7] Hyperglycemia, in the absence of hyperinsulinemia, exerts its own independent effect on muscle glucose uptake and suppress endogenous glucose production in a dose dependent fashion. The majority (~80-85%) of glucose that is taken up by peripheral tissues, in an insulin dependent manner, is disposed of in muscle, with only a small amount (~4-5%) being metabolized by adipocytes. Another 10% is disposed of by splanchnic tissues through non insulin dependent mechanisms. Although fat tissue is responsible for only a small amount of total body glucose disposal, it plays a very important role in the maintenance of total body glucose homeostasis. Insulin is a potent inhibitor of lipolysis and even small increments in the plasma insulin concentration exert a potent antilipolytic effect, leading to a marked reduction in adipose tissue release of fatty acids and subsequently a decrease in plasma free fatty acids (FFA) level. The decline in plasma FFA concentration facilitates an increased glucose uptake in muscle and contributes to the inhibition of hepatic glucose production. Thus, changes in the plasma FFA concentration in response to increased plasma levels of insulin and glucose play an important role in the maintenance of normal glucose homeostasis.[12-15] Glucagon also plays a central role in the regulation of glucose homeostasis.[9,16]

During the post-absorptive state (10-12 hours fasting overnight), hepatic glucose output depends on a delicate equilibrium between basal glucagon secretion (stimulatory effect), and basal insulin secretion (inhibitory effect). Approximately 75% of the total effect depends on the stimulatory action of glucagon.[96]

Normal glucose homeostasis

The metabolic response to ingested carbohydrate is markedly different in individuals with normal glucose tolerance compared to those with T2DM. Individuals with normal glucose metabolism have a typical insulin, glucose, and glucagon profile in plasma in response to the ingestion of a carbohydrate meal.

In the post-absorptive state, the majority of glucose that is removed from the body occurs in insulin-independent tissues. Approximately 50% of all glucose utilization occurs in the brain, another 25% of glucose uptake occurs in the splanchnic area (liver plus gastrointestinal tissues) and the remaining 25% uptake of glucose in the post-absorptive state takes place in insulin-dependent tissues, primarily muscle. Basal glucose utilization averages ~2.0 mg/kg.min and is precisely matched by the rate of endogenous glucose production. Approximately 85% of endogenous glucose production is derived from the liver, and the remaining amount is produced by the

kidney. Approximately half of basal hepatic glucose production is derived from glycogenolysis and half from glyconeogenesis.[6-11]

Prediabetes

Diabetes mellitus is defined as a cluster of metabolic disorders, characterized by hyperglycemia high enough to significantly increase the incidence of a specific an unique type of microangiopathy (retinopathy, nephropathy and neuropathy).

Prediabetes is a condition in which blood glucose levels are higher than normal, but not high enough for a diagnosis of diabetes. Prediabetes, also known as Dysglycemia, usually have no symptoms. People may have this condition for several years without noticing anything. Prediabetes can be separated into two different conditions: impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), depending on the type of test and timing (fasting *vs* postprandial) used for diagnosis.

IFG and IGT represent intermediate states of abnormal glucose regulation that exist between normal glucose homeostasis and diabetes. IFG is now defined by an elevated fasting plasma glucose (FPG) concentration (≥ 100 and < 126 mg/dl).[92] IGT is defined by an elevated 2-h plasma glucose concentration (≥ 140 and < 200 mg/dl) after a 75-g glucose load on the oral glucose tolerance test (OGTT) in the presence of an FPG concentration < 126 mg/dl.[92]

The pathophysiology of IFG seems to include the following key defects: reduced hepatic insulin sensitivity, stationary beta cell dysfunction and/or chronic low beta cell mass, altered GLP-1 secretion and inappropriately elevated glucagon secretion.[93] Conversely, the prediabetic state of isolated IGT (IGT without IFG) is mainly characterized by reduced peripheral (muscle) insulin sensitivity, near-normal hepatic insulin sensitivity and a reduced second phase insulin secretion. Individuals developing combined IFG/IGT exhibit severe defects in both peripheral and hepatic insulin sensitivity, as well as a progressive loss of beta cell function.[93] In conclusion, the transition from the prediabetic states to overt type 2 diabetes is characterized by a non-reversible vicious cycle that includes severe deleterious effects on glucose metabolism.

Type 2 Diabetes and obesity

Obesity is a complex disorder, where genetic predisposition interacts with environmental exposures to produce a heterogeneous phenotype.[17] Today, we know that some of these obesity phenotypes are associated with a high risk of developing T2DM.[18] There is also strong evidence that, for a given adiposity, there is a large heterogeneity in the metabolic risk mainly linked to the location of excessive adipose tissue. Visceral adipose tissue accumulation is an important predictive factor of lipid, glucose or atherogenic disturbances, while location of adipose tissue in the lower part of the body is not associated with increased metabolic alterations.

BMI *vs* DMT2 risk

Many epidemiologic studies have shown that body mass index (BMI) is a powerful predictor of type 2

Table I
Pathophysiology of the prediabetic states

Pathophysiology	*i-IFG*	*i-IGT*	*IFG/IGT*
Muscle			
Insulin sensitivity	Unaltered	Reduced	Reduced
Liver			
Insulin sensitivity	Reduced	Unaltered	Reduced
Hepatic glucose production	Elevated	Unaltered	Elevated
Pancreas			
First-pashe insulin response	Reduced	Reduced or unaltered	Reduced
Disposition index	Reduced	Reduced	Reduced
Glucagon secretion	Elevated	Elevated	Elevated
Gut			
GLP-1 secretion	Reduced or elevated	Reduced or elevated	¿?
GIP secretion	Unaltered	Reduced or elevated	¿?
Adipose tissue			
Insulin sensitivity	Reduced	Reduced	¿?
NEFA release	Unaltered	Elevated	¿?
Adipocytokine release	¿?	¿?	¿?
Brain	¿?	¿?	¿?
Kidney	¿?	¿?	¿?

diabetes.[19,20] For example, Field et al.[21] reported that both men and women with a BMI of 35.0 were 20 times more likely to develop diabetes than were their same-sex peers with a BMI between 18.5 and 24.9. In another investigation from the Nurses' Health Study, overweight and obesity was the single most important predictor of type 2 diabetes in 30-55-y-old women.[22]

Furthermore, this general obesity measure has consistently been associated with adverse health outcomes, but certain sub-phenotypes of obesity have been recognized that appear to deviate from the apparent dose-response relationship between BMI and its consequences. Ruderman and others[23,24] identified metabolically obese normal-weight (MONW) individuals who, despite having a normal-weight BMI, demonstrate metabolic disturbances typical of obese individuals. These disturbances include insulin resistance (IR) and increased levels of central adiposity, low levels of high density lipoprotein-cholesterol (HDL-C) and elevated levels of triglycerides, dysglycemia and hypertension. This clustering of risk factors has been called the metabolic syndrome (MetS).[25] Others have described metabolically healthy obese (MHO) individuals, who, despite having BMI exceeding 30 kg/m^2, are relatively insulin sensitive and lack most of the metabolic abnormalities typical of obese individuals.[26,27] MONW and MHO individuals are interesting because these phenotypes separate obesity from its usual metabolic consequences, offering insight into risks associated with risk factor clustering or IR that are largely independent of overall obesity (MONW) or risks associated with obesity that are largely independent of adiposity's intermediate metabolic abnormalities (MHO). Characteristics of BMI-metabolic risk sub-phenotypes have been described in selected study samples, but their prevalence in a community-based sample is not well established.

Fat distribution *vs* T2DM risk

It has been theorized that the reduced normal inhibitory action of insulin ("insulin resitance") on Hormone Sensitive Lipase (HSL) in adipocytes, accelerates lipolysis and raises the levels of FFAs, which worsen both peripheral and hepatic insulin resistance.[28] However, despite the strong association, visceral fat does not seem to have a direct role in the development of peripheral insulin resistance. On the other hand, visceral fat is an important source of inflammatory cytokines such as TNF-alpha, TGF-beta, and IL6 that. can directly affect insulin-mediated glucose uptake.[29] Visceral adipocytes are more sensitive than subcutaneous adipocytes to the catecholamines (mainly epinephrine), ACTH and glucagon lipolytic effects and less sensitive to the insulin antilipolytic and fatty acid re-esterification effect,[29] a phenomenon which could further enhance free fatty acids efflux (FFA) in those who are predisposed to store fat in the visceral area. Furthermore, the venous effluent of visceral fat depots leads directly into the portal vein, resulting in greater FFA flux to the liver in viscerally obese individuals than in those with predominantly subcutaneous obesity. Although visceral fat depots have been estimated to represent only approximately 20% of total body fat mass in men and 6% in women,[31,32] approximately 80% of hepatic blood supply is derived from the portal vein.[33] This not only promotes hepatic fat accumulation but can also cause hepatic insulin resistance.[34] While there is a consensus that visceral fat has a strong association with cardiovascular risk factors, particularly dyslipidemia, hypertension and hyperinsulinemia,[35] this relationship has been challenged by Abate et al.[36] and Goodpaster et al.[37] These researchers found that abdominal subcutaneous fat, as determined by magnetic resonance imaging and computed tomography, was at least as strong a correlate of insulin sensitivity (evaluated by the euglycemic clamp) as visceral fat and retained independent significance after adjusting for visceral fat.[37]

Cellular and metabolic disorders

Insulin resistance requires increased insulin output both in the basal state and in response to stimulation, to maintain normal glucose tolerance, whereas improvements in insulin sensitivity place the β-cell in the position of having to reduce insulin release to avoid hypoglycemia. These changes in insulin sensitivity that require adjustment of insulin output can occur quite rapidly or over longer periods of time.[44,45] The mechanisms responsible for these changes clearly vary and involve changes in both β-cell function and β-cell mass, although in most instances it appears that functional changes predominate (at least in the short term). In addition to functional adaptation to such rapid changes in insulin sensitivity, the β-cell must also alter its activity when this critical modulator changes for more prolonged periods. Under such conditions one envisages both -cell secretory function and β-cell mass playing complementary roles.

Islets of Langerhans Dysfunction

The most notable alteration that occurs in the islets of Langerhans in type 2 diabetes is the amyloid deposition derived from the polypeptide hormone islet amyloid polypeptide (IAPP, "amylin"). In 1986 it was understood that it is a polymerization product of a novel β-cell regulatory product.[46,47] It has been argued that the amyloid may not be of importance since there is no strict correlation between the degree of islet amyloid infiltration and the disease. However, it is hardly discussable that the amyloid is important in subjects where islets have been destroyed by

pronounced islet amyloid deposits. Even when there is less islet amyloid the deposits are widely spread, and -cells show ultrastructural signs of cell membrane destruction.[48,49] It is suggested that type 2 diabetes is heterogeneous and that in some individuals aggregation of IAPP into amyloid fibrils could determine a progressive loss of β-cells.

Loss of mass and β-cell function

As in DMT1, prospective studies of DMT2 indicate a progressive decline in -cell function preceding relatively abrupt diabetes onset.[50,51] However there is no means to establish to what extent, if at all, this decline in β-cell function is due to impaired β-cell mass or simply due to declining function. Autopsy studies of patients with T2DM have revealed a β-cell mass of ~0-65% compared to body mass index matched non-diabetic patients controls.[52] There is also increased β-cell apoptosis compared to controls,[53] implying that the loss of β-cell mass is likely progressive unless there is concurrently increased β-cell formation. In a study in which pancreatic tissue from patients with type 2 diabetes mellitus and control subjects was obtained from 124 autopsies, the rate of β-cell replication and neogenesis was similar (indeed, very low) in all cases, with no difference between diabetic and control groups. However, the frequency of β-cell apoptosis was increased 10-fold in the lean and 3-fold in the obese cases of type 2 diabetes (64, 65). So that, the real determinant of lower β-cell mass in T2DM is an increased rate of apoptosis.

Several studies have linked type 2 diabetes with a variety of proapoptotic mechanisms,[60] including glucose-induced synthesis of IL-1,[61,62] endoplasmic reticulum (ER) stress,[63] mitochondrial overload and pro-islet amyloid polypeptide secretion.[66] Given the wide range of β-cell mass in nondiabetic humans, the possibility exists that vulnerability to T2DM is based in part upon the β-cell mass accomplished as an adult. In the face of insulin resistance, those individuals with the lowest β-cell mass would have the highest requirement per β-cell for pro-insulin and pro-islet amyloid polypeptide synthesis and processing.

– *Disposition index:* Current evidence points to β-cell dysfunction as the first demonstrable defect with limited capacity to compensate for the presence of insulin resistance. However, the modulating effect of insulin sensitivity on β-cell function has to be considered for the assessment of insulin release in individuals at risk of developing DM2. The nature of this relationship is such that insulin sensitivity and β-cell function are inversely and proportionally related, whereby the product of these two parameters is constant, being referred to as the disposition index,[54] and in turn can be interpreted as a measure of the ability of the β-cell to compensate for insulin resistance. Mathematically, this relationship is described by the hyperbolic relationship between the acute insulin response (AIR) and the metabolic action of insulin to stimulate glucose disposal (M) and is referred to as glucose homeostasis, with glucose concentration assumed to remain constant along the hyperbola.

Loss of α-cell function

Despite the importance of the α-cell and glucagon secretion in the regulation of glycaemia and nutrient homeostasis, little is known about the physiology of these cells compared with the overwhelming information about β-cells. Several factors may explain this lack of information regarding glucagon secretion. First, the scarcity of this cell population in islets of animal models such as mice and rats along with several technical limitations of conventional methods for evaluation of α-cell function has made it more difficult to study α-cell s than beta-cells.[55] Second, the lack of functional identification patterns has also been an important limitation in α-cell research. Abnormal α-cell function is an important determinant of the magnitude of hyperglycemia found in diabetes.

