Review Article

The Effect of Bariatric Surgeries on Nonalcoholic Fatty Liver Disease

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ABSTRACT

Objective: A review of published data addressing hepatic histopathological, metabolical, and functional changes following gastric banding, sleeve gastrectomy, gastric bypass surgery, and biliopancreatic with duodenal switch surgeries on nonalcoholic fatty liver disease (NAFLD). NAFLD is currently the most common chronic liver disease. Owing to the strong relationship between obesity and NAFLD, the idea of weight reduction as a method to treat NAFLD has rapidly emerged. Bariatric surgery has proved to be the most efficient method for weight reduction; hence, their beneficial effects on NAFLD have been evaluated by several studies. A literature review of published data was performed during the years 2012-2014 using PubMed with the following key words: Bariatric, NAFLD, steatosis, sleeve gastrectomy, gastric bypass, gastric banding, biliopancreatic diversion with duodenal switch, obesity, and insulin resistance (IR). Exclusion criteria were non-English articles and inherited NAFLD, pregnancy-induced NAFLD, and children. The majority of published data are in favor of indicating that bariatric surgeries improve the histologic and metabolic changes associated with NAFLD. The suggested mechanisms are: The reversal of IR, reduction of inflammatory markers, and improved histological features of NAFLD. Accordingly, bariatric surgeries are potentially one of the future methods in treating patients with morbid obesity and NAFLD. However, some questions remain unanswered, such as whether timing of surgery, type of surgery most effective, and whether bariatric surgeries are capable of curing the disease. Long-term and well-designed prospective studies are needed to address these issues.

Key Words: Bariatric, gastric bypass, gastric banding, insulin resistance biliopancreatic diversion with duodenal switch, nonalcoholic fatty liver disease, obesity, steatosis, sleeve gastrectomy

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Increased consumption of high-density food and declining physical activity have led to an epidemic of obesity.[1] Obesity affects health adversely, thereby increasing comorbid metabolic disorders such as type 2 diabetes mellitus (T2DM), hypertension, hyperlipidemia, and steatohepatitis.[2] This hepatic pathology is part of a wide spectrum of liver pathologies known as nonalcoholic fatty liver disease (NAFLD),[3-7] which is becoming the most common type of chronic liver disease.[8-10]

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OBESITY

Definition

Obesity is defined by the World Health Organization (WHO) as an abnormal or excessive fat accumulation that may impair health, with body mass index (BMI) greater than or equal to 30 kg/m^2.[11] Obesity is associated with metabolic alterations including insulin resistance (IR), hyperinsulinemia, dyslipidemia, hypertension, endothelial dysfunction, pro-atherogenic and chronic inflammatory status.[12-15]

Prevalence

WHO and International Obesity Task Force reported that 312 million adults worldwide are obese. WHO also reported that an estimate of more than 1.4 billion adults, were overweight. Of these overweight adults, over 200 million men and nearly 300 million women are obese. Overall, more than one in 10 of the world's adult

population are obese,[16] with Middle East, Pacific Islands, Southeast Asia, and China being the areas at greatest risk.[17] In Saudi Arabia, obesity is increasing with an overall prevalence of 35.5%; in comparison, females were significantly more obese than males with a prevalence of 44% and 26.4%, respectively.[18]

NONALCOHOLIC FATTY LIVER DISEASE

Definition

NAFLD is a spectrum of diseases that is associated with fatty infiltration of the liver that starts with simple fat accumulation (steatosis), which may progress into hepatic inflammation, termed as nonalcoholic steatohepatitis (NASH), with or without accompanying hepatic fibrosis/cirrhosis, with some patients eventually developing hepatocellular carcinoma.[19-21] It was first reported by Ludwig in 1979, who described it as an alcoholic-like liver disease in nonalcoholic people.[22] Until the last decade little information existed about the pathogenesis, etiology, or progression of the disease.

