Changes in Level of Ghrelin Post Laparoscopic Sleeve Gastrectomy

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ABSTRACT

Background: *Although sleeve gastrectomy classified as a restrictive procedure in treatment of morbid obesity, it seems to be more than just a mechanicalbarrier to food consumption because the removal of the gastric fundusand part of the body of the stomach. as the fundus the main source of ghrelin hormone , sleeve gastrectomy results in a significant reductionof serum ghrelin levels and alterations in gastric emptying.* ***The aim of the study*** *is to detect the effect of laparoscopic sleeve gastrectomy on the level of ghrelin hormone and its role in weight loss, and to detect a correlation between EBWL and drop in ghrelin hormone level.* ***Methods****: The study included 30 morbidly obese patients with BMI from 46.2 to 62.2 Kg/m2 with obesity related comorbidities and had failed trials of conservative management , all of them underwent LSG and the ghrelin level was measured preoperatively at the day of the admission then after 1 month of the operation.* ***Results:*** *In the present study , the drop in the body weight 1 month after sleeve gastrectomy was 9.3%, the drop in ghrelin hormone level was 21.25%.* ***Conclusion:*** *the decrease in the appetite of all patients indicates that the resection of the main source of ghrelin hormone play an important role in the postoperative weight loss. However no correlation was found between the percentage of EBWL and the percentage of ghrelin hormone drop 1 month following laparoscopic sleeve gastrectomy.*
Keywords: *Key words : stomach - ghrelin- sleeve gastrectomy*

INTRODUCTION

Obesity is the second leading cause of preventable death after smoking. Annually, obesity-related diseases account for 400,000 of premature deaths.**(SAGES 2008)**

A combination of genetics, environmental issues, and behavioral factors may contribute to the condition.Consumption of high-calorie foods, consumption of too much food, and a sedentary lifestyle all work together to create this condition. Obesity is associated with the development of diabetes mellitus, hypertension, dyslipidemia, arthritis, sleep apnea, cholelithiasis, cardiovascular disease, and cancer. **(NIH 1998 & SAGES 2008**)

Morbid obesity is defined as severe obesity that threatens one's health and can shorten lifespan**.** Obesity can be treated medically and surgically. Medical treatment for obesity is difficult, because the amount of weight lost is small and patients tend to regain most of the weight. Operations designed to result in significant and long-lasting weight loss in patients who are severely obese are called bariatric surgery.

The term *bariatric surgery* is derived from the Greek words *baros* (weight) and *iatreia* (medical treatment)**.** Body mass index (BMI) describes relative weight for height and correlates significantly with an individual's total body fat BMI is based on height and weight and applies to adults of both sexes. BMI is calculated as follows: BMI equals weight in kg/height in m^2 or weight in lb/height in square inches.**(1)**

Although several classifications and definitions for degrees of obesity are accepted, the most widely accepted is the World Health Organization (WHO) criteria based on BMI. Under this convention for adults, grade 1 overweight (commonly and simply called overweight) is a BMI of 25-29.9 kg/m^2. Grade 2 overweight (commonly called obesity) is a BMI of 30-39.9 kg/m^2. Grade 3 overweight (commonly called severe or morbid obesity) is a BMI greater than or equal to 40 kg/m^2.

The surgical literature often uses a different classification to recognize particularly severe obesity. In this setting, a BMI greater than 40 kg/m^2 is described as severe obesity, a BMI of 40-50 kg/m^2 is termed morbid obesity, and a BMI greater than 50 kg/m^2 is termed super obesity.

The definition of obesity in children involves BMIs greater than the 85th (commonly used to define overweight) or the 95th (commonly used to

define obesity) percentile, respectively, for age-matched and sex-matched control subjects.[2]

Ghrelin is synthesized as a preprohormone, consisting of a 23 amino acid signal peptide, the mature 28 amino acid ghrelin sequence and a 66 amino acid C-terminal region coding for obestatin[3].

Ghrelin needs to have an octanoyl group attached to Ser to be biologically active This posttranslational modification is mediated by the enzyme ghrelin-O-acyltransferase (GOAT), a member of the membraneboundacyltransferase family, in the endoplasmic recticulum[4].

