**Name of Journal:** *World Journal of Experimental Medicine*

**Manuscript NO:** 67367

**Manuscript Type:** REVIEW

**Weight regain after bariatric surgery: Promoters and potential predictors**

Demerdash HM. Weight regain after bariatric surgery

Hala Mourad Demerdash

**Hala Mourad Demerdash,** Department of Clinical Pathology, Alexandria University Hospitals, Alexandria 21311, Egypt

**Author contributions:** Demerdash HM is in charge of all the works of this manuscript.

**Corresponding author: Hala Mourad Demerdash, MD, PhD, Consultant Physician-Scientist, Professor,** Department of Clinical Pathology, Alexandria University Hospitals, Azaareta, Khartoum Square, Alexandria 21311, Egypt. demerdashh@yahoo.com

**Received:** April 22, 2021

**Revised:** June 7, 2021

**Accepted:** September 14, 2021

**Published online:**

**Abstract**

Obesity is globally viewed as chronic relapsing disease. Bariatric surgery offers the most efficient and durable weight loss approach. However, weight regain after surgery is a distressing issue as obesity can revert. Surgical procedures were originally designed to reduce food intake and catalyze weight loss, provided that its role is marginalized in long-term weight maintenance. Consequently, it is essential to establish a scientifically standardized applicable definitions for weight regain, which necessitates enhanced comprehension of the clinical situation, as well as have realistic expectations concerning weight loss. Moreover, several factors are proposed to influence weight regain as psychological, behavioral factors, hormonal, metabolic, anatomical lapses, as well as genetic predisposition. Recently, there is a growing evidence of utilization of scoring system to anticipate excess body weight loss, along with characterizing certain biomarkers that identify subjects at risk of suboptimal weight loss after surgery. Furthermore, personalized counseling is warranted to help select bariatric procedure, reinforce self-monitoring skills, motivate patient, encourage mindful eating practices, to avoid recidivism.

**Key Words:** Weight regain; Bariatric surgery; Hormones; Diet; Exercise; Genetic factors

Demerdash HM. Weight regain after bariatric surgery: Promoters and potential predictors. *World J Exp Med* 2021; In press

**Core Tip:** Obesity constitutes an enormous health struggle worldwide. Weight regain after bariatric surgery is a distressing issue that requires extensive study; various influencing factors as well as predicting biomarkers must be considered carefully before making decision for surgery, selecting bariatric procedure as well as close long term monitoring and support are essential.

**INTRODUCTION**

Morbid obesity is the consequence of cumulative imbalances between energy intake and energy expenditure[1]. It is a serious chronic disease causing various comorbidities reducing affected persons’ well-being and lifespan. Bariatric surgery is an option in morbidly obese subjects when lifestyle and non-surgical strategies evidenced incompetent. It produces superior reduction in body weight along with relief of associated comorbidities compared to nonsurgical interventions[2]. There are several reputable techniques adopted in management of morbid obesity worldwide. However, Laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) are two most common weight loss procedures due to their significant weight reduction and durability[3,4].

Following bariatric surgery, body contouring occurs when operated subject finally achieves the required body mass index (BMI) in a comprehensive and stable basis, exhibiting proper nutritional, psychological and clinical aspects[5]. Since during weight loss, those subjects may encounter nutritional depletion along with metabolic adaptation, which compromises healing demands and the whole response to surgical stress[6,7]. Consequently, expected weight loss after successful surgical procedure progresses through several anticipated phases[3] (Table 1). However, stability phase outcome is frequently humbled in considerable number of patients, with regain of 5-10 kg, after weight stabilization which is expected and considered normal[4]. Though, in long-term surveillance, there is growing perception concerning the possibility of weight regain after bariatric surgery[6]. Kraschnewski *et al*[8] stated that less than 20% of operated subjects who achieved expected weight loss through various surgical procedures within the first year, experienced variable extent of weight regain within five years.

**IDENTIFICATION OF POSTOPERATIVE WEIGHT REGAIN**

In order to determine weight regain, it is essential to comprehend the definition of weight stability. Considering that it is expected to observe minor fluctuations in body weight. Rubin defined weight stability as less than 2.5 kg variation in body weight per month over the preceding three months[9]. Given that this issue is subjective; Various literatures proposed a postoperative period of 12-18 mo till body weight becomes stable, with no more fluctuations through the succeeding 4-6 mo[10-12]. Accordingly, definition for weight regain requires careful description by determining patient characteristics, such as baseline BMI, age, gender, surgical procedure, general health perceptions, preoperative comorbidities[13].

Voorwinde *et al*[14] introduced six definitions for weight regain after bariatric surgery based on reports of various researches: (1) An increase of more than 10 kg from body weight denoting weight regain after achieving desired weight stability; (2) An increase of more than 25% excess weight loss (% EWL) after achieving weight stability phase; (3) An increase in BMI of 5 kg/m2 after attaining steady BMI; (4) Weight regain to a BMI more than 35 kg/m2 from baseline after long standing follow up *e.g.,* five years; (5) Any weight regain; and (6) An increase more than 15% of total body weight from baseline after long period follow up *e.g.,* five years[14]. This is determined by using following equation (total body weight at end of follow up period – total body weight at baseline/ total body weight at baseline × 100 > 15[13,15].

Percentage of EWL refers to reduction in body weight after bariatric surgery. In brief, a subject whose ideal body weight ought to be 70 kg but weighs 130 kg before bariatric procedure, implies 60 kg excess body weight. Appropriately, an optimum weight loss response is generally termed as 50% EWL[10,16]. Then long term postoperative expected weight loss is approximately two-thirds (2/3) of initial body weight (60 kg excess weight) or 40 kg[17]. The ideal weight is customarily determined on the basis of body mass index of 25 kg/m2[13]. This is obtained from a formula where the square of subject’s height in meters is multiplied by 25. For instance, if subject’s height is 1.8 m: (1.8 × 1.8) × 25 then ideal body weight is 81 kg[13].

In pursuit for clinically applicable outcome indicators, some authors referred to percentage of total weight loss (%TWL) as the most accurate metric for calculating weight loss post-operative[10,12]. They claimed that %TWL is minimally affected by perplexing preoperative variables as initial BMI, age, comorbidities particularly diabetes. Therefore, %TWL is simple, easy to estimate and understand[12,18]. It is often utilized in appraising behavioral and pharmacotherapeutic literature[18].

%TWL is determine by formula: Pre-operative body weight – Current body weight) / (Pre-operative body weight) × 100**[**12].

Some authors recommend that %TWL applied routinely to quantify weight loss and suggest that ≥ 20%TWL within 12 mo become the established benchmark to identify good responders to weight loss surgery along with reporting of remission or improvement of obesity comorbidities. As well as to track long-term weight regain after bariatric surgery[18,19]. However, Corcelles *et al*[20] concluded that use of single variable such as %TWL to delineate weight-loss outcomes can generate deceptive evaluation of patients results. Consequently, they recommended use of more than one definition for weight loss including change in BMI or BMI loss percent EWL, percent %TWL, percent excess BMI loss, and percent total BMI loss[20].

***Weight changes in two most common bariatric procedures: LRYGB vs LSG***

In terms of short-term outcome; RYGB yields 60%- 80% of excess body weight loss (EBWL) within the first year. It is generally recommended for morbid obesity with BMI over 40[18,19]. On the other hand, LSG yields weight loss at a slower, steadier rate, about 60% of excess body weight is lost within first 18 mo[21,22]. However, several studies revealed that both procedures are equally effective measures for short-term obesity management (< 36 mo) in super obese subjects[23,24].

Pertaining to long-term outcomes; five years postoperative follow up significant weight regain is sporadic for patients undergoing RYGB 2.5%, whereas patients undergoing LSG 14.6%[11]. This conclusion was supported by other studies[25,26]. It is worth mentioning that bariatric surgery was originally intended to downsize the stomach in an attempt to reduce food intake and prompt weight loss, but research studies approved that it has a minimal role in long-term weight loss maintenance[15,16,27].

**DETERMINANTS OF WEIGHT REGAIN**

The etiology of weight regain tends to be multifactorial including behavioral and dietary habits, mental health, anatomical changes, hormonal variations and genetic aspects[27,28]. Certainly, it results from a combination of components, which vary among individuals’ overtime[29]. Moreover, anticipation of weight regain should be mandatory in consultation with all parties; patient, surgeon and nutritionist prior to surgery, as it may influence patient’s ability to avoid weight regain[28]. Madan *et al*[30] have observed that only 10% of patients could recall being enlightened about the possibility of weight regain after surgery.

***Dietary habits and behavioral practices.***

Negative eating habits and lack of dietary modifications are risks to long-term postoperative failure. Therefore, to obtain maximum benefit from surgery, patients should be encouraged to adhere to appropriate dietary habits[31]. Since, weight regain commonly occur as result of poor assortment of healthy diets rather than excessive intake[29]. Sawamoto *et al*[32] reported that persistence of poor preoperative eating behavior after surgery was associated with 68.6% failure rate. Also, Felsenreich *et al*[33] found that unhealthy eating habit correlated with rate of 59% weight regain within 10 years after surgery. Nikiforova *et al*[34] obtained similar results, they proposed the explanation for weight regain include; sleeve or pouch dilation according to procedure performed, enhanced ghrelin levels, lifestyle behaviors and lack of follow-up support. Additionally, Mitchell *et al*[35] found a higher incidence of weight regain among subjects who consumed limited number of meals, less than 5 small frequent meals, and often skipped breakfast. Owing to a false belief that decrease in number of meals aids supplementary weight loss, whereas actually ingestion of numerous small meals per day augments diet-induced thermogenesis and stimulates smaller insulin secretion[32].

**Healthy dietary deeds acknowledged among weight loss maintainers[36]:** (1) Commitment to daily intake of breakfast as it assists stabilization of blood glucose level[31]; (2) Consumption of ample amounts of water, as optimal hydration prevent oxidative stress, while losing more than 2% of body water causes altered body temperature control, increased both physical and mental fatigue[36]; (3) Greater protein intake about 1.0-1.5 g/kg of ideal body weight per day, restriction of sugar less than 5 gm per serving and less than 30% of daily calories fat[30,37]; and (4) Ingestion of nutrients with low glycemic index and high dietary fibers contents such as fruits and vegetables prolong intestinal absorption[31]. Accordingly, Nutritional follow-up monitoring is consistently regarded as a vital element of medical management after bariatric surgery[38].

***Mental health and psychiatric disorders***

In this respect adverse eating behaviors could be a crucial factor; including emotional binge eating described as episodes of overeating even when not hungry, on exposure to emotional stimuli or stress to extent of causing gastrointestinal discomfort[31]. Similarly, Grazing is repetitive unplanned eating of minor quantities of food with loss of control over this feeding, associated with some psychological disturbance[39]. Also, distracted passive eating implies hyperphagia in presence of an element disturbing one’s attention from the quantity of food ingested as chatting with a friend or watching television[27,40]. Moreover, some individuals may display cravings for fats and sweets, described as addictive personality or could be regarded as cortisol-mediated response to stress[41]. Sugar craving phenomenon may possibly be induced by central metabolic actions, as serotonin or dopamine imbalance, altered leptin levels[41]. Cognitive behavioral consideration proves more effective in curing maladaptive eating disorders than sole nutritional counselling without managing psychological part[42,43]. Authentically, psychological conditions as grazing could lead to weight regain postoperatively, regardless of surgery type in about 16%-39% of patients post-operatively[44-46]. This considerably high incidence necessitates accurate assessment, close monitoring and attention to guidelines for nutritional management postoperatively recommending eating slowly, chewing food thoroughly, and increasing the frequency of meals[42].