Kleiner proposed the NASH activity score (NAS), which is designed by the Pathology Committee of the NASH Clinical Research Network to grade the active histological features of NASH. The score is the sum of all features: Steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2); ranging from 0 to 8. Score less than 3 is not NASH, whereas a score equal to or more than 5 is a definite NASH.[23]

Prevalence

Due to the modern lifestyle we are living, NAFLD prevalence is increasing in today's population,[24] being the most common chronic liver disease.[25,26] It is estimated to occur in approximately 30% of the general population in western countries,[27] and it ranges from 65% to 92.3% in morbidly obese patients (BMI > 35 kg/m^2),[3-6] with up to 25% of them having NASH.[7] Moreover, the estimated prevalence of NAFLD in Saudi Arabia is 7%-10% of the general population.[26]

NAFLD Pathophysiology

The exact cause of NAFLD is still unknown; however, many theories have been proposed. The most quoted theory was the "2-hit" hypothesis, which states that NAFLD is initiated with hepatocyte accumulation of triglycerides (TGs) resulting in steatosis. This makes hepatocytes more prone to the second hit, played by the inflammatory cytokines, adipokines, mitochondrial dysfunction, and oxidative stress, which lead to steatohepatitis and/or fibrosis.[28,29] It is important to note that TGs themselves are not hepatotoxic[30]; however, they are considered as markers for increased hepatic exposure to potentially toxic-free fatty acids (FFAs).[31]

More recently, a third hit "inadequate hepatocyte proliferation" was proposed to the hypothesis. Normally the loss of hepatocytes stimulates its multiplication. However, the presence of inflammatory mediators and radical oxygen species may hinder hepatocyte replication. This results in further damage and increased number of hepatic progenitor described as oval cells,[32] which have the ability to differentiate into hepatocyte-like cells. The degree of oval cell activation and intermediate hepatocyte-like cells have shown positive correlation with fibrosis stage. In addition, these cells are also implicated in the pathogenesis of hepatocellular carcinoma that could be a possible consequence of NAFLD.[31,32]

Most attention has been focused recently on the effect of IR on the development and progression of NAFLD. IR is a condition in which a certain amount of insulin does not produce the expected biological effect on insulin-sensitive tissue.[33] In IR, there is an increased influx of FFAs into the liver, which undergoes either β-oxidation or esterification with glycerol to form TGs, resulting in an additional source of fat in the liver. FFAs are known to have a negative effect on insulin action on targeted peripheral tissue.[34] There is also evidence that FFAs can directly lead to hepatotoxicity via oxidative stress and activation of inflammatory pathways such as TNF-α[35] and leptin, which are produced by macrophages and adipocyte, respectively.[36,37] Some studies have suggested that the toxic effect of unesterified FFAs could be prevented by hepatic TG accumulation.[31,38]

Obese patients are in a chronic inflammatory state, which is correlated with IR as elevation of both tumor necrosis factor-α (TNF-α) and monocyte chemotactic protein-1 (MCP-1) which causes impairment of adipocyte insulin sensitivity.[39-41] In addition to IR and hyperinsulinemia being caused by obesity, there is also ground for a considerable possibility that IR contributes to the development of obesity. The latter happens by increasing the circulating insulin leading to weight gain.[42,43] Inflammation and activation of several immune pathways in obese patients affect hepatic lipid metabolism, leading to hepatic injury.[28,29,44] Adipose tissue inflammation starts by recruitment and stimulation of monocytes in the adipose tissue by chemokines such as MCP-1 and osteopontin.[14,39,45] The hypertrophied visceral adipocytes in morbidly obese patients release chemokines that lead to further macrophage infiltration into the adipose tissue. This will result in the production of proinflammatory cytokines, and these inflammatory modifications create what is known as "adipocyte dysregulation."[2,46]

Recently, dysregulated adipocytokines were divided into "offensive" and "defensive" adipocytokines. Offensive adipocytokines include plasminogen activator inhibitor-1,[47] TNF-α,[40,48] interleukin-6 (IL-6),[49] MCP-1,[41] and angiotensinogen.[50] Examples of defensive adipocytokines

are Adiponectin[51-53] and leptin.[54-56] The dysregulation of adipocytokines such as these contributes to obesity-related metabolic disorders including NAFLD.[2] However, the mechanisms by which TG accumulation leads to abnormal expression of adipocytokines and development of the metabolic syndrome have not been fully clarified.

