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ORIGINAL ARTICLE

Sleeve Gastrectomy in Metabolic Syndrome for Nonmorbid Obese Patients: Is this the Future for Diabetes Treatment?

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ABSTRACT

During the development of surgical treatments, there have been so many improvements and challenging task that have lead surgeons to treat patients with new procedures and new indications.

Gastrectomy surgery initially was performed for cancer surgery. Now it is a worldwide performed procedure for complete healthy stomachs, but the main indication its weight loss, and all the physiological improvements that this procedure will bring to the patients' health.

During the bariatric surgery development, there have been different choices for different indications and different patients, depending on a variety of conditions and data that take evidence based medicine, to approve that this procedures can be accepted in the surgical field.

All the studies that have been showing improvement of medical conditions in obese patients, and had compared different type of procedures (Gastric Bypass, Duodenal Switch, Biliopancreatic Divertion, Sleeve Gastrectomy), led surgeon in different part of the world to take indications of surgery beyond weight loss. Being proved by previous analysis, that most of the patients get remission or cure, of comorbidities before an statistically significant weight loss, this study was led to perform vertical sleeve gastrectomy in patients with overweight, nonobese, that where diagnosed with metabolic syndrome (MS). Ten patients where operated (f = 6 m = 4), all of them met at least three criteria for MS (National Cholesterol Education Program Adult Treatment Panel III Citeria), 100% had diabetes mellitus (DM) as a criteria. After surgery the patients where followed up to 12 months and the mean body mass index (BMI) achieved overall was 22.58 kg/m^2 being the minimum 18.8 kg/m^2 (f = 22.28 m = 22.44). The total mean weight loss overall was 64.95 $\pm$ 12.6 kg, and the mean percentage of weightloss was 35% of initial weight with no clinical significance in the patients and 70% had remission of DM.

Keywords: Bariatric surgery, Diabetes remission, Metabolic surgery, Metabolic syndrome, Nonobese, Sleeve gastrectomy.

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INTRODUCTION

Obesity and its comorbidities have been the pillars of procedures and investigations to reduce the morbidity and mortality of this preventable disease. Obesity is the second cause of preventable deaths in US after smoking, therefore, this disease is making of bariatric surgery, one of the most performed gastrointestinal procedures in US. In obese patients, main indication of consult in bariatric clinics is not the esthetic aspect but a clinical problem due to morbidity that causes severe weight, like hypertension, diabetes, gout, etc.

Bariatric surgery was initiated in the 1990, with the specific indication of treatment of morbid obese patients, and the main goal of this procedures is to establish an anatomical restructure, for restrictive and metabolic gastrointestinal absorption modification.[1] The main objective of this procedures is to reduce weight, but during the experience of surgeon performing and investigating long-term outcomes of this procedures, it's been shown that comorbidities are improved even before weight loss begins.[2]

Therefore, the metabolic changes that this procedures involves, and the metabolic improvement in patients with metabolic syndrome (MS), took expert surgeons in this field to research if it is possible to improve diabetes mellitus (DM), hypertension, dyslipidemia, which all are diagnostic criteria of MS. And with several data published of improvement of this criteria with deferent type of bariatric procedures, in nonmorbid obese patients,[3-6] we decided to add more data performing a restrictive gastric procedure that can improve MS and remission of DM in nonobese patients.

METABOLIC SYNDROME

Metabolic syndrome (MS) was described by The World Health Organization (WHO) in 1998. Based that insulin resistance was the center pillar to the pathophysiology of MS, the WHO criteria had to determine insulin resistance in patients. Fasting glucose level above 100 mg/dl or impaired glucose tolerance (IGT), defined as a glucose level above 140 mg/dl, after ingestion of 75 gm of glucose load during an oral glucose tolerance test. Alternatively, other measures could serve as evidence of insulin resistance, such as an elevated homeostatic model assessment of insulin resistance (HOMA-IR)

value. In addition to this absolute requirement for insulin resistance, two additional criteria of five, have to be met, to stablish MS. These included obesity, hypertension, dyslipidemia and microalbuminuria.