***Physical activity and lifestyle***

Physical inactivity is considered a valuable component criticized of having a role in weight regain along with as sleep deprivation (sleeping less than the recommended amount) and television watching more than two hours daily, all may be associated with reduced sensitivity to the internal satiety signals[36]. Similarly, Petit et al deduced that sleep deprivation augments mood changes, upsets glucose metabolism and appetite regulation[47]. They suggested that sleep replenishes glucose stores in neurons while the awake cycle depicts recurrent glycogen breakdown[47].

Corresponding to American College of Sports Medicine proposals for weight loss and prevention of weight regain for adults; entailed performance of 150 min per week of moderate or vigorous physical activity [moderate < 3-6 metabolic equivalents (METs), vigorous > 6 METs][48]. In view that experts assessed exercise performance in MET. Where one MET is expressed as the amount of energy spent to rest quietly, for average adult one calorie per every 2.2 pounds of body weight per hour[49]. This signifies that moderate activity is enough to burn 3 to 6 times as much energy per minute than lying quietly[50]. American Society for Metabolic and Bariatric Surgery encourages the increase in physical activity to a minimum of 30 min per day[48]. Notably, within the first year postoperative, physical activity contributes to enhanced oxygen consumption with prompt adaptability in heart rate and improved lipid profile[51]. While, Freire *et al*[52] depicted that it has a negligible effect on short-term weight loss, but assists long term weight loss maintenance. Some studies reported that subjects engaged in moderate to vigorous physical activity achieved a greater % EBWL compared to others less physically active 2-5 years postoperative[53-55].

***Anatomical modifications***

RYGB bears a long-term failure rate of 20%-35%, particularly in super-obese population (BMI > 50 kg/m2) due to gastro-gastric fistula or disrupted staple line[56]. Gastro-gastric fistula is a communication between pouch and stomach remnant, which permits food to cross duodenum reducing restrictive and malabsorptive potentials of RYGB, but is alleviated by surgical revision as biliopancreatic diversion or duodenal switch[57]. Even though wide gastrojejunostomy or pouch dilatation could be [anticipated](https://www.merriam-webster.com/thesaurus/anticipated#verb), if pouch is > 6 cm in length or > 5 cm in width[58,59]. Although, subjects who develop large pouches (> 50 mL) may comprise comparable weight loss to those with normal sized pouches[59]. However, this never omit contribution of large pouch to weight regain[57,58].

Consequently, Dayyeh *et al*[59] found that dilated gastrojejunal stoma after RYGB produces early gastric pouch emptying, they concluded that its’ diameter was correlated with weight regain. While in LSG weight regain may result from physiologic dilation of stomach remnant in the long run, or failure of complete removal of the gastric fundus[60]. This entails reduction in post-prandial satiety, allowing increased volume of food consumed, to the extent that 59% of patients regained more than 20% of their lost body weight[60,61].

***Hormonal/metabolic imbalance***

**Summary of gut hormone changes after surgery**: A chief focus after performing bariatric surgery is time interval of satiety hormones signifying early sense of fullness with smaller meals based on their release site[62]. Additionally, there is an overall agreement that great improvement in glycemic control accomplished are likely to be associated with alterations in the secretion of gastrointestinal hormones including hunger (ghrelin), satiety [glucagon-like peptide-1 (GLP-1) and peptide tyrosine tyrosine(PYY)], and energy balance[63].

LSG reduces the size of the stomach; stimulus for gut hormones secretion specifically GLP-1 is obtained by proximal alimentary signals, *e.g.,* increased cholecystokinin derived by entrance of hydrochloric acid, amino acids, or fatty acids into duodenum[64,65]. These changes influence release of ghrelin, PYY, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) as well as other gut hormones[65,66]. On the other hand, RYGB approach, eliminates the stomach and proximal small intestine, creating a small pouch and direct connection with distal gut, consequential variations in gut hormones secretion results from abrupt exposure of intestinal epithelium to nutrients, with subsequent stimulation of L- cells[66]. This is coupled with significantly suppressed ghrelin, elevated GLP1, PYY levels, along with high pH of undigested chyme possibly contributing to diminished food intake and altered energy expenditure, leading to weight loss[66,67]. Also, exclusion of the upper segment of the intestine, where the GIP producing K-cells are present, would entail diminished levels of GIP, and is likely to constrain fat accumulation and intuitively supports long-term weight loss maintenance[68].

***Hormonal disparity associated with weight regain***

**GLP-1:** Acts to lower blood glucose by stimulating insulin release and inhibiting glucagon secretion[65]. GLP-1 is decomposed by ubiquitous dipeptidyl peptidase-IV (DPP-IV) enzyme[69]. Conversely, DPP-IVexpression seems to be mediated by epigenetic influences as hyper- methylation of the DPP*-*IV promoter due to unhealthy lifestyle or genetic predisposition[69]. Also, deregulation of metalloproteinases coincident with fibrosis in different adipose tissue depots were found to induce insulin resistance in adipocytes and skeletal muscle cells[70]. Specifically, morbidly obese subjects coupled with insulin resistance undergoing bariatric surgery, may confront suboptimal response of GLP-1 associated with possibility of weight regain[71]. Those subjects achieve better response in terms of glycemic control and weight loss upon management with postoperative DPP-IV inhibitors[72].

**Ghrelin/leptin ratio:** A range of subjects may display a robust neuroendocrine-metabolic starvation feedback to initial weight loss that promotes metabolic energy preservation and favors weight regain after bariatric surgery[73]. Furthermore, Serum leptin is expected to decline by 50% after the first postoperative week, with an additional decrease during the first postoperative year[67]. Consequently, good responders revealed greater ghrelin to leptin ratio during fasting and post-prandial preoperative assessment contrasted with those who encountered weight regain[73]. On the other hand, operated patients who gradually regain weight, encountered resistance to the satiety-inducing effects of leptin[74]. The condition is characterized by elevated circulating leptin levels and decreased leptin sensitivity[75].

**Growth hormone:** Growth hormone (GH) is another sporadic factor principally regulated by two hypothalamic peptide hormones: GH-releasing hormone (GHRH) and somatostatin[76]. Though, further brain signaling pathways are participating in the control of GH secretion. Obese subjects may exhibit multiple endocrine defects that correspond to body composition variations, as increased visceral fat and decreased fat-free mass[77]. Theoretically, combination of various somatotropic axis alterations might be accountable for diverse scores of GH and insulin growth factor-1 (IGF-1) deficiency in obese subjects. Among the underlying neuroendocrine alterations of low plasma GH levels in obesity, associated with GHRH, somatostatin dysregulation[77]. Few studied recommended preoperative evaluations of GH/IGF-1[78]. They proposed that prevalence of persisting GH and/or IGF-1 levels below the normal range for six months after surgery was correlated with a significantly insufficient weight loss[77,78]. The GH/IGF-1 axis is assessed by evaluating serum IGF-1 Levels and the GH peak after stimulation by (GHRH + arginine hydrochloride)[78].

**Reactive hypoglycemia:** Establishes another hypothesis for weight regain as a consequence of dumping syndrome, mediated by hypersecretion of GIP and GLP-1, which may induce B cell expansion and insulin hypersecretion as long term consequences[79,80]. Besides this, Hypoglycemia ensues in 64%-82% of subjects within 5 years postoperative. The assumption for its occurrence involve refined pancreatic B cells function and mass, improved insulin sensitivity, diminished ghrelin level[80,81]. Since glucose is perceived as a chief appetite mediator, several attacks of hypoglycemia due to substantial insulin hypersecretion after meals, may trigger appetite[82]. Relatedly, direct effect of insulin on lipid accumulation since one of major function of insulin is inhibition of lipolysis[81,83]. Hence existing information reveals that attenuated postprandial gut hormone feedback /or reactive hypoglycaemia may show a correlation between eating disorders and hormonal imbalance[75,84].

**Female menopause:** Female menopause would apparently reduce effectiveness of bariatric-surgery outcome; given that estrogens mediate the effects of reproductive axis function on weight regulation[85]. Asarian *et al*[86] concluded that surgery seems more effective for pre-menopausal women (or post-menopausal women receiving hormone replacement therapy) than climacteric women with lower levels of estrogen. Because estrogens powerfully regulate the satiating effect of gut hormones as GLP-1[76,85].

***Genetic predisposition***

Authentically, it is largely proposed that genetic and environmental aspects could modify the outcome of bariatric surgery, especially in the long run[87,88]. Exceedingly high baseline BMI > 50 kg/m2 is be associated with concomitant fast postoperative weight loss, besides greater risk of postoperative weight regain[89,90].

Numerous genes were identified as obesity related genes, and mutations of any produces rare monogenic forms predispose to obesity; including leptin gene, leptin receptor, pro-opiomelanocortin (POMC), melanocortin 4 receptor, melanocortin 3 receptor, fat mass and obesity-associated (FTO), insulin induced gene 2, G protein-coupled receptor 24, corticotropin releasing hormone receptor and corticotropin releasing hormone receptor[91]. Remarkably, mutations in the zone of leptin/melanocortin pathway in the central nervous system being essential in regulation of energy homeostasis appears to result in enhanced appetite and reduced satiety, consequently early postoperative failure[89].

Accordingly, generation of genome-wide association studies (GWAS) provides a reasonably rich source of information to illustrate the molecular mechanisms connecting gene regulation, lifestyle and environmental factors in defining the risk of obesity[92,93]. Thus GWAS has improved comprehension of common genetic variants and collectively elucidated approximately 6% of the variation in adult BMI[93,94]. Correspondingly, the current hypothesis asserts that patients carrying none or few number of risk alleles of obesity show more efficient weight loss after bariatric surgery than carriers of multiple risk variants[95]. Genetic risk scores is computed by summarizing risk related variants across the genome, through gathering information from various predictive single nucleotide polymorphism (SNP)[91].

Unfortunately, in spite of intensive genetic research, the molecular mechanisms are barely clarified[91,95]. The epigenetic alterations preceding or post-translational regulatory genes without changes in the nucleotide sequence, particularly methylation of DNA cytosine (C) represents an extremely stable modification[96]. Particularly epigenetic markers, in subjects who regained the weight loss induced by nutritional or surgical intervention displayed differential DNA methylation patterns in leukocytes or subcutaneous adipose tissue or compared to subjects successfully maintained their weight loss over a short or long periods[97].

Eventually, the methylation of genes involved in metabolic pathways exhibited changes after bariatric surgery. For example, weight regain is associated with hyper methylation of POMC and in turn, revealed higher melanocyte stimulating hormone-positive neurons[97]. On the other side, low methylation of neuropeptide Y gene is linked to hunger and satiety controlling peptides as ghrelin[98]. Furthermore, distinctive variants of FTO gene interrelate with dietary subscription, as high-protein regime benefits weight loss and improvement of body configuration in carriers of the FTO risk allele rs1558902, while carriers of FTO rs9939609 allele attained better weight loss response to low-fat hypocaloric diet[99].

