Journal of
Obesity & Weight Loss Therapy

Alwahsh and Ramadori, J Obes Weight Loss Ther 2015, 5:5
DOI: 10.4172/2165-7904.1000280

Mini Review Open Access

How Does Bariatric Surgery Improve Type II Diabetes? The ''Neglected'' Importance of the Liver in Clearing Glucose and Insulin from the Portal Blood

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Received date: August 24, 2015; **Accepted date:** October 26, 2015; **Published date:** October 30, 2015

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Abstract

The pandemic of obesity due to food "addiction" has led to a dramatic increase in rates of Type II Diabetes Mellitus (T2DM). T2DM is characterized by increased glucose and insulin (but not of the C-peptide) serum levels. Increase of insulin serum level without increase of insulin synthesis is supposed to be due to insulin resistance. Reduction of body weight (BW) through reduction of calories uptake is the most effective measure to treat T2DM and metabolic syndrome in obese patients.

Appetite suppressant drugs which potentially reduce BW have several side effects, and as "lifestyle modifiers" are not approved of as potential antidiabetic drugs. In addition to the treatment of extreme (BMI ≥ 40) obesity, surgeons have expanded the offer of bariatric surgery as therapeutic option for diabetic, "non-morbid" (BMI ≤ 35) obesity. As a "collateral effect" of this surgical intervention, acute and long-term improvement of T2DM has been observed. Although several hypotheses to explain this improvement have been reported, the exact mechanism underlying the reduced hyperglycemia and hyperinsulinemia immediately after surgery is unclear. Though long-term effects of the different operations have not yet been studied thoroughly.

Besides weight-loss, bariatric surgery may also reduce lipid accumulation in the liver. Reverse of the hepatic lipid deposition may improve clearance of glucose and insulin from the liver and consequently lead to reduction their concentrations in the peripheral blood. This mechanism has not, however, been considered when effects of bariatric surgery on glucose metabolism have been reported. In fact, a few reports on limited patients number already published have given information about changes of liver size and/or liver lipid content at different time points post-operation. Future prospective studies should focus on the changes in glucose and lipid metabolism induced in the liver by the various types of surgical interventions.

Keywords: Roux-en-Y-gastric bypass; Biliopancreatic diversion; Laparoscopic sleeve gastrectomy; Non-alcoholic fatty liver disease; Insulin clearance; Insulin resistance; Hepatic steatosis; Body weight loss

Introduction

Prevalence of Type II Diabetes Mellitus (T2DM) is increasing dramatically worldwide. T2DM is mainly due to Insulin Resistance (IR), that is, the cells do not respond sufficiently to the insulin or higher insulin concentration is needed to exert the normal insulin effect. T2DM is diagnosed as glycated hemoglobin, HbA1c >6.3% (45 mmol/mol), fasting plasma glucose >126 mg/dL, >200 mg/dL during oral glucose-tolerance test (OGTT) or random testing [1], and increased insulin level. Obesity is an important risk factor for both T2DM and non-alcoholic fatty liver disease (NAFLD). More than one-third of U.S. adults are obese. These patients are also relatively insensitive to the effects of leptin; a satiety hormone produced mainly in subcutaneous fat tissue [2].

Due to the anatomical linkage, the liver clears most of the absorbed nutrients as well as gastrointestinal hormones via portal blood. The ingestion of sugar-enriched diets triggers insulin secretion from the pancreas, and the absorbed glucose and the secreted insulin are delivered to the liver. NAFLD is usually seen among the overweight (body mass index, BMI 25-29.9) or obese people (≥ 30). NAFLD is a wide range of conditions caused by an accumulation of fat within the hepatocytes, which could advance to a progressive form, the non-alcoholic steatohepatitis (NASH). The consumption of fructose; which can be used as sweetener in juice beverages and soft drinks, and of high-fat-diet (HFD), "Western diet", with/out light-to-moderate alcohol intake could cause simple liver steatosis, NASH with progression to liver cirrhosis an even cancer [3-5].

Body weight (BW) loss improves insulin action; the major factor involved in the pathogenesis of T2DM, and is considered a primary therapy for obese patients who have T2DM [6]. Unfortunately, most T2DM patients especially those with morbid extreme obesity fail to achieve successful weight loss and adequate glycemic control from medical therapy or lifestyle modifiers. In contrast, bariatric surgery causes marked weight loss and almost complete remission of T2DM in most patients shortly after the operation. In fact, most patients with severe obesity who undergo bariatric surgery have NAFLD, which is associated IR, T2DM, hypertension, and obesity-related dyslipidemia [7]. Here, we would like to emphasize the significance of liver in glucose homeostasis and IR after bariatric surgery-accompanied BW loss and remission of T2DM.

