INTRODUCTION

Obesity is a leading preventable cause of death worldwide, with increasing rates in adults and children. Authorities view it as one of the most serious public health problems of the 21st century. It is a pan-endemic health problem in both developed and developing countries. Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health, leading to reduced life expectancy and increased health problems. It increases the likelihood of various diseases, particularly heart disease, type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis. Obesity is most commonly caused by a combination of excessive food energy intake, lack of physical activity, and genetic susceptibility, although a few cases are caused primarily by genes, endocrine disorders, medications, or psychiatric illness. The World Health Organization (WHO) predicts that overweight and obesity may soon replace more traditional public health concerns such as malnutrition and infectious diseases as the most significant cause of poor health ***(Must et al., 1999).***

Mini gastric bypass or single anastomosis bypass has shorter operating time, less re-routing of the intestines, one fewer anastomosis (connection of intestines) decreasing anastomosis leak percentage due to fewer sites for leakage and internal hernia, easy to reverse and revise, technically easier for the surgeon, and similar weight loss and recovery. It is

considered a restrictive and mal-absorptive surgery aiming to reduce calorie intake, reduce appetite and reduce calorie absorption to result in weight loss .The stomach is stapled along the lesser curvature with a bougie inserted and starting from the gastric incisura in order to create a long tube. The jejunum is lifted usually 200cm from the ligamentum of Treitz and anastomosed to the gastric tube ***(Rutledge, 2001).***

Mini gastric bypass induces significant and long-term remission of T2DM and improvement of metabolic/cardiovascular risk factors in severely obese patients. The short-term (decreased caloric intake) and long-term results (decreased fat mass and body weight) of bariatric surgery complementarily lead to improvement in glucose metabolism, insulin resistance, change in adipocytokines release, and quality of life. Currently, mini gastric bypass surgery is well accepted as a feasible therapeutic option for T2DM management in patients who are inadequately controlled by healthy lifestyle and medical treatment ***(Li et al., 2012; Brethauer at al., 2013).***

Although Mini gastric bypass procedure is an effective therapy for weight loss, it alters normal digestion and nutrient absorption of gastrointestinal system. These alterations can be mild with no apparent sequelae, or cause life-threatening complications including severe malnutrition which occurs in approximately 4.7% of the patients postoperatively as a result of protein, carbohydrate and lipid malabsorption. Gastric bypass also can lead to increased glycogen like Peptid-2 and

associated with markedly suppressed ghrelin levels (which is a hormone that increases food intake in rodents and humans) possibly contributing to the weight-reducing effect of the procedure ***(Le Roux et al., 2010).***

Gastric bypass procedure has a long term effect on bile dependent vitamins "e.g. Vit A,D,E,K" especially vitamin D metabolism, calcium and bone mineral density. In addition, vitamin D is also needed for the intestinal absorption of calcium. By creating a Roux anastomosis there is poor mixing of bile salts with fat, which results in impaired fat absorption and ultimately may produce malabsorption of vitamin D with subsequent hypocalcaemia, hyperparathyroidism and bone resorbtion ***(De Prisco et al., 2005)***

Mini gastric bypass has an effect on other hormones like insulin, leptin and gut hormones ***(Liou et al., 2007; Wang et al., 2005).***

Aim of the Work

To highlight the metabolic effect of Gastric Bypass on body physiology and how these changes encountered after operation serve in losing weight.

Chapter 1

PATHOPHYSIOLOGY OF OBESITY

Introduction:

Obesity is becoming a global epidemic in both children and adults It is an unintended consequence of the economic, social, and technological advances realized during the past several decades. The food supply is low in cost and abundant, and palatable foods with high caloric density are readily available in prepackaged forms and in fast-food restaurants. Labor-saving technologies have greatly reduced the amount of physical activity that used to be part of everyday life. Finally, the widespread availability of electronic devices in the home has promoted a sedentary lifestyle, particularly among children.