Another epigenetic element is small non-coding RNAs (21-22 nucleotides), they are crucial for post-transcriptional regulation of gene expression. Single-stranded micro-RNA (miRNA) binds to a complementary target messenger RNA (mRNA) to disrupt translational processes[100]. Some studies reported short- and long-term miRNA profile changes after bariatric surgery in diverse tissues of both animal and humans that were associated with weight regain/or failure to achieve the desired body weight[101,102]. Accordingly, Obesity provoked changes in miRNA concentration within adipose tissues which promotes chemotaxis of macrophages and other immune cells towards the adipocytes. These miRNAs further impose chronic low grade inflammation, which sequentially may alter miRNA profile[103]. For example, miR-365 and miR-574, are proposed in adipose tissue hypertrophy through regulation of Early B cell factor 2 specific brown fat selective role involved in adipocyte differentiation *via* regulation of Peroxisome proliferator-activated receptor Gamma PPARγ, a ligand-activated transcription factor, involved in numerous cellular functions as lipid metabolism, glucose homeostasis and impediment of oxidative stress[104]. Therefore, they may represent prospective targets for non-surgical therapy of obesity and postulate novel biomarkers for predicting bariatric surgery outcomes[103].

**PREDICTORS OF WEIGHT REGAIN:**

An essential measure during evaluation of patients with obesity prior to surgery; is identification of attributes or biomarkers that could deduce improvement of the metabolic profile of candidates that benefits from surgery on long term. Also, to categorize subjects more susceptibility to regain weight after surgery[32].

***A greater weight reduction during early weight loss phase postoperative***

Initial prosperous weight loss within the first few months postoperative anticipated long term weight loss at 4 and 8 years, examining long-term impression of intensive lifestyle intrusion on obesity associated comorbidities and mortality[35,105]. Also, Vogels *et al*[106] assumed that comparatively high baseline BMI and fat mass were correlated with concomitant long-term weight loss maintenance during two years follow up period (< 10% regain). Alvarado *et al*[107] deduced better response upon requesting morbidly obese subjects to lose around 4.5-9 kg of weight, in few weeks instantaneously prior to bariatric surgery, they attained improved postoperative weight loss. Similarly, some studies assessed preoperative weight loss of less than 5% or 5%-10% of total body weight was accompanied with superior outcome[108,109], However, other studies concluded that extremely high baseline BMI above 50 kg/m2 was correlated with inferior postoperative weight loss (below 50% EWL)[110,111].

***Baseline insulin sensitivity***

Insulin regulates numerous metabolic processes within serval organ in body. Consequently, reduced sensitivity to insulin action is termed insulin resistance, *i.e.*, suboptimal response of various metabolic functions to normal insulin levels in blood[112]. It has a prime influence in predicting vulnerability to weight regain, and may be concluded through insulin resistance as defined by HOMA-IR[113]. Hence high baseline plasma insulin may be indicative of postoperative insulin resistance[112]. Similarly, Antuna-Puente *et al*[114] proposed that subjects with high plasma triglyceride concentrations were found to be insulin resistant. Kong *et al*[115] recommended applying a combination of biomarkers including elevated baseline fasting plasma insulin and inflammatory biomarkers as IL-6 levels, and the number of HAM56+ cells (macrophages) in subcutaneous white adipose tissue (WAT) to anticipate opposition to weight loss as well as susceptibility to weight regain with a prediction accuracy of 75%.Estimation of pancreatic β cell function (insulin secretion) and insulin sensitivity were calculated by using following formulas[116,117]:

(1) HOMA-IR = [Fasting insulin (uU/mL) × Fasting blood glucose (nmol/L)]/22.5.

(2) HOMA-β = [20 × fasting insulin (uU/mL)]/[Fasting blood glucose (mmol/L)-3.5].

(3) Quantitative insulin-sensitivity check index (QUICKI)= 1/[log fasting plasma insulin (uU/mL) + log fasting blood glucose(mg/dL)].

(4) Oral glucose tolerance test (OGTT): Fasting blood samples are drawn, then subject ingest 75 gm glucose load for OGTT. Glucose and insulin are measured in all blood samples obtained, usually at 0, 60, and 120 min or only 0 and 120 min during the OGTT.

(5) Matsuda index = 10000√ (FPI × FPG) × (x GPC × x IPC). Where FPI is fasting plasma insulin expressed as μU/mL, FPG is fasting plasma glucose expressed as mg/dL, x GPC is mean plasma glucose concentration after the load and x IPC is the mean insulin concentration after the load[117].

Expected normal ranges for above parameters: HOMA-IR normal range is less than 1.4, HOMA-β reference value is less than 81.7, while QUICKI index is less than 0.4 and MATSUDA index non diabetic range is less than 4.5[116,117].

***Plasma concentrations of total cysteine***

Plasma cysteine level is strongly connected with enlarged fat mass, probabilities of developing obesity and could be used as predictor of weight regain[118,119]. Cysteine is an essential sulfur-containing amino acid, that can form disulfide linkages, which simultaneously regulate protein structure and stability[120]. Circulating total cysteine (tCys) exists either as free cysteine homogeneous (cystine) or mixed (*e.g.*, homocysteine-cysteine) disulfides, and albumin-bound cysteine[121]. While cellular cysteine is the rate limiting precursor of intracellular antioxidant glutathione and prevail principally in reduced form[122]. Since plasma tCys is predominantly oxidized, high levels tCys, presume unfavorable outcomes, and is often related to obesity[120].

In addition, Cysteine enhances the activity of stearoyl-CoA desaturase-1 (SCD-1), which is a key enzyme for synthesis of monounsaturated fatty acids. SCD-1 introduces a single double bond at the Δ9, 10 of long-chain acyl-CoA substrates[123]. Its chief products are palmitoleic acid and oleic acid; the largely copious fatty acids in cholesterol esters, membrane phospholipids and triglycerides[123]. The activity of SCD-1 is also associated with the levels of sulfur containing amino acid, particularly cysteine. So SCD-1 suppression results in diminished fat deposits (regardless of food intake), enhanced insulin sensitivity and greater basal energy expenditure[123,124]. Accordingly, high plasma tCys observed to be positively linked to elevated total cholesterol, low density lipoprotein-cholesterol and triglycerides[125]. As it effectively inhibits hormone-sensitive lipase, and promotes adipocyte triglyceride and glucose uptake[125]. Hanvold *et al*[126] concluded that profound tCys elevation two years after RYGB was associated with weight regain.

***Plasma adipokines***

Some adipokines have displayed the ability to influence weight regain owing to their roles in energy expenditure and or food intake as adiponectin, retinol-binding protein 4 (RBP4), angiotensin converting enzyme (ACE) activity[127].

**RBP4:** RBP4 is transport protein for retinol (Vitamin A) secreted mainly by the liver and to a lesser extent by the adipose tissue. Munkhtulga *et al*[128] stated that the minor allele of regulatory RBP4 SNP was found to augment adipocyte RBP4 expression and was correlated with elevated BMI in Asian population. Wang *et al*[129] reported higher baseline RBP4 associated with compromised weight loss, they elucidated increased release of RBP4 in obese WAT owing to the presence of hypertrophic adipocytes during weight regain.In view that RBP4 carrying retinol is a precursor of ligands of retinoid X receptor, which activates peroxisome proliferator activated receptors modulating transcription of genes involved in fat metabolism and adipogenesis[130]. In this respect, elevated RBP4 level reflects stimulated adipocyte proliferation, adipogenesis and accordingly weight regain[131].

Additionally, RBP4 Links to insulin resistance through RBP4 associated effects comprising increased hepatic gluconeogenesis by [accentuating](https://www.merriam-webster.com/thesaurus/accentuate) the exhibition of phosphoenolpyruvate carboxykinase enzyme in the liver which simultaneously suppresses insulin signaling in skeletal muscle by blocking insulin-stimulated phosphorylation of insulin receptor substrate-1[132]. Moreover, glucose transporter GLUT4 protein level in human adipocytes correlates positively with the rate of glucose clearance and inversely with circulating RBP4 level[133].

**ACE:** ACE gene polymorphisms are associated with BMI and obesity[134]. Provided that immense amounts angiotensin II (Ang II), product of ACE activates adipocyte differentiation and consequently influence adipose tissue mass[135]. Moreover, Wang *et al*[136] observed that greater reduction in ACE level was coupled with stable body weight during follow-up and abstained tendency to weight regain. Velkoska *et al*[137] demonstrated the effect of ACE inhibitors on body weight management by reducing body water or *via* reduction in energy intake.

ACE is a carboxypeptidase that is expressed in many tissues including adipose tissue but predominantly in the vascular endothelium, brain and lung. The enzyme is anchored to cell membranes and is shed into the plasma by enzymatic cleavage[138]. Furthermore, a positive association between the weight loss induced change in serum ACE concentration and weight regain during *ad libitum* feeding (free feeding)[138,139]. A causal association appears between ACE and weight regain. However, the underlying mechanism remains unclear, in spite of the fact that ACE plays a role in many processes other than the regulation of blood pressure, such as inflammation, fibrosis and the regulation of food intake by the hypothalamus by reinforcing thermogenesis (though corticotrophin releasing hormone-autonomous mechanism)[136].

**Fibroblast growth factor 21:** Fibroblast growth factor 21 (FGF21) is a “myokine.” that stimulates the oxidation of fatty acids, production of ketone bodies, and inhibition of lipogenesis[141]. Kharitonenkov *et al*[141] proposed that it could be a prospective metabolic regulator and a potential anti-diabetic drug. FGF21 mRNA is expressed in gastrointestinal tract, brain, skeletal muscle, brown adipose tissue, and heart[142]. FGF21 is a molecule with a very short half-life of 1-2 h in absence of specific stimuli, due to enzymatic cleavage by fibroblast activation protein α (FAP), a serine protease that inactivates FGF21[143]. Interestingly, FAP is secreted from muscle during physical exercise[144]. Also, FGF21 is removed from circulation by renal clearance[140].

FGF21 acts as a fasting-induced hormone intended for the adaptive response to starvation and consumption of energy derived from tissues breakdown[145]. Several studies hypothesized relationship between energy expenditure, body weight regulation and FGF21[145-147]. Through provoking energy expenditure with acute low-protein diet (3% causes almost an average energy expenditure (adaptive thermogenesis) can identify individuals who are able to disperse the excess calories consumed as heat (“spendthrift”) opposed to those who are incapable (“thrifty”)[145]. The extent of the elevation in serum FGF21 level in condition of acute low-protein overfeeding is positively correlated with the acute change in 24-h energy expenditure. While poor responders (Thrifty) show an attenuated FGF21 response to acute low-protein feeding, therefore are vulnerable to weight gain over 6 mo[145,146]. Provided that individuals don’t suffer liver, cardiac, kidney or muscle disease which may interfere with test results[147].

**CONCLUSION**

Bariatric surgery is a tool to achieve significant weight loss, to obtain maximum benefit must adapt pre and postoperative follow up. Also, the role of a nutritionist in bariatric surgery team has expanded ahead diet counseling, to address individual barriers and counsel morbidly obese subjects by ensuring they understand selected bariatric procedures, offering education, identify individual factors that may predict weight regain, reinforce self-monitoring skills, encourage mindful eating practices, supply appropriate nutritional supplements, and motivate daily physical activity, provide close support and follow-up to avoid relapse.

