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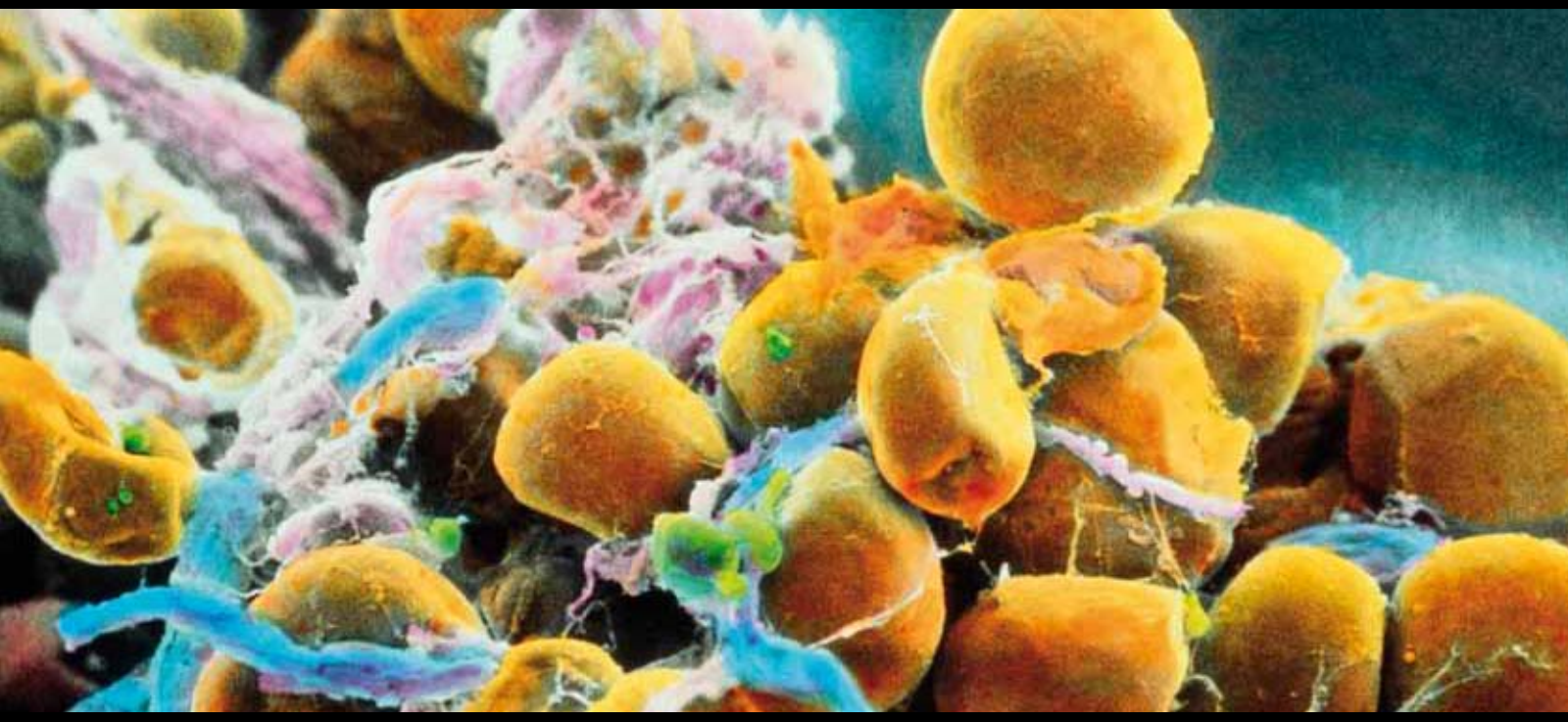
Metabolic Effects of Bariatric Surgery

Guest Editors: Francesco Saverio Papadia, Monica Nannipieri, Wojciech Konrad Karcz, and Robert N. Cooney



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Editorial Board

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Editorial

Metabolic Effects of Bariatric Surgery

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Obesity and its associated comorbidities are an ongoing health care problem worldwide [1]. It is well known that obese patients are at increased risk for the development of diabetes, hypertension, hyperlipidemia, sleep apnea, osteoarthritis, and other degenerative diseases [2]. Bariatric surgery has demonstrated to achieve, on top of significant weight reduction, also long-term control of metabolic comorbidities in morbidly obese patients [3].

In particular, glycemic control of morbidly obese diabetic patients improves markedly after surgery, and bariatric surgery has been recently proposed as a treatment for diabetic, obese class 1 patients in a statement by the International Diabetes Federation [4]. Nonetheless, most of the evidence on the benefits of bariatric surgery in morbidly obese diabetic patients available today is based on retrospective reviews, and even the few prospective trials have some limitations [5].

A recently published, very critical review [6] states that bariatric surgery does not "cure" diabetes. In addition, whether this acute "cure" will continue to be a long-term benefit in reducing cardiovascular disease morbidity and mortality as well as cancer mortality for patients with type 2 diabetes has to be documented in future studies. Therefore, before large-scale application of bariatric surgery to non-bariatric candidates, outside of controlled clinical trials, can be considered or recommended, sufficient long-term data on outcome and complications has to be collected and reported.

In this issue, a wide spectrum of topics have been addressed, ranging from preclinical to clinical reports. Particular attention has been focused on long-term reports.

Bariatric surgery with a metabolic indication, "metabolic surgery", is here to stay. It is our duty to ensure that its development is driven by sound evidence and good clinical judgement.

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Review Article

Pregnancy after Bariatric Surgery: A Review

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Maternal obesity is a major cause of obstetric morbidity and mortality. With surgical procedures to facilitate weight loss becoming more widely available and demanded and increasing number of women becoming pregnant after undergoing bariatric surgery, it is important and timely to consider the outcome of pregnancy following bariatric surgery. This paper aims to synthesize the current evidence regarding pregnancy outcomes after bariatric surgery. It concludes that bariatric surgery appears to have positive effects on fertility and reduces the risk of gestational diabetes and preeclampsia. Moreover, there appears to be a reduced incidence of fetal macrosomia post-bariatric procedure, although there remains uncertainty about the increased rates of small-for-gestational age and intrauterine growth restricted infants, as well as premature rupture of membranes in this group. A number of case reports highlight that pregnancy following bariatric surgery is not without complications and it must be managed as high risk by the multidisciplinary team.

1. Introduction

The epidemic of obesity in middle- and high-income countries has led to an increased prevalence of obese women of reproductive age, conveying enormous consequences for the health of both mother and child. Maternal obesity (defined as BMI $\geq$ 30 at the first antenatal consultation) has become one of the most commonly occurring risk factors in obstetric practice [1], and the prevalence of obesity in pregnancy has risen dramatically in recent years. In the UK, 33% of pregnant women are overweight or obese [2]. Indeed, the Centre for Maternal and Child Enquiries (CMACE) has selected obesity in pregnancy as its principal project for 2008–2011, with emphasis that in the UK, between 2000–2003 approximately 35% of the women who died in pregnancy, childbirth, or in the postpartum period were obese. Furthermore, approximately 30% of mothers who had a stillbirth or neonatal death were obese [3].

Obese women have an increased risk of stillbirth or intrauterine fetal death [4]. They are at greater risk of preterm labour, miscarriage and fetal chromosomal anomalies, as well as macrosomia. Obese women are more likely to suffer from thromboembolism, gestational diabetes, pregnancy-induced hypertension, and preeclampsia. They have a greater incidence of dysfunctional labour, caesarian section [5] and associated perioperative morbidity, as well as postpartum haemorrhage. Therefore, weight loss after surgery has the potential to confer enormous health benefit for mother and child.

The health burden of obesity is driving increasing numbers of people, including women of reproductive age, to seek long-term treatment to facilitate weight loss. However, few anti-obesity interventions have been found to be helpful. Comparing surgery with nonoperative means of weight loss, the National Institute for Health and Clinical Evidence concluded.

> *Surgery remains more effective than a non-surgical approach for people who are obese (BMI > 38 for women, >34 for men) in the longer term (measured up to 10 years after surgery) [6].*

A number of gastric banding procedures, many now done laparoscopically, have been shown to produce dramatic weight loss, and many women become pregnant after such procedures. Does weight loss by these surgical means confer the assumed health benefits of weight reduction? What are the risks to pregnancies post-bariatric procedures?

Increasing numbers of research papers have sought to quantify the benefits for maternal and child health in such pregnancies, as well as highlighting potential complications of pregnancy after these procedures. This paper summarises the current evidence regarding pregnancy after bariatric surgery to draw conclusions regarding maternal, fetal and infant risks and benefits, and to highlight areas in which further robust research is required before recommendations can be made.

2. Fertility

There is a vast amount of evidence supporting the negative effects of obesity on fertility and on IVF outcomes. Characterised by a hyperinsulinaemic and potentially hyperandrogenaemic state, obesity may lead to oligo/amennorhoea, often in association with polycystic ovarian syndrome. The relative risk of anovulatory infertility has been found to be as high as 3.1 in patients with BMI > 27 [7]. Weight reduction has been shown to readdress this hormonal imbalance and increase fecundity in obese and overweight women [8]. It is therefore postulated that bariatric surgery improves menstrual regularity and ovulation in anovulatory obese women, thus restoring fertility.

Assessing fertility by a proxy of normalization of menstrual cycles, as well as lessening of symptoms of PCOS, a number of studies have demonstrated resumption of ovulation after bariatric surgery and associated weight loss. In a retrospective patient survey-based study, Teitelman et al. found a preoperative anovulatory rate of approximately half of women undergoing bariatric surgery (largely Roux-en-Y gastric bypass), with resumption of regular menstrual patterns in 71.4% and a positive correlation between degree of weight loss and likelihood of resolution of menstrual dysfunction [9]. Furthermore, a prospective study of 17 obese patients with PCOS found decreased hirsutism and blood levels of testosterone, androstenedione, dehydroepiandrosterone sulfate, as well as normalization of menstrual cycles in all women after bariatric surgery [10].

Less has been published exploring the effect of bariatric surgery on spontaneous and IVF treatment-related fertility rates, largely as most studies rely on retrospective case-control studies from women who were able to get pregnant and whose pre-conception fertility histories were available [11]. Nevertheless, a number of small studies comparing fertility rates before and after surgery do report improvements in fertility [12–14].

3. Pregnancy Related Medical Complications

There is increasing evidence to suggest that weight loss after bariatric surgery may improve maternal and perinatal outcomes by reducing obesity-associated obstetric risk factors. Although there is a paucity of robust randomized control trials in this area, a number of recent case-control and cohort studies demonstrate that women who have had preconceptual bariatric surgical procedures may have lower rates of obesity-related pregnancy complications such as gestational diabetes and hypertensive disorders than either historical controls or women who had pregnancies before their bariatric procedures [15, 16].

In a retrospective cohort study of US insurance claims of 585 women who had undergone bariatric procedures, Bennett et al. found that women who had delivered after their bariatric procedure ($N = 269$) had substantially lower rates of preeclampsia and eclampsia (odds ratio 0.20, 95% confidence interval 0.09 to 0.44), chronic hypertension complicating pregnancy (0.39, 0.20 to 0.74), and gestational hypertension (0.16, 0.07 to 0.37), even after adjustment for age, multiple pregnancy, surgical procedure, and preexisting diabetes [17]. Similarly, in a large retrospective study of all women between 1988–2006 who delivered after bariatric surgery in a tertiary unit in Israel, Weintraub et al. found a significant reduction in the rates of gestational diabetes mellitus (17.3% versus 11.0%; $P = 0.009$) and hypertensive disorders in pregnancy (23.6% versus 11.2%; $P = 0.001$) after analyzing 301 deliveries preceding bariatric surgery and 507 following surgery [18]. Wittgrove et al., in a retrospective study of 36 post Roux-en-Y gastric bypass pregnancies, found decreased rates of gestational diabetes mellitus, hypertensive disorders, as well as fetal macrosomia in the postsurgery group [19].

Not all studies concur with these results. Patel et al. did not find a statistically significant difference in pregnancy-induced hypertension, preeclampsia, nor gestational diabetes mellitus between postlaparoscopic Roux-en-Y treated patients and obese and nonobese controls [20]. Moreover, higher rates of gestational diabetes and chronic hypertension have been reported in patients postbariatric surgery, although this association was shown to be nonsignificant after adjustment for confounding factors [21].

4. Perinatal Outcome

As described above, bariatric surgery and the weight loss associated therewith appears to decrease obesity-related maternal morbidity. It therefore follows that perinatal outcome, particularly those associated with disorders such as gestational diabetes and preeclampsia, would be improved following bariatric surgery and pre-pregnancy weight loss. However, there lacks good evidence to support improved perinatal outcomes following pregnancy postbariatric surgery, although there is little evidence to suggest adverse outcomes.

5. Birth Weight

Maternal obesity is known to have implications on birth weight, particularly an increased risk of macrosomia (birth weight > 4000 g) [22]. A number of retrospective and prospective observational studies have sought to define the impact of bariatric surgery on birth weight.

Pregnancy following bariatric surgery has also been demonstrated to reduce fetal macrosomia (birth weight > 4000 g). Patel et al. found a significant decrease in mean birthweight and the incidence of macrosomia after Roux-en-Y gastric bypass compared with severely obese patients,

and similar to those of nonobese and obese patients [20]. Similarly, Weintraub et al. found a significant reduction in the incidence of macrosomia in women who delivered before bariatric surgery compared with those who delivered before (7.6% versus 3.2%; $P = 0.004$) [18]. Importantly, when comparing women with previous bariatric surgery ($n = 298$) with all deliveries ($n = 159210$) irrespective of maternal weight, women who had previous bariatric surgery were more likely to have macrosomic babies (OR 2.1, 95% CI: 1.4–3.0, $P < 0.001$) [21].

Although there seems to be evidence to demonstrate a reduced incidence of macrosomia after bariatric surgery, the study by Sheiner et al. demonstrated an apparently increased rate of intrauterine growth restriction with a history of bariatric surgery (5% versus 2%; $P < 0.001$), as well as premature rupture of membranes (OR 1.9, $P = 0.001$), although this association was not persistent after multivariable analysis (OR 1.4, $P = 0.063$) [21]. Patel et al. demonstrated that the incidence of SGA after RYGB was higher (11.5%) compared with nonobese patients (0.5%, $P < 0.001$), but not significantly different from obese (2.6%) and severely obese patients (3.7%) [21]. Although Ducarme et al. demonstrated the rates for low birth weight (<10% centile) were lower amongst postbariatric surgery patients compared with controls (7.7% versus 10.6%) [23], neither Richards et al. [24] nor Dixon et al. [25] demonstrated significant differences in the incidence of SGA infants in post-bariatric surgery patients compared with controls.

A reduced risk of macrosomia is not supported by all studies. In a prospective study of 79 consecutive pregnancies following laparoscopic adjusted gastric banding in comparison with the same patient's penultimate pregnancies before surgery, Dixon et al. found that although the pregnancy maternal weight gain was lower in those who had undergone surgery, there was no significant difference in birth weight between the two groups [25].

Timing of pregnancy after bariatric surgery has not been demonstrated to affect birth weight. In a small retrospective review, Dao et al. demonstrated that of 34 patients who became pregnant after bariatric surgery between 2001–2004, there was no significant difference in birth weight or premature labour between the 21 patients who fell pregnant within 1 year after surgery and the 13 who became pregnant >1 year after the procedure [26].

6. Premature Birth and Miscarriage

From the literature, it seems that the rate of premature delivery does not seem to significantly differ in pregnancies after bariatric surgery, compared control groups matched for BMI [20, 24, 25], nor with those prebariatric surgery [14, 19, 25]. Nevertheless, a very recent meta-analysis of 84 cohort and case control studies has suggested that although the overall risk of preterm birth is similar in overweight, obese women and women of normal weight, the risk of induced preterm birth was increased in overweight and obese women (relative risk 1.30, 1.23–1.37), with causes presumably related to increased medical complications in pregnancy necessitating early delivery. It is also found that the overall risk of spontaneous or induced preterm birth before 32 weeks completed gestation is increased after bariatric surgery [27].

While one small case series of 9 patients reports a miscarriage rate decline of 33.3% to 7.8% in patients following bariatric surgery, [28] with the presurgery pregnancies as the control group, there is a lack of robust evidence to demonstrate a significant effect of bariatric surgery on miscarriage rate. Whilst a higher miscarriage rate (21.6%) was demonstrated in bariatric surgery preoperative patients compared with the general population, this was not reduced postoperatively (26%) despite a reduction in BMI [29].

7. Perinatal Death and Congenital Malformations

Despite the above-described apparent increase in IUGR and premature rupture of membranes (albeit before multivariable analysis), Sheiner et al. did not find a significant difference in perinatal mortality between those with a history of bariatric surgery [21]. Comparing all pregnancies of patients with and without previous bariatric surgery ($N = 159210$), the perinatal mortality rate was not significantly different between the groups. However, a number of observational studies have highlighted the importance of further research into the potential increase in congenital malformations following bariatric surgery; a prospective cohort of 239 pregnancies after BPD reported two birth malformations, one infant dying from surgery for meconium obstruction and two deaths from "unknown causes" [30].

8. Maternal Nutritional Deficiencies

Concern rightly exists surrounding the theoretical potential for nutritional deficiencies for mother and infant after bariatric surgery, particularly malabsorptive procedures. Published outcomes of adverse nutritional deficiencies in women who have undergone bariatric surgery are rare, although case reports do exist detailing deficiencies in iron, B12, calcium, and vitamin D after malabsorptive procedures which have the potential to lead to fetal complications including neural tube defects, low birth weight, neonatal hypocalcaemia or rickets [31]. Eerdekens et al. report on 5 cases of severe neonatal intracranial bleeding resulting in three neonatal deaths and two severely disabled infants, in births following bariatric surgery, all possible related to vitamin K deficiency [32]. Whilst disturbances of coagulation as a result of vitamin K deficiency was proved only in one of the cases (maternal gastric outlet obstruction 2 years post gastric banding), it highlights that careful attention to maternal and fetal nutrition must be made a crucial element of care in such pregnancies.

9. Surgical Complications

An increase in intra-abdominal pressure, displacement of organs by a gravid uterus, and a predisposition to vomiting in pregnancy poses risk to the pregnant woman post

bariatric surgery. A systematic review of 75 research papers by Maggard et al. described 20 reports of complications requiring surgical intervention during pregnancy following bariatric surgery including 14 bowel obstructions, 1 gastric ulcer, 4 band events and 1 staple line stricture, resulting in 3 maternal, and 5 neonatal deaths [11]. Such reports highlight the importance of treating a pregnant woman after bariatric surgery as high-risk pregnancy although these rates may not indeed be higher than in the normal population when reporting bias is accounted for.

10. Conclusions

The evidence presented above is strongly suggestive that patients who undergo bariatric surgery may have lower risk of maternal complications such as preeclampsia and gestational diabetes compared with obese controls or pre-surgery pregnancies. Furthermore, it seems that bariatric surgery may reduce the risk of fetal macrosomia, although the risk of growth restriction or low birth weight is not clear and risk of nutritional deficiencies appears rare. Isolated case reports detailing intestinal obstruction and other surgical emergencies during pregnancy in women who have had bariatric surgery need further quantification, although it is clear that pregnancy postbariatric surgery is not without risks. Clearly, careful attention must be paid to women who have had previous surgery to ensure adequate maternal and fetal nutrition, as well as the early recognition of potential complications.

Unfortunately, the level of evidence regarding maternal and fetal outcomes after bariatric surgery is limited to observational case control and cohort studies; no definitive studies comparing pregnancy outcomes between different bariatric operative techniques have been performed, nor do any randomized control trials exist to definitively characterize the reproductive potential of bariatric surgery, nor are they likely to be feasible. Further research is needed to clarify the benefits and risks of prepregnancy bariatric surgery to better equip the multidisciplinary team with informed advice and management of preconceptual, antenatal, delivery, and postnatal care for these women.

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Research Article

Improvement of Type 2 Diabetes Mellitus in Obese and Non-Obese Patients after the Duodenal Switch Operation

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Introduction. Type 2 diabetes mellitus (T2DM) is one of the most important obesity-related comorbidities. This study was undertaken to characterise the effect of the biliopancreatic diversion with duodenal switch (BPD-DS) in morbidly obese and nonmorbidly obese diabetic patients. *Methods*. Outcome of 74 obese diabetic patients after BPD-DS and 16 non-obese diabetic patients after BPD or gastric bypass surgery was evaluated. Insulin usage, HbA_{1c}-levels, and index of HOMA-IR (homeostasis model assessment of insulin resistence) were measured. *Results*. A substantial fraction of patients is free of insulin and shows an improved insulin sensitivity early after the operation, another fraction gets free of insulin in a 12-month period after the operation and a small fraction of long-term insulin users will not get free of insulin but nevertheless shows an improved metabolic status (less insulin needed, normal HbA_{1c}-levels). *Conclusion*. BPD-DS leads to an improvement of T2DM in obese and non-obese patients. Nevertheless, more data is needed to clarify indications and mechanisms of action and to adjust our operation techniques to the needs of non-obese diabetic patients.

1. Introduction

Obese patients' lifetime and life quality are not only limited by obesity itself but also by associated disorders, in particular type 2 diabetes mellitus (T2DM). Patients need medication, regular subcutaneous injections, and should keep a diet. Frequently, the diabetes is poorly controlled, which leads to various complications, even failure of organs. Serious vascular diseases may occur, and some patients need dialysis or surgery because of diabetes related complications. Fortunately bariatric surgery shows effects not only on body weight but also on glucose homoeostasis. In the long-term some operations show better results concerning diabetes than concerning weight loss. Patients remain overweight but experience remission from diabetes [1]. The question arises if we should rather talk of "diabetes surgery" than "bariatric surgery" when operating an obese patient with T2DM [2]. The next step would consequently be the "antidiabetic" operation of non-obese patients with inadequately controlled diabetes [3–5]. The "Standards of Medical Care in Diabetes" published yearly by the American Diabetes Association, for the first time, mentions surgical therapy in 2009 [6]. They recommend bariatric surgery for adults with BMI >35 kg/m^2 and type 2 diabetes, especially if the diabetes or associated comorbidities are difficult to control with lifestyle and pharmacologic therapy. However, they state that there is currently insufficient evidence to generally recommend surgery in patients with BMI <35 kg/m^2 outside of a research protocol. These recommendations were assumed without any change for 2010 [7]. Similar recommendations were made by the Diabetes Surgery Summit Consensus Conference in 2010: surgery should be considered for patients with BMI >35 kg/m^2 who are inadequately controlled by lifestyle and medical therapy. A surgical approach may also be appropriate as an nonprimary alternative to treat inadequately controlled diabetes in patients with a BMI of 30–35 kg/m^2 [8]. The biliopancreatic diversion with duodenal switch (BPD-DS) is a well-established bariatric operation with encouraging effects on glucose homeostasis and diabetes [9, 10]. In the present study, we present our first results concerning improvement of T2DM in morbidly obese and also in nonmorbidly obese patients. As outcome parameters usage of

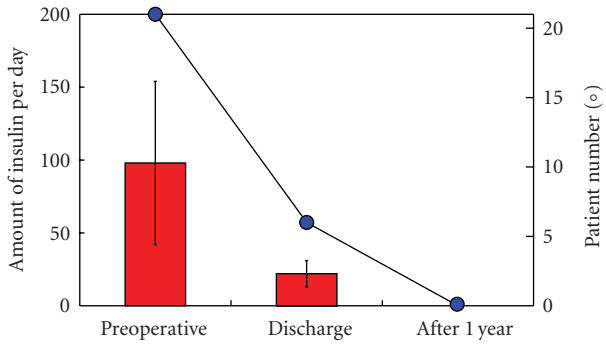

Figure 1: Reduction of insulin usage prior to BPD-DS, at discharge and one year after the operation. Blue dots indicate the number of patients in need of insulin (right scale). Red bars indicate the mean amount of insulin used per day (left scale, whiskers indicate standard deviation).

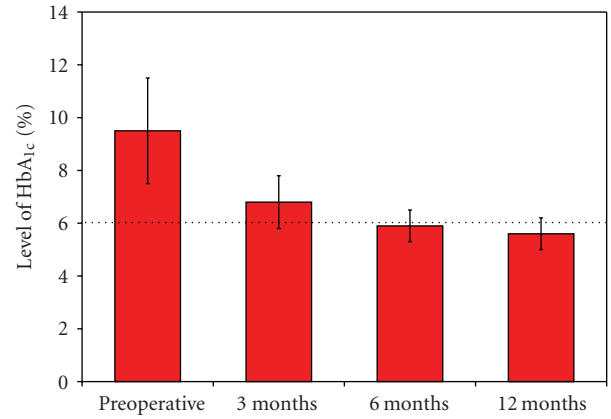

Figure 2: HbA_{1c} levels prior to BPD-DS and 3, 6, and 12 months after the operation. Red bars indicate the mean levels of HbA_{1c}, whiskers indicate standard deviation.

insulin, HbA_{1c}-levels and HOMA-IR index were measured [11].

2. Patients and Methods

Patients: as a first group, 21 obese patients (9 male/12 female) with insulin-dependent T2DM received a biliopancreatic diversion with duodenal switch (BPD-DS). Mean age was 51 years (26–67), mean preoperative BMI was 46 kg/m^2 (35–56), mean duration of diabetes was 10,5 years (2–30), and preoperative duration of insulin treatment was 6.5 years (0,5–25) with a mean usage of 98 (25–250) units of insulin per day. Mean preoperative HbA_{1c} was 9,5% (6,0–14,0). Body weight, usage of insulin or oral antidiabetic drugs and HbA_{1c} levels were evaluated 3, 6, and 12 months after surgery.

Retrospective analysis of sixteen diabetic patients (8 male/8 female) with a BMI <35 kg/m^2 (mean BMI 32, 26–34,5) was also performed, mean age was 56 years (36–68). Mean duration of diabetes was 16 years (4–40), mean duration of insulin therapy was 6 years (1–12), and mean daily amount of insulin used was 92 IU (30–140). These patients received either BPD-DS ($n = 7$), BPD-Scopinaro ($n = 5$), or Roux-en-Y gastric bypass ($n = 4$). All patients with BMI <35 kg/m^2 knew that intestinal bypass surgery is not yet a standard procedure to treat diabetes and signed an informed consent.

To evaluate early improvements of insulin sensitivity, HOMA-IR index was measured at the day of surgery and 3, 7, 14, and 21 days after BPD-DS in a group of 27 obese patients (21 patients using insulin before surgery). Mean preoperative HOMA-IR index was 14,3.

Seventy-four patients after BPD-DS operations between February 2005 and January 2009 were retrospectively evaluated concerning postoperative outcome in relation to preoperative duration of insulin therapy. Mean age was 50 years (26–68), mean BMI was 47 kg/m^2. BPD-DS operations were conducted with a common channel of 100 cm in an open approach. All operations were performed at the Department of Surgery, St. Josef Hospital Monheim, Germany.

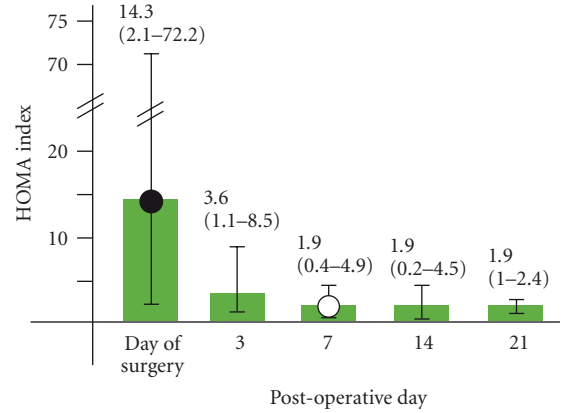

Figure 3: HOMA index at the day of surgery and 3, 7, 14, and 21 days after BPD-DS (27 patients). Green bars indicate mean HOMA index (whiskers indicate minimum and maximum values). Seven days after the operation, the mean HOMA index reaches a normal value <2.

3. Results

3.1. Remission of Insulin-Dependent Type 2 Diabetes Mellitus after BPD-DS. In group one, mean preoperative BMI was 46 kg/m^2 (35–56), mean preoperative duration of insulin treatment was 6.5 years with a mean usage of 98 units of insulin per day. At time point of discharge, 15 patients did not need insulin any more and one year after the operation insulin therapy was terminated in all patients (Figure 1). HbA_{1c} levels decreased from preoperatively 9.5 (mean) to 5.9 (mean) and 5.6 (mean) after 6 and 12 months without any dietary restriction (Figure 2). Only one patient needed an antidiabetic drug one year after the operation. In the group of non-obese patients, similar results were seen; at discharge, 13 patients were free of insulin, and, one year after the operation all patients were free of insulin. Patients after BPD-DS and BPD-Scopinaro showed slightly better results than patients after gastric bypass (data not shown).

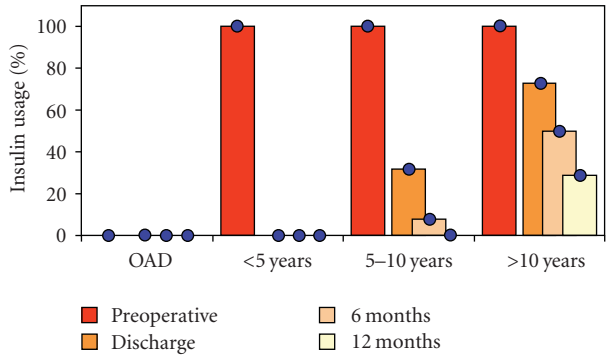

Figure 4: Reduction of insulin usage after BPD-DS dependent on preoperative duration of insulin usage. Group I "OAD" was treated by oral antidiabetic drugs only and used no insulin postoperatively. Group II used insulin for less than 5 years preoperatively and needed no insulin at discharge and after. Group III used insulin for 5 to 10 years. Thirty-seven percent of patients in this group needed insulin at discharge (light brown bar), but all patients in this group were free of insulin 1 year after the operation. Group IV used insulin for more than 10 years. Seventy-three percent of patients in this group needed insuline at discharge (light brown bar), 23% of patients in this group still needed insuline 1 year after the operation (white bar).

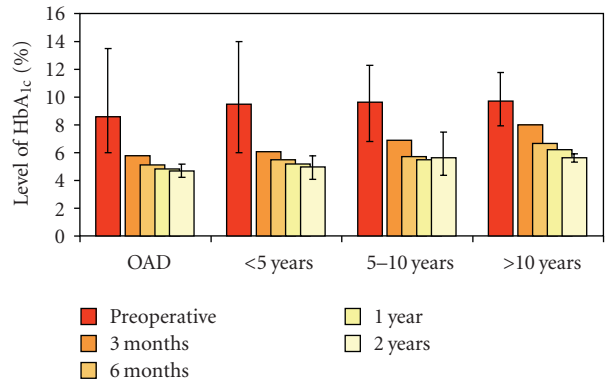

Figure 5: HbA_{1c} levels after BPD-DS dependent on preoperative duration of insuline usage. Group I "OAD" was treated by oral antidiabetic drugs only. HbA_{1c} levels were below 6% as early as 3 months after the operation. Group II used insulin for less than 5 years preoperatively and also showed normal levels of HbA_{1c} from 3 months after the operation on. Group III used insulin for 5 to 10 years. Mean HbA_{1c} normalized 6 months after the operation. Group IV used insulin for more than 10 years. Mean HbA_{1c} in this group normalized not until 2 years after the operation. Shown are mean values and additionally minimum/maximum values for preoperative and 2 years data.

3.2. Decrease of Insulin Resistance in the Early Postoperative Phase. Mean HOMA-IR index decreased from a preoperative value of 14.3 to 3.6, and 1.9 three and 7 days after surgery (Figure 3). There was no significant difference whether the patients were treated with oral antidiabetics or with insulin. Also, three patients who were discharged from hospital with small amounts of insulin (maximally 36 units per day) had a low postoperative HOMA-IR index of 1.3 to 2.6. No dependence of BMI on the postoperative course of insulin resistance could be detected.

3.3. Influence of Preoperative Duration of Insulin Therapy on Postoperative Outcome. According to their need for insulin, patients in group 3 were divided into 4 groups: 15 patients were treated with oral antidiabetic medication, 25 used insulin for less than 5 years, 23 used insulin for 5–10 years, and 11 used insulin for more than 10 years. At discharge from hospital, all patients in groups I and II were free of insulin. Thirty-three percent of patients in group III, still needed insulin at the time of discharge, but all of them were free of insulin 12 months after the operation. In group IV, 73% needed insulin at the time of discharge, 23% still needed small amounts of insulin 12 months after the operation (Figure 4). HbA_{1c} levels also decreased continuously in all groups. Mean levels below 6% were reached 3 month after surgery in groups I and II, 6 month after surgery in group III and 2 years after surgery in group IV (Figure 5).

4. Discussion

In this study, we evaluated short- and long-term effects on T2DM in patients after BPD-DS. In general, we saw encouraging results. This is of major importance since T2DM is one of the most important obesity-related comorbidities. Diabetes itself leads to a vast amount of diseases and complications of different organs.

In a group of 21 obese patients with insulin-dependent T2DM, we evaluated insulin usage and HbA_{1c} levels 6 and 12 months after BPD-DS. These patients had used insulin for a mean time of 6.5 years, and they had a mean usage of 98 units of insulin per day. Twelve months after the operation, they were all free of insulin with normalized HbA_{1c} levels and without any dietary restriction (Figure 2). Most other studies on BPD/BPD-DS include a substantial fraction of patients with T2DM who do not need insulin at the time point of operation but they report similar results, diabetes is resolved in the majority of cases after 1 year [1, 12]. Remarkably, 15 patients were free of insuline at the time point of discharge, where a weight reduction is not yet achieved and, in the other patients, a significant reduction of insulin doses could be observed.

In a second collective of patients, the HOMA-IR index was measured to obtain more information about changes of insulin sensitivity in the early postoperative phase [12]. HOMA-IR is a product of serum insulin and blood glucose level after 12 h of fasting with values >2 providing evidence for insulin resistance and levels >5 in patients with T2DM [11]. We saw that after BPD-DS, the insulin sensitivity determined by the HOMA-IR index increased rapidly and usually nearly normalized within few days after surgery. The restoration of insulin sensitivity was independent on severity and duration of diabetes and also independent on BMI and the usage of oral antidiabetic medication.

Finally, to further evaluate whether the remission of T2DM depends on the duration and severity of diabetes, 74 patients were divided into 4 groups according to their

need for insulin: we could see that even patients with a long history of insulin-dependent T2DM have a good chance for remission. However, in the group with a usage of insulin >10 years the chance of remission is significantly lower and a small percentage of patients will not be completely free of insulin—probably due to secondary beta-cell failure. Nevertheless, HbA_{1c} of these patients is significantly lower and less insulin is required which helps to control diabetes-associated complications and organ damages. As a summary of the data, it can be said that a substantial fraction of the patients is free of insulin and shows an improved insulin sensitivity early after the operation, another fraction gets free of insulin in a 12-month period after the operation and a small fraction of long-term insulin users will not get free of insulin but nevertheless shows an improved metabolic status (less insulin needed, normal HbA_{1c}-levels).

The effects of gastrointestinal surgery on glucose metabolism are not understood in detail. The restrictive effect of bariatric surgery and the reduced caloric intake might lead to an improvement of glucose homeostasis and T2DM in the long run. This effect is equivalent to a diet and accompanied by weight loss and can be seen after restrictive operations like gastric banding [13]. A more pronounced effect can be observed after gastric bypass surgery and BPD and occurs significantly earlier, actually a few days after surgery, long before a loss of excess weight is achieved. Other mechanisms beside the "dietary" effect must exist [14]. In the early postoperative period, those mechanisms are independent of weight loss, later on they might be additive to the dietary-effect which can be seen after restrictive surgery. The "foregut hypothesis" states that the exclusion of the duodenum and proximal jejunum from the transient of nutrients are crucial for this effect, since it has also been seen in diabetic patients after subtotal gastrectomy due to ulcus or cancer [15–17]. The neuronal, hormonal, or chemical signalling pathways which influence insulin secretion and glucose homeostasis, and, thus, provide a link between "foregut" and beta cells are subject of various studies.

The question that consequently arises is the following: should BPD-DS be performed in non-obese patients with poorly controlled diabetes? It is not self-evident to expect that we will observe similar results in non-obese patients, because obesity itself might change the patients' metabolic status and mechanisms of regulation as well as levels and effects of hormones.

However, we have seen very similar results concerning usage of insulin and HbA_{1c} in a population of 16 patients with T2DM and a BMI $<35\,kg/m^2$. The next important issue is that the weight-reductive operations, which have been developed, have an antidiabetic effect but they might not be the optimal antidiabetic operations in non-obese patients. Consequently, procedures may have to be optimized for non-obese patients with T2DM, resulting in novel antidiabetic procedures. It has to be determined, for example, if less gastric restriction—or no gastric restriction, like in case of the isolated duodenal switch—leads to similar anti-diabetic results. It has to be found out where to place the distal anastomosis to obtain optimal anti-diabetic results and minimal side effects like diarrhea or nutritional deficiencies. As seen in bariatric surgery for morbid obesity, there will not probably be only a single "anti-diabetic" operation but several options, depending on the patients' comorbidities, weight, and, most likely, also duration and therapy of the patients' diabetes.

As a conclusion, we characterized the short- and medium-term effects of BPD-DS on T2DM. Preliminary results also show a good anti-diabetic effect in non-morbidly obese patients. Indications, mechanisms of action, and development of new surgical procedures to treat diabetes will be of major interest in the near future.

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Review Article

Tissue-Specific Effects of Bariatric Surgery Including Mitochondrial Function

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A better understanding of the molecular links between obesity and disease is potentially of great benefit for society. In this paper we discuss proposed mechanisms whereby bariatric surgery improves metabolic health, including acute effects on glucose metabolism and long-term effects on metabolic tissues (adipose tissue, skeletal muscle, and liver) and mitochondrial function. More short-term randomized controlled trials should be performed that include simultaneous measurement of metabolic parameters in different tissues, such as tissue gene expression, protein profile, and lipid content. By directly comparing different surgical procedures using a wider array of metabolic parameters, one may further unravel the mechanisms of aberrant metabolic regulation in obesity and related disorders.