Short- and long-term effects of bariatric surgery on insulin sensitivity and BW loss

Currently, the best treatment method to achieve weight loss in morbid obese persons (BMI ≥ 40) by inducing a negative balance between energy intake (or absorption) and energy expenditure, is the bariatric surgery [8]. The obtained BW loss is primarily due to a mechanical restriction of food intake (e.g., gastric banding) and/or malabsorptive procedures (e.g., gastric bypass). The effectiveness of bariatric surgery in abolishing T2DM ranges from 43% with gastric banding to 98% with Biliopancreatic Diversion (BPD) with/out duodenal switch [9,10]. Little is known of the exact underlying mechanisms of the improvement of insulin sensitivity and glycemia [10], but mechanisms like the "foregut" and the "hindgut" hypotheses have been proposed [11].

Recent publications showed that many patients had lost about one-third of their BWs and an improvement of T2DM acutely post-bariatric operation [6,12]. In addition, the bypass of duodenum and proximal jejunum by nutrients enhanced insulin sensitivity, inhibited lipolysis, and increased insulin clearance in glucose-tolerant and diabetic obese subjects. These results may further our knowledge of the effects of bariatric surgery on both IR and T2DM [13].

Improvement in T2DM is seen in 80-98% of obese diabetic patients who undergo gastric bypass or BPD. This improvement is evident early after the operation before significant weight loss has occurred, though the exact mechanism remains unclear. Studies have focused on changes in the entero-insular axis, which is mediated in part by the interaction of incretin hormones, e.g., the Glucagon-Like Peptide-1 (GIP1) and Glucose-Dependent Insulinotropic Polypeptide (GIP), on the beta islet cells of the pancreas. The responsible mechanisms for the supposed increased GLP1 synthesis are still a matter of debate [14]. Other mechanisms which have been postulated focus on the adipo-insular axis; the actions of adiponectin and leptin seem to have an important role in IR, but their action depends on weight loss [11].

Every year more than 100.000 morbid obese people get different operations for weight loss, however, few studies report long-term follow-up post-operation in cohorts with adequate retention rates. Data from a recently published Cochrane review is based just on 1798 patients (22 trials!) reported, and Yang et al. studied 3-years effects of Laparoscopic Sleeve Gastrectomy (LSG) versus Roux-En-Y Gastric Bypass (RYGP) on T2DM patients (BMI ≥ 28-35 kg/m^2) [15]. Interestingly, it was found that 78.6% in the LSG and 85.2% in the RYGB group achieved complete remission of T2DM with HbA1c <6.0% without taking diabetic medications, and 89.3% LSG *vs.* 92.6% RYGB group gained successful treatment of diabetes with HbA1c ≤ 6.5%. RYGB group had significantly greater BW loss than the LSG group. Serum lipids in each group were also greatly improved [15].

Futhermore, the influence of gender on long-term (5-years) weight loss and comorbidity improvement after LSG and RYGB was investigated. The LSG was more effective in obese male than female patients regards to the percentage of excess BMI lost (%EBMIL), with no difference in comorbidities. However, RYGB procedure elicited similar results in both genders in terms of % EBMIL and comorbidities [16].

In a systemic review about bariatirc surgery of 7371 clinical studies since 1946 performed on patients with a BMI ≥ 35, had >2 years of outcome information, and had follow-up measures for at least 80% of the initial cohort, it was found that for T2DM (HBA1c<6.5% without medication), sample-size-weighted remission rates were 66.7% for RYGP and 28.6% for gastric band. For hyperlipidemia (cholesterol <200 mg/dL, HDL>40 mg/dL, LDL<160 mg/dL, and triglycerides<200 mg/dL), remission rates were 60.4% for RYGP and 22.7% for gastric band. It is conuded that RYGP has better outcomes than gastric band procedures for long-term loss, T2DM control and remission, hypertension, and hyperlipidemia [17].

Importantly, Madsbad et al. reported that with all three of these procedures, remission of diabetes is associated with early increases in insulin sensitivity in the liver and later in peripheral tissues (Figure 1). The LSG and RYBG are also associated with improved insulin secretion and an exaggerated postprandial rise in GLP1 [18].