**REFERENCES**

1 **McLaughlin L**, Hinyard LJ. The Relationship Between Health-Related Quality of Life and Body Mass Index. *West J Nurs Res* 2014; **36**: 989-1001 [PMID: 24473057 DOI: 10.1177/0193945913520415]

2 **Janik MR**, Rogula T, Bielecka I, Kwiatkowski A, Paśnik K. Quality of Life and Bariatric Surgery: Cross-Sectional Study and Analysis of Factors Influencing Outcome. *Obes Surg* 2016; **26**: 2849-2855 [PMID: 27179520 DOI: 10.1007/s11695-016-2220-2]

3 **Angrisani L**, Santonicola A, Iovino P, Formisano G, Buchwald H, Scopinaro N. Bariatric Surgery Worldwide 2013. *Obes Surg* 2015; **25**: 1822-1832 [PMID: 25835983 DOI: 10.1007/s11695-015-1657-z]

4 **Garg H**, Priyadarshini P, Aggarwal S, Agarwal S, Chaudhary R. Comparative study of outcomes following laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy in morbidly obese patients: A case control study. *World J Gastrointest Endosc* 2017; **9**: 162-170 [PMID: 28465782 DOI: 10.4253/wjge.v9.i4.162]

5 **Mendes FH**, Viterbo F. Defining "Weight Stability" for Post-Bariatric Body Contouring Procedures. *Aesthetic Plast Surg* 2017; **41**: 979-980 [PMID: 28175967 DOI: 10.1007/s00266-017-0800-8]

6 **Lauti M**, Kularatna M, Hill AG, MacCormick AD. Weight Regain Following Sleeve Gastrectomy-a Systematic Review. *Obes Surg* 2016; **26**: 1326-1334 [PMID: 27048439 DOI: 10.1007/s11695-016-2152-x]

7 **King WC**, Hinerman AS, Belle SH, Wahed AS, Courcoulas AP. Comparison of the Performance of Common Measures of Weight Regain After Bariatric Surgery for Association With Clinical Outcomes. *JAMA* 2018; **320**: 1560-1569 [PMID: 30326125 DOI: 10.1001/jama.2018.14433]

8 **Kraschnewski JL**, Boan J, Esposito J, Sherwood NE, Lehman EB, Kephart DK, Sciamanna CN. Long-term weight loss maintenance in the United States. *Int J Obes (Lond)* 2010; **34**: 1644-1654 [PMID: 20479763 DOI: 10.1038/ijo.2010.94]

9 **Rubin JP,** Capla J. Staging and combining procedures. In:Rubin JP, Jewel ML, Richter DF, Uebel CO (eds) Body contouring and liposuction, 1st ed. Elsevier, Amsterdam, 2013; **55**: 593-603

10 **Ponce J**, Nguyen NT, Hutter M, Sudan R, Morton JM. American Society for Metabolic and Bariatric Surgery estimation of bariatric surgery procedures in the United States, 2011-2014. *Surg Obes Relat Dis* 2015; **11**: 1199-1200 [PMID: 26476493 DOI: 10.1016/j.soard.2015.08.496]

11 **Puzziferri N**, Roshek TB 3rd, Mayo HG, Gallagher R, Belle SH, Livingston EH. Long-term follow-up after bariatric surgery: a systematic review. *JAMA* 2014; **312**: 934-942 [PMID: 25182102 DOI: 10.1001/jama.2014.10706]

12 **Grover BT,** Morell MC, Kothari SN, Borgert AJ, Kallies KJ, Baker MT. Defining Weight Loss After Bariatric Surgery: a Call for Standardization. *Obes Surg* 2019; **29**: 3493-3499 [PMID: 31256357 DOI: 10.1007/s11695-019-04022-z]

13 **Amundsen T**, Strømmen M, Martins C. Suboptimal Weight Loss and Weight Regain after Gastric Bypass Surgery-Postoperative Status of Energy Intake, Eating Behavior, Physical Activity, and Psychometrics. *Obes Surg* 2017; **27**: 1316-1323 [PMID: 27914028 DOI: 10.1007/s11695-016-2475-7]

14 **Voorwinde V,** Steenhuis IHM, Janssen IMC, Monpellier VM, van Stralen MM. Definitions of Long-Term Weight Regain and Their Associations with Clinical Outcomes. *Obes Surg* 2020; **30**: 527-536 [PMID: 31677016 DOI: 10.1007/s11695-019-04210-x]

15 **Adams TD**, Davidson LE, Litwin SE, Kim J, Kolotkin RL, Nanjee MN, Gutierrez JM, Frogley SJ, Ibele AR, Brinton EA, Hopkins PN, McKinlay R, Simper SC, Hunt SC. Weight and Metabolic Outcomes 12 Years after Gastric Bypass. *N Engl J Med* 2017; **377**: 1143-1155 [PMID: 28930514 DOI: 10.1056/NEJMoa1700459]

16 **Arterburn DE,** Olsen MK, Smith VA, Livingston EH, Van Scoyoc L, Yancy WS Jr, Eid G, Weidenbacher H, Maciejewski ML. Association between bariatric surgery and long-term survival. *JAMA* 2015; **313**: 62-70 [PMID: 25562267 DOI: 10.1001/jama.2014.16968]

17 **Maciejewski ML**, Arterburn DE, Van Scoyoc L, Smith VA, Yancy WS Jr, Weidenbacher HJ, Livingston EH, Olsen MK. Bariatric Surgery and Long-term Durability of Weight Loss. *JAMA Surg* 2016; **151**: 1046-1055 [PMID: 27579793 DOI: 10.1001/jamasurg.2016.2317]

18 **Hatoum IJ**, Kaplan LM. Advantages of percent weight loss as a method of reporting weight loss after Roux-en-Y gastric bypass. *Obesity (Silver Spring)* 2013; **21**: 1519-1525 [PMID: 23670991 DOI: 10.1002/oby.20186]

19 **Boza C**, Gamboa C, Salinas J, Achurra P, Vega A, Pérez G. Laparoscopic Roux-en-Y gastric bypass *vs* laparoscopic sleeve gastrectomy: a case-control study and 3 years of follow-up. *Surg Obes Relat Dis* 2012; **8**: 243-249 [PMID: 22285881 DOI: 10.1016/j.soard.2011.08.023]

20 **Corcelles R**, Boules M, Froylich D, Hag A, Daigle CR, Aminian A, Brethauer SA, Burguera B, Schauer PR. Total Weight Loss as the Outcome Measure of Choice After Roux-en-Y Gastric Bypass. *Obes Surg* 2016; **26**: 1794-1798 [PMID: 26803753 DOI: 10.1007/s11695-015-2022-y]

21 **Lee WJ**, Pok EH, Almulaifi A, Tsou JJ, Ser KH, Lee YC. Medium-Term Results of Laparoscopic Sleeve Gastrectomy: a Matched Comparison with Gastric Bypass. *Obes Surg* 2015; **25**: 1431-1438 [PMID: 25648253 DOI: 10.1007/s11695-015-1582-1]

22 **Arman GA**, Himpens J, Dhaenens J, Ballet T, Vilallonga R, Leman G. Long-term (11+years) outcomes in weight, patient satisfaction, comorbidities, and gastroesophageal reflux treatment after laparoscopic sleeve gastrectomy. *Surg Obes Relat Dis* 2016; **12**: 1778-1786 [PMID: 27178613 DOI: 10.1016/j.soard.2016.01.013]

23 **Abouelela MS,** Mourad FA, Reyad HA. Comparison between effectiveness of mini gastric bypass and sleeve gastrectomy in weight reduction in super obese patients. *Egypt J Surg* 2020; **39**: 338-343 [DOI: 10.4103/ejs.ejs\_211\_19]

24 **Magouliotis DE**, Tasiopoulou VS, Svokos AA, Svokos KA, Sioka E, Zacharoulis D. One-Anastomosis Gastric Bypass Versus Sleeve Gastrectomy for Morbid Obesity: a Systematic Review and Meta-analysis. *Obes Surg* 2017; **27**: 2479-2487 [PMID: 28681256 DOI: 10.1007/s11695-017-2807-2]

25 **Weiner RA,** Weiner S, Pomhoff I, Jacobi C, Makarewicz W, Weigand G. Laparoscopic sleeve gastrectomy-influence of sleeve size and resected gastric volume. *Obes Surg* 2007; **17**: 1297-1305 [PMID: 18098398 DOI: 10.1007/s11695-007-9232-x]

26 **Fezzi M,** Kolotkin RL, Nedelcu M, Jaussent A, Schaub R, Chauvet MA, Cassafieres C, Lefebvre P, Renard E, Bringer J, Fabre JM, Nocca D. Improvement in quality of life after laparoscopic sleeve gastrectomy. *Obes Surg* 2011; **21**: 1161-1167 [PMID: 21298508 DOI: 10.1007/s11695-011-0361-x]

27 **Cena H**, De Giuseppe R, Biino G, Persico F, Ciliberto A, Giovanelli A, Stanford FC. Evaluation of eating habits and lifestyle in patients with obesity before and after bariatric surgery: a single Italian center experience. *Springerplus* 2016; **5**: 1467 [PMID: 27652042 DOI: 10.1186/s40064-016-3133-1]

28 **Johnson Stoklossa C**, Atwal S. Nutrition care for patients with weight regain after bariatric surgery. *Gastroenterol Res Pract* 2013; **2013**: 256145 [PMID: 24348530 DOI: 10.1155/2013/256145]

29 **Al-Najim W**, Docherty NG, le Roux CW. Food Intake and Eating Behavior After Bariatric Surgery. *Physiol Rev* 2018; **98**: 1113-1141 [PMID: 29717927 DOI: 10.1152/physrev.00021.2017]

30 **Madan AK,** Tichansky DS, Taddeucci RJ. Postoperative laparoscopic bariatric surgery patients do not remember potential complications. *Obes Surg* 2007; **17**: 885-888 [PMID: 17894146 DOI: 10.1007/s11695-007-9164-5]

31 **Chapman CD**, Benedict C, Brooks SJ, Schiöth HB. Lifestyle determinants of the drive to eat: a meta-analysis. *Am J Clin Nutr* 2012; **96**: 492-497 [PMID: 22836029 DOI: 10.3945/ajcn.112.039750]

32 **Sawamoto R**, Nozaki T, Nishihara T, Furukawa T, Hata T, Komaki G, Sudo N. Predictors of successful long-term weight loss maintenance: a two-year follow-up. *Biopsychosoc Med* 2017; **11**: 14 [PMID: 28592990 DOI: 10.1186/s13030-017-0099-3]

33 **Felsenreich DM**, Langer FB, Kefurt R, Panhofer P, Schermann M, Beckerhinn P, Sperker C, Prager G. Weight loss, weight regain, and conversions to Roux-en-Y gastric bypass: 10-year results of laparoscopic sleeve gastrectomy. *Surg Obes Relat Dis* 2016; **12**: 1655-1662 [PMID: 27317599 DOI: 10.1016/j.soard.2016.02.021]

34 **Nikiforova I,** Barnea R, Azulai S, Susmallian S. Analysis of the Association between Eating Behaviors and Weight Loss after Laparoscopic Sleeve Gastrectomy. *Obes Facts* 2019; **12**: 618-631 [PMID: 31747668 DOI: 10.1159/000502846]

