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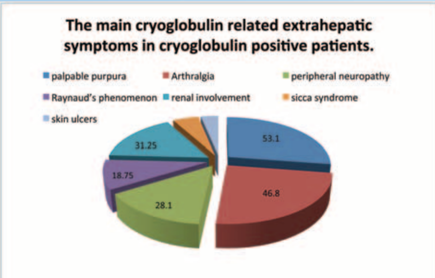

Figure 1: Main cryoglobulin-related extrahepatic symptoms in cryoglobulin-positive patients. (Page 461).

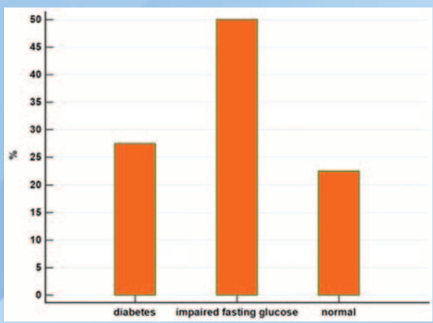

Figure 1: (Frequency of patients without prior history of diabetes (n=120) according to fasting blood glucose.) (Page 589).

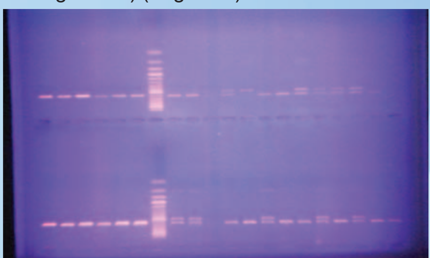

Figure 1:PCR product bands at 557 base pair (bp) and interleukin-12B gene polymorphism bands at 557, 454 and 103 bp. (Page 809).

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The significance of bariatric surgery in Egyptian patients with metabolic syndrome: a multicenter study

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Background
Obesity and metabolic syndrome (MS) are global health concerns, with high rates of cardiovascular morbidity and mortality. The current guidelines recommend lifestyle modifications as the best initial treatment for obesity and MS. However, lifestyle interventions have modest effects and high 1-year failure rates. Bariatric surgery offers more weight loss with sustained effect in the long term.
Aim
The aim was to assess the effect of bariatric surgery on MS and all its components and to detect the probable risk factors for persistent MS after bariatric surgery in Egyptian patients.
Patients and methods
This prospective multicenter study included 250 obese patients who underwent bariatric surgery and completed 1 year of postoperative follow-up. The patients were evaluated preoperatively and at 1, 6, and 12 months postoperatively for presence of MS and its components according to criteria of the third report of National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III).
Results and discussion
After 1 year of follow-up, the percentages of patients who had MS, obesity, type 2 diabetes mellitus, hypertension, hypertriglyceridemia, and low high-density lipoprotein-cholesterol were significantly decreased from 92, 100, 84, 50, 74, and 50% to 17, 2, 8, 17, 42, and 25%, respectively. Smoking, family history of obesity, and less percentage of excess weight loss were the most important risk factors for persistence of MS after bariatric surgery.

Keywords:
bariatric surgery, diabetes, dyslipidemia, excess weight loss, hypertension, metabolic syndrome, obesity

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Introduction

Obesity is a global health epidemic and is defined as a BMI 30 kg/m^{2}or higher. According to the severity, obesity is divided into three categories: class 1 (BMI 30–35), class 2 (BMI 35–40) and class 3 (BMI≥40). Obese patients have an increased risk of premature mortality, with significantly higher incidence of hypertension, dyslipidemia, type 2 diabetes mellitus (T2DM), metabolic syndrome (MS), coronary artery disease, stroke, renal failure, obstructive sleep apnea and malignancy, such as breast, endometrial, colon and liver cancers, as well as gallbladder disease, osteoarthritis, fatty liver disease, pregnancy disorders and depression [1].

Additionally, obese patients may be exposed to weight-based social and health system discrimination that results in mood disorders and decreased quality of life [2].