1. Introduction

Bariatric surgery represents a highly successful treatment strategy for obesity and secondary diseases such as type 2 diabetes mellitus (T2DM), at least in morbidly obese patients [1]. Though similar effects may be obtained with lifestyle intervention [2], many morbidly obese patients do not succeed in making sufficient permanent lifestyle changes [3]. The success rate of surgery varies depending on the surgical procedure and individual factors including lifestyle/nutrition, age, gender, and genetics/epigenetics [4, 5]. Besides being an effective treatment for obesity that decreases mortality and morbidity, bariatric surgery confers some health risk including renal stone formation and oxalate nephropathy (calcium oxalate crystals in the kidney) [6]. Due to changes to the gastrointestinal tract with malabsorptive surgery, absorption of vitamins and minerals is affected and bariatric surgery patients are advised to take micronutrient supplements [7].

It is of utmost importance to fully understand the metabolic changes induced by bariatric surgery, as it may lead to novel treatment strategies for obesity and related health problems. Because morbidly obese patients undergoing bariatric surgery effectively and consistently lose excess body weight and reduce obesity-related comorbidity, they represent a very useful patient group for studying mechanisms that regulate metabolic health. The most common surgical procedures are today performed laparoscopically and include adjustable gastric band (LAGB), sleeve gastrectomy (LSG), Roux-en-Y gastric bypass (RYGB), and biliopancreatic diversion (BPD). BPD often includes duodenal switch (BPD/DS) and sleeve gastrectomy. RYGB and BPD show the best long-term results in terms of fat loss [8, 9] and diabetes resolution [1]. Whereas LAGB and LSG exert their effects through reduced ventricular volume and food intake, RYGB and BPD (with sleeve gastrectomy) combine this effect with malabsorption of nutrients by means of bypassing a substantial part of the small intestine. In addition, the intestinal reconfiguration results in a rapid improvement of diabetes within days in most patients, which cannot be entirely ascribed to energy restriction or fat loss [10]. This intriguing observation has led to the hypothesis that

regulatory factors in the small intestine, including peptide hormones and nerve signals, are critical in modulating glucose homeostasis. Thus, the metabolic effects of bariatric surgery are both dependent and independent of fat loss.

In the present paper, our overall aim was to describe central mechanisms that may mediate the beneficial effects of bariatric surgery on metabolic health. Our specific objective was first to summarize the most important findings regarding fat loss-independent effects of bariatric surgery. Because of the scarcity of data on the acute effects of surgery on various metabolic parameters, we also discuss longer-term metabolic effects that may result from a combination of fat loss and intestinal surgery, including effects on mitochondria. Finally, our objective was to provide new perspectives for future research regarding the metabolic effects of bariatric surgery.

2. Acute Metabolic Effects of Bariatric Surgery

In the weeks following bariatric surgery, patients are limited to consumption of liquids and their nutrient intake becomes drastically reduced. Thus, when evaluating the metabolic effects of bariatric surgery, one must consider the isolated impact of reduced energy intake versus weight loss. In healthy lean subjects, energy restriction may induce a "starvation diabetes" marked by hepatic and peripheral insulin resistance [11]. In obese individuals, on the other hand, energy restriction may improve glycemic control and insulin sensitivity independently of weight loss during the first days [12]. The metabolic effects of weight loss may begin to be substantial after 7–10 days of energy restriction [13]. In diabetic obese individuals, four days of energy restriction improved hepatic insulin sensitivity leading to suppressed hepatic glucose output and reduced fasting glucose levels [14].

However, energy restriction cannot fully account for the acute improvement in glycemic control after intestinal bypass. Studies comparing intestinal bypass (RYGB) to energy-restrictive procedures, both of which require patients to consume only liquids in the first weeks postsurgery, show a specific acute effect on glucose metabolism after RYGB. In contrast to RYGB [5, 15], the LAGB procedure showed no amelioration of diabetes until a considerable degree of weight loss had occurred in a randomized controlled trial of obese diabetic patients [16]. Kashyap et al. showed that only RYGB and not LSG improved postprandial insulin secretion and sensitivity despite similar reductions in weight and fasting insulin levels (subjects were compared 1–3 weeks before versus 1 week after surgery) [17]. Similarly, a randomized controlled trial of diabetic patients by Peterli et al. showed that RYGB but not LSG increased meal-induced insulin responses 1 week postsurgery, while effects of the different surgical procedures were similar at 3 months, when similar weight loss was achieved [18]. These observations clearly point towards mechanisms of acute glucose control that are unique to intestinal bypass and that are independent of energy restriction and weight loss.

The acute effects of bariatric surgery on glycemic control and metabolic health likely involve a combination of several factors, including insulin secretion, peripheral insulin sensitivity, and hepatic insulin sensitivity. Distinct effects have been observed with the BPD and RYGB procedures. The effects of BPD are more due to intestinal reconfiguration and malabsorption, while RYGB involves a greater restriction of gastric volume (to 30 ml versus 300–400 ml with BPD). BPD rapidly improved insulin sensitivity along with a reduction in insulin secretion and normalization of blood glucose levels 1 week [19] as well as 1 month postsurgery, measured by euglycemic-hyperinsulinemic clamp [20]. On the other hand, RYGB did not improve peripheral insulin sensitivity 2 weeks or 1 month postsurgery, also measured by euglycemic-hyperinsulinemic clamp [21, 22]. Rather, RYGB may acutely reduce hyperglycemia by increasing food-induced insulin secretion via increased release of incretins [18, 23], in some cases resulting in episodes of hypoglycaemia [24, 25]. It should be noted that another study of RYGB patients before versus 6 days after surgery found significant improvement in peripheral insulin sensitivity measured by intravenous glucose tolerance tests and homeostatic model assessment (HOMA) [15]. However, euglycemic-hyperinsulinemic clamp is a superior technique for measuring insulin resistance. It is possible that improvements in hepatic rather than peripheral insulin sensitivity may represent a key mechanism of glucose control after RYGB. A study in mice suggested that restoration of glucose control after RYGB may be due to reduced endogenous glucose output via improved hepatic insulin sensitivity, and also altered intestinal gluconeogenesis [26].

The proposed hypotheses attempting to explain the surgery-specific effects on glucose metabolism remain speculative. Various mechanisms are likely to contribute [10]. The lower intestinal (hindgut) hypothesis proposes that exclusion of the proximal intestine leads to a more rapid delivery of nutrients to the lower intestine, resulting in increased release of gut hormones that regulate glucose metabolism (e.g., glucagon-like peptide-1 (GLP-1), peptide Y (PYY), and oxyntomodulin secreted by L-cells in the distal small intestine and parts of the colon) [27, 28]. It is possible that central effects of GLP-1 may contribute to reducing hepatic insulin resistance and glucose production [29]. Importantly, a stimulatory effect on the circulating levels of incretins such as GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), which augment insulin secretion, was not observed with energy restriction in diabetic patients [23]. It is interesting to note that secretion of GIP, which is produced in K-cells in the proximal intestine, was found to be increased after RYBG [27] but decreased after BPD [19, 20]. GIP has been shown to promote energy storage in adipose tissue, and inactivation of GIP in mice was shown to improve insulin resistance [30]. Moreover, the upper intestinal (foregut) hypothesis postulates that the proximal intestine that is bypassed with RYGB and BPD releases one or more factors with adverse effects on glucose metabolism. In polygenic diabetic rats (Goto-Kakizaki), Rubino et al. found that duodenal-jejunal bypass enhanced glucose metabolism independently of food intake and body weight [31]. The mechanism may involve reduced nutrient contact with the excluded duodenum [32]. In diabetic humans with a 60 cm

flexible plastic sleeve inserted to inhibit nutrient contact with duodenal mucosa (endoluminal duodenal sleeve), glycemic control both after and between meals improved considerably already after 1 week without significant weight loss [33].

Neuronal signalling has been implicated as a critical factor in the postsurgery control of glucose metabolism. The vagus nerve is a critical regulator of the digestive process as well as of appetite regulation in the gut-brain-gut axis, and vagotomy (resection of the vagus nerve) has been used to treat obesity [34]. More recently, blockage of vagus activity by an implanted medical device has shown promising effects on weight loss in humans [35]. Randomized controlled trials are needed to confirm this effect, and possible acute effects on glucose metabolism would be of particular interest. An acute effect of vagotomy to reduce insulin secretion was demonstrated several decades ago in rats [36]. Hepatic glucose production is centrally regulated via the hepatic branch of the vagus nerve [37]. Thus, vagus nerve function may at least partially mediate the acute effects of intestinal bypass surgery on glucose metabolism.

3. Long-Term Effects on Insulin Sensitivity, Glucose Metabolism, and Metabolic Tissues

While it is difficult to isolate the fat loss-dependent and independent effects of bariatric surgery, long-term studies of bariatric patients indicate that a greater loss of excess body weight associates with an improved effect on diabetes [1]. When performed in morbidly obese patients, the RYGB and BPD/DS procedures often reduce body weight to about half the original weight within the two first years, followed by a stable weight for at least 10 years [8, 9]. Although bariatric patients usually remain obese after surgery with a body-mass index (BMI) above 30, their metabolic profile is in many respects similar to that of healthy, lean individuals. A prospective study of whole body and muscle insulin sensitivity before and one year after bariatric surgery found that weight-stable RYGB patients were more comparable to lean than weight-matched controls [38]. However, this beneficial effect of fat loss is not specific to bariatric surgery, since shorter-term nutritional intervention and exercise have also been shown to induce weight loss-independent improvements in glucose homeostasis [39, 40]. Nonetheless, bariatric surgery allows for relatively controlled long-term prospective studies of both moderate and profound fat loss and has provided important insight into the altered functions of metabolic tissues in (morbid) obesity.

3.1. Bariatric Surgery and the Functions of Adipose Tissue and Skeletal Muscle. Adipose tissue performs functions that are critical to metabolic health, providing a storage buffer for surplus energy and secreting peptide hormones, cytokines, lipids and other molecules, thereby coordinating metabolic regulation with other organs [41]. Obesity is characterized by increased fat mass and altered adipose tissue function, involving cellular stress responses, changes in extracellular matrix, infiltration of immune cells such as macrophages, chronic inflammation, and potential aberration of adipogenesis, angiogenesis, and tissue remodelling. These changes are related to increased ectopic lipid accumulation and secretion of adipokines with potential adverse systemic effects [42, 43].

Bariatric surgery may improve adipose tissue function via various mechanisms, including an acute reduction in energy intake, changes in the endocrine and immune-related functions of the gut, and profound reductions in adipose tissue mass [44]. There is a paucity of information on the acute effects of bariatric surgery on adipose tissue function in humans. In cultured human subcutaneous adipocytes, GIP together with insulin was found to activate lipoprotein lipase [45], suggesting that altered GIP levels after bariatric surgery may affect lipid uptake in adipose tissue [46].

Several long-term studies of bariatric patients have revealed important insights into the alterations of adipose tissue function in obesity. Endoplasmic reticulum stress is increased in obesity, markers of which were strongly reduced in both subcutaneous adipose tissue and liver tissue 1 year after RYGB [47]. Moreover, a reduction in macrophage infiltration and the expression of chemoattractant and pro-inflammatory genes was observed in a global gene expression study of subcutaneous adipose tissue before versus 3 months after RYGB [48]. Our recent microarray study of subcutaneous adipose tissue before versus 1 year after BPD/DS corroborates these findings, showing a substantial reduction in genes related to immunity and defense functions [49]. These studies have also demonstrated that bariatric surgery, most likely due to the profound fat loss, strongly alters the expression of genes involved in extracellular matrix functions [49, 50]. While similar observations have been made in dietary intervention studies [51, 52], the differential gene expression after bariatric surgery may be specific to the extreme degree of fat loss and possibly also some effects of the gastrointestinal changes after surgery.

Muscle insulin resistance may be a critical factor in the pathogenesis of diabetes and metabolic complications including fatty liver [53]. Bariatric surgery was found to decrease intramyocellular lipids measured by Oil-red-O staining 3 and 9 months after RYGB or LAGB [54]. The study also found reduced gene expression of *SCD1* and *PDK4* in skeletal muscle after 3 months, whereas *PPARα*, *MCAD*, *CPT1*, and *UCP3* were down-regulated only at the 9-month time point. Greco et al. showed a significant reduction in intramyocellular lipids 6 months after BDP [55]. A magnetic resonance spectroscopy study also found significant reductions in intramyocellular lipids already 1 month after BPD [56], while this early effect was not reported in a study of seven RYGB patients [57]. Further studies should be performed to verify whether there is a surgery-specific effect on intramyocellular lipids. It is tempting to speculate whether a reduced circulating level of GIP specifically after BPD may play a role, since suppression of GIP may reduce lipid storage in skeletal muscle and liver as in adipose tissue [46].

3.2. Bariatric Surgery and Liver Function. The liver is a critical organ for maintaining metabolic homeostasis in the body. Lipid homeostasis is typically disrupted in obese

individuals, reflected by chronically elevated plasma lipid levels. Together with adipose tissue, the liver is the main lipidemic organ during systemic hyperlipidimia, and the development of insulin resistance and diabetes [58]. The liver takes up free fatty acids (FFAs) released from adipose tissue, as well as circulating triglycerides (TGs). The FFAs are either degraded by β-oxidation or repackaged to TGs in very low-density lipoprotein particles and released into the bloodstream.

Steatosis (fatty liver) occurs when there is an imbalance between lipogenesis and fatty acid oxidation. When the rate of hepatic fatty acid uptake from plasma and *de novo* fatty acid synthesis predominates over the rate of fatty acid oxidation and triglyceride export, triglycerides will be deposited in the liver. The resulting liver injury is often associated with obesity, and 95% of individuals with class III obesity (BMI $\geq$ 40 kg/m^2) have alterations in routine liver biopsies due to steatosis, steatohepatitis, or fibrosis [59]. These liver abnormalities are known as nonalcoholic fatty liver disease (NAFLD) which increases the risk of developing T2DM, dyslipidemia, and hypertension [60]. It is unknown whether alterations in hepatic glucose, FA, and lipoprotein metabolism and inflammation are causes of NAFLD, or whether these abnormalities are increased in the presence of NAFLD. Increased hepatic β-oxidation will generate reactive oxygen species and promote the development from steatosis to the inflammatory stage nonalcoholic steatohepatitis (NASH). Reduced lipid storage efficiency in adipose tissue and increased rates of adipose tissue lipolysis in obesity promote ectopic lipid accumulation, challenging the liver with high amounts of FFAs [43].

The amelioration of NAFLD and liver function by bariatric surgery may be an important contributor to the systemic improvement of energy homeostasis. Most studies have shown improved liver histology and liver function as well as insulin sensitivity in obese subjects with NAFLD and NASH after bariatric surgery [61]. The weight loss and reduced energy overload improve liver parameters, and the less severe steatosis is fully reversible. In accordance with this, LAGB changed the hepatic adipokine levels of NAFLD patients in an anti-inflammatory direction, increased the adiponectin protein level, and decreased the leptin receptor mRNA level 6 months after surgery [62]. Another study found that a gene with a central role in lipid peroxidation, *CYP2E1*, was significantly reduced in liver after weight loss following bariatric surgery [63]. Hepatic lipid peroxidation, as measured by the malondialdehyde (MDA) level, was reduced and liver steatosis decreased from 17% prior to surgery to 2% several months after. These studies show that bariatric surgery can improve the more progressed NASH disease. The amelioration of NAFLD and liver function by bariatric surgery may be an important contributor to the systemic improvement of energy homeostasis. However, the lack of randomized clinical trials so far makes it difficult to conclude on the use of bariatric surgery for treatment of NASH [64].

Intriguingly, no reduction in intrahepatocellular lipid levels was observed 1 month after RYGB while insulin sensitivity markedly improved [57]. This was surprising given the strong link between hepatic lipid levels and insulin resistance. On the other hand, hepatic lipid content was markedly reduced by 6 and 12 months. Of note, neither visceral adipose tissue mass nor intramyocellular lipid levels correlated with the improvements in insulin sensitivity. These observations should be validated in short-term randomized studies with increased power and in subjects undergoing different forms of bariatric surgery. This may provide important new insight into the mechanisms whereby bariatric surgery affects the systemic metabolic homeostasis via the individual metabolic tissues. Development of insulin resistance in the liver may also partly result from the altered secretion of metabolic and inflammatory adipokines from adipose tissue [58, 65]. The general metabolic effects of bariatric surgery are summarized in Figure 1.

4. Mitochondria in Obesity and Diabetes Mellitus

4.1. Mitochondria before Bariatric Surgery. Mitochondrial metabolism is essential in maintaining normal physiological function in human cells, for example, by providing energy in the form of ATP and performing fatty acid (FA) oxidation. These metabolic functions are reduced in insulin-responsive tissues (muscle and adipose tissue) in obesity and T2DM. No consensus has been reached so far whether insulin resistance is a result of reduced mitochondrial density and whether it is the cause or consequence of mitochondrial dysfunction [66–76]. In general, insulin regulates protein synthesis, glycolysis, and glucose storage in muscle and liver, lipid synthesis, and storage in liver and adipose tissue, and inhibits gluconeogenesis and ketogenesis in liver [77]. In particular, insulin signalling was shown to influence mitochondrial DNA and protein synthesis and affect mitochondrial respiration and ATP production [78]. Factors that may cause mitochondrial dysfunction include genetic defects, age, physical inactivity, and nutritional overload. These factors may exert changes in mitochondrial size and content, activity and coupling of mitochondrial respiration, copy numbers of the mitochondrial genome, reactive oxygen species (ROS) production, FA oxidation, and more.

Altered gene expression and protein levels may reflect the status of mitochondrial function in obesity and related diseases. Reduced expression of specific genes in myocytes was proposed to result in mitochondrial dysfunction in patients with T2DM. For example, the expression of several genes encoding enzymes involved in the electron transport chain was reduced in muscle of family history-positive nondiabetic subjects and subjects with T2DM [79, 80]. However, this reduced mRNA expression was not reflected in a reduced respiratory rate per mitochondrion in insulin-resistant muscle [66]. The expression of several genes of the FA oxidation pathway was also decreased in skeletal muscle in T2DM [80]. Moreover, genes related to mitochondrial biogenesis, such as peroxisome proliferator-activated receptor γ coactivator-1 (*PGC-1α* and *PGC-1β*), were similarly downregulated in diabetes [79, 80]. Another study attributed the decreased skeletal muscle FA oxidation in obesity to

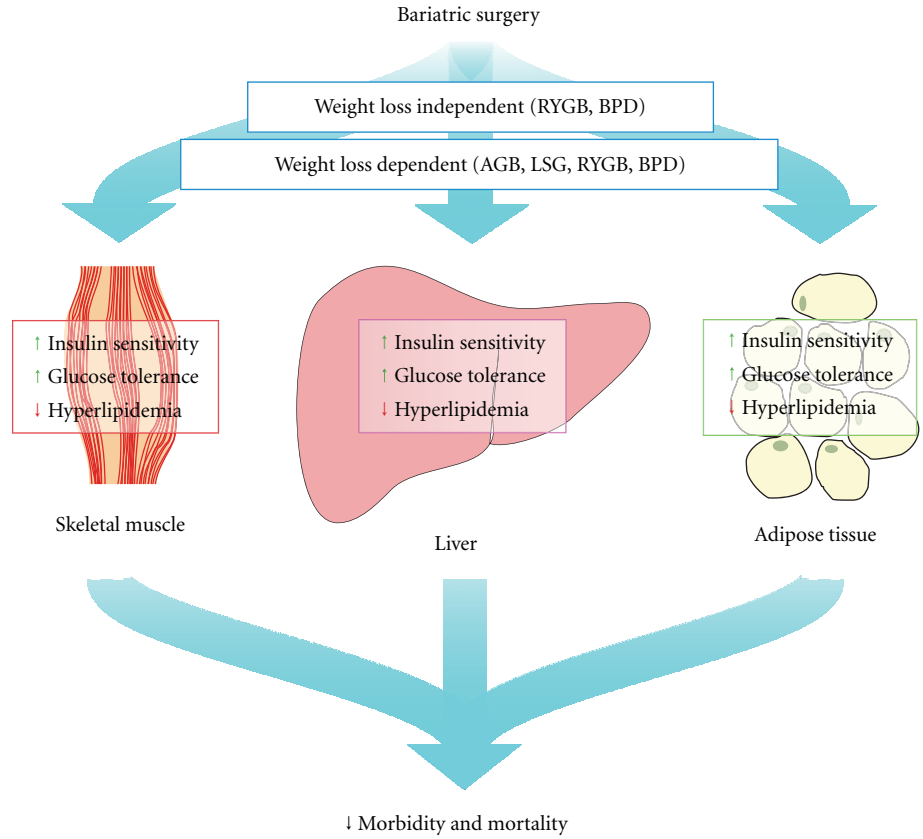

Figure 1: Scheme of the metabolic changes in response to adjustable gastric band (AGB) and laparoscopic sleeve gastrectomy (LSG), whose metabolic effects are mainly dependent on weight loss, and Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD), whose metabolic effects are also independent of weight loss.

reduced mitochondrial content (and not to intrinsic mitochondrial defects), but showed no reduction in the protein levels of PGC-1α, PGC-1β, peroxisome proliferator-activated receptor α (PPARα), or the mitochondrial transcription factor A (TFAM). Instead, the protein level of PPARγ was increased, possibly due to decreased FA oxidation [81]. Furthermore, it has been proposed that mitochondrial fusion and metabolism in obese and non-obese T2DM patients is impaired due to reduced expression of mitofusin 2 (MFN2) in skeletal muscle [82–84]. MFN2 is an outer mitochondrial- and endoplasmic reticulum membrane protein with fusion activity important for mitochondrial dynamics and morphology [83–85]. MFN2 transcriptional activation is regulated by both PGC-1α and β and the estrogen-related receptor α (ERRα). More studies are needed to delineate the molecular mechanisms responsible for altered mitochondrial function in obesity.

It is of potential interest to compare different adipose tissue depots regarding mitochondrial function. Increased visceral (intra-abdominal) adipose tissue mass is particularly associated with risk of metabolic disease relative to subcutaneous fat. Diabetic humans show decreased expression of respiratory rate genes in visceral adipose tissue compared to healthy humans [87]. It has also been shown that visceral adipose tissue contains twice as many, but smaller, mitochondria per milligram of tissue than the subcutaneous depot [87]. This resulted in visceral fat eliciting lower mitochondrial respiration than subcutaneous fat, when expressed per cell. However, per milligram tissue visceral fat was metabolically more active than subcutaneous fat.

4.2. Mitochondrial Regulatory Pathways and Biogenesis after Bariatric Surgery. Mitochondrial function is destabilized in obesity and T2DM, but few studies have specifically investigated the effect of bariatric surgery on mitochondrial metabolism in myocytes and adipocytes. Bariatric surgery has been shown to induce severalfold changes in the expression of genes encoding proteins involved in mitochondrial function and biogenesis in muscle and adipose tissue. In a global gene expression study of subcutaneous adipose tissue before versus 1 year after BPD/DS [49], we observed an altered expression of certain genes involved in the mitochondrial electron transport chain. These alterations included an up-regulation after surgery of *ATP5G2*, which encodes a subunit of the mitochondrial ATP synthase, and of *COX5B*, the nuclear-encoded Vb subunit of the cytochrome c oxidase (COX) complex. The multi-subunit COX complex transfers electrons from cytochrome c (CYCS)

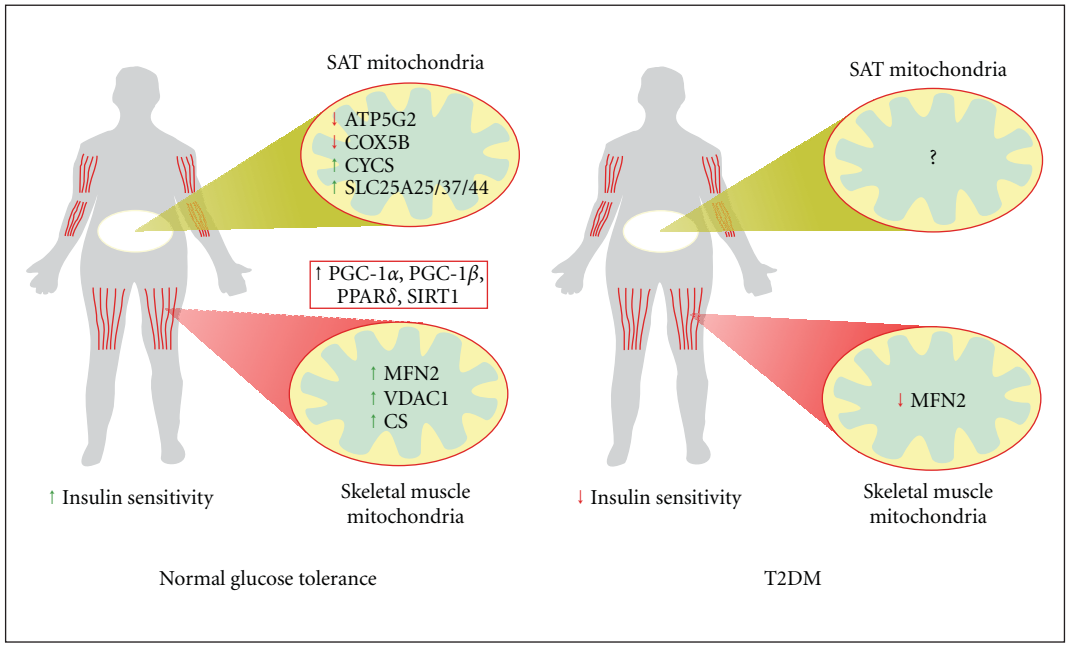

Figure 2: Summary of altered mitochondrial and mitochondrial biogenesis (boxed) gene expression in skeletal muscle of morbidly obese patients with normal glucose tolerance or type 2 diabetes mellitus (T2DM) [86] and in subcutaneous adipose tissue (SAT) one year after BPD/DS surgery [49]. Arrows indicate the direction of the altered gene expression after bariatric surgery.

to molecular oxygen to form water. The expression of *CYCS*, on the other hand, which is also an intermediate in apoptosis, was down-regulated in adipose tissue after bariatric surgery. In addition, three genes of the solute carrier family (*SLC25A25*, *SLC25A37*, *SLC25A44*), involved in shuttling phosphate, iron, and adenine nucleotides across the inner mitochondrial membrane, were significantly down-regulated postsurgery. Another study investigated alterations in skeletal muscle mitochondrial function two years after BPD surgery, comparing morbidly obese patients to patients with normal glucose tolerance (NGT) and T2DM [86]. It was demonstrated that BPD surgery increased insulin sensitivity in both NGT and T2DM patients, an effect that did not correlate with induced mitochondrial gene expression in the diabetic patients (Figure 2). NGT patients showed an increased expression of genes regulating mitochondrial biogenesis in skeletal muscle, including *PGC-1α*, *PGC-1β*, *PPARδ*, and *SIRT1* (a gene that regulates PGC-1*α* expression in liver and muscle) [86]. The expression of other mitochondrial genes such as *MFN2* and the constitutive genes porin (*VDAC1*) and citrate synthase (*CS*) were also significantly increased in the NGT patients. In the diabetic patients, no change was observed with the exception of *MFN2* which was down-regulated. Moreover, a differential oxidative profile in line with the mitochondrial gene expression could be observed in the two groups. Glucose oxidation during fasting was higher in the NGT group and lipid oxidation was higher in the diabetic group after BPD surgery. These results suggest a differential regulation of mitochondrial function in response to BPD in patients with NGT and T2DM, respectively.

5. Future Perspectives

Many aspects of the metabolic effects of bariatric surgery remain inadequately addressed or unanswered. There is convincing evidence that bariatric surgery exerts acute effects on metabolism that are independent of energy restriction and fat loss. The role of incretins on the metabolic functions of the liver, adipose tissue, and skeletal muscle should be further investigated. Molecular biology tools including global gene expression analysis and proteomics should be applied on tissue biopsies and isolated cell fractions collected before and shortly after bariatric surgery. Since certain biopsies are difficult to obtain from humans (e.g., postoperative visceral fat), the rat may be a useful model for studying the acute as well as long-term metabolic effects of bariatric surgery in all tissues [88–90]. In humans, short-term randomized controlled trials with increased power and direct comparison of different surgical procedures should be performed, and these would be strengthened by simultaneous measurement of tissue-specific metabolic parameters. More detailed analysis of parameters such as mitochondrial function may reveal novel mechanisms that may be targeted for more successful treatment of obesity and related diseases. The acute and long-term effects of specific bariatric surgery procedures on tissue and mitochondrial functions should be further investigated.

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Review Article

Metabolic Bone Disease in the Bariatric Surgery Patient

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Bariatric surgery has proven to be a life-saving measure for some, but for others it has precipitated a plethora of metabolic complications ranging from mild to life-threatening, sometimes to the point of requiring surgical revision. Obesity was previously thought to be bone protective, but this is indeed not the case. Morbidly obese individuals are at risk for metabolic bone disease (MBD) due to chronic vitamin D deficiency, inadequate calcium intake, sedentary lifestyle, chronic dieting, underlying chronic diseases, and the use of certain medications used to treat those diseases. After bariatric surgery, the risk for bone-related problems is even greater, owing to severely restricted intake, malabsorption, poor compliance with prescribed supplements, and dramatic weight loss. Patients presenting for bariatric surgery should be evaluated for MBD and receive appropriate presurgical interventions. Furthermore, every patient who has undergone bariatric surgery should receive meticulous lifetime monitoring, as the risk for developing MBD remains ever present.

1. Introduction

Although obesity is noted throughout recorded history, the prevalence of obesity rapidly reached pandemic proportions during the second half of the 20th century. Paralleling the pandemic, surgical treatment approaches came into vogue, stemming at least in part from the observation that patients who had undergone gastrectomy experienced significant and durable weight loss. It was not until the early 1970s when the development of metabolic bone disease was linked to gastrointestinal surgeries, most notably following gastrectomy, that rapidly became a well-known cause of osteomalacia. Advances in the field of bariatric surgery have addressed many of the more serious postoperative complications in spite of the untoward consequences of bariatric surgery and dramatic weight loss on skeletal health persist.

2. Normal Nutrient Absorption: It Is All about the Bones

Recalling the nutrients essential for bone health and their primary sites of gut absorption helps to illustrate why metabolic bone disease is commonly seen in bariatric surgery patients (Figure 1).

Minerals such as calcium, magnesium, and many trace elements are absorbed predominantly in the proximal small bowel. Calcium absorption is also driven by physiologic need and can be absorbed via active transport throughout the duodenum, the ileum, and, to a lesser degree, the jejunum and colon when need be [1]. Proteins and fats are absorbed in the proximal bowel after the prerequisite actions of pancreatic enzymes. The water-soluble vitamins are absorbed in the proximal small bowel with the exception of B_{12} which is absorbed principally in the terminal ileum. Vitamin D and the other so-called "fat-soluble" vitamins are mainly absorbed by passive diffusion in the proximal and mid small intestine in a process that is not fat-dependant per se but highly dependant on the presence of bile salts [2–4].

3. Bariatric Surgery and MBD: A Causal Relationship Established

Gastrointestinal surgeries resulting in weight loss had their beginnings in the 1940s originally designed to treat, among other maladies, gastric ulcers. By the early 1950's this clinical observation led to the first intestinal bypass surgeries performed expressly for weight reduction. The

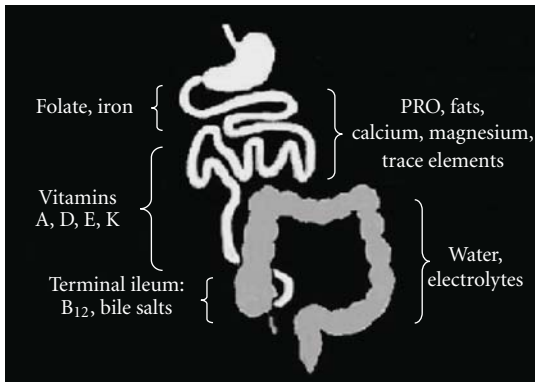


Figure 1: Primary sites of absorption of nutrients essential for bone health.

earliest procedures bypassed a great deal more of the small intestine than modern day procedures and did indeed result in dramatic weight loss but were accompanied by severe diarrhea, electrolyte imbalance, hepatic failure, and a high rate of mortality. In the 1960s procedures such as the "14–4" jejuno-ileal bypass where all by 14 inches of proximal jejunum were bypassed and anastamosed to the terminal ileum (4 inches), promoted significant weight loss with relatively fewer complications but severe malabsorption, protein and vitamin deficiencies, renal oxalate stones, and hepatic failure led to unacceptable complication and mortality rates [5].

The first articles identifying metabolic bone disease following gastrointestinal surgeries were published in the 1970's most notably following gastrectomy and jejuno-ileal bypass [6]. In fact, the prevalence and severity of nephrolithiasis following the 14–4 surgery necessitated surgical reversal in many patients by the fifth postsurgical year, and forced the abandonment of the procedure later that decade.

Since then, publications citing a causal relationship between bariatric surgery and metabolic bone disease number into the multiple of hundreds. The time from surgery to diagnosis ranges from 8 weeks to greater than 32 years, and no bariatric procedure to date has been exempt [7–12]. But undoubtedly the most profound clinical findings have been in older patients who underwent weight loss surgery in the 1970s and were subsequently treated for chronic renal oxalate stones and "severe osteoporosis" when in fact chronic, severe malabsorption, and steatorrhea resulted in profound metabolic derangement, nutrient deficiencies, and osteomalacia [9, 13].

Today there are multiple, safe, effective bariatric procedures that are classified by their predominant mechanism of action. Restrictive procedures such as gastric banding and the gastric sleeve promote weight loss by reducing the size of the stomach thereby severely limiting oral intake. Malabsorptive procedures bypass some portion of the small intestine and promote weight loss by decreasing the absorption of calorie-containing nutrients. And combination procedures, such as the Roux-en-Y gastric bypass and biliopancreatic diversion, limit the size of the stomach as well as bypass part of the small intestine.

Exclusively restrictive procedures, formerly presumed not to alter bone metabolism, appear to place patients at risk of MBD due to inadequate intake of calcium, vitamin D, and protein [14, 15]. Regardless of the surgical procedure, profound deficiencies can and do occur and as a result, all patients who have undergone a surgical weight loss procedure should undergo routine screenings for metabolic bone disease.

4. Voluntary Weight Loss: Involuntary Bone Loss

Voluntary weight loss of approximately 10% on the part of an obese or overweight individual, whether it is achieved as a result of bariatric surgery or dieting, results in bone loss at all sites of 1-2% [16–19]. This loss appears to vary among populations in that premenopausal women less than 45 years of age may be able to lose a moderate amount of weight without a significant increase in fracture risk, while a study of overweight men found a 7% weight loss resulted in a 1% bone loss [20].

Specifically, weight reduction decreases calcium absorption through several proposed mechanisms, with a subsequent rise in PTH and increase in bone resorption, and the percentage of bone lost as a result of weight loss correlates strongly with the velocity at which the weight is lost. Proposed mechanisms include effects due to increased levels of circulating cortisol, and decreased levels of circulating estrogen, IGF-1, leptin, ghrelin, and GLP-2, particularly in patients who have undergone bariatric surgery [20].

Postsurgically, rapid weight loss of 50 kg to greater than 100 kg is not uncommon among successful bariatric patients, and this combined with severely restricted oral intake, decreased calcium absorption, and vitamin D deficiency places these patients at extremely high risk for the rapid development of MBD [10, 21, 22]. One large study noted the development of metabolic bone disease in greater than 70% of patients having undergone a malabsorptive procedure, a second study detected increased markers of bone resorption as soon as 8 weeks after bariatric surgery, regardless of whether the patient underwent a malabsorptive or restrictive bariatric procedure, and yet another study that examined patients 12 months after undergoing gastric banding found that 48% had a statistically significant bone mineral reduction of greater than three percent [7, 9,14].

Attempts to protect the skeleton and mitigate the activation of the calcium-PTH axis during weight reduction with supplemental calcium and vitamin D have had mixed results. One current hypothesis supports the fact that the usual recommended intake of calcium is inadequate to during weight loss, and higher levels of 1600–1800 mg/day should be recommended, while the required level of supplemental Vitamin D during periods of rapid weight loss remains unclear [23, 24].

Inadequate protein intake also has a detrimental effect on bone and may play a key role in the development of MBD in this population. The intake of lean protein is highly emphasized in the immediate postoperative period as a body

protein-sparing strategy; however tolerance, compliance, and malabsorption issues frequently result in inadequate intake and frank protein deficiency. This is discussed in further detail below.

5. Four Paradoxes of Bariatrics and MBD

As medical professionals, we made assumptions every day regarding our patients, fostered at least in part by the ever-increasing speed at which we must see, assess, diagnose, and treat. Although many suppositions are both legitimate and accurate, consider the following commonly made assumptions that are, in fact, fundamental paradoxes when it comes to bariatric patients and the risk for metabolic bone disease.

5.1. Obesity ≠ Well-Nourished. The first paradox to consider in approaching the morbidly obese patient is that the presence of obesity does *not* equate to being well nourished. In fact, body mass index (BMI) quantifies body mass, not nutrition status, and should not be presumed to be a surrogate marker for the nutritional status of the individual. Recognizing this fact allows the clinician to maintain an appropriately high index of suspicion for underlying deficiencies that could serve as clues to the presence of metabolic bone disease.