35 **Mitchell JE**, Christian NJ, Flum DR, Pomp A, Pories WJ, Wolfe BM, Courcoulas AP, Belle SH. Postoperative Behavioral Variables and Weight Change 3 Years After Bariatric Surgery. *JAMA Surg* 2016; **151**: 752-757 [PMID: 27096225 DOI: 10.1001/jamasurg.2016.0395]

36 **Parrott JM,** Craggs-Dino L, Faria SL, O'Kane M. The Optimal Nutritional Programme for Bariatric and Metabolic Surgery. *Curr Obes Rep* 2020; **9**: 326-338 [PMID: 32451780 DOI: 10.1007/s13679-020-00384-z]

37 **Popkin BM**, D'Anci KE, Rosenberg IH. Water, hydration, and health. *Nutr Rev* 2010; **68**: 439-458 [PMID: 20646222 DOI: 10.1111/j.1753-4887.2010.00304.x]

38 **Schiavo L,** Pilone V, Rossetti G, Iannelli A. The Role of the Nutritionist in a Multidisciplinary Bariatric Surgery Team. *Obes Surg* 2019; **29**: 1028-1030 [PMID: 30617913 DOI: 10.1007/s11695-019-03706-w]

39 **Pizato N**, Botelho PB, Gonçalves VSS, Dutra ES, de Carvalho KMB. Effect of Grazing Behavior on Weight Regain Post-Bariatric Surgery: A Systematic Review. *Nutrients* 2017; **9** [PMID: 29206132 DOI: 10.3390/nu9121322]

40 **Bowman SA**. Television-viewing characteristics of adults: correlations to eating practices and overweight and health status. *Prev Chronic Dis* 2006; **3**: A38 [PMID: 16539779]

41 **Drewnowski A**. Obesity, diets, and social inequalities. *Nutr Rev* 2009; **67 Suppl 1**: S36-S39 [PMID: 19453676 DOI: 10.1111/j.1753-4887.2009.00157.x]

42 **Rudolph A**, Hilbert A. Post-operative behavioural management in bariatric surgery: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev* 2013; **14**: 292-302 [PMID: 23294936 DOI: 10.1111/obr.12013]

43 **Conceição EM**, Mitchell JE, Machado PPP, Vaz AR, Pinto-Bastos A, Ramalho S, Brandão I, Simões JB, de Lourdes M, Freitas AC. Repetitive eating questionnaire [Rep(eat)-Q]: Enlightening the concept of grazing and psychometric properties in a Portuguese sample. *Appetite* 2017; **117**: 351-358 [PMID: 28712976 DOI: 10.1016/j.appet.2017.07.012]

44 **White MA**, Kalarchian MA, Masheb RM, Marcus MD, Grilo CM. Loss of control over eating predicts outcomes in bariatric surgery patients: a prospective, 24-month follow-up study. *J Clin Psychiatry* 2010; **71**: 175-184 [PMID: 19852902 DOI: 10.4088/JCP.08m04328blu]

45 **Colles SL**, Dixon JB, O'Brien PE. Grazing and loss of control related to eating: two high-risk factors following bariatric surgery. *Obesity (Silver Spring)* 2008; **16**: 615-622 [PMID: 18239603 DOI: 10.1038/oby.2007.101]

46 **Leahy CR**, Luning A. Review of nutritional guidelines for patients undergoing bariatric surgery. *AORN J* 2015; **102**: 153-160 [PMID: 26227519 DOI: 10.1016/j.aorn.2015.05.017]

47 **Petit JM,** Burlet-Godinot S, Magistretti PJ, Allaman I. Glycogen metabolism and the homeostatic regulation of sleep. *Metab Brain Dis* 2015; **30**: 263-279 [PMID: 25399336 DOI: 10.1007/s11011-014-9629-x]

48 **Mechanick JI**, Kushner RF, Sugerman HJ, Gonzalez-Campoy JM, Collazo-Clavell ML, Spitz AF, Apovian CM, Livingston EH, Brolin R, Sarwer DB, Anderson WA, Dixon J, Guven S; American Association of Clinical Endocrinologists; Obesity Society; American Society for Metabolic & Bariatric Surgery. American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. *Obesity (Silver Spring)* 2009; **17 Suppl 1**: S1-70, v [PMID: 19319140 DOI: 10.1038/oby.2009.28]

49 **Ainsworth BE**, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000; **32**: S498-S504 [PMID: 10993420 DOI: 10.1097/00005768-200009001-00009]

50 **Shada AL**, Hallowell PT, Schirmer BD, Smith PW. Aerobic exercise is associated with improved weight loss after laparoscopic adjustable gastric banding. *Obes Surg* 2013; **23**: 608-612 [PMID: 23196991 DOI: 10.1007/s11695-012-0826-6]

51 **Shah M**, Snell PG, Rao S, Adams-Huet B, Quittner C, Livingston EH, Garg A. High-volume exercise program in obese bariatric surgery patients: a randomized, controlled trial. *Obesity (Silver Spring)* 2011; **19**: 1826-1834 [PMID: 21681226 DOI: 10.1038/oby.2011.172]

52 **Freire RH**, Borges MC, Alvarez-Leite JI, Toulson Davisson Correia MI. Food quality, physical activity, and nutritional follow-up as determinant of weight regain after Roux-en-Y gastric bypass. *Nutrition* 2012; **28**: 53-58 [PMID: 21885246 DOI: 10.1016/j.nut.2011.01.011]

53 **Marc-Hernández A**, Ruiz-Tovar J, Aracil A, Guillén S, Moya-Ramón M. Effects of a High-Intensity Exercise Program on Weight Regain and Cardio-metabolic Profile after 3 Years of Bariatric Surgery: A Randomized Trial. *Sci Rep* 2020; **10**: 3123 [PMID: 32080310 DOI: 10.1038/s41598-020-60044-z]

54 **Josbeno DA**, Kalarchian M, Sparto PJ, Otto AD, Jakicic JM. Physical activity and physical function in individuals post-bariatric surgery. *Obes Surg* 2011; **21**: 1243-1249 [PMID: 21153567 DOI: 10.1007/s11695-010-0327-4]

55 **Monpellier VM**, Janssen IMC, Antoniou EE, Jansen ATM. Weight Change After Roux-en Y Gastric Bypass, Physical Activity and Eating Style: Is There a Relationship? *Obes Surg* 2019; **29**: 526-533 [PMID: 30392103 DOI: 10.1007/s11695-018-3560-x]

56 **Maleckas A**, Gudaitytė R, Petereit R, Venclauskas L, Veličkienė D. Weight regain after gastric bypass: etiology and treatment options. *Gland Surg* 2016; **5**: 617-624 [PMID: 28149808 DOI: 10.21037/gs.2016.12.02]

57 **Filho AJ**, Kondo W, Nassif LS, Garcia MJ, Tirapelle Rde A, Dotti CM. Gastrogastric fistula: a possible complication of Roux-en-Y gastric bypass. *JSLS* 2006; **10**: 326-331 [PMID: 17212889]

58 **Jiang HP**, Lin LL, Jiang X, Qiao HQ. Meta-analysis of hand-sewn *vs* mechanical gastrojejunal anastomosis during laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Int J Surg* 2016; **32**: 150-157 [PMID: 27107663 DOI: 10.1016/j.ijsu.2016.04.024]

59 **Abu Dayyeh BK**, Lautz DB, Thompson CC. Gastrojejunal stoma diameter predicts weight regain after Roux-en-Y gastric bypass. *Clin Gastroenterol Hepatol* 2011; **9**: 228-233 [PMID: 21092760 DOI: 10.1016/j.cgh.2010.11.004]

60 **Heneghan HM**, Yimcharoen P, Brethauer SA, Kroh M, Chand B. Influence of pouch and stoma size on weight loss after gastric bypass. *Surg Obes Relat Dis* 2012; **8**: 408-415 [PMID: 22055390 DOI: 10.1016/j.soard.2011.09.010]

61 **Topart P**, Becouarn G, Ritz P. Pouch size after gastric bypass does not correlate with weight loss outcome. *Obes Surg* 2011; **21**: 1350-1354 [PMID: 21660641 DOI: 10.1007/s11695-011-0460-8]

62 **le Roux CW**, Welbourn R, Werling M, Osborne A, Kokkinos A, Laurenius A, Lönroth H, Fändriks L, Ghatei MA, Bloom SR, Olbers T. Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass. *Ann Surg* 2007; **246**: 780-785 [PMID: 17968169 DOI: 10.1097/SLA.0b013e3180caa3e3]

63 **Begg DP,** Woods SC. The endocrinology of food intake. *Nat Rev Endocrinol* 2013; **9**: 584-597 [PMID: 23877425 DOI: 10.1038/nrendo.2013.136]

64 **Jacobsen SH**, Olesen SC, Dirksen C, Jørgensen NB, Bojsen-Møller KN, Kielgast U, Worm D, Almdal T, Naver LS, Hvolris LE, Rehfeld JF, Wulff BS, Clausen TR, Hansen DL, Holst JJ, Madsbad S. Changes in gastrointestinal hormone responses, insulin sensitivity, and beta-cell function within 2 weeks after gastric bypass in non-diabetic subjects. *Obes Surg* 2012; **22**: 1084-1096 [PMID: 22359255 DOI: 10.1007/s11695-012-0621-4]

65 **Beglinger S**, Drewe J, Schirra J, Göke B, D'Amato M, Beglinger C. Role of fat hydrolysis in regulating glucagon-like Peptide-1 secretion. *J Clin Endocrinol Metab* 2010; **95**: 879-886 [PMID: 19837920 DOI: 10.1210/jc.2009-1062]

66 **Peterli R**, Steinert RE, Woelnerhanssen B, Peters T, Christoffel-Courtin C, Gass M, Kern B, von Fluee M, Beglinger C. Metabolic and hormonal changes after laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy: a randomized, prospective trial. *Obes Surg* 2012; **22**: 740-748 [PMID: 22354457 DOI: 10.1007/s11695-012-0622-3]

67 **Korner J**, Inabnet W, Febres G, Conwell IM, McMahon DJ, Salas R, Taveras C, Schrope B, Bessler M. Prospective study of gut hormone and metabolic changes after adjustable gastric banding and Roux-en-Y gastric bypass. *Int J Obes (Lond)* 2009; **33**: 786-795 [PMID: 19417773 DOI: 10.1038/ijo.2009.79]

68 **Rao RS**, Kini S. GIP and bariatric surgery. *Obes Surg* 2011; **21**: 244-252 [PMID: 21082290 DOI: 10.1007/s11695-010-0305-x]

69 **Gilbert MP**, Pratley RE. GLP-1 Analogs and DPP-4 Inhibitors in Type 2 Diabetes Therapy: Review of Head-to-Head Clinical Trials. *Front Endocrinol (Lausanne)* 2020; **11**: 178 [PMID: 32308645 DOI: 10.3389/fendo.2020.00178]

70 **Divoux A**, Tordjman J, Lacasa D, Veyrie N, Hugol D, Aissat A, Basdevant A, Guerre-Millo M, Poitou C, Zucker JD, Bedossa P, Clément K. Fibrosis in human adipose tissue: composition, distribution, and link with lipid metabolism and fat mass loss. *Diabetes* 2010; **59**: 2817-2825 [PMID: 20713683 DOI: 10.2337/db10-0585]