The evidence for this can be summarized as follows: Fasting hyperglycemia and insulin requirements are lower in pancreatectomized patients lacking glucagon.[56] Moreover, in such individuals[56] and in insulin-dependent diabetics whose glucagon secretion is suppressed with somatostatin,[57] hyperglycemia following acute withdrawal of insulin is markedly diminished. The failure to suppress glucagon secretion appropriately after meal ingestion increases postprandial hyperglycemia in people with impaired glucose tolerance and diabetes. Nevertheless, the above studies suggest association, and investigations using selective glucagon secretion or receptor antagonists would help to fully evaluate contribution of glucagon dysfunction in the pathogenesis of diabetes.[58]

Lipotoxicity

Diabetes is associated with dyslipidemia and characterized by an increase in circulating free fatty acids (FFAs) and changes in lipoprotein profile. In healthy humans, besides the insulin resistance and hyperinsulinemia induced by an acute elevation of FFAs, there is also an increase in glucose-stimulated insulin secretion after prolonged "low grade" FFA infusion (48 and 96 h)[37,38] but not in nondiabetic individuals genetically predisposed to developing DM2.[38] In healthy control subjects, the FFA-induced insulin resistance was compensated by the enhanced insulin secretion, whereas persistently elevated FFAs may contribute to progressive β-cell failure (β-cell lipotoxicity) in individuals genetically predisposed to DMT2 and also has been implicated as an acquired cause of impaired β-cell

function, as individuals progress from IGT to overt type 2 diabetes mellitus. Within the beta cell, long-chain fatty acids are converted to their fatty acyl-CoA derivatives, which lead to increased formation of phosphatidic acid and diacylglycerol. These lipid intermediates activate specific protein kinase C isoforms, which enhances the exocytosis of insulin. Long-chain fatty acyl-CoA also stimulate exocytosis, cause closure of the K+-ATPase channel, stimulate Ca2+-ATPase and increase intracellular calcium, thus augmenting insulin secretion. In contrast to these acute effects, chronic beta cell exposure to elevated fatty acyl-CoA inhibits insulin secretion through operation or activation of the Randle cycle. Increased fatty acyl-CoA levels within the beta cells also stimulate ceramide synthesis, which augments inducible nitric-oxide synthase. The resultant increase in nitric oxide increases the expression of inflammatory cytokines, including interleukin-1 and tumor necrosis factor alfa, which impair β-cell function and promote beta cell apoptosis.

Glucotoxicity

Unger and colleagues first introduced the concepts of glucotoxicity.[59] In their initial glucose toxicity paper, they put forward the concept that continuous overstimulation of the β-cell by glucose could eventually lead to depletion of insulin stores, worsening of hyperglycemia, and finally deterioration of β-cell function. The main action of the glucotoxicity on the pathophysiology of T2DM is the formation of reactive oxygen species (ROS) through its relationship with oxidative stress that affects the beta cells. Reports that β-cells have very low levels of antioxidant enzymes compared with other tissues suggest that the β-cell is particularly vulnerable for oxidative stress.[67]

Once glucose enters cells, it is primarily and progressively metabolized to glyceraldehyde-3-phosphate, 1:3 bis-P-glycerate, glyceraldehyde-3-phosphate, and pyruvate. Pyruvate then enters the tricarboxylic acid cycle to undergo oxidative phosphorylation, during which formation of ATP and ROS occurs. However, when excess glucose is available to the cell, alternative pathways exist through which excess glucose can be shunted and ROS can be formed from glucose.[66]

Alterations in incretins profiles

To date, only glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide 1 (GLP-1) fulfill the definition of an incretin hormone in humans. Furthermore, studies have shown that these two peptides potentiate glucose-stimulated insulin secretion in an additive manner, likely contribute equally to the incretin effect and together can fully account for the majority of the incretin effect in man. The actions of both are receptor-mediated. Incretins bind to specific heterotrimeric membrane receptors in beta cells, resulting in activation of adenyl cyclase and increased cellular cAMP levels, enhancing in this way the release of insulin. The profiles of these two incretins are altered in patients with T2DM.[68] While GIP concentration is normal or modestly increased in patients with T2DM[84] the insulinotropic actions of GIP are significantly diminished.[85] Thus, patients with T2DM have an impaired responsiveness to GIP with a possible link to GIP-receptor downregulation or desensitization. In contrast to GIP, the secretion of GLP-1 has been shown to be deficient in patients with T2DM.[85]

– *GLP1: Secretion, metabolism and influence in T2DM:* Glucagon-like peptide 1 (GLP-1) is an intestinal hormone that exerts profound effects in the regulation of glycemia, stimulating glucose dependent insulin secretion, proinsulin gene expression, and -cell proliferative and anti-apoptotic pathways, as well as inhibiting glucagon release, gastric emptying, and food intake.[69] Although the proglucagon gene is expressed in enteroendocrine L-cells and pancreatic β-cells,[70] GLP-1 is synthesized by post-translational processing of proglucagon only in the intestine. The L-cells are predominantly located in the ileum and colon, although have also been localized in the stomach and proximal gut[98] and have been identified as open-type epithelial cells that are in direct contact with nutrients in the intestinal lumen.[71] Furthermore, L-cells are located in close proximity to both neurons and the microvasculature of the intestine,[72,73] which allows the L-cell to be affected by both neural and hormonal signals. Bioactive GLP-1 exists in two equipotent forms, GLP-$1^{7\text{-}36\ NH2}$ and GLP-$1^{7\text{-}37}$, in the circulation, of which the first one is predominant.[74] Secreted GLP-1 is rapidly degraded by the ubiquitous enzyme dipeptidyl peptidase IV (DPP-IV),[75] resulting in an extremely short half-life for GLP-1 of ~2 min.[74] Nutrient ingestion is the primary physiological stimulus to the L-cell and results in a biphasic pattern of GLP-1 secretion. An initial rapid rise in circulating GLP-1 levels occurs 15-30 min after a meal, followed by a second minor peak at 90-120 min.[76] Glucose and fat have been found to be potent stimulators of GLP-1 secretion when ingested,[77] but also after direct administration into the intestinal lumen[75,78] or into perfused ileal segments (79). Unlike glucose and fat, protein does not appear to stimulate proglucagon-derived peptide secretion from L-cells,[77] although protein hydrolysates have been found to stimulate GLP-1 release in a perfused rat ileum model and in inmortalized human L-cells.[79,80] Several studies suggest that impairments at the level of the L cell may account, at least in part, for the reduced GLP-1 secretion that is observed in patients with type 2 diabetes,[81,82] as well as in obesity.[83] This common view that GLP-1 secretion in T2DM patients is deficient and that this applies to a lesser degree in individuals with impaired

glucose tolerance has been recently review by Nauck et al.[98] This review summarises the literature on the topic, including a meta-analysis of published studies on GLP-1 secretion in individuals with and without diabetes after oral glucose and mixed meals and the findings does not support the contention of a generalized defect in nutrient-related GLP-1 secretory responses in type 2 diabetes patients, which has been the rationale for replacing endogenous incretins with GLP-1 receptor agonists or re-normalising active GLP-1 concentrations with dipeptidyl peptidase-4 inhibitors.[98]

– *GIP: Secretion, metabolism and influence in T2DM:* GIP is a single 42 amino acid peptide derived from the processing of a 153 amino acid precursor, whose 10 Kb spanning gene is located on chromosome 17 in humans. Is secreted in a single bioactive form by K cells and released from the proximal small intestine (duodenum and jejunum), in response to the oral ingestion of carbohydrates and lipids. GIP receptors are expressed in the pancreatic islets, gut, adipose tissue, heart, pituitary, adrenal cortex and in several regions of the brain.[88] As GLP-1, GIP is rapidly degraded by the enzyme DPP-IV, that cleaves the biologically active forms at the position 2 alanine (N-terminal), resulting in inactive or weak antagonist peptide fragments. When incretins are administered intravenously in normal subjects and in diabetic patients, the plasma half-life (t1/2) of exogenous GIP is about 5-7 minutes.[86,87,97]

These findings suggest that the majority of GIP and GLP-1 released in the portal circulation is inactivated by DPP-4 before entry into the systemic circulation. In addition to cell-surface membrane-bound form, DPP-4 also exists as a soluble protein in the circulation. Thus, a minor amount of secreted incretins reach the pancreatic β-cells. The effects of GIP are mediated after binding to specific plasma membrane receptors. They belong to the 7 trans-membrane-domain receptor family coupled to G proteins. Binding of GIP to their respective receptor causes the activation of adenyl cyclase via G protein, and leads to an increase of intracellular cyclic AMP levels. Subsequent activation of protein kinase-A results in a cascade of intracellular events, such as increased concentrations of cytosolic Ca2+ and, in the case of pancreatic β-cells, enhanced exocytose of insulincontaining granules. Other signalling pathways may also be activated such as MAP kinase, phospho-inositol-phosphate PIP3, and protein kinase B (PKB) pathways.[88] Results of studies in humans as well as studies in mice lacking both the GIP and the GLP-1 receptors showed an additive effect on insulin secretion.[89] There is experimental evidence indicating that GIP regulates fat metabolism in adipocytes, including enhanced insulinstimulated incorporation of fatty acids into triglycerides, stimulation of lipoprotein lipase activity, stimulation of fatty acids synthesis.[90] In addition GIP has been shown to promote β-cell proliferation and cell survival in islet cell line studies.[91]

Summary

The pathophysiology of T2DM is multi-faceted and includes deficient insulin secretion from pancreatic islet cells, insulin resistance in peripheral tissues, and inadequate suppression of glucagon production. These processes result in inadequate uptake, storage, and disposal of ingested glucose accompanied by elevated hepatic glucose production and hyperglycemia. As now believed, insulin resistance is very much part of the natural history of Type 2 diabetes and may be present many years before the clinical diagnosis. Loss of -cell mass in the pancreatic islets can progress to a clinically significant degree even in patients with IGT, such that at the time of diagnosis of DMT2, a significant number of cells may already be lost. The glucose sensitivity of the beta cell is also progressively deteriorated. Thus, early in the development of T2DM, fasting glucose concentrations are often within normal ranges while postprandial hyperglycemia is already present.

Obesity and type 2 diabetes mellitus are linked in several ways. Obesity is implicated in the pathological process culminating in the development of type 2 diabetes[94,95] through the promotion of both insulin resistance and secretion deficit. Fat distribution, in particular visceral fat, with an excess FFA release secondary to lack of inhibition of lipolysis by insulin (insulin resistance at the visceral adipocytes) may aggravate the state through an overstimulation of ectopic fat accumulation in skeletal muscles and liver, which deteriorates insulin sensitivity in these tissues. Moreover, ectopic FFA accumulation in the pancreas, mediated by their fatty acyl-CoA derivatives, can also deteriorate insulin secretion.

The incretin hormones include glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP), both of which may also promote proliferation/neogenesis of beta cells and prevent their decay (apoptosis). Both hormones contribute to insulin secretion from the beginning of a meal and their effects are progressively amplified as plasma glucose concentrations rise. The current interest in the incretin hormones is due to the fact that the incretin effect might be reduced in patients with T2DM, even though this concept has been challenged recently. In addition, there is hyperglucagonaemia, which is not suppressible by glucose and stimulates basal glucose output from the liver. In such patients, the secretion of GIP is near normal, but its effect on insulin secretion, particularly the late phase, is severely impaired. They potentiate glucose-induced insulin secretion and may be responsible for up to 70% of postprandial insulin secretion.

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Influences of the diabetes surgery on pancreatic β-cells mass

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Abstract

In diabetes mellitus type 2 (DMT2), malfunction and apoptosis of β-cell provoke a deficient insulin secretion. Generally, has been sustained that β-cell function is severely compromised in type 2 diabetes before the disease appears and then continues to decrease linearly with time. Diversionary bariatric procedures such as gastric bypass, biliopancreatic diversion, one anastomosis gastric by-pass (BAGUA) and others that bypasses the foregut, induce a rapid non-weight-loss-associated improvement in glycemic control, especially if treated early before irreparable β-cell damage has occurred. The antidiabetic effect of bariatric operations is likely due to the improvement in the hormonal dysregulation associated with the development of diabetes. Now we know that the bariatric surgery through the reorganization of the gastrointestinal tract can affect to β-cells mass homeostasis, stopped apoptosis and stimulate the replication and neogenesis. These effects are caused mainly by three stimuli: caloric restriction, rapid transit of food to the ileum and the exclusion of an intestinal portion including the stomach, duodenum and part of the jejunum. Several mechanisms have been proposed for this exciting effect that may provide key insights into the pathogenesis of type-2 diabetes. All of these mechanisms include from gut hormones such as ghrelin to second messengers such as AKT system or protein kinase B. Although not all the processes involved in the homeostasis of β-cells are clear, we can explain some of the effects of bariatric surgery exerted on this important set of endocrine cells, which are essential in diabetes control.

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Key words: *Bariatric surgery. Pancreas β-cells. Diabetes mellitus.*

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INFLUENCIA DE LA CIRUGÍA DE DIABETES SOBRE LA MASA DE CÉLULAS BETA PANCREÁTICAS

Resumen

En la diabetes mellitus tipo 2 (DMT2) se puede observar una disfunción de las células así como un alto índice de apoptosis, este hecho, da lugar a una deficiente secreción de insulina. La función de este tipo celular se ve gravemente comprometida incluso antes de que aparezcan los primeros síntomas de la enfermedad y luego continúa disminuyendo linealmente con el tiempo. Los procedimientos bariátricos derivativos como el bypass gástrico, la derivación biliopancreática, el bypass gástrico de una anastomosis (BAGUA) y otras técnicas quirúrgicas donde se puentea el intestino proximal, inducen una rápida mejora del control glucémico no asociada a la pérdida de peso, sobre todo si se trata a tiempo, antes de que la enfermedad provoque un daño irreparable en el conjunto de las células pancreáticas. El efecto antidiabético de las operaciones bariátricas se debe, probablemente, a la mejora en la desregulación hormonal asociada con el desarrollo de la diabetes. Ahora sabemos que la cirugía bariátrica mediante la reorganización del tracto gastrointestinal puede afectar a la homeostasis de la masa de células-β, deteniendo la apoptosis y estimulando la replicación y la neogénesis. Estos efectos son causados principalmente por tres estímulos: la restricción calórica, el tránsito rápido de alimentos a través del íleon y la exclusión de una porción intestinal que incluye parte del estómago, el duodeno y una gran porción del yeyuno. Se han propuesto varios mecanismos para explicar este interesante efecto que pueden proporcionar información clave en la patogénesis de la diabetes tipo 2. Estos mecanismos incluyen desde hormonas intestinales tales como la grelina a segundos mensajeros tales como el sistema AKT o la proteína quinasa B. Aunque aun no conocemos todos los procesos implicados en la homeostasis de las células , sí se pueden explicar algunos de los efectos que ejerce la cirugía bariátrica sobre este importante conjunto de células endocrinas, que son esenciales en el control de la diabetes.