In 2001, the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) defined the MS if three or more of the following five criteria are met: waist circumference over 40" in men or 35" in women, blood pressure over 130/85 mm Hg, fasting triglyceride (TG) level over 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl in men or 50 mg/dl in women and fasting blood sugar over 100 mg/dl. This definition does not require that any specific criterion be met, only that at least three of five criteria are met. This definition will not imply that the main cause of MS is the insulin resistance or obesity.

METABOLIC EFFECT OF BARIATRIC PROCEDURES

The Role of the Intestinal Hormones

Previous investigations have demonstrated the rising levels of intestinal hormones segregated to luminal space during postoperative stages of bariatric patients. Neuroendocrinal stimulation and negative feedback in hormones in obese patients are marking an important role in DM control and stimulation. Parietal cells in gut secrete hormones that will directly and indirectly act over glycemic control. The peptides made in the gut and released into the circulation plays a crucial role in the regulation of energy homeostasis, by signals that influence the central melanocortin system.[18] These gut hormones cause hunger and satiety effects and thus, have an integral role in appetite regulation. Therefore, a gut-brain axis can be established to maintain and regulate insulin/incretin secretion and glucagon/glucose blood levels. This gut hormones include: glucagon-like peptide-1 (GLP-1), peptide YY (PYY), ghrelin, cholecystokinin (CCK), glucose-dependent insulinotropic polypeptide (GIP), oxyntomodulin (OXM), and pancreatic polypeptide (PP). This hormones act as an incretin by augmenting the insulin response to nutrients and slowing gastric emptying inhibiting the glucagon secretion in a glucose-dependent manner.

Studies performed in laboratory models, GLP-1 has been shown to expand islet mass by stimulating pancreatic β-cell proliferation and induction of islet neogenesis, and it also promotes cell differentiation.[20] A recent study by Laferrère et al showed early after Roux en-Y gastric bypass (RYGB), the greater GLP-1 and GIP release and improvement of incretin effect are related not to weight loss but rather to the surgical procedure itself,[20] suggesting that this could contribute to improved glycemic control after RYGB even in patients with less obesity.

The ghrelin hormone (GH) is a 28 amino acid peptide presenting a unique n-octanoylation modification on its serine in position three, catalyzed by ghrelin O-acyl transferase. Ghrelin is mainly produced by a subset of stomach cells and also by the hypothalamus, the pituitary and other tissues. Transcriptional, translational, and post-translational processes generate ghrelin and ghrelin-related peptides. Homo- and heterodimers of growth hormone secretagogue receptor, and as yet unidentified receptors, are assumed to mediate the biological effects of acyl ghrelin and desacyl ghrelin, respectively. Ghrelin exerts wide physiological actions throughout the body, including growth hormone secretion, appetite and food intake, gastric secretion and gastrointestinal motility, glucose homeostasis, cardiovascular functions, anti-inflammatory functions, reproductive functions and bone formation.

Ghrelin hormone its produced in parietal cells of the fundus of the stomach, thus, in patients that undergo SG, the fundus its removed, improving the weight loss effect and gut hormonal response to GH suppression.

It is been described that GH levels after SG are lower than in patients with RYGB, and the overall evaluation after 12 months, ghrelin levels maintained suppressed and significant suppression after food intake was observed.[22]

BACKGROUND

Several studies and have been performed to establish long-term outcomes for metabolic changes in bariatric surgery, and the main body mass index (BMI) weight loss in different procedures for morbid obese patients.[1,8] And several meta-analysis and randomized trials, have showed that complete and partial remission of diabetes, in morbid obese patients (defined as completely no diabetes medication intake and maintained normalized glucose levels), after 5 years follow-up, its 78%[10] and the reduction of overall death, in this group of patients, its more than 90%.[11]

The effects on weight loss, and metabolic changes between the different bariatric procedures will depend on the patient selection for each procedure, and an adequate preparation and follow-up, regardless of the main BMI of the patient before surgery. And adequate selection of patients to undergo bariatric procedures will improve the patient's outcomes. Therefore, the American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic and Bariatric Surgery, have already suggested guidelines for bariatric procedures, and suggested that bariatric procedures could be performed in patients ranging from 30 to 34.9 BMI,

with diabetes, and quoting the lack of long-term data to stablish complete and long-term resolution.[9]

The importance of metabolic changes with bariatric procedures have being reported in some studies, such as De Paula[12] et al that have demonstrated an 82% of diabetes resolution, even in normal and overweight patients, with a mean BMI of 23.1 and 28.3 respectively.