71 **Woelnerhanssen B**, Peterli R, Steinert RE, Peters T, Borbély Y, Beglinger C. Effects of postbariatric surgery weight loss on adipokines and metabolic parameters: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy--a prospective randomized trial. *Surg Obes Relat Dis* 2011; **7**: 561-568 [PMID: 21429816 DOI: 10.1016/j.soard.2011.01.044]

72 **Sarkar J,** Nargis T, Tantia O, Ghosh S, Chakrabarti P. Increased Plasma Dipeptidyl Peptidase-4 (DPP4) Activity Is an Obesity-Independent Parameter for Glycemic Deregulation in Type 2 Diabetes Patients. *Front Endocrinol (Lausanne)* 2019; **10**: 505 [PMID: 31402899 DOI: 10.3389/fendo.2019.00505]

73 **Sima E,** Webb DL, Hellström PM, Sundbom M. Non-responders After Gastric Bypass Surgery for Morbid Obesity: Peptide Hormones and Glucose Homeostasis. *Obes Surg* 2019; **29**: 4008-4017 [PMID: 31338735 DOI: 10.1007/s11695-019-04089-8]

74 **Ochner CN**, Gibson C, Shanik M, Goel V, Geliebter A. Changes in neurohormonal gut peptides following bariatric surgery. *Int J Obes (Lond)* 2011; **35**: 153-166 [PMID: 20625384 DOI: 10.1038/ijo.2010.132]

75 **Pan H**, Guo J, Su Z. Advances in understanding the interrelations between leptin resistance and obesity. *Physiol Behav* 2014; **130**: 157-169 [PMID: 24726399 DOI: 10.1016/j.physbeh.2014.04.003]

76 **Savastano S**, Di Somma C, Barrea L, Colao A. The complex relationship between obesity and the somatropic axis: the long and winding road. *Growth Horm IGF Res* 2014; **24**: 221-226 [PMID: 25315226 DOI: 10.1016/j.ghir.2014.09.002]

77 **Edén Engström B**, Burman P, Holdstock C, Ohrvall M, Sundbom M, Karlsson FA. Effects of gastric bypass on the GH/IGF-I axis in severe obesity--and a comparison with GH deficiency. *Eur J Endocrinol* 2006; **154**: 53-59 [PMID: 16381991 DOI: 10.1530/eje.1.02069]

78 **Savastano S,** Angrisani L, Di Somma C, Rota F, Savanelli MC, Cascella T, Orio F, Lombardi G, Colao A. Relationship between growth hormone/insulin-like growth factor-1 axis integrity and voluntary weight loss after gastric banding surgery for severe obesity. *Obes Surg* 2010; **20**: 211-220 [PMID: 19636643 DOI: 10.1007/s11695-009-9926-3]

79 **Erion KA,** Corkey BE. Hyperinsulinemia: a Cause of Obesity? Curr Obes Rep 2017; 6: 178-186 [PMID: 28466412 DOI: 10.1007/s13679-017-0261-z]

80 **van Beek AP**, Emous M, Laville M, Tack J. Dumping syndrome after esophageal, gastric or bariatric surgery: pathophysiology, diagnosis, and management. *Obes Rev* 2017; **18**: 68-85 [PMID: 27749997 DOI: 10.1111/obr.12467]

81 **Roslin M**, Damani T, Oren J, Andrews R, Yatco E, Shah P. Abnormal glucose tolerance testing following gastric bypass demonstrates reactive hypoglycemia. *Surg Endosc* 2011; **25**: 1926-1932 [PMID: 21184112 DOI: 10.1007/s00464-010-1489-9]

82 **Varma S**, Clark JM, Schweitzer M, Magnuson T, Brown TT, Lee CJ. Weight regain in patients with symptoms of post-bariatric surgery hypoglycemia. *Surg Obes Relat Dis* 2017; **13**: 1728-1734 [PMID: 28844575 DOI: 10.1016/j.soard.2017.06.004]

83 **Gumbs AA**, Modlin IM, Ballantyne GH. Changes in insulin resistance following bariatric surgery: role of caloric restriction and weight loss. *Obes Surg* 2005; **15**: 462-473 [PMID: 15946423 DOI: 10.1381/0960892053723367]

84 **Schauer PR**, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, Navaneethan SD, Singh RP, Pothier CE, Nissen SE, Kashyap SR; STAMPEDE Investigators. Bariatric Surgery *vs* Intensive Medical Therapy for Diabetes - 5-Year Outcomes. *N Engl J Med* 2017; **376**: 641-651 [PMID: 28199805 DOI: 10.1056/NEJMoa1600869]

85 **Asarian L**, Geary N. Modulation of appetite by gonadal steroid hormones. *Philos Trans R Soc Lond B Biol Sci* 2006; **361**: 1251-1263 [PMID: 16815802 DOI: 10.1098/rstb.2006.1860]

86 **Asarian L,** Abegg K, Geary N, Schiesser M, Lutz TA, Bueter M. Estradiol increases body weight loss and gut-peptide satiation after Roux-en-Y gastric bypass in ovariectomized rats. *Gastroenterology* 2012; **143**: 325-7.e2 [PMID: 22609384 DOI: 10.1053/j.gastro.2012.05.008]

87 **Sarzynski MA**, Jacobson P, Rankinen T, Carlsson B, Sjöström L, Bouchard C, Carlsson LM. Associations of markers in 11 obesity candidate genes with maximal weight loss and weight regain in the SOS bariatric surgery cases. *Int J Obes (Lond)* 2011; **35**: 676-683 [PMID: 20733583 DOI: 10.1038/ijo.2010.166]

88 **Speliotes EK**, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, Lango Allen H, Lindgren CM, Luan J, Mägi R, Randall JC, Vedantam S, Winkler TW, Qi L, Workalemahu T, Heid IM, Steinthorsdottir V, Stringham HM, Weedon MN, Wheeler E, Wood AR, Ferreira T, Weyant RJ, Segrè AV, Estrada K, Liang L, Nemesh J, Park JH, Gustafsson S, Kilpeläinen TO, Yang J, Bouatia-Naji N, Esko T, Feitosa MF, Kutalik Z, Mangino M, Raychaudhuri S, Scherag A, Smith AV, Welch R, Zhao JH, Aben KK, Absher DM, Amin N, Dixon AL, Fisher E, Glazer NL, Goddard ME, Heard-Costa NL, Hoesel V, Hottenga JJ, Johansson A, Johnson T, Ketkar S, Lamina C, Li S, Moffatt MF, Myers RH, Narisu N, Perry JR, Peters MJ, Preuss M, Ripatti S, Rivadeneira F, Sandholt C, Scott LJ, Timpson NJ, Tyrer JP, van Wingerden S, Watanabe RM, White CC, Wiklund F, Barlassina C, Chasman DI, Cooper MN, Jansson JO, Lawrence RW, Pellikka N, Prokopenko I, Shi J, Thiering E, Alavere H, Alibrandi MT, Almgren P, Arnold AM, Aspelund T, Atwood LD, Balkau B, Balmforth AJ, Bennett AJ, Ben-Shlomo Y, Bergman RN, Bergmann S, Biebermann H, Blakemore AI, Boes T, Bonnycastle LL, Bornstein SR, Brown MJ, Buchanan TA, Busonero F, Campbell H, Cappuccio FP, Cavalcanti-Proença C, Chen YD, Chen CM, Chines PS, Clarke R, Coin L, Connell J, Day IN, den Heijer M, Duan J, Ebrahim S, Elliott P, Elosua R, Eiriksdottir G, Erdos MR, Eriksson JG, Facheris MF, Felix SB, Fischer-Posovszky P, Folsom AR, Friedrich N, Freimer NB, Fu M, Gaget S, Gejman PV, Geus EJ, Gieger C, Gjesing AP, Goel A, Goyette P, Grallert H, Grässler J, Greenawalt DM, Groves CJ, Gudnason V, Guiducci C, Hartikainen AL, Hassanali N, Hall AS, Havulinna AS, Hayward C, Heath AC, Hengstenberg C, Hicks AA, Hinney A, Hofman A, Homuth G, Hui J, Igl W, Iribarren C, Isomaa B, Jacobs KB, Jarick I, Jewell E, John U, Jørgensen T, Jousilahti P, Jula A, Kaakinen M, Kajantie E, Kaplan LM, Kathiresan S, Kettunen J, Kinnunen L, Knowles JW, Kolcic I, König IR, Koskinen S, Kovacs P, Kuusisto J, Kraft P, Kvaløy K, Laitinen J, Lantieri O, Lanzani C, Launer LJ, Lecoeur C, Lehtimäki T, Lettre G, Liu J, Lokki ML, Lorentzon M, Luben RN, Ludwig B; MAGIC, Manunta P, Marek D, Marre M, Martin NG, McArdle WL, McCarthy A, McKnight B, Meitinger T, Melander O, Meyre D, Midthjell K, Montgomery GW, Morken MA, Morris AP, Mulic R, Ngwa JS, Nelis M, Neville MJ, Nyholt DR, O'Donnell CJ, O'Rahilly S, Ong KK, Oostra B, Paré G, Parker AN, Perola M, Pichler I, Pietiläinen KH, Platou CG, Polasek O, Pouta A, Rafelt S, Raitakari O, Rayner NW, Ridderstråle M, Rief W, Ruokonen A, Robertson NR, Rzehak P, Salomaa V, Sanders AR, Sandhu MS, Sanna S, Saramies J, Savolainen MJ, Scherag S, Schipf S, Schreiber S, Schunkert H, Silander K, Sinisalo J, Siscovick DS, Smit JH, Soranzo N, Sovio U, Stephens J, Surakka I, Swift AJ, Tammesoo ML, Tardif JC, Teder-Laving M, Teslovich TM, Thompson JR, Thomson B, Tönjes A, Tuomi T, van Meurs JB, van Ommen GJ, Vatin V, Viikari J, Visvikis-Siest S, Vitart V, Vogel CI, Voight BF, Waite LL, Wallaschofski H, Walters GB, Widen E, Wiegand S, Wild SH, Willemsen G, Witte DR, Witteman JC, Xu J, Zhang Q, Zgaga L, Ziegler A, Zitting P, Beilby JP, Farooqi IS, Hebebrand J, Huikuri HV, James AL, Kähönen M, Levinson DF, Macciardi F, Nieminen MS, Ohlsson C, Palmer LJ, Ridker PM, Stumvoll M, Beckmann JS, Boeing H, Boerwinkle E, Boomsma DI, Caulfield MJ, Chanock SJ, Collins FS, Cupples LA, Smith GD, Erdmann J, Froguel P, Grönberg H, Gyllensten U, Hall P, Hansen T, Harris TB, Hattersley AT, Hayes RB, Heinrich J, Hu FB, Hveem K, Illig T, Jarvelin MR, Kaprio J, Karpe F, Khaw KT, Kiemeney LA, Krude H, Laakso M, Lawlor DA, Metspalu A, Munroe PB, Ouwehand WH, Pedersen O, Penninx BW, Peters A, Pramstaller PP, Quertermous T, Reinehr T, Rissanen A, Rudan I, Samani NJ, Schwarz PE, Shuldiner AR, Spector TD, Tuomilehto J, Uda M, Uitterlinden A, Valle TT, Wabitsch M, Waeber G, Wareham NJ, Watkins H; Procardis Consortium, Wilson JF, Wright AF, Zillikens MC, Chatterjee N, McCarroll SA, Purcell S, Schadt EE, Visscher PM, Assimes TL, Borecki IB, Deloukas P, Fox CS, Groop LC, Haritunians T, Hunter DJ, Kaplan RC, Mohlke KL, O'Connell JR, Peltonen L, Schlessinger D, Strachan DP, van Duijn CM, Wichmann HE, Frayling TM, Thorsteinsdottir U, Abecasis GR, Barroso I, Boehnke M, Stefansson K, North KE, McCarthy MI, Hirschhorn JN, Ingelsson E, Loos RJ. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* 2010; **42**: 937-948 [PMID: 20935630 DOI: 10.1038/ng.686]

