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MINIREVIEWS

# Effect of bariatric surgery on humoral control of metabolic derangements in obese patients with type 2 diabetes mellitus: How it works

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## Abstract

Obesity and diabetes is a co-pandemic and a major health concern that is expanding. It has many psychosocial and economic consequences due to morbidity and mortality of this disease combination. The pathophysiology of obesity and related diabetes is complex and multifactorial. One arm of this disease process is the genetic susceptibility. Other arm is dependent on the intricate neuro-humoral factors that converge in the central nerve system. Gut hormones and the adipose tissue derived factors plays an important role in this delicate network. Bariatric surgery provides the only durable option for treatment of obesity and furthermore it provides a remission in the concomitant diseases that accompany obesity. This review provides a brief insight to all these mechanisms and tries to deduce the possible reasons of remission of type 2 diabetes after bariatric surgery.

**Key words:** Type 2 diabetes; Morbid obesity; Bariatric surgery



**Core tip:** Metabolic surgery in obese individuals results weight loss and beneficial effects on type 2 diabetes mellitus and metabolic syndrome.

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## INTRODUCTION

Obesity is considered as abnormal accumulation of

**Table 1 World Health Organization classification of obesity**

| Classification | WHO class | BMI (kg/m$^2$) |
|---|---|---|
| Underweight | | ≤ 18.5 |
| Normal | | 18.5-24.9 |
| Overweight | | 25.0-29.9 |
| Obesity | I | 30.0-34.9 |
| | II | 35.0-39.9 |
| Extreme obesity | III | 40 |

Adapted from Aronne[4]. WHO: World Health Organization; BMI: Body mass index.

excess energy as fat tissue that results in major health problems and reduced life span of the individual[1]. Obesity is a major health problem and is now considered a worldwide pandemic. Its incidence increasing in an alarming rate and by 2015 around a million people is expected to be overweight worldwide[2]. Furthermore, it is considered as a government political problem for it results in economic, social losses due to morbidity and mortality during the course of the disease[3]. The risk stratification of obesity is made according to World Health Organization's proposed classification of obesity (Table 1)[4]. Increasing body mass index (kg/m$^2$) the morbidity and mortality rate of the patient increases. Obesity causes many concomitant systemic diseases. Among the diseases that occur with obesity are diabetes, hypertension, coronary artery diseases, dyslipidaemias, non-alcoholic fatty liver disease and metabolic syndrome are pronounced[5]. There are many problems when dealing with obese patient. For since it is a multifactorial disease the treatment is very hard furthermore there are many social security related problems when dealing with bariatric patient. There are also psychosocial implications against obese people such as job interview bias, unavailability of public bills and inability of social security coverage for obesity related diseases[6].

Obesity is multifactorial disease and many neuro-humoral factors are orchestrated in appetite control and energy haemostasis of the individual. Detailed review of these factors is out of the scope of this text. Here we will examine briefly the central nervous system related and gut humoral factors related control mechanisms of the appetite of the individual and furthermore we will give detailed information regarding type 2 diabetes mellitus (T2DM) and obesity pandemic. Later on, we will try to summarize the effects of bariatric surgery on humoral factors of obesity and diabetes.

### Role of central nervous system in control of appetite

Central nervous system as a pivotal point in orchestration of anorectic and orexigenic signals received from the periphery. Mainly the arcuate nucleus of the central nervous system integrates all the input[7]. This area of the brain contains neuropeptide YY rich neurons. The main orexigenic stimulus comes from Ghrelin and the anorectic stimuli come from the Glucagon like peptide-1 (GLP-1), plasma peptide tyrosine tyrosine 3-36 (PYY3-36), cholecystokinin and *etc*. All these stimuli integrate at the arcuate nucleus and this causes the individual to seek food in discrete time points between daily activities[8-10]. This is one of the main points that is deranged in the obese individual and a continuous eating behaviour occurs in the obese patient.