There are two main anatomical mechanisms in which bariatric surgery takes its effects. The first it is creating anatomical change to minimize the space of food intake, and creating a hormonal effect, directly changing hunger stimulation by hormones that are produced in specific cells in gastric fundus, such as GH. And the second, it is creating secreting limbs for the gastric and biliopancreatic digestive juices, to bypass a specific gastrointestinal segment that it is responsible of absorptive mechanisms.

There are procedures that are created to stablish this two anatomophysiological effects at the same time, like duodenal switch with pancreatobiliary diversion. And all of this mechanisms have proved to produce adequate glycemic control, with weight loss effects, depending on each procedure, in nonmorbid obese patients and in patients only with overweight patients.[12,14]

Based on this findings the medical-surgical field has encountered a new perspective of clinical outcome. The treatment of metabolic disorders, without obese morbidity.

Several studies have evaluated different types of bariatric procedures. Performed in patients under 35 BMI, even in patients with normal weight, all of them have achieved glycemic control, regardless of weight control mechanisms (Table 1).[13] In some of them, the role of gastric hormones and the relation between gastric anatomy and insulin resistance have been analyzed and described.[3,6,14]

Results in insulin resistance and β-cell dysfunction tests, showed different type of improvements with different procedures. Not all studies have evaluated this variables. But, it described that the nonweight loss effect of bariatric surgery in nonobese patients has an direct impact on the incretin pancreatic-stimulation.[19] Therefore, weight loss has a very important effect on improving insulin sensitivity and reversing MS, even in patients with BMI < 30%.

Table 1: Glycemic control in patients that overcome bariatric procedures

Case study	*Cases*	*Female*	*Male*	*Mean BMI*	*% Glycemic control*
M Frenken[15]	16	8	8	32	100
Kwang Yeol Paik[16]	12	4	8	27.9	66
Wu Q, Xiao Z, Cheng Z, Tian H[6]	8	5	3	31.5	83
M Cerci, MI Bellini, F Russo[7]	25	15	10	33.2	86
Ricardo V Cohen[3]	66	40	26	32.5	88
Aureo L DePaula[17]	202	59	143	29.7	86.40
Total	358	131	198	31.13	85

The procedures described in different studies includes RYGB, sleeve gastrectomy, bilio-pancreatic diversion with duodenal switch, and Ileal interposition with sleeve gastrectomy. In Table 1 shows an overall percentage of glycemic control at 12 months period after the procedure have being performed. And some of them describe that patients had achieved glycemic control without medication even before the hospital discharge and 72 hours after surgery.[7] The main percentage of patients that acquire glycemic control, after the procedures, varies from 60 to 100%, with a mean 85%. And the studies vary in the description of DM remission as some authors describe partial remission as main HbA1 < 6.5% without diabetes medication, and others < 7.0%, and complete remission if HbA1 < 5.6%. But the findings in each study have showed, overall, that bariatric procedures are better treatment of long-term patients with DM that medical therapy alone,[21] and surgical treatment will have a direct effect on other comorbidities, resolving hypertension in 58%, sleep apnea in 80%, hypertriglyceridemia resolved in 58%, hypercholesterolemia resolved in 64%,[3] and a prediction of 10 years risk of cardiovascular disease for each patient, calculated using the United Kingdom Prospective Diabetes Study (UKPDS) risk engine,[18] fell substantially after surgery 71%.[3] This are comorbidities of mild obesity that medical therapy for DM itself will not cure.

METHODOLOGY

Source of Data

This study was carried out in Guatemala city in a nutrition, bariatric and metabolic clinic, Metabolik, and the patients that were selected for surgery where operated with minimal access approach in an advanced laparoscopy center. Patients were selected from a multispecialty clinic specialized in diabetes and diabetes complications and over 125 patients charts, 32 where selected as candidates for preoperative evaluation, and 10 patients were selected for surgery.