89 **Schwartz MW**, Seeley RJ, Campfield LA, Burn P, Baskin DG. Identification of targets of leptin action in rat hypothalamus. *J Clin Invest* 1996; **98**: 1101-1106 [PMID: 8787671 DOI: 10.1172/JCI118891]

90 **Frayling TM**, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 2007; **316**: 889-894 [PMID: 17434869 DOI: 10.1126/science.1141634]

91 **Herrera BM**, Lindgren CM. The genetics of obesity. *Curr Diab Rep* 2010; **10**: 498-505 [PMID: 20931363 DOI: 10.1007/s11892-010-0153-z]

92 **Seyednasrollah F**, Mäkelä J, Pitkänen N, Juonala M, Hutri-Kähönen N, Lehtimäki T, Viikari J, Kelly T, Li C, Bazzano L, Elo LL, Raitakari OT. Prediction of Adulthood Obesity Using Genetic and Childhood Clinical Risk Factors in the Cardiovascular Risk in Young Finns Study. *Circ Cardiovasc Genet* 2017; **10** [PMID: 28620069 DOI: 10.1161/circgenetics.116.001554]

93 **Orozco G**, Barrett JC, Zeggini E. Synthetic associations in the context of genome-wide association scan signals. *Hum Mol Genet* 2010; **19**: R137-R144 [PMID: 20805105 DOI: 10.1093/hmg/ddq368]

94 **Izquierdo AG**, Crujeiras AB. Obesity-Related Epigenetic Changes After Bariatric Surgery. *Front Endocrinol (Lausanne)* 2019; **10**: 232 [PMID: 31040824 DOI: 10.3389/fendo.2019.00232]

95 **Belsky DW**, Moffitt TE, Sugden K, Williams B, Houts R, McCarthy J, Caspi A. Development and evaluation of a genetic risk score for obesity. *Biodemography Soc Biol* 2013; **59**: 85-100 [PMID: 23701538 DOI: 10.1080/19485565.2013.774628]

96 **Crujeiras AB**, Diaz-Lagares A, Sandoval J, Milagro FI, Navas-Carretero S, Carreira MC, Gomez A, Hervas D, Monteiro MP, Casanueva FF, Esteller M, Martinez JA. DNA methylation map in circulating leukocytes mirrors subcutaneous adipose tissue methylation pattern: a genome-wide analysis from non-obese and obese patients. *Sci Rep* 2017; **7**: 41903 [PMID: 28211912 DOI: 10.1038/srep41903]

97 **Nilsson EK**, Ernst B, Voisin S, Almén MS, Benedict C, Mwinyi J, Fredriksson R, Schultes B, Schiöth HB. Roux-en Y gastric bypass surgery induces genome-wide promoter-specific changes in DNA methylation in whole blood of obese patients. *PLoS One* 2015; **10**: e0115186 [PMID: 25710379 DOI: 10.1371/journal.pone.0115186]

98 **Crujeiras AB,** Campion J, Díaz-Lagares A, Milagro FI, Goyenechea E, Abete I, Casanueva FF, Martínez JA. Association of weight regain with specific methylation levels in the NPY and POMC promoters in leukocytes of obese men: a translational study. *Regul Pept* 2013; **186**: 1-6 [PMID: 23831408 DOI: 10.1016/j.regpep.2013.06.012]

99 **Zhang X**, Qi Q, Zhang C, Smith SR, Hu FB, Sacks FM, Bray GA, Qi L. FTO genotype and 2-year change in body composition and fat distribution in response to weight-loss diets: the POUNDS LOST Trial. *Diabetes* 2012; **61**: 3005-3011 [PMID: 22891219 DOI: 10.2337/db11-1799]

100 **Krol J,** Loedige I, Filipowicz W. The widespread regulation of microRNA biogenesis, function and decay. *Nat Rev Genet* 2010; **11**: 597-610 [PMID: 20661255 DOI: 10.1038/nrg2843]

101 **Hubal MJ**, Nadler EP, Ferrante SC, Barberio MD, Suh JH, Wang J, Dohm GL, Pories WJ, Mietus-Snyder M, Freishtat RJ. Circulating adipocyte-derived exosomal MicroRNAs associated with decreased insulin resistance after gastric bypass. *Obesity (Silver Spring)* 2017; **25**: 102-110 [PMID: 27883272 DOI: 10.1002/oby.21709]

102 **Ortega FJ**, Mercader JM, Moreno-Navarrete JM, Nonell L, Puigdecanet E, Rodriquez-Hermosa JI, Rovira O, Xifra G, Guerra E, Moreno M, Mayas D, Moreno-Castellanos N, Fernández-Formoso JA, Ricart W, Tinahones FJ, Torrents D, Malagón MM, Fernández-Real JM. Surgery-Induced Weight Loss Is Associated With the Downregulation of Genes Targeted by MicroRNAs in Adipose Tissue. *J Clin Endocrinol Metab* 2015; **100**: E1467-E1476 [PMID: 26252355 DOI: 10.1210/jc.2015-2357]

103 **Manning P**, Munasinghe PE, Bellae Papannarao J, Gray AR, Sutherland W, Katare R. Acute Weight Loss Restores Dysregulated Circulating MicroRNAs in Individuals Who Are Obese. *J Clin Endocrinol Metab* 2019; **104**: 1239-1248 [PMID: 30383229 DOI: 10.1210/jc.2018-00684]

104 **Arner P**, Kulyté A. MicroRNA regulatory networks in human adipose tissue and obesity. *Nat Rev Endocrinol* 2015; **11**: 276-288 [PMID: 25732520 DOI: 10.1038/nrendo.2015.25]

105 **Unick JL**, Neiberg RH, Hogan PE, Cheskin LJ, Dutton GR, Jeffery R, Nelson JA, Pi-Sunyer X, West DS, Wing RR; Look AHEAD Research Group. Weight change in the first 2 months of a lifestyle intervention predicts weight changes 8 years later. *Obesity (Silver Spring)* 2015; **23**: 1353-1356 [PMID: 26110890 DOI: 10.1002/oby.21112]

106 **Vogels N**, Westerterp-Plantenga MS. Successful long-term weight maintenance: a 2-year follow-up. *Obesity (Silver Spring)* 2007; **15**: 1258-1266 [PMID: 17495202 DOI: 10.1038/oby.2007.147]

107 **Alvarado R**, Alami RS, Hsu G, Safadi BY, Sanchez BR, Morton JM, Curet MJ. The impact of preoperative weight loss in patients undergoing laparoscopic Roux-en-Y gastric bypass. *Obes Surg* 2005; **15**: 1282-1286 [PMID: 16259888 DOI: 10.1381/096089205774512429]

108 **Livhits M**, Mercado C, Yermilov I, Parikh JA, Dutson E, Mehran A, Ko CY, Gibbons MM. Preoperative predictors of weight loss following bariatric surgery: systematic review. *Obes Surg* 2012; **22**: 70-89 [PMID: 21833817 DOI: 10.1007/s11695-011-0472-4]

109 **Melton GB**, Steele KE, Schweitzer MA, Lidor AO, Magnuson TH. Suboptimal weight loss after gastric bypass surgery: correlation of demographics, comorbidities, and insurance status with outcomes. *J Gastrointest Surg* 2008; **12**: 250-255 [PMID: 18071836 DOI: 10.1007/s11605-007-0427-1]

110 **Pajecki D**, Dalcanalle L, Souza de Oliveira CP, Zilberstein B, Halpern A, Garrido AB Jr, Cecconello I. Follow-up of Roux-en-Y gastric bypass patients at 5 or more years postoperatively. *Obes Surg* 2007; **17**: 601-607 [PMID: 17658018 DOI: 10.1007/s11695-007-9104-4]

111 **Ochner CN**, Jochner MC, Caruso EA, Teixeira J, Xavier Pi-Sunyer F. Effect of preoperative body mass index on weight loss after obesity surgery. *Surg Obes Relat Dis* 2013; **9**: 423-427 [PMID: 23434275 DOI: 10.1016/j.soard.2012.12.009]

112 **Arner P**, Andersson DP, Bäckdahl J, Dahlman I, Rydén M. Weight Gain and Impaired Glucose Metabolism in Women Are Predicted by Inefficient Subcutaneous Fat Cell Lipolysis. *Cell Metab* 2018; **28**: 45-54.e3 [PMID: 29861390 DOI: 10.1016/j.cmet.2018.05.004]

113 **Eriksson-Hogling D**, Andersson DP, Bäckdahl J, Hoffstedt J, Rössner S, Thorell A, Arner E, Arner P, Rydén M. Adipose tissue morphology predicts improved insulin sensitivity following moderate or pronounced weight loss. *Int J Obes (Lond)* 2015; **39**: 893-898 [PMID: 25666530 DOI: 10.1038/ijo.2015.18]

114 **Antuna-Puente B**, Disse E, Faraj M, Lavoie ME, Laville M, Rabasa-Lhoret R, Bastard JP. Evaluation of insulin sensitivity with a new lipid-based index in non-diabetic postmenopausal overweight and obese women before and after a weight loss intervention. *Eur J Endocrinol* 2009; **161**: 51-56 [PMID: 19429699 DOI: 10.1530/EJE-09-0091]

115 **Kong LC**, Wuillemin PH, Bastard JP, Sokolovska N, Gougis S, Fellahi S, Darakhshan F, Bonnefont-Rousselot D, Bittar R, Doré J, Zucker JD, Clément K, Rizkalla S. Insulin resistance and inflammation predict kinetic body weight changes in response to dietary weight loss and maintenance in overweight and obese subjects by using a Bayesian network approach. *Am J Clin Nutr* 2013; **98**: 1385-1394 [PMID: 24172304 DOI: 10.3945/ajcn.113.058099]

116 **Henríquez S**, Jara N, Bunout D, Hirsch S, de la Maza MP, Leiva L, Barrera G. Variability of formulas to assess insulin sensitivity and their association with the Matsuda index. *Nutr Hosp* 2013; **28**: 1594-1598 [PMID: 24160221 DOI: 10.3305/nh.2013.28.5.6512]

117 **DeFronzo RA**, Matsuda M. Reduced time points to calculate the composite index. *Diabetes Care* 2010; **33**: e93 [PMID: 20587713 DOI: 10.2337/dc10-0646]