Obesity may be caused by environmental factors, medical conditions, disabilities, medications, unhealthy food choices, meal timing, chronic sleep deprivation, long-term stress (elevated cortisol), nicotine smoking and aging. Environmental causes for weight gain can start in utero with improper maternal nutrition in addition to poverty or sedentary lifestyle with inactive work and low physical activities [3].

Medical conditions that commonly cause weight gain include hypothyroidism, polycystic ovary syndrome, Cushing's syndrome and psychiatric disorders, such as binge eating disorder and night eating syndrome. Some medications may cause weight gain such as corticosteroids, insulin, thiazolidinediones, tricyclic antidepressants, selective serotonin reuptake inhibitors, anticonvulsants and β-adrenergic blockers [4,5].

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Meal timing (night-time eating) and unhealthy food choices, including excessive consumption of high-caloric foods such as sugar and refined carbohydrates, potato chips, French fries, sugar-sweetened beverages and processed meats, contribute to the most weight gain [6].

MS is a constellation of obesity, fasting hyperglycemia or T2DM, blood pressure greater than 130/85 or hypertension and dyslipidemia. The pathophysiology of MS is complex, with insulin resistance (IR) being the pivotal underlying mechanism. In obese patients, the visceral adipose tissue acts as an endocrine organ producing multiple cytokines and adipokines, which in turn produce a systemic low-grade inflammation affecting mainly the blood vessels of the vital organs causing significant cardiovascular morbidity and premature death [7,8].

The recent guidelines for management of obesity recommended early identification of overweight and obese persons, patient education on the benefits of weight loss, dietary modification, more physical exercises and the choice of a proper bariatric surgery. Lifestyle modification (low-caloric diet and physical exercises) remains the gold standard approach with the goal of losing 5–10% of body weight. Patients' education about lifestyle interventions is recommended to be on-site, to last for at least 6 months, with more than 14 sessions, and to continue for at least a year [9].

Lifestyle interventions lead to modest weight loss. However, the results are not usually maintained, with the 1-year failure rate being greater than 95%. Moreover, in most cases, they have little effects on cardiovascular morbidity and mortality, kidney failure, and progression of nonalcoholic steatohepatitis (NASH) to liver cirrhosis or hepatocellular carcinoma [10].

Bariatric surgery, which is recommended for patients with BMI greater than 40 or BMI greater than 35 with obesity-related comorbidities, produces a greater and more sustained weight loss with greater effects on obesity-related comorbidities than all other options of obesity management, reducing the mortality risk by 89% in those morbidly obese patients. Bariatric surgery improves obesity and MS by body weight reduction, loss of visceral fat, gastric volume restriction, malabsorption and alterations of gut hormones. Gut hormonal alterations include increased release of glucagon-like peptide 1, peptide YY, ghrelin, gastrin, glucagon and cholecystokinin. These hormonal changes induce early satiety and excess insulin release. Weight loss efficacy depends on the initial patient weight and the type of surgical procedure, as gut hormonal alterations occur with Roux en-Y gastric bypass (RYGB) more commonly than other procedures [11,12].

Recent studies showed that bariatric surgery produced remission of T2DM with improved diabetic nephropathy and retinopathy more than lifestyle intervention and medical therapy. Moreover, bariatric surgery was shown to improve the histological features of NASH even in the advanced stages of NASH fibrosis [10,13,14].

Bariatric surgery is divided into restrictive procedures and a combination of restrictive and malabsorptive procedures. Restrictive procedures include laparoscopic gastric plication, laparoscopic adjustable gastric band and laparoscopic sleeve gastrectomy (SG). However, SG is well known to produce changes in intestinal hormones, bile acid metabolism, microbioma and the gut-brain signaling. The restrictive and malabsorptive procedures include mainly RYGB and biliopancreatic diversion. According to the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) registry report 2017, the most commonly performed bariatric surgeries worldwide were RYGB (46.3%) and SG (43.6%) [15,16].