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Palabras clave: *Cirugía de la obesidad. Células-β. Diabetes tipo 2.*

Introduction

β-cell mass regulation represents a critical issue for understanding diabetes, a disease characterized by a deficiency in the number of pancreatic β cells. The number of islet β cells present at birth is mainly generated by the proliferation and differentiation of pancreatic progenitor cells, a process called neogenesis. Shortly after birth, β-cell neogenesis stops and a small proportion of cycling β cells can still expand the cell number to compensate for increased insulin demands, but at a slower rate. The low capacity for self-replication in the adult is too limited to result in a significant regeneration following extensive tissue injury. In addition, chronically increased metabolic demands can lead to β-cell failure to compensate. Neogenesis from progenitor cells inside or outside islets represents a more potent mechanism leading to robust expansion of the β cell mass, but it may require external stimuli. Recent studies[1,2] have demonstrated that it is possible to regenerate and expand the β-cell mass using hormones and growth factors like glucagon-like peptide-1, gastrin, epidermal growth factor, and others. Treatment with these external stimuli can restore a functional β-cell mass in diabetic animals.[3]

Malfunction and β-cell apoptosis

The triggering factor in DMT2 is β-cell failure, which involves a decrease in β cell mass and deterioration of key β cell functions such as glucose-stimulated insulin secretion (GSIS). We know that obesity often leads to insulin resistance, but not all obese people develop DMT2. Likewise, we can also see how normal weight people develop insulin resistance just as obese. A study comparing the β cell mass in obese diabetic/obese nondiabetic note that β cells was decrease in individuals with T2DM.[4] Similarly, β cell apoptosis is increased in obese humans with glucose intolerance or diabetes. Genetic background has an important role in determining the susceptibility of β cells to decompensation and progression to DMT2. This is demonstrated using rodent models.[5] Genes responsible for obesity and insulin resistance interact with environmental factors (increased fat/caloric intake and decreased physical activity), resulting in the development of obesity and insulin resistance. These increase secretory demand on β-cells. If the β-cells are normal, their function and mass increase in response to this increased secretory demand, leading to compensatory hyperinsulinaemia and the maintenance of normal glucose tolerance. By contrast, susceptible β-cells have a genetically determined risk, and the combination of increased secretory demand and detrimental environment result in β-cell dysfunction and decreased β-cell mass, resulting in progression to impaired glucose tolerance, followed, ultimately, by the development of DMT2.

The mechanisms through death in the β cell occurs are related to work overload in the endoplasmic reticulum (ER) and constitutive upregulation of pyruvate cycling that affects the performance of the mitochondria and glucose sensitivity. Overnutrition and increased lipid supply induce enzymes of beta-oxidation, such as carnitine palmitoyltransferase-1 (CPT1), resulting in increased acetyl CoA levels, allosteric activation of pyruvate carboxylase (PC) and deregulation of pyruvate cycling. This leads to basal insulin hypersecretion and loss of the glucose-stimulated increment in pyruvate cycling flux, thereby blunting glucose stimulated insulin secretion. Finally, insulin hypersecretion is accompanied by amylin secretion, which in humans can form amyloid fibrils that accumulate at the surface of β-cells to induce dysfunction and apoptotic death. The increased demand for insulin biosynthesis increases demand (workload) in the ER, gradually leading to ER stress and increased protein misfolding. ER stress is initially relieved by the unfolded protein response (UPR), mediated by the transcription factor XBP1, but over time, the UPR becomes less effective and the deleterious effects of ER stress lead to cell death, mediated by IRE1.

AKT cell signaling system is involved in the apoptosis process, in a crucial way. This signaling system is activated through receptors on the cell surface. When

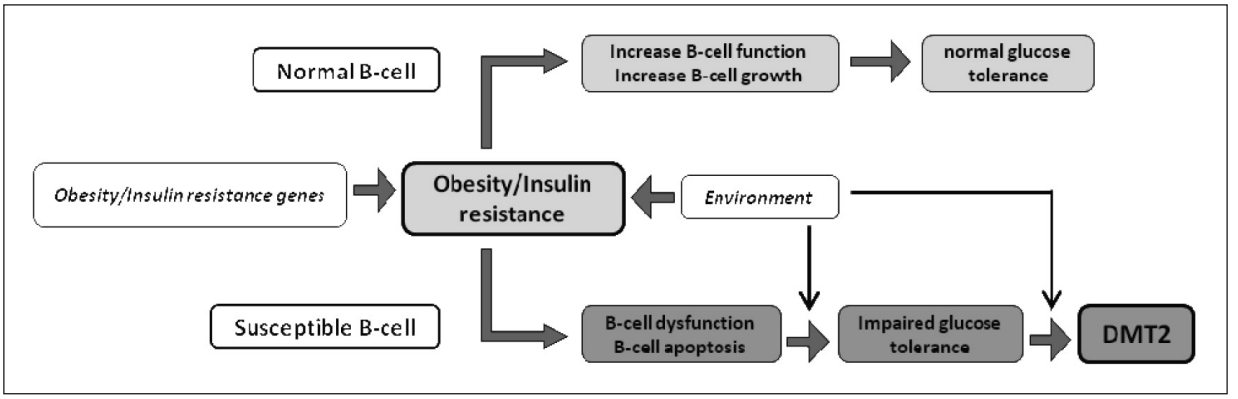

Fig. 1.—Relationship between genes and environment with insulin resistance and its effect on normal β cells and susceptible β cells individuals.

activated induces the production of second messengers as PIP3, phosphatidyl-inositol 3,4,5-triphosphate, which carries the signal from the cell surface to the cytoplasm. PIP3 activates the serine/threonine kinase PDK1 (3-phosphoinositide-dependent protein kinase-1) enzyme, which is able to return activated protein kinase B or AKT. The proteins phosphorylated by protein kinase B promote cell survival and its unphosphorylated form promotes apoptosis.

Regeneration of β-cells

In the remission of T2DM is obvious to think that the recovery of β-cell mass is an important factor. But seems clear that pancreas has a slow rate of β-cell turnover. Whereby β-cells replicate and new islets are formed, probably from exocrine duct cells through the process of neogenesis.[6,7,8] The rate of β-cell replication seems to slow with age and neogenesis can be stimulated by injury. We can cause a chemical damage by administration of streptozotocin or alloxan, two drugs that destroy the β-cell selectively. Another way to study pancreas regeneration is causing tissue damage by surgery, in this case a partial pancreatectomy (70%) or subtotal (90-95%) can be performer. Otherwise, we can use duct ligation like model of tissue injury. In the last case, a partial pancreas destruction and inflammation exist due to exocrine secretion products release. In all experiments, an increase in the mitotic ability of the pancreas occurs after tissue damage, producing a partial regeneration of the endocrine and exocrine pancreas.[9,10] Depending experimental model used, it is observed a higher or lower increase in β-cell replication rate, indicating that endocrine regeneration is caused by a replication increased, similar to observed in the physiological increase which occurs during adult growth. However, in other cases is observed an increase in replication rate of pancreatic ducts and it is possible to measure Pdx-1 expression and insulin in ductal cells.[11] This suggests that in these cases regeneration is produced by a neogenesis activation, through the stem cells or precursor cells activation. The results indicate that these cells will differentiate to β-cell using the same molecular mechanisms that occur during embryogenesis. Moreover it has been demonstrated that exist several substances able to stimulate regenerative processes when administered to animal models. GLP1 promotes the proliferation and neogenesis of -cells, reduces β-cell apoptosis, and increases differentiation of exocrine-like -cells toward a more differentiated β-cell phenotype.[12] The betacellulin, EFGs (epidermal growth factor) growth factor family promotes the regeneration of β-cells in both rats and mice pancreatectomized perfused with alloxan.[13] Also the combination of different factors such as gastrin and EGF, induce β-cell growth in mice treated with alloxan or in mice with a duct ligation.[14] Therefore, we could think that if bariatric surgery is able to stimulate some of these hormones secretion will be able to activate cells replication and neogenesis (small scale).

Bariatric surgery types

Not all bariatric procedures have the same effect on weight loss and diabetes remission, certain procedures are more effective than others and its effect occurs a few days after the intervention. The two major types are classified as purely restrictive procedures and a mix of restrictive and malabsorptive procedures; last one technique includes an intestinal bypass. Purely restrictive procedures (laparoscopic adjustable gastric banding, sleeve gastrectomy, vertical gastroplasty) limit gastric volume and, therefore, restrict the intake of calories by inducing satiety. Afterward, patients lose approximately 10% to 20% of their total body weight. Furthermore, multiple studies, including a randomized controlled trial,[15] have shown remission of type 2 diabetes with these techniques but not with conventional medical therapy. The effect is primarily mediated by weight loss and improved insulin sensitivity, both of which occur several months following surgery. On the other hand, a second category described as intestinal bypass procedures, that include one anastomosis gastric bypass (BAGUA), gastric bypass Y-Roux, biliopancreatic diversion, and other techniques derived from these, have a different mechanism of action. The stomach is partitioned, with the proximal portion then connected to the jejunum. The distal portion of the stomach, duodenum and early jejunum is then connected downstream from the gastrojejunal anastomosis to the mid to distal jejunum. In this type of intervention, type 2 diabetes often resolves within days or weeks after surgery, long before that a significant weight loss has occurred.[16,17]

Bariatric surgery effects

Intestinal reconfiguration provokes by BAGUA, BPD and RYGB procedures causes different stimuli on the gastrointestinal tract. These stimuli are due to the effect of caloric restriction, exclusion of a great part of the stomach and duodenal bypass. Causing, in the case of by-pass, a rapid transit of food through the gut and avoiding contact with that intestinal portion. These effects are related to the rapid remission of T2DM.[18]

Caloric restriction

This effect is produced by the resection of a large part of the stomach, limiting food intake. Caloric restriction lowers blood sugar, resulting in a decrease in insulin secretion. This reduces lipogenesis in white adipose tissue (WAT), thereby decreasing the production of TNFα and increases adiponectin, enhancing

insulin sensitivity in metabolically active tissues such as muscle and liver, again decreasing blood glucose levels.[19] Some studies relate caloric restriction with expression of SIRT-1.[20] This protein, a homolog of the yeast protein silent information regulator 2 (Sir2), which encodes an NAD^+ (nicotinamide adenine dinucleotide) dependent histone deacetylase may play a key role in the regulation of β-cell apoptosis. SIRT1 is only expressed in islets, but not in the exocrine pancreas[21, 22,23] which indicates that SIRT1 may be involved in the special physiological function of islets. The SIRT1 binding promoter region of uncoupling protein 2 (UCP2) directly represses the expression of the UCP2 gene and regulates glucose-stimulated insulin secretion (GSIS). Increased SIRT1 expression significantly promotes GSIS. According to the physiological functions of SIRT1 substrates and the special effects of SIRT1 in islet β-cells, it is reasonable to believe that SIRT1 expression is not only involved in regulating β-cell function to secrete insulin, but also is associated with the apoptosis of β-cells. SIRT 1 inhibits β-cells apoptosis by repressing the UCP2 gene transcription (mitochondrial uncoupling protein), increasing mitochondria energy efficiency and release of the endoplasmic reticulum stress. However, transcription repression of UCP2 by SIRT1 appears to be counteracted during the fast, slowing the synthesis of ATP and insulin response, possibly by a ratio NAD/NADH decrease in the pancreas. SIRT1 also could promote beta-cells survival during oxidative stress by FOXO1 and subsequent activation of transcription factors NeuroD and Mafa, increasing resistance to stress.[24] FOXO 1 activate by SIRT 1 also involved in the regulation of glucose, promoting gluconeogenic gene transcription during stress.

Ghrelin levels decreased?

Ghrelin is a 28-amino acid orexigenic hormone secreted from the duodenum and stomach. In addition to contribute to marked decrease in appetite and food intake observed after bariatric surgery, ghrelin may also improve glucose tolerance. Ghrelin may stimulate insulin-regulating hormones, suppress adiponectin (a hormone insulin sensitizer), decreased hepatic insulin sensitivity at the level of phosphatidyl inositol-3-kinase and inhibit the secretion of insulin by β-cells.[25] The physiological significance of ghrelin as inhibitor of insulin secretion was demonstrated in a study of ghrelin-deficient mice$^{ob/ob}$ which showed low levels of uncoupling protein 2 (UCP2) in pancreatic islets. As seen above, the decrease in the levels of this protein leads to increased insulin secretion and inhibition of β-cell stress, thus improving their survival and function. These mice showed greater sensitivity to insulin and improved glucose tolerance that the mice able to synthesize ghrelin.[110] Because 90% of ghrelin synthesis is performed on that portion of the intestinal tract, which has been excluded from the stimulus of food, is feasible to believe that compromise secretion of ghrelin may contribute to antidiabetes effects of bariatric surgery.[27] Ghrelin levels after these procedures were extremely low throughout the 24-h period, a paradoxical response in the face of profound weight loss. Since then, eight other groups have shown in prospective studies that ghrelin levels fall after bariatric surgery (or at least are more suppressed by food intake), and four cross-sectional studies have confirmed abnormally low levels in operated patients compared with controls.[28] Three other groups found no significant change in human ghrelin levels after bariatric surgery but interpreted this as impairment in the expected increase of ghrelin with weight loss. In contrast, four groups have reported normal increases in ghrelin with surgery induced weight loss. These heterogeneous findings suggest that differences in surgical techniques, possibly involving treatment of the vagus nerve,[29] might account for the disruption of ghrelin secretion in most but not all cases.