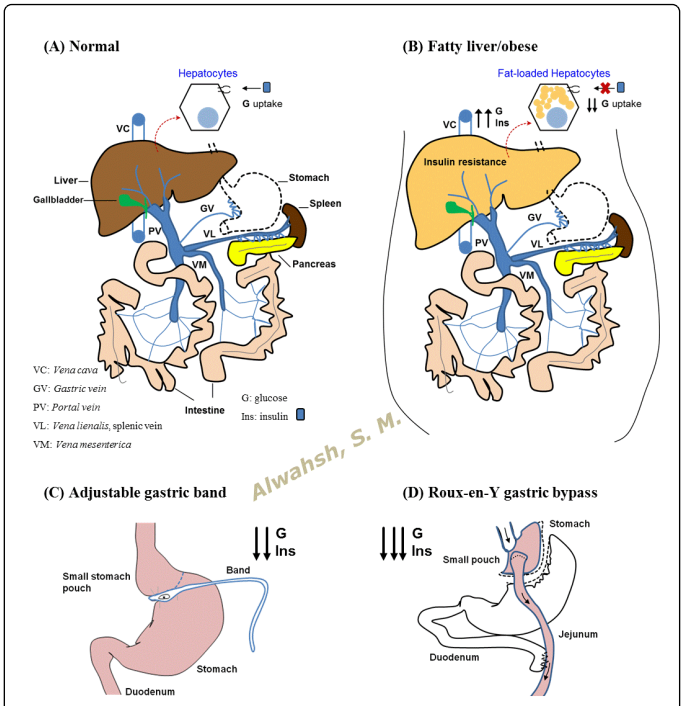

Figure 1: The liver maintains blood glucose level and it is the major site of insulin clearance in healthy subject (A), in case of obesity (B), the ingested glucose, and consequently, the secreted pancreatic insulin bypass the fatty liver due to hepatic IR. Bariatric surgery leads to a restricted calorie intake (C) and/or reduced food absorption (D) which, in turn, lowers insulin production; results in weight-loss and improvement of the fatty liver and IR. Subsequently, this rapidly improves T2DM after the surgery.

Bariatric surgery, the liver and insulin insensitivity

The liver is the major site for insulin clearance as it takes up about 75% of insulin presents in portal blood [13,19]. It has been shown that a direct connection of portal vein with the inferior vena cava-portacaval shunt-, thus bypassing the liver entry; increased of peripheral blood insulin and blood and urinary glucose levels [20]. Insulin clearance is impaired in T2DM and obesity, and severity of the changes of IR has been correlated with the severity of hepatic steatosis [21]. After bariatric surgery there is a sudden decrease of nutrients ingestion. People claim that this is not enough to explain the improvement of the serum glucose level and of the HBA1c.

Bariatric surgery may also reduce lipid deposition in the liver [7]. This effect has not, however, been considered when effects of bariatric surgery on glucose metabolism have been reported, especially as most published studies [17] of bariatric surgery are retrospective. In fact, none of the studies published so far has given information about changes of liver size and/or liver fat content post-bariatric operation. By reporting changes in histology after bariatric surgery, none of the studies published so far has given information about changes of liver size and/or quantitative liver lipid content post-bariatric operation.

A common presentation of pancreatic pathologies is jaundice, which occurs due to the obstruction of the common bile duct and is the classical symptom of pancreatic head malignancies and consequent impaired liver function. In the context of chronic liver disease, markers for common bile-duct obstruction and liver cell damage are associated with the development of IR, metabolic syndrome and T2DM [22]. Remarkably, surgically reversible blood glucose dysregulation diagnosed concomitantly with a (peri-) pancreatic tumor appears secondary to compromised liver function due to tumor compression of the common bile duct and the subsequent increase in IR. It can be categorized as "cholestasis-induced diabetes" and thereby distinguished from other forms of hyperglycemic disorders [23].

Raffaelli et al. studied the changes in the levels of diurnal leptin, insulin and free fatty acid in severely obese (BMI ≥ 40 kg/m^2) women before and 6-months after BPD [2]. Amazingly, they reported that BPD, a malabsorptive bariatric operation that drastically reduces circulating lipid levels, improves IR independently of weight loss. They demonstrated that normalization of insulin sensitivity after bariatric surgery was associated with a reduction in 24-h free fatty acid concentrations and changes in the pattern of leptin peaks in plasma. Bariatric surgery improves the metabolic dysfunction of obesity, and this may be through a reduction in circulating free fatty acids and modification of leptin metabolism [2]. Raised FFA levels decrease the ability of insulin to suppress hepatic glucose output and to promote peripheral glucose uptake, which are supposed to be the major features of IR [2]. In contrast, overnight reduction of FFA levels with acipimox, a drug used to treat hypertriglyceridemia, has been reported to improve IR in obese subjects [24].