5.2. Morbid Obesity ≠ Better Bone Quality. Morbid obesity has historically been viewed as having a protective effect against the development of osteoporosis. But the second paradox to be attentive to in this population is that although the bone mineral density as measured by dual-energy X-ray absorptiometry (DXA) may be normal, it does not equate to normal (or better) bone quality. In fact, sequestration of vitamin D in the adipocytes, frank vitamin D and calcium deficiencies, and secondary hyperparathyroidism (HPTH) are common in extremely obese individuals presenting for bariatric surgery, and all can have a profound effect on bone quality [8, 9, 21, 25]. Studies attempting to define the prevalence of vitamin D deficiency have identified rates in excess of 60% among patients selected to undergo weight loss surgery [9, 26]. Similarly, the prevalence of elevated PTH in this population ranges from 25% to 48% [9, 27].

5.3. Morbid Obesity ≠ Central DXA. The third paradox is that bariatric surgery patients are at high risk for bone loss but DXA, the gold standard for bone density measurement, has limited utility in this population. Weight limitations of DXA tables have typically been 250–275 pounds. Newer and larger machines can accommodate upwards of 450 pounds but this is still insufficient to accommodate many bariatric patients. Forearm DXA imaging remains the only statistically validated option for assessing bone mineral density and fracture risk in patients who exceed the recommended table weight limit, and should be used for presurgical screening and postsurgical surveillance in this population.

The use of serial DXA in patients who have experienced dramatic weight loss is not without controversy. Discussed elsewhere in the literature, it is important to note that there are some studies that have identified statistically significant accuracy errors in serial central DXA measurements in this population [28].

5.4. Abnormal DXA ≠ Osteoporosis. Despite the presence of long-standing morbid obesity, many patients will have abnormally low bone mineral density test results. But abnormal DXA results do not always represent primary osteoporosis, and abnormal DXA results should never evoke a "knee-jerk" reflex response on the part of the clinician to diagnose osteoporosis and start a bisphosphonate. In fact, indiscriminate use of bisphosphonates in this patient population can result in life-threatening complications—more on this in a moment.

Abnormal DXA in a bariatric surgery patient often represents secondary bone disease due to nutritional deficiencies, and when secondary bone disease is present, it should become the focus of treatment interventions. A clue to the presence of secondary bone disease may be seen in abnormally low Z-scores. Recall that Z-scores for a reference population are matched to age as well as gender. If the bone mineral density has changed only because of normal aging, Z-scores would be expected to be zero, however if the Z-scores are significantly low, this should raise the index of suspicion as to the presence of underlying deficiencies.

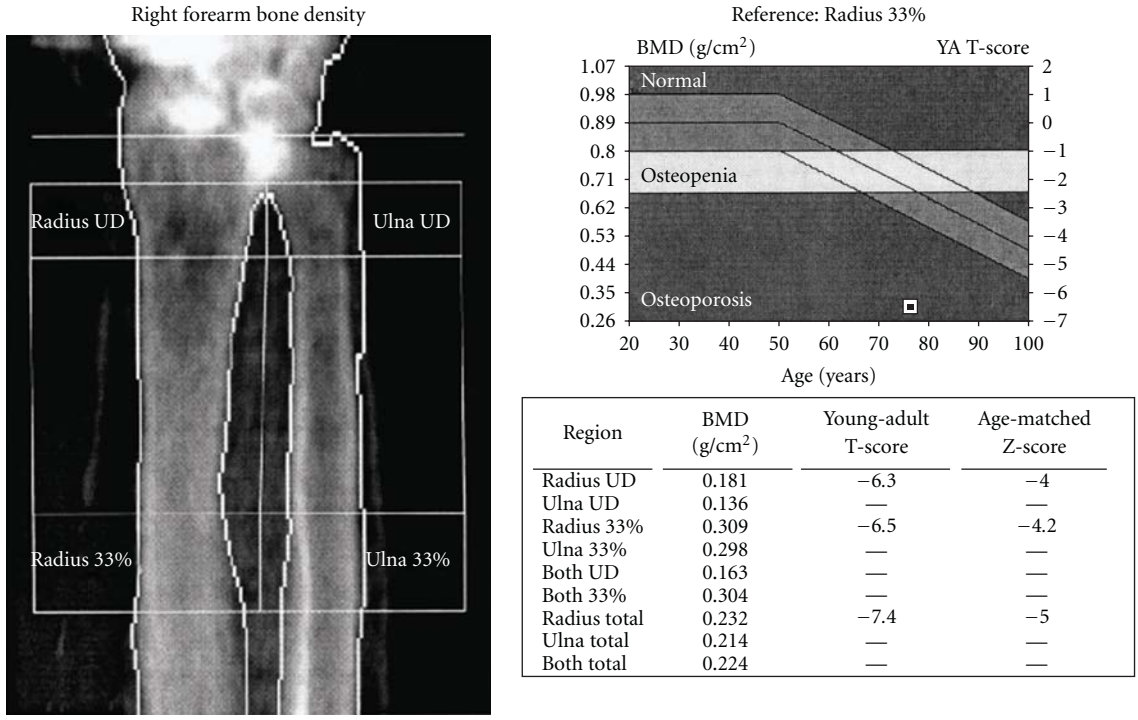
6. Case in Point

The DXA image seen in Figure 2 is the nondominant forearm of a woman who recently presented for evaluation and treatment of hypocalcemia. Her medical history was remarkable for bariatric surgery in 1974, chronic renal stones since 1979, and she had been wheelchair bound for 10 years due to numerous fragility fractures and profound proximal weakness. Biochemical indices were significant for hypocalcemia, undetectable 25-hydroxyvitamin D, elevated alkaline phosphatase, intact parathyroid hormone five times the upper range of normal and very low urine calcium. The T-scores clearly exceed the World Health Organization criteria for osteoporosis, but the Z-scores in concert with the clinical presentation are even more telling.

Delineating secondary bone disease from low peak bone mass often requires additional clinical data and a skilled specialist, but in this case the grossly abnormal biochemical indices and patient presentation is sufficient to confidently make the correct diagnosis and select the appropriate course of treatment.

7. Other Clues to the Presence of Metabolic Bone Disease

Months to years prior to the diagnosis of metabolic bone disease, many patients have nonspecific and vague symptoms that are often incorrectly diagnosed as fibromyalgia, rheumatoid arthritis, polymyalgia rheumatica, Paget disease, or depression [8]. But as in other aspects of clinical medicine, there is still no substitute for a thorough history and physical exam. Additionally, bariatric surgery patients should be



Region	BMD (g/cm^2)	Young-adult T-score	Age-matched Z-score
Radius UD	0.181	−6.3	−4
Ulna UD	0.136	—	—
Radius 33%	0.309	−6.5	−4.2
Ulna 33%	0.298	—	—
Both UD	0.163	—	—
Both 33%	0.304	—	—
Radius total	0.232	−7.4	−5
Ulna total	0.214	—	—
Both total	0.224	—	—

Figure 2: DXA-Forearm.

asked about their nutrition practices including protein intake and the use of supplements.

Proximal weakness or complaints of muscle loss; deep, dull, poorly localizing bone pain, and increasing difficulty arising from a chair or ascending a flight of stairs all serve as clues to the possible presence of vitamin D deficiency and osteomalacia. A history of frequent stooling, steatorrhea, or kidney stones should also heighten clinical suspicion of abnormal calcium metabolism and risk for bone loss.

Finally, undersupplementation in this patient population can rapidly lead to MBD in that maintenance of normal nutrition status and the associated lab parameters typically requires daily protein and supplements in doses that far exceed the current RDAs. It is imperative for clinicians to have a high index of suspicion for the presence of MBD if a patient reports taking only an over-the-counter multivitamin and 500 mg of calcium daily, with little attention paid to the diet.

8. Calcium Oxalate Stones

In the intact GI tract, bile acids and free fatty acids are absorbed in the proximal intestine, calcium forms an insoluble precipitate with oxalates, and calcium oxalates are harmlessly excreted in the stool. In the malabsorptive gut, unabsorbed fatty acids bind calcium thereby making it unavailable to bind oxalates, and lingering bile acids and free fatty acids promote increased colonic permeability. The unbound oxalates are readily absorbed in the distal gut resulting in hyperoxaluria thereby increasing the likelihood of oxalate deposition in the renal parenchyma [29, 30]. One recent study noted a mean time to the development of the first stone after roux-en-y gastric bypass (RNYGB) of 2.9 years with a range of 1 month to 13 years [29].

Although there is evidence that a low-oxalate diet may decrease the risk of stone formation by 20 percent, it is important to keep in mind that dietary oxalates only account for 10–20 percent of total oxalates, with hepatic synthesis accounting for 40–50 percent, and ascorbic acid metabolism accounting for the remaining 40–50 percent [31]. Oxalates are a ubiquitous component of plants, cereal grains, leafy, and root vegetables, therefore an oxalate-free diet is clearly not possible, and further restriction of the diet following bariatric surgery, with its inherent risks for nutritional inadequacy, is inadvisable. Emphasis on adequate water intake, avoidance of dietary fats and supplemental vitamin C, and supplementation with calcium citrate which helps to increase urinary pH and retard calcium oxalate crystal formation, have all been demonstrated to be beneficial in preventing calcium oxalate stones in this population [31–33].

9. 2008 AACE/TOS/ASMBS Guidelines

There have been a wide variety of recommendations put forth in the literature for perioperative screening, risk stratification, and management of MBD in bariatric patients [34–37]. With the 2008 publication of the American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic and Bariatric Surgery (AACE/TOS/ASMBS) medical guidelines for perioperative support of the bariatric surgery patient, there are now evidence-based practice guidelines that include recommendations for testing and management of skeletal and mineral disorders [38]. Although the guidelines serve as an excellent

general guide, essential information specifically addressing bone disease in this population is still lacking. Specifically, evidence-based guidelines need to be put forth regarding presurgical bone assessment, the preferential use of calcium citrate, the use of cholecalciferol (D3) over D_2 or D analogs; the efficacy of UV-B light in patients resistant to oral repletion; the risk for fat-soluble vitamin deficiencies with long-term use of bile acid sequestrants commonly used to treat postoperative diarrhea, and both the risks and questionable efficacy of oral bisphosphonates in this population.

10. Recommendations

Presurgically, in addition to the biochemical indices recommended in the AACE/TOS/ASMBS guidelines which include 25-hydroxyvitamin D and a bone marker of resorption such as urine n-telopeptide (NTX), obtain a baseline DXA, even if only the forearm can be imaged because of weight limitations. If the DXA is abnormal, pursue further investigation and treatment as appropriate, with a high index of suspicion for secondary bone disease.

Postsurgically, repeat the DXA in one year, then follow the International Society for Clinical Densitometry (ISCD) guidelines in determining when best to obtain future bone density studies [39].

11. Calcium Supplementation

Calcium citrate has been demonstrated to have better bioavailability, superior fractional uptake in bone, and efficacy in normalizing markers of bone turnover when compared to other commercially available calcium supplements [40]. Citrate is metabolized to bicarbonate which has a neutralizing affect on urine, thereby also decreasing the risk of nephrolithiasis.

An optimal daily intake of calcium based on the specific bariatric surgical procedure is currently unknown however attempts to optimize calcium intake is essential, particularly during periods of rapid weight loss [23, 24]. Absorption, separate from the issue of compliance, can be problematic for some patients, therefore judicious monitoring is advised. It is important to remember that calcium homeostasis is a tightly regulated process, maintained by a combination of gut absorption, bone resorption, and renal reabsorption. In the absence of adequate dietary calcium and/or absorption, calcium will be resorbed from bone in order to support calcium-dependant processes; therefore the serum calcium is an unreliable measure of adequate calcium intake. Quantifying urine calcium can assist in assessing the adequacy of calcium intake in that abnormally low urine calcium in the presence of normal renal function suggests inadequate intake and/or absorption. Table 1 provides a summary of current recommendations for this unique population [13, 41].

Table 1: Recommended daily calcium and vitamin D_3^* intake.

Adult women and men	Calcium	Vitamin D_3
During periods of rapid weight loss	1,500–2000 mg	1,000 IU
Morbidly obese patients	1,500 mg	2,000 IU
Post-Bariatric surgery patients	1,500–2000 mg	2,000 IU–100,000+ IU

*Doses listed are for maintenance of normal levels. Repletion of vitamin D often requires significantly higher doses.

11.1. Vitamin D. Serum 25-hydroxyvitamin D remains the most accurate marker of vitamin D status, and has well-established, strong associations with vitamin D deficiency, fragility fractures, and secondarily elevated parathyroid hormone.

Correction of vitamin D deficiency in bariatric surgery patients requires more than just an over-the-counter multivitamin. Repletion has been safely achieved by giving 50,000 IU to 100,000 IU cholecalciferol daily for one to two weeks followed by a maintenance dose of 50,000 one to three times weekly. Ergocalciferol as well as the various vitamin D analogs have not demonstrated the efficacy achieved with cholecalciferol in normalizing blood values or addressing symptoms [42, 43].

The absorption of vitamin D is dependant upon the presence of bile acids. Predictably, it has been demonstrated that taking cholecalciferol with the largest meal of the day promotes improved uptake [44]. And for patients who are unable to achieve normal serum levels with oral supplementation, UV-B phototherapy is an effective alternative [3, 4, 45, 46]. Having said that, the use of tanning beds, although advocated by few, is not recommended due to the fact that the average tanning bulb emits 95% UVA and 5% UVB radiation, imparts a 4-fold to 15-fold higher dose of UVA and 2-fold higher dose of UVB than summer, noontime casual sun exposure, and have been implicated in the development of skin cancers [47, 48].

11.2. Cholestyramine. Originally marketed as an effective drug for the reduction of plasma cholesterol because of its ability to sequester intestinal bile acids, cholestyramine is now commonly prescribed for the symptomatic relief of diarrhea. When the drug is used on a short-term basis, there does not seem to be cause for concern however, when prescribed long term as is often the case in bariatric surgery patients, there is an increased risk for alterations in vitamin and mineral metabolism due to the resin's bile acid-binding characteristics [49], and risk of bowel obstruction [50, 51].

Studies conducted in rodents that date back to the 1970s demonstrated a net negative balance for calcium, inadequate vitamin D absorption, and a subsequent increase in parathyroid hormone secretion due to cholestyramine. Frank osteomalacia was also noted but was found to be reversible with vitamin D supplementation [49]. Subsequent human studies confirmed the relationship between chronic use of bile acid resins, impaired vitamin D absorption, and osteomalacia [52] while at least one longitudinal study refutes the effect on the availability of vitamin D and the development of secondary hyperparathyroidism [53].

The evidence regarding the risk of bowel obstruction due to cholestyramine is more scanty, almost exclusively in the pediatric population, and predominantly in the form of case reports dating back to the late 1960s [54, 55]. The lone exception is a review published in 2007 that while examining safety considerations noted that moderate-to-severe constipation was common, and subsequently compelled the authors to recommend that cholestyramine and other bile acid sequestrants are to "be avoided in patients with recent abdominal surgery and in patients with recent or repeated episodes of intestinal obstruction" [56].

12. Bisphosphonate Use in Bariatric Surgery Patients

When a bone loss disease occurs in a bariatric surgery patient, secondary disease should be suspected first, and it is the secondary disease that deserves the primary focus of treatment interventions. The etiology of confirmed vitamin D deficiency, hypocalcemia, elevated alkaline phosphatase, secondary hyperparathyroidism, and accompanying signs and symptoms should be clearly delineated to the degree possible, and appropriate treatment interventions initiated. Abnormal DXA may be indicative of both primary and secondary disease however aggressive treatment of the underlying cause of the secondary disease can result in significant improvements in BMD [41].

Clinical and biochemical resolution of secondary bone disease in the presence of persistently abnormal DXA should prompt treatment considerations for primary bone disease, however concern remains when considering the use of oral bisphosphonates in bariatric surgery patients due to the lack of safely and efficacy data. Specifically, tolerance has not been established in the surgical gut, and risk of ulceration at surgical anastamosis has not been defined. Efficacy of oral bisphosphonates has also come into question following intestinal procedures after which the drug may be malabsorbed. It is for these reasons that if a bisphosphonate is indicated, unless there is evidence to the contrary, intravenous administration is recommended.

13. Protein and Bone Health

A systematic review of protein and bone health concluded that diets containing 1.0–1.5 g/kg protein are typically optimal for bone health [57]. This is particularly worrisome, in that this suggests the current RDA of 0.8 g protein/kg is insufficient to promote calcium homeostasis. Similarly, the common practice of prescribing 60 to 80 grams of protein after bariatric surgery is often wholly inadequate. It is essential to use an adjusted body weight that approximates metabolically active tissue when calculating protein needs as there is also a link between excessive protein intake, calciuria, and increased fracture risk [58, 59].

14. Bariatric Osteomalacia: An Evolving Concept

Prior to recent investigations in metabolic bone disease and bariatric surgery, improvement in bone density as a result of vitamin D supplementation had been demonstrated however, the changes were small, of questionable clinical significance, and occurred exclusively in trabecular bone [60].

Bariatric osteomalacia appears to be a unique disorder in that profound improvement in symptoms and bone mineral density measurements have been observed in response to aggressive oral repletion with pharmacologic doses of cholecalciferol and calcium citrate (Figure 3). It has been proposed that these observed responses may be unique to bariatric surgery patients, is a synergistic and graded response of D3 and calcium citrate based on the magnitude of the deficiencies, and that D3 likely has a hormonal effect on cortical bone that is more pronounced in this patient population [41, 61]. Studies are currently underway in an effort to confirm the observations, characterize the pathophysiology, and define diagnosis, treatment, and preventative guidelines for this increasingly common disorder.

15. Summary

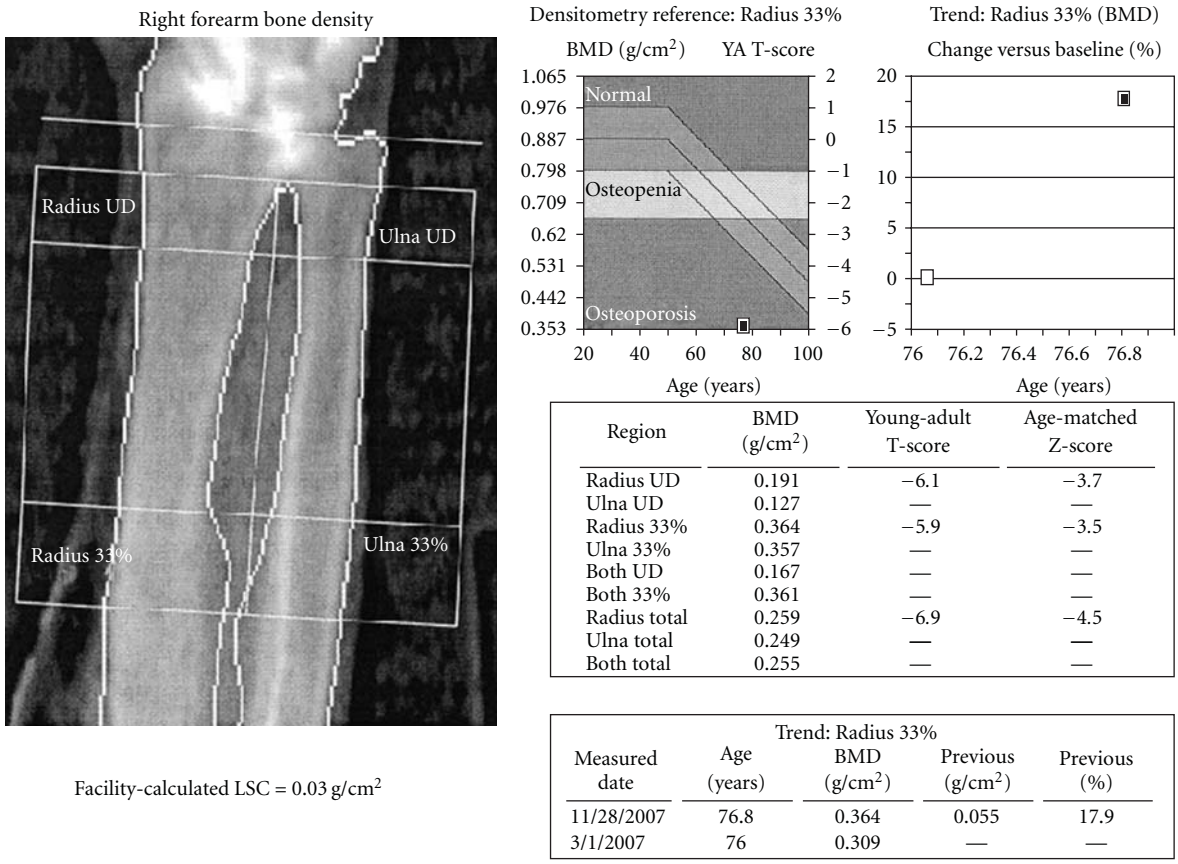
Bariatric surgery has proven to be an effective and life-saving measure that provides sustainable weight loss but it is not without risk of complications, to include metabolic bone disease.

There is a causal, multifactorial relationship between bariatric surgery and MBD and for that reason MBD remains an ever-present risk in bariatric surgery patients. Patients presenting for bariatric surgery should be evaluated for MBD and receive appropriate presurgical interventions. Postsurgically, the importance of consuming adequate protein and the correct combination of vitamins and minerals cannot be overstated, remembering that no bariatric surgical procedure is risk-free when it comes to the development of metabolic bone disease.

As clinicians, we cannot assume that our morbidly obese patients are well nourished or that they have normal bone quality. Dual-energy X-ray absorptiometry can be used to help assess bone status in the morbidly obese, however if the DXA table limitations prevent imaging the hips and spine, the nondominant forearm is a validated option for quantifying bone mineral density.

Not all abnormal DXA results represent primary osteoporosis and in fact, in the bariatric population, secondary bone disease is the norm and when the diagnosis has been confirmed, treating the underlying cause of the secondary disease must take precedent. DXA Z-scores, if abnormally low, suggest the presence of secondary MBD, however it is important to remember that secondary disease can be present even in the presence of normal scores. Clues such as proximal weakness, a history of renal oxalate stones, chronic steatorrhea, and undersupplementation should serve to alert the clinician to the possible presence of metabolic bone disease.

In addition to the AACE/TOS/ASMBS guidelines, a baseline and one year postoperative DXAs are recommended. The use of calcium citrate and cholecalciferol (vitamin D3) are the recommended forms of these supplements, and in order to achieve and maintain normal serum levels, very



Region	BMD (g/cm²)	Young-adult T-score	Age-matched Z-score
Radius UD	0.191	−6.1	−3.7
Ulna UD	0.127	—	—
Radius 33%	0.364	−5.9	−3.5
Ulna 33%	0.357	—	—
Both UD	0.167	—	—
Both 33%	0.361	—	—
Radius total	0.259	−6.9	−4.5
Ulna total	0.249	—	—
Both total	0.255	—	—

Facility-calculated LSC = 0.03 g/cm²

Trend: Radius 33%				
Measured date	Age (years)	BMD (g/cm²)	Previous (g/cm²)	Previous (%)
11/28/2007	76.8	0.364	0.055	17.9
3/1/2007	76	0.309	—	—

Bone mineral density change: 17.9% increase at the radius 33% over an 8-month period
Associated clinical changes: decreased bone and muscle pain, no further calcium oxalate stones, improved endurance and strength, ambulating independently

Figure 3: Bone remineralization following aggressive oral repletion with cholecalciferol and calcium citrate.

high doses are often required in the bariatric postoperative patient.

Caution is advised when considering the use of certain medications to treat common problems in this patient population. Cholestyramine or other bile acid sequestrants used to control diarrhea in this patient population increase the risk of exacerbating vitamin D malabsorption and osteomalacia, and may increase the risk of bowel obstruction. The use of bisphosphonates for presumed osteoporosis carries the risk of life-threatening hypocalcemia; efficacy has not been well established in this population, and the risk for ulceration from oral preparations at the surgical anastamosis has yet to be delineated.

Finally, there is emerging evidence that bariatric osteomalacia is a unique and increasingly common phenomenon in bariatric surgery patients that can have a subtle clinical presentation but potentially devastating consequences if left unrecognized. Investigations into the underlying mechanism of the disease, the response to aggressive repletion, and effective preventive strategies are ongoing. The treatment regimen at this point in time includes the use of cholecalciferol and calcium citrate with frequent monitoring and dose adjustments to attain and maintain normal lab parameters.

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Research Article

Semiquantitative Assessment of Bowel Habits and Its Relation with Calcium Metabolism after Gastric Bypass Surgery: A Retrospective Study

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Background. Calcium malabsorption after bariatric surgery may be harmful to skeletal health and demands for optimal skeletal management. *Methods*. 103 Patients were evaluated retrospectively at 12 months after surgery. The evaluation included a questionnaire about stool frequency and consistency and laboratory assessments. *Results*. 103 Patients, 27 males and 76 females, were included in the study. 83 Patients had an alimentary limb of 100 cm and 20 patients one of 150 cm. At 12 months after surgery, 77.7% reported changes of bowel habits, albumin adjusted calcium levels were normal in all but 2 patients, and PTH levels were increased in 35%. Correlations between semiquantified bowel scores (fecal scores) and data from the laboratory demonstrated increasing PTH values along with more frequent and softer/watery stools (RR 30.5, CI 6.2–149.2, $P < .001$). There was a trend for higher PTH levels in patients with an alimentary limb of 150 cm. Normal PTH levels were more frequently found in case of calcium and vitamin D3 use (RR 14.3, CI 3.6–56.5, $P < .001$). *Conclusion*. This study demonstrates interrelationships between semi-quantified fecal scores, PTH levels, and the compliance of taking calcium/vitamin D3 suppletion. However, prospective randomized studies are necessary to show causal relationships.

1. Introduction

Bariatric surgery still remains the most effective treatment for morbid obesity, leading to a reduction of comorbidities in the long term [1]. Roux-en-Y-Gastric Bypass (RYGB) is one of the most frequently performed procedures in the United States and is also widely practiced in Europe [2–4]. Calcium and vitamin D deficiencies, which frequently arise after surgery, may be overlooked because of their slow development. However, they may give rise to secondary hyperparathyroidism (2°HPT) as the body attempts to counter the deficits [5]. Obviously, sufficient dietary calcium and vitamin D are necessary to prevent this condition, which can be difficult to achieve because of the bypassed proximal part of the small intestine. This is the obvious reason for the recommendation of supplying adequate amounts of dietary calcium and vitamin D after surgery [6–8]. Long-lasting 2°HPT for years is believed to be an important contributing factor for increased bone turnover and consequent bone loss. Indeed, epidemiologic data have shown that gastric surgery can lead to a state of 2°HPT with an increased risk of osteoporotic fractures [9–11].

Besides inadequate dietary intake of calcium to compensate for suboptimal calcium absorption, changes of bowel habits after gastrointestinal surgery may also interfere. It is of note that morbidly obese patients frequently have fecal incontinence due to a rise in intra-abdominal pressure with compression and stretch of the pelvic floor and of the muscles and nerves around the anal sphincter complex and in the vicinity of the supporting endopelvic fascia [12]. After bariatric surgery, many patients initially experience less fecal incontinence due to substantial weight loss and associated improvements of intra-abdominal mechanics [13, 14]. For obvious reasons, patients may even have a lowered frequency and hardened consistency of defecation in comparison to the situation prior to the operation. Nevertheless, more frequent

Table 1: Preoperative demographics and laboratory data prior to gastric bypass surgery.

Parameters		
Patient no.	103	
Males/Females	27/76[1]	
Age (yr)	42.3 ± 9.7	
BMI (Kg/m^2)	48.6 ± 6.2	
Body weight (Kg)	144.3 ± 21.9	
Alimentary limb		
Patient no. with *100* cm	83	
Patient no. with *150* cm	20	
		Patients with abnormal lab. values
Calcium (mmol/L)[2]	2.31 ± 0.07	2[3]
Vitamin D (nmol/L)	50.4 ± 22.4	
Insufficiency <30 (nmol/L)		18 (17%)
Deficiency <50 (nmol/L)		32 (31%)
PTH (pmol/L)	5.1 ± 1.0	10 (10%)

[1]The number of males versus females was statistically different ($P < .05$). [2]Serum calcium was adjusted for albumin concentrations. [3]1 Patient had a corr. serum calcium of 2.63 and 1 patient of 2.10 mmol/L.

and looser stools are common in operated patients [15–17]. Studies in laboratory animals elaborating on intestinal calcium absorption have shown that intestinal calcium kinetics depends on intestinal transit time [18]. Similar observations were found after RYGB due to the inability of the small intestine to bind and absorb calcium [19].

To our knowledge, no previous studies were published about interactions between bowel habits after surgery and changes of calcium metabolism. The aim of the present study is to investigate relationships between semiquantified stools scores according to patient reports, compliance for the daily use of extra calcium, and calcium metabolism.

2. Patients and Methods

During a period of 3 years, 423 morbidly obese patients underwent laparoscopic RYGB. Patients were eligible for the study if laboratory data were available at baseline and at 11 to 13 months after surgery. A total of 103 patients, 27 males and 76 females, were eligible, and these were invited to discuss the purpose of the study; all consented to participate. The objectives of the study were (1) to evaluate bowel habit changes after surgery; (2) to evaluate relationships between (1) and laboratory assessments; (3) to evaluate relationships between (1) and (2) with the daily use of a formulation, containing 1 g of elementary calcium and 880 to 1000 IU Vitamin D3. The medical ethical committee of Rijnstate Hospital, Arnhem, The Netherlands approved the study.

Table 2: Biochemical data categorized according to normal or increased PTH levels at 12 months after gastric bypass surgery.

PTH (pmol/L)	PTH ≤ 6.8	PTH > 6.8	Normal
Patient no.	67	36	
Calcium	2.34 ± 0.08	2.31 ± 0.11	2.10–2.55 mmol/L
Vitamin D	47.5 ± 27.5	40.3 ± 20.3	30–100 nmol/L
Albumin	38.6 ± 3.0	38.6 ± 4.0	35–50 g/L
PTH	4.3 ± 1.4*	9.5 ± 2.8*	1.3–6.8 pmol/L

Lab. results are represented as (mean ± 1SD). *Significant by one-way ANOVA with $P < .0001$.

All patients were planned for surgery. All patients underwent surgery in a single center for bariatric surgery (Rijnstate Hospital Alysis Zorggroep, The Netherlands). Laparoscopic RYGB was performed by 2 dedicated bariatric surgeons who used standard techniques. According to protocol, patients with a BMI >40 kg/m^2 received a 45 cm biliopancreatic limb, and a 100 cm alimentary limb, while patients with a BMI >50 kg/m^2 received a 150 cm alimentary limb. 20 Patients received a 150 cm limb and 83 patients received a 100 cm limb. 22.2% of all males received a 150 cm limb versus 18.8% of all females, meaning no statistical difference in sex distribution. Patients were advised to take daily multivitamins in addition to omeprazol 40 mg (once daily for 6 months) [20] and low molecular heparin SC (fraxiparine 5700 IU once daily for 6 weeks); patients were advised to take a daily calcium/vitamin preparation (CaD 1000/880 sachets, containing calcium citrate and vitamin D3) or, if they refused to take CaD, to try a different formulation containing calcium carbonate and vitamin D3 (Calcichew 500/400 chewing tablets b.i.d.).

After written informed consent, each participant was requested to complete a questionnaire about his/her bowel habits prior to and at 12 months after surgery. Fecal frequency was scored on a five-point scale ranging from less than twice a week (1 point), every two days (2 points), once a day (3 points), twice a day (4 points) to more than twice a day (5 points). In addition, fecal consistency was scored on a five-point scale ranging from watery stools (5 points), watery to solid stools (4 points), normal stools (3 points), firm stools (2 points) to hard stools with concomitant constipation (1 point). Summation of fecal consistency and frequency scores yielded a "fecal score" (FS). Compliance in taking additional calcium and vitamin D3 was arbitrarily defined as daily use with the maximal exception of one day per week. Patients who reported taking the supplement for 5 or less days a week were categorized as noncompliant. For the current analysis, we recorded (1) compliance with regular use of calcium and vitamin D3 containing formulations, (2) the number of patients who requested to switch from liquid formulations (sachets) to chewing tablets, and (3) the number of patients who used laxatives or constipating agents, at least weekly. Calcium, albumin, vitamin D, and PTH at baseline (before surgery) and at 12 months after surgery were used in the final analysis of the study.

Table 3

(a) Changes of bowel habits according to frequency and consistency scores before and after gastric bypass surgery

Time	Baseline frequency	12 mo. frequency	Baseline consistency	12 mo. frequency
Patient no.	*103*	103	*103*	103
Frequency/ Consistency				
<2 per week/ constipated	*9*	6	*12*	8
3 times per week/firm	*23*	19	*26*	14
1 day/normal	*55*	44	*62*	48
2 per day/solid to watery	*13*	19	*2*	27
>2 per day/liquid	*3*	15	*1*	6

Number of patients with frequency and consistency scores ranging from 1 to 5 points.

(b) Fecal scores before and after gastric bypass surgery

Fecal score	Baseline	12 Months
2	7	8
3	4	8
4	12	17
5	29	27
6	39	17
7	8	12
8	4	9
9	0	4
10	0	1

Fecal scores are the summation of stool frequency and consistency ranging from 2 to 10 points and disclosed a significant increase post surgery (γ^2-test: $P < .01$).

2.1. Statistical Analysis. The datasheet was analyzed using SPSS16, statistical software. All data are reported as mean ± 1SD unless otherwise specified; $P < .05$ was considered significant. Results were compared using independent sample *t*-tests, Chi square-tests, relative risk calculation, and one-way ANOVA. Logistic regression was used to differentiate between variables.

3. Results

Demographic data of the included 103 patients, prior to surgery, are listed in Table 1. There were 27 males and 76 females ($P < .05$). All patients were Caucasians. 8 Patients (7.7%) were regular tobacco users, 12 patients were on antidiabetic drugs (11.6%), and 1 patient used prednisone. 6 females were postmenopausal; 1 of them was on hormonal replacement therapy.

2 Patients were diagnosed with a leakage at the gastrojejunostomy and were oversewn successfully, respectively, on the first and third postoperative days. Both patients were discharged within a week after the second operation. Other 2 patients had their gallbladder removed at 6 and 8 months after surgery. There were no other surgical complications.

The excess weight loss (EWL) was >25% for the entire group of 103 patients and exceeded more than half in 83 participants (81%). EWL of the total group at 12 months had decreased by (mean ± 1SD) 63.5 ± 19.5%. The BMI of the whole group decreased from 48.2 ± 6.2 kg/m^2 before surgery to 33.9 ± 5.5 kg/m^2 at 12 months.

Serum calcium concentrations corrected for albumin were normal in 101 patients (98%); vitamin D insufficiency (<50 nmol/L) was demonstrated in 63 patients of whom 32 patients (31%) had vitamin D deficiency (<30 nmol/L). PTH levels were increased (>6.8 pmol/L) in 36 patients (35%), see Table 2.

Notably, none of the patients were regular laxative users, and 79 out of 103 patients (77.7%) reported permanent changes of their bowel habits. Each patient estimated stool frequency and consistency on two 5-point scales ranging from stools less than twice a week to more than twice a day and from watery to hard stools. The summation of each score (frequency plus consistency scores) yielded a fecal score (FS). Memorized stool frequency and consistency data before surgery and at 12 months are listed in Table 3(a) and the distribution of fecal scores (FS) (from 2 to 10 points) in Table 3(b). Each score disclosed a significant change comparing frequency of stools (F), consistency of stools (C), and the fecal score (FS). In general, there was a significant shift towards more frequent and less consistent stools, which overall had resulted in higher fecal scores for (F: $P < .05$, C: $P < .0001$, and FS: $P < .01$).

Laboratory assessments disclosed no significant changes of corrected calcium and vitamin D levels (calcium before surgery 2.31 mmol/L and at 12 months 2.34 mmol/L, vitamin D before surgery 50.4 nmol/L and at 12 months 45.0 nmol/L), while mean PTH levels increased from 5.1 to 6.1 pmol/L ($P = .02$). Before surgery, 10 patients had increased PTH levels, while 4 of them (40%) had also increased PTH levels at 12 months. Before surgery, 32 out of 93 patients had normal PTH levels but developed raised PTH levels at 12 months (34.4%) (NS). PTH levels compared for each domain of stool habits (frequency (F), consistency (C), and fecal score (FS)) per tertile at 12 months, showed no significant changes for F and C. However, PTH levels rose significantly along with tertile FS (RR 30.5, CI 6.2–149.2, $P < .001$), see Table 4.

At 12 months, calcium and vitamin D levels were similar between patients with an alimentary limb of 100 cm ($n = 83$) and 150 cm ($n = 20$) (100 cm: calcium: 2.31 mmol/L, vitamin D 46 nmol/L and 150 cm: calcium: 2.33 mmol/L, vitamin D 42 nmol/L). In addition, there was a trend towards higher PTH levels after inclusion of all patients using two-sided Student *t*-test: 100 cm: PTH: 5.6 pmol/L and 150 cm: PTH 7.9 pmol/L ($P = .001$). PTH levels were not significantly significant after inclusion of compliant calcium/vitamin D3 users (logistic regression) (RR 3.2, CI 0.9–11.8, $P = .08$). At 12 months, there were 36 patients (35%) with increased PTH levels. 24 of these patients had a 100 cm alimentary limb (67%), and 12 patients had a 150 cm alimentary limb (33%).

Table 4: Laboratory results according to fecal scores calculated for each tertile.

Fecal score	Low	Intermediate	High	*P*-value
Patient numbers (Point range per tertile fecal score)	33 (2–4)	44 (5-6)	26 (7–10)	
Calcium (mmol/L) (Patient numbers with hypocalcemia)	2.35 ± 0.09 (0)	2.32 ± 0.09 (0)	2.34 ± 0.11 (1)	.43
Vitamin D (<30 nmol/L/<50 nmol/L)	41 ± 21.0 (11/22)	51 ± 29.8 (11/25)	39.5 ± 20.4 (10/16)	.12
PTH (≥6.8 pmol/L)	4.9 ± 2.3 (4)	5.8 ± 3.2 (13)	8.0 ± 3.4 (19)	<.001
Patients with an alimentary limb of 150 cm (% of total)	3 (9)	10 (23)	7 (26)	.17*

*P value by γ^2-test, all other comparisons were performed by one-way ANOVA.