Study Period

Patients were preselected in a retrospective manner, collecting information in medical records from January 2010 to May 2014. Evaluation of patients preselected was performed during July 2014, and procedures where performed during August to September 2014.

Method of Collection of Data

Information of patients admitted and evaluated with diagnostic and treatment of DM where collected from files.

Patients were selected as candidates based on parameters previously standardized, and they were contacted to perform a re-evaluation of DM diagnostic and treatment. A total of 32 patients where re-evaluated by nutritionist, internal medicine, phycologist, and laparoscopic surgeon. Only 10 patients where candidates for surgery after multispecialty evaluation, surgery information and consent, and contraindication of procedure has being ruled out.

Patients where admitted 24 hours previous to the procedure and stapled sleeve gastrectomy was performed. Invagination of the stapled line was done in all the patients with absorbable continuous intracorporeal suture and drainage was placed in all the patients as well. Gastrography was performed 24 hours after the procedure in all the patients.

Inclusion Criteria

Diagnostic of MS as described above. Tree criteria of five of the NCEP-ATP III definition for the MS. According to the NCEP-ATP III definition, MS is present if three or more of the following five criteria are met: waist circumference over 40'' in men or 35'' in women, blood pressure over 130/85 mm Hg, fasting TG level over 150 mg/dl, fasting HDL cholesterol level less than 40 mg/dl in men or 50 mg/dl in women and fasting blood sugar over 100 mg/dl or hemoglobin alpha 1 (HbA1) ≥7.5%. Because this parameters are based on a different standard physiognomy type, diet, economical status and socioeconomically environment, for this study we used the body mass index (BMI) as parameter of inclusion, and were included patients ranging from BMI >25 Kg/m² and <35 Kg/m².

Exclusion Criteria

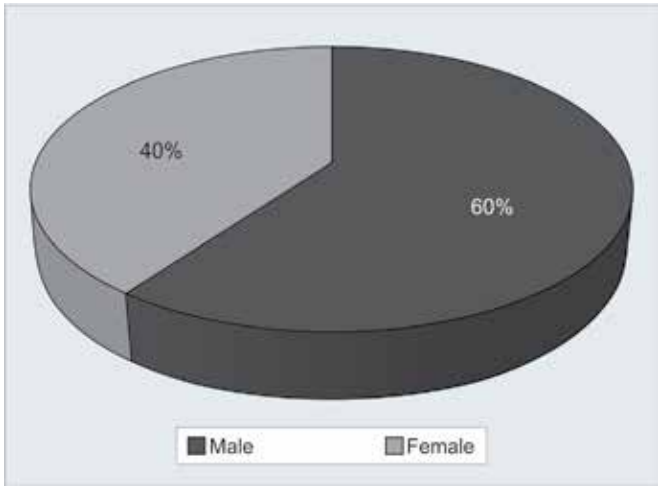
- Age over 55 years
- Diabetes diagnosed or treatment over 5 years
- Contraindications for surgery over evaluation by specialists.

Postoperative Follow-up

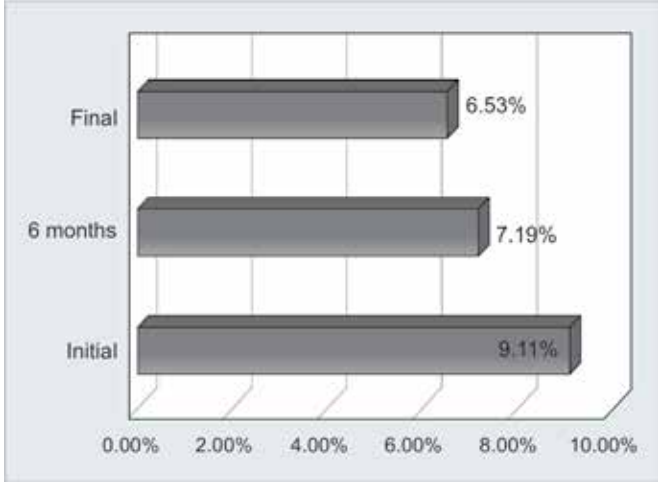
All patients were followed-up 2 weeks, 3, 6 and 12 months after the procedure, performing blood test and nutritional evaluation to gather the data of weight loss and MS criteria. Preoperative and postoperative data are presented.