GOAT uses predominantelyoctanoic acid derived from the diet as substrate for ghrelin octanoylation [5].

The unacylated form of ghrelin does not bind to the GRLN-receptor. Nevertheless, it is present in much higher levels than the acylated form in plasma and tissue The ghrelin receptor is a G-protein coupled receptor of which two alternatively spliced variants exist [6].

The GHS-R1a form (GRLN-R) is a classical 7-transmembrane domain receptor and is the active form of the receptor. The GHS-R1b form is truncated, with only 5-transmembrane domains, and without any clear physiological function. The GRLN-R has a constitutive activity of about 50% of the maximal activity10 and is able to dimerize with the dopamine receptor subtype 1, the cannabinoid 1 receptor, the melanocortin 3 receptor and the 5-HT2C receptor in the brain, in this way attenuating GRLN-R signaling.[7]

Similar to ghrelin, the GRLN-R is also widely distributed, suggesting a pleiotropic function for ghrelin.[8]

The gastric fundus contains 10 to 20 times more ghrelin per 1 gram of tissue than the duodenum with diminishing concentrations being found in the jejunum and ileum.[9]

Ghrelin levels rise before every meal and decline with food intake, suggesting a role for ghrelin as a meal initiation factor.[10]

Ghrelin release during fasting is mediated via activation of the autonomic nervous system. There is evidence for the involvement of both cholinergic and adrenergic neurotransmission, involving b1 adrenergic receptors onthe ghrelin cell, in the release of ghrelin.[11]

Plasma ghrelin levels in humans decline sharply after each meal.[10]

Ghrelin stimulates food intake when administered both peripherally and centrally by communicating directly, via the bloodstream, or indirectly, via GRLN-Rs on vagal afferents, with the arcuate nucleus in the hypothalamus.[12] Ghrelin also appears to be involved in the rewarding properties of food intake.[13]

In addition to these central effects, ghrelin is also an adiposity signal, altering expression of enzymes involved in storage and oxidation of fat in adipocytes.[14]

PATIENTS & METHODS

This study had been conducted in Cairo University hospitals in the period between February 2013 and August 2013. The study comprises 30morbidly obese patients indicated for bariatric surgery after failure of conservative measures for management of their morbid obesity. All patients in the study have tried and failed, for at least 6 months, to lose weight using diet, exercise and/or medication.

The age of the study population ranged between 24 and 45 years with averageof 34.2 years. The study comprises 9 malesand 21 females.

The BMI of the study population ranged from 46.2to 62.2 kg/m^2 with average 52.5 kg/m^2.Their weight ranged from 110 to 200 kg with average 135.9 kg& height from 150 to 182 cm with average 161.2cm.

Different options for management of morbid obesity were discussed in details with the patients with emphasis on the benefits and more importantly the potential complications and side effects of the different bariatric surgical procedures.

Inclusion Criteria

Subjects are considered appropriate candidates for the study if they fulfill the following criteria:

Obese patients with BMI more than 40 or more than 35 with co- morbidity

Exclusion Criteria

Sweet eaters and patients with GERD.

Technique

Laparoscopic Sleeve Gastrectomy:

All procedures took place under general anaesthesia with the patient lying in supine position. After induction of 15 mmHg pneumoperitoneum, 5 trocars were inserted with sizes of 5, 10 and 12 mm. Division of the

gastroepiploic, short gastric and posterior fundic vessels is done starting at 4 cm proximal to the pyloric ring all the way till the angle of His using the (ultracision Harmonic scalpel) **(Harmonic; Ethicon Endosurgery, Cincinnati, OH, USA)**

Once the dissection part is over, a 36 Frbougie is introduced orally by the anaesthisiologist through the oesophagus and inside the stomach. The surgeon then guides it along the lesser curvature and into the pyloric channel and duodenal bulb.

