

Impact of bariatric surgery on non-alcoholic fatty liver disease: an integrative review

Impacto da cirurgia bariátrica na doença hepática gordurosa não alcoólica: uma revisão integrativa

Impacto de la cirugía bariátrica en la enfermedad del hígado graso no alcohólico: una revisión integrativa

Received: 10/05/2021 | Reviewed: 10/12/2021 | Accept: 10/14/2021 | Published: 10/17/2021

Antônio Alves Júnior

ORCID: <https://orcid.org/0000-0002-5034-6187>
Universidade Federal de Sergipe, Brasil
E-mail: aalves@infonet.com.br

Tereza Virgínia Silva Bezerra do Nascimento

ORCID: <https://orcid.org/0000-0002-6706-6907>
Universidade Federal de Sergipe, Brazil
E-mail: terezahepato@gmail.com

João Augusto Cegarra Quintiliano

ORCID: <https://orcid.org/0000-0001-8618-8056>
Universidade Federal de Sergipe, Brazil
E-mail: quintiliano.ja@gmail.com

Julia Maria Salgado Carvalho

ORCID: <https://orcid.org/0000-0002-7064-6558>
Universidade Federal de Sergipe, Brazil
E-mail: juliaslgd@gmail.com

Roberta Kayane Silva Leal

ORCID: <https://orcid.org/0000-0002-0858-5942>
Universidade Federal de Sergipe, Brazil
E-mail: robertakayane@hotmail.com

Maria Rosa Melo Alves

ORCID: <https://orcid.org/0000-0002-7532-3512>
Universidade Federal de Sergipe, Brazil
E-mail: rosa.alves.biomed@gmail.com

Márcio Bezerra Santos

ORCID: <https://orcid.org/0000-0001-9962-6537>
Universidade Federal de Sergipe, Brazil
E-mail: marciobezerra.ufs@outlook.com

Carlos Anselmo Lima

ORCID: <https://orcid.org/0000-0003-4269-7320>
Universidade Federal de Sergipe, Brazil
E-mail: ca.lima01@gmail.com

Marcos Antônio Nunes Prado

ORCID: <https://orcid.org/0000-0001-5244-5843>
Universidade Federal de Sergipe, Brazil
E-mail: nunes.ma@outlook.com

Abstract

The present study aims to demonstrate the results of the impact of bariatric surgery on non-alcoholic fatty liver disease through secondary sources available in the literature. A literature review was carried out with the descriptors "Non-alcoholic Fatty Liver Disease" OR "NAFLD" AND "Bariatric Surgery"; "Doença Hepática Gordurosa não Alcoólica" OR "DHGNA" AND "Cirurgia Bariátrica" in the databases: Latin American and Caribbean Health Sciences Literature, through the Virtual Health Library, and Medical Literature Analysis and Retrieval System Online (Medline), through PubMed. Cohort-type studies addressing the effects of bariatric surgery on non-alcoholic fatty liver disease published in the last 5 years were included in the review. Thirty-one studies were identified, of which 10 were excluded for not performing postoperative evaluation and 8 were excluded for not containing the methodological criteria, totaling 13 studies. The current literature presents data suggestive of the association between bariatric surgery and the regression of non-alcoholic fatty liver disease, however, the studies observed present wide variations in methodological applications and samples with heterogeneous profiles, which makes it difficult to generalize the results. More studies are needed so that it is possible to document with greater evidence and reproducibility the action of different types of bariatric surgery on the rate of this liver disease regression.

Keywords: Non-alcoholic fatty liver disease; Bariatric surgery; Diagnostic techniques and procedures; Digestive system diseases.

Resumo

O presente estudo tem como objetivo demonstrar os resultados do impacto da cirurgia bariátrica na DHGNA através de fontes secundárias disponíveis na literatura científica. Foi realizada uma revisão da literatura com os descritores "Fatty Liver" OR "NAFLD" AND "Bariatric Surgery"; "Doença Hepática Gordurosa não Alcoólica" OR "DHGNA" AND "Bariatric Surgery" nas bases de dados: Literatura Latino-Americana e do Caribe em Ciências da Saúde, por meio da Biblioteca Virtual em Saúde, e Análise de Literatura Médica e Sistema de Recuperação Online (Medline), por meio do PubMed. Estudos do tipo coorte que abordam os efeitos da cirurgia bariátrica na NAFLD