BARIATRIC SURGERIES

Due to the strong association of NAFLD with obesity,[3-7,57-60] weight loss proved to have a beneficial effect on NAFLD.[5,60,61] In patients who have failed dietary manipulation and weight reduction exercise programs, bariatric surgeries have proved to be the most effective way for durable, marked, and sustained weight loss.[62-66]

Types of Bariatric Surgeries

There are 3 principles of bariatric operations, categorized in respect to their mechanism: (1) Restrictive procedures, which decrease the stomach size to limit the intake of solids; (2) malabsorptive procedures, which limit the absorption of nutrients by shortening the small intestine; thus decreasing the surface area that is exposed to food; and (3) combined, restrictive, and malabsorptive.[67] Laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy (SG), and gastric bypass (GBP) have become the most preferred procedures worldwide.[68] Restrictive and combined procedures have shown very promising effects on liver function and histology[7] [Figure 1].

Gastric Banding

In 1978, Wilkinson and Peloso reported the first gastric banding procedure. At that time it was neither adjustable nor laparoscopic.[69,70] The techniques of adjustable banding were proposed in the early 1980s, and with the emergence of laparoscopy in the mid-1990s the band insertion was done laparoscopically.[70] LAGB involves making a small proximal gastric pouch by inserting a gastric band around the superior end of the stomach [Figure 1a]. This band is linked to an injection port in the skin through a tube, which gives its adjustability.[70] LAGB accounts for 42.3% of bariatric procedures.[68] Irrespective of its purely restrictive principles in weight reduction, LAGB showed significant weight loss with excess weight loss (EWL) of 58.8 ± 30.0%, 56.8 ± 35.0%, and 58.4 ± 46.6%, at 1, 3, and 5 years, respectively, with a failure rate (%EWL\50%) of 40.4%, 43.5%, 46.3%, and 55% at 1, 3, 5, and 7 years, respectively.[71,72]

Sleeve Gastrectomy

In 1993, Hess and Marceau introduced SG as a restrictive component of biliopancreatic diversion (BPD; a malabsorptive procedure). Initially it was not intended as a standard single procedure.[73] In 2008, it became a common procedure, making up to 5.4% of the total number of performed bariatric surgeries.[68] In this procedure, the surgeon removes 75% of the stomach, resulting in a sleeve-like structure extending from the esophagus until the duodenum [Figure 1c].[73] Although SG is a restrictive procedure, it results in marked reduction of Ghrelin production; a pleiotropic hormone secreted from neuroendocrine P/D1 cells of the stomach fundus; a hormone involved in appetite and its reduction decreases hunger and improves satiety.[74,75] SG results in EWL of 55.81% at 1 year and 67.42% at 2 years.[76,77]

Gastric bypass

Currently, GBP surgery is considered to be the most effective surgical intervention in morbidly obese patients.[20,78] It accounts for 49.3% of bariatric surgeries.[68] Here the surgeon splits the stomach into two pouches; a smaller proximal and a larger distal pouch, and connects both ends to the anatomically manipulated small intestines [Figure 1d]. GBP is considered as a restrictive procedure with mild malabsorptive effect. GBP shows tremendous systemic beneficial effects starting with ghrelin level reduction,[79] marked sustained weight loss,[20,78,80,81] with an EWL of 64% 1 year after the surgery,[82] and 64.9% 7 years later.[83]

Biliopancreatic Diversion with Duodenal Switch

In 1976, Scopinaro reported the first BPD procedure.[84] Hess[85] and Marceau[73,86] created duodenal switch by uniting the Demeester method[87] with Scopinaro's to avoid duodenogastric reflux in the original BPD.[84] BPD with or without duodenal switch (DS) comprises SG with redirection of the small intestine forming two distinct routes (the shorter route collects food from the stomach, the longer route transfers bile from the liver) with a common canal [Figure 1e]. Unlike GBP, BPD with DS (BPD/DS) is mainly malabsorptive with slight restrictive effect.[85] BPD/DS accounts for 0.8% of all bariatric surgeries,[68] as it is a complex procedure with long operative time and higher risk of complications.[88] However, BPD/DS provides the greatest and most sustained weight loss with an EWL of 85% in 1 year[88] and 75% in 10 years.[89]