The World Health Organization (WHO) estimates that worldwide, more than one billion people are overweight, and 300 million are classified as obese. Additionally, the prevalence of overweight and obese young people is increasing rapidly in both the industrialized and developing world, constituting a global epidemic ***(WHO, 2015).***

Obesity is associated with numerous co-morbidities such as cardiovascular diseases (CVD), type 2 diabetes, hypertension, certain cancers, and sleep apnea/sleep-disordered breathing. In fact, obesity is an independent risk factor for CVD, and CVD risks have also been documented in obese children. Obesity is associated with an increased risk of

morbidity and mortality as well as reduced life expectancy. Health service use and medical costs associated with obesity and related diseases have risen dramatically and are expected to continue to rise. Besides an altered metabolic profile, a variety of adaptations/alterations in cardiac structure and function occur in the individual as adipose tissue accumulates in excess amounts, even in the absence of co-morbidities. Hence, obesity may affect the heart through its influence on known risk factors such as dyslipidemia, hypertension, glucose intolerance, inflammatory markers, obstructive sleep apnea/hypoventilation, and the prothrombotic state, in addition to as-yet-unrecognized mechanisms. On the whole, overweight and obesity predispose to or are associated with numerous cardiac complications such as coronary heart disease, heart failure, and sudden death because of their impact on the cardiovascular system ***(Zhang et al., 2016).***

Measurement of obesity:

Obesity is most widely measured via the body mass index (BMI). BMI is calculated as weight divided by the square of the height and given in units of kg/m^2. BMI is reliable, objective, and easily calculated. For this reason, the use of BMI has become widely accepted by investigators and clinicians and has been formally recommended by the WHO. A BMI between 18.5 and 24.9 kg/m^2 is generally considered normal. Patients with a BMI between 25 and 29.9 kg/m^2 are considered overweight, and those with a BMI greater than or equal to 30

kg/m 2 are considered to be obese,(WHO 2014). Obesity is further subclassified into class I, class II, and class III obesity as indicated in Table 1. Patients with a BMI greater than 40 kg/m^2 (class III obesity) are considered to be "morbidly obese," and those with a BMI greater than 50 kg/m 2 are classified as "super-obese." The term "super-super obese" is less commonly used to describe a BMI above 60 kg/m^2 ***(WHO, 2014).***

Table (1): WHO classification of obesity ***(WHO, 2014).***

Classification	Body mass index (kg/m2)	Risk of co-morbidities
Underweight	<18.5	Low
Normal range	18.5 to 24.9	Average
Overweight	>25.0	Increased
Pre-obese	25.0–29.9	Increased
Obese class I	30.0–34.9	Moderate
Obese class II	35.0–39.9	Severe
Obese class III	>40	Very severe

Metabolic Predictors of Weight Gain

The development of obesity occurs when the caloric intake is disproportionate to the energy expended. Three metabolic factors have been reported to be predictive of weight gain: a low adjusted sedentary energy expenditure, a high respiratory quotient (RQ; carbohydrate-to-fat oxidation ratio), and a low level of physical activity ***(Ravussin et al., 1989).***

The resting metabolic rate (RMR):

The resting metabolic rate (RMR) is strongly correlated to fat-free mass (FFM) in both men and women However, RMR is only one component of the total daily energy expenditure, which also includes the thermic effect of food and physical activity ***(Swinburn et al., 1994)***. Daily energy expenditure can be measured in a respiratory chamber or in free-living people by the doubly labeled water method. The contribution of low energy expenditure to the development of obesity was evaluated in several studies of Pima Indians. In a study of 95 subjects, the mean 24-hour adjusted energy expenditure was 36.3 kcal/kg FFM, but it varied considerably among the participants, from 28 to 42 kcal/kg FFM. Notably, this thermogenic response was correlated inversely with the change in body weight over a 2-year follow-up ($r = -0.39, p < 0.001$). People with low adjusted energy expenditure were four times more likely to gain 7.5 kg during follow-up than those with high adjusted energy expenditure. Similar results were found in a second group of 126 subjects who were followed up for 4 years. Of those with low RMR, 28% had a 10-kg body weight gain during follow-up compared with <5% of those with high RMR. Finally, in a group of 94 siblings from 36 families, the 24-hour energy expenditure tended to aggregate in families, such that some families showed low levels and others had high levels of energy expenditure. This finding suggests that energy expenditure may have a familial determinant ***(Ravussin et al., 1988).***

High respiratory quotient (RQ):