According to the definition used in the current study, there were 82 compliant calcium/vitamin D3 users (80%). High PTH levels (PTH >6.8 pmol/L) were found in 21 patients who belonged to this group compliant for suppletion (26%) against 15 patients who belonged to the 21 remaining noncompliant suppletion users (71%) (RR 14.3, CI 3.6–56.5, $P < .001$). In the subgroup of 36 patients with high PTH levels, 21 patients (58%) were compliant suppletion users (PTH: 9.2 ± 2.8 pmol/L) and 15 patients (42%) were not compliant (PTH: 9.9 ± 2.7 pmol/L) (NS).

The reasons for noncompliant suppletion use were being principally against regular use of any prescribed drug, frequently forgetting, and taste aversion against calcium formulations. 69 of the 82 compliant suppletion users (84%) had decided to switch from sachets (liquid formulation) to chewing tablets, while the remaining 13 patients (16%) continued to take sachets. The main reasons for changing from sachets to tablets were nonpalatability reported by 54 patients (78%) and/or the inability to drink large volumes reported by 30 patients (43%). There were 6 reports on dumping-like symptoms with sachets.

4. Discussion

The results of the current study showed significant changes of bowel habits after surgery, which went into the direction of a higher stool frequency, less consistency, and consequent higher fecal scores. There were no correlations with either frequency or consistency and PTH levels, while fecal score and PTH levels were positively correlated. There was also an interaction between compliance for calcium/vitamin D3 suppletion and PTH levels, but it should be emphasized that the current results are nothing but associations, which implicates that prospective intervention studies are needed to clarify how these factors interact. Moreover, it is entirely unclear whether additional calcium and vitamin D supplements are beneficial in suppressing PTH levels and ultimately affect incident osteoporotic fractures in later life. An additional uncertainty is the effect of omeprazol 40 mg (once daily for 6 months) on calcium metabolism after surgery. Indeed, proton pump inhibitor therapy increases the risk to skeletal fracture in the long term, possibly by inhibiting intestinal calcium absorption [21, 22]. Obviously, prospective randomized clinical trials should be long lasting as osteoporotic fractures usually occur much later in life.

Elevation of PTH, even in the presence of unchanged corrected calcium and vitamin D levels, is compatible with 2°HPT [5]. In fact, RYGB serves as a model for 2°HPT exclusively due to inadequate calcium absorption. A study on calcium metabolism of patients who had undergone RYGB and matched controls showed that the patients needed an extra amount of 750 mg calcium per day to maintain similar PTH levels [23]. These calculations were made at 9 months after surgery, meaning that calcium metabolism was still influenced by skeletal calcium effluxes due to high bone turnover [23, 24]. Yet, no calcium balance studies have been published that deal with operated patients with a stable body weight to provide information on the optimal amount of dietary calcium. Notably, too much extra dietary calcium may be harmful because of calcium-related constipation. It has been shown previously that calcium salts bind to free fatty acids and fecal bile acids in the colonic lumen, forming calcium soaps. In other words, calcium suppresses intestinal motility indirectly through binding at the colon level leading to less free fatty acids and to bile acids that are toxic to the colonic mucosa to provoke frequent and watery stools [25].

It is an open question whether increased PTH levels due to chronic calcium malabsorption after RYGB are relevant to future skeletal health. Bone loss after bariatric surgery can be partly ascribed to the direct and secondary effects of rapid weight loss and partly to 2°HPT-related bone loss. Moreover, shortly after bariatric surgery, there will be substantial bone loss, which is obviously driven by the catabolic state of the ongoing weight reduction and not by 2°HPT. Most of this type of rapid bone loss occurs at the hip and ceases with stabilization of body weight. The loss of bone mineral density after surgery occurs mainly at the hip and pelvis, varying between 5 and 10% [23, 24, 26]. However, these analyses were performed around 12 months after surgery, during rapid bone loss. Thus far, there are no data, for example, after a decade available in the literature. Most of the available data come from histological studies of operated patients with a jejunoileal bypass, showing that full-blown

osteomalacia was common after this particular procedure [27]. However, jejunoileal bypass surgery is fraught with many long-term complications, among which is vitamin D deficiency, and the operation has therefore been abandoned. Since no histology data are available from obese patients after RouxenY bypass surgery, the jejunoileal bypass bone samples are unique and could help to understand some of the skeletal health issues that should be dealt with. In a comparative histomorphometry study in 21 patients 3–14 years after intestinal bypass surgery for obesity, osteomalacia was found in one-third of all patients. Biopsies of those without osteomalacia disclosed a marked reduction of trabecular thickness, partly as the result of 2°HPT and partly because of insufficient osteoblastic synthesis. This picture differs from that of age-related bone loss and postmenopausal osteoporosis which share loss of density rather than thickness of trabecular plates [28]. Biopsies from 16 middle-aged males after partial gastrectomy with Billroth II anastomosis revealed high bone turnover (leading to bone loss) due to body weight reduction after-surgery and/or 2°HPT [11]. Finally, there is a histological proof for insufficient osteoblastic recruitment and activity, probably due to deficits of unidentified nutrients resulting from the malabsorption caused by bypassing critical parts of the small intestines [28]. In a bone biopsy study among 41 patients after partial or total biliopancreatic bypass, it was found that defective mineralization and a decrease of bone formation rate were present in spite of serum 25-hydroxyvitamin D concentrations being normal [29]. These biopsy data underscore the concept that in one way or another essential nutrients are needed to support bone formation.

This study has several limitations, mainly related to its retrospective and cross-sectional design. However, it underlines the need for more prospective intervention studies in gastric bypass patients, even though this procedure is considered the gold standard, suggesting safety. In the meantime, it remains advisable to consider bone mineral density in the assessments of risk factors prior to surgery, particularly in women.

In conclusion, 12 months after gastric bypass surgery, there was a positive relationship between bowel habits (i.e., the summation of stool frequency and consistency scores) and PTH levels with an interaction for the compliance with calcium/Vitamin D suppletion. This finding is based on fecal score and an arbitrarily chosen definition of compliance. The current study underscores the importance of professional management of bowel habits and tailor-made calcium/vitamin D suppletion. Long-term prospective intervention studies are critical to evaluate efficacy as well as side effects and should be undertaken in the near future.

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Clinical Study

Influence of Sleeve Gastrectomy on NASH and Type 2 Diabetes Mellitus

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Background. Nonalcoholic fatty liver disease is present in up to 85% of adipose patients and may proceed to nonalcoholic steatohepatitis (NASH). With insulin resistance and obesity being the main risk factors for NASH, the effect of isolated sleeve gastrectomy (ISG) on these parameters was examined. *Methods.* 236 patients underwent ISG with intraoperative liver biopsy from December 2002 to September 2009. Besides demographic data, pre-operative weight/BMI, HbA1c, AST, ALT, triglycerides, HDL and LDL levels were determined. *Results.* A significant correlation of NASH with higher HbA1c, AST and ALT and lower levels for HDL was observed ($P < .05$, <.0001, <.0001, <.01, resp.). Overall BMI decreased from 45.0 ± 6.8 to 29.7 ± 6.5 and 31.6 ± 4.4 kg/m^2 at 1 and 3 years. An impaired weight loss was demonstrated for patients with NASH and patients with elevated HbA1c (plateau 28.08 kg/m^2 versus 29.79 kg/m^2 and 32.30 kg/m^2 versus 28.79 kg/m^2, resp.). Regarding NASH, a significant improvement of AST, ALT, triglyceride and HDL levels was shown ($P < .0001$ for all). A resolution of elevated HbA1c was observed in 21 of 23 patients. *Summary.* NASH patients showed a significant loss of body weight and amelioration of NASH status. ISG can be successfully performed in these patients and should be recommended for this subgroup.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) describes a wide spectrum of liver pathologies from simple steatosis to steatohepatitis (NASH) and cirrhosis [1]. NAFLD has a prevalence of 10% to 24% in the general population. Its prevalence in obese persons is between 50% and 85%, and 65–90% in those with Type 2 Diabetes mellitus (T2DM) [2].

For patients diagnosed with NASH, 15–20% may develop cirrhosis [3]. Given the fact that patients with NASH can enter a final cirrhotic pathway, it is not surprising that NASH appears to portend an increased risk of hepatocellular carcinoma [4].

Liver function test (lft) abnormalities are common in patients with NAFLD, with elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) usually no greater than four times the upper limit of normal and a variable AST/ALT ratio, although ALT usually predominates [5]. Several noninvasive models have been established to differentiate steatosis from NASH. It is not clear to date whether biopsy is needed for the diagnosis of NASH [6].

The pathophysiology of NASH is regarded as a continuous process with two major factors. The first factor is considered to be insulin resistance resulting in steatosis by increased elaboration of free fatty acids (FFA) that are absorbed by the liver. The second factor is a series of complex interactions between hepatocytes, stellate cells, adipose cells, Kupffer cells, inflammatory mediators, and reactive oxygen species that result in inflammation (NASH) or cirrhosis [7]. Here, the adipose tissue, whose function goes far beyond gathering energy supplies, seems to play a key role, being an essential endocrine organ producing a number of proteins demonstrating auto- and paracrine effects [8].

Unlike other chronic diseases such as T2DM, there are no formal treatment algorithms for patients with NAFLD. Currently, management of NAFLD consists of modifying the underlying risk factors including medical therapy [9–14]. To induce weight loss in NASH patients, bariatric surgery is discussed as a potential alternative.

Sleeve gastrectomy was first introduced by Hess and Marceau as a restrictive component of biliopancreatic diversion with duodenal switch; it was initially not intended as a standard single procedure [15]. Reported weight loss after isolated sleeve gastrectomy (ISG) is good and ranges from 33% to 83.3% of EWL at the 1-year followup [16, 17]. Today sleeve gastrectomy is performed as a stand-alone procedure with a low operative risk. The most common complication is staple line insufficiency and staple line bleeding [18]. Although it is mainly a restrictive procedure, resolution of T2DM occurs in 50% to over 94% of patients after ISG by 1-year followup [19, 20].

The impact of bariatric surgery on NASH has been examined for several bariatric interventions such as gastric bypass or duodenal switch operations. Based on the data reported for isolated sleeve gastrectomy regarding weight loss and amelioration of T2DM, we examined the effect of ISG on NASH and NASH-related comorbidities using clinical and biological data.

2. Material and Methods

2.1. Patients. A review of prospectively collected data was conducted for 236 consecutive patients, undergoing ISG at Polyclinique Priollet, Châlons en Champagne, France from December 2002 to September 2009. Laparoscopic Sleeve Gastrectomy was performed as previously described using a 36 French calibration tube. Methylene blue was injected intraoperatively to check for leakage [21].

Data collected included demographic data, preoperative weight/BMI, HbA1c levels, liver functions tests (AST and ALT), and lipid profiling (triglycerides, HDL, and LDL). Early followup examinations were conducted at 6 weeks and 6 months after ISG, the later followup time span was yearly. All data were entered prospectively into a custom-designed database. Approval for the surgery and prospective audit was granted by the institution's clinical board.

2.2. Histological Assessment. Liver biopsy was conducted percutaneously during ISG under laparoscopic guidance using a 14-gauge 200 mm Tru Cut Biopsy needle (CareFusion). The biopsies were taken from the central part of the left lobe of liver. All liver biopsy specimens were stained with H&E, PAS, Masson trichrome, Perls and Van Gieson. For the assessment of liver histology, one pathologist and a second observer evaluated all biopsies according to the semiquantitative scoring system for NAFLD proposed by Brunt et al. [22].

2.3. Statistics. Statistical analysis was conducted using Prism 5 for Mac OS X (GraphPad Software, Inc.)

One and two-way ANOVA were used to compare and evaluate biological data. Spearman's correlation was applied to asses a correlation between two variables. A P-value $< .05$ was considered significant.

Table 1: Patient characteristics.

Variable	
Number of patients	236
female %	87
Age at operation (years)	37.9 ± 10.0*
Weight (kg)	119.5 ± 19.4*
BMI kg/m^2	45.0 ± 6.8*
Liver biopsy	
NASH	87
normal liver histology	35
mean degree of steatosis	33.6 ± 24.7*
HbA1c > 6.5%	23

*mean ± standard deviation.

3. Results

Isolated sleeve gastrectomy was performed in 236 patients with a mean BMI of 45 ± 6.8 kg/m^2 (Table 1). In order to assess liver histology, intraoperative liver biopsy was accomplished in all patients. From the 223 histologic samples that could be finally evaluated, diagnosis was as follows: 35 patients with normal liver, 77 with steatosis, 87 with NASH, 18 with fibrosis, 3 with cirrhosis, 2 with siderosis, and one patient with chronic hepatitis (Table 1). Patient followup was conducted up to 3 years with a median overall followup of 12 months. Among the clinical and biological data analysed, NASH was significantly correlated with higher HbA1c, AST, and ALT levels and lower levels for HDL (Spearman's correlation <.05, <.0001, <.0001, <.01, resp.). Elevated ALT levels could only be detected in 2 of 33 patients with normal liver histology, but in 33 of 65 patients with NASH (Fisher's exact test $P < .0001$). Other biological data were similar in both groups (Table 3). Interestingly, there was a significant correlation between a progressing liver disease from normal liver histology over steatosis to NASH and rising HbA1c levels (Pearson's correlation $P < .01$).

Our main objective was to determine if NASH has an impact on the primary outcome after ISG, and equally important to analyze the effect of ISG on NASH.

Overall, ISG led to substantial weight loss with a BMI reduction of 44% within 1 year (Table 2). Comparing patients with normal liver histology to patients diagnosed with NASH, a significant reduction of body weight was seen in both groups with a marginally larger preoperative BMI in NASH patients (44.2 ± 5.6 kg/m^2 versus 45.9 ± 8.3 kg/m^2; NS). Nonlinear regression analysis suggested equal initial weight loss in both groups with an impaired reduction of BMI for NASH patients beginning after the 9-month followup (plateau 28.08 kg/m^2 versus 29.79 kg/m^2, Figure 1). Overall, patients with normal liver histology presented with a significantly better weight reduction (Two-way ANOVA $P < .05$). Determining HbA1c levels, 23 patients were considered diabetic prior to the operation. Histologic evaluation of

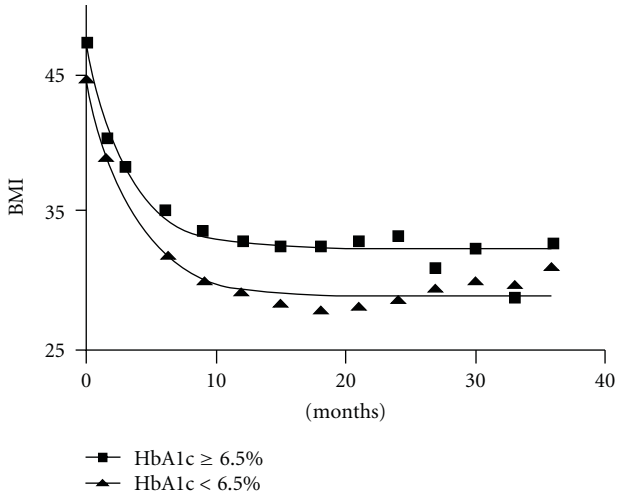

Figure 1: Course of BMI after ISG for patients with HbA1c ≥ 6.5% versus patients with HbA1c < 6.5%. Nonlinear regression 95% CI plateau 31.12 to 33.49 kg/m^2 versus 28.31 to 29.26 kg/m^2, respectively, two-way ANOVA $P < .0001$.

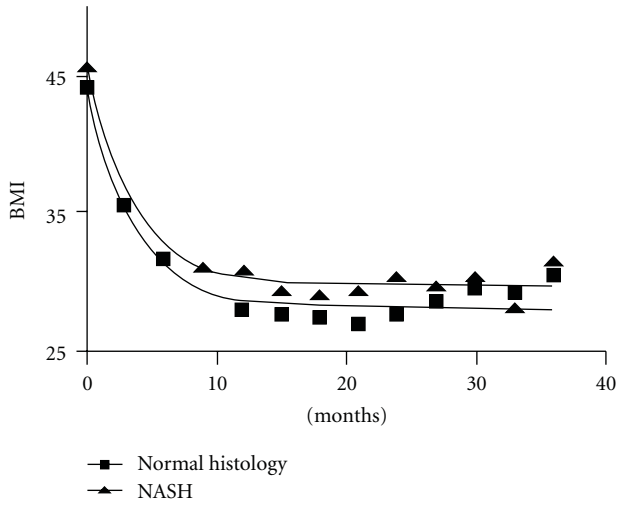

Figure 2: Course of BMI after ISG for patients with normal liver histology versus patients with NASH. Nonlinear regression 95% CI plateau 27.27 to 28.89 kg/m^2 versus 28.69 to 30.89 kg/m^2, respectively, two-way ANOVA $P < .05$.

this subgroup revealed only 2 patients with normal liver histology, 4 with steatosis, 14 with NASH, 1 with cirrhosis, 1 with fibrosis, and 1 with chronic hepatitis. There was a highly significant difference in weight reduction compared to non-diabetic patients, (two-way ANOVA $P < .001$). Nonlinear regression analysis revealed a broader difference in plateau level comparing NASH patients to patients with normal liver histology (plateau for HbA1c > 6.5% 32.30 kg/m^2 versus HbA1c ≤ 6.5% 28.79 kg/m^2, Figure 2).

Regarding biological data, ISG could significantly improve HbA1c levels in all patients (Kruskal-Wallis $P < .0001$, Table 2). In the 23 patients diagnosed with diabetes prior to sleeve gastrectomy, median HbA1c levels normalized within 12 months (HbA1c 7.1% versus 5.6%, resp.). A significant reduction of HbA1c levels could also be shown for NASH patients (Kruskal-Wallis $P < .01$). In patients who presented with normal liver histology, sleeve gastrectomy had no effect on HbA1c; however, mean HbA1c was not above the cutoff level of 6.5% at any given time point (Table 3).

Regarding lipids, ISG had a significant impact on triglyceride levels. Overall mean triglyceride levels could be reduced by 37.5% after 1 year (Table 2). In patients with NASH, initial triglyceride levels were higher than in patients with normal liver histology (1.8 ± 1.4 mmol/L versus 1.4 ± 0.7 mmol/L). Although a significant reduction of triglycerides was seen in both groups, NASH had a significantly impairing impact on triglyceride levels (two-way ANOVA $P < .05$, Table 3).

Overall, analysis of the remaining lipid profile showed no influence of ISG on cholesterol, HDL, or LDL levels (Table 2). Subgroup analysis revealed no significant impact on either cholesterol or LDL levels. HDL levels again remained unchanged for patients with normal liver histology. In contrast, NASH patients presented a significant improvement of HDL (Kruskal-Wallis $P < .0001$, Table 3).

Transaminase levels were examined as a representative test for liver function and liver injury. In preoperative data,

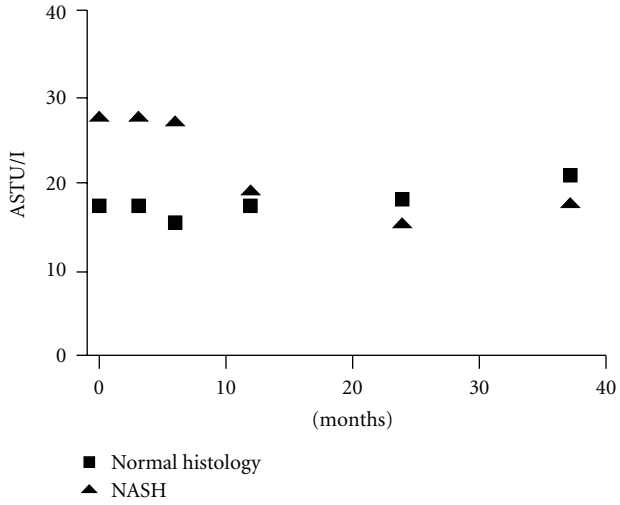

Figure 3: Course of AST levels over a 3-year followup. A significant reduction of AST levels could be shown for NASH patients (ANOVA $P < .01$).

a strong correlation could be seen between high transaminase levels and histologically diagnosed NASH (Spearman's correlation $P < .0001$ and <.0001 for ALT and AST, resp.). For patients with NASH, transaminase levels could be reduced by over 50% within 6 months, achieving similarity to the levels of patients with normal histology. This effect remained stable throughout the followup period. For patients with normal histology, transaminase levels were low and remained unchanged after sleeve gastrectomy (Figure 3).

4. Discussion

In the present study, we report a mean BMI loss of 15.3 kg/m^2 and 13.4 kg/m^2 at 12 and 39 months after ISG. This goes

Table 2: Overall clinical and biological data at 1- and 3-year followup.

Variable	Before surgery	1 year after surgery	3 years after surgery	*P* value
BMI kg/m^2	45.0 ± 6.8	29.7 ± 6.5	31.6 ± 4.4	<.0001
HbA1c %	5.8 ± 1.1	5.3 ± 0.5	5.4 ± 1.2	<.0001
AST level U/L	22.7 ± 11.9	18.14 ± 9.9	20.0 ± 10.8	<.0001
ALT level U/L	34.2 ± 21.2	19.8 ± 14.8	23.01 ± 17.2	<.0001
Triglyceride level mmol/L	1.6 ± 1.1	1.0 ± 0.4	1.0 ± 0.5	<.0001
Cholesterol level mmol/L	5.1 ± 1.1	5.1 ± 1.0	5.1 ± 1.3	NS
LDL level mmol/L	3.1 ± 0.8	3.1 ± 1.0	3.1 ± 1.6	NS
HDL level mmol/L	1.3 ± 0.5	1.26 ± 0.5	1.6 ± 0.4	<.0001

Figures presented as mean ± standard deviation; *P* value determined with Kruskal-Wallis test.

Table 3: Separate consideration of clinical and biological data at 1- and 3-year followup for patients with NASH and normal liver histology.

Variable	Before surgery		1 year after surgery		3 years after surgery		*P* value		*P* difference
	Normal liver	NASH	Normal liver	NASH	Normal liver	NASH	Normal liver	NASH	
BMI kg/m^2	44.2 ± 5.6	45.9 ± 8.3	28.2 ± 4.9	30.8 ± 8.8	30.3 ± 5.6	30.8 ± 5.3	<.0001	<.0001	<.05
HbA1c %	5.4 ± 0.5	6.1 ± 1.4	5.2 ± 0.4	5.4 ± 0.4	4.9 ± 0.4	5.2 ± 0.5	NS	<.01	<.001
AST level U/L	17.9 ± 4.8	27.9 ± 14.4	18 ± 11.2	19.2 ± 9.3	19.2 ± 11.0	17.2 ± 2.4	NS	<.01	NS
ALT level U/L	23.9 ± 9.1	42.1 ± 25.3	25.8 ± 27.3	17.5 ± 7.3	22.0 ± 16.1	12.2 ± 1.9	NS	<.0001	NS
Triglyceride level mmol/l	1.4 ± 0.7	1.8 ± 1.4	0.9 ± 0.3	1.0 ± 0.3	0.8 ± 0.3	0.9 ± 0.4	<.05	<.0001	<.05
Cholesterol level mmol/L	5.3 ± 0.8	5.0 ± 1.0	5.7 ± 1.5	5.0 ± 0.8	4.8 ± 1.1	5.2 ± 0.9	NS	NS	NS
LDL level mmol/L	3.3 ± 0.7	3.0 ± 0.8	3.6 ± 0.9	3.1 ± 0.8	2.7 ± 1.1	3.3 ± 0.7	NS	NS	NS
HDL level mmol/L	1.4 ± 0.4	1.2 ± 0.4	1.7 ± 0.7	1.5 ± 0.3	1.5 ± 0.5	1.5 ± 0.3	NS	<.0001	NS

Figures presented as mean ± standard deviation; separate *P* values for NASH and normal liver histology were determined with Kruskal-Wallis test, *P* difference determined with two-way ANOVA.

along with data recently published on 200 patients with isolated sleeve gastrectomy, reporting a weight loss from 45.5 kg/m^2 to 30.6 kg/m^2 and 31.7 kg/m^2 at 12 and 18 months, respectively, using a 48 Fr calibration tube [23]. A Greek centre, at which a 38 Fr bougie was used, reported a comparable weight loss from 45.3 kg/m^2 to 30.5 kg/m^2 for 246 patients undergoing ISG [24]. In a series of 163 patients undergoing ISG using a 36 French calibration tube, weight loss from 45.9 kg/m^2 to 33.1 kg/m^2 and 31.6 kg/m^2 was presented at 1- and 2-year followup. Bougie size does not seem to have an impact on initial weight loss; however, sleeve dilatation and a consequent regain of weight occur for larger bougies [18, 25].

A diabetic metabolism with high insulin levels and thus inadequate glucose and lipid homoeostasis is expected to lead to poor weight loss after obesity surgery. This is supported by evidence found by Caiazzo et al., who reported an impaired weight loss for diabetic patients after laparoscopic gastric banding (LAGB) at one-year followup [26]. Schauer et al. showed a comparable effect on EWL% after laparoscopic gastric bypass (LGB) [27]. Similar findings are presented by Mathurin et al., who reported a significantly lower weight loss for patients presenting with insulin resistance prior to obesity surgery (laparoscopic gastric banding and bypass) [28]. However, these findings remain controversial, as others report no difference regarding weight loss in their subgroup analysis [29].

Our data suggest a significantly impaired weight loss for patients with elevated HbA1c levels at baseline despite a good resolution of HbA1c, suggesting elevated Hb1Ac level as a predictor for poor weight loss. However, weight loss is still highly significant in this group.

Comparing weight loss of patients diagnosed with NASH during the operation to patients with normal liver histology, an impairment in loss of BMI is evident. This phenomenon can partly be explained by the impaired weight loss of diabetic patients; however, only 14 of 87 patients with NASH showed an HbA1c above 6.5%. Certainly, changes in adipokine profiling play a pivotal role in NASH pathology. New studies simultaneously evaluating NASH and adipokine profiling should further evaluate this context.

Dixon et al. examined the effect of LAGB on the histopathological features of NAFLD, performing two consecutive liver biopsies and determining plasma aminotransferase concentrations at a median followup time of 30 months. This group could show a significant correlation of aminotransferase concentrations and presence of NASH at the first and second biopsies. An aminotransferase decrease of 38% could best and significantly predict the change in NASH status [30].

Ulitzky et al. identified diabetes, ALT, and triglyceride levels as independent risk factors for NASH in multivariate analysis [31]. In our cohort, we could show a strong correlation of preoperatively determined ALT and HbA1c levels with histologically confirmed NASH. A limitation of our study is the lack of a second liver biopsy, which prevents clearly defining the effect of sleeve gastrectomy on liver histology. In the NASH subgroup, however, we could

show a significant reduction of triglyceride, HbA1c, and ALT levels, resulting in a significant reduction of NASH incidence, when applying the Ulitzky model [32]. Furthermore, patients diagnosed with NASH presented with a 39% decrease in AST level.

Lacking a distinct algorithm, NASH therapy is mainly based on the reduction of underlying risk factors. With obesity being the single most significant risk factor, weight loss surgery is widely discussed for the management of NASH. A recently conducted Cochrane research concerning this subject analyzed 21 independent studies. Among the bariatric procedures used, the majority of the studies were conducted with Roux-en-Y gastric bypass (13) and adjustable gastric banding (6). Regarding histological outcomes, eighteen studies reported a significant improvement in the degree of steatosis and eleven studies reported an improvement in histological markers of inflammation. In 11 of 16 studies lfts improved in the course of followup, aggravation could not be observed [33]. In concordance with the data presented above, our data suggest amelioration of NASH after ISG.

An amelioration of T2DM after ISG is currently under intensive discussion. Abbatini et al. showed a 80.9% resolution of T2DM after ISG over a 3-year followup [34]. In a series of 39 consecutive patients with preoperatively diagnosed T2DM undergoing ISG, Vidal et al. presented a resolution of HbA1c levels below 6.5% in 94.6% at 1-year followup. Furthermore, they could show a 50% to 80% resolution of metabolic syndrome associated figures such as triglyceride and HDL levels, suggesting ISG as a successful strategy for the management of different cardiovascular risk components of the metabolic syndrome [20]. In our subgroup analysis of patients with elevated HbA1c, the median HbA1c level was within normal ranges for 87% of patients at 1- and 3-year followup.

The mechanism of T2DM resolution after sleeve gastrectomy is widely discussed. Some believe that hormonal regulation plays a key role [20, 34]. In this regard, Peterli et al. measured higher GLP-1 levels following ISG [35]. This stimulation may be caused by a progressed gastrointestinal passage after sleeve gastrectomy. Comparison of small bowel transit time from patients after ISG to controls showed a significant reduction in transit time from 298.1 ± 9.2 to 199 ± 65.7 minutes [36]. Also, an increase on PYY can be seen after ISG with possible amelioration of glucose control [37, 38].

Overall, ISG is a restrictive operation. Weight loss is greatest in the first months after operation, so it does not seem surprising to see rapid amelioration of T2DM. In a recent, study performing LSG in nonmorbidly obese T2DM patients resulted in a resolution of T2DM in up to 50% 1 year after operation. The effect is related more to a decrease of insulin resistance because of calorie restriction and weight loss rather than to an increase of insulin secretion [19].

Besides weight loss, the amelioration of T2DM most likely seems to create the condition for resolution of NASH after ISG. Mathurin et al. proposed that remaining insulin resistance is the main risk factor for nonresolution of NASH after obesity surgery [28]. Furthermore, insulin sensitisers such as Pioglitazone and Rosiglitazone can be applied as medical treatment for NASH [10, 11]. The GLP-1 agonist Exenatide could be administered with success; however, data are scarce [39, 40].

Changes in adipokine profiling add to this effect, especially given the fact that only 14 of 87 patients with NASH had HbA1c levels above 6.5%. For adiponectin, it was demonstrated that lower adiponectin levels are associated with increased severity of hepatic inflammation. A repletion of adiponectin in mice resulted in significant improvements in steatosis and inflammation [41, 42]. For TNF-α elevated plasma concentrations, as can be detected in obese patients, mediated hepatic injury by inhibition of mitochondrial electron transport and release of reactive oxygen species that stimulate lipid peroxidation [43]. Clearly more research is needed to further clarify these correlations.

5. Conclusion

ISG conducted in 236 patients resulted in a significant and sustained weight loss comparable to data presented by others. Although a significant difference was seen between NASH patients and patients with normal histology, NASH patients showed a highly significant loss of body weight. For this subgroup, amelioration of HbA1c levels and equally important amelioration of liver histology could be demonstrated. ISG can be successfully performed in NASH patients and, as a fairly easy and safe bariatric intervention to conduct, it can be particularly recommended for this subgroup.

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W. K. Karcz and D. Krawczykowski are contributed equally to this work.

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Clinical Study

Fourteen- Year Long-Term Results after Gastric Banding

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Background. Gastric banding (GB) is a common bariatric procedure that is performed worldwide. Weight loss can be substantial after this procedure, but it is not sufficient in a significant portion of patients. Long-term rates for associated complications increase with every year of follow up, and only a few long-term studies have been published that examine these rates. We present our results after 14 years of postoperative follow up. *Methods*. Two hundred patients were operated upon form 01.02.1995 to 31.01.2009. Data collection was performed prospectively. In retrospective analysis, we analyzed weight loss, short- and long-term complications, amelioration of comorbidities and long-term outcome. *Results*. The mean postoperative follow up time was 94.4 months (range 2–144). The follow up rate was 83.5%. The incidence of postoperative complications for slippage was 2.5%, for pouch dilatation was 9.5%, for band migration was 5.5% and 12.0% for overall band removal. After 14 years, the reoperation rate was 30.5% with a reoperation rate of 2.2% for every year of follow up. Excess weight loss was 40.2% after 1 year, 46.3% after 2 years, 45.9% after 3 years, 41.9% after five years, 33.3% after 8 years, 30.8% after 10 years, 33.3% after 12 years and 15.6% after 14 years of follow up. *Conclusion*. The complication and reoperation rate after GB is high. Nevertheless, GB is still a therapeutic option in morbid obese patients, but the criteria for patient selection should be carefully evaluated.

1. Introduction

Demographic studies worldwide have shown a recent increase in the incidence of morbid obesity, and this condition has been identified as a major public health problem. Nonoperative treatments for weight loss offer limited success and have a high rate of failure. Currently, a Swedish obese subject study has shown that operative treatment of morbid obesity is the only effective therapy [1]. Besides weight reduction, the amelioration of obesity-associated comorbidities is an important consequence of surgical treatment of morbid obesity. Among the variety of restrictive and malabsorptive bariatric procedures, gastric banding has been performed in most countries worldwide. In Germany, GB (besides RYGBP) is the most performed bariatric procedure according to data from a nationwide survey [2].

Because GB has the advantages of being less invasive and a reversible procedure, it has been the procedure of choice for the treatment of morbid obesity for several years in Europe. In 2009, it was the most performed bariatric procedure in the USA.

The aim of our study was to analyze long-term results after GB from 1995 to 2009 and to assess the efficacy of GB for weight loss, improvement of comorbidities, and the incidence of complications.

2. Materials and Methods

2.1. Patients. Between February 1st 1995 and January 31st 2009, in 200 morbid obese patients, GB was performed at the Municipal Hospital in Gera, Germany. All patients were carefully selected according to IFSO-Guidelines [3].

Data collection was performed prospectively and analyzed retrospectively.

Preoperative characteristics of the patients are listed in Table 1. The operation was performed in 41 (20.5%) men and 159 (79.5%) women with a mean age of 41.5 years. The preoperative BMI was 47.9 kg/m^2. The mean BMI in men was

Table 1: Demographic data.

	Gender (%)	Age (years)	BMI (kg/m^2)
Men	20.5	41.5	52.0
Women	79.5	41.7	46.8
Total	100.0	41.5	47.9

Table 2: Operation data.

		Patients total	Mean operation time (min)
Total	(*n*)	200	128.1
Open surgery	(*n*)	39	117.7
Conversion rate	(*n*)	12	253.3
Laparoscopic approach	(*n*)	161	126.1
Perigastric approach	(*n*)	137	141.3
Pars flaccida technique	(*n*)	63	99.5

52.0 kg/m^2, which was significantly higher than in women (46.8 kg/m^2).

2.2. Operative Technique and Data. Between February 1st 1995 and June 15th 1997, 39 (19.5%) procedures had been performed by one surgeon using open approach technique.

In June 1997, we started the GB procedure with a laparoscopic technique used in 80.5% of operations (Table 2). From June 1997 to February 2001, all Lap Bands were placed using perigastric approach. This technique was used in 68.5% of patients. Conversion rate of laparoscopic technique was 7.4% during the first 100 laparoscopic operations. After introduction of the pars flaccida technique in March 2001, we performed all GB procedures (31.5%) with the pars flaccida technique by a standardized laparoscopic approach to avoid posterior slippage. The space between the left crus and the band was closed to avoid lateral slippage by a stitch between the greater curvature and the left crus. We formed a small pouch of less than 20 cc. The pouch was secured by 3 to 5 gastrogastric stitches to avoid anterior slippage.

We used 11 SAGB (SAGB; Obtech, Ethicon Endo-Surgery) and 189 Lap-Band bands (INAMED Health, Santa Barbara, CA).

2.3. Postoperative Management. The patients were followed in our hospital. The first consultation and clinical examination was performed six weeks postoperatively and then every three months for the first two years of followup. Followup examinations were performed twice a year or whenever needed after the second postoperative year.

A liquid diet was recommended for the first 5 days postoperatively. A normal diet was introduced thereafter. During each visit, a standardized fup was performed with documentation of weight, eating behavior, and a short clinical examination. Band adjustments were very rare. The band was adjusted only in cases of weight loss less than 2 kg per month or a less than 25% change in the EBWL after 3 months. In the case of discomfort from a normal diet or reflux symptoms, the filling of the band was reduced. The injection volume depended on the weight loss and the patient's tolerance as well as his or her eating behaviors.

Table 3: Reasons for band removal.

Patients	(*n*)	24
Overall removal rate	(%)	12.0
Discomfort	(*n*)	5
Excellent excessive weight loss	(*n*)	1
Migration	(*n*)	11
Slippage	(*n*)	2
During cholecystectomy (at out-of-town hospitals)	(*n*)	2
Peritonitis	(*n*)	1
Stomach wall necrosis	(*n*)	1
Epiphrenic esophageal diverticula	(*n*)	1

3. Results

3.1. Followup. Followup data were available from 83.5% of patients. The mean followup time was 94.4 (6–144) months.

3.2. Slippage. The slippage rate was 2.5% ($n = 5$). After an open approach in 3 patients, slippage occurred with a mean followup time of 10.3 (1–24) months. After laparoscopy in 2 patients, slippage occurred with a mean followup time of 18 (12–24) months. The operation was performed in all patients in perigastric approach. After introduction of pars flaccida technique, slippage rate decreased to zero.

3.3. Pouch Dilatation (PD). During the postoperative course, the great majority of our patients developed PD (9.5%, $n = 19$). A total of 12 patients were operated on by an open technique, and 7 patients underwent a laparoscopic technique. After introduction of the pars flaccida technique, pouch dilatation no longer occurred.

3.4. Band Migration. Band migration occurred in 5.5% ($n = 11$) of cases. In all patients, the operation was performed using a perigastric placement of the band.

3.5. Band Removal. Band removal was performed in 24 (12%) patients. Five patients wished to have the band removed due to discomfort. In one patient, the band was removed due to her excellent excessive weight loss. In 18 patients, the band had to be removed in case of long-term complications such as band migration in 11 cases and slippage in 2 cases. In 2 cases, the band was removed at an out-of-town hospital without any described reason after a cholecystectomy. Epiphrenic esophageal diverticula, gastric wall necrosis, and acute peritonitis were the reasons for band removal among the other patients (Table 3).