Complications and Side Effects

Although LAGB is considered as the safest of all bariatric surgeries, it has its own complications. These include pouch enlargement,[90] band slip,[91] and band erosion[92] with rates of 12%, 3.2%, and 1.66%, respectively, as well as esophageal dysmotility, which was a poorly appreciated complication affecting 68.8% of patients in the long term.[93] SG has minimal complications, with staple line leak as the most common complication (4%).[94,95] All bariatric surgeries share the need for postoperative multivitamin and multimineral supplements to minimize the risk of deficiencies. The most common deficiencies encountered were of iron and vitamin B12.[96-98] Malabsorptive procedures result in substantial weight loss, but have the highest complication rates and

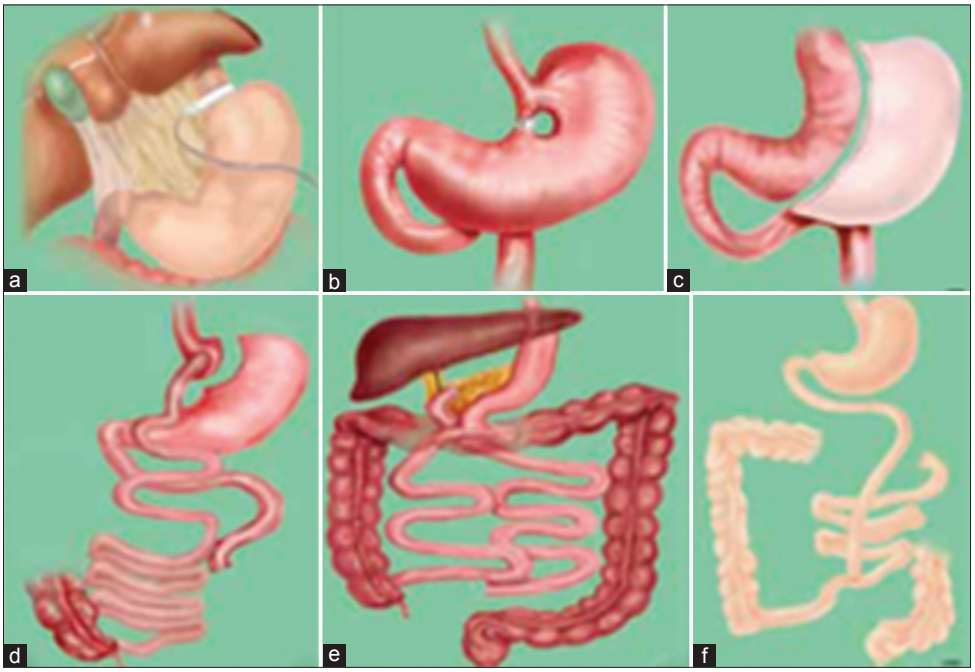

Figure 1: Bariatric surgical procedure. (a) Laproscopic adjustable gastric banding; (b) Vertical banding gastroplasty; (c) Laproscopic adjustable gatseric banding; (d) Roux-en-Y gastric bypass; (e) Biliopancreaatic diversion; (f) Jejunoileal bypass

serious side effects with a total complication rate of 23% for GBP and 25% for BPD.[99-106]

With GBP, the most commonly reported complications were anastomotic stricture (8.9%), intestinal obstruction (7.3%), gastrointestinal bleeding (4%), staple line leakage (1.6%),[107] and dumping syndrome.[67] BPD complications include hepatic failure (explained by rapid weight loss).[100] Complications also comprise gastric leak (0.07%),[89] marginal ulcers (0.3%),[108] and duodenal stump leak (0.02%),[89] but no dumping syndrome.[85] Furthermore, it has been reported that patients with protein depletion may require revisions and reversals of their surgeries with rates of 3.7% and 0.61%, respectively.[89] Unfortunate mortality was reported in 0.1% of patients undergoing LAGB or SG, in 0.5% of those who had undergone GBP, and in 1.1% in those who had PBD.[109]

Effects of Bariatric Surgeries

Besides the previously mentioned benefits (EWL) and complications of bariatric surgeries, the following text focuses mainly on the metabolic, inflammatory, histologic, and liver function changes.