### Peripheral axis

Peripheral axis consists of gut related hormones with vagus and the adipose tissue related humoral factor; namely the adipokines. These are all potent short and long terms stimuli for the control of energy haemostasis in the individual and as a result of this there is the food seeking behaviour characteristics of humans (and most vertebrates) ae determined.

### Role of gut related hormones in obesity

Several factors secreted from the gastrointestinal tract regulate the caloric intake and the food seeking behaviour of the individual[7,8]. There are factors that increase the adipogenesis and there are counteracting factors that reduce the appetite and reduce adipose tissue formation. Main orexigenic factors secreted from the gastrointestinal system are ghrelin and insulin. The counteracting mechanisms on the other hand are GLP-1, NYY3-36, *etc*[9,10]. Furthermore vagus and the autonomic system are important afferent inputs of the gastrointestinal system to the arcuate nucleus forming the gut-brain feedback mechanisms[11,12].

Ghrelin is a 28-amino acid peptide. It has been shown to be produced from the fundic mucosa. In animal models, it was shown that ghrelin increased feeding and weight gain and had an orexigenic role in energy balance. The clock genes *PER1* and *PER2* ghrelin levels peak before meals and quickly decrease following meals. Arcuate nucleus in the central nervous system exhibits ghrelin receptors[13,14].

Insulin has many roles in energy balance. Serum glucose levels elevated after a meal stimulate insulin release by pancreatic beta cells. Additional secretagogues of insulin are amino acids such as alanine, glycine, and arginine, acetylcholine produced from vagal nerve endings, and incretins such as GLP-1 and glucose-dependent insulinotropic polypeptide[7,8]. Although central effects of insulin is reduced appetite and weight loss in preclinical studies in obese individuals show higher basal insulin levels[8].

GLP-1 has an important role in increasing secretion of insulin from the pancreas[7]. Both *in vivo* and *in vitro* researches have showed that GLP-1 increase insulin secretion in the beta cell. Moreover, glucagon secretion is inhibited by GLP-1 while insulin sensitivity is increased[7,15].

PYY3-36 is an anorectic factor on the arcuate nucleus through the Y2 receptors expressed at the neuronal level. It shows peak levels 1-2 h following the meals and the rise in serum levels are observed within 15 min following eating[8,16]. PYY3-36 anorectic effect is possibly facilitated by the vagus nerve[16].