3.6. Reoperation. Among the above-mentioned complications, 61 (30.5%) patients required reoperation. In 5

Table 4: Overall reoperation rate

	(n)	(%)
Removal rate without slippage and migration	9	4.5
Slippage	5	2.5
Pouch dilatation	19	9.5
Migration	11	5.5
Disconnection	9	4.5
Reoperation due to failure	8	4.0
Patients in total	61	30.5
Reoperation rate per year of FUP		2.2

patients, the band was explanted without any substitution. The total number of patients requiring reoperation was significantly higher in the open approach group (31.3%, $n = 43$) versus the pars flaccida group (3.2%, $n = 3$). Data for reoperation are shown in Table 4. The reoperation rate was 2.2% per year.

3.7. Weight Loss after Gastric Banding. Weight loss after gastric banding is summarized in Table 5.

3.8. Changes in Comorbidities. During the postoperative period, 85.7% of patients who had previously suffered from diabetes prior to bariatric surgery could significantly reduce their insulin doses. In 14.3% of patients, diabetes was resolved, completely. Amelioration of hypertension was observed in 82.2% of patients.

3.9. Postoperative Mortality. There was no early postoperative mortality.

During the followup period, four patients (3 female and 1 male) died. The mean age of these patients was 64.1 (range 50.5–70) years. Two patients died due to their severe comorbidities 6 months and 96 months after GB. One patient died due to gastric cancer 36 months after GB [4]. Another woman died after repair of an abdominal wall hernia 132 months after band implantation.

4. Discussion

GB is beside RYGBP the most frequently performed bariatric operation worldwide. According to the data of a meta-analysis study, this procedure has been carried out in 95% of countries performing bariatric surgery [5].

When GB was introduced, the results were excellent in comparison with other restrictive bariatric procedures.

In the literature, only a few prospective randomized studies have been reported. These studies compared GB with RYGBP or/and SG. In addition, randomized trials comparing different kinds of bands (low- and high-pressure bands) were also performed. Single center studies report data with low evidence on the complication rates, outcome, and amelioration of comorbidities. In general, patient's outcome after GB is influenced by the incidence of long-term complications. These include slippage, pouch dilatation, and band migration as well as port-site complications and esophageal dilatation. Nevertheless, there are only a few studies examining long-term results with a time period longer than 10 years available in the literature.

In our clinical experience, the results obtained after 14 years show a high complication rate and a weight regain after the 5th year of followup. These data are comparable with data published by Lanthaler et al. [6]. In their data describing young patients, weight loss was very successful within the first 4 years postoperatively [6]; thereafter, the BMI increased slowly. However, the reason for weight regain after that time was not described in detail. In our experience, most of the patients change their eating behaviors to liquids and sweets leading to a high calorie intake.

Nevertheless, an improvement in obesity-related comorbidities was observed in most patients. However, complete resolution of diabetes was less than reported in a published meta-analysis [4]. Reasons for this difference may have been the high BMI of our patients and the early onset of diabetes prior to surgery.

In our retrospective examination with preoperative data collection, the majority of our patients were female, which is consistent with data from the literature [5, 6]. The BMI (47.5 kg/m^2) in our patients was higher than in most published studies due to the reimbursement problems of bariatric surgeries in Germany.

4.1. Slippage and Pouch Dilatation. Over time, the complication rates for incidences of slippage and pouch dilatation decreased. The drop in the complication rate was the result of a switch from the perigastric to a pars flaccida technique as well as the introduction of next generation bands and the development of band devices especially made for the connecting tube and the port system.

In fact, there was a decrease in the slippage rate from 3.6% in the perigastric approach to 0% in the pars flaccida technique [7].

Pouch dilatation is a long-term complication after GB. The incidence of pouch dilatation is influenced by the surgical approach (open versus laparoscopic) and the technique (perigastric versus pars flaccida). Opening the lesser sac during open band placement leads to a higher incidence of pouch dilatation than the laparoscopic approach, which creates a small retrogastric channel. Data in the literature examining the incidence of pouch dilatation are mostly heterogeneous because most studies include different approaches and techniques. Otherwise, there are only a few reports with a followup period of more than 5 years.

4.2. Band Migration. Intragastric band migration is characterized by a "silent" migration of the band into the stomach [8, 9]. Peritonitis symptoms are usually absent, and there are limited retrospective data obtained from long-term studies available [10, 11]. The incidence of band migration ranges from 0.6% to 14.4% according to the literature [10–13]. In a few studies, band migration has been considered as a complication associated with the first 2 postoperative years, which is caused by intraoperative gastric perforation [6, 14–16].

Table 5: Excess body weight loss in comparison with literature.

Author	Year	n	EWL in %							
Years of FUP			1	2	3	5	8	10	12	14
Belachewet al. [24]	2002	763	40	50.0				50		
O'Brien and Dixon[25]	2002	706	47	52	53.0	57.0				
Weiner et al. [26]	2003	984					59.3			
Martikainen et al. [27]	2004	123	36	38		30.0				
Biagini and Karam [28]	2008	591	66.7	72.6			82.3			
Strohet al. [2]	2009	200	40.2	46.3	45.9	41.9	33.3	30.8	33.3	15.6
			$n = 175$	$n = 157$	$n = 147$	$n = 122$	$n = 80$	$n = 53$	$n = 15$	$n = 1$

In our data, most patients with band migration had an uncritical uptake of nonsteroidal antirheumatic agents, bronchospasmolytic drugs, and anticoagulant substances. Specifically, 26.6% of patients were treated with nonsteroidal antirheumatic substances, 20.2% with anticoagulant substances, and 0.6% with bronchospasmolytic drugs. Therefore, in our opinion, these medications should be considered as potential causes of band migration. Chronic inflammation at the tissue area covered by the band could be a further reason for developing erosion. In our experience, band migration occurs by 30–86 months postoperatively [17]. In addition, the erosion rate has been shown to increase over the long-term followup period [18].

Band erosion can lead to a life-threatening condition in cases of upper gastrointestinal bleeding and bowel obstruction. Therefore, finding a correct diagnosis is essential. In our study, we did not see any port infection in the first 3 postoperative months and after band filling. In the literature, port infection has been reported to be the first symptom of erosion [19]. However, our own data revealed varying intervals between the onset of port infection and the occurrence of erosion.

Thus, the treatment depends on symptomatology. We favor band removal in cases of complete erosion using gastroscopy and an AMI Band Cutter (CJ Medical, Buckinghamshire, Great Britain) [17].

In the literature, a correlation of erosion rate with the band type (high-pressure versus low-pressure bands) has not been described [20].

At the end of the 1990s, repositioning of the band in cases of slippage and pouch dilatation was widely performed. However, data from our study indicated a higher incidence of gastric band migration, and data in the literature have shown disappointing results [17, 18, 21]. Thus, in cases of slippage and pouch dilatation, most published results and our findings reveal no indication for rebanding [18]. We believe band removal in cases of erosion accompanied by a simultaneous "rebanding" should not be performed because there is a potential risk of infection of the new band. This conclusion is based on the different causes of band erosion, a significantly higher migration rate following intraoperative gastric perforation and the currently available data in the literature. In addition, because of the high failure rate after band revision, a conversion to a Roux-en-Y gastric bypass or biliopancreatic diversion needs to be considered.

4.3. Amelioration of Comorbidities. According to data from a German nationwide survey on bariatric surgery, our reported patients had a significantly higher age and BMI compared with data obtained in the meta-analysis on bariatric surgery patients [5]. In addition, significantly more patients suffered from type-II diabetes mellitus and arterial hypertension in our study. Thus, the consequential higher rate of comorbidities was due to the occurrence of a severe metabolic syndrome. However, the impact of a high preoperative BMI on weight reduction needs to be investigated through a long-term study.

4.4. Reoperation Rate. The reintervention rate per year of followup in our patients was 2.2%. These data correspond to the literature, which reports a reoperation rate between 3 and 4% per year of followup [18].

4.5. Excess Weight Loss. Concerning the EBWL, the literature reports an EBWL of 47.5% from a meta-analysis study. This meta-analysis reported a progression in weight loss for the first 3 years after GB, which was followed by a stable level of weight loss out to 8 years with no detectable regain of weight [22]. Data of long-term studies with a followup time of more than five years are shown in Table 5. Studies comparing weight loss after perigastric technique to pars flaccida approaches have not shown any influence of operation technique on EWL [23]. GB results in a continuous weight loss during the first 3 years and is sustained for up to 5 years. These results are in concordance with data from the Italian Band Group, but not with weight loss patterns observed in Australian data [14, 23]. We believe the patients in our study had a lower weight loss due to the higher preoperative BMI and the higher incidence of diabetes type II. For better long-term results, we suggest interdisciplinary teamwork to reduce long-term complication rates, increase weight loss, and ameliorate comorbidities.

5. Conclusion

GB has been shown to be a safe and efficient bariatric procedure when performed by an experienced surgeon

using a standardized operation technique. The importance of a close and standardized followup by an experienced multidisciplinary team and the surgeon can result in a decreased complication rate, increased weight loss, and reduced comorbidities.

Furthermore, there are no data in the literature addressing specific criteria, which allow the selection of patients for either restrictive or malabsorptive procedures so as to improve final outcome. To guarantee long-term success after bariatric surgery and to avoid complications, particularly when following combined procedures, lifelong postoperative care is required, which is a specific concern for obesity surgery. Moreover, there is a limited amount of long-term followup data available in the literature and these are from just a few single center studies. Thus, researchers and clinicians should prospectively enroll all patients as indicated by the German multicenter observational study for quality assurance in obesity surgery. This study annually registered parameters such as weight reduction, amelioration of comorbidities, and long-term complications. Subsequently, these data were used to assess the surgical treatment of morbid obesity in Germany [2].

Abbreviations

EWL: Excess weight loss
Fup: Followup
GB: Gastric banding
PD: Pouch dilatation
RYGBP: Roux-en-Y Gastric Bypass.

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Research Article

Gastric Bypass Promotes More Lipid Mobilization Than a Similar Weight Loss Induced by Low-Calorie Diet

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Background. Recently, we found large reductions in visceral and subcutaneous fat one month after gastric bypass (GBP), without any change in liver fat content. *Purpose*. Firstly to characterize weight loss-induced lipid mobilization after one month with preoperative low-calorie diet (LCD) and a subsequent month following GBP, and secondly, to discuss the observations with reference to our previous published findings after GBP intervention alone. *Methods*. 15 morbidly obese women were studied prior to LCD, at GBP, and one month after GBP. Effects on metabolism were measured by magnetic resonance techniques and blood tests. *Results*. Body weight was similarly reduced after both months (mean: −8.0 kg, $n = 13$). Relative body fat changes were smaller after LCD than after GBP ($-7.1 \pm 3.6\%$ versus $-10 \pm 3.2\%$, $P = .029$, $n = 13$). Liver fat fell during the LCD month (-41%, $P = .001$, $n = 13$) but was unaltered one month after GBP (+12%). *Conclusion*. Gastric bypass seems to cause a greater lipid mobilization than a comparable LCD-induced weight loss. One may speculate that GBP-altered gastrointestinal signalling sensitizes adipose tissue to lipolysis, promoting the changes observed.

1. Introduction

Gastric bypass (GBP) surgery markedly reduces body weight with predominant losses of body fat and smaller reductions of lean body mass and bone mass [1]. The efficiency of GBP in treating morbid obesity is widely recognized, and its effect to improve glucose intolerance and diabetes is remarkable. In addition to the caloric restriction imposed by the operation, altered gastrointestinal hormonal signalling [2–4] is generally thought to contribute to the beneficial effect of GBP in resolving diabetes [5, 6].

In a recent study using magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS), we observed a larger relative reduction in visceral fat depot than subcutaneous fat at one month following GBP, and furthermore, an unexpected lack of change in liver fat [7]. At this time point, the morbidly obese subjects had lost an average of four BMI units, and the insulin sensitivity, as calculated by HOMA index, had improved by 34%. Fasting concentrations of free fatty acids (FFA) and beta-hydroxybutyric acid were elevated, reflecting lipolysis and flux of free fatty acids to the liver. In general, an inverse relationship between liver fat content and insulin sensitivity has been described [8, 9]. In this regard, the situation observed one month after GBP represents a notable disconnect.

Short periods of low-calorie diet (LCD) prior to gastric bypass are increasingly recommended by surgeons in order to preoperatively reduce body weight and liver volume and thereby facilitate the surgical procedure [10, 11]. To provide further insights into lipid dynamics after GBP, we evaluated a group of morbidly obese women prior to one month of preoperative LCD, at surgery, and one month after the GBP. The metabolic balance was examined by blood tests, and changes of the lipid depots were analyzed with a novel

MRI setup, including postprocessing and MRS. Significant differences between the two treatment periods with respect to the changes in total amount of body fat as well as liver fat were observed.

2. Materials and Methods

2.1. Subjects and Study Design. Fifteen morbidly obese women with the characteristics summarized in Table 1 were recruited from the waiting list for laparoscopic gastric bypass at the Department of Surgery, University Hospital in Uppsala, Sweden. None of the subjects had a specific hepatic disease disorder resulting in fatty liver or a history of alcohol abuse. The local ethics committee approved the study, and written consent was obtained from all subjects. This study was performed also to determine to what extent a one-month LCD treatment would reduce liver volume and facilitate the surgical procedures (to be published).

The study procedures were based on three main visits, separated by one month. At each of these visits, blood samples were drawn after overnight fasting. MR investigations were performed at the same day in a fed state. *First visit:* MRI/MRS was carried out in the forenoon, and the LCD treatment was initiated, after consultation with a dietician, during the afternoon. To increase motivation and thereby improve LCD compliance, a meeting with a dietician was held after approximately one week of LCD. *Second visit:* MRI/MRS was performed in the evening and the GBP the following day. *Third visit:* MRI/MRS was performed in the afternoon.

2.2. Low-Calorie Diet. LCD treatment (Modifast, Inpolin AB, Stockholm) was initiated one month prior to the GBP. All participants received information and instructions from the same physician and a trained dietician. The LCD regimen ad modum Modifast, containing 30 E% protein, 49 E% carbohydrates, and 21 E% fat, was prescribed. Total calorie intake was set to total energy expenditure, as calculated by Harris-Benedict, minus 1000 kcal/day. A lower limit of 860 kcal/day was used. The resulting total calorie intake averaged 959 ± 149 kcal/day.

2.3. Surgery. Laparoscopic gastric bypass surgery was performed at the Department of Surgery, Uppsala University Hospital according to clinical routine [12]. A five-port technique with circular stapling of the gastrojejunostomy was used. The proximal jejunum was divided 30 cm distal to the ligament of Treitz, and a 70-cm Roux-limb was created. The small bowel continuity was restored by an enteroanastomosis. The left liver lobe was then elevated by an Endopaddle (Ethicon Endosurgery, Johnson&Johnson, Cincinnati, OH). The angle of His was opened as well as the bursa five cm distal to the gastroesophageal junction on the lesser curvature. The pouch was divided by a horizontal 45 mm cutting linear stapler and two vertical 60 mm rows. The anvil of the 25 mm circular stapler was passed transorally and placed in the right-angled corner in-between the two first stale lines. The Roux-limb was passed anticolic, antigastric and anastomosed to the pouch end-to-side by the circular stapler (Covidien, Norwalk, CT). Finally, the anastomosis was checked by air under water, and the portholes were closed. The patients were given preoperative antibiotics and thromboprophylaxis by subcutaneous low-molecular-weight heparin (LMWH) for 14 days. In each recruited patient, the laparoscopic gastric bypasses could be performed and the postoperative course was uneventful, except in one patient who had the enteroanastomosis corrected.

2.4. Blood Analyses. Blood was collected after an overnight fast, and serum and plasma were prepared and stored at −70°C until analysis. Fasting plasma glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), free fatty acids (FFA), apolipoproteins A1 and B, and liver enzymes were measured with routine laboratory techniques. Insulin was analyzed with an AutoDELFIA automatic immunoassay system (Wallac Oy, Turku, Finland). Growth hormone (GH), glucagons, and NT-pBNP were determined with assays in routine use at Clinical Chemistry, Uppsala University Hospital. Beta-hydroxybutyrate was spectrophotometrically determined in plasma with an enzymatic end-point method [13]. Leptin and adiponectin were analyzed in plasma samples as previously described [14]. The homeostasis model assessment (HOMA, mmol/L) index was calculated by multiplying fasting plasma glucose mmol/L and fasting insulin mU/L and then dividing by 22.5 [15].

2.5. Magnetic Resonance Acquisition. The MR measurements were performed using a 1.5T clinical scanner (Achieva; Philips Healthcare, Best, The Netherlands) modified to allow imaging during arbitrary table speed. A special 3D gradient echo sequence was used to collect three images with different echo times (TE) from each axial slice during continuous table motion [16]. Imaging parameters were as follow: TR 5.9 ms, TE 1.36/3.22/5.09 ms, flip angle 3 degrees, elementary signal sampling field of view (FOV) (in motion direction) 112 mm, virtual FOV 530×377×2000 mm^3, and voxel size 2.07×2.07×8.00 mm^3. The table speed was set to 6.5 mm/s resulting in a whole-body scan time of 5 min, 15 sec. Shallow breathing was instructed during acquisition of the abdominal region to reduce potential respiration inducing motion artefacts. Subjects were imaged in supine position with the arms extended above the head.

To evaluate liver fat, single-volume localized ^{1}H-spectroscopy was performed in a 3 × 3 × 3 cm^3 volume of interest positioned in the right liver lobe, avoiding major vessels and bile ducts. A PRESS acquisition was used with the parameters TR/TE, 3000/44 ms, with 16 excitations without water suppression and 32 with water suppression (1024 samples, 1000 Hz bandwidth) during free shallow breathing.

2.6. Magnetic Resonance Data Processing. Whole-body water and fat images were reconstructed using the multiecho image data as previously described [17]; see Figure 1. Visceral and abdominal subcutaneous adipose tissue (VAT and SAT) was automatically measured from the reconstructed water

Table 1: Subject characteristics of the 15 females at baseline and after one month of low-calorie diet (LCD) and one month after gastric bypass (GBP).

	Baseline	Post LCD		Post GBP	
	Mean ± SD	Mean ± SD	*P* value	Mean ± SD	*P* value
Age (years)	34.7 ± 7.88				
Weight (kg)	121.3 ± 13.4	113.9 ± 12.0	<.001	105.8 ± 12.0	<.001
BMI (kg/m^2)	42.9 ± 3.02	40.3 ± 2.93	<.001	37.4 ± 2.99	<.001
Total fat Volume (L)	69.3 ± 7.55 [a]	64.3 ± 6.85 [a]	<.001	58.0 ± 7.65 [a]	<.001
Total water Volume (L)	42.9 ± 4.53 [a]	40.8 ± 3.82 [a]	<.001	38.8 ± 4.44 [a]	<.001
VAT (L)	5.31 ± 0.97 [a]	4.91 ± 0.88 [a]	.002	4.39 ± 0.73 [a]	<.001
SAT abd (L)	21.3 ± 2.93 [a]	19.8 ± 2.73 [a]	.003	17.8 ± 3.10 [a]	<.001
Liver fat (%)	9.72 ± 6.31 [a]	5.69 ± 4.24 [a]	.001	5.89 ± 3.93 [a]	.736
Liver volume (L)	2.17 ± 0.38 [a]	1.90 ± 0.23 [a]	.001	1.89 ± 0.28 [a]	.841
Liver fat Volume (mL)	218 ± 154	107 ± 78.0	<.001	111 ± 70.8	.376
Hemoglobin (g/L)	139 ± 7.54	140 ± 7.26	.845	136 ± 6.77	.099
EVF (%)	41.2 ± 2.40	40.8 ± 2.51	.458	39.3 ± 2.23	.115
Na (mmol/L)	136 ± 0.99	137 ± 1.64	.041	139 ± 1.62	.007
K (mmol/L)	3.95 ± 0.20	3.67 ± 0.25	.009	3.65 ± 0.23	.793
Creatinine (umol/L)	58.9 ± 3.75	65.9 ± 6.34	.000	58.7 ± 5.90	.003
Albumin (g/L)	41.3 ± 2.26	44.5 ± 3.23	.001	43.3 ± 2.72	.221
ALT (ukat/L)	0.43 ± 0.15	0.93 ± 0.60	.007	0.57 ± 0.26	.015
AST (ukat/L)	0.47 ± 0.11	0.62 ± 0.23	.045	0.48 ± 0.12	.034
GT (μkat/L)	0.65 ± 0.72	0.74 ± 0.81	.119	0.53 ± 0.28	.179
Glucose (mmol/L)	5.14 ± 0.67	4.73 ± 0.83	.005	5.03 ± 0.49	.082
Insulin (mU/L)	22.9 ± 7.82	17.1 ± 8.15	<.001	13.3 ± 5.52	.096
HOMA index	5.32 ± 2.18	3.63 ± 1.93	<.001	2.99 ± 1.33	.241
Growth hormone (ug/L)	0.46 ± 0.52	1.05 ± 0.97	.008	1.49 ± 1.11	.146
Glucagon (pmol/L)	73.4 ± 20.8	69.4 ± 17.9	.149	75.8 ± 18.2	.024
BNP (ng/L)	44.7 ± 27.4	46.3 ± 28.4	.847	93.7 ± 71.5	.011
Leptin (mg/L)	17.4 ± 4.91	12.8 ± 8.43	.000	10.3 ± 3.29	.001
Adiponectin (Ug/mL)	7.49 ± 2.97	8.37 ± 8.43	.302	8.13 ± 3.56	.662
Cholesterol (mmol/L)	4.79 ± 1.14	4.43 ± 1.05	.002	4.29 ± 0.92	.349
HDL (mmol/L)	1.08 ± 0.19	0.93 ± 0.15	.001	0.95 ± 0.19	.550
LDL (mmol/L)	3.07 ± 0.96	2.85 ± 1.05	.125	2.64 ± 0.84	.145
LDL/HDL	2.93 ± 1.10	3.27 ± 1.44	.092	2.95 ± 1.05	.094
Triglycerides (mmol/L)	2.17 ± 1.28	1.80 ± 0.76	.255	1.80 ± 0.54	1.000
ApoA1 (g/L)	1.33 ± 0.14	1.10 ± 0.12	<.001	1.11 ± 0.11	.829
ApoB (g/L)	0.96 ± 0.32	0.89 ± 0.28	.048	0.88 ± 0.25	.775
ApoB/ApoA1	0.73 ± 0.25	0.82 ± 0.28	.014	0.79 ± 0.23	.290
FFA (mmol/L)	0.58 ± 0.23	0.85 ± 0.33	.011	0.89 ± 0.28	.739
Beta-hydroxybutyrate (mmol/L)	0.07 ± 0.05	0.31 ± 0.28	.007	0.34 ± 0.22	.613

[a]Data from the 13 subjects who completed the MR investigations. BMI: body mass index, VAT: visceral adipose tissue volume, SAT: subcutaneous adipose tissue volume in the abdominal subvolume, EVF: erythrocyte volume fraction. ALT: alanine transaminase, AST: aspartate aminotransferase, GT: gamma glutamyltransferase, BNP: B-type natriuretic peptide, FFA: free fatty acids.
Statistical significance evaluated from baseline to post-LCD, and post-LCD to post-GBP.

and fat images as previously described [16]. Coefficients of variation (CVs) of repeated investigations have previously been determined to be 2.3% ± 2.6% and 2.3% ± 2.1%, for VAT and SAT, respectively. Estimates of total fat and water volumes were calculated by summing the signals in the fat and water fraction images, respectively [16]; see Figure 1. To reduce the effect from differences in the amount of arms and feet included in the image volumes only, manually determined subvolumes (from the top of the head to the axial slice above the feet with "smallest areas") were analyzed. The fat volume is derived mainly from adipose tissues while the water volume originates mainly from lean tissue.

Spectroscopy data was analyzed using jMRUI [18] (version 3.0; www.mrui.uab.es), employing water as internal

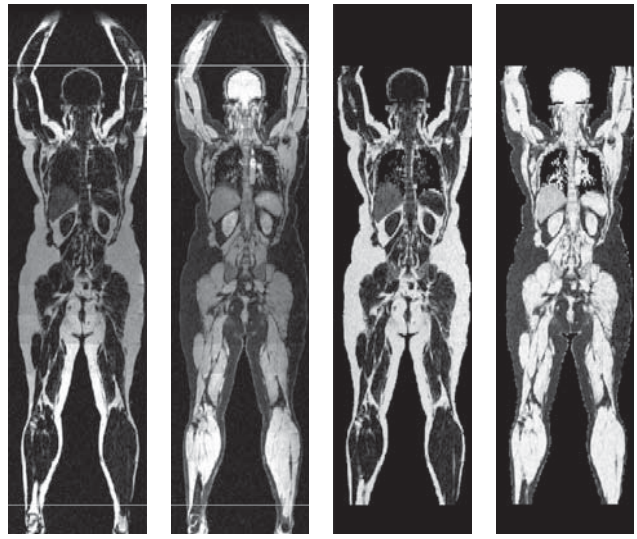

Figure 1: Illustration of image data employed from one subject included in the study. Reconstructed fat and water images are shown in (a) and (b), respectively. The horizontal lines delineate the subvolumes analysed in (c) and (d), where the fat- [fat/(fat+water)] and water-fraction [water/(fat+water)] images calculated and used to estimate total fat and water volumes are shown, respectively. Note that the intensity variations seen in (a) and (b) are removed by the use of fraction images. The intensity in each pixel estimates its absolute fat and water contents, and by integrating the pixel contents, total volumes are obtained. Note that fat infiltration of the liver (greyish and measured to approximately 25%) can be seen in (c).

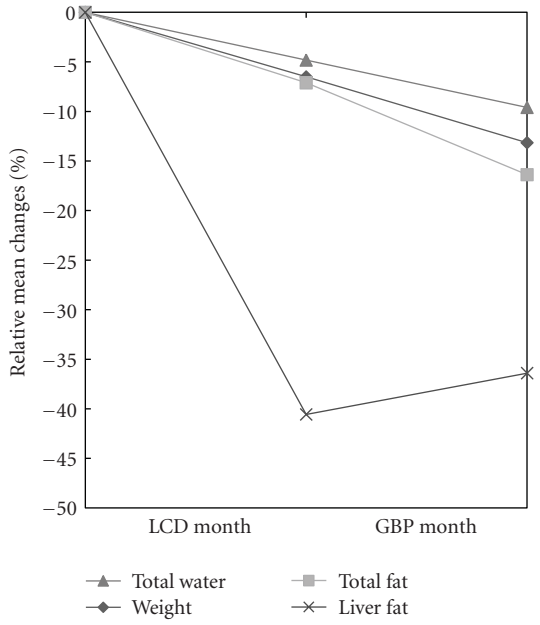

Figure 2: Relative mean changes of weight, total fat, total water, and liver fat during the LCD and the GBP months ($n = 13$).

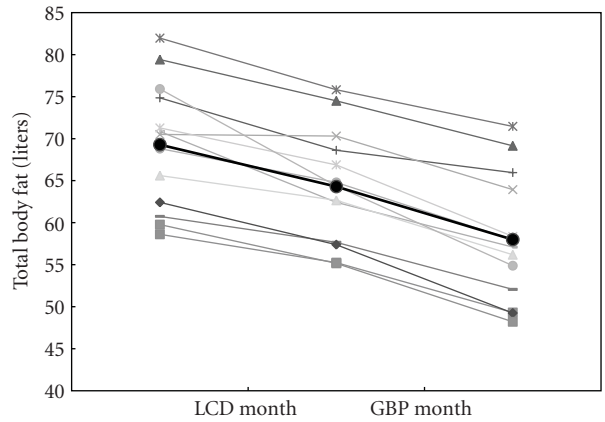

Figure 3: Individual total body fat volumes measured using prior to one month of LCD, at surgery, and at one month postGBP ($n = 13$). Mean body fat volume is illustrated by the thicker line.

reference, facilitating liver fat measures in percent. Spectral line intensities were determined by time domain fitting, using the nonlinear least-squares AMARES algorithm [19]. No spectral preprocessing was applied.

Liver volumes were assessed by manual segmentation in axial slices of the reconstructed water images by two experienced operators using the software ImageJ (version 1.40 g, http://rsbweb.nih.gov/ij/). Average liver volumes were used. The liver fat assessment using MRS gives liver fat concentration (%). If this concentration changes, one does not know if that is a result of change in liver fat content or if the total liver volume has changed for other reasons. Since liver volume was also assessed in this study, the total liver fat volume was calculated by multiplying concentration and volume.

2.7. Statistics Analysis. Two-sided, paired t-tests were used to test for differences between absolute values between the time

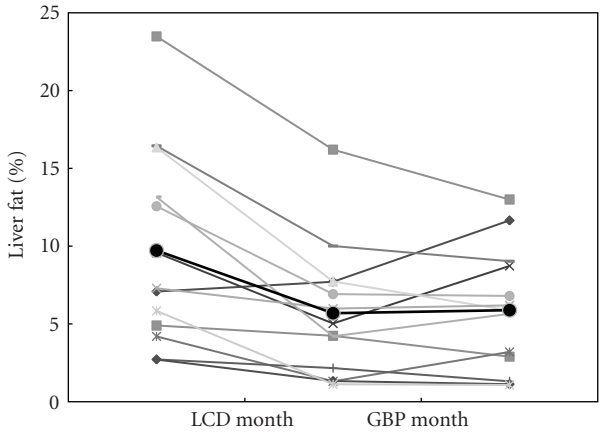

Figure 4: Liver fat concentrations (%) determined using MRS at the three time points ($n = 13$). The thicker line illustrates mean liver fat concentration.

points in Table 1 and between relative changes in Table 2. P values of <.05 were considered statistically significant.

3. Results

The patients lost comparable amounts of body weight during the two months, on average 7.47 ± 2.59 kg during the first month with LCD and 8.09 ± 1.70 kg during the postoperative month ($P = .497/.148$, for absolute/relative changes, resp., $n = 15$). The weight reductions in 13 subjects successfully analyzed with MRI/MRS were 8.03 ± 2.28 and 8.03 ± 1.76 kg, respectively. The relative decrease in total body fat was greater during the GBP month (from −7.1% ± 3.6% to −10.0 ± 3.2%, $P = .029$, $n = 13$). The reductions in the visceral and abdominal subcutaneous fat depots were on average −7.3% and −6.6%, respectively, after LCD and −10.3% and −10.3% after GBP. The estimated water volumes showed similar changes during the LCD and the GBP month, −4.8% and −5.0%, respectively.

The measurements at the different time points are shown in Table 1 and the relative changes in Table 2. The MRI/MRS data is reported for the 13 subjects successfully analysed at all three time points. One subject cancelled all MR investigations and another subject cancelled her third. The relative mean changes in weight, total fat and water volumes and also in liver fat are shown in Figure 2. The absolute fat volumes and liver fat measurements are shown in Figures 3 and 4, respectively.

Liver volume decreased significantly over the LCD-month but not during the GBP month. Corresponding changes in liver fat were determined to be −40.6% ± 25.3%, ($P = .001$) and +12.4% ± 51.7%, ($P = .736$).

Biochemically, alterations in fasting glucose and insulin levels took place during the two periods, resulting in increased insulin sensitivity as reflected by the HOMA indices. Free fatty acids concentrations increased from 0.58 to 0.85 mmol/L after LCD and to 0.89 mmol/L one month after the operation. The beta-hydroxybutyrate concentrations increased by several folds during LCD, from a mean of 0.07 to 0.31 umol/L and remained elevated one month after surgery, 0.34 umol/L.

The patients studied had, at baseline, cholesterol and apolipoprotein A and B within the normal reference ranges and slightly elevated triglycerides. After diet and surgery, changes within the reference ranges were noted. Leptin fell during both LCD and GBP. Adiponectin tended to increase after LCD and was not further altered over the postoperative month. Mean values of growth hormone prior to LCD, at surgery, and at one month after GBP were 0.46, 1.05, and 1.49 ug/L, glucagon 73, 69, and 76 pmol/L, and NT-pBNP 45, 46, and 94 ng/L, respectively.

Alanine transaminase (ALT) increased after LCD from 0.43 to 0.93 μkat/L and fell into the normal range to 0.57 the month after surgery. Aspartate aminotransferase (AST) and gamma glutamyltransferase (GT) showed similar patterns of lesser magnitude.

4. Discussion

The extent of weight loss after the month with LCD and that at the first month after GBP were similar, yet the mobilization of body fat was larger after the operation than after the LCD. Furthermore, the amount of liver fat was not lowered one month after GBP, which it was after the month of LCD. Free fatty acids and the beta-hydroxybuturate concentrations were elevated and tended to be higher one month after GBP, compared to after one month of LCD. Collectively, the findings indicate a more marked flux of fatty acids from the adipose tissues to the liver and subsequent incorporation into triglycerides during the month after GBP compared to the LCD month.

A limitation of the design used in this study is that the effects seen during the month after GBP are not only influenced by the GBP surgery but also by effects of the preoperative LCD. The restriction of the caloric intake during the preoperative LCD month most likely reduces the initial lipolytic effects seen after GBP. Despite this, the results from the current study indicate instead an increased lipolysis after GBP.

The observation of unchanged liver fat one month after surgery is in good agreement with our previous prospective report on lipid mobilization over a year-long period after GBP, in which at one month after surgery, there likewise was no change in liver fat, despite marked changes in subcutaneous and visceral depots [7]. The patients of the previous study were also of female gender and had similar age, weight, and BMI (35 years range 22–47, 122 ± 13 kg, and 43.7 ± 4.1 kg/m^2, resp.) as the subjects of this study. Thereby, they can be regarded as a historical control group of obese subjects undergoing gastric bypass without a preoperative LCD period. These subjects lost, on average, 11.0 kg body weight and 8.4 liters of adipose tissue (also assessed using whole-body MRI) the first month after GBP. This should be compared to the reductions of 7.4 kg body weight and 5.0 liters of adipose tissue measured after the LCD month in the current study. It seems likely that the lesser degree of weight loss during the month after GBP in the present study

Table 2: Relative changes (%) over the low-calorie diet (LCD) and postGBP periods.

	LCD month	GBP month	*P* value
Weight / BMI	−6.08 ± 1.77	−7.17 ± 1.60	.148
Total Fat Volume	−7.11 ± 3.58 [a]	−10.0 ± 3.19 [a]	.029
Total Water Volume	−4.82 ± 2.29 [a]	−4.98 ± 2.69 [a]	.898
VAT	−7.28 ± 6.92 [a]	−10.3 ± 6.40 [a]	.326
SAT abd	−6.55 ± 6.73 [a]	−10.3 ± 5.32 [a]	.171
Liver Fat	−40.6 ± 25.3 [a]	+12.4 ± 51.7 [a]	.011
Liver Volume	−12.0 ± 7.54 [a]	−0.40 ± 8.33 [a]	.013
Liver Fat Volume	−47.2 ± 24.5	13.6 ± 55.9	.006
Hemoglobin	0.27 ± 3.73	−2.72 ± 6.17	.195
EVF	−0.87 ± 5.04	−3.27 ± 7.81	.409
Na	0.79 ± 1.34	1.32 ± 1.62	.473
K	−6.78 ± 8.83	−0.19 ± 10.1	.184
Creatinine	11.9 ± 8.32	−10.4 ± 11.0	<.001
Albumin	7.84 ± 7.08	−2.32 ± 7.90	.009
ALT	138 ± 180	−26.5 ± 29.3	.007
AST	43.1 ± 88.2	−16.4 ± 25.5	.047
GT	14.9 ± 38.1	−3.81 ± 39.3	.282
Glucose	−8.01 ± 8.53	8.01 ± 13.2	.008
Insulin	−27.0 ± 20.1	−12.5 ± 43.8	.339
HOMA index	−32.2 ± 22.2	−2.47 ± 60.2	.141
Growth hormone	348 ± 621	422 ± 1070	.835
Glucagon	−3.54 ± 17.1	10.6 ± 15.3	.055
BNP	34.1 ± 97.5	146 ± 173	.078
Leptin	−25.7 ± 14.6	−18.3 ± 19.9	.182
Adiponectin	16.0 ± 47.3	76.8 ± 310	.504
Cholesterol	−7.11 ± 7.31	−2.13 ± 11.4	.269
HDL	−13.3 ± 12.5	2.46 ± 13.3	.023
LDL	−6.91 ± 17.1	−5.23 ± 15.1	.830
LDL/HDL	12.4 ± 21.2	−7.36 ± 16.6	.043
Triglycerides	−6.01 ± 37.8	7.10 ± 29.7	.409
Ap-lipA1	−16.6 ± 8.11	1.09 ± 9.80	.001
Ap-lipB	−5.97 ± 13.0	0.15 ± 10.8	.268
ApB/A1	15.3 ± 20.6	−2.30 ± 14.4	.050 (.0497)
FFA	74.4 ± 109	20.9 ± 589	.186
Beta-hydroxybutyrate	482 ± 651	103 ± 220	.080

[a]Data from the 13 subjects who completed the MR investigations. BMI: body mass index, VAT: visceral adipose tissue volume, SAT: subcutaneous adipose tissue volume in the abdominal subvolume, EVF: erythrocyte volume fraction. ALT: alanine transaminase, AST: aspartate aminotransferase, GT: gamma glutamyltransferase, BNP: B-type natriuretic peptide, FFA: free fatty acids.
Statistical significance evaluated from differences in relative changes over the LCD and GBP months.

is influenced by the prior weight loss that took place during the preoperative LCD month.

The similar weight losses measured in this study suggest that the caloric intakes over the two periods were comparable. Average caloric intake three to six months after gastric bypass surgery has been estimated to be 960–1000 kcal/day [20, 21], that is, close to that of the LCD employed (average 959 kcal/day). The patients were advised a diet with an energy content and macronutrient composition similar to that of the LCD. After an operation, patients typically take multiple, small meals in order to lower a risk of dumping and/or postprandial hypoglycemic episodes. We did not collect dietary records in attempts to calculate detailed energy, protein, lipid, and carbohydrate intake.