Rapid transit of food

The result of this effect is an unabsorbed nutrients increase in the distal intestine, enhancing the release of GLP-1 by L cells, thus improving glucose homeostasis. The original physiological role described for GLP1 was like an incretin hormone that stimulates insulin secretion in a glucose-dependent manner.[30,31] GLP1 also increases transcription of the gene encoding insulin and enhances both the stability of the mRNA encoding insulin and biosynthesis of insulin by mechanisms that involve pathways that are both dependent on and independent of cAMP and protein kinase A, as well as pathways that increase the intracellular concentration of Ca2+. In addition, GLP1 improves β-cell function by inducing the expression of sulfonylurea receptor and inwardly rectifying K+ cannel (KIR6.2) in β-cells. It also prevents the downregulation of mRNA encoding KIR6.2 and the downregulation of ATP-sensitive K+ channel activity induced by high levels of glucose. GLP-1, with PYY and oxyntomodulin are synthesized in the ileum and colon through stimulation of L cells by nutrients. After BPD, the food goes directly from the stomach to the ileum and GLP-1 levels appear unquestionably high. This effect may be less obvious in the case of RYGB because the intestinal bypass is lower. However, have been measured elevated levels of GLP-1, PYY and oxyntomodulin in both types of bariatric surgery.[32] Further support for the effect of rapid transit, comes from ileal interposition procedure. In this type of surgery, a segment of the L-cell-rich ileum is transplanted into the upper intestine near the duodenum-jejunum boundary, thereby increasing its exposure to ingested nutrients. This reconfiguration of the digestive tract provoke a greatly enhances postprandial GLP-1 and PYY levels. Ileal

interposition with no gastric restriction or malabsorption, results in improved glycemic control, with or without weight loss depending on the rodent model or humans studied.[33,34] It is unclear the main process through which it enhances the insulin secretion, as predicted from increases in the incretin GLP-1, or improves insulin sensitivity, and the results of different experiments support both possibilities.

The exclusion of the intestinal segment

Several studies in rats have demonstrated that exclusion of the proximal small intestine from contact with ingested nutrients is a critical component in the mechanism improving glucose tolerance after bariatric operations that bypass the proximal small intestine.[35,36] Dr. Francesco Rubino, with his model of duodenal-jejunal by-pass (DJB), was the first to provide strong evidence supporting this model. In this variant of RYGB, the stomach remains intact but excludes the proximal intestine of food contact.[35] In Goto-Kakizaki rats (GK), used as an experimental animal model of T2DM without obesity, this operation improves diabetes quickly and permanently, even without reduction in food intake or weight loss.[37,38,39] GK rats subjected to DJB with duodenal exclusion followed by DJB without duodenal exclusion, or vice versa, experienced reversible remission and reconstitution of T2DM. Diabetes was eliminated or restored based on the absence or presence, respectively, of nutrient passage through the duodenum.[36] To try to explain these results we must return to the increase in GLP-1 synthesis measured after bariatric surgery with duodenal bypass, which seems to have, as we explained before, an important role in maintaining β-cell mass. The initial rapid rise in GLP-1 secretion must be mediated indirectly, through a neuro/endocrine pathway, rather than through direct interactions of the luminal contents with L-cells.[40] Figure 2 shows GLP-1 secretion regulation by neuro/endocrine pathway. After a meal, nutrients in the duodenum activate a proximal-distal neuroendocrine loop, which stimulates GLP-1 secretion from L-cells in the ileum and colon. In rodents, GIP, released from K-cells, activates vagal afferents, which subsequently causes GLP-1 secretion through vagal afferents and enteric neurons that release acetylcholine (Ach) and peptide release gastrin (GRP). Movement of nutrients toward more distal sections of the intestine leads to the direct interaction of nutrients with L-cells, which also stimulates GLP-1 secretion. Placement glucose or fat into the duodenum of rodents, which were prevented nutrients contact to the ileum, which excluded the possibility of direct interaction between luminal nutrients and L-cells, induced an immediate and prolonged stimulation of the L-cell that was comparable in magnitude to increments in GLP-1 observed when nutrients were placed directly into the ileum.[41] Furthermore, when nutrients were placed in the duodenum of the rat, a prompt rise in glucose-dependent insulinotropic peptide (GIP) levels was also observed, and infusion of GIP or treatment of primary rat L-cells in culture with GIP also stimulated GLP-1 secretion,[42,43] thus implicating GIP in the proximal regulation of GLP-1 secretion. The more important role of the vagus nerve in mediating the proximal-distal

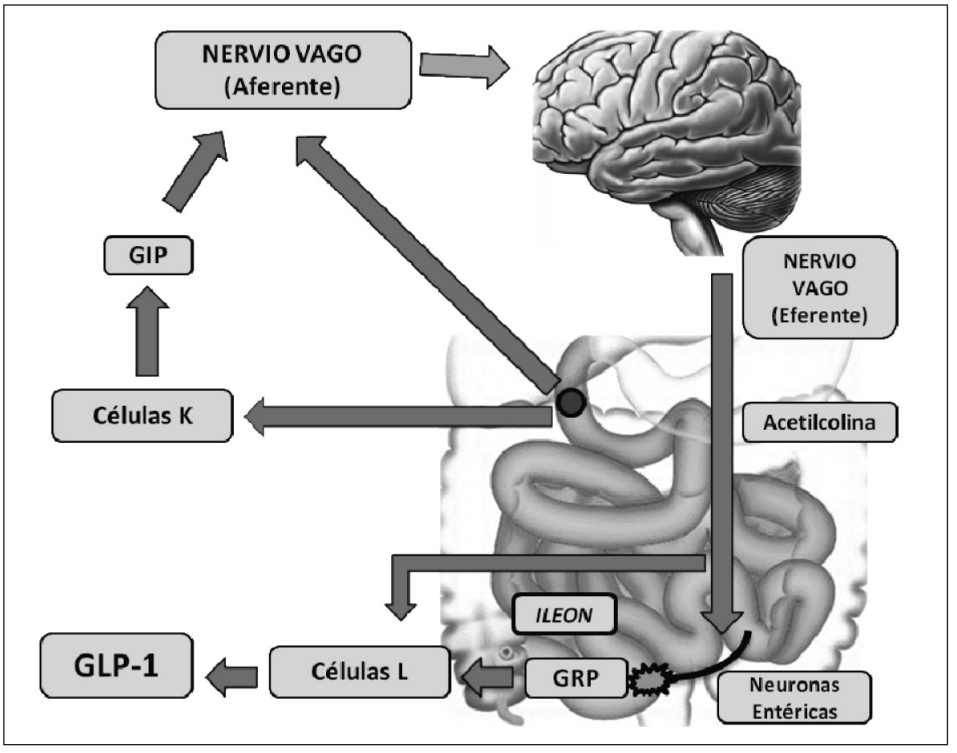

Fig. 2.—GLP-1 secretion regulation by neuro/endocrine pathway.

loop was elucidated when L-cell stimulation by placement of fat into the duodenum or by infusion of physiological concentrations of GIP was completely abrogated by sub-diaphragmatic vagotomy.[42]

Sumary

The studies summarized in this article have greatly advanced our understanding of the molecular and biochemical mechanisms that are involved in the development of type 2 diabetes. In morbid obesity, bariatric surgery with duodenal and proximal jejunum bypass causes rapid and profound metabolic adaptations; insulin sensitivity improves in proportion to the weight loss, and β-cell glucose sensitivity increases independently of weight loss. Furthermore the improvement of glucose homeostasis is greater after this surgery than after other weight loss methods. The mechanisms involved in the remission of T2DM include: 1) caloric restriction, which through the SIRT 1 protein, inhibits beta-cell apoptosis by repressing UCP2 gene transcription (mitochondrial uncoupling protein), increased mitochondrial energy efficiency and the release of endoplasmic reticulum stress. 2) Possible compromised ghrelin secretion in some cases, with decrease in the levels of UCP 2, which leads to increased insulin secretion and inhibition of β-cell stress, thus improving their survival and function. 3) Enhanced nutrient stimulation of L-cell peptides from the lower intestine provokes a GLP-1 levels increase. This protein, increases transcription of the gene encoding insulin and enhances both the stability of the mRNA encoding insulin and biosynthesis of insulin, improve the beta-cells survival. 4) Exclusion of the upper intestine from contact with ingested nutrients that provoke again GLP-1 increased levels, this time by neuro/endocrine pathway. Moreover, these mechanisms cause deregulations in many hormones and second messengers levels, all related to glucose homeostasis, survival and regeneration of beta cells, and probably additional unknown effects. Characterization and identification of other contributing factors are compelling research objectives that promise not only to guide surgical design but also to reveal novel targets for pharmacological therapy of diabetes. Molecular biology tools including global gene expression analysis and proteomics should be applied on tissue biopsies and isolated cell fractions collected before and shortly after bariatric surgery. Since certain biopsies are difficult to obtain from humans, the rat may be a useful model for studying the acutest well as long-term metabolic effects of bariatric surgery in all tissues.[44, 45]

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Influence of diabetes surgery on gut hormones and incretins

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Abstract

The dramatic rise in the prevalence of obesity and type 2 diabetes mellitus (T2DM) has become a major global public health issue. There is increasing evidence that metabolic surgery is more effective than diet and exercise for diabetes remission and weight loss. Moreover, the rapid time course and disproportional degree of T2DM improvement after metabolic procedures compared with equivalent weight loss with conservative treatment, suggest surgery-specific, weight-independent effects on glucose homeostasis. Gut hormones has been proposed as one of the potential mechanisms for the weight-independent diabetes remission and long-term weight loss after these procedures. In this review we discuss the available current metabolic procedures and we review the current human data on changes in gut hormones after each metabolic procedure.

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Key words: *Bile acid. Metabolic surgery. Enteroinsular axis.*

INFLUENCIA DE CIRUGÍA DIABETES SOBRE HORMONAS INTESTINALES E INCRETINAS

Resumen

El espectacular aumento de la prevalencia de la obesidad y la diabetes mellitus tipo 2 (DMT2) se ha convertido en un importante problema de salud pública mundial. Hay evidencias crecientes de que la cirugía metabólica es más eficaz que la dieta y el ejercicio para remisión de la diabetes y la pérdida de peso. Por otra parte, el inmediato y elevado grado de mejora de la DM2 tras los procedimientos metabólicos en comparación con la equivalente pérdida de peso mediante el tratamiento conservador, sugieren efectos específicos de la cirugía, peso-independientes en la homeostasis de la glucosa. Se han propuesto a las hormonas intestinales como uno de los posibles mecanismos para la remisión de la diabetes peso-independiente y la pérdida de peso a largo plazo la después de estos procedimientos. En esta revisión se discuten los procedimientos metabólicos actuales disponibles y se revisan los datos humanos actuales sobre los cambios en las hormonas intestinales después de cada procedimiento metabólico.

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Palabras clave: *Ácidos biliares. Cirugía metabólica. Eje enteroinsular.*

Introduction

Type 2 diabetes mellitus (T2DM) is a heterogeneous disorder and, while its causes have yet to be fully explained, obesity is considered as the primary risk factor.[1] The term "diabesity" has been used to show the strong relationship between the two conditions.[2] It has been estimated that the risk of developing T2DM is increased 93-fold in women and 42-fold in men who are severely obese compared to those with a normal weight.[3,4] A healthy diet and exercise remain the cornerstones of T2DM treatment; bariatric surgery is undoubtedly more effective in the remission and improvement of T2DM compared to lifestyle modifications and pharmacotherapy.[5] Due to the dramatic effects of these operations on the resolution of T2DM and metabolic syndrome, these procedures are now considered as "metabolic" operations, particularly as many of their metabolic actions occur before any noticeable weight loss.[6,7]

Thus far there is only one randomised controlled trial that has investigated bariatric surgery as a treatment of T2DM compared to conservative non surgical treatment. It compared adjustable gastric banding (AGB) to conventional medical T2DM therapy with a focus on weight loss by diet and exercise. After 2 years, remission of T2DM was significantly higher in those who received surgery (73% *vs* 13%).[5] The Swedish Obese Subjects study, a large cohort prospective study has clearly shown the impressive effects of surgery on the prevention and sustained remission of T2DM (72% at 2 years and 36% at 10 years of patients with T2DM preoperatively remained free of the disorder) when compared with well-matched controls treated medically.[8] A meta analysis that preceded the consensus meeting from the

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American Diabetes Association where complete remission of diabetes was defined as a fasting glucose < 5.6 mmol/L and a HbA1c < 6% after 1 year of treatment,[9] reported that 78.1% of T2DM patients had complete "remission", and the condition was improved or resolved in 86.6% of cases.[10]

The effectiveness and the speed at which T2DM goes into remission differ between the various procedures.[6] The rapid resolution of T2DM cannot entirely be explained by weight loss alone and some procedures like RYGB, biliopancreatic diversion (BPD) and sleeve gastrectomy (SG) improve glycaemia within days, long before any significant weight loss occurs.[6,11,12]

Indeed, there is increasing evidence that alterations in circulating gut hormone concentrations by surgery play a key role in improved glucose homeostasis. As the gastrointestinal tract is the largest endocrine organ in the body, many of these hormones are contributing to the regulation of glucose homeostasis, working through the so-called entero-insular axis.[13]

In this article we will summarise the current evidence on the changes after metabolic procedures in fasting and postprandial circulating levels of the gut hormones. The focus will be on those hormones implicated in glucose and energy homeostasis such as Glucagon like Peptide-1 (GLP-1), Peptide YY (PYY), glucose-dependent insulinotropic polypeptide (GIP) and ghrelin.