Metabolic Changes

Consistently reported outcome of bariatric surgeries have shown improvement in many metabolic aspects, studies have proved that bariatric surgeries along with medical therapy achieved glycemic control in significantly more than medical therapy alone. In a 2-year prospective study on 18 patients undergoing GBP, by Furuya *et al*., 8 had T2DM at baseline and 2 after surgery ($P < 0.05$), 11 had hyperlipidemia at baseline and 3 after surgery ($P < 0.05$), and IR (measured by HOMA) was closer to normal after surgery ($P < 0.05$)[78]. Moschen *el al* showed complete resolution of T2DM ($P < 0.05$), and they also reported a decrease in HOMA index, as it was 5.5 before, and 2.4 1 year later ($P < 0.05$).[110] Karcz *et al*. reported that 23 patients had T2DM prior to SG, 12 months later the median hemoglobin A1c levels dropped and remained within normal range 2 years after.[111] Mathurin *et al*. assessed IR using the quantitative insulin sensitivity check index (QUICKI), which was 3.2 at baseline and declined to 2.84 a year after surgery and remained consistent for 5 years ($P < 0.05$) along with a significant decline in serum TGs ($P < 0.05$). A decline in IR has been proved to be an early indicator of an improvement in liver histology (steatosis and ballooning).[30] A randomized clinical trial by Schauer *et al*.[112] showed that bariatric surgery in 99 patients (RYGB and LSG) has resulted in a significantly lower glycemic control measured by the percentage of glycosylated hemoglobin ($P = 0.02$) and HOMA-IR ($P < 0.01$), when compared with intensive medical therapy (41 patients). Another study by Mingrone *et al*. targeted patients with DM and then randomly assigned to either medical therapy or bariatric surgery (RYGB, BPD).[113]. The surgical group patients (60 patients) had a significantly better glycemic ($P < 0.001$) and a better lipid control ($P < 0.001$) [Table 1].

Inflammatory Changes

It has been shown that weight loss due to bariatric surgeries is associated with a significant reduction in hepatic expression

Table 1: Comparison between the metabolic effects after bariatric surgeries between selected studies

Study	Type of surgery	Longest follow-up	Fasting glucose (mg/dL)	Fasting insulin (mU/L)	HOMA index	Triglycerides (mg/dL)
Dixon[61]	LAGB	25.6±10 months	Improved*	Improved*	N/A	Improved*
Klein[80]	GBP	12 months	Improved*	Improved*	Improved*	Improved*
Furuya[78]	RYGB	24 months	Improved*	N/A	Improved*	Improved*
Moschen[110]	LAGB	72 months	Improved*	Improved*	Improved*	N/A
Mathurin[30]	Bariatric surgeries	1 year	Improved*	N/A	N/A	Improved*
Karcz[111]	LSG	36 months	N/A	N/A	N/A	Improved*
Schauer+[112]	RYGB LSG	12 months	Improved	N/A	Improved	N/A
Mingrone[113]	RYGB BPD	2 years	Improved	N/A	N/A	Improved

BPD: Biliopancreatic diversion, DS: Duodenal switch, GBP: Gastric bypass, RYGB: Roux en y gastric bypass, LAGB: Laparoscopic adjustable gastric banding, LSG : Laparoscopic sleeve gastrectomy: LFT: N/A: not available. *P<0.05. +These studies had a control group on medical therapy