To account for the larger reduction in fat after GBP compared to the LCD period but similar weight losses during the two periods, a somewhat larger reduction in nonfat compartments should have taken place during the LCD month. With the MRI technique used, only two compartments are visualized as images generated from protons in fat and water molecules. The fat volumes primarily reflect the adipose tissue even though bone marrow and fatty infiltrated tissues/organs also contribute. The water volumes reflect the nonfat lean tissue of muscles, organs, and brain. Bone

marrow and water content in adipose tissue also contribute. In this study, the change in water volumes did not differ between the LCD and GBP months, in contrast to the change in fat volumes. A limitation of our study is that we did not perform any measurements by DEXA, which would provide information on changes in lean tissue and bone.

There was an increase in liver enzymes during LCD and a trend towards normalization over the month following the operation. In general, morbid obesity is associated with some degree of steatohepatitis and elevation of liver enzymes, changes that improve upon long-term weight loss [22]. Marked diet-induced weight loss over shorter periods of time has been found to increase liver enzymes [23, 24] by mechanisms that are not fully understood [25]. In some studies, the increase in enzymes has been transitory and suggested to reflect an adaptation of the hepatocytes. In this study, the difference in enzyme levels one month after LCD compared to one month after GBP might reflect such adaptation, as the daily average intake and composition of nutrients supposedly were similar during the two periods. In support of such notion, we have observed that patients operated with gastric bypass without a preoperative LCD treatment and examined one month after the operation displayed elevated liver enzymes (unpublished).

Any caloric restriction causes a breakdown of fat, driven by hormone-sensitive lipase in adipocytes and by lipoprotein lipase in heart and skeletal muscles. Lipolysis in white adipose tissue is mainly controlled by the antilipolytic effect of insulin and a stimulatory effect of norepinephrine released from sympathetic nerve endings and acting via beta-adrenergic receptors [26]. Lipolysis is also influenced by humoural factors such as circulating catecholamines, growth hormone, thyroid hormones, and glucagon. Recently, natriuretic peptides have been added to the list of lipolytic hormones [27]. In this study, GH baseline concentrations increased throughout and thereby conceivably contributed to promote lipolysis. Increases in GH levels after GBP have been described by us [28] and others [29]. The BNP levels were unchanged during the LCD month while they were seen to increase during the GBP month. We are not aware of any prior reports of BNP levels determined after gastric surgery.

In a recent report, centrally administered GLP-1 was found to stimulate sympathetic flow and lipolysis of body fat [30]. An increased secretion of GLP-1 is a prominent finding in patients who have been operated with gastric bypass [4, 31]. Hypothetically, a central GLP-1 mechanism might play a role for the enhanced lipolysis after GBP. Glucagon stimulates glycogenolysis and fatty acid oxidation in the liver and has been shown also to stimulate lipolysis in adipocytes [32, 33]. In patients operated with GBP, a remarkable response with a rise in glucagon following food intake has been observed [34, 35]. Possibly, postprandial increases in glucagon levels might contribute to the enhanced mobilization of body fat after GBP surgery.

In conclusion, the mechanism behind an enhanced lipolysis after GBP seems multifactorial. The caloric restriction imposed by the surgical procedure is the main driver of lipolysis, to which altered gastrointestinal signalling, for example, meal-stimulated increases in GLP-1 and glucagon, and sympathetic nerve outflow to the adipose tissue in autonomic nerves conceivably contribute. It is likely that FFAs are utilized as energy source in heart and skeletal muscle and lower the need for glucose, which in turn lowers insulin secretion in the nonfed state and thereby promotes lipid mobilization. Lipolysis might also be stimulated by increased fasting levels of lipolytic hormones, for example, growth hormone, BNP, catecholamines. An increased flux of FFA from adipose tissues depots would promote the maintained triglyceride levels in the liver one month after GBP. To obtain further insights into the phenomenon of enhanced lipolysis, studies of diurnal hormone and catecholamine dynamics could be of interest.

Acknowledgments

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Conflict of Interests

The authors declare that they have no conflicts of interests.

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Review Article

Safety, Effectiveness, and Cost Effectiveness of Metabolic Surgery in the Treatment of Type 2 Diabetes Mellitus

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Remission of type 2 diabetes mellitus with metabolic surgery is a field of active investigation and development. The extraordinary results obtained in diabetic patients with BMI > 35 kg/m^2 have led investigators to query if similar results could be achieved in patients with BMI < 35 kg/m^2. A few studies have been recently conducted to evaluate the safety, effectiveness, and cost effectiveness of bariatric surgery in diabetic patients with BMI BMI < 35 kg/m^2. However, stronger evidence would be required before insurance coverage is extended for bariatric surgery to all type 2 diabetic patients, in addition to those with BMI ≥ 35 kg/m^2 for whom eligibility is already established. In addition, the hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery are yet to be determined. This paper will review the evidence about safety, effectiveness, and cost effectiveness of bariatric surgery in type 2 diabetes mellitus remission and the potential socioeconomic impact of offering bariatric surgery to diabetic patients with BMI BMI < 35 kg/m^2.

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is a major cause of morbidity and mortality around the world. The prevalence of T2DM in the US was 8% in 2008 [1]. According to the American Diabetes Association, the total estimated cost of diabetes in 2007 was $174 billion [2]. The traditional goal for medical treatment of T2DM has been to delay the appearance of end-organ complications. In contrast, surgical treatment for T2DM is currently being evaluated as a potential "cure" for T2DM. Several studies have demonstrated that obese diabetic patients who undergo bariatric surgery experience complete T2DM remission, maintaining euglycemia without medications for more than 10 years [3]. Additionally, following some gastrointestinal (GI) procedures, T2DM resolves within days to weeks, long before the occurrence of major weight loss [4]. Bariatric surgery as a modality to treat obesity in the US is reserved for patients with BMI ≥ 35 kg/m^2 and the presence of serious comorbidities (T2DM, moderate or severe obstructive sleep apnea (OSA), pseudotumor cerebri, and severe steatohepatitis), or BMI > 40 kg/m^2 and minor comorbidities (mild OSA, hypertension (HTN), insulin resistance, glucose intolerance, dyslipidemia, impaired quality of life, or activities of daily living) [5]. However, some recent publications also suggest that conventional bariatric surgery results in remission of T2DM in patients with BMI < 35 kg/m^2 [6, 7]. In addition, novel antidiabetic GI procedures have been developed by groups outside the US to treat T2DM patients with BMI < 35 kg/m^2 [8, 9]. In view of the growing enthusiasm for surgical interventions to treat T2DM, the 1st diabetes surgery summit (DSS) was held in Rome in March 2007 to develop guidelines for the use of GI surgery to treat T2DM. The DSS position statement included that a surgical approach may be appropriate as a nonprimary alternative to treat inadequately controlled T2DM in suitable surgical candidates with BMI 30–35 kg/m^2 and that novel GI surgical techniques (duodenal-jejunal bypass, ileal interposition, sleeve gastrectomy, and endoluminal sleeves) should be used only in the context of IRB-approved trials [10]. The growing interest in offering surgical therapy to T2DM patients with BMI < 35 kg/m^2 within the world surgical community has not yet spread to the US surgical community. A major limitation for the development of the field of metabolic surgery in the US is

the absence of insurance coverage for bariatric procedures in T2DM patients with BMI < 35 kg/m^2. Several studies have demonstrated that adjustable gastric banding (AGB) and Roux-en-Y gastric bypass (RYGB) are cost effective at 5-year followup in comparison to conventional treatment (CT) for T2DM in patients with BMI ≥ 35 kg/m^2 [11–14]. One study has also shown cost effectiveness of bariatric surgery in patients with T2DM and BMI ≥ 30 and <40 kg/m^2 [15]. The purpose of this paper is to review the existing literature about safety, effectiveness, and cost effectiveness of bariatric surgery in T2DM remission and the potential socioeconomic impact of offering bariatric surgery to diabetic patients with BMI < 35 kg/m^2.

2. Morbidity and Mortality of Bariatric Surgery

Trends in mortality in bariatric surgery were reported by Buchwald et al. [16] in 2007. This systematic review and meta-analysis included 360 studies for a total of 85,000 patients with a mean BMI of 47.4 kg/m^2. In contrast to the popular belief that bariatric surgery is a drastic measure to treat obesity because of its associated risks, this study demonstrates that mortality from laparoscopic RYGB (LRYGB) is comparable to mortality from laparoscopic cholecystectomy, which is considered to be a safe operation by the general public. Mortality rates from LRYGB in this study were 0.16% within 30 days and 0.09% from 30 days to 2 years. Similarly, a 30-day postoperative mortality of 0.3% after RYGB or laparoscopic AGB (LAGB) was reported by the Longitudinal Assessment of Bariatric Surgery (LABS) Consortium, a 10-center prospective trial involving 4776 patients undergoing bariatric surgery. This study also reported a composite end point of death or serious complication of 4.1% within 30 days after surgery [17]. Gastric bypass surgery has been associated with decreased long-term total mortality in severely obese patients, as demonstrated by Adams et al. [18] in 2007. This retrospective cohort study compared the long-term mortality of 7925 patients who underwent gastric bypass surgery matched for age, sex, and BMI to severely obese control subjects who applied for driver's licenses, using the National Death Index. During a mean followup of 7.1 years, adjusted long-term mortality from any cause in the surgery group decreased by 40%, as compared with that in the control group (37.6 versus 57.1 deaths per 10,000 person-years, $P < .001$); cause-specific mortality in the surgery group decreased by 56% for coronary artery disease (2.6 versus 5.9 per 10,000 person-years, $P = .006$), by 92% for diabetes (0.4 versus 3.4 per 10,000 person-years, $P = .005$) and by 60% for cancer (5.5 versus 13.3 per 10,000 person-years, $P < .001$) However, rates of death not caused by disease, such as accidents and suicide, were 58% higher in the surgery group than in the control group (11.1 versus 6.4 per 10,000 person-years, $P = .04$). Sjöström et al. [19] also reported a survival benefit of bariatric surgery over conventional treatment for obesity. This prospective controlled study compared 2010 patients who underwent bariatric surgery (AGB: 376; RYGB: 265; vertical banded gastroplasty: 1369) to 2037 patients who received conventional treatment (matched control group). The unadjusted overall hazard ratio was 0.76 in the surgery group ($P = .04$), as compared with the control group, and the hazard ratio adjusted for sex, age, and risk factors was 0.71 ($P = .01$). The most common causes of death were myocardial infarction and cancer. Perioperative complications were experienced by 13% of patients, which included bleeding (0.9%), thromboembolic events (0.8%), wound complications (1.8%), abdominal infection (2.1%), pulmonary symptoms (6.2%), and miscellaneous (4.8%). Postoperative complications requiring reoperation were experienced by 2.2%.

3. Effectiveness of Bariatric Surgery in T2DM Remission in Patients with T2DM and BMI ≥ 35 kg/m^2

The bariatric literature has consistently demonstrated a significant effect of bariatric surgery in T2DM remission in patients with BMI ≥ 35 kg/m^2. T2DM resolution or remission has usually been defined as HbA_{1C} values ranging from <6% to <7% in the absence of antidiabetic medications. The prospective, controlled Swedish Obese Subjects Study by Sjöström et al. [20] reported a significant difference in the prevalence of diabetes between the surgery group and the conventional treatment group (2 years: 1% versus 8%, $P < .001$; 10 years: 7% versus 24%, $P < .001$). Participants who underwent surgery were more likely to recover from diabetes (2 years: 72% versus 21%, $P < .001$; 10 years: 36% versus 13%, $P < .001$). A systematic review and meta-analysis of bariatric surgery by Buchwald et al. [3] included 136 studies for a total of 22,094 patients; mean baseline BMI was 46.9 kg/m^2 (32.3–68.8). The studies that reported resolution of T2DM included a total of 1846 patients. Diabetes resolution rates were 98.9% after biliopancreatic diversion (BPD), 83.7% after RYGB and 47.9% after AGB. Another systematic review by Levy et al. [21] confirmed that bariatric surgery was highly effective in obtaining weight reduction in morbidly obese patients of up to 60% of the excess weight, along with resolution of preoperative diabetes in more than 75% of the cases.

4. Cost Effectiveness of Bariatric Surgery in Patients with T2DM and BMI ≥ 35 kg/m^2

Ackroyd et al. [11] established a payer-perspective cost effectiveness and budget impact (BI) model of AGB and RYGB versus CT in patients with BMI ≥ 35 kg/m^2 and T2DM in Germany, UK, and France (Table 1). The base case time scope was 5 years, and the annual discount rate for utilities and costs was 3.5%. In Germany and France, both RYGBP and AGB yielded a cost decrease and were thus dominant in terms of incremental cost-effectiveness ratio (ICER) compared to CT. In the UK, RYGBP and AGB yielded a cost increase but were cost-effective. The authors concluded that, in patients with T2DM and BMI ≥35 kg/m^2, AGB and RYGBP are effective at 5-year followup in cost-saving in Germany and France and are cost effective in the UK with a moderate BI versus CT. Anselmino et al. [12] replicated this model in Austria, Italy, and Spain. In Austria

Table 1: Cumulative cost per patient over 5 years including cost of therapy, cost of complications, and cost of prevalent T2DM [11].

Study	Conventional therapy	Laparoscopic adjustable gastric banding	Laparoscopic gastric bypass
Germany	€17197	€13610	€12166
France	€19276	€14796	€13399
United Kingdom	£7083	£9072	£9121

Table 2: Summary results for the base-case analysis [13].

35-year time horizon	Bariatric surgery	Medical management	Difference
Life expectancy, y	11.536 (0.424)	10.870 (0.187)	+0.6666 (0.460)
Quality-adjusted life expectancy, y	6.782 (0.479)	5.883 (0.105)	+0.8999 (0.493)
Total costs (2007, dollars)	83,482 (3191)	63,722 (2296)	+19,760 (3861)
Management	9117	11,621	−2504
Cardiovascular disease	34,811	37,824	−3013
Renal	3592	4539	−947
Eye	3769	3963	−194
Ulcer/neuropathy/amputation	5915	5776	+139
Surgery	23,131	0	+23,131
Incremental cost per life-year gained (2007, dollars)	—	—	29,676
Incremental cost per QALY gained (2007, dollars)	—	—	21,973

and Italy, both AGB and RYGBP are cost saving and are thus dominant in terms of ICER compared to CT. In Spain, AGB and RYGBP yield a moderate cost increase but are cost effective, assuming a willingness to-pay threshold of 30,000 euro per quality adjusted life year (QALY). Under worst-case analysis, AGB and RYGBP remain cost saving or around breakeven in Austria and Italy and remain cost effective in Spain.

A similar study was conducted in the US by Ikramuddin et al. [13]. The analysis showed that compared with medical management, RYGB surgery for obese diabetic patients has a cost effectiveness ratio of $22,000 per QALY gained (Table 2). The authors concluded that, in the US, RYGB surgery is cost-effective from a payer's perspective. From a third-party payer's perspective, Crémieux et al. [14] evaluated the return on investment for bariatric surgery in the United States. Morbidly obese patients aged 18 years or older were identified in an employer claims database of more than 5 million beneficiaries. Each of the 3651 patients who underwent bariatric surgery during this period was matched to a control subject who was morbidly obese and never underwent bariatric surgery. Total healthcare costs for bariatric surgery patients and their controls were recorded for 6 months before surgery through the end of their continuous enrollment. The study suggested that the total cost of laparoscopic bariatric surgery is fully recovered after 25 months. These returns on investment result from reductions in prescription drug costs, physician visit costs, and hospital costs (including emergency department visits and inpatient and outpatient visits). The reduced costs are associated with multiple major diagnosis categories, including diabetes mellitus, coronary artery disease, hypertension, and sleep apnea. Similarly, a review of 15 years of experience in a French university hospital reported that bariatric surgery is cost effective after 3.5 years [22].

5. Effectiveness of Bariatric Surgery in T2DM Remission in Patients with BMI < 35 kg/m^2

Recent publications suggest that the beneficial effects of bariatric surgery in type 2 diabetic patients are not limited to patients with BMI ≥ 35 kg/m^2. O'Brien et al. [23] completed a randomized clinical trial that included 80 adults with BMI between 30 kg/m^2 and 35 kg/m^2. They reported a significant resolution of the metabolic syndrome in patients undergoing laparoscopic adjustable gastric banding. Patients in this study were assigned to a program of very-low-calorie diets, pharmacotherapy, and lifestyle change for 24 months (non-surgical group) or to placement of a laparoscopic adjustable gastric band. The metabolic syndrome was initially present in 38% of patients in each group and was present in 24% of nonsurgical patients and 3% of surgical patients at the completion of the study ($P < .002$). A second nonblinded randomized controlled trial was conducted by Dixon et al. [24] from December 2002 through December 2006, which included 60 obese patients with BMI >30 and <40 recently diagnosed with type 2 diabetes. CT reflected the best available medical management including consultation with a diabetes educator every 6 weeks, medical therapies as determined by an experienced endocrinologist specialized in diabetes, and lifestyle modification programs. In addition to all aspects of CT, surgical therapy involved the placement

of a LAGB. Remission of T2DM (fasting glucose level <126 mg/dL and HbA_{1C} < 6.2% while taking no glycemic therapy) was observed in 73% of patients in the surgical group and in 13% of patients in the conventional therapy group. Remission of T2DM was related to weight loss and lower baseline HbA_{1C}.

Cohen et al. [25] also demonstrated that obese patients with a BMI of <35 kg/m^2 and severe comorbidities can benefit from LRYGB. A total of 37 patients (mean BMI 32.5 kg/m^2) who had tried to lose weight with no success and had been undergoing clinical treatment with no resolution or improvement of their life-threatening comorbidities (T2DM, HTN, lipid disorder, GERD, and sleep apnea) underwent LRYGB. After extensive explanation and documentation, the Brazilian insurance companies approved the procedure in 3 cases, and international (nonAmerican) insurance companies approved the procedure in 4 cases. The followup range was 6–48 months. The mean excess weight loss was 81%. Thirty-six patients had total remission of their comorbidities. One patient still had mild hypertension, but with a reduction in the number of antihypertensive drugs used. No surgery-related complications were reported.

Remission of T2DM in patients with BMI < 35 kg/m^2 after LRYGB was also published by Lee et al. [26]. This was a retrospective study of prospectively collected data that included 201 patients with impaired fasting glucose or T2DM. Among the 201 patients, 44 (21.9%) had BMI < 35 kg/m^2 and 157 (78.1%) had BMI ≥ 35 kg/m^2. One year after surgery, fasting plasma glucose returned to normal in 89.5% of BMI < 35 kg/m^2 T2DM and 98.5% of BMI ≥ 35 kg/m^2 patients ($P = .087$). The treatment goal of T2DM (HbA_{1C} < 7.0%, LDL < 150 mg/dl, and triglyceride <150 mg/dl) was met in 76.5% of BMI < 35 kg/m^2 and 92.4% of BMI ≥ 35 kg/m^2 patients ($P = .059$). Major perioperative complications occurred in 4.5% of patients with BMI < 35 kg/m^2 and no perioperative mortality. The authors concluded that despite a slightly lower response rate of T2DM treatment, patients with include BMI < 35 kg/m^2 still had an acceptable T2DM resolution, and this treatment option can be offered to this group of patients. A recent study demonstrated T2DM remission and reduced cardiovascular risk after gastric bypass in Asian Indians with BMI < 35 kg/m^2. A total of 15 consecutive patients with T2DM and a BMI of 22–35 kg/m^2 underwent RYGB. The data were prospectively collected before surgery and at 1, 3, 6, and 9 months postoperatively. The BMI decreased postoperatively by 20%, from 28.9 ± 4.0 kg/m^2 to 23.0 ± 3.6 kg/m^2 ($P < .001$). All antidiabetic medications were discontinued by 1 month after surgery in 80% of the subjects. At 3 months and thereafter, 100% were euglycemic and no longer requiring diabetes medication. The fasting blood glucose level decreased from 233 ± 87 mg/dL to 89 ± 12 mg/dL ($P < .001$), and the HbA_{1C} decreased from 10.1% ± 2.0% to 6.1% ± 0.6% ($P < .001$). Their waist circumference, presence of dyslipidemia, and hypertension improved significantly. The predicted 10-year cardiovascular disease risk (calculated using the United Kingdom Prospective Diabetes Study equations) decreased substantially for fatal and nonfatal coronary heart disease and stroke. No mortality, major surgical morbidity, or excessive weight loss occurred [27].

6. Cost Effectiveness of Bariatric Surgery in Patients with T2DM and BMI < 35 kg/m^2

Cost effectiveness of surgically induced weight loss for the management of T2DM has also been demonstrated for patients with BMI >30 and <40 kg/m^2. Keating et al. [15] published the within-trial cost efficacy of surgical therapy relative to CT for achieving remission of recently diagnosed T2DM in class I and II obese patients. The efficacy results were derived from a 2-year randomized controlled trial conducted by Dixon et al. [24]. Trial intervention costs included LAGB surgery, mitigation of surgical complications, outpatient medical consultation, pathology, medical investigations, weight loss assisted therapies, and medication. During the first 6 months of the trial, mean intervention costs per patient were approximately sevenfold greater for surgical patients than for CT patients. The difference between costs in each intervention group decreased with each subsequent 6-month period until the last 6 months of the trial, when intervention costs were equivalent in both groups. The ICER for surgical therapy (relative to CT, 16,600 Australian dollars) was lower than the comparable ICER for CT (relative to no intervention, 25,500 Australian dollars). Modeling cost effectiveness over a longer time period, Keating et al. [28] concluded that after 10 years the return on investment of surgical therapy is fully recovered through savings in health care costs to treat T2DM in the surgical group.

7. Discussion

A significant existing body of literature has proven that bariatric surgery is safe, effective, and cost effective as a treatment for T2DM in patients with BMI ≥ 35 kg/m^2. A rapidly growing body of literature has demonstrated that bariatric surgery is also safe, effective and cost-effective as a treatment for T2DM in patients with BMI > 30 and <35 kg/m^2. However, most data collection on weight loss surgery has relied on administrative data sets, single-institution studies, and other sources that are not weight loss surgery specific. The results from weight loss surgery specific databases, which have been implemented since 2004 (i.e., NIH-sponsored longitudinal assessment of bariatric surgery consortium, the ACS-Bariatric Surgery Center Network, and the ASMBS/SRC Centers of Excellence Program), could identify areas for improvement and optimize outcomes and patient care [29].

There is still controversy in the US health system about extending coverage for bariatric surgery to all obese patients with diabetes, in addition to those with BMI ≥ 35 kg/m^2 for whom eligibility is already established. This approach would result in immediate costs of several hundred billion dollars. There is concern that such expenditures would redirect scarce resources away from prevention efforts [30]. Although the studies quoted above refute this argument, opponents to expanding metabolic surgery argue that at least one recent study suggests that maintenance of weight loss over time may

be no better in surgical patients than in those who lost weight without surgery [31]. Weight regain may be associated with deceleration in the rate of recovery from comorbidities after bariatric surgery [20].

It is important to promote funding for projects that study the safety, effectiveness, and cost effectiveness of metabolic surgery in T2DM patients. The Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial was designed to evaluate the efficacy of two bariatric surgery procedures (laparoscopic sleeve gastrectomy and RYGB) in comparison to advanced medical therapy in patients with T2DM with modest obesity with BMI of 27–42 kg/m^2. This single site, prospective, randomized controlled trial will enroll 150 subjects who will be followed. The primary end point will be the rate of biochemical resolution of T2DM at 1 year as measured by HbA1c < 6%. The safety and adverse event rates will also be compared between the three arms of the study [32]. The creation and development of similar parallel trials would help to validate the results derived from STAMPEDE.

It is also important to promote funding for projects that investigate the hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery. It appears that other mechanisms besides weight loss contribute to the higher rates of T2DM remission after RYGB in comparison with AGB [33]. Potential mechanisms underlying the direct antidiabetic impact of RYGB include enhanced nutrient stimulation of lower intestinal hormones (e.g., glucagon-like peptide-1), altered physiology from excluding ingested nutrients from the upper intestine, compromised ghrelin secretion, modulations of intestinal nutrient sensing, and regulation of insulin sensitivity, and other changes yet to be fully characterized [34]. Elucidation of the antidiabetic mechanisms of RYGB may help develop more potent and efficacious drugs in the future treatment of T2DM.

Although cost effectiveness of bariatric surgery in patients with T2DM and BMI < 35 kg/m^2 have been reported in at least 2 well-conducted studies, more good quality evidence is required before extending coverage for all T2DM patients. It is unclear if all T2DM would be potential candidates for metabolic surgery or if only patients that meet certain criteria (e.g., duration of T2DM, BMI, established cardiovascular disease, insulin dependency, C-peptide levels, etc.) would benefit while others would not. The socioeconomic impact of obtaining T2DM remission via metabolic surgery is yet to be determined and should be an area of active investigation.

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Research Article

Effect of Laparoscopic Adjustable Gastric Banding on Metabolic Syndrome and Its Risk Factors in Morbidly Obese Adolescents

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We examined the effect of laparoscopic adjustable gastric banding (LAGB) on weight loss, inflammatory markers, and components of the Metabolic Syndrome (MeS) in morbidly obese adolescents and determined if those with MeS lose less weight post-LAGB than those without. Data from 14–18 yr adolescents were obtained at baseline, 6 and 12 months following LAGB. Significant weight loss and improvements in MeS components were observed 6 months and one year following LAGB. The incidence of MeS declined 56.8% after 6 months and 69.6% after 12 months. There was no significant difference in amount of weight lost post-LAGB between those with and without MeS at either timepoint. Correlations between change in weight parameters and components of MeS in those with and without MeS at baseline were examined and found to vary by diagnostic category. LAGB is effective for short-term improvement in weight, inflammatory markers, and components of MeS in morbidly obese adolescents.

1. Introduction

Over the past 30 years, the prevalence of adult obesity in the United States has doubled while that of adolescent obesity has tripled [1]. Current estimates classify 15.5% of US children and adolescents as overweight (body mass index (BMI) between 85th and 95th percentile for age), 4% as obese (BMI between 95th and 99th percentile for age), and 4% as morbidly obese (BMI $\geq$ 99th percentile for age). These children are at risk of developing serious obesity-related comorbidities such as type 2 diabetes, dyslipidemia, hypertension, and metabolic syndrome (MeS). The necessity for early, aggressive treatment of obesity stems from the need to not only alleviate the medical and psychosocial comorbidities experienced in adolescence but also to decrease the risk of premature mortality in adulthood.

MeS affects an estimated 1/3 to 1/2 of morbidly obese adolescents [2] and likely contributes to the increased morbidity and mortality seen in adulthood. Pediatric MeS, just as adult MeS, is associated with a significantly elevated risk of cardiovascular disease and type 2 diabetes. Additionally, risk of MeS in adulthood is associated with its presence in childhood and adolescence [3, 4].

Adolescent obesity has significant long-term consequences, as there is a dose-dependent relationship between BMI in adolescence and risk of morbidity and mortality in adulthood [5]. Alarmingly, studies show that childhood obesity, particularly adolescent obesity, is a key predictor of adult obesity, and up to 77% of children will carry their obesity into adulthood [6]. The dangers of adult obesity include a reduction of median survival by 8–10 years in adults with BMIs between 40 and 45 kg/m^2 [7].

Increasing evidence suggests that traditional nonsurgical weight loss methods are ineffective and that bariatric surgery is the most sustainable and effective treatment for weight loss in the morbidly obese [8–11]. Presently, the most common surgical options for adolescents are Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding (LAGB), with

gastric bypass comprising more than 90% of US adolescent cases in 2003 [1]. LAGB is associated with a five- to ten-fold lower mortality rate and three-fold lower complication rate than gastric bypass, has the advantages of adjustability and reversibility, and has been associated with sustained weight loss and improved comorbidities in adults [12]. There is little long-term data on LAGB in adolescents however, since the procedure is not FDA approved for use in individuals under the age of 18 yrs.

While a handful of promising national and international studies demonstrating the safety and efficacy of LAGB in morbidly obese adolescents have been published [8–11, 13–19], few report on the effects of LAGB-induced weight loss on MeS. The aim of this study was to evaluate the effects of LAGB on weight, inflammatory markers, and components of MeS in morbidly obese adolescents and to determine if those with MeS lose less weight post-LAGB than those without as a consequence of their preoperative metabolic derangements.

We hypothesize that LAGB will result in a significant amount of excess weight loss, which will be accompanied by improvements in markers of inflammation as well as in measures diagnostic of MeS. We further postulate that MeS may represent a more advanced state of metabolic derangement, in which the patient is more resistant to weight loss. Therefore, those who carry a diagnosis of MeS will lose less weight compared to those who do not.

2. Methods

This is an IRB-approved, prospective, nonrandomized single center study conducted under an FDA-approved Investigational Device Exemption. An initial feasibility trial of 15 adolescents with followup was performed with interim safety and effectiveness data submitted to the FDA. The FDA subsequently granted approval to implant up to 125 additional patients with evaluation and followup identical to the initial 15. All adolescents who underwent LAGB were entered into a database and included in the data analysis. Subjects with 6-month (6 m) and/or 12-month (12 m) post-LAGB anthropometric and/or metabolic data were included in this report, which assessed weight, BMI, waist circumference (WC), systolic and diastolic blood pressure (BP) percentiles, triglycerides (TG), high-density lipoprotein (HDL), fasting blood sugar (FBS), C-reactive protein (CRP), % weight loss (%WL), and % excess weight loss (%EWL). Inclusion and exclusion criteria are described in Table 1. The BMI guidelines used were consistent with NIH criteria for bariatric surgery in adults [20].

2.1. Presurgical Methods. Subjects were recruited from among those enrolled in weight management programs at Columbia University Medical Center (CUMC) or referred by private pediatricians to the Center for Adolescent Bariatric Surgery. Consent was obtained from parents or caregivers and assent obtained from each subject. Both adolescents and their parents or caregivers were actively involved in the screening process, during which medical, social, psychiatric, and weight histories were obtained. As part of the protocol, subjects who met criteria for entry were enrolled at CUMC in either a 6 m lifestyle modification program if they had no prior programmatic weight loss experience or a 3 m program if they had documentation of participation in prior programs. During this time, subjects met monthly with a nurse practitioner/exercise specialist and a registered dietician, one to three times with an endocrinologist, and twice with a psychiatrist or psychologist and the pediatric surgeon. At the end of the lifestyle modification program, those subjects who demonstrated active participation and willingness to make changes were offered LAGB, while those having difficulty with program compliance were encouraged to continue with medical weight management. Prior to undergoing LAGB, baseline evaluations including anthropometric measurements, fasting blood studies (comprehensive metabolic panel, lipids, and nutrition panel), and an oral glucose tolerance test were performed. In addition, an electrocardiogram, chest X-ray, sleep study, and abdominal ultrasound with attention to the liver and gallbladder were completed for preoperative clearance. A bone age was performed to document skeletal maturity, and a serum HCG was carried out in females to ensure negative pregnancy.

Comorbidities were diagnosed by medical staff using the following criteria. Diagnosis of MeS was made using the 2003 Cook criteria for adolescents with modification of the FBS criterion to the November 2003 ADA criterion of >100 mg/dl as abnormal. Thus, we used the presence of any 3 of the following: TG $\geq$ 110 mg/dL, HDL $\leq$ 40 mg/dL, FBS $\geq$ 100 mg/dL, WC (cm) $\geq$ 90th percentile for ethnicity, age and sex, and BP (mmHg) $\geq$ 90th percentile for age, height, and sex [21]. Hypertension was defined as systolic and/or diastolic BP greater than the 95th percentile for age, sex, and height [22]. Dyslipidemia was defined by the presence of fasting HDL $\leq$ 40 mg/dl, LDL $\geq$ 110 mg/dl, TG $\geq$ 110 mg /dl, and/or total cholesterol $\geq$200 mg/dl.

Height was measured using a stadiometer to the nearest 0.1 cm; weight was measured using a digital readout scale to the nearest 0.1 kg. WC was measured at the anterior superior iliac spine to the nearest 0.5 cm. BP was measured with an aneroid sphygmomanometer while subjects were seated. Three readings for each of systolic and diastolic BPs were obtained, and the average of the measurements was used. Blood samples were obtained after an overnight fast. Serum glucose, HDL, and TG were run on an Olympus A42700 analyzer (Olympus America Inc, Melville NY). CRP was measured by nephelometry using a BN2 immunoassay (Siemens Industry, USA).

2.2. Surgical Methods. LAP-BAND (LAP-BAND System; Allergan Corp, Santa Barbara, CA) is a silicone ring with an adjustable inner diameter that is positioned around the proximal stomach just distal to the gastroesophageal junction, creating a small proximal gastric pouch. Kink-resistant tubing connects the the band to a subcutaneous access port. Saline can be injected into or withdrawn from the port to adjust the diameter of the band. LAP-BAND controls the outlet diameter of the upper stomach pouch, limiting emptying rate and causing a feeling of early satiety and subsequent weight loss.

All surgical procedures were performed at the Morgan Stanley Children's Hospital of New York by a pediatric surgeon (JZ). Placement of the LAP-BAND was performed laparoscopically with the patient under general anesthesia. The LAP-BAND was placed using 5 trocar sites according to the pars flaccida technique, which has been described in detail elsewhere [23]. The LAP-BAND was left empty at the end of placement to allow for postoperative swelling. Patients were observed in the hospital overnight, and a contrast esophagram was performed to confirm band position and assess pouch emptying prior to discharge.

2.3. Follow-Up Assessment. Patients were instructed to return for followup visits for assessment of weight changes, for nutritional advice, and for postsurgical monitoring and adjustments at weeks 2, 4, 6, and 8, then monthly for the initial 12 m, with plans for followup at 15, 18, and 24 m, and semiannually thereafter for a total of 5 years. Fasting laboratory evaluations (including comprehensive metabolic panel, nutritional panel, lipids, and oral glucose tolerance test) were performed at postoperative months 6 and 12 with biannual assessments intended for the next 5 yrs. The first band adjustment occurred 5–6 weeks post-LAGB. Subsequent band adjustments were tailored to the individual's needs, including feelings of hunger and satiety, as well as pain with or without vomiting. The overall goal for weight loss was 1–1.5 lbs per week, which is consistent with other studies [16, 24]. Patients were instructed to follow a pureed diet in the first postoperative week, a blended diet for postoperative weeks 2–3, a soft diet for postoperative weeks 4–6, and a well-balanced low-fat diet for postoperative week 7 and beyond. In addition, patients were instructed to continue physical activity, to eat 3 small meals per day, to avoid liquids 30 minutes before and 30 minutes after eating, and to stop eating when full.

Ideal body weight was derived by multiplying the square of each subject's baseline height by the BMI at the 85th percentile for each subject's sex and age using the CDC growth charts (2000). There is no consensus with respect to the optimal BMI to use when determining ideal body weight for children and adolescents. Our goal was to have subjects achieve a weight and BMI within normal range for their age. While a BMI at the 85th percentile is at the uppermost limit of normal, it is within the normal range and a realistic goal for our study subjects. Excess weight (EW) was calculated by subtracting ideal body weight from actual baseline weight. %EWL was calculated by dividing the amount of weight lost at 6 m or 12 m post-LAGB by the EW and multiplying by 100. %WL was calculated by dividing the amount of weight lost at 6 m or 12 m post-LAGB by baseline weight and multiplying by 100.

2.4. Statistical Analysis. Pearson correlation was used to identify associations among changes in weight and indices of the MeS at both 6 m and 12 m. Fisher's exact test was used to assess the change in the proportion of subjects meeting MeS criterion at 6 m and 12 m. Logistic regression with dichotomously coded MeS status (improved versus unimproved) was used to assess which weight change measure was most highly associated with change in MeS status. Linear mixed models for repeated measures were used to check whether average within-subject changes over time represented statistically reliable changes from baseline. The 6 m and 12 m cohorts were analyzed separately. A P-value less than.05 was considered statistically significant, and data are expressed as counts and percentages or means and standard error of the mean (SEM). No adjustments for analysis of multiple outcome measures were made.

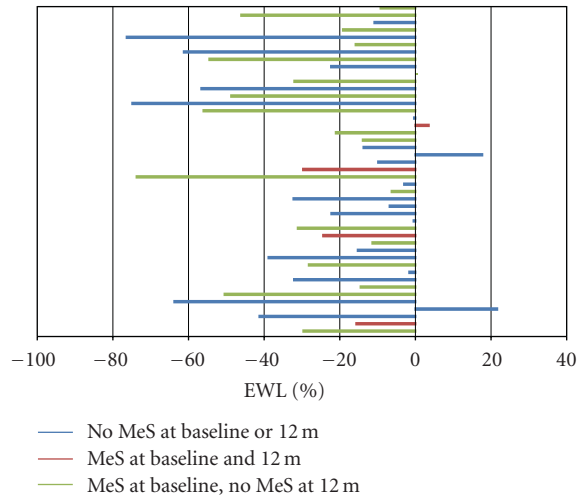

Figure 1: %EWL 12 m post-LAGB.

3. Results

All procedures were performed laparoscopically. There were no operative deaths. Early complications included 1 exploration for bleeding, 1 repositioning of a misplaced band, and 1 exploration for presumed bowel obstruction which proved to be prolonged ileus. One patient developed aggravation of plantar fasciitis requiring analgesics and physical therapy. There were 2 minor wound complications. Late complications included 3 band displacements which required laparoscopic repositioning and 5 port repositions. No patient required band removal.

From March 2006 through June 2010, 108 adolescents (31 males, 77 females) underwent LAGB. At the time of this report, all subjects were at least 6 m post-LAGB and 88 (81.5%) presented for followup. These 88 adolescents (36 Hispanic, 13 African-American, 33 Caucasian, and 6 mixed ethnicity) had baseline age 16.8 ± 0.1 yrs, BMI 45.9 ± 1.0 kg/m^2, and EW 66.9 ± 3.0 kg. Thirty-seven subjects had MeS. Mean %WL at 6 m post-LAGB was 7.5 ± 0.9%, ranging from a loss of 24.8% to a gain of 12.7%. The mean %EWL equaled 17.1 ± 2.2%, ranging from 86.8% of excess weight lost to 27.3% of excess weight gained. Fifteen patients gained weight at the 6 m time point with mean weight gain of 6.1 ± 1.1 kg.