Patients and methods

This is a prospective multicenter study, carried out in the University Hospitals of Zagazig, Banha, and Tanta Faculties of Medicine in Egypt. The study included 250 obese patients who underwent laparoscopic bariatric surgery (either SG or RYGB) from February 2015 till December 2017 and completed at least 1 year of follow-up postoperatively. The study was approved by the boards and the ethical committees of the three centers. Written informed consents were obtained from all patients.

Preoperatively, all patients were evaluated regarding full history taking, thorough clinical examination particularly for blood pressure, weight and height, with endocrine and nutritional evaluation. Investigations included complete blood count, liver and kidney functions tests, coagulation profile, serum thyroid stimulating hormone, 8 a.m. serum cortisol level, fasting blood sugar, glycosylated hemoglobin (HbA1c), fasting lipid profile [particularly serum triglycerides (TG) and high-density lipoprotein (HDL)-cholesterol], in addition to abdominal ultrasound.

The patients were also evaluated preoperatively for the presence of MS according to criteria of NCEP-ATP III where at least three of the following criteria identify presence of MS (obesity defined as BMI ≥30 kg/m^2, fasting blood glucose ≥100 mg/dl or T2DM, blood pressure ≥130/85 mmHg or hypertension, serum TG level ≥150 mg/dl, and/or serum HDL-cholesterol <50 mg/dl for women or <40 mg/dl for men) [17].

The inclusion criteria included BMI greater than 40 kg/m^2 or BMI greater than 35 kg/m^2 with obesity-related comorbidities, for example, T2DM, hypertension, dyslipidemia, MS and NASH.

The exclusion criteria included obesity secondary to genetic abnormalities or endocrine disorders such as hypothyroidism and Cushing's syndrome, and the patients who did not complete 1 year of follow-up after the surgery.

All patients were followed at 1, 6, and 12 months postoperatively, with emphasis on the clinical and laboratory criteria of MS.

Remission of T2DM, hypertension, and dyslipidemia was defined as fasting glucose level less than 100 mg/dl in addition to HbA1c less than 6.5%, blood pressure less than 140/90 mmHg and fasting serum TG and HDL-cholesterol less than 150 mg/dl and greater than 40 mg/dl for men or greater than 50 mg/dl for women, respectively, without the use of medications for at least 3 months.

The collected data were analyzed using the statistical package for the social sciences (IBM SPSS) software version 22.0 (2013; IBM Corp., Chicago, Illinois, USA). Analysis for quantitative variables was done using analysis of variance test whereas qualitative data were analyzed using χ^2-test for differences between proportions. Univariate and multivariate analyses were done to determine the probable risk factors of persistent MS after bariatric surgery. The level of significance was taken at *P* value less than 0.05.

Results

Our prospective multicenter study included 250 obese patients, of which 67% were females and 26% were smokers, with a mean age of 34 years. After 1 year of follow-up, the percentage of patients who have MS, obesity, diabetes, hypertension, hypertriglyceridemia and low HDL- cholesterol was significantly decreased from 92, 100, 84, 50, 74, and 50% to 17, 2, 8, 17, 42, and 25%, respectively. Our results showed that remission of T2DM, HTN, hypertriglyceridemia & MS occurred in ~90%, 66%, 44% & 81% of patients, respectively. There were no statistically significant differences between the preoperative clinical characteristics of SG and RYGB patients, except for that higher percentage of SG patients had hypertriglyceridemia than RYGB patients. Statistically significant percentages of SG patients had faster obesity resolution 6 months than RYGP patients postoperatively. However, RYGB patients had more statistically significant 1-year percentage of excess weight loss and higher percentage of infection after surgery.

Discussion

Obesity is a chronic disease resulting from excessive visceral fat deposition to the degree that causes multiorgan damage secondary to IR and systemic low-grade inflammation. It represents a global epidemic with significant cardiovascular morbidity and mortality. MS, which includes obesity, T2DM, hypertension, and dyslipidemia, carries a high risk of ischemic heart disease, stroke, NASH and renal failure [18].