Metabolic surgery techniques

During the RYGB the stomach is divided into the upper stomach pouch, which is 15- to 30 mL in volume and the lower, gastric remnant. The stomach pouch is then anastomosed to the jejunum, through a gastrojejunal anastomosis in a so called Roux-en-Y fashion. The continuity of the bowel is restored via a jejunojejunal anastomosis, between the excluded biliary limb and the alimentary limb, performed at 75-100 cm distally from the gastrojejunostomy.[14,15]

SG is a relatively new procedure increasing in popularity. It originated as part of the duodenal switch operation and later has been used as a first stage procedure for the very obese and high risk patients. In SG the stomach is transected vertically creating a gastric tube and leaving a 150 to 200 mL pouch. The remaining stomach is excised.[16]

BPD includes a partial gastrectomy, leaving a 400 mL gastric pouch. The small bowel is divided 250 cm proximally to the ileocecal valve and the alimentary limb is connected to the gastric pouch to create a Roux-en-Y gastroenterostomy. An anastomosis is performed between the excluded biliopancreatic limb and the alimentary limb at 50 cm proximally to the ileocecal valve.[17] In the biliopancreatic diversion with duodenal switch (BPD-DS) a vertical sleeve gastrectomy is constructed and the division of the duodenum is performed immediately beyond the pylorus. The alimentary limb is connected to the duodenum while the biliopancreatic limb is anastomosed to the ileum 75 cm proximally to the ileocecal valve.[18]

Adjustable gastric banding (AGB) involves the insertion of an adjustable plastic and silicone ring around the proximal aspect of the stomach, immediately below the gastroesophageal junction creating a small proximal pouch.[19]

Novel operations are geared toward the treatment of T2DM and not necessarily to induce weight loss per se. Among the most prominent of these operations are the duodenal-jejunal bypass and the ileal interposition. First described by Rubino,[20] the duodenal-jejunal bypass (DJB) is a stomach-sparing bypass of a short portion of proximal intestine, a gastric bypass without the stomach stapling. DJB has been shown to improve T2DM in both lean and obese animal models and it is currently being investigated in early human trials.

The ileal interposition (II), previously called "transposition" involves the removal of a small segment of the ileum with its vascular and nervous supply and its insertion into the proximal small intestine. Overall, early studies of humans undergoing ileal interposition have shown promising results, and the procedure is now combined with SG when weight loss is also desirable [sleeve gastrectomy with ileal interposition (SG-ileal interposition)].[21]

Gut hormones implicated in glucose homeostasis

Enteroinsular axis

The enteroinsular axis as a concept was introduced by Unger and Eisentraut in 1969 and describes the connection between the gut and the pancreatic islets.[22] Creutzfeldt suggested that this axis encompasses nutrient, neural and hormonal signals from the gut to the islet cells.[23] The main gut hormones involved in the enteroinsular axis are GLP-1 and GIP which are also called "incretins", whilst ghrelin and PYY seems to play a less prominant role in glucose homeostasis. The incretin effect, defined by Creutzfeld, describes "the phenomenon of oral glucose eliciting a greater insulin response than intravenous glucose, even when the same amount of glucose is infused or an equivalent rise in glycaemia is caused by the parenteral route".[23] GLP-1 and GIP, which are the dominant peptides responsible for nutrient-stimulated insulin secretion account for 50% to 60% of nutrient-stimulated insulin release.[13,24]

GLP-1

GLP-1 synthesized by the L-cells located mainly in the ileum at the distal gastrointestinal tract. A major physiologic role of GLP-1 is stimulation of insulin release in response to nutrient ingestion. Moreover, GLP-1 exerts its glucose-lowering effects through inhibition of gastric emptying, which delays digestion and blunts postprandial glycaemia, restoration of

insulin sensitivity and inhibition of glucagon secretion. Additionally, GLP-1 acts on the central nervous system to induce satiety and decrease food intake.[24-26]

GIP

GIP is an incretin which is secreted from K cells in the duodenum in response to absorbable carbohydrates and lipids. GIP is degraded rapidly in the plasma by the enzyme dipeptidyl peptidase 4 (DPP4) to GIP,[3-42] which is biologically inactive. The main physiologic role of GIP, which is a less potent insulin secretagogue than GLP-1, is the stimulation of pancreatic β-cells to increase the glucose-dependent insulin secretion.[24,26] Moreover, GIP causes a postprandial rise of glucagon and promotes lipoprotein lipase activity. Its secretion is associated with the induction of β-cell proliferation and the enhanced resistance to apoptosis.[27]

Other gut peptides associated with the enteroinsular axis

Ghrelin

Ghrelin is a peptide mainly produced from the X/A-like cells of the stomach and to a lesser degree from the small intestine and acts on the hypothalamus to regulate appetite. Ghrelin is a known orexigenic hormone, it stimulates appetite and food intake. Furthermore, ghrelin impairs insulin sensitivity and also inhibits insulin secretion. Circulating ghrelin concentrations increase with fasting and decrease following nutrient ingestion. Moreover, ghrelin levels increase with diet-induced weight loss.[25,28]

PYY

PYY is a peptide released into the circulation by intestinal endocrine L-cells of the distal gut following food ingestion along with GLP-1. PYY is released postprandially in proportion to the calories ingested and has an inhibitory effect on gastrointestinal mobility. It increases satiety, reduces food intake and delays gastric emptying.[25,29,30] In addition to regulating appetite and body weight, PYY exerts glucoregulatory properties especially in rodents.[25] Thus, elevated levels of PYY after bariatric surgery could contribute to the improved glucose homeostasis.

GLP-1 levels after metabolic surgery

GLP-1 levels after RYGB

In the vast majority of the studies, fasting GLP-1 levels do not change significantly postoperatively and only a few studies have reported increased levels postoperatively.[31-45] Postprandial GLP-1 levels are increased after RYGB and have a higher peak at 15 to 30 minutes after meal ingestion compared to preoperative responses.[31,36,43] The postprandial GLP-1 levels gradually increase during the first two years after the operation.[41,42] These changes in postprandial GLP-1 levels are independent of weight loss and the caloric reduction during the early postoperative period.[31,37]

GLP-1 levels after BPD

Fasting GLP-1 levels are increased from the first postoperative week.[46-48] Similar to RYGB, postprandial GLP-1 levels are increased after BPD from the first postoperative week and these changes are independent of weight loss.[47,48]

GLP-1 levels after AGB

The vast majority of AGB studies did not find any significant change of fasting GLP-1 levels at the postoperative follow-up.[33,49-52] Furthermore, three studies that measured the postprandial GLP-1 levels after meal did not find any significant difference compared to preoperatively up to 12 months postoperatively.[33,49,52]

GLP-1 levels after SG

Fasting GLP-1 levels preoperatively and 3 months postoperative are similar after SG.[40,53] Postprandial AUC and peak levels of GLP-1 at 30 minutes after the ingestion of a meal do increase as early as the first postoperative week.[40,53]

GLP-1 levels after experimental procedures

The only human study that reports GLP-1 levels after DJB reports found increased postprandial levels of GLP-1 at 1 month postoperatively when at 6 months there was no significant change compared to preoperatively.[54] Similarly to the results after DJB, a study by DePaula et al. which investigated the changes in GLP-1 levels after SG with ileal interposition found that postprandial levels of GLP-1 were significantly increased after the procedure.[55]

GIP levels after metabolic surgery

GIP after RYGB

The findings on fasting GIP levels after RYGB are inconclusive. The majority of the studies reported no changes in fasting GIP,[31,35-37] but some showed decreased levels of GIP,[42,56] especially in T2DM patients.[32] Regarding postprandial GIP levels after

RYGB, many studies report no significant changes in postprandial AUC levels,[31,35-37,43] but there is a cross-sectional study which found decreased postprandial GIP levels compared to controls.[56] Lafferere reported that postoperative postprandial GIP levels had an increased peak at 30 minutes after meals, however Hansen did not confirm this finding.[31,35]

GIP levels after BPD

Active fasting GIP levels decreased immediately after the BPD.[47] In addition, GIP postprandial levels after BPD are decreased from the first postoperative week after the biliopancreatic diversion and this change is independent of the weight loss.[47,48]

GIP levels after AGB

Usinger et al. and Shak studied fasting GIP levels in 8 and 24 patients after AGB respectively.[50,52] Both of them did not find any significant changes postoperatively.[50,52] Postprandial GIP levels did not change after AGB.[52,56]

GIP levels after experimental procedures

In the only study that has been performed to investigate GIP levels after DJB, the investigators didn't find any postprandial changes in GIP levels.[54] On the other hand, studies after SG with ileal interposition showed a significant increase in postprandial GIP levels postoperatively in patients with T2DM.[55]

Ghrelin

Ghrelin levels after RYGB

Several studies have assessed the impact of metabolic surgery on circulating ghrelin profiles, measuring either total (acyl- and desacyl-ghrelin) or acyl-ghrelin in the fasting and/or meal-stimulated state. The majority of the studies on fasting ghrelin levels have shown either no significant change[33,39,57-59] or decreased levels,[40,60-64] especially in the early postoperative period. However, a significant number of long-term follow-up studies have reported increased fasting ghrelin levels.[65-67] It is noteworthy that in many studies which reported decreased ghrelin levels immediately postoperatively, there was a trend for increased levels in longer follow-up.[64,65,67,68]

The findings on postprandial ghrelin levels after RYGB are also inconclusive, as there are groups which showed no changes,[64,69] increases[49] and decreases[33,40] following surgery. The majority of the studies have shown decreased or no significant change in postprandial ghrelin levels in the early postoperative period (first six weeks).[33,40,49,64,69] The differences in the methodologies between the different studies are probably one of the main reasons behind the discrepant findings.[70] Blood samples for hormone assays were collected and processed in diverse ways (i.e., tubes chilled or not; with or without protease or DDP-4 inhibitors; acidified or not; diverse commercial assays; different durations of centrifugation). Moreover, there were differences in the experimental meals, (including their carbohydrate and lipid content), follow-up and also blood sampling points.[45] Furthermore, the technical variations between the same surgical procedures may be partially responsible for the published differences as the variable damage of the vagus nerve and the difference in gastric fundus management may affect ghrelin levels.[71-73] Glucose homeostasis may also play a role in gut hormone responses after the same bariatric procedure. Hyperinsulinaemia and insulin resistance per se are associated with ghrelin suppression in obese individuals.[73,74]

Ghrelin levels after BPD and BPD-DS

Similar to RYGB, the findings regarding ghrelin levels after BPD are inconclusive; some groups have reported increases,[75,76] others no change[77,78] and one reported decreases.[62] After a growth hormone- releasing hormone/arginine test post-BPD ghrelin levels are increased 18 months postoperatively compared to baseline.[78] Moreover, the 24 hour production of ghrelin has been found to be increased after BPD.[79] Regarding BPD-DS, Kotidis reported that total fasting ghrelin was decreased 18 months postoperatively.[80]

Ghrelin levels after AGB

Fasting ghrelin levels are increased in the majority of the studies after AGB;[81-85] however there is also a significant number of studies which report no significant differences in fasting ghrelin levels compared to preoperatively.[86,87] Two studies have measured prospectively ghrelin postprandial levels and did not find significant changes up to twelve months postoperatively.[33,49]

Ghrelin levels after SG

All the studies that have measured fasting ghrelin levels, with a follow-up of up to 5 years after SG have found decreased levels.[40,57,84,87,88] The only study that reported on postprandial ghrelin levels was a randomised controlled trial which found decreased levels at 1 week and 3 months compared to preoperatively, but also RYGB.[40]

Ghrelin levels after experimental procedures

Fasting and postprandial ghrelin levels are significantly decreased after the SG with ileal interposition.[55]

PYY levels after metabolic surgery

PYY levels after RYGB

Fasting PYY levels after RYGB have been studied extensively after gastric bypass with prospective follow-up up to 2 years.[41] Similarly to GLP-1, in the vast majority of cases baseline PYY levels remained unchanged after RYGB.[33,39,40,49,57] Postprandial PYY AUC and PYY peak levels are increased after RYGB from the second postoperative day and these changes appear to be independent of weight loss.[33,39,40,41,49,58,59,89] Moreover, PYY postprandial levels are increased progressively after RYGB.[41]

PYY levels after BPD and BPD-DS

García-Fuentes demonstrated in a group of 38 patients that total fasting PYY levels are increased after BPD.[90] However, a recent study on fasting and postprandial PYY levels after BPD-DS reported that they are increased compared to preoperatively.[91] The rapid gastric emptying in combination with the anatomical changes has been proposed as the main reasons.[91]

PYY levels after AGB

All studies which have measured PYY levels after AGB have found no change in postoperative fasting PYY levels.[33,49] Furthermore, prospective studies that have measured PYY AUC and PYY peak levels after AGB did not report any change postoperatively.[33,49]

PYY levels after SG

The results regarding fasting PYY fasting levels after LSG are inconclusive. Karamanakos studied fasting PYY levels at 1, 3, 6 and 12 months postoperatively and found that total fasting PYY levels increased postoperatively from the first month.[57] Peterli however reported that fasting total PYY levels decrease at 1 week and 3 months after the operation when Valderas did not find any significant change 2 months postoperatively.[40,89] Postprandial PYY levels increased from the early postoperative period with a significant peak of PYY levels at 30 minutes after meal ingestion.[40,89]

PYY levels after experimental procedures

Postprandial PYY levels in humans after SG-ileal interposition were elevated 16 months postoperatively.[55]

Possible mechanisms for the changes in gut hormone levels after metabolic procedures

Significant differences between the hormonal profiles of bariatric procedures have been shown in this study. A number of possible physiological mechanisms have been proposed for these differences.