However, the bariatric surgery-induced weight loss can be explained by reduced consumption of high-fat/ fructose-containing diets and alcohol [25]; the nutrients that cause hepatic steatosis, hepatomegaly, and consequently IR, when consumed in extensive amounts [3,5]. This suggests that the reappearance of the hyperglycemia, insulinemia and IR in patient's long-time postoperation is due to the accumulation of fats in the liver, which in turn reduces liver's ability to take up insulin and glucose from the portal blood .This reduction becomes even greater when hepatocellular damage and consequent reduction of liver function occur. This indicates the central role of the liver in glucose and insulin homeostasis.

The prevalence of and predictive markers for NAFLD in 184 morbidly obese patients undergoing bariatric surgery were assessed. It has been found that the prevalence of NAFLD was 84%, and non-invasive markers include the age, waist circumference, serum ALT activity, and serum triglyceride level are efficient for the diagnosis and management of NAFLD in morbidly obese patients [26].

Recently, we reproduced the situation of hyperinsulinemia and hyperglycemia in presence of NAFLD conditions observed in humans by inducing feeding rats with different hypercaloric diets. Rats were reared on chow, Lieber-DeCarli (LDC), LDC+30% kJ ethanol and 30% kJ fructose (L-EF) for 28-days. L-EF diet caused liver dysfunction, hypertriglyceridemia, and low HDL-cholesterol. Furthermore, we [4] found that the mRNA expression of hepatic insulin receptor substrate-1/2 was significantly reduced in the L-EF group, accompanied by hyperglycemia and decreased C-peptide:insulin ratio, pointing to hepatic IR and reduced insulin and glucose clearance (Figure 2). While the effect of metformin on BW may be due to the frequent gastrointestinal side effect with reduction of the introduction of nutrients, GLP-1 may influence the appetite at the brain level.

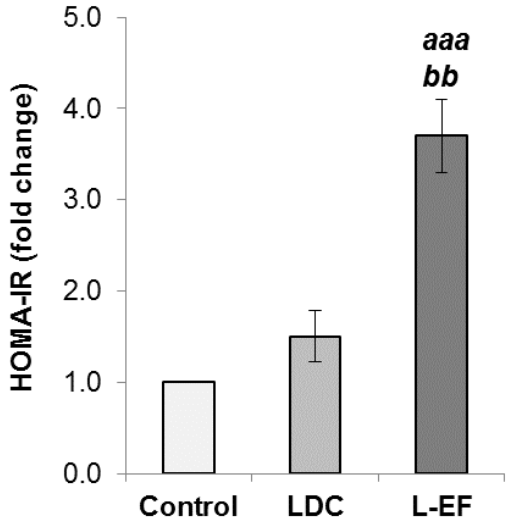

Figure 2: Rats were fed chow, Lieber-DeCarli (LDC), or LDC+ 30% kJ ethanol and 30% kJ fructose (L-EF) for 28-days. The homeostatic model assessment of insulin resistance (HOMA-IR) index was calculated as HOMA-IR = (I0 × G0)/22.5, where I0 = fasting insulin in μU/mL and G0 = fasting plasma glucose in mmol/L. ^{aaa}indicates significant difference P<0.001 vs. LDC, and ^{bb}P<0.001 vs. control by unpaired t-Test.

The current evidence suggests that bariatric surgery for patients with severe obesity decreases the grade of steatosis, hepatic inflammation, and fibrosis. However, further long-term studies are required to confirm the true effects before recommending bariatric surgery as a potential treatment for NASH [7]. Thanos et al. have examined the long-term effects of RYGB on the rat brain's response to the anticipation of palatable high-fat *vs.* regular diet [27]. They found that RYGB alters brain activity in areas involved in reward expectation and taste processing when anticipating a palatable fatty food. Thus, specific cerebellar regions with altered metabolism following RYGB may help identify novel therapeutic targets for treatment of obesity [27].

Conclusions

Bariatric surgery is effective in improving IR and glucose metabolism primarily by reducing calorie intake; consequently reducing BW and lipid deposition in the liver, and by improving insulin-dependent glucose uptake in the hepatocyte. This effect is the best explanation for T2DM-improvement after bariatric surgery. However, more research is needed to advance our understanding of the alterations induced in the liver by different bariatric surgical

procedures that improve metabolic function and contribute to the resolution of T2DM.

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