RQ is the second potential metabolic predictor of weight gain. A low RQ of 0.7 suggests that a person is oxidizing more fat than carbohydrate, whereas a ratio of 1.0 suggests that more carbohydrate than fat is being oxidized. The relationship between RQ and weight gain was evaluated in nondiabetic Pima Indians who were fed a weight-maintenance diet. In a group of 152 subjects, the 24-hour RQ varied from 0.799 to 0.903. Notably, the 24-hour RQ correlated with changes in body weight during a mean follow-up of 25 months (r = 0.27, $p < 0.01$). Subjects in the 90th percentile of RQ were 2.5 times more likely to gain at least 5 kg than those in the 10th percentile, and this effect was independent of 24-hour energy expenditure ***(Zurlo et al., 1990).***

Decreased physical activity:

It is believed that a sedentary lifestyle also has an impact on weight gain, but it remains to be shown in a well-designed longitudinal study. According to the 1996 Surgeon General's Report on Physical Activity and Health, participation in physical activity decreases with age. In each age group, more women than men do not participate in physical activity.

Pathophysiology of obesity:

Obesity is an exaggeration of normal adiposity and is a central player in the pathophysiology of diabetes mellitus, insulin resistance, dyslipidemia, hypertension, and

atherosclerosis, largely due to its secretion of excessive adipokines. Inflammatory, insulin-resistant, hypertensive, and thrombotic-promoting adipokines, which are atherogenic, are counterbalanced by anti-inflammatory and anti-atherogenic adipocyte hormones such as adiponectin, visfatin, and acylation-stimulating protein, whereas certain actions of leptin and resistin are pro-atherogenic. Adiponectin is protective against liver fibrosis due to its anti-inflammatory effect, whereas inflammatory cytokines such as tumor necrosis factor-α are detrimental for both fatty liver and pancreatic insulin release. Obesity contributes to immune dysfunction from the effects of its inflammatory adipokine secretion and is a major risk factor for many cancers, including hepatocellular, esophageal, and colon ***(Tartaglia et al., 1995).***

Mechanisms of controlling weight gain:

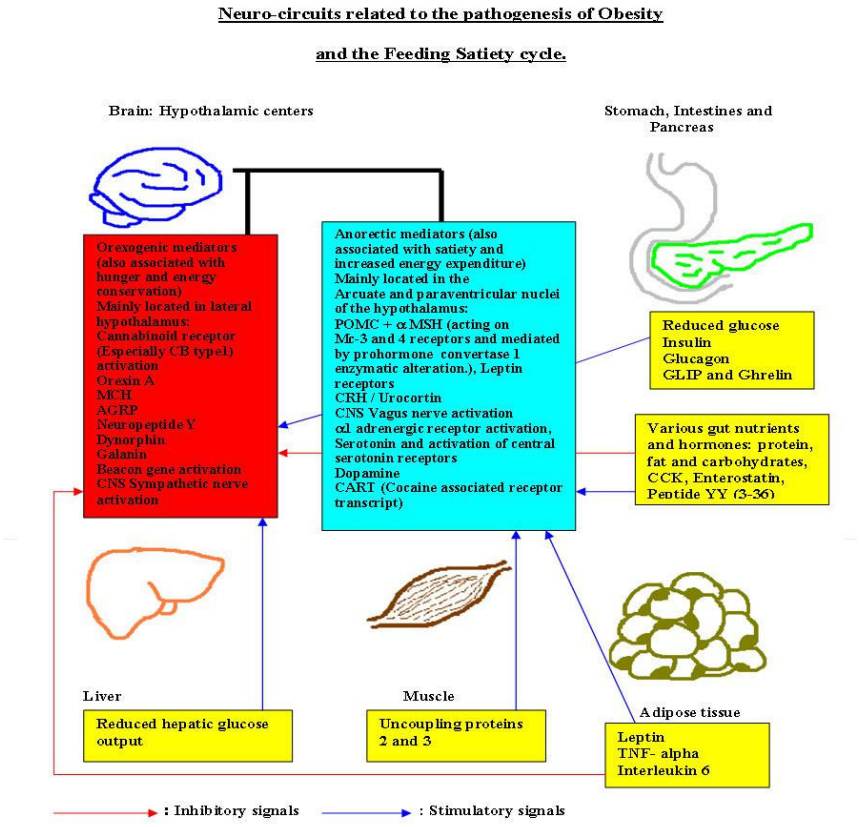

Figure (1): Neuro circuits related to the pathogenesis of obesity

1-CNS Regulation of food intake

The hypothalamus is the region that integrates and co-ordinates the signals influencing the energy balance ***(figs. 2 & 3).*** In addition to signals from neuropeptides and neurocytokines, hypothalamic centers involved in energy homeostasis can also be influenced by metabolic substrates ***(Ahima et al., 2008).***