Anatomical differences between the procedures

Long term changes in ghrelin levels after BPD and RYGB remain inconclusive as discussed above, but it appears that both operations result in decreased or unchanged levels in the early postoperative period, following which concentrations increased progressively. BPD-DS and SG are associated with decreased ghrelin levels. The fact that in both these operations the fundus of the stomach, which is the main location of ghrelin producing cells does not have contact with food, lead to speculation that its presence could play a significant role on circulating ghrelin levels.[73] Further-

Table I
The profile of the gut hormones' changes after RYGB, BPD-DS, SG, AGB

	RYGB	*BPD*	*SG*	*AGB*	*BPD-DS*
Fasting GLP-1	↔	↑	↔	↔	–
GLP-1 AUC	↑	↑	↑	↔	–
Fasting PYY	↔	↑	↑ or ↔ or ↓	↔	↑
PYY AUC	↑	–	↑	↔	↑
Fasting GIP	↔	↓	–	↔	–
GIP AUC	↔	↓	–	↔	–
Fasting ghrelin	↔ or ↓ or ↑	↔ or ↑	↓	↑ or ↔	↓
Ghrelin AUC	↔ or ↓	↑	↓	↔	–

↔: No significant change in the majority of studies; ↑: Significant increased in the majority of studies; ↓: Significant decreased in the majority of the studies; –: No studies for this parameter; GLP-1: Glucagon Like Peptide-1; PYY: Peptide YY; GIP: gastric inhibitory polypeptide/glucose – dependent insulinotropic polypeptide; RYGB: Roux- en-Y Gastric Bypass; BPD: Biliopancreatic Diversion; SG: Sleeve Gastrectomy; AGB: Adjustable Gastric Banding; BPD-DS: Biliopancreatic Diversion with Duodenal Switch; AUC: Area Under the Curve.

more, in two recent randomised controlled trials, ghrelin levels were significantly lower after SG compared to RYGB and this could also be partially explained by the anatomical differences in the stomach postoperatively.[40,57] On the other hand, ghrelin levels remain unchanged or increased after AGB due to the body's response to a diet-like induced weight loss.

Consistent with the lower intestinal hypothesis, the majority of the metabolic operations such as BPD, BPD-DS, RYGB, DJB and SG with ileal interposition known for rapid postoperative glycaemic control, create gastrointestinal shortcuts for food to access the distal bowel. After BPD and BPD-DS, which conduct food directly from the stomach to the distal jejenum and ileum, postprandial GLP-1 and PYY excursions are unquestionably increased. Despite that RYGB and DJB bypass less jejenum, increased GLP-1 and PYY levels occur progressively. Consistent with elevated postprandial GLP-1 secretion, post-RYGB patients display an increased incretin effect.[36] SG with ileal interposition also increases GLP-1 and PYY postprandial levels, as a segment of the L-cell-rich ileum is transplanted into the upper intestine near the duodenum-jejunum boundary, thereby increasing its exposure to ingested nutrients. As predicted, this operation greatly enhances postprandial GLP-1 and PYY secretion with no gastric restriction or malabsorption and results in improved glycaemic control.[55]

The different limb length after the intestinal bypass procedures seems to play a role on GIP postprandial levels. In procedures with very long limbs, such as BPD, the GIP levels are decreased.[47,48] In RYGB and DJB, with shorter limbs, postprandial GIP levels remain unchanged, when after SG with ileal interposition rapid gastric emptying and the quick contact of undigested food with the K-cells leads to increased postprandial GIP levels.[55]

Changes in gastric emptying

The rapid gastric emptying that occurs after some of the procedures could lead to early contact of the food with the ileum creating an enhanced gut hormones response from the L-cells (PYY and GLP-1). Gastric emptying is accelerated after RYGB from the third postoperative day and accompanied by shortened intestinal time in morbidly obese patients.[34,42] This was accompanied by an increased postprandial GLP-1 response. SG and BPD-DS are also associated with increased gastric emptying[91-93] although one study suggested no change postoperatively.[94] Further support to the rapid gastric emptying is provided from the presence of dumping symptoms after SG.[95]

Differences in bile acids secretion

A recent study has shown that ghrelin levels in obese patients are negatively correlated with bile acids levels when PYY and GLP-1 postprandial levels are positively correlated with specific types of bile acids.[96] Moreover, increased bile acid secretion after RYGB has been associated with GLP-1 peak levels.[97] More studies in bile acids changes after metabolic procedures and their associations with changes in gut hormones levels postoperatively are necessary in order to understand the role of bile acids in gut hormone secretion and glucose and energy homeostasis.

Gut hypetrophy and differences in DPP-4 activity

Following BPD, significant gut hypertrophy has been reported in both humans and rats.[98] This could explain the increased GLP-1 and PYY fasting levels after BPD and BPD-DS, as well as the increased postprandial levels. On the other hand, the activity of the enzyme DPP-4 which degrades the GLP-1, GIP and PYY is reduced after RYGB,[99] but does not change after BPD.[46] The association between DPP-4 activity and the differences in the fasting and postprandial levels of GLP-1, GIP and PYY after RYGB compared to BPD still needs further exploration.

Conclusion

Each metabolic procedure has a unique gut hormone profile. These differences in gut hormones secretion may partially explain the different rate and effectiveness as regards the glycaemic control and the weight loss of these procedures. Future work with more standardized protocols is needed to finally confirm the differences in hormonal profile after various metabolic procedures. Using what we have learnt about gut hormones from metabolic surgery will allow us to refine our surgical procedures and may help those patients that are not eligible or able to have metabolic surgery.

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Other aspects of bariatric surgery: liver steatosis, ferritin and cholesterol metabolism

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Abstract

Bariatric surgery developed in the late 1970 to treat severe hyperlipidemias in overweight individuals, not necessarily obese. Several techniques have been developed, and the concept has come first of a surgery for morbid obesity, then of a cure for diabetes in morbid obesity. There are other aspects of bariatric surgery that deserve attention, beyond BMI and diabetes, such as hypertension, poor life expectancy, increased prevalence of cancer, congestive heart failure, social inadequacy. The aim of this presentation is to review some recent development in clinical research, in the fields of liver steatosis, ferritin metabolism, and cholesterol metabolism.

Liver steatosis, also called fatty liver encompasses a graduation of diseases with different clinical relevance and prognosis. NAFLD correlates with atherosclerosis, insulin resistance and diabetes mellitus. There is now evidence that weight loss, obtained through diet or restrictive surgery, reduces the prevalence (and the severity) of NAFLD.

An other issue is represented by serum ferritin concentrations, that are strongly associated with fibrosis, portal and lobular inflammation in NAFLD patients, especially in the presence of obesity. Body iron contributes to excess oxidative stress already at non iron overload concentrations. Moreover, serum ferritin is an important and independent predictor of the development of diabetes. Weight loss is accompanied by reduction of ferritin, more after restrictive than malabsorptive surgery.

Metabolic changes are greater after malabsorptive or mixed surgery than after purely restrictive surgery, and this has been ascribed to a greater weight loss. Studies comparing the two kinds of surgery indicate that, for the same amount of weight loss, decrease of cholesterol is greater with the former than with the latter techniques, and this difference is mainly due to a greater reduction of intestinal absorption of cholesterol. In the choice of surgery for the single patient, among other aspects, malabsorptive surgery seems to be more indicated in subjects with hyperlipidemia, especially with high cholesterol levels.

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Key words: *Bariatric surgery. Liver steatosis. Ferritin. Cholesterol metabolism.*

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OTROS ASPECTOS DE LA CIRUGÍA BARIÁTRICA: ESTEATOSIS HEPÁTICA, METABOLISMO DE FERRITINA Y COLESTEROL

Resumen

La cirugía bariátrica se desarrolló a finales de la década de los 70 para tratar la hiperlipidemia severa en personas con sobrepeso, no necesariamente obesos. A lo largo de los años se han desarrollado varias técnicas quirúrgicas que han sido utilizadas en primer lugar en la obesidad mórbida y posteriormente en el tratamiento de la diabetes. Hay otros aspectos de la cirugía bariátrica que merecen atención más allá del IMC y la diabetes, como la hipertensión, la pobre esperanza de vida, una mayor prevalencia de cáncer, insuficiencia cardíaca e inadaptación social. El objetivo de este artículo es revisar los recientes avances clínicos en campos de investigación relacionados con la esteatosis hepática, el metabolismo de ferritina y el metabolismo del colesterol.

La esteatosis hepática, también llamada hígado graso abarca una serie de las enfermedades con diferente pronóstico y relevancia clínica. El Hígado Graso No Alcohólico (NAFLD siglas en ingles) se correlaciona con la aterosclerosis, resistencia a la insulina y diabetes mellitus. Hoy en día existen evidencias de que la pérdida de peso que se obtiene a través de la dieta o cirugía restrictiva, reduce la prevalencia (y la gravedad) de la NAFLD.

Otro tema de estudio incluye las concentraciones de ferritina sérica, que están fuertemente asociadas con la fibrosis e inflamación lobular y portal en pacientes con NAFLD, especialmente en presencia de obesidad. El exceso de hierro corporal en obesos contribuye a un aumento del estrés oxidativo debido a una sobrecarga en su concentración. Por otra parte, la ferritina sérica es un indicador importante e independiente del desarrollo de la diabetes. La pérdida de peso se acompaña de una disminución de la ferritina. Esta disminución es más evidente tras una cirugía restrictiva que tras una malabsortiva.

Los cambios metabólicos son mayores después de una cirugía malabsortiva o mixta que tras una cirugía puramente restrictiva, y esto se ha atribuido a una mayor pérdida de peso. Estudios que comparan los dos tipos de cirugía indican que, para la mismo índice de pérdida de peso, la disminución de colesterol es mayor con las primeras técnicas que con las últimas, y esta diferencia se debe principalmente a una mayor reducción de la absorción intestinal del colesterol. En la elección de la cirugía para un paciente concreto, entre otros aspectos, la cirugía de malabsorción parece estar más indicada en sujetos con hiperlipemia, especialmente con altos niveles de colesterol.

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Palabras clave: *Cirugía bariátrica. Esteatosis hepática. Ferritina. Metabolismo colesterol.*

Introduction

Metabolic surgery has been proposed as the new name of bariatric surgery, but was developed in the late 1978 to treat severe hyperlipidemias in above-normal body weight individuals, not necessarily obese; the Program on the Surgical Control of the Hyperlipidemias (POSCH) can be considered the beginning of the era of bariatric surgery.[1] Several techniques have been developed later, and the concept has come first of a surgery for morbid obesity, then of a cure for diabetes in morbid obesity. Nevertheless, there are other aspects of bariatric surgery that deserve attention, as raised Body Mass Index BMI) and diabetes are not the only co-morbidities of obesity; think of hypertension, poor life expectancy, increased prevalence of cancer, congestive heart failure, social inadequacy. Given the strict links between obesity, chronic sub-clinical inflammation, insulin resistance, diabetes, the metabolic syndrome, and steatosis, the aim of this presentation is to review some recent development in clinical research, basic and surgical.

Liver steatosis

Liver steatosis, also called fatty liver encompasses a graduation of diseases with different clinical relevance and prognosis; simple NAFLD (non Alcoholic Fatty Liver Disease) is more frequent and less severe than NASH (Non Alcoholic Steato Hepatitis), as the former is a benign condition, the latter can proceed to cirrhosis and probably also to hepatocellular carcinoma.[2]

Prevalence of NAFLD has been defined through biopsies (that is considered the gold standard for the diagnosis, in that a differentiation between steatosis, steatosis plus fibrosis, steatohepatitis is possible), autopsy series, and non-invasive methods such as liver ultrasound, liver enzymes (ALT and AST plus GGT), magnetic resonance imaging (MRI). Though considered the gold standard, biopsies are not suitable for population studies; one would wander whether it is ethical to perform repeat liver biopsies for research purposes. Expectedly, the prevalence of NAFLD varies in different studies, that is in different populations, and using different criteria and methodologies; in summary, NAFLD (and NASH) affect a significant proportion of adults of both sexes. NAFLD is quite frequent in obesity, in diabetes, in metabolic syndrome, and is expected to increase worldwide due to the obesity epidemics, and is also increased with increasing alcohol consumption.[2,3]

NAFLD correlates with atherosclerosis, insulin resistance and diabetes mellitus,[4,5] whatever the method of assessment of NAFLD. In the large European population (RISC Study) NAFLD, evaluated through the fatty liver index, was associated with increased CHD risk, low-density lipoprotein cholesterol, systolic blood pressure, and intima-media-thickness, and inversely associated with insulin sensitivity, high-density lipoprotein cholesterol, adiponectin, and physical activity.[4] Based on liver biopsies, about three quarters of bariatric surgery patients have liver steatosis, and about a quarter have fibrosis.[6] There have been attempts to predict frequency and severity of fatty liver based on liver function tests; in 200 patients, multivariate analysis identified six predictive factors for NASH: the diagnosis of HT, DM, sleep apnea, AST > 27 IU/L, ALT > 27 IU/L, and non-black race;[7] however, In 139 patients undergoing bariatric surgery, NASH was found in 57 (41%): age, gender, race, BMI, DM, HT, and liver function tests and triglyceride, cholesterol, iron, and prealbumin measurements were not strong predisctors of NASH [8]. Imaging has been proposed as a surrogate of liver biopsies; ultrasound, compared with biopsy, has an accuracy 0.81%;[6] a recent meta-analysis indicates that the diagnostic accuracy is greater for magnetic resonance imaging (MRI), chemical-shift MRI and for spectroscopy-MRI;[9] the two latter techniques correlate, and accurately estimate the severity of steatosis.[10,11] During the last 5 years we have developed a MRI chemical-shift analysis to differentiate NAFLD from other infiltrative liver disorders such as glycogenosis.[12-14] This technique requires simple MRI instruments, correlates with ultrasound, and preliminary data indicate a high frequency of NAFLD in obese subjects, paralleled by frequent elevation of liver enzymes.[15]

The next question is: what is the effect of weight loss on NAFLD? There is now abundant evidence that weight loss, obtained through diet or restrictive surgery, reduces the prevalence (and the degree) of NAFLD; this applies to biopsies, to ultrasound studies, to MRI studies, as well as to liver function tests, and the different criteria seem to yield the same kind of information; also NASH seems to regress to simple NAFLD.[15-20] The drop of AST and ALT correlates with loss of visceral fat.[21] Interestingly, the effect of malabsorptive surgery (biliointestinal bypass) is less clear (liver enzymes),[22] but there is no recent data showing worsening of NAFLD or NASH after bariatric surgery.