DATA EVALUATION

Ten patients were operated, 60% (n = 6) male, 40% (n = 4) female (Graph 1). The overall mean age was 36.2 ± 17 years. All of the patients met criteria for MS, being fasting glucose plasma levels the criteria present in 100%, with a mean value of 242.5 mg/dl (f = 239 m = 248) and all the patients with preoperative HbA1 >7.9 (mean 9.11 ± 1.7) (Graph 2). The mean weight was 52.79 Kg (f = 81.36 m = 82.95) with a BMI of 29.4 Kg/m² (f = 28.69, m = 30.07) (Graph 3). Dyslipidemia was present in 80% of cases with mean TGs and human leukocyte antigen (HLA) of 200.5 mg/dl and 39.3 mg/dl respectively. Diagnostic of hypertension was made with routine blood pressure and was present in 80% of the patients but only four (50%) of them were under treatment. After the procedure, patients were routinely evaluated and data gathered after 12 months period. The mean BMI achieved overall was 22.58 Kg/m² being the minimum 18.8 Kg/m² (f = 22.28, m = 22.44) (Table 3). The total mean weight loss overall was 64.95 ± 12.6 Kg, and the mean percentage of weight loss was 35% of initial weight (Table 2). The hemoglobin A1c below 7% was achieved by 80% of patients and below 6.5% by 60% (Graph 4). Fasting glucose levels decreased overall from 242.80 to 98.50 mg/dl. The overall HbA1 decreased from 9.1% to 6.6%. Triglycerides levels decreased from



Graph 1: Gender of patients



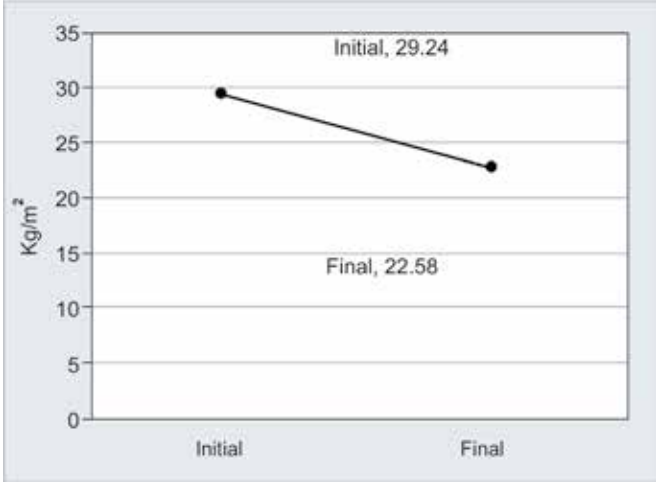
Graph 2: hemoglobin alpha 1 overall improvement after sleeve gastrectomy

Table 2: Total weight loss (kg)

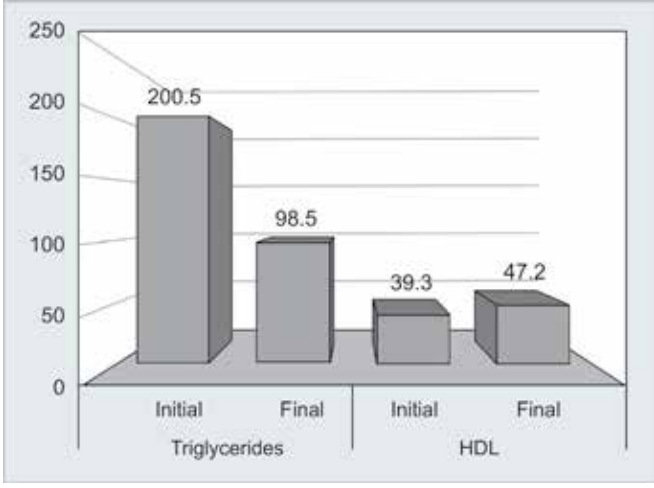
Patient	*Initial*	*6 Months*	*12 Months*	*Total weight loss*	*Percentage*
1	45.45	38.18	27.49	17.96	39.52
2	35.54	28.79	22.45	13.08	36.82
3	38.22	30.96	26.94	11.29	29.53
4	35.95	29.12	21.84	14.11	39.25
5	35.54	28.43	21.61	13.93	39.20
6	32.64	28.07	23.02	9.62	29.48
7	33.47	30.79	25.87	7.60	22.72
8	38.22	30.88	20.07	18.15	47.48
9	40.91	31.09	21.76	19.15	46.80
10	38.22	34.02	28.92	9.31	24.35
Mean	37.42	31.03	24.00	13.42	35.87