The recommended approach for management of obesity and MS includes lifestyle modifications (diet and exercises), medications and bariatric surgery. Although lifestyle interventions remain the gold standard for obesity management and the best initial treatment for other components of MS, they have high failure rate at 1 year, with unsatisfied effects on cardiovascular morbidity and mortality. Bariatric surgery offers a widely accepted alternative approach for management of obesity and other features of MS, with more initial weight loss that is sustained on the long term in comparison to lifestyle interventions and medications [10].

The aim of our study was to evaluate the effects of bariatric surgery on MS and all its components and to determine the probable risk factors of persistent MS after bariatric surgery in Egyptian patients.

Our prospective multicenter study included 250 obese patients, of which 67% were females and 26% were smokers, with a mean age of 34 years. Family history of obesity and DM was present in 42 and 59% of patients, respectively. Our results showed also statistically

Table 1 Preoperative and postoperative demographic data of the study patients

	Preoperatively (at baseline) (*N*=250) [*n* (%)]	Postoperative (*N*=250) [*n* (%)]		
		1 month postoperatively	6 months postoperatively	12 months postoperatively
Age (years)		33.6±8.9		
Sex: female		167 (66.8)		
Smoking	64 (25.6)	59 (23.6)	60 (24)	66 (26.4)
Diabetes	209 (83.6)	153 (61.2)	67 (26.8)	21 (8.4)
Hypertension	125 (50)	84 (33.6)	51 (20.4)	42 (16.8)
Obesity (BMI $>30\,kg/m^2$)	250 (100)	243 (97.2)	105 (42)	6 (2.4)
Hyper-TG	186 (74.4)		165 (66)	104 (41.6)
Low HDL-cholesterol	125 (50)		109 (43.6)	63 (25.2)
HbA1c (%)	9.4±1.7	7.9±2.6	7.1±0.7	1.2±5.1
Family history of diabetes		146 (58.4)		
Family history of obesity		105 (42)		
MS	231 (92.4)			43 (17.2)

HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; MS, metabolic syndrome; TG, triglycerides.

significant improvement of MS and all its features after bariatric surgery. After 1 year of follow-up, the percentage of patients who have MS, obesity, diabetes, hypertension, hypertriglyceridemia and low HDL-cholesterol was significantly decreased from 92, 100, 84, 50, 74, and 50% to 17, 2, 8, 17, 42, and 25%, respectively, as shown in Table 1.

Our results showed that remission of T2DM occurred in ∼90% of patients. This goes in agreement with the results of Ahluwalia [18], Buchwald *et al.* [19] and Cohen *et al.* [20] who reported remission of T2DM in 88.4, 88, and 78.1%, respectively, after bariatric surgery.

However, our results were more than those reported by Schauer and colleagues, Panunzi and colleagues and National Database for the American Society for Metabolic and Bariatric Surgery, which reported remission rates of DM of 42, 71 and 62% with RYGB and 52% with SG, respectively [21–23].

This can be explained by the relatively lower mean age of our patients (34 years), thus, the less duration and fewer complications of diabetes as well as the preoperative and postoperative endocrine and nutritional assessment allowing better perioperative glycemic control. Therefore, our patients had lower diabetes remission scores, which indicates better chance for diabetes remission as reported by Ugale *et al.* [24].

Our results showed remission of hypertension in 66.4% of patients. This is comparable to the results of Schiavon *et al.* [25], Lee *et al.* [26], and Ahluwalia [18] who reported remission rates of hypertension after bariatric surgery of 63, 58, and 58%, respectively.

The remission effect of bariatric surgery on hypertension could be owing to relief of renal vessel compression by fatty tissue, remission of the systemic inflammation and its proliferative effects on the vascular endothelium, and probably owing to hypometylation of CpG sites (cg00875989 and cg09134341), which were metylated in obese patients before the surgical treatment and were associated with hypertension [27,28].