Sixty-two subjects (57%) provided blood work for evaluation. Baseline and 6 m post-LAGB anthropometric

Table 1: Patient selection criteria.

Inclusion Criteria	Exclusion Criteria
– 14–18 yrs old at time of enrollment	– History of prior bariatric surgery or intent to have additional bariatric surgery in the next year
– BMI $\geq$ 40 kg/m^2 or $\geq$ 35 kg/m^2 and at least 1 comorbidity	– History of GI tract anomalies, severe cardiopulmonary disease, coagulopathy, hepatic insufficiency or cirrhosis
– Obesity for at least 5 yrs with documented attempts at diet and medical management	– History of gastric or esophageal surgery
– Bone age at least 13.5 (F) and 14.5 (M)	– History of chronic aspirin and/or NSAID use
– Emotional maturity	– Pregnancy or intent to become pregnant in the next year
– Use of appropriate contraception (F)	– Eating disorders with self-induced vomiting
– Understanding and willingness to comply with protocol	– Inability to understand the intervention and followup

(F): female; (M): male; NSAID: non-steroidal anti-inflammatory drug.

Table 2: Clinical characteristics and MeS variables at baseline and at 6 m post-LAGB ($N = 62$).

Variable	Timepoint		
	Baseline	6 m post-LAGB	P†
BMI (kg/m^2)	47.8 ± 0.95 (35.7–86.2)	44.0 ± 1.0 (28.6–81.9)	< .0001
Weight (kg)	134.9 ± 3.6 (83.9–201.7)	125.5 ± 3.6 (69.4–195.5)	< .0001
WC (cm)	136.1 ± 2.4* (107.5–188)	127.8 ± 2.4 (91.8–177.5)	< .0001
Systolic BP (%ile)	70.9 ± 3.3$^\#$ (6–100)	59.6 ± 3.3 (5–99)	.0056
Diastolic BP (%ile)	74.5 ± 2.8$^\#$ (23–100)	62.3 ± 2.8 (6–99)	.0015
TG (mg/dl)	1.30 ± 0.10 (0.44–5.57)	1.18 ± 0.10 (0.32–4.27)	*.065*
FBS (mg/dl)	4.62 ± 0.06 (3.39–6.44)	4.70 ± 0.06 (3.77–5.77)	NS
HDL (mg/dl)	1.09 ± 0.03 (0.75–1.81)	1.12 ± 0.03 (0.75–1.68)	NS
CRP (mg/L)	93.3 ± 10.5* (2.29–440.0)	66.7 ± 10.5 (3.05–363.8)	.0002

Data are presented as Mean ± SEM (Range). $^\dagger P$-value for changes in variables between baseline and 6 m post-LAGB. $^*N$: 59. $^\#N$: 60.

Table 3: Clinical characteristics and MeS variables at baseline and 12 m post-LAGB ($N = 29$).

Variable	Timepoint		
	Baseline	12 m post-LAGB	$P^\dagger$
BMI (kg/m^2)	48.8 ± 1.4 (35.9–65.4)	42.9 ± 1.5 (27.7–65.8)	<.0001
Weight (kg)	135.0 ± 5.2 (94.5–198.4)	120.2 ± 5.2 (68.4–167.6)	<.0001
WC (cm)	135.4 ± 3.6* (109.5–168)	123.5 ± 3.5 (87–165)	<.0001
SBP (%-ile)	71.1 ± 5.0 (6–98)	58.1 ± 5.1 (5–100)	.019
DBP (%-ile)	71.7 ± 3.9 (25–100)	68.0 ± 4.0 (16–98)	NS
TG (mg/dl)	1.30 ± 0.13 (4.97–3.15)	1.22 ± 0.13$^\#$ (4.07–4.38)	NS
FBS (mg/dl)	4.80 ± 0.11 (3.94–7.44)	4.66 ± 0.11 (4.05–6.16)	NS
HDL (mg/dl)	1.10 ± 0.05 (0.78–1.66)	1.19 ± 0.05$^\#$ (0.73–1.68)	.029
CRP (mg/L)	77.1 ± 11.4* (7.0–257.1)	53.3 ± 11.4$^\#$ (2.1–221.9)	.024

Data are presented as Mean ± SEM (Range). $^\dagger P$ -value for changes in variables between baseline and 12 m post-LAGB. $^*N$: 27. $^\#N$: 28.

Table 4: P-values for correlations among weight change measures and components of MeS at 6 m post-LAGB by MeS status at baseline.

Variable	No MeS ($N = 51$)			Yes MeS ($N = 37$)		
	%EWL	%WL	BMI	%EWL	%WL	BMI
WC (cm)	<0.0001	0.01	<0.0001	0.0024	0.0004	0.0005
HDL (mg/dl)	NS	NS	NS	NS	NS	NS
TG (mg/dl)	NS	0.0098	0.004	NS	NS	NS
CRP (mg/dl)	NS	NS	NS	NS	NS	NS
FBS (mg/dl)	NS	0.019	0.013	NS	NS	NS
SBP %ile	NS	NS	*0.06*	NS	NS	NS
DBP %ile	NS	NS	NS	NS	NS	NS

Table 5: *P*-values for correlations among weight change measures and components of MeS at 12 m post-LAGB by MeS status at baseline.

Variable	No MeS ($N = 22$)			Yes MeS ($N = 23$)		
	%EWL	%WL	BMI	%EWL	%WL	BMI
WC (cm)	<0.0001	<0.0001	<0.0001	0.043	0.009	0.002
HDL (mg/dl)	NS	NS	NS	0.032	0.047	*0.08*
TG (mg/dl)	NS	NS	NS	NS	NS	NS
CRP (mg/dl)	NS	NS	NS	NS	NS	NS
FBS (mg/dl)	NS	0.046	0.037	NS	NS	NS
SBP %ile	NS	NS	NS	NS	NS	NS
DBP %ile	*0.067*	NS	*0.065*	NS	NS	NS

data of subjects who had blood work assessed were not significantly different from that of subjects who did not (data not shown). There were significant improvements in BMI, weight, WC, systolic and diastolic BP% iles, and CRP (Table 2). MeS resolved in 21 of the adolescents diagnosed at baseline (56.8%; $P < .0004$). No significant differences were observed in %EWL, %WL, or change in BMI between those with MeS at baseline and those without (data not shown). Resolution of MeS did not significantly correlate with change in BMI, %WL, or %EWL (P = NS).

At the time of this report, 84 adolescents were at least 12 m post-LAGB. Forty-five adolescents (50.6%; 17 male, 28 female) attended 12 m followup visits. These 45 adolescents (19 Hispanic, 6 African-American, 17 Caucasian, and 3 mixed ethnicity) had baseline age 17.2 ± 0.2 yrs, BMI 45.8 ± 1.5 kg/m^2, and EW 69.4 ± 4.3 kg. Twenty-three subjects had MeS. The %WL for this group was 10.9 ± 1.2%, ranging from a 43.0% loss to a gain of 9.1%. Mean %EWL was 25.9 ± 3.6% ranging from an excess weight loss of 76.4% to an excess weight gain of 21.6% (Figure 1). Four adolescents had net weight gains, the mean of which was 6.1 ± 2.8 kg (range 0.6–13.5 kg).

Twenty nine (35%) provided bloodwork for evaluation. There were no differences in the anthropometric data between those who came for bloodwork and those who did not (data not shown). Significant improvements in BMI, weight, WC, systolic BP %ile, CRP, and HDL one year after LAGB were observed (Table 3). MeS resolved in 16 of the adolescents diagnosed at baseline (69.6%; $P = .0003$). There were no significant differences in %EWL, %WL, or change in BMI between those who had MeS at baseline and those who did not (data not shown). Resolution of MeS correlated to %EWL, nearing statistical significance ($P = .06$) but did not correlate to %WL or BMI (P = NS).

Tables 4 and 5 demonstrate correlations of components of MeS with parameters of weight change in those with and without MeS at 6 m and 12 m post-LAGB. At 6 m post-LAGB, %WL, BMI, and %EWL (Table 4) correlated significantly with WC in those who did not have MeS at baseline. BMI and %WL also correlated significantly with change in TG and FBS in this cohort. In those with MeS at baseline, BMI, %EWL, and %WL only correlated with change in WC (Table 4). One year post-LAGB, %EWL, BMI, and %WL correlated significantly with WC in those who did not have MeS at baseline (Table 5). %WL and BMI, correlated significantly with change in FBS as well. In those with MeS at baseline, %EWL, BMI and %WL correlated with WC and HDL (Table 5).

4. Discussion

This study examined the effects of LAGB on a diverse population of morbidly obese adolescents with respect to changes in weight and resolution of MeS. Our results indicate that LAGB is effective in most morbidly obese adolescents for achieving weight loss and decreasing the frequency of MeS. Similar to other adolescent LAGB series, there were no intraoperative or postoperative deaths, and the complication rate was comparable to what has previously been reported [8–10, 14–19]. Our study showed weight loss at 6 m and 12 m post-LAGB, which is consistent with results of other studies, but of smaller magnitude. Post-LAGB weight gain was observed in 15 of 88 adolescents at 6 m post-LAGB and in 4 of 45 adolescents at 12 m post-LAGB. While Widhalm et al. also reported weight gain in 4 of 7 adolescents post-LAGB, they began gaining at 44 m after surgery [17]. Although they did not report adolescents who gained weight postoperatively, Silberhumer et al. and Angrisani et al. did describe failure rates of 3 out of 50 at 1-year followup and 5 out of 25 at 5-year followup, respectively, defining failure as %EWL < 25% [13, 14].

Possible explanations for the insufficient weight loss and weight gain in our subjects include lack of social support, failure to change eating habits, and failure to incorporate recommended exercise. Degree of adherence to followup appointments could further contribute to disappointing outcomes. Possible reasons for lack of followup may include difficulty in attending appointments due to school, work, or other obligations; inability to finance appointments due to loss of health insurance; satisfaction with weight loss such that no need was felt to see the medical team; embarrassment at the lack of weight loss or presence of weight gain; lack of desire to undergo blood testing and/or consume glucola for the 2-hour oral glucose tolerance test. We were unable to provide monetary or other incentives for attending followup visits and complying with lifestyle modifications. Such enticements may have increased our compliance rate and resulted in even better weight loss results. Information regarding changes in body composition,

including percent fat mass, was not obtained during the study. It is possible that for some adolescents muscle accrual is occurring but not being accounted for when they step on the scale. We plan to assess body fat percentage of our study subjects in future visits in order to better understand body compositional changes that are occurring with weight changes. We are also investigating factors relating to subject compliance in order to understand which adolescents will succeed post-LAGB, thus enabling us to better screen future candidates.

There is increasing evidence that resolution of obesity-related comorbidities such as MeS with weight loss can be seen in adolescents as it has been in adults [16, 19, 25]. Holterman et al., using the International Diabetes Federation guidelines, reported a 34% reduction of MeS in 10 adolescent girls at 6 m and a 68% reduction at 9 m post-LAGB [16]. Our data show comparable post-LAGB improvement with a 56.8% resolution of MeS 6 m post-LAGB and a 69.6% resolution of MeS 12 m post-LAGB. Both series noted near statistically significant improvement in TG 6 m post-LAGB, but this was not sustained at the 12 m time point in our subjects. This is likely a reflection of dietary changes, which incorporated more carbohydrate-rich foods and fewer fatty foods. Consistent with Holterman et al., who saw improvements in systolic BP following LAGB, we saw significant improvement in systolic BP 6 m and 12 m post-LAGB. In addition, we saw significant improvement in diastolic BP at the 6 m time point that was not sustained 12 m after surgery. Change in HDL approached statistical significance 6 m post-LAGB and was significant one year following surgery, probably a reflection of the increase in physical activity in our subjects over time.

Studies indicate that 10% WL can lead to resolution of a number of adiposity-related comorbidities [26]. In our study, subjects lost only 7.5% WL 6 m following surgery, but this gave them a %EWL of 17.1%. This degree of EWL was accompanied by a significant resolution of MeS in these subjects, manifested by significant improvement in a number of components that define the disease. One year following surgery, with %WL of 10.9% and %EWL of 25.9%, an even greater percentage of subjects had resolution of MeS. It is possible therefore that lesser degrees of WL than the generally recommended 10% in the morbidly obese population will result in significant health-related improvement and that the utilization of %EWL to assess co-morbidity risk reduction may be of benefit in the morbidly obese population.

Similar to the observations of Widhalm et al., we also observed improvements in CRP, an inflammatory biomarker that independently predicts future vascular events [19]. Decreased CRP has been associated with reductions in the occurrence of adverse cardiovascular outcomes [27]. In our adolescents, CRP decreased significantly at 6 m post-LAGB and continued to decrease at 12 m post-LAGB. This improvement is important since 20.5% of our subjects had at least three risk factors for cardiovascular disease at baseline, which included obesity, sedentary lifestyle, dyslipidemia, elevated BP, impaired glucose tolerance, and impaired FBS. LAGB-induced weight loss appears to eliminate some of these risk factors, in addition to reducing CRP levels, all of which may lead to improved cardiovascular health in this group of adolescents.

This is one of the first studies to date to examine correlations of MeS components to changes in weight in adolescents following bariatric surgery. At both 6 m and 12 m post-LAGB, change in WC was correlated with %EWL, %WL, and change in BMI, irrespective of MeS status. This is similar to findings by Coppen et al., who observed significant correlation between weight change and WC following a 75.5% decrease in MeS following 10 weeks of diet-induced weight loss in a group of 6–19 year old [28]. No relationships were observed with any other metabolic parameter of MeS in this study. Our results showed that in those without MeS at baseline, %WL and change in BMI correlated with change in FBS and TG 6 m post-LAGB, findings that were not observed in those who had MeS prior to surgery. Despite weight loss and improvements in individual components of MeS, no significant relationship existed between these components and weight loss in those with MeS prior to surgery. This suggests that another factor may serve as a link between weight change and MeS components and is relevant only in those who have the syndrome.

12 m following LAGB, %WL and change in BMI continued to correlate with FBS but not with TG in those who did not have MeS at baseline. The fact that there was no significant improvement in TG levels 12 m post-LAGB could explain this finding. Interestingly, in those who did have MeS at baseline, change in HDL correlated significantly with %EWL and %WL. It is as yet unclear what the significance and implications of these findings are. Further studies examining the relationship between MeS components and weight change will help shed more light into this matter.

This study is limited by the lack of a control group undergoing conventional diet and exercise, as was present in a study by O'Brien et al. [8]. The short-term nature of our study precludes an assessment of the long-term impact of LAGB on comorbidities; however, long-term followup is ongoing with a goal of a total of 5 years of postsurgical followup. Our study is not unique in its difficulty with ensuring followup [24]. The number of subjects who presented for followup metabolic evaluation was less than the total number of subjects who presented for followup anthropometric assessment. There were no significant differences in weight change between those who had laboratory data for evaluation and those who did not, suggesting that our conclusions from the laboratory assessments may be extended to the entire group at each time point.

Our study adds to the limited literature documenting the effectiveness of LAGB in achieving not only weight loss with limited adverse effects, but also resolution of comorbidities, particularly MeS in morbidly obese adolescents. We found that MeS does not hinder weight loss in our study subjects and that a number of components of MeS improve with less than the %WL currently recommended for improvement. The option of using %EWL as a goal for improvement of comorbidities in the morbidly obese and obese population is introduced; further studies into this matter are warranted.

We show that correlations between parameters of weight change and components of MeS indeed are different between those with and without MeS prior to undergoing surgical weight loss. Future research into the implications of these relationships is necessary. Only continued long-term followup can clarify the role of LAGB amongst the various weight loss treatments available and whether the diagnosis of MeS alters the response of the individual components of MeS to weight loss.

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Research Article

A Model of Insulin Resistance in Mice, Born to Diabetic Pregnancy, Is Associated with Alterations of Transcription-Related Genes in Pancreas and Epididymal Adipose Tissue

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Objective. This study is conducted on a model of insulin-resistant (IR) mice born to dams which were rendered diabetic by the administration of streptozotocin. *Methods*. Adult IR and control offspring were selected and we determined the mRNA expression of transcription factors known to modulate pancreatic and adipose tissue activities and inflammation. *Results*. We observed that serum insulin increased, and the mRNA of insulin gene transcription factors, Pdx-1, Nkx6.1 and Maf-A, were upregulated in IR mice pancreas. Besides, their pancreatic functional capacity seemed to be exhausted as evidenced by low expression of pancreatic Glut2 and glucokinase mRNA. Though IR offspring exhibited reduced epididymal adipose tissue, their adipocytes seemed to be differentiated into macrophage-like cells, as they exhibited upregulated CD14 and CD68 antigens, generally expressed by macrophages. However, there was no peripheral macrophages infiltration into epididymal adipose tissue, as the expression of F4/80, a true macrophage marker, was undetectable. Furthermore, the expression of IL-6, TNF-α and TLR-2, key players of insulin resistance, was upregulated in the adipose tissue of IR offspring. *Conclusion*. Insulin resistant state in mice, born to diabetic pregnancy, alters the expression of function-related genes in pancreas and epididymal adipose tissue and these offspring are prone to develop metabolic syndrome.

1. Introduction

Hyperglycemia, related to insulin resistance, is due to a decrease in peripheral glucose uptake, and to an increase in hepatic glucose production [1]. In order to induce insulin resistance, most of the investigators have adopted a strategy in which they feed the rodents with high-fat diets [2, 3]. However, this dietary intervention is not well standardized, and the high-fat-induced phenotype varies distinctly among different studies [3]. It is obvious that appropriate animal models are crucial to study the pathogenesis and therapy of this complex metabolic disorder. From a scientific and an ethical point of view, it is reasonable to obtain a disease model which should resemble to the pathogenesis in human beings.

In our laboratory, we have developed a model of insulin resistance in macrosomic rats born to streptozotocin- (STZ-) induced diabetic dams [4, 5]. These macrosomic offspring of diabetic dams were hyperglycemic, hyperinsulinemic, and they exhibited high serum and liver lipid levels during adulthood. Recently, we have also developed a model of insulin resistance in mice born to the STZ-induced diabetic animals [6]. The pups and their diabetic mothers were fed the standard laboratory chow. These offspring developed

a marked hyperinsulinemia, hyperglycemia, and insulin resistance at adulthood [6]. In the present report, we assessed the pancreatic β-cell functions by determining the mRNA levels of Glut2 and glucokinase. We also examined the expression of some major insulin gene transcription factors like pancreatic and duodenal homeobox- (Pdx-) 1, NK6 transcription factor related-locus-1 (Nkx6.1), and Maf-A [7, 8]. Nkx6.1 is important for the terminal differentiation of β-cells [8] and is known to influence glucose-induced insulin secretion [9]. Pdx-1 regulates the transcription of insulin, glucokinase, and islet amyloid polypeptide [7, 8]. Moreover, Pdx-1 and Maf-A can exert their positive actions separately on the promoter and their effects are additive [10]. Therefore, we determined the expression of pancreatic mRNA of these transcription factors in order to respond to the question whether they are involved in the β-cell adaptation in response to insulin resistance.

Because adipokines, secreted by adipose tissue, play crucial role in the onset of type II diabetes and obesity [11], we determined the mRNA encoding for leptin and adiponectin in epididymal adipose tissue. Moreover, macrophages have been shown to infiltrate several organs, including adipose tissue, during inflammatory processes [12]. We, therefore, investigated the expression of mRNA of CD14, CD68, and F4/80 antigens in the epididymal adipose tissue of these animals. CD14 has been shown to bind to lipopolysaccharide (LPS) which interacts with Toll-like receptors (TLR) [13], and this spurred us to examine the expression of TLR-2 mRNA in epididymal adipose tissue. The mRNA expression of tumour necrosis factor- (TNF-) α and interleukin- (IL-) 6 was determined as these agents are also known to be secreted in adipose tissue [14]. In order to shed light whether T cells infiltrate the adipose tissue of insulin-resistant (IR) mice, we also investigated the mRNA expression of T cell receptor-alpha (TCRα), regulated on activation of normal T cell expressed and secreted (RANTES) and its receptor CCR-5 in the epididymal adipose tissue.

All the aforementioned parameters were studied in adult control and IR mice which were, respectively, the descendents of control and diabetic dams, since the rationale of the present study is to explore the metabolic consequences of a pathologic model of insulin resistance of *in utero* exposure to hyperglycemia, that is, diabetic pregnancy.

2. Materials and Methods

2.1. Animals and Design. The study was performed on wild type C57BL/6J mice (Charles River, Les Oncins, France) at age of 3 months. The insulin-resistant (IR) offspring of diabetic mice were obtained as described elsewhere [6]. Briefly, after mating, the first day of gestation was determined by the presence of spermatozoids in vaginal smears. Pregnant mice ($n = 8$, at age of 3 months), housed individually in wood-chip-bedded plastic cages at constant temperature (25°C) and humidity (60 ± 5%) with a 12 hours light-dark cycle, were rendered diabetic by five daily intraperitoneal injections of streptozotocin (40 mg/kg body weight in 0.1 M citrate buffer, pH 4.5), starting on day 5 of gestation [15]. Another group of pregnant mice ($n = 8$) were also injected with the vehicle alone and considered as control groups. The glycemia was followed during gestation of mice as we described previously [6]. All diabetic dams included, in this study, had the fasting blood glucose levels above 1.23 g/L. The success rate in obtaining the diabetic dams was 87.5%. In the litters of diabetic dams, the mean proportion of hyperglycemic pups at birth was 94.6 ± 3%. Only 12 male offspring born to diabetic dams, which were hyperglycemic at birth and showed a hyperglycemia and a hyperinsulinemia at 3 months of age, were selected and included in the study, since reproductive hormones have been associated with prevalence, susceptibility, and severity of obesity and autoimmune disease [16, 17]. The nonhyperglycemic pups of diabetic mothers were excluded, as maternal diabetes related to fetal hyperglycemia was the criterion for the selection of our experimental population [5]. However, these nonhyperglycemic offspring of diabetic mothers were not hyperinsulinemic, neither at birth nor at adulthood. They had normal growth and did not show any significant difference from the control pups in serum lipids.

The dams and offspring (after weaning) were fed the standard laboratory chow. The principles of laboratory animal care (NIH publication No. 86-23, revised 1985) were followed, as well as specific national laws (e.g., the current version of the German Law on the Protection of Animals) where applicable. The experimental protocol was also approved by the Regional Ethical Committee.

2.2. Oral Glucose-Tolerance and Insulin-Tolerance Tests. Oral glucose-tolerance test (OGTT) was carried out in 12 hyperglycemic offspring and 12 control offspring after a 15-h fast. Briefly, a single dose of glucose was orally administrated (3 g/kg body weight) to the mice. Glycemia was measured using One Touch ULTRA Glucometer (LifeScan, Johnson and Johnson, USA), every 5 or 10 minutes for 2 hours following glucose loading, by cutting off the tip of tail and squeezing it gently.

For intraperitoneal insulin-tolerance test (IPITT), a single dose of insulin (0.5 U/kg body weight; Actrapid Novo, Copenhagen, Denmark) was injected intraperitoneally after 4-h fast and, as in the oral glucose-tolerance tests, glycemia was measured every 5 or 10 minutes for 2 hours, following insulin injection.

2.3. Blood, Liver, Pancreas, and Epididymal Adipose Tissue Samples. After overnight fasting, animals (3 months-ages) were anesthetized with pentobarbital (60 mg/kg body weight). Blood was drawn from the abdominal aorta. Serum was obtained by low-speed centrifugation (1000 g × 20 minutes) and used for glucose (glucose oxydase method, Beckman Instruments, USA) and insulin determination (ELISA kit, LINCO Research Inc, St. Charles, MO, USA). Pancreas, epididymal adipose tissue, and livers, after removal, were weighed then frozen in liquid nitrogen and used for total RNA extraction.

2.4. Determination of Serum and Liver Lipids. After total lipid extraction, according to the method of Bligh and Dyer [18] serum or liver triglyceride (TG) and free fatty acids (FFA) were separated on silica gel by thin layer chromatography (TLC) and the purified fractions of FFA and TG were quantified by gas liquid chromatography [6, 19].

2.5. Real-Time RT-PCR Quantification Assay. Total RNA was prepared using Trizol reagent (Invitrogen Life Technologies, Groningen, The Netherlands) according to the manufacturer's instructions. The integrity of RNA was electrophoretically checked by ethidium bromide staining and by the OD absorption ratio OD260 nm/OD280 nm more than 1.9. One microgram of total RNA was reverse transcribed with Superscript II RNAse H-reverse transcriptase using oligo (dT) according to the manufacturer's instructions (Invitrogen Life Technologies, France). Real-time PCR was performed on an iCycler iQ real-time detection system (Bio-Rad, Hercules, CA, USA) as described elsewhere [6]. Briefly, the amplification was done by using SYBR Green I detection (SYBR Green JumpStart, Taq ReadyMix for Quantitative PCR, Sigma). Oligonucleotide primers, used for mRNA analysis, were based on the sequences of mice gene in GenBank database. The sequence of the reference gene used for normalization of RT-PCR gene expression data is the β-actin (forward: 5′-AGAGGGAAATCGTGCGTGAC-3′; reverse: 5′-CAATAGTGATGACCTGGCCGT-3′). All mice RT-PCR primer sets used to amplify the genes in these studies are presented in Table 1. All determinations were performed, in duplicates using two dilutions of each assay to achieve reproducibility. Results were evaluated by iCycler iQ software including standard curves, amplification efficiency (E), and threshold cycle (Ct). Relative quantitation of mRNA expression of a large number of signalling factors in different groups was determined using the ΔΔCt method, in which ΔΔCt = ΔCt of gene of interest-ΔCt of $\boldsymbol{\beta}$ actin. ΔCt = Ct of interest group - Ct of control group. Relative quantity (RQ) was calculated as follows: $\mathrm{RQ} = (1 + E)^{(-\Delta\Delta\mathrm{Ct})}$.

2.6. Statistical Analysis. Results are shown as means ± SEM. Statistical analysis of data was carried out using STATISTICA (version 4.1, Statsoft, Paris, France). Data were evaluated by analysis of variance. Duncan's Multiple-Range test and the Student's t-test were employed for the comparison between diabetic and control dams, and the IR offspring with their corresponding controls, respectively. Differences were considered significant at $P < .05$.

Table 1: Gene regions amplified and their corresponding primer sequences used for RT-PCR.

Genes amplified	Primer sequences
Mouse RANTES	F: 5′-GCAGTCGTGTTTGTCACTCG-3′
	R: 5′-TAGGACTAGAGCAAGCGATGAC-3′
Mouse CCR5	F: 5′-GCCTAAACCCTGTCATCTATGC-3′
	R: 5′-ATATTTCCCGGCCCTGATAAAAG-3′
Mouse MCP-1	F: 5′-GAGAGCCAGACGGGAGGAAG-3′
	R: 5′-TGAATGAGTAGCAGCAGGTGAG-3′
Mouse CD68	F: 5′-TTCAGGGTGGAAGAAAGGTAAAGC-3′
	R: 5′-CAATGATGAGAGGCAGCAAGAGG-3′
Mouse IL-6	F: 5′-CCGCTATGAAGTTCCTCTCTGC-3′
	R: 5′-ATCCTCTGTGAAGTCTCCTCTCC-3′
Mouse TCRα	F: 5′-CCTCTACAGCAGCGTTCTCATCC-3′
	R: 5′-GGGTAGGTGGCGTTGGTCTCTTTG-3′
Mouse CD14	F: 5′-GCGTGTGCTTGGCTTGTTG-3′
	R: 5′-CAGGGCTCCGAATAGAATCCG-3′
Mouse F4/80	F: 5′-TCCAGCACATCCAGCCAAAGC-3′
	R: 5′-CCTCCACTAGCATCCAGAAGAAGC-3′
Mouse TLR-2	F: 5′-CTACAGTGAGCAGGATTCC-3′
	R: 5′-CAGCAAAACAAGGATGGC-3′
Mouse TNF-α	F: 5′-CTCTTCTCATTCCTGCTTGTGG-3′
	R: 5′-AATCGGCTGACGGTGTGG-3′
Mouse SREBP-1c	F: 5′-CATCAACAACCAAGACAGTC-3′
	R: 5′-CCAGAGAAGCAGAAGAGAAG-3′
Mouse FAT/CD36	F: 5′-TGCTCTCCCTTGATTCTGCTGC-3′
	R: 5′-TTTGCTGCTGTTCTTTGCCACG-3′
Mouse Adiponectin	F: 5′-GCCGCTTATGTGTATCGCTCAG-3′
	R: 5′-GCCAGTGCTGCCGTCATAATG-3′
Mouse Leptin	F: 5′-ACACACGCAGTCGGTATCC-3′
	R: 5′-GAGTAGAGTGAGGCTTCCAGG-3′
Mouse Glucokinase	F: 5′-AGAAGGCTCAGAAGTTGGAGAC-3′
	R: 5′-GGATGGAATACATCTGGTGTTTCG-3′
Mouse Insulin	F: 5- TGGCTTCTTCTACACACCCAT-3′
	R: 5′-CTCCAGTGCCAAGGTCTGAA-3′
Mouse Glut2	F: 5′-TGTGGTGTCGCTGTTTGTTG-3′
	R: 5′-AATGAAGTTTGAGGTCCAGTTGG-3′
Mouse C/EPB-β	F: 5′-AGCTGAGCGACGAGTACAAG-3′
	R: 5′-AGCTGCTCCACCTTCTTCTG-3′
Mouse Maf-A	F: 5′-ATCACTCTGCCCACCATCAC-3′
	R: 5′-CGCCAACTTCTCGTATTTCTCC-3′
Mouse Nkx6-1	F: 5′-GGGTCTTCCTCCTCCTCCTC-3′
	R: 5′-GGTCTGGTGTGTTTTCTCTTCC-3′
Mouse Pdx-1	F: 5′-CTACTGCCTTCGGGCCTTAG-3′
	R: 5′-TTGGAACGCTCAAGTTTGTACC-3′

3. Results

3.1. Glycemia during Oral Glucose- and Insulin-Tolerance Tests. During OGTT, the glycemia was higher in the offspring of diabetic dams as compared with their corresponding controls (Figure 1(a)). The area under glucose curve during the time of the test was 304.95 g/L ∗ 120 minutes for offspring of diabetic dams, as compared to that of control offspring which was 175.80 g/L ∗ 120 minutes. Two hours after glucose loading, glycemia was not back to its basal value in hyperglycemic offspring. In response to insulin injection, the decrease in glycemia was less marked in hyperglycemic offspring, suggesting decreased insulin sensitivity, that is, an insulin resistance in these mice (Figure 1(b)). Though, in IR offspring (hyperglycaemic), glycemia was back to its basal value, 120 minutes after insulin injection, it remained lower in controls.

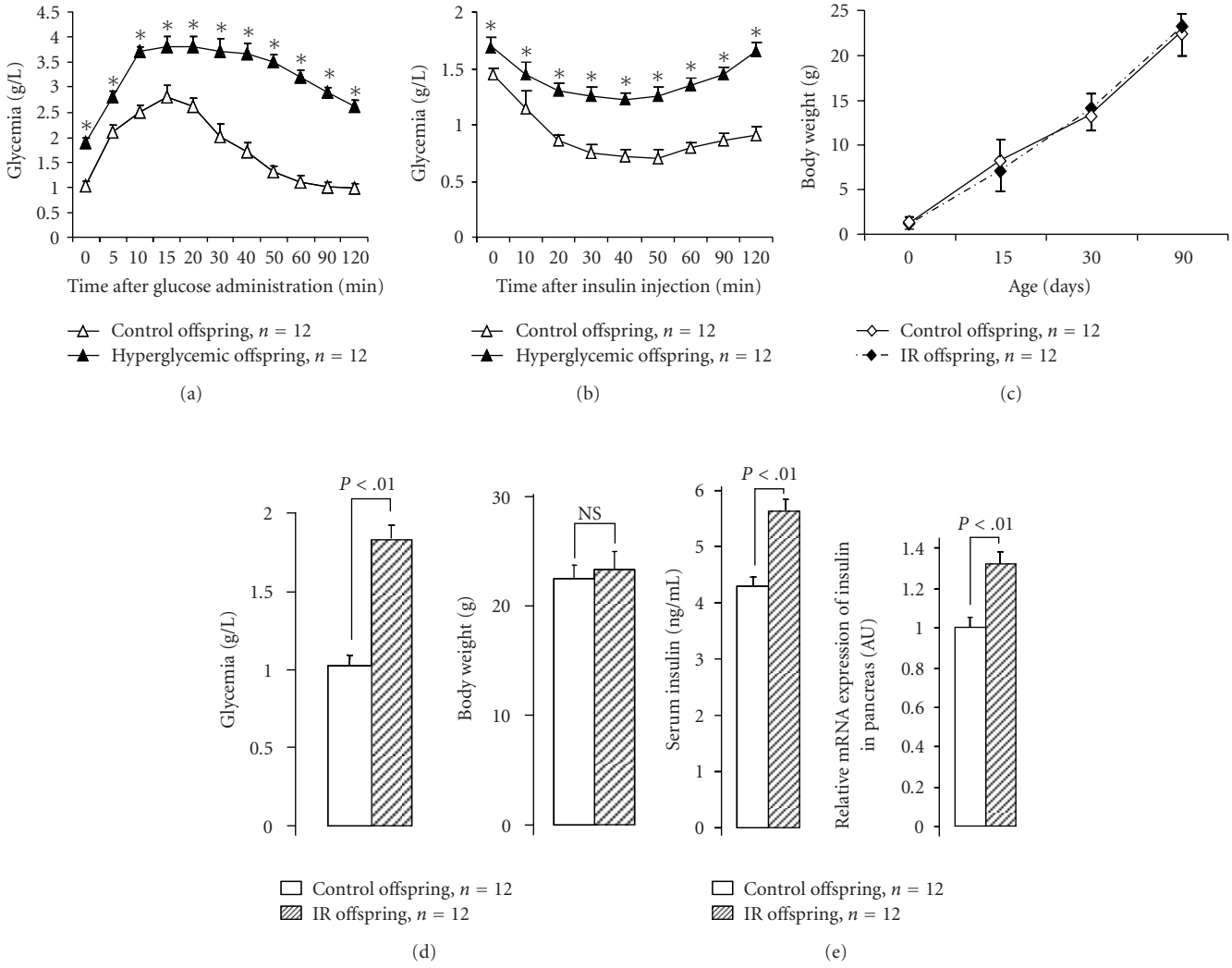

Figure 1: (a) *Oral glucose-tolerance tests (OGTT).* Glycemia during OGTT (3 g/kg-body weight) was measured after a 15-h fast, every 5–10 minutes, for 120 minutes following glucose administration. (b) *Intraperitoneal insulin-tolerance tests (IPITT).* Glycemia during IPITT (0.5 U/kg body weight) was measured after a 4-h fast, every 5–10 minutes, for 120 minutes following insulin injection. $^*P < .01$ significant difference between control offspring (open triangle) and hyperglycemic offspring (solid triangle). (c) *Evolution of the body weight of the offspring from birth until 3 months of age.* Open Square corresponds to control offspring and Solid Square to IR offspring. (d) *Glycemia and body weight at 3 months.* (e) *Serum insulin and insulin mRNA expression in the pancreas.* Glycemia, serum insulin, and its mRNA expression were determined as described in Section 2. The offspring were weighed during the study until the age of 3 months. The dams and the offspring after weaning were fed the standard laboratory chow. Values are means ± SEM, $n = 12$ per group of animals. AU: arbitrary units.

3.2. Glycemia, Body Weight, and Serum Insulin Concentration and Its mRNA Expression in Pancreas. There was no significant difference in the body weight between control and IR offspring, from their birth until 3 months of age (Figure 1(c)). However, the IR offspring were hyperglycemic and hyperinsulinemic and expressed high level of insulin transcript compared with their controls (Figures 1(d) and 1(e)).

3.3. Maf-A, Nkx6-1, Pdx-1, C/EBP-β, Glut 2, and Glucokinase mRNA Expression in the Pancreas. It is well known that glucose stimulates insulin release [9]. Moreover, Glut2 and glucokinase (GK) are implicated in the regulation of glucose metabolism gene transcription in β-cells [20, 21]. Besides, some factors like Pdx-1, Nkx6.1, and Maf-A are required for insulin gene transcription [7, 8]. Assessment of the beta-cell functionality may need hyperglycemic clamp study and glucose-tolerance test. As we have performed the glucose-tolerance test and assessed some major insulin gene transcription factors, we therefore examined the relative quantitative expression of mRNA encoding for these factors in the pancreas and assessed, in the β-cells, the levels of Glut2 and glucokinase mRNA. Indeed, while C/EBP-β mRNA was undetectable, IR offspring expressed higher Maf-A, Nkx6-1, and Pdx-1 transcripts than their corresponding controls (Figure 2(a)). Glut2 and GK mRNA expressions were downregulated in IR offspring compared to controls (Figure 2(b)).