Gastric transection begins 4 to 6 cm proximal to the pylorus. A 60-mm, green or gold cartilage, is placed across the antrum through the right midepigastric port and fired. The second stapler is placed approximately 1 to 2 cm from the border of the lesser curvature in the direction of the GE junction. The bougie must be held in position during this part of the procedure until completion of the stomach transection to avoid stapling across a displaced bougie.

Sequential firings of the stapler along the border of the bougie on the lesser curvature completes the gastric transection at the left crus. After completing the transection, the entire staple line is inspected carefully to make sure that the staples are well formed especially at the antrum where the stomach is thickest. The transected stomach then is removed through one of the 10-mm port sites. After completion of the gastric transection the integrity of the staple line is tested by Methylene blue with the pylorus compressed by a surgical grasper. Methylene blue is injected (via the bougie) into the stomach and the staple line is inspected carefully to exclude macroscopic leaks of the suture line. The dye is then removed from the stomach, as is the bougie. All trocar sites are closed with 0 Vicryl (Ethicon) using a suture passer to prevent abdominal wall hernias.

Ghrelin assay:

Venous sample were collected in pre-child tube preoperatively at the day of hospital admission & 1 month following the operation. After centrifugation at 4 ºC serum was separated and stored – 20 ºC

Postoperative follow up:

In the postoperative period, all patients were given 3rd generation cephalosporins, anticoagulants, analgesics, proton pump inhibitors and antiemetics. Gastrographin meal was done to all patients on the 1st day postoperative to exclude any leakage or stricture. In day one, all patients started oral fluids (if tolerated) after performing the study. Most patients were discharged 24-72 h postoperative after meeting the discharge criteria of no bleeding, no leakage and no other complications.

The patients were evaluated for changes in comorbid conditions and quality of life (QOL), in addition to weight loss& symptoms &signs of any complication .sample taken from patient one month after operation to measure the level of ghrelin hormone .

RESULTS

The number of cases done was 30 morbid obese patients (9males ,21 females). All procedures were performed laparoscopically without conversions.

Age : The age of cases ranged between 24 and 45 years with a mean ±SD34.2 ±6.3years. Height The height of cases ranged between 150 and182 cm with a mean ±SD161.2 ±6.9 cm .

Weight before operation.The age of cases ranged between 110and 200 kg with a mean ±SDof 135.9±16.8 kg

Weight 1 month after operationThe age of cases ranged between 99and 180 kg with a mean±SDof 122.4±15.8 of kg

BMI before operation The BMI of cases ranged between 62.22 kg/m^2and46.2kg/m^2 years with a mean±SD52.5±4.6 of kg/m^2

BMI 1 month after operation The BMI of cases ranged between 56.9 $kg/m^2$and 41kg/m^2 years with a mean±SD47.3±4.5 of kg/m^2

Ghrelin hormone level before operation The ghrelin hormone levelof cases ranged between 13µg/Land 22µg/L years with a mean±SD16.0±2.3µg/L

Ghrelin hormone level 1 month after operation The ghrelin hormone level of cases ranged between 7.5µg/L and16µg/L years with a mean±SD12.6±1.8µg/L.

Table(2): Nostatistical correlation between the ghrelin hormone drop and EBWL after one month

	Mean± SD	**Test value**	**X_2**
Weight in kg before operation	135.9±16.8	36.437	**<0.001**
weight in kg one month after operation	122.4±15.8		
BMI before operation	52.5±4.6	44.066	**<0.001**
BMI) after operation	47.3±4.5		
Ghrelin before operation (µg/L)	16.0±2.3	7.991	**<0.001**
Ghrelin after operation (µg/L)	12.6±1.8		

Correlation between drop in body weight and drop in ghrelin postoperative

	Ghrelin difference	
	r	**P value**
EBWL after 1 month	0.085	0.656

DISCUSSION

Our main objective was to examine the changes in the circulating level of ghrelin hormone after LSG and their role in underlying mechanism of weight loss.