Our results showed that remission of hypertriglyceridemia occurred in 44% of patients, whereas remission of low HDL-cholesterol occurred in ∼50% of cases. These results were comparable to those of Cohen and colleagues who reported remission of hypertriglyceridemia in 58% of cases and remission of hypercholesterolemia in 64% of cases. However, our results were less than those reported by Yang *et al.* [29] and Zhang *et al.* [30], who observed a 100 and 92.5% remission of dyslipidemia after RYGB and 75 and 84.6% after SG, respectively, after 3 years of follow-up [20].

Our results showed remission of MS as defined by NCEP-ATPIII criteria in 81.3% of patients. This is comparable to the results of Martini *et al.* [31] and Boza *et al.* [32] who reported MS remission in 86 and 76% of cases, respectively, after bariatric surgery.

Before bariatric surgery as shown in Table 2, our study showed that presence of obesity, hypertension or dyslipidemia had no statistically significant effect on occurrence of MS. Only diabetes was significantly more common in obese patients with MS than those without MS. This is in agreement with Martini *et al.* [31] who reported that diabetes and higher HbA1c were the only significant

Table 2 Variables of metabolic syndrome in patients with and without metabolic syndrome at baseline and 1 year postoperatively

	Preoperatively (at baseline) (*N*=250) [*n* (%)]		*P* value	1 year postoperatively (*N*=250) [*n* (%)]		*P* value
	With MS (*N*=231)	Without MS (*N*=19)		With MS (*N*=43)	Without MS (*N*=207)	
BMI (kg/m^2)	42.1 (38.6–46.1)	40.9 (35.5–45.6)	0.167	30.9 (30.1–32.1)	25.9 (21.2–32.1)	<0.001
Diabetes	198 (85.7)	11 (57.9)	*<0.001*	18 (41.9)	3 (1.4)	<0.001
Hypertension	112 (48.5)	13 (68.4)	0.096	31 (72.1)	11 (5.3)	<0.001
Obesity	231 (100)	19 (100)	N/A	5 (11.6)	1 (0.5)	<0.001
Hyper-TG	173 (74.9)	13 (68.4)	0.533	39 (90.7)	4 (1.9)	<0.001
Low HDL-cholesterol	119 (51.5)	6 (31.6)	0.096	42 (97.7)	21 (10.1)	<0.001

HDL, high-density lipoprotein; MS, metabolic syndrome; TG, triglycerides

Table 3 Risk factors for persistent metabolic syndrome 1 year after bariatric surgery

	12 months postoperatively (*N*=250) [*n* (%)]		*P* value
	With MS (*N*=43)	Without MS (*N*=207)	
Age (years)	34.8 (22–46)	30.8 (21–40)	0.242
Sex: female	29 (67.4)	138 (66.7)	0.922
Smoking	19 (44.2)	47 (22.7)	<0.004
BMI (kg/m^2)	30.9 (30.1–32.1)	25.9 (21.2–32.1)	0.439
Family history of obesity	27 (62.8)	78 (37.7)	<0.003
Family history of DM	23 (53.5)	123 (59.4)	0.476
% WL at 1 year	26.1%	36.6%	0.019
SG	33 (76.6)	123 (59.4)	0.02
RYGB	10 (23.4)	84 (40.6)	

DM, diabetes mellitus; MS, metabolic syndrome; RYGB, Roux en-Y gastric bypass; SG, sleeve gastrectomy; WL, weight loss.

metabolic disorder preoperatively in patients with persistent MS.

However, after bariatric surgery, all features of MS were significantly more common in patients with persistent MS than in those with resolved MS, indicating a highly significant improvement of all features of MS after bariatric surgery, as shown in Table 2. These results match those of Eid *et al.* [33] and Casella *et al.* [34], who reported statistically significant improvement of all components of MS after bariatric surgery.

In Table 3, we compared patients who had persistent MS and those who had resolution of MS after bariatric surgery regarding their preoperative clinical characteristics, type of surgery performed, postoperative BMI and percentage of excess weight loss to assess the predictors of persistent MS after bariatric surgery. Our results showed that smoking, family history of obesity and less percentage of excess weight loss were the most important risk factors for persistence of MS after bariatric surgery. Moreover, we found a similar effect of both SG and RYGB on resolution of MS after bariatric surgery. However, RYGB was more statistically associated with MS resolution than persistence.