Ferritin

Serum ferritin concentrations and BMI are strongly associated with fibrosis, portal and lobular inflammation in NAFLD patients.[23] Diabetes and metabolic syndrome are the main contributors to high ferritin levels in obesity.[24] Growing evidence has shown that even moderately increased iron stores, represented by high-normal ferritin concentrations, are associated with diabetes.[25-28] More recently the results from prospective studies from Caucasian populations suggested that iron overload could predict the development of abnormal glucose metabolism.[29]

It is unclear whether elevated ferritin may simply be another marker of insulin resistance or whether

elevated ferritin concentrations identify iron stores that may contribute to the pathogenesis of altered metabolic states. A recent study has suggested that body iron contributes to excess oxidative stress already at non iron overload concentrations.[30] Moreover, serum ferritin has been identified as an important and independent predictor of the development of diabetes[31] and high concentrations of ferritin, together with low oral glucose insulin sensitivity, have been identified as independent markers of fibrosis in NASH.[32]

It has been hypothesized that iron could be an important cofactor in the pathogenesis and progression of some cases of NASH[31] since NAFLD subjects have increased hepatic fatty acid oxidation, and increased production of ROS.[30-32] In a large cohort of NASH patients, 21.1% had hyper-ferritinemia while only 7.4% had signs of peripheral iron overload and 9% had signs of hepatic iron overload.[31]

Among other things, weight loss is accompanied by reduction of inflammation, and ferritin is both a storage protein for iron and a marker of inflammation; ferritin decreases after surgery, more after restrictive than malabsorptive surgery.[33-36] Considering the close relationship between obesity, insulin resistance and development of NAFLD, we studied their association with hepatic profile and ferritin concentrations.[34] Since bariatric surgery-weight loss is associated with reduced insulin resistance, restored glucose tolerance, reduced hepatic steatosis, and improved liver enzymes, we repeated the analyses after laparoscopic gastric banding surgery to evaluate the impact of weight loss on the association between hepatic profile, ferritin concentrations, and insulin resistance. In our group of 169 obese subjects (89 with normal liver enzymes, 70 with raised liver enzymes), before bariatric surgery, ferritin concentrations were increased proportionally to ALT concentrations, although, in general, within normal ranges and similar in NGT, IGT, and T2DM. A positive correlation was observed between ferritin plasma concentrations and insulin resistance. After surgery, however, we did not observe a significant decrease in plasma ferritin concentrations despite the improvement in hepatic function and insulin resistance. However, the correlations between ferritin, ALT, and insulin resistance remained suggesting that ferritin may simply identify a new phenotype of insulin resistance.[34]

Cholesterol metabolism

Metabolic changes are greater after malabsorptive or mixed surgery (bilio-pancreatic diversion, gastric by-pass) than after purely restrictive surgery (vertical banded gastroplasty, gastric banding, intra-gastric balloon), and this has been ascribed to a greater weight loss; no surprise that disappearance of comorbidities like diabetes mellitus happens more frequently after the former than after the latter interventions.[37] Even though improvement of hyperlipidemia was present in a fair proportion of subjects undergoing gastric banding (triglycerides 78%, 94%, 87%; cholesterol 77%, 91%, 100% with gastric banding, gastric bypass, and bilio-pancreatic diversion, respectively, the degree of reduction of cholesterol levels was clearly different (-0.30, 0.96, 1.97 mmol, respectively). We reported decreased cholesterol levels after bilio-intestinal by-pass (an other malabsorptive surgery)[22] or after bilio-pancreatic diversion,[38] but not after gastric banding. The cholesterol reduction that we and others have reported after after bilio-intestinal by-pass, bilio-pancreatic diversion, or gastric by-pass is a quite dramatic phenomenon and is likely due to the major reduction in bile acid re-absorption in the intestine, and possibly to altered regulation of the feedback mechanisms controlled by nuclear protein such as LXR, FXR and PPAR; these transcriptional factors are involved in bile acid and cholesterol metabolism, occurring in patients undergoing after bilio-intestinal by-pass, bilio-pancreatic diversion or gastric by-pass (which cause malabsorption and also reduced bile re-absorption), but not gastric banding (a purely restrictive bariatric procedure).[39] It is also possible that reduced gastric volume and reduced production of gastric lipase, as well as reduced secretion of cholecystokinin (that physiologically stimulates digestive enzyme secretion such as lipases and proteases) might result in a marked decrease in the hydrolysis of triacylglycerols, with a reduction of the absorption of free fatty acids.[40] Both bilio-pancreatic diversion and gastric by-pass include partial gastric resection, or functional gastric disconnection; therefore, gastric by-pass and bilio-pancreatic diversion can not be regarded as purely restrictive or purely malabsorptive surgical techniques. we hypothesized that, aside from greater weight loss, a specific effect of malabsorptive surgery on cholesterol metabolism might exist, probably mediated by intestinal milieu.[41,42] We also observed that, at six months, weight loss was similar with gastric banding and with bilio-intestinal by-pass.[22] Therefore we performed a comparison of gastric banding, intra-gastric balloon, and bilio-intestinal by-pass, and hypocaloric diet (1,200 kcal/day), on glucose and cholesterol levels in morbid obesity. We could confirm that, at 6 months, weight loss is similar with the three surgical techniques, greater than with diet, and that glucose metabolism was also similarly affected; however, serum cholesterol and LDL-cholesterol levels were affected in a significant way only by bilio-intestinal by-pass.[43] Then we evaluated intestinal cholesterol absorption, endogenous cholesterol synthesis, and cholesterol catabolism through the bile acids pathway, and we found that after bilio-intestinal by-pass, together with decreased cholesterol levels, intestinal cholesterol absorption is reduced, associated with enhanced cholesterol synthesis and enhanced cholesterol catabolism; in contrast, after gastric banding there is no change in cholesterol levels, in cholesterol absorption, synthesis, and only a marginal increase in cholesterol catabolism.[44]

Conclusion

Decision on which surgical procedure to choose for the individual obese patients is a complex matter, that has to take into consideration expectations, invasiveness and reversibility, surgical mortality, drawbacks of each surgical procedure;[45,46] among other aspects, malabsorptive surgery seems to be more indicated in subjects with hyperlipidemia, especially with high cholesterol levels.

Declaration

The authors have no conflict of interests with the contents of this paper.

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Influence of diabetes surgery on a gut-brain-liver axis regulating food intake and internal glucose production

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Abstract

It has long been known that the brain, especially the hypothalamus, can modulate both insulin secretion and hepatic glucose fluxes, via the modulation of the sympathetic system (promoting glycogen breakdown) and the parasympathetic system (stimulating glycogen deposition). Central insulin signalling or hypothalamic long-chain fatty acid oxidation can also control insulin's suppression of endogenous glucose production. Interestingly, intestinal gluconeogenesis can initiate a portal glucose signal, transmitted to the hypothalamus via the gastrointestinal nervous system. This signal may modulate the sensation of hunger and satiety and insulin sensitivity of hepatic glucose fluxes as well. The rapid improvements of glucose control taking place after gastric bypass surgery in obese diabetics has long been mysterious. Actually, the specificity of gastric bypass in obese diabetic mice relates to major changes in the sensations of hunger and to rapid improvement in insulin sensitivity of endogenous glucose production. We have shown that an induction of intestinal gluconeogenesis plays a major role in these phenomena. In addition, the restoration of the secretion of glucagon like peptide 1 and consequently of insulin plays a key additional role to improve postprandial glucose tolerance. Therefore, a synergy between incretin effects and intestinal gluconeogenesis might be a key feature explaining the rapid improvement of glucose control in obese diabetics after bypass surgery.

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Key words: *Gastric bypass. Brain. Liver. Intestinal gluconeogenesis. Insulin sensitivity. Glucagon-like peptide 1.*

INFLUENCIA DE LA CIRUGÍA DE DIABETES SOBRE EL EJE INTESTINO-CEREBRO-HÍGADO QUE REGULA INGESTA ALIMENTARIA Y PRODUCCIÓN INTERNA DE GLUCOSA

Resumen

Se sabe desde hace tiempo que el cerebro, especialmente el hipotálamo, puede modular la secreción de insulina y los flujos hepáticos de glucosa mediante la modulación del sistema simpático (promoviendo la degradación del glucógeno) y el sistema parasimpático (estimulando el depósito de glucógeno). La señalización central de la insulina o la oxidación hipotalámica de los ácidos grasos de cadena larga también pueden controlar la producción de la glucosa endógena por la supresión de la insulina. De forma interesante, la gluconeogénesis intestinal puede iniciar una señal de glucosa portal, que se transmite al hipotálamo a través del sistema nervioso gastrointestinal. Esta señal puede modular la sensación de hambre y la saciedad, así como la sensibilidad a la insulina de los flujos hepáticos de glucosa. Las mejorías rápidas del control de la glucosa que ocurren tras la cirugía de derivación gástrica en los diabéticos obesos siguen siendo un misterio. En realidad, la especificidad de la derivación gástrica en ratones obesos diabéticos se relaciona con cambios importantes en las sensaciones de hambre y con una mejoría rápida de la sensibilidad a la insulina de la producción endógena de glucosa. Hemos demostrado que la inducción de la gluconeogénesis intestinal desempeña un papel principal en estos fenómenos. Además, la restauración de la secreción del péptido 1 de tipo glucagón y, por consiguiente, de la insulina, desempeña un papel clave adicional en la mejora de la tolerancia a la glucosa postprandial. Por lo tanto, la sinergia entre los efectos de la incretina y la gluconeogénesis intestinal podría ser un elemento clave en la mejora rápida del control de la glucosa en los diabéticos obesos tras la cirugía de derivación.

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Palabras clave: *Derivación gástrica. Cerebro. Hígado. Gluconeogénesis intestinal. Sensibilidad a la insulina. Péptido 1 de tipo glucagón.*

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Introduction

The worldwide increase of obesity, now considered as an epidemic, has necessitated the development of new therapeutic approaches of this metabolic state. In the case of morbid obesity, which also increased dramatically, bariatric surgery may be relevant when the patient is in treatment failure with respect to the control of body weight. Two types of gastric surgery are generally used. The best known, gastric banding is restrictive. Its aim is to reduce the size of the stomach using a gastric band. A second type of technique, more invasive, is the so-called gastric bypass, which in addition to reducing stomach creates a diversion of food into the distal small intestine, with the aim to associate a malabsorption of nutrients. There are different variants of the bypass surgery, such as the "Roux-en-Y", duodenojejunal exclusion, or biliopancreatic diversion (see 1 for review). However, all produce similar metabolic effects.

A question still unresolved 5 years ago relates to the mechanisms underlying the metabolic differences observed between the major surgeries for morbid obesity, especially when obesity is associated with type 2 diabetes. Both types of operation induce substantial weight loss. However, "bypass" patients generally refer to their physician a significant loss of their feelings of hunger, which is not the case of "banding" patients. Patients also frequently mention changes in the appetite for fatty food. Weight loss is also greater after bypass than after banding.[1] The various hypotheses proposed, generally based on differences in the induced secretion of gastrointestinal hormones that influence the phenomena of hunger and satiety (ghrelin, cholecystokinine, glucagon like peptide-1 (GLP-1)), have proved insufficient to explain the major difference between the two techniques. For example, the secretion of ghrelin, an orexigenic hormone, is unaffected by gastric bypass.[2] In addition, the results relating to the secretion of GLP-1, a hunger-curbing hormone, were sometimes contradictory among different studies.[3,4] Another unexplained feature of gastric bypass in obese diabetics is a dramatic improvement in their diabetes.[5] This improvement takes place very rapidly (within some days), i.e. well before any weight loss induced by surgery.[5] In contrast, patients treated using the banding technique show an improvement in their diabetes much later, once they have lost weight. The mechanism involved here was still unexplained. The term "metabolic surgery" applied to the gastric bypass was born from these observations.

Central control of endogenous glucose production

Endogenous glucose production (EGP) is a crucial function, which allows the body to maintain plasma glucose concentration around 1 g/L in absence of food, i.e. between the periods of assimilation of meals and during the night. It is admitted that increased EGP is a feature of type 2 diabetes, and that the augmentation of EGP determines that insulin resistance without diabetes finally becomes frank diabetes.[6] Three organs only can perform this function, because they are the only organs known to express glucose-6-phosphatase (Glc6Pase), the key enzyme of EGP.[6] All three organs express all the enzymes needed for glucose synthesis,[7-9] and are able to release glucose, e.g. during fasting.[10-12] In line with this key role in fasting glucose homeostasis, Glc6Pase together with phosphoenolpyruvate carboxykinase (PEPCK), the other key regulatory enzyme of EGP, are regulated by nutrients and hormones (notably insulin) at the level of gene expression and enzymatic activity in the liver, kidney and small intestine.[7-10,13-17] Among the three organs capable of EGP, the liver is often regarded as the major contributor. This is essentially due to its specific capacity of glycogen storage, a store of glucose that it can mobilize via the activation of glycogenolysis. This allows it to rapidly and finely tune blood glucose concentration. The other two organs (kidney and intestine) do not exhibit this capacity, and it is generally observed that they increase their participation in EGP as fasting in lasting.[6,11,13,18,19] For this reason, a vast majority of previous studies about the regulation of EGP have focused on hepatic glucose fluxes.