Cholecystokinin (CCK) is liberated by the small intestine into the circulation in response to the contact with nutrients such as fatty acids, and influences satiety by actions on CCK receptors located on peripheral vagal afferent terminals, which transmit neural signals to the brainstem ***(Ochner et al., 2011).***

The true effects of this hormone in patients submitted to surgeries that promote duodenal bypass are still unknown. The absence of nutrient passage through the duodenum and, therefore, the lack of stimulus to its production apparently markedly decrease its effects after these surgeries ***(Ochner et al., 2011).***

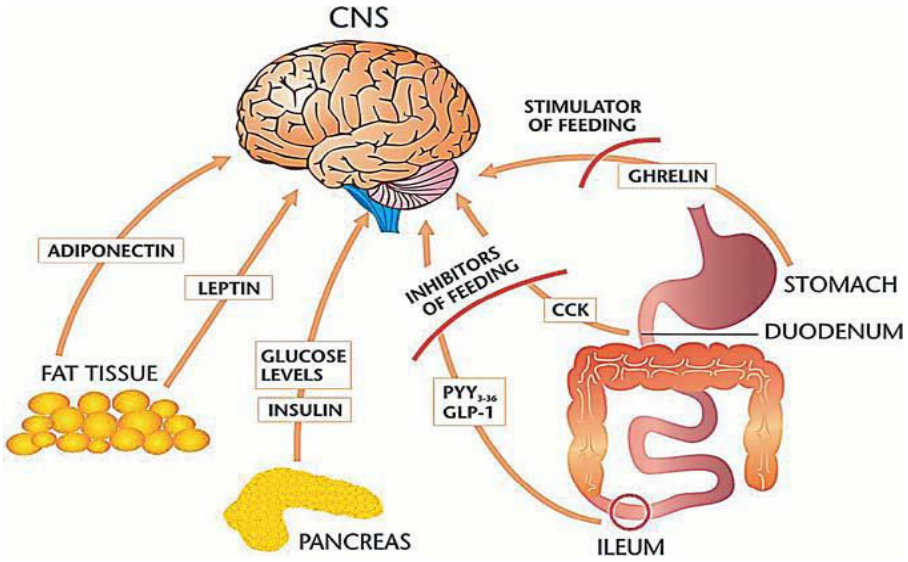

Figure (2): Normal afferent signals.

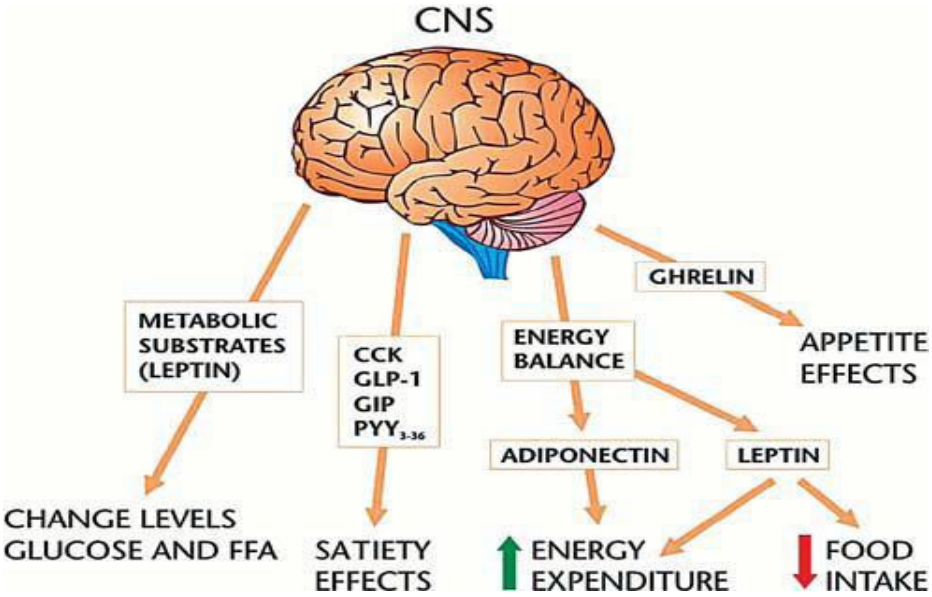

Figure (3): Normal efferent signals

2-Gastrointestinal hormones and food intake

Many techniques in obesity surgery, which involve modification in the digestive tract, like the RYGB, lead consequently to a true short circuit in the production of intestinal hormones as well as the signalization to the CNS ***(fig. 4).*** A considerable segment of small intestine is bypassed, resulting in a much shorter gastrointestinal tract ***(Cohen et al., 2005).***