There are multiple theories that explain the relationship between smoking and MS. Smoking is thought to increase adiposity, IR, leptin resistance, endothelial dysfunction and induce low-grade systemic inflammation. It also increases triglyceride levels and reduction in HDL-cholesterol by increasing sympathetic activity [35,36].

The metabolic effects of tobacco smoking are variable. Nicotine is known to have appetite-suppressing effects that may help weight loss. However, nicotine is a sympathomimetic that increases IR, mostly through enhancing catecholamines release. It also increases visceral fat production in relation to total body fat owing to excess cortisol production [37].

Our results showed that family history of obesity is a statistically significant risk factor for persistent MS after bariatric surgery. This goes in agreement with Lent *et al.* [38] who reported that familial predisposition, genetic and environmental factors, parental obesity and familial dietary habits are significant risk factors for obesity, type 2 DM and MS in bariatric surgery patients.

We also found that the percentage of excess weight loss is a statistically significant predictor of MS resolution after bariatric surgery. The less percentage of excess weight loss after bariatric surgery gives a higher chance of persistence of MS. This copes with the results of Batsis *et al.* [39] who reported that the percentage of excess weight loss after bariatric surgery was a significant predictor of MS resolution.

As shown in Table 4, there were no statistically significant differences between the preoperative clinical characteristics of SG and RYGB patients,

Table 4 Comparison between sleeve gastrectomy and Roux en-Y gastric bypass patients regarding preoperative clinical characteristics and postoperative outcomes

	SG % (*N*=156) [*n* (%)]	RYGB % (*N*=94) [*n* (%)]	*P* value
Age	35±7.2	34±5.7	0.253
Sex: female	98 (62.8)	69 (73.4)	0.085
Smoking	42 (26.9)	22 (23.4)	0.539
BMI	41.3±2.5	41.7±3.2	0.272
DM	127 (81.4)	82 (87.2)	0.231
HTN	81 (51.2)	44 (46.8)	0.501
Low HDL	76 (48.7)	49 (52.1)	0.603
High TG	125 (80.1)	61 (64.9)	0.008
Family history of obesity	70 (44.9)	35 (37.2)	0.233
% WL at 1 year	52.8	66.1	0.034
Absent obesity 6 months postoperatively	99 (63.5)	46 (48.9)	0.022
Bleeding	1 (0.6)	1 (1.1)	0.666
Infection	1 (0.6)	4 (4.3)	0.043
Leakage	None	2 (2.1)	0.069
Mortality	None	None	NA

DM, diabetes mellitus; HDL, high-density lipoprotein; HTN, hypertension; MS, metabolic syndrome; NA, not available; RYGB, Roux en-Y gastric bypass; SG, sleeve gastrectomy; WL, weight loss.

except for that higher percentage of SG patients had hypertriglyceridemia than RYGB patients. Statistically significant percentages of SG patients had faster obesity resolution 6 months postoperatively than RYGP patients. However, RYGB patients had more statistically significant 1-year percentage of excess weight loss and higher percentage of infection after surgery. This goes in agreement with Arapis *et al.* [40] who reported better weight loss and more postoperative complication in RYGB patients compared with SG patients.

Conclusion

Obesity and MS are major worldwide health problems with significant cardiovascular morbidity and premature mortality. Bariatric surgery is an accepted option for management of MS in a selected group of patients with a better and more sustained weight reduction in the long term. Bariatric surgery produced a significant resolution of MS and all its features (obesity, T2DM, hypertension and dyslipidemia) after 1-year follow-up. The most important detected risk factors for persistent MS after bariatric surgery were smoking, family history of obesity and less percentage of excess weight loss after surgery. Moreover, RYGB was more commonly associated with MS resolution.

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Conflicts of interest

There are no conflicts of interest.

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