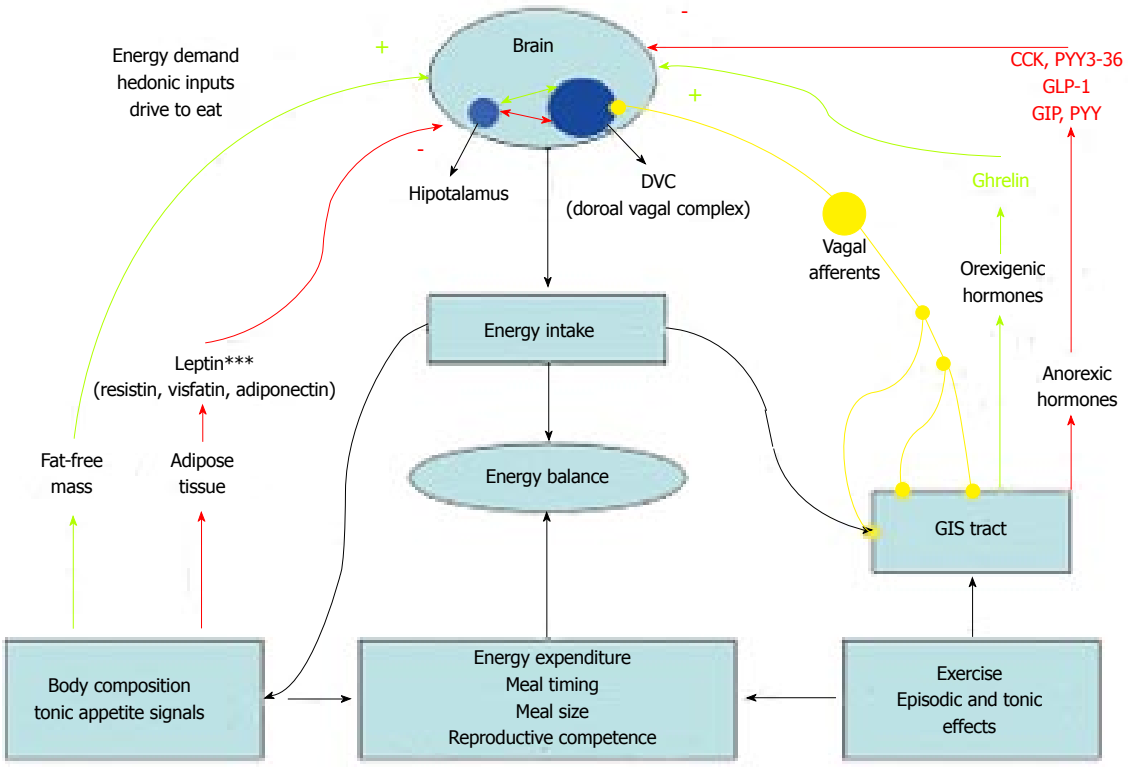


**Figure 1 Factors produce a tendency towards insulin resistance and diabetes in the obese patients.** DVC: Dorsal vagal complex; CCK: Cholecystokinin; GLP-1: Glucagon-like peptide-1; PYY: Peptide YY; GIP: Gastric inhibitory polypeptide.

### *Role of adipose tissue in obesity*

Leptin and adiponectin are the two main humoral factors secreted from the adipose tissue and that play a role in the energy haemostasis of the individual. They all together form the adipose-brain feedback axis[8].

Leptin is produced in white and brown adipose tissue, placenta, ovaries, skeletal muscle, stomach, breast, bone marrow, pituitary, and liver[8]. Engineer and Garcia have showed that leptin affects hypothalamus, where it inhibits NPY/AgRP receptor neurons while stimulates α-MSH neurons[17]. In contrast to ghrelin, leptin acts on appetite and energy balance[7,18]. Harvey *et al*[8] has reported leptin resistance in obese patients.

Adiponectin is secreted from white adipose tissue[8]. Serum adiponectin levels are negatively correlated to serum insulin and glucose levels, body fat mass, and waist-to-hip ratio. It has been shown that fasting adiponectin levels have been reduced in the obese individuals[19]. Nevertheless, the response to a meal appear to be exaggerated in obese subjects.

### *Relationship between obesity and diabetes*

Obesity is associated to many medical conditions, probably the most disturbing may be T2DM. Both obesity and T2DM are mainly related with insulin resistance[3]. The nonesterified fatty acids (NEFAs) secreted from adipose tissue in obese population may lead to the theory that insulin resistance and β-cell dysfunction are probably related[20,21]. Adipose tissue affects body metabolism by secreting hormones, glycerol, leptin, cytokines, adiponectin, proinflammatory substances, and NEFAs. Increased NEFA secretion is detected both in obesity and T2DM, and it is related with insulin resistance in both situations. In humans, insulin resistance starts to develop shortly after an acute increase of plasma NEFA levels.

Intra-abdominal fat is linked to the genes that secrete specific types of proteins responsible for the production of energy[22,23]. Omental adipocytes secrete larger amount of adiponectin than the subcutaneous-derived adipocytes[24,25]. Furthermore, adiponectin secreted from omental adipocytes is negatively associated with weight gain. The excretion of NEFAs to different tissue may be affected by their source. Abdominal fat is considered more lipolytic than subcutaneous fat, and it does not respond simply to the antilipolytic action of insulin, which makes intra-abdominal fat more significant in causing insulin resistance and diabetes[26]. All these factors produce a tendency towards insulin resistance and diabetes in the obese patients (Figure 1).