118 **Newgard CB**, An J, Bain JR, Muehlbauer MJ, Stevens RD, Lien LF, Haqq AM, Shah SH, Arlotto M, Slentz CA, Rochon J, Gallup D, Ilkayeva O, Wenner BR, Yancy WS Jr, Eisenson H, Musante G, Surwit RS, Millington DS, Butler MD, Svetkey LP. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell Metab* 2009; **9**: 311-326 [PMID: 19356713 DOI: 10.1016/j.cmet.2009.02.002]

119 **Elshorbagy AK**, Valdivia-Garcia M, Refsum H, Butte N. The association of cysteine with obesity, inflammatory cytokines and insulin resistance in Hispanic children and adolescents. *PLoS One* 2012; **7**: e44166 [PMID: 22984471 DOI: 10.1371/journal.pone.0044166]

120 **Elshorbagy AK**, Nurk E, Gjesdal CG, Tell GS, Ueland PM, Nygård O, Tverdal A, Vollset SE, Refsum H. Homocysteine, cysteine, and body composition in the Hordaland Homocysteine Study: does cysteine link amino acid and lipid metabolism? *Am J Clin Nutr* 2008; **88**: 738-746 [PMID: 18779291 DOI: 10.1093/ajcn/88.3.738]

121 **Lima A,** Ferin R, Bourbon M, Baptista J, Pavão ML. Hypercysteinemia, A Potential Risk Factor for Central Obesity and Related Disorders in Azores, Portugal. *J Nutr Metab* 2019; **2019**: 1826780 [PMID: 31321096 DOI: 10.1155/2019/1826780]

122 **Lu SC**. Regulation of glutathione synthesis. *Curr Top Cell Regul* 2000; **36**: 95-116 [PMID: 10842748 DOI: 10.1016/s0070-2137(01)80004-2]

123 **Flowers MT**, Ntambi JM. Role of stearoyl-coenzyme A desaturase in regulating lipid metabolism. *Curr Opin Lipidol* 2008; **19**: 248-256 [PMID: 18460915 DOI: 10.1097/MOL.0b013e3282f9b54d]

124 **Poloni S**, Blom HJ, Schwartz IV. Stearoyl-CoA Desaturase-1: Is It the Link between Sulfur Amino Acids and Lipid Metabolism? *Biology (Basel)* 2015; **4**: 383-396 [PMID: 26046927 DOI: 10.3390/biology4020383]

125 **Elshorbagy AK**, Valdivia-Garcia M, Graham IM, Palma Reis R, Sales Luis A, Smith AD, Refsum H. The association of fasting plasma sulfur-containing compounds with BMI, serum lipids and apolipoproteins. *Nutr Metab Cardiovasc Dis* 2012; **22**: 1031-1038 [PMID: 21550220 DOI: 10.1016/j.numecd.2011.01.008]

126 **Hanvold SE**, Vinknes KJ, Bastani NE, Turner C, Løken EB, Mala T, Refsum H, Aas AM. Plasma amino acids, adiposity, and weight change after gastric bypass surgery: are amino acids associated with weight regain? *Eur J Nutr* 2018; **57**: 2629-2637 [PMID: 28856439 DOI: 10.1007/s00394-017-1533-9]

127 **Kwon Y,** Kim S, Lim Y, Park Y. Review on Predictors of Weight Loss Maintenance after Successful Weight Loss in Obesity Treatment. *J Korean Med Obes Res* 2019; **19**: 119-136 [DOI: 10.15429/jkomor.2019.19.2.119]

128 **Munkhtulga L**, Nagashima S, Nakayama K, Utsumi N, Yanagisawa Y, Gotoh T, Omi T, Kumada M, Zolzaya K, Lkhagvasuren T, Kagawa Y, Fujiwara H, Hosoya Y, Hyodo M, Horie H, Kojima M, Ishibashi S, Iwamoto S. Regulatory SNP in the RBP4 gene modified the expression in adipocytes and associated with BMI. *Obesity (Silver Spring)* 2010; **18**: 1006-1014 [PMID: 19851303 DOI: 10.1038/oby.2009.358]

129 **Wang P**, Menheere PP, Astrup A, Andersen MR, van Baak MA, Larsen TM, Jebb S, Kafatos A, Pfeiffer AF, Martinez JA, Handjieva-Darlenska T, Hlavaty P, Viguerie N, Langin D, Saris WH, Mariman EC; Diogenes consortium. Metabolic syndrome, circulating RBP4, testosterone, and SHBG predict weight regain at 6 months after weight loss in men. *Obesity (Silver Spring)* 2013; **21**: 1997-2006 [PMID: 23408763 DOI: 10.1002/oby.20311]

130 **Plutzky J**. The PPAR-RXR transcriptional complex in the vasculature: energy in the balance. *Circ Res* 2011; **108**: 1002-1016 [PMID: 21493923 DOI: 10.1161/CIRCRESAHA.110.226860]

131 **Kotnik P**, Fischer-Posovszky P, Wabitsch M. RBP4: a controversial adipokine. *Eur J Endocrinol* 2011; **165**: 703-711 [PMID: 21835764 DOI: 10.1530/EJE-11-0431]

132 **Esteve E**, Ricart W, Fernández-Real JM. Adipocytokines and insulin resistance: the possible role of lipocalin-2, retinol binding protein-4, and adiponectin. *Diabetes Care* 2009; **32**: S362-S367 [PMID: 19875582 DOI: 10.2337/dc09-S340]

133 **Graham TE**, Yang Q, Blüher M, Hammarstedt A, Ciaraldi TP, Henry RR, Wason CJ, Oberbach A, Jansson PA, Smith U, Kahn BB. Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. *N Engl J Med* 2006; **354**: 2552-2563 [PMID: 16775236 DOI: 10.1056/NEJMoa054862]

134 **Bouwman FG**, Boer JM, Imholz S, Wang P, Verschuren WM, Dollé ME, Mariman EC. Gender-specific genetic associations of polymorphisms in ACE, AKR1C2, FTO and MMP2 with weight gain over a 10-year period. *Genes Nutr* 2014; **9**: 434 [PMID: 25322899 DOI: 10.1007/s12263-014-0434-2]

135 **Frigolet ME**, Torres N, Tovar AR. The renin-angiotensin system in adipose tissue and its metabolic consequences during obesity. *J Nutr Biochem* 2013; **24**: 2003-2015 [PMID: 24120291 DOI: 10.1016/j.jnutbio.2013.07.002]

136 **Wang P**, Holst C, Wodzig WK, Andersen MR, Astrup A, van Baak MA, Larsen TM, Jebb SA, Kafatos A, Pfeiffer AF, Martinez JA, Handjieva-Darlenska T, Kunesova M, Viguerie N, Langin D, Saris WH, Mariman EC; Diogenes consortium. Circulating ACE is a predictor of weight loss maintenance not only in overweight and obese women, but also in men. *Int J Obes (Lond)* 2012; **36**: 1545-1551 [PMID: 22270380 DOI: 10.1038/ijo.2011.278]

137 **Velkoska E**, Warner FJ, Cole TJ, Smith I, Morris MJ. Metabolic effects of low dose angiotensin converting enzyme inhibitor in dietary obesity in the rat. *Nutr Metab Cardiovasc Dis* 2010; **20**: 49-55 [PMID: 19361967 DOI: 10.1016/j.numecd.2009.02.004]

138 **Grobe JL**, Grobe CL, Beltz TG, Westphal SG, Morgan DA, Xu D, de Lange WJ, Li H, Sakai K, Thedens DR, Cassis LA, Rahmouni K, Mark AL, Johnson AK, Sigmund CD. The brain Renin-angiotensin system controls divergent efferent mechanisms to regulate fluid and energy balance. *Cell Metab* 2010; **12**: 431-442 [PMID: 21035755 DOI: 10.1016/j.cmet.2010.09.011]

139 **Vink RG**, Roumans NJ, Mariman EC, van Baak MA. Dietary weight loss-induced changes in RBP4, FFA, and ACE predict weight regain in people with overweight and obesity. *Physiol Rep* 2017; **5** [PMID: 29122953 DOI: 10.14814/phy2.13450]

140 **Staiger H**, Keuper M, Berti L, Hrabe de Angelis M, Häring HU. Fibroblast Growth Factor 21-Metabolic Role in Mice and Men. *Endocr Rev* 2017; **38**: 468-488 [PMID: 28938407 DOI: 10.1210/er.2017-00016]

141 **Kharitonenkov A**, Adams AC. Inventing new medicines: The FGF21 story. *Mol Metab* 2014; **3**: 221-229 [PMID: 24749049 DOI: 10.1016/j.molmet.2013.12.003]

142 **Zhen EY**, Jin Z, Ackermann BL, Thomas MK, Gutierrez JA. Circulating FGF21 proteolytic processing mediated by fibroblast activation protein. *Biochem J* 2016; **473**: 605-614 [PMID: 26635356 DOI: 10.1042/BJ20151085]

143 **Tezze C**, Romanello V, Sandri M. FGF21 as Modulator of Metabolism in Health and Disease. *Front Physiol* 2019; **10**: 419 [PMID: 31057418 DOI: 10.3389/fphys.2019.00419]

144 **Vinales KL**, Begaye B, Bogardus C, Walter M, Krakoff J, Piaggi P. FGF21 Is a Hormonal Mediator of the Human "Thrifty" Metabolic Phenotype. *Diabetes* 2019; **68**: 318-323 [PMID: 30257977 DOI: 10.2337/db18-0696]

145 **Fazeli PK**, Lun M, Kim SM, Bredella MA, Wright S, Zhang Y, Lee H, Catana C, Klibanski A, Patwari P, Steinhauser ML. FGF21 and the late adaptive response to starvation in humans. *J Clin Invest* 2015; **125**: 4601-4611 [PMID: 26529252 DOI: 10.1172/JCI83349]

146 **Kim KH**, Lee MS. FGF21 as a Stress Hormone: The Roles of FGF21 in Stress Adaptation and the Treatment of Metabolic Diseases. *Diabetes Metab J* 2014; **38**: 245-251 [PMID: 25215270 DOI: 10.4093/dmj.2014.38.4.245]

147 **Parmar B**, Lewis JE, Samms RJ, Ebling FJP, Cheng CC, Adams AC, Mallinson J, Cooper S, Taylor T, Ghasemi R, Stephens FB, Tsintzas K. Eccentric exercise increases circulating fibroblast activation protein α but not bioactive fibroblast growth factor 21 in healthy humans. *Exp Physiol* 2018; **103**: 876-883 [PMID: 29663541 DOI: 10.1113/EP086669]

**Footnotes**

**Conflict-of-interest statement:** There is no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** April 22, 2021

**First decision:** May 12, 2021

**Article in press:**

**Specialty type:** Endocrinology and metabolism

**Country/Territory of origin:** Egypt

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** DeSousa K **S-Editor:** Wu YXJ **L-Editor: P-Editor:**

**Figure Legends**

**Table 1 Phases of weight changes after bariatric surgery**

|  |  |
| --- | --- |
| **Phase name** | **Phase description** |
| Weight loss Phase  | Initial prompt weight loss period during which convalescent patient could lose up to 25 kg in the first month, this period persists for up to six months[3] |
| Pre-stability Phase  | Afterwards, weight loss slacks off for approximately one year[3] |
| Stability Phase  | Ultimately, through the subsequent two years usually convalescent patients attain lowermost body weight, (having lost about 50% of the excess body weight) is maintained in the majority (70%-80%) of patients, irrespective of surgical procedure performed[2] |