of several factors involved in hepatic inflammation such as MCP-1 and interleukin-8 (IL-8).[80] Weight loss has also been shown to regulate hepatic fibrogenesis by decreasing several inflammatory and fibrogenesis factors, including transforming growth factor-β1, tissue inhibitor of metalloproteinase 1, α-smooth muscle actin, and collagen-α1,[80] which inhibits the activity of matrix metalloproteinases.[80] Along the same lines, Moschen *et al*. showed significant systemic reduction in C-reactive protein (mg/dL) from 0.86 to 0.42, TNF-α (pg/mL) from 2.36 to 0.8, and leptin serum levels from 27.4 to 15.15 (ng/mL) after 1-year of surgery ($P < 0.05$); however, the hepatic leptin expression [messenger ribonucleic acid (mRNA), and protein level] was not affected.[110] Serum levels of adiponectin rose significantly from 7.46 to 8.95 μg/mL ($P < 0.05$) 1 year after LAGB. Adiponectin protein expression (done via immunohistochemistry) in liver biopsies increased significantly ($P < 0.05$) after LAGB. This study supports the hypothesis that weight loss in morbidly obese patients is associated with increased levels of anti-inflammatory adipocytokines and decreased levels of pro-inflammatory adipocytokines. Also, Moschen *et al*. considered the effects of weight loss on the hepatic or adipose tissue expression of IL-6, adiponectin, and TNF-α in 20 morbidly obese patients undergoing LAGB, with 6 months follow up. For IL-6, they reported significant reduction in serum, subcutaneous tissues (25.9-fold), and hepatic mRNA expression ($P < 0.05$). Nevertheless, serum TNF-α was undetectable at both baseline and follow up, hepatic TNF-α expression remained the same, but subcutaneous TNF-α had a 2.1-fold reduction ($P < 0.05$). In addition, their results showed noticeable increase in subcutaneous adiponectin expression.[114]

Biochemical Liver Changes

Although it is not ideal to use liver enzymes as an accurate reflection of NAFLD status, most of the studies used aspartate transaminase (AST) and alanine transaminase (ALT) to evaluate NAFLD effect on liver function at baseline and after bariatric surgeries. Papadia *et al*. intended to assess the risk factors for acute liver damage after BPD. They included 99 patients, AST levels were elevated 2 months after BPD ($P < 0.05$), this elevation was followed by a significant drop 10 months later ($P < 0.05$).[115] Keshishian *et al*. reported a transient elevation of AST (130%) and ALT (160%) 6 months after BPD/DS.[116] However, these levels were normalized in 1 year, and persisted for 3 years. Moschen *et al*. stated that 7 out of 30 patients had an elevated ALT at baseline; 3 remained elevated at 6 months, but in 12 months from the procedure; only 1 patient continued having elevated ALT.[110] In the Swedish obese subjects paper, a recent prospective controlled study, they examined the long-term effect of bariatric surgery on transaminase levels in 2 and 10 years.

At 2 years, results showed lower serum ALT and AST levels and no change in the control group but at 10 years ALT levels continued to drop, whereas AST increased.[117] It is worth mentioning that limited studies looked into albumin as a reflection of liver function, with no reports yet of significant changes.[20] None of the reviewed studies reported results of protein C and S, or coagulation profile [Table 2].

Histological Changes

Steatosis

A prospective study by Clark *et al*. aimed to evaluate liver histological effect before and after GBP surgery in 16 patients. They showed an improvement in histological features of NAFLD (based on Brunt criteria) with regression of steatosis in 13 (81%) of the patients ($P < 0.05$).[81] No patient had an increase in steatosis after 305 ± 131 days from an open GBP surgery. This study was limited by the small sample size, and nonprotocolized criteria of the second biopsy.[81] Similarly, Furuya *et al*., showed that (33%) of their patients displayed variable degrees of steatosis prior to surgery, which disappeared in 89% after 2 years ($P < 0.05$)[78]. Moschen *et al*. found reduction of liver steatosis in 14 out

Table 2: Comparison between the biochemical liver changes after bariatric surgeries

Study	Surgical intervention	Follow-up	Changes in LFT (IU/L) (*P* value)	
			AST	ALT
Papadia[115]	BPD	12 months	Declined*	Declined*
Dixon[61]	LAGB	25.6±11 months	Declined*	Declined*
Clark[81]	GBP	305±131 days	Declined^	Declined^
Keshishian[116]	DS	48 months	Same as baseline^	Declined^
Furuya[78]	RYGB	2 years	Declined^	Declined^
Moschen[110]	LAGB	6/12 months	Declined*	Declined*
Karcz[111]	LSG	2 years	Declined*	Declined*
Burza et al+	GB/vertical banded gastroplasty/ RYGB	2/10 years	Declined initially Increased in ten years*	Declined*