### *Fecal fat, and fecal biliary acids in obesity*

The cytotoxicity of fecal bile acids is associated with their concentration in fecal water, and particularly is related to the concentration of secondary bile acids[27,28]. Total bile acid levels in fecal water were decreased meaningfully in the course of orlistat treatment. The decrease in fecal water bile acids during orlistat treatment mainly was caused by a large reduction in deoxycholic acid. Small reductions were observed in fecal water with both the orlistat and placebo groups for all the other bile acids. This is relevant in that the

secondary bile acids, which include deoxycholic acid, are the bile acids most frequently associated in colonic cell hyperproliferation[29,30].

## BARIATRIC SURGERY AND OBESITY RELATED METABOLIC CHANGES

Bariatric surgery consists of various interventions which can be divided as restrictive, malabsorptive, or combined restrictive and malabsorptive. The number of bariatric interventions (*i.e.*, metabolic surgery) for the treatment of obesity is in exponential increase. This is partially due to effective and long-lasting weight loss; in addition, a good deal of improvement of co-morbidities after surgery compared with diet and physical activity[7]. In this subsection we will briefly evaluate the changes in the levels of above mentioned factors with respect to various bariatric procedures and at the end try to draw certain conclusion regarding the metabolic effects of bariatric (metabolic) surgery. We will briefly summarize the effect of bariatric surgery on each of the adipose and gut humoral factors.

In the case of ghrelin there are many report regarding Roux-en-Y gastric bypass (RY-GBP) and the serum ghrelin levels detected in various set points starting from ranging between 14 d postoperatively to 2 years[31,32]. Most of the researchers have found decreased ghrelin levels postoperatively and these results have been compared to non-resectional restrictive procedures such as adjustable gastric banding (AGB). Therefore we can say that the final effect of procedures involving gastric transection reduces the serum ghrelin levels[33,34].

The changes in ghrelin after sleeve gastrectomy (SG) were measured in different studies. Shak *et al*[35] stated that fasting ghrelin levels are decreased up to 5 years of follow-up. Moreover, some studies tried to evaluate and compare the effects of RY-GBP or AGB with the SG on fasting ghrelin levels, which showed to be decreased[36]. These studies showed that the ghrelin suppression after both SG and RY-GBP may be part of the mechanism that contributes to diabetes remission[35,36].

Serum insulin levels sow rapid drop with RY-GBP, biliopancreatic diversion and duodenal switch and SG however with AGB although insulin drops the incretin effect is not observed[7,35-38].

A strong GLP-1 response was reported 10 years after RY-GBP, suggesting a long-lasting effect. Furthermore, in T2DM patients, an improved GLP-1 response to meal intake is not enough to preserve normal glucose tolerance in the long term after RY-GBP. Similarly, some studies have shown unaffected fasting GLP-1 and a noteworthy increase in response to a glycemic challenge[39,40]. Studies have shown a significantly increased fasting level of PYY3-36 following RY-GBP. Following the AGB, fasting PYY3-36 or meal-stimulated response is variable and inconclusive[41,42]. Data regarding the effects on leptin are inconclusive and therefore research regarding area is urgently needed. Furthermore, adiponectin studied in RY-GBP in only one study and was found be increased following surgery[43]. This study is not enough to draw conclusions and therefore multi-centric high patient volume studies are needed to evaluate the role of metabolic surgery on adipose-brain axis in obesity.

Clinically all these changes in the humoral effects that the bariatric surgery produces is seen as remission of diabetes in obese individuals postoperatively. Even in patients who continue to have diabetes postoperatively have a better quality of life due to reduced medications and a better glycaemic control. This has been extensively studied and currently here even meta-analysis regarding this subject showing very good results in almost all procedure types[44-47].

## CONCLUSION

Metabolic surgery in obese individuals results weight loss and beneficial effects on T2DM and metabolic syndrome.

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