Ghrelin is a potent orexigenic polypeptide hormone that is produced from endocrine cells in oxyntic glands of gastric fundus.[15]

Although LSG classified as a restrictive procedure , sleeve gastrectomy seems to be more than just a mechanical barrier to food consumption because the removal of gastric fundus and part of body of stomach result in significant reduction of serum ghrelin levels.[16]

Our study is conducted in 30 morbid obese patient (9males, 21 females) their age range from 24 to 45 years, their height range from (150 to 182 cm) and their preoperative data according to weight range from (110 to 200kg) with mean of 135.9kg, BMIrange from 62.22to 46.2 kg/m^2 with mean of 52.5 kg/m^2 and ghrelin hormone level range from 22 to 13 µg/L with mean of 16 µg/L .

Post operative data one month after operation showed drop in body weight that range from 99to 180 kg with mean of 122.4 kg with percentage of drop 9.3%,drop in BMI that range from 41to 56.9 kg/m^2 with mean 47.3 kg/m^2 with percentage of drop 9.9%, drop in level of ghrelin that range from 7.5 to 16 µg/L with mean 12.6 µg/L with percentage of drop 21.25%.

Study on 11 morbid obese patients (3 males , 8 females) with average of age 35.2 ± 10.7 year old , average of body weight 120.2 ±19.8 kg , average of BMI 44.7 ±5.3 these patients were investigated before and 1week ,3 month and 1 year after surgery there was marked reduction in body weight and BMI. The average body weight 1 week after operation was 116.9 ± 18.7 kg ,3 months after operation average weight was104±17.7 kg ,1 year after operation the average weight was86.3±15.6 .Average BMI 1 week after operation 43.4 ±5.2 kg/m^2 , 3 months after operation 39.8± 5.8 kg/m^2,1 year after operation 32.5 kg/m^2

In same study ghrelin hormone there was reduction in level of ghrelin hormone . Preoperative average level was 451±36 pg/ml .1week , 3 month and 1 year after operation the average level was 302±18,305±22 and 363±17pg/ml respectively with percentage drop in level of ghrelin hormone 33.4%, 32.3%,19.5% respectively.[17]

Another study on 15 morbid obese patients (3 males ,12 females)with average weight 130 kgm , average BMI 46.8kg/m^2 . these patients were investigated preoperative , 6 months and 12 month after operation . There was marked decrease in level of ghrelin hormone post operatively. Preoperative level of ghrelin was 23.69 pg/ml , 6 month after operation 15.58 pg/ml,1 year after operation 15.43pg/ml. with percentage drop in level of ghrelin hormone 34.3%,34.8 respectivly.[18]

Another study on 16 morbid obese patients with average age 30.6±7.8 years ,average weight 122±18.1 kg, average BMI45.1±3.6.patient were assigned to LSG pt were reevaluated 1,3,6,and 12 month after operation.

Average preoperative ghrelin hormone level was 638±189 pg/ml, average ghrelin hormone

level 1,3 month after operation was 550±136 ,610±188pg/ml respectively with percentage drop in level of ghrelin hormone 16%, 4% respectively.[19]

Although we believe that this study can be of great benefit for the better understanding the hormonal mechanism of action of laparoscopic sleeve gastrectomy, yet more patients and longer periods of follow up are needed.

SUMMARY & CONCLUSION

Laproscopic sleeve gastrectomy has proven a very effective bariatric operation and now considered the leading bariatric procedure in many bariatric centers worldwide.

Ghrelin regulate the secretion of growth hormone release and is potent orexigenic (appetite-stimulating) peptide. This effect of ghrelin is mediated by the activation of ghrelin receptors in the hypothalamus / pituitary area.

Because the gastric fundus, known as the main localization of ghrelin producing cells, is resected by sleeve gastrectomy ,plasma ghrelin level is expected to decrease following surgery.

In the present study , the drop in the body weight 1 month after sleeve gastrectomy was 9.3%, the drop in ghrelin hormone level was 21.25% and decrease in the appetite of all patients indicates that the resection of the main source of ghrelin hormone play an important role in the postoperative weight loss. However no correlation was found between the percentage of EBWL and the percentage of ghrelin hormone drop 1 month following laparoscopic sleeve gastrectomy.

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