Table 3: Body mass index reduction overall

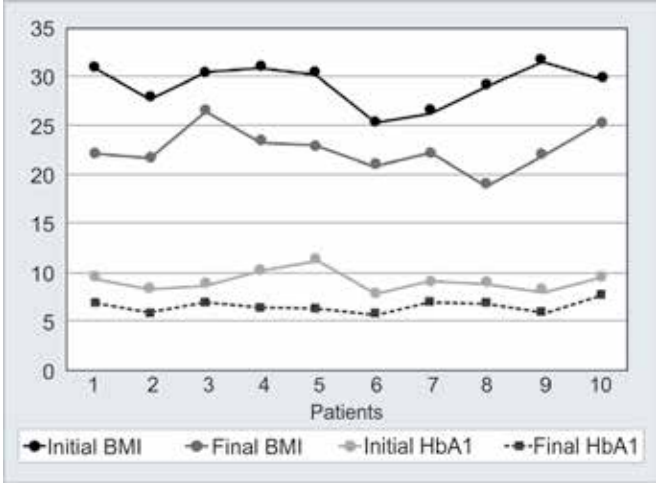
	BMI reduction		
Patient	*Initial*	*6 Months*	*Final*
1	30.86	25.93	22.22
2	27.70	22.44	21.61
3	30.52	28.08	26.55
4	30.89	25.02	23.17
5	30.16	24.13	22.92
6	25.45	21.88	20.87
7	26.40	24.29	22.18
8	29.10	23.57	18.91
9	31.51	23.95	22.06
10	29.79	26.52	25.32
Mean	29.24	24.58	22.58



Graph 3: Mean BMI reduction overall



Graph 5: Lipids improvement overall after 12 months



Graph 4: Body mass index and HbAl decrease over 12 months period after sleeve gastrectomy

a mean of 200.5 to 98.5 mg/dl, and mean HDL raised from 39.3 to 47.20 mg/dl (Graph 5). From the 80% of the patients that had hypertension, blood pressure had normalized (< 140/90 mm Hg) in 90% of the patients without hypertension treatment. Only one patient continued with oral medication for hypertension and DM but had improvement in the overall clinical evaluation.

One patient had gastric leak that was observed and treated with drainage and had to continue with special nutritional support and clinical evaluation during 3 weeks.

CONCLUSION

The MS was diagnosed in 10 patients according to the NCEP-ATP III definition. And the overall outcome of the patients was that 90% of the patients had less than three criteria out of five described to diagnose MS. The total temporary remission without medication of DM was achieved in 60% and no patient suffered from malabsorption complications or went underweight. The overall BMI reduction for nonobese patients with sleeve gastrectomy was 22.6 Kg/m² and the minimum achieved by one patient was 18.91 Kg/m² without complications and with an adequate nutritional evaluation and support. There is still a lot of information to be gathered, and it would make the surgical knowledge even wider, to make international general consensus about the procedures, processes and variables to be analyzed and measured during the surgical treatment of nonobese metabolic patients. But the data gathered so far, indicate that performing a restrictive,

malabsorptive gastrointestinal procedure, can cause a remission of one of the most worldwide challenging illness and improving the quality of life of the patients that undergo a metabolic surgical procedure.

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