AST: Aspartate transaminase, ALT: Alanine transaminase, BPD: Biliopancreatic diversion, DS: Duodenal switch, GBP: Gastric bypass, RYGB: Roux en y gastric bypass , LAGB: Laparoscopic adjustable gastric banding, LFT: Liver function test. *P<0.05: ^P>0.05. +This study had a control arm

of 18 patients ($P < 0.001$) using the modified classification system from Kleiner.[110] Keshishian *et al*., reported the effect of DS 697 patients who were followed with a median of 6, 12, 18 months, and annually for 4 years. The histology results were only available in 78 out of 697 patients. These 78 patients had a second liver biopsy with a time interval ranging from 6 months to 3 years; depending on the need for a second operative procedure. Based on subjective assessment, the severity of steatosis had more than 50% reduction compared with baseline readings.[116] Mathurin *et al*. studied 381 patients who underwent bariatric surgeries with protocol liver biopsies at three intervals, first intraoperatively, second 1 year after, and a third 5 years later. They used the NAFLD activity score (NAS) to evaluate the NAFLD histological changes, and the 5-grade scale for fibrosis assessment.[30] They revealed significant reduction of liver steatosis from 37% before surgery to 16% in 5 years ($P < 0.01$). They reported that patients with persistent steatosis had higher BMI, IR, TG, ALT, and gamma glutamyl transferase than patients without steatosis.[30]

Ballooning and Inflammation

Most studies did not show improvement in inflammation such as the one by Mathurin *et al* ($P > 0.05$).[30]" However, some showed changes. Clark *et al*. studied 16 paired liver biopsies, 15 showed inflammation in the initial biopsy, and 12 revealed a significant reduction ($P < 0.01$) after a mean follow up of 305 ± 131 (SD) days from the surgery.[81] Many studies have shown that hepatocyte ballooning improves after bariatric surgeries such as Mathurin *et al*. (CI 95%)[30] Clark *et al*. ($P < 0.05$),[81] Furuya *et al*.,[78] and Moschen *et al*. ($P < 0.05$).[110]

Fibrosis

Most of the studies showed significant improvement of fibrosis. Clark *et al*. reported 14 patients with some degree of perisinusoidal fibrosis at the time of GBP. Of these, 6 patients showed improvement in the fibrosis score by one point; however, 8 patients had no change in the second biopsy. Similarly, of the 13 patients with portal fibrosis at baseline, 6 had improvement in their fibrosis score by one point, whereas the remaining 7 had no change. None of the patients showed development or progression at the time of follow up ($P = 0.01$, 0.01, and 0.003, respectively).[81] Likewise, Furuya *et al*., reported that fibrosis disappeared in 75% patients ($P < 0.05$), with no worsening at the time of the second biopsy.[78] Moschen *et al*., did not detect any changes in liver fibrosis 6 months after the LAGB surgery ($P = 0.27$).[110] On the other hand, Mathurin *et al*. showed worsening of the extent of fibrosis from baseline to 1 and 5 years in 20% of patients, whereas there was no change in 80% of patients ($P = 0.01$).[30] At 5 years, the progression of fibrosis was detected in patients with higher IR, BMI, and NAS. This unexpected effect may be attributed to the very high starting body weight of the patients included in this study.

Nonalcoholic Steatohepatitis

Dixon *et al*. studied the improvement of liver histology including NASH and cirrhosis with LAGB-induced weight loss.[61]. They evaluated 197 patients, 36 had a second biopsy, which was not protocolized with a mean follow up of 25.6 ± 11 months, 23 had NASH. Over all change was significant ($P < 0.05$)-19 cases (82%) had resolution or remission of NASH, 2 (9%) had improvement without resolution, and 2 (9%) remained unchanged.[61] Similar results were obtained by Keshishian *et al*.[116] and Moschen *et al*.[110]

Mathurin *et al*. had 99 patients with NASH at baseline, 5 years later only 30 patients remained with NASH ($P < 0.01$).[30] Nonetheless, this marked improvement was observed in the first year of follow up, with no significant change from 1 to 5 years ($P > 0.05$).[30]

CONCLUSION

This review demonstrates the effect of bariatric surgery on the metabolic, biochemical, and histopathological parameters of NAFLD. Due to the complexity of the disease, additional clinical studies with stronger methodology, longer follow up, and with a larger sample size are needed to confirm the sustainability of these effects. Moreover, the significant morbidities as well as the rare mortality rates from bariatric surgeries do need to be considered and clearly explained to the patient.

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