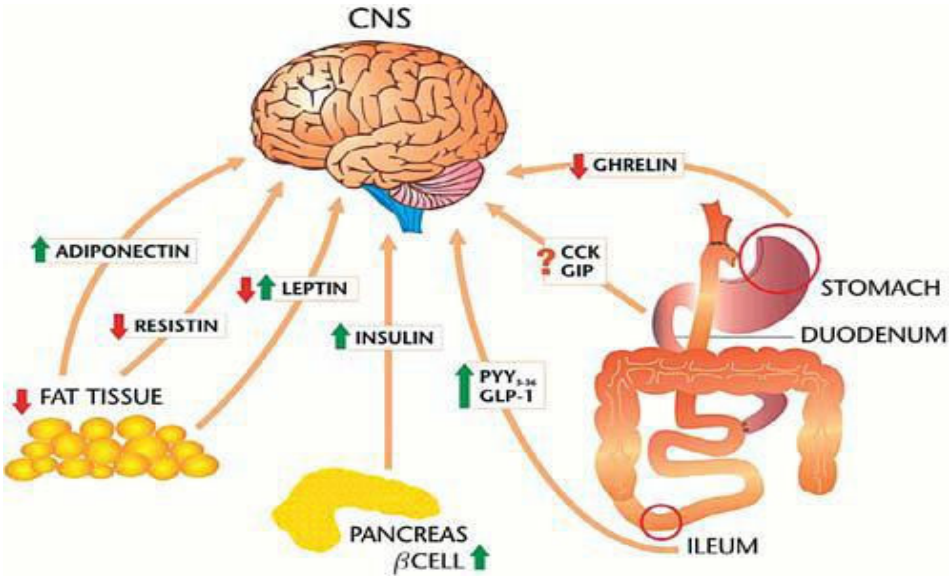

Figure (4): Efferent and afferent signals after RYGB

It is fundamental to understand that, each time we eat, we produce a variety of stimuli, both mechanical and chemical in the enteroendocrine cells, and as a consequence, the production of substances like hormones, enzymes, vitamin absorption factors, etc., lead to many effects in the signals to the CNS. The surgeries that modify this -natural passage obviously confound this entire system ***(Malik et al., 2008).***

The most studied intestinal hormones in obesity surgery today are Cholecystokinin (CCK), ghrelin and oxytomodulin (OXM).

Cholecystokinin:

This is one of the most studied hormones. It is a powerful satiation trigger and is secreted primarily in two forms: CCK -

33, also known as alimentary secreted from duodenum and jejunum cells, and CCK-8, the cerebral made in the CNS. That produced in the duodenum has very well defined functions in the digestive process, like stimulating gallbladder emptying, pancreatic enzyme secretion, gastric emptying, and acid production in the stomach. Surgeries like bypass exclude the duodenum, and the true effects in all this signalization will be altered ***(Cohen et al., 2005).***

Ghrelin:

Ghrelin is unique among gut hormones in stimulating food intake, and its chronic administration to rat's causes obesity. However, its levels have been shown to be smaller in the obese when compared to people of normal weight. The place with the highest ghrelin concentration is the gastric fundus. When this gastric segment is disconnected and isolated, there is a hypothesis that a fatigue in this hormone production exists, which stops acting. In humans, the serum concentration levels of ghrelin increase before meals and decrease after them ***(Zhany et al., 2014).***

Three studies confirmed a decrease in fasting ghrelin levels after laparoscopic sleeve gastrectomy (LSG). A prospective, double-blind study comparing RYGB and LSG confirmed a significant postprandial suppression of ghrelin postoperatively, while there was no change in the RYGB group. In the same study, the marked suppression of ghrelin levels after LSG was associated with greater appetite reduction and