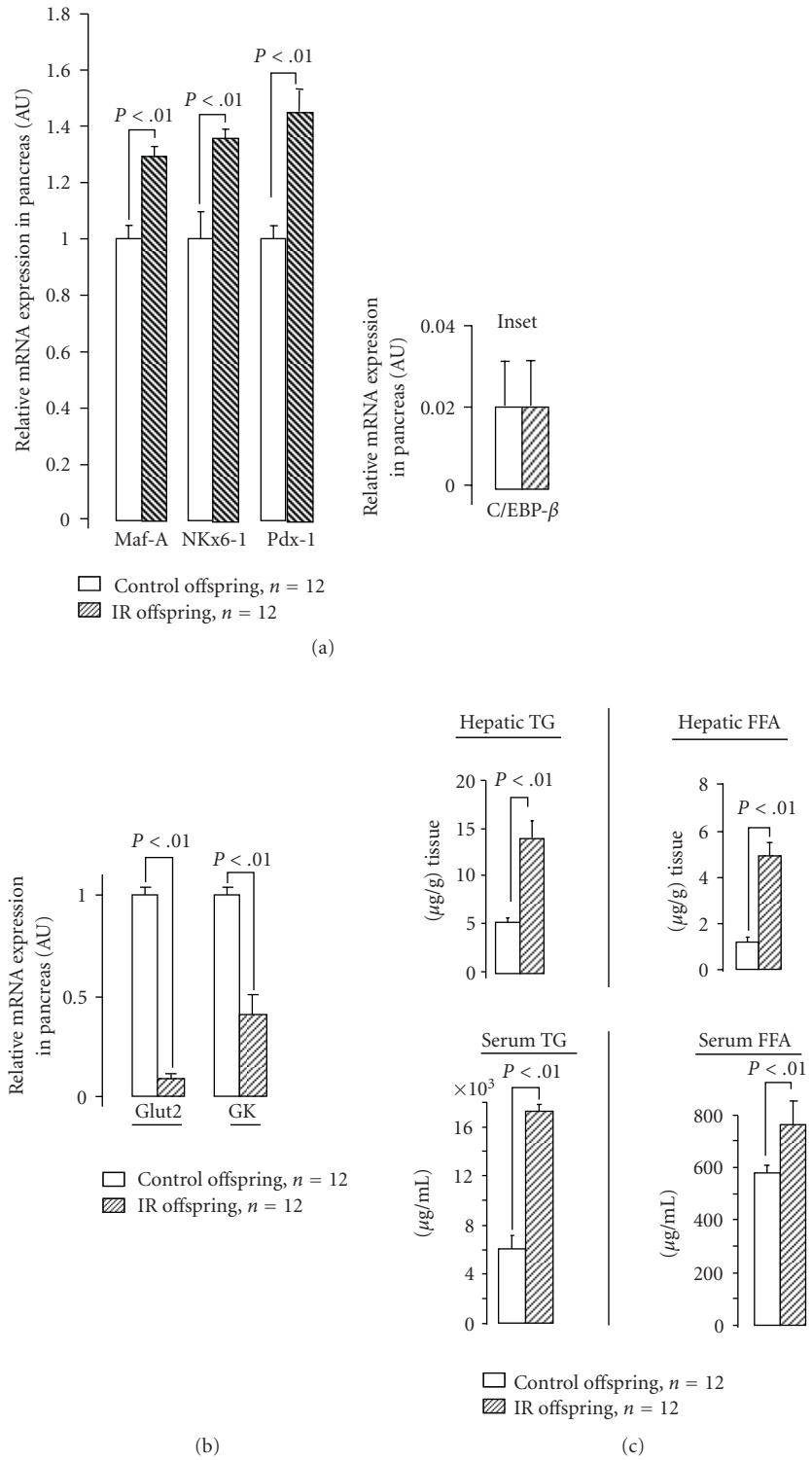

Figure 2: *Maf-A, Nkx6-1, Pdx-1, and C/EBP-β* (a), *Glut2 and GK* (b) *mRNA expression in the pancreas of IR and control offspring*. The expression of mRNA was quantitatively analyzed by employing real-time RT-PCR as described in Section 2. AU: arbitrary units. (c) *Serum and hepatic triglyceride (TG) and free fatty acids (FFA) in IR and control offspring*. The lipids were determined in serum and liver as described in Section 2. Values are means ± SEM, $n = 12$ per group of animals.

3.4. Serum and Hepatic TG and FFA Concentrations. Insulin resistance has been associated with hyperlipidemia [22]. Indeed, in the present study, IR offspring highly accumulated of TG and FFA in their liver and serum as compared to control animals (Figure 2(c)).

3.5. Adiposity, Adiponectin, Leptin, TNF-α, and IL-6 mRNA Expression in Epididymal Adipose Tissue. Obesity has been linked to high adiposity and hyperlipidemia [6, 23]. Moreover, it has been reported that chronic inflammation in fat plays crucial role in the development of insulin resistance [22]. Therefore, we assessed the weight of epididymal adipose tissue as well as the obesity-related parameters such as adiponectin and leptin and proinflammatory markers (TNF-α and IL-6). Indeed, IR offspring exhibited reduced epididymal adipose tissue mass than the control offspring (Figure 3(a)). The quantity of epididymal adipose tissue was positively correlated with the expression of mRNA of adiponectin ($R^2 = 0.87$ in controls offspring versus $R^2 = 0.90$ in IR offspring) and leptin ($R^2 = 0.85$ in controls offspring versus $R^2 = 0.95$ in IR offspring) (Figures 3(a) and 3(b)). Conversely, IR offspring showed increased expression of proinflammatory markers which are IL-6 and TNF-α in their epididymal adipose tissue (Figure 3(c)).

3.6. Liver Weight and FAT/CD36, SREBP-1c, TNF-α and IL-6, mRNA Expression in the Liver. While the IR offspring exhibited reduced epididymal adipose tissue mass, they showed higher liver weight than that of the controls (Figure 3(d)). Consequently, the liver of IR offspring exhibited features of steatosis. Furthermore, FAT/CD36 is actively implicated in the uptake of lipids and, hence, may contribute to high lipid contents in the liver. Moreover, chronic inflammation has been reported as a link between insulin resistance and obesity, associated with lipid accumulation [22, 24]. We therefore examined the expression of lipid transporters and some proinflammatory markers in liver. Indeed, while the expression of FAT/CD36 mRNA was upregulated, that of SREBP-1c mRNA was downregulated in the liver of IR offspring compared to controls (Figure 3(e)). There was no significant difference in expression of IL-6 mRNA (1.00 ± 0.12 versus 1.11 ± 0.14) and TNF-α mRNA (1.00 ± 0.10 versus 0.90 ± 0.15) in the liver of both groups of mice.

3.7. CD14, CD68, F4/80, TCRα, TLR-2, MCP-1, RANTES, and CCR5 mRNA Expression in Epididymal Adipose Tissue. Macrophages and T cells accumulation in adipose tissue characterized the inflammation in obesity [12, 14]. Since inflammation has appeared as a link between insulin resistance and obesity and diabetes [24], we examined the level of macrophage and T cell markers in the epididymal adipose tissue of insulin-resistant offspring. While none of the mRNA expression of F4/80, MCP-1 (infiltrated macrophages' marker), TCRα, RANTES, and CCR5 (infiltrated T cells' markers) was detectable from all animal groups, IR offspring expressed high level of CD14, CD68, and TLR-2 mRNA in their epididymal adipose tissue as compared to controls (Figures 4(a) and 4(b)).

4. Discussion

High-fat diet feeding induces obesity and metabolic disorders in rodents [3]. However, this dietary intervention is not well standardized. The question which type of high-fat diet is best to the model of human metabolic alterations remains unanswered. On the other hand, the use of monogenic models (such as the ob/ob mouse or the Zucker-(fa/fa) fatty rat) or pharmacologically-induced obesity models (such as the gold-thioglucose mouse) has raised some problems concerning the interpretation of the observed effects. The question of whether the results obtained arise from the obese phenotype or the model's genetic/pharmacological background is difficult to solve completely. These observations prompt researchers to generate obesity in animals by using fat-enriched (high-fat) diet strategies for several years now. Indeed, several studies have revealed that high-fat diets promote hyperglycemia and whole body insulin resistance, and their effects on target organs have been examined. Based on this experience, it is generally accepted that high-fat diets can be used to generate a valid rodent model for the metabolic syndrome with insulin resistance and altered beta-cell function [25–27]. However, the real difficulty is the definition of the term "high-fat diet" itself and the standardization of the exact fat content and fat composition of the diets. Various high-fat diets have been used with relative fat fractions between 20% and 60% energy as fat, and the basic fat component varies between animal-derived fats [3]. Consequently, all these diets are summarized under the term high-fat diets in the literature. This has inevitably led to a considerable variability in the results reported. In the present study, we propose a new model of pathological insulin resistance associated with maternal diabetic pregnancy. Therefore, the present study is designed to shed light on the pathophysiological model of insulin resistance, related to diabetic pregnancy in mice. The insulin-resistant (IR) offspring, in our laboratory, have been obtained from pregnant animals which were rendered diabetic by the administration of streptozotocin [4–6]. As far as the model design is concerned, we would like to mention that maternal streptozotocin administration before pregnancy affects fertility and impairs embryo development during the preimplantation period [28]. However, like in the present study, the induction of diabetes by streptozotocin injection on day 5 of gestation has no effect on embryo development [29]. Moreover, we induced diabetes during the second half of the first trimester of pregnancy with five low doses of streptozotocin starting on day 5 of gestation to mimic type 1 diabetic pregnancy, following a T lymphocyte-dependent process [30, 31]. Moreover, the administration of low doses of streptozotocin to rodents represents a good model of diabetes development, and this is for several reasons: (i) islet lesions in this experimental model resemble to those of human insulitis, with a predominance of $CD8^+$ T cells [30], (ii) the animals used are normal and do not have an underlying immune abnormalities like BB rat, being lymphopenic with few peripheral $CD8^+$ T cells [32], and NOD mice which have systemic immune abnormalities [33], (iii) the onset of diabetes is controlled, and (iv) the Th1/Th2

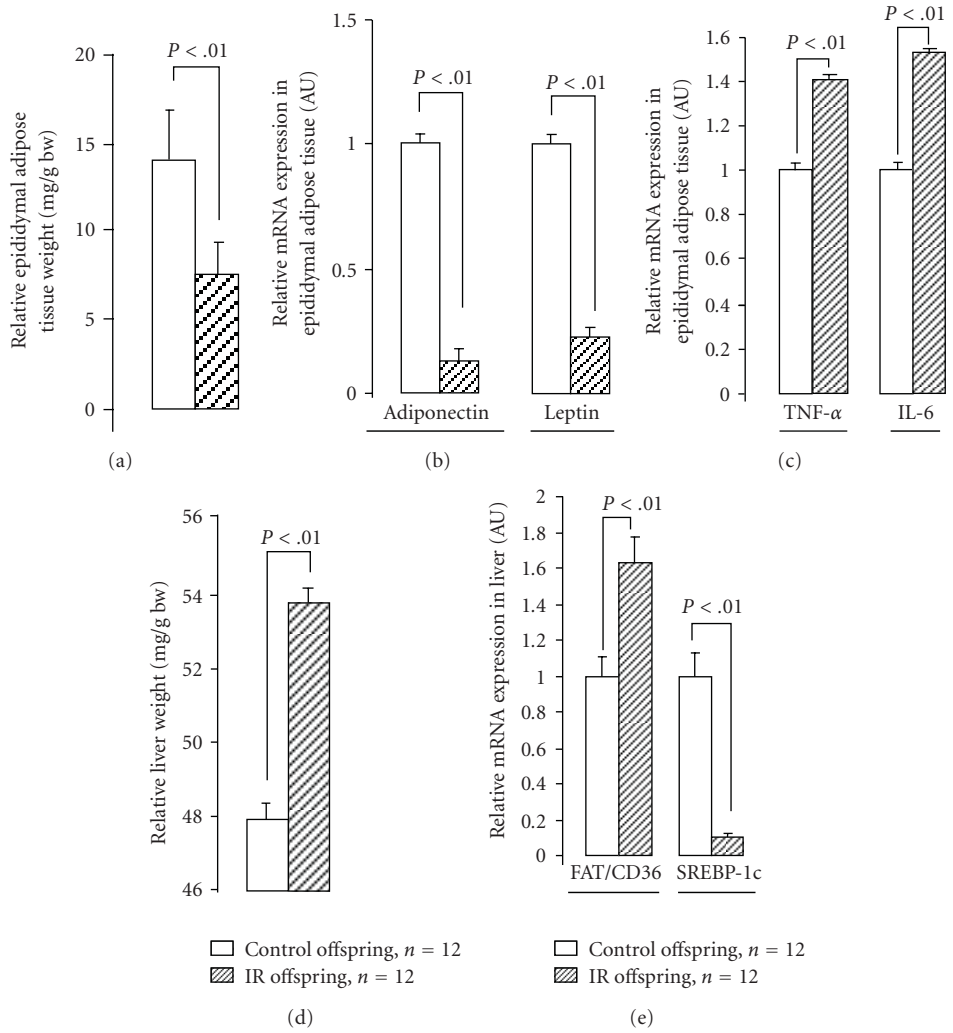

Figure 3: *Relative epididymal adipose tissue weight* (a) *and adiponectin and leptin* (b), *and TNF-α and IL-6* (c) *mRNA expression in epididymal adipose tissue. Relative liver weight* (d) *and FAT/CD36 and SREPB-1c mRNA expression in liver* (e) *of IR and control offspring.* The liver and epididymal adipose tissue weights are expressed as milligrams (mg) of the tissue per grams (g) of body weight of mice. The expression of mRNA was quantitatively analyzed by employing real-time RT-PCR as described in Section 2. Values are means ± SEM, $n = 12$ per group of animals. AU: arbitrary units. The quantity of epididymal adipose tissue was positively correlated with the mRNA expression of adiponectin and leptin two obesity-related parameters; R^2 = coefficient of correlation between the mass of epididymal adipose tissue and the level of the expression of adipokines (*adiponectin and leptin)* in each group of animals.

dichotomy can be observed during diabetes in these animals [30, 34]. These IR offspring of diabetic dams showed, after OGTT, a high hyperglycemia compared with control offspring. Moreover, the IPITT demonstrated decreased insulin sensitivity in these mice. These observations confirmed a real insulin resistance in these offspring [35, 36].

The first and foremost question is how the hyperglycemia modulates pancreatic β-cell functions. We observed that IR mice born to diabetic dams had higher serum insulin levels and pancreatic insulin transcripts than control mice, in accordance with our previous observations [5, 6]. Pancreatic β-cells produce and store insulin in response to physiological demand, and hyperglycemia, within 15 minutes, results in the activation of a complex network of intracellular signalling pathways that trigger insulin release [37]. The hyperinsulinemic state of IR offspring may be due to high expression of the major insulin gene transcription factors which are Pdx-1, Maf-A, and Nkx6 in their pancreas [38]. Indeed, other investigators have shown that the deletion of Pdx-1 gene in the pancreas results in abnormally low insulin concentrations [39]. In our study, the glucose-induced hyperinsulinemia does not seem to be mediated by C/EBP-β as the expression of this repressor of insulin gene was not significantly altered in both groups of animals. Pancreatic β-cell function is associated to glucokinase activity [21]. IR mice exhibited low expression of glucokinase and Glut2 mRNA in the pancreas and this phenomenon might be responsible for impaired glucose transport and metabolism, thus contributing to high glucose concentration in these animals, as suggested by Ahlgren et al. [39] that reduced

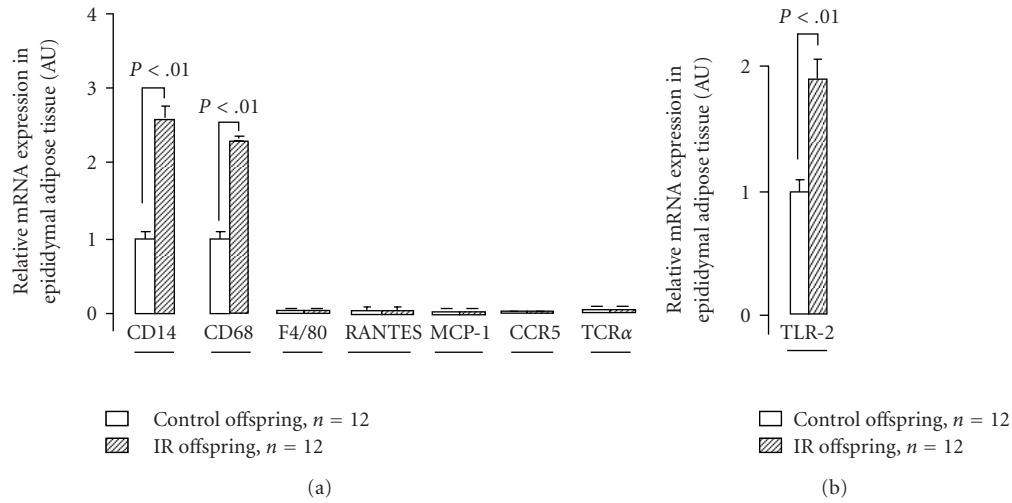

Figure 4: *The mRNA expression of CD14, CD68, F4/80, RANTES, CCR5, MCP-1, TCRα* (a), *and TLR-2* (b) *in epididymal adipose tissue of IR and control offspring.* The expression of mRNA was quantitatively analyzed by employing real-time RT-PCR as described in Section 2. Values are means ± SEM, $n = 12$ per group of animals. AU: arbitrary units.

Glut2 levels lead to hyperglycemia. Indeed, glucose has been shown to stimulate insulin release and the transcription of insulin gene and translation of the nascent mRNA in pancreatic β-cells [9]. Several investigators have interestingly demonstrated both *in vivo* and in primary culture *in vitro*, that the effect of glucose on glycolytic and lipogenic genes in GK knockout hepatocytes is lost because of the impaired ability of these cells to efficiently metabolize glucose [40]. Moreover, other investigators have shown that downregulation of SREBP-1c expression induces a markedly decrease in Glut2 expression [41]. Thus, we can state that the hyperglycemic state in IR offspring might be also due to the marked decreased expression of GK and Glut2, as these animals, in addition, exhibited low expression of SREBP-1c which may contribute to decreased level of Glut2 [41]. However, it is useful to specify that this hyperglycemia in IR mice might also be due to low insulin sensitivity in target peripheral organs.

While the IR offspring exhibited reduced epididymal adipose tissue mass, they showed increased liver weight than the control offspring and, consequently, the liver of IR offspring showed features of steatosis. This could, at least in part, account for their similar body weight despite reduced epididymal adipose tissue mass in IR offspring which also abundantly accumulated FFA and TG [5, 6]. It has been well established by several studies that diabetes mellitus induces hyperlipidemia in mothers and in their obese offspring [5, 42, 43]. In diabetic rats, high levels of triglyceride in maternal circulation may create a steep concentration gradient across the placenta, which accelerates their transport and deposition in fetal tissues [43]. This hypertriglyceridemia persists with age and has been linked to the development of insulin resistance and hyperlipogenesis [44]. Besides, IR offspring exhibited high levels of CD36/FAT which will again participate in high uptake of lipids by liver and will ultimately contribute to liver steatosis in these animals. Furthermore, the mRNA of SREBP-1c is downregulated in IR offspring. SREBP-1c controls the transcription of lipogenic genes. Hence, a high accumulation of TG and FFA in the liver, due to high expression of FAT/CD36, might be responsible for the low expression of SREBP-1c in these animals. On the other hand, some authors have demonstrated, *in vivo* and *in vitro*, that hepatic GK is required for synergistic action of SREBP-1c and ChREBP on glycolytic and lipogenic gene expression [40]. Other investigators have observed altered expression and activity of SREBP-1c in GK-knockout mice [45]. As the IR mice, in our study, expressed low GK, we can state that reduced expression of SREBP-1c might be due to the low expression of glucokinase mRNA.

Adipokines, secreted by adipose tissue, are required for a number of metabolic processes [46]. In this study, adiponectin and leptin levels were positively correlated with the epididymal adipose tissue mass which decreased in IR offspring. These observations are in accordance with our previous results in macrosomic infants of gestational diabetic women [47]. Furthermore, Guerre-Millo et al. [48] have also shown that high-fat diet-fed mice exhibited higher glucose levels and lower adiponectin concentrations than the standard diet animals. Hence, reduced adiponectin will again contribute to insulin resistance as this adipokine, an anti-inflammatory agent, has been shown to enhance insulin sensitivity [49, 50]. In our study, IL-6 and TNF-α mRNA are upregulated in the epididymal adipose tissue of IR offspring. It has been recently shown that adipose tissue, during insulin-resistant state, secrete IL-6 and TNF-α [14]. Moreover, high levels of TNF-α and IL-6 may also downregulate the expression of adiponectin [51].

In IR offspring, increased IL-6 might not only diminish insulin sensitivity by suppressing insulin signal transduction but also interfere with anti-inflammatory effect of insulin, and might favour inflammation during insulin-resistance state, as demonstrated by Dandona et al. [24]. Furthermore,

IL-6 has been shown to be one of the mediators of hyperinsulinemic state [52]. It is interesting to mention that 10%–35% of the body's basal circulating IL-6 is derived from adipose tissue and a positive correlation has been found between insulin resistance and circulating IL-6 [24]. Thus, we can state that hyperglycemia may be one of the factors implicated in IL-6 expression [24].

As far as inflammation in adipose tissue is concerned, we observed that CD14 and CD68 mRNA expression, but not F4/80, was upregulated in epididymal adipose tissue of IR offspring. These observations suggested that the adipocytes seemed to be differentiated into macrophage-like cells, as they expressed upregulated transcripts of CD14 and CD68 antigens, generally expressed by macrophages. However, there was no peripheral macrophages infiltration into epididymal adipose tissue, as the expression of F4/80, a true macrophage marker, was downregulated. Our results are in close agreement with those of Khazen et al. [53] who have reported that murine and human adipose tissue express CD14 and CD68, but not F4/80, both at protein and mRNA levels. Besides, Cousin et al. [54] have demonstrated that preadipocytes can be differentiated into macrophage-like cells which are stained with MOMA-2, a marker of monocyte-macrophage lineage, but are negative for F4/80. Besides, the lack of expression of MCP-1, a monocytes/macrophages chemoattractant, provides an additional argument for the absence of macrophages in epididymal adipose tissue of these animals. Moreover, it has been reported that RANTES and its receptor CCR5 are expressed principally on infiltrated T cells in adipose tissue during insulin resistance in high-fat diet-fed animals [14]. In our study, we could not detect both RANTES and CCR5 mRNA in epididymal adipose tissue of the IR mice. Furthermore, we did not observe the expression of TCR-alpha mRNA, suggesting that T cells are not infiltrated in epididymal adipose tissue of these mice. These findings corroborate the study of Xu et al. [22] who did not observe infiltration of T cells in white adipose tissue of both genetic and high-fat diet-induced mouse models of insulin resistance.

In vitro differentiated adipocytes have been shown to express TLR-2 [55] and the polymorphism of TLR-2 gene significantly correlates with a higher risk of insulin resistance [56]. We observed that TLR-2 mRNA expression increased in epididymal adipose tissue of IR mice and these observations corroborate the report of Murakami et al. [36] who have shown that the adipocytes, in rats fed a high-fat diet, coexpress TNF-α and TLR-2, and these adipocytes do not express F4/80. Besides, these authors [36] have suggested that adipocytes coexpressing TNF-α and TLR-2 might be "pathological" cells in fat tissue, promoting the development of insulin resistance as seen in metabolic syndrome. Finally, we observed that IR offspring exhibited a high level of FFA in serum and liver. Murakami et al. [36] have also shown that increased FFA level may activate inflammatory pathway in adipocytes, and TLR-2 seems to contribute to this pathway by inducing TNF-α production.

Therefore, the novelty of our study is that, in this model of insulin resistance without obesity, the inflammatory state of epididymal adipose tissue of IR offspring is intrinsic to this organ which cells seemed to be differentiated into macrophage-like cells, but not because of the macrophages or T cell infiltration.

5. Conclusion

To sum up, our study demonstrates that the hyperinsulinemia, observed in IR offspring of diabetic dams, appears as a pathological model of insulin resistance which is associated with altered expression of genes of insulin transcription factors and glucose metabolism-related enzymes. Our study will help understand the mechanisms of insulin resistance in offspring, born to diabetic mothers, as several studies have shown that these offspring are prone to develop metabolic syndrome [5, 44].

Conflict of Interests

All of the authors have nothing to declare as far as the conflict of interests is concerned.

Abbreviations

IR:	Insulin-resistant
GK:	Glucokinase
Pdx-1:	Pancreatic and duodenal homeobox-1
Nkx6.1:	NK6 transcription factor related-locus-1
MCP-1:	Monocyte-chemoattractant protein-1
RANTES:	Regulated on activation of normal T cell expressed and secreted
ChREBP:	Carbohydrate response element-binding protein
SREBP1c:	Sterol response element-binding protein 1c
FAT/CD36:	Fatty acid translocase
TG:	Triglyceride
TLR:	Toll-like receptor
FFA:	Free fatty acids.

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Clinical Study

Vitamin A Deficiency after Gastric Bypass Surgery: An Underreported Postoperative Complication

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Introduction. Few data are available on vitamin A deficiency in the gastric bypass population. *Methods*. We performed a retrospective chart review of gastric bypass patients ($n = 69$, 74% female). The relationship between serum vitamin A concentration and markers of protein metabolism at 6-weeks and 1-year post-operative were assessed. *Results*. The average weight loss at 6-weeks and 1-year following surgery was 20.1 ± 9.1 kg and 44.1 ± 17.1 kg, respectively. At 6 weeks and 1 year after surgery, 35% and 18% of patients were vitamin A deficient, (<325 mcg/L). Similarly, 34% and 19% had low pre-albumin levels (<18 mg/dL), at these time intervals. Vitamin A directly correlated with pre-albumin levels at 6 weeks ($r = 0.67$, $P < 0.001$) and 1-year ($r = 0.67$, $P < 0.0001$). There was no correlation between the roux limb length measurement and pre-albumin or vitamin A serum concentrations at these post-operative follow-ups. Vitamin A levels and markers of liver function testing were also unrelated. *Conclusion*. Vitamin A deficiency is common after bariatric surgery and is associated with a low serum concentration of pre-albumin. This fat-soluble vitamin should be measured in patients who have undergone gastric bypass surgery and deficiency should be suspected in those with evidence of protein-calorie malnutrition.

1. Introduction

Obesity, defined as a body mass index (BMI) ≥ 30 kg/m^2, is a chronic disease with major health and economic implications and is recognized as one of the greatest contributors of excessive morbidity and mortality in the 21st century. Approximately 30% of the American population is obese, making it the leading nutritional disorder in our society [1]. This trend has escalated to epidemic proportions with a disproportionate increase in persons with superobesity, defined as those with a BMI ≥ 50 kg/m^2.

In 1991, the National Institutes of Health issued a consensus statement concluding that in the morbidly obese, bariatric surgery is the most successful intervention for long-term weight loss [2]. Significant weight loss following bariatric surgery reduces the inherent obesity-specific comorbidities, lowers cardiovascular risk, and provides a survival benefit in this escalating patient population [3, 4]. Weight loss surgery has become increasingly utilized, with greater than 225,000 procedures performed in the United States in 2008 according to the American Society of Metabolic and Bariatric Surgery [5].

Due to the malabsorption induced by the procedure, in conjunction with a reduced gastric volume and alterations in eating behaviors, there is an increased risk of developing certain mineral and vitamin deficiencies. Retinol deficiency is more commonly associated with malabsorptive weight loss surgical interventions, and fewer studies have reported

this outcome with Roux-en-Y gastric bypass surgery [6, 7]. Routine postoperative laboratory surveillance at our institution identified a direct recurring coupling of deficiencies of serum retinol and prealbumin concentration; this association has not been previously described in the gastric bypass literature.

2. Methods

We performed a retrospective chart review of 122 obese patients (96 women, 26 men) who underwent Roux-en-Y gastric bypass surgery at William Beaumont Hospital in Royal Oak, Michigan, USA. Fifty-four charts had incomplete data and were excluded from analysis; the remaining 69 subjects served as our study population. The patient population was preapproved for surgery from a multidisciplinary perspective at the William Beaumont Hospital Weight Control Center. The surgeries were performed between October 2005 and July 2007 by two affiliated bariatric surgeons. Data were obtained from William Beaumont Hospital's electronic chart system (One Chart, EPIC systems Corporation) and operative reports.

Serum markers of nutrition were assessed including: prealbumin, albumin, total protein, and retinol. Roux limb measurements were analyzed as a potential mediator of malabsorption, and liver function studies were obtained. Patients were interviewed at baseline and follow-up intervals by our team of bariatric dietitians for nutritional compliance with dietary protein intake. Confidentiality was protected by assigning patients' anonymous numbers, and the study was approved by the hospital's Human Investigation Committee.

3. Postoperative Treatment

Our protocol at the William Beaumont Hospital Weight Loss Center involves regular follow-up outpatient visits at 6 weeks, 3, 6, 9, and 12 months with a multidisciplinary team that includes a dietitian, exercise physiologist, psychologist, and bariatrician. The dietitian works to optimize dietary intake and assess for food intolerances. A comprehensive nutritional intake routinely evaluates macronutrient composition. Routines recommendations include consuming a higher daily intake of lean protein (approximately 1.2 g/kg of ideal body weight), which generally corresponds to 55–80 and 70–110 grams for women and men, respectively. Other important dietary principles include avoidance of excessive sugars (>5 grams per serving), which can promote a Dumping Syndrome, and inclusion of <30% of daily intake from fat per day to avoid steatorrhea. Patients are also counseled to minimize the consumption of partially saturated and hydrogenated fats. We routinely recommend a chewable multivitamin twice daily, calcium citrate 500 mg three times daily with 400 IU of vitamin D, ferrous sulfate 30 mg daily separated by 2 hours from the calcium compound, and 1000 mcg of cyanocobalamin daily to prevent vitamin and mineral deficiencies. Laboratory surveillance of commonly reported mineral and vitamin deficiencies as well as protein levels prompted a tiered response of additional treatments as needed.

Table 1: Baseline demographic variables.

	Baseline
Mean age (yrs)	48.8 ± 12.6
Female (%)	73.9
Weight (kg)	64.8 ± 13.2
BMI (kg/m^2)	51.2 ± 9.4
Roux limb length (cm)	113.6 ± 33.1

4. Statistical Analysis

Demographics and baseline characteristics are reported as means ± standard deviation (SD) or counts with percent frequencies as appropriate. Spearman correlations were completed between weight change and vitamin A levels with all the continuous variables at both 6 weeks and 1 year. Univariate comparisons between patients meeting their protein goal and those that did not were made using either a test for normally distributed data or Wilcoxon rank tests for the outliers. Categorical variables were examined using Pearson's chi-square as appropriate (expected frequency > 5; otherwise Fisher's Exact tests were used). These same tests were completed between patients with and without vitamin A deficiency. Statistical significance was chosen at $P \leq .05$. All analyses used The SAS System for Windows version 9.2, Cary, NC.

5. Results

Baseline demographic information of our study population is in Table 1. Weight loss at 6 weeks and 1 year following surgery was 20.1 ± 9.1 kg and 44.1 ± 17.1 kg, respectively (Figure 1(a)). At 6 weeks and 1 year, 35% and 18% of patients were vitamin A deficient (<325 mcg/L). Similarly, 34% and 19% had low prealbumin levels (<18 mg/dL) at these time intervals (Figure 1(b)). Vitamin A directly correlated with prealbumin levels at 6 weeks ($r = 0.67$, $P < .001$), and 1-year ($r = 0.67$, $P < .0001$). There was no significant correlation between roux length measurement and serum vitamin A concentrations, at 6 weeks and 1 year ($r = 0.008$ and -0.008, resp.; $P = .96$ for both). Similarly, the correlations between the roux length and prealbumin concentrations at 6 weeks or 1 year were insignificant ($r = -0.08$; $P = .55$ and $r = -0.001$; $P = .99$). Achieving dietary protein intake goal, defined as average daily dietary protein intake within 5 grams of intake goal or greater on average, was also not associated with serum levels of vitamin A at 6 weeks or 1 year ($P = .41$; $P = .24$, resp.). No significant correlations between vitamin A levels and markers of liver function (aspartate aminotransferase and alanine aminotransferase) were observed at 6 weeks ($P = .29, .98$, resp.) or at 1 year ($P = .34, .99$, resp.). Vitamin K assessments were not included in the study methodology and cannot be commented on. We examined the associations between zinc, protein, and vitamin A in various forms and did not identify any significant relationships.

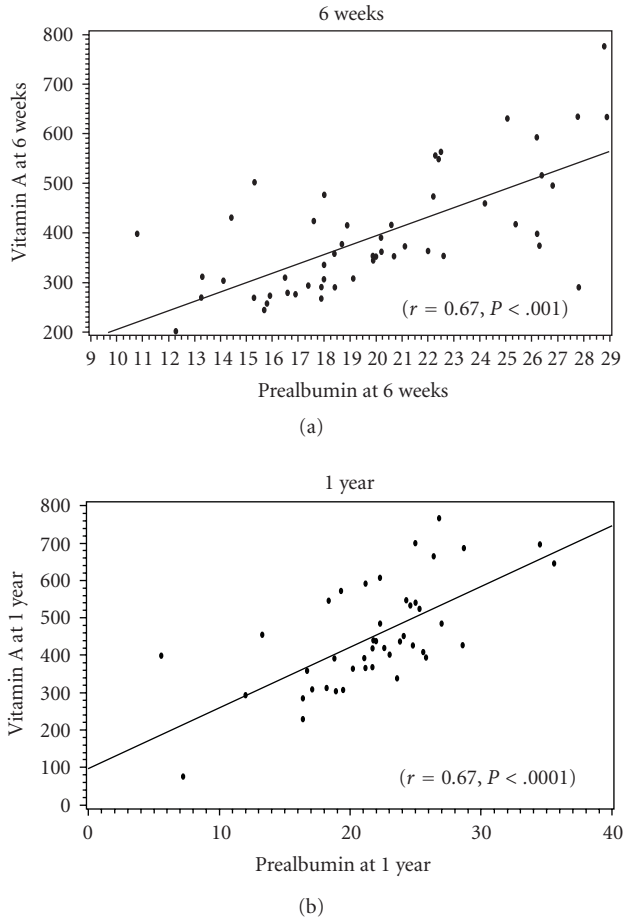

Figure 1

6. Discussion

Vitamin A is an essential fat-soluble vitamin absorbed through the small intestine as either retinol (animal derived) or carotene (plant and vegetable derived). Subsequently, it is converted to retinyl palmitate and hydrolyzed to bound retinyl binding protein that transports vitamin A to tissues. Several potential mechanisms may exacerbate vitamin A deficiency in a postoperative gastric bypass patient. First, the deficiency may arise from surgically bypassing the duodenum and first portion of the jejunum, promoting an iatrogenically induced malabsorption. Second, drastic decreases in the dietary intake of many micronutrients like carotenoids and retinol, especially in early recovery, are likely to occur. In addition, traditional dietary recommendations after gastric bypass include a low-fat diet which potentially limit the absorption of fat-soluble vitamins. This patient subset may also be at risk due to confounding nonalcoholic steatohepatitis, higher rates of cirrhosis, or both, which may interfere with maintaining vitamin A storage and production. Finally, higher levels of oxidative stress may also occur after gastric bypass surgery, which can interfere with vitamin A absorption and processing.

Vitamin A deficiency is rarely described in Western society; however, worldwide, it remains the most common etiology of visual disturbances, including blindness. Vitamin A deficiency has been ascribed to a wide variety of ophthalmologic complications including conjunctival and corneal xerosis, keratomalacia, retinopathy, visual loss, and nyctalopia. Moreover, retinol supports photosensitive pigmented cells of the retinal rods and cones that are necessary for optimal visual acuity.

Serum retinol levels and protein-calorie malnutrition have been correlated among children and infants in developing nations. Vitamin A deficient children treated with an augmented dietary protein intake demonstrated an increase in serum protein markers as well as serum retinol levels [8]. In this extreme clinical scenario, retinol deficiency was successfully managed through this dietary intervention alone, without the addition of vitamin A rich foods or vitamin A supplementation [9]. The present findings support the intimate interaction that serum retinol levels have to carrier proteins which determine the bioavailability of serum retinol concentration and reinforce the interdependent relationship of these nutritional markers. As such, total body stores of vitamin A may not be truly deficient; in reality, limited access to nutritional protein binding and transport capacity may underlie these serum retinol findings. These data suggest that addressing the nutritional protein levels is necessary in conjunction with deficient serum retinol concentrations.

There are several case series describing vitamin A deficiency with visual disturbances involving patients who have had gastric or intestinal surgery [6, 7, 10]. None of our patients complained of visual disturbance; however, ocular complaints may have been underreported in the scope of this paper because many clinical features especially early in the course of retinol deficiency can be vague or nonspecific and may not have been recognized as clinically relevant. Additionally, these variables were assessed over a relatively short follow-up interval. It is important to acknowledge this potential complication after bariatric surgery in patients who undergo longstanding iatrogenic malabsorption with limited nutritional protein stores [10] and consider appropriate diagnostic testing and referral for ophthalmologic assessment, when appropriate.

7. Limitations

Our investigation has all the limitations of a small retrospective study. The study cohort was obtained via available data. Accordingly, our population was limited to those patients who were compliant with their baseline evaluation, 1-year follow-up exam and serial laboratory testing. Subjects with missing preoperative or postoperative lab values were excluded from the analysis, which may have biased our study in representing a more compliant subset of patients. Because we captured these data in the scope of clinical management, multivitamin brands and additional retinol supplementation may have varied according to patient preference and our treatment methodology. We also did not account for other potential confounding variables, including physical activity, nutritional compliance, or the duration of supplementation.

Accordingly, we are not able to make treatment recommendations for these deficiencies. Nevertheless, vitamin A deficiency is of escalating interest in clinical centers and will likely be the focus of future research. Finally, baseline vitamin A levels were not obtained.

8. Conclusion

We noted a striking, direct relationship between postoperative nutritional protein levels and vitamin A concentrations in our gastric bypass populations. Vitamin A deficiency is common after gastric bypass and is directly associated with a low serum prealbumin concentration, a measure of protein-calorie malnutrition. This fat-soluble vitamin deficiency should be considered in postoperative patients and deficiency should be strongly suspected in those with evidence of protein calorie malnutrition. Improving awareness and understanding of total body vitamin A utilization is of paramount importance in the ongoing medical management of this at-risk population.

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