In addition to the control by insulin, the hypothalamus, via the modulation of the sympatheticparasympathetic balance, takes part in the control of whole body glucose metabolism, notably at a liver level. The hypothalamus influences insulin secretion,[20] glucose utilization in the skeletal muscle[21] and liver glucose storage and production.[22,23] Particularly, the nervous efferents connecting the hypothalamus to the liver tightly control EGP via the regulation of hepatic glycogen storage.[22,23] More specifically, neurons in the ventromedial hypothalamus control the stimulation of liver glycogenolysis, through the activation of the sympathetic system. Conversely, neurons in the lateral hypothalamus stimulate liver glycogenogenesis, via the activation of the parasympathetic system. Additional circuits from the paraventricular nucleus to the liver have also been involved in the control of hepatic glycogen storage, via a modulation of the sympathetic-parasympathetic balance. In addition, the paraventricular nucleus has been suggested to also serve as a relay for signals from both the ventromedial and the lateral hypothalamus to the liver.[22]

Furthermore, the role of the hypothalamus in the control of hepatic glucose production has been recently specified, either in rats or in mice with targeted gene mutations affecting insulin receptor expression and signalling. A key role for insulin within the hypothalamus has been suggested. Hence, insulin's suppression of EGP is decreased in rats with decreased insulin signalling in the hypothalamus.[24,25] Moreover, insulin receptor-KO mice with partial restoration of insulin receptor in the brain, liver and pancreatic b-cells are rescued from neonatal death and diabetes ketoacidosis.

However, despite a full restoration of insulin signalling in the liver, they still exhibit defects in the control of HGP by insulin, due to persisting partial deficiency of insulin signalling in the arcuate and paraventricular hypothalamic nuclei.[26] At an intracellular mechanistic level, a central sensing of long chain fatty-acids, through their oxidation, and a relay via hypothalamic ATP-dependent potassium channels, has been suggested to be involved in the suppression of EGP by insulin.[27-29] Moreover, the descending nerve fibres of the hepatic branch of the vagus have been shown to convey a causal efferent signal to the liver.[28,29] In addition, the efferent signal is also able to regulate both hepatic Glc6Pase and PEPCK gene expression.[29]

Among the most recent advances in the central control of both glucose and energy homeostasis, the role of AMP-activated protein kinase (AMPK), a key fuel sensor enzyme expressed in the whole body — including the brain— occupies a central place.[30] Hypothalamic AMPK, indeed, is a key target of both insulin and leptin, which are two major hormones able to curb hunger and to control glucose homeostasis. Both hormones inhibit AMPK, which in turn modifies the activity of acetyl-CoA carboxylase and the lipid metabolism of those neurons involved in the control of food intake and glucose metabolism.[30] As a result, the neurons expressing the neuromediators acting on the melanocortin receptors of type 3 (controlling energy expenditure) and of type 4 (controlling food intake), may coordinately regulate both glucose and energy homeostasis under the control of leptin and/or insulin.[3]

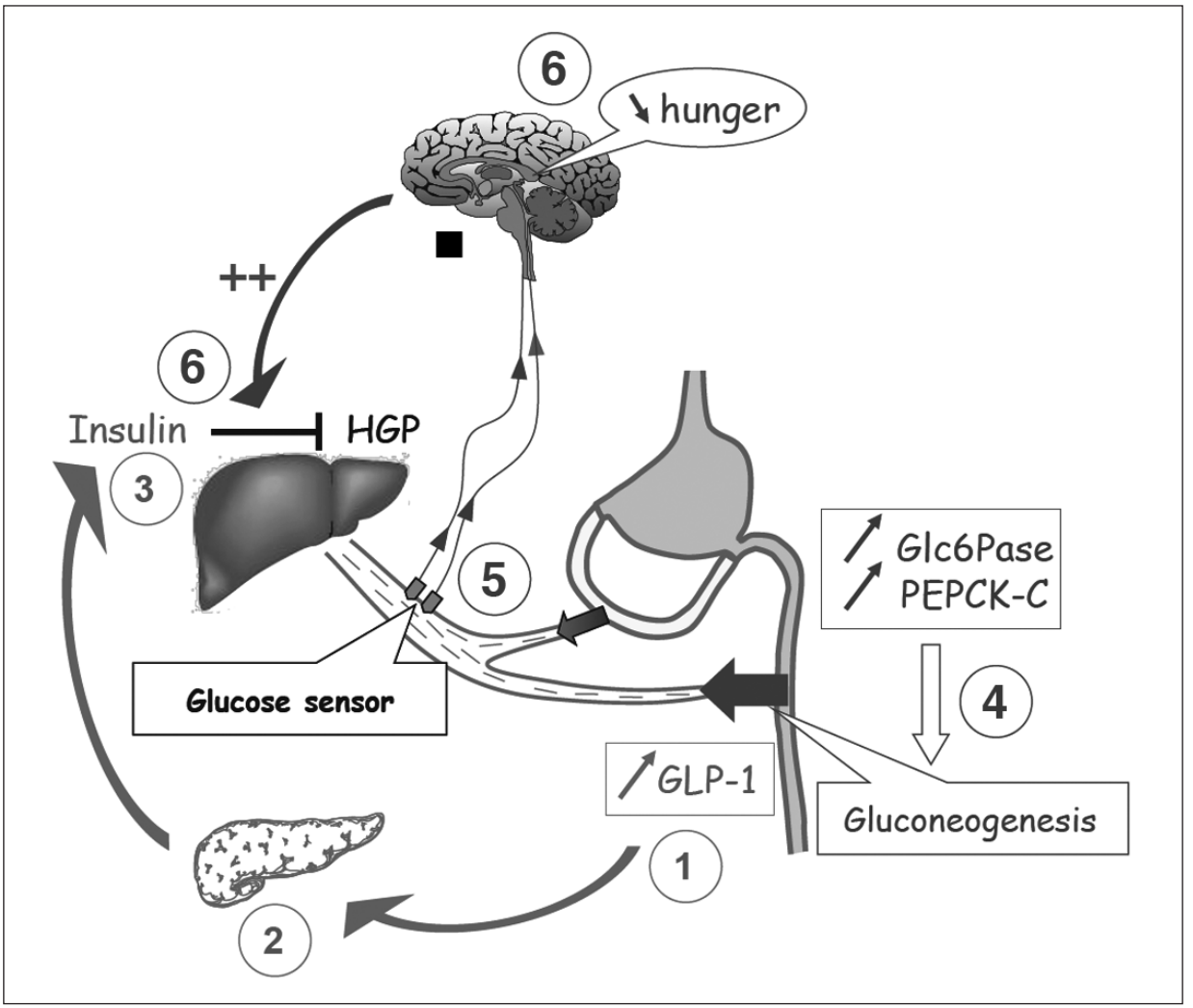

Fig. 1.—Synergy between IGNG and GLP-1 in the control of food intake and glucose homeostasis after gastric bypass: The two pathways operate in synergy. (1) the derivation of food in the distal small intestine (the grey route in the scheme) causes increased secretion of GLP-1 in response to the meal. (2) This stimulates secretion of insulin. (3) Insulin inhibits hepatic glucose production (HGP). (4) the derivation of food in the distal small intestine induces gene expression of IGNG in this portion, which expresses little or no IGNG in the "out of surgery" situation. The genes of IGNG are thus expressed strongly over the length of the small intestine. This leads to the release of glucose into the portal blood, which lasts between meals, and adds to the proximal IGNG to activate the portal glucose sensing system. (5) The portal glucose sensor transmits the information to the brain via the afferent nervous system. (6) The brain's response involves a decrease in hunger and an enhanced suppression of hepatic glucose production by insulin.

Role of a gut-brain-liver axis in gastric bypass

To understand the metabolic differences between gastric banding and gastric bypass, two mouse models representing the two types of surgery have been developed. For the bypass, a simple enterogastroanastomose (EGA) without reducing the size of the stomach was performed (fig. 1). Before surgery, mice were fed for 12 weeks with a diet enriched in fat and sugars to make them obese and insulin-resistant. The sham-operated mice recover their pre-surgical food intake in a few days. On the contrary, the EGA mice reduce their food intake by 70% immediately after the operation.[6] It should be emphasized that they have a normal size of the stomach, which strongly suggests that this decrease is due to a diminution of their feelings of hunger. On the contrary, even if the banded mice eat less, due to the size restriction of their stomach, they tend to increase their food intake again after one week. They eventually die if we do not restrict their food, exhibiting notably a strong expansion of the esophagus, suggesting that their feelings of hunger are always present.

What is the role of GLP-1?

The different hormonal hypotheses frequently proposed were studied. None has helped to explain the observed differences in food intake for the two surgeries. Regarding the possible role of GLP-1, a hypothesis that was often put forward (see above), EGA mice recover significant secretion of the hormone (and consecutively of insulin) in response to an oral glucose load[31] (fig. 1). Since both GLP-1 and insulin are anorectic, it was crucial to study the possible role of GLP-1. This was done using exendin-9, a potent antagonist of GLP-1 receptor. Continuous infusion of exendin-9 canceled insulin secretion in response to a glucose load, reflecting the effectiveness of the antagonist, but only partially reversed the effects of EGA on food intake. This strongly suggests that GLP-1 may have an important role in the recovery of insulin secretion after bypass, and thus in the observed improvement of glucose homeostasis in general, but that neither GLP-1 nor insulin, would play the key role in reducing food intake.[31]

What is the role of the portal glucose signal and intestinal gluconeogenesis?

On decreased hunger

Since the eighties, we know that glucose, when infused into the portal blood of fasting animals, results in a decrease of their food intake.[32] It is also established that this signal, often called "portal glucose signal" is detected in the walls of the portal vein, and is transmitted by nervous afferents to the nervous centers — hypothalamus and nucleus of the solitary tract—, which are the major areas of control of energy homeostasis.[33] This particular location of the glucose sensor gives the intestinal gluconeogenesis (IGNG)[34] the potential to be a player in the control of feelings of food intake.[35] IGNG, ideally located just upstream the site of detection of glucose, allows the intestine to release glucose into the portal vein and thus to activate the portal glucose signal. We have provided the proof of concept of this new paradigm by demonstrating that induction of IGNG and activation of portal glucose signal is the causal link between the ingestion of protein-enriched meals and their well-known effects of satiety, property used for a long time by nutritionists to help their obese patients to loose weight.[36]

Thus, we considered the hypothesis of a possible role of IGNG in the appetite suppressant effects of gastric bypass. Hence, we showed that a strong induction of expression of regulatory genes of gluconeogenesis, glucose-6 phosphatase and phosphoenolpyruvate carboxykinase-C, occurs in the distal small intestine of EGA mice and not in "sham" or "band" mice.[31] In the normal situation, the gluconeogenic function is expressed in the proximal intestine mainly, and virtually not in the distal small intestine.[37-39] As in rats fed high-protein diet, the induction of genes in EGA mice results in a release of glucose into the portal blood (fig. 1). This lasts during the post-absorptive period.[31] A demonstration of its causal role in the sharp decrease of food intake in EGA mice was provided by two complementary approaches. 1) The inactivation of the portal vein afferents at the time of surgery completely cancels the suppression of subsequent food intake induced by EGA. 2) No effect of EGA is observed on food intake of mice invalidated for the gene of the glucose transporter Glut2, the glucose carrier necessary for the detection of portal glucose in rodents.[31]

On improved glucose control

The portal glucose signal, in addition to its effects on food intake, is also likely to interfere with control of glucose homeostasis. Notably, it has been strongly suggested that it inhibits the production of glucose by the liver.[40] It seemed logical to think that it could also play a causal role in improving glycemic control induced by gastric bypass. To study glucose tolerance and insulin sensitivity in mouse models of "banding" and EGA equivalent in nutritional conditions, the different groups of mice were fed on a "pair-fed" basis, adjusted on the consumption of EGA mice. EGA mice showed an improvement in glucose tolerance and insulin sensitivity at 10 days after surgery. While weight loss was the same as that of "banding" or "sham" mice, the two latter do not show significant improvement in their glucose control.[31] By experiments of hyperinsulinemic euglycemic clamp, the improve-

ment was shown to relate to the inhibition by insulin of EGP, more specifically in the liver (fig. 1). EGA mice, probably because of increased insulin sensitivity, have a decreased expression of the gene of glucose-6 phosphatase in the liver.[31] Note that many hypotheses were considered to try to explain this improved insulin sensitivity (based on changes in leptin, adiponectin, resistin, TNF, AMPK activity, etc.). None accounted for the improvements observed. Similarly, "EGA" mice treated with exendin-9 show a partial reversal of their glucose tolerance, due to the cancellation of insulin secretion, but are still sensitive to insulin during the insulin tolerance test. However, the benefits of the EGA do not take place in KO-Glut2 mice, or in mice after denervation of the portal vein, which demonstrates again the crucial role of the portal nervous sensing of glucose in these effects. Taken together, these data strongly suggest that, if the restoration of secretion of GLP-1 and insulin has an important role in improving glucose tolerance, it is the gut-brain-liver axis of induction of IGNG and activation of the portal glucose signal which is the mechanical link accounting for improved insulin sensitivity after gastric bypass. It is interesting to note that in the particular nutritional situation that are the high-protein diets, insulin suppression of endogenous glucose production is potentiated as in EGA.[41] In this situation also, the effect occurs at the level of production of glucose by the liver, which is particularly evident from improved liver glycogen storage during the clamp.[41]

Both incretin effect and intestinal gluconeogenesis explain the benefits of bypass on glucose control

In conclusion, the specificity of bypass surgery in terms of benefits on glucose and energy homeostasis can be summarized as follows. Without excluding other mechanisms (many of them could play a role after the remodeling of the structure of the digestive system), the specificity of gastric bypass in obese mice relates to major changes in the sensations of hunger and to rapid improvement of glucose control. 1) The induction of IGNG plays a major role in changing the sensations of hunger, and in restoring insulin sensitivity of endogenous glucose production. 2) The restoration of the secretion of GLP-1 and insulin plays a key additional role, in this context of insulin sensitivity recovered, in the improvement of postprandial glucose tolerance. It is noteworthy that the occurrence of a net portal release of glucose during the post-absorptive period has been recently confirmed 6 days after gastric bypass in morbid obese.[42] Moreover, the improvement of insulin sensitivity (and not the changes in GLP-1 or insulin secretions) has been recently suggested underlying the improvement in glucose metabolism shortly after bypass in obese diabetics.[43] The findings in mice may therefore perfectly apply to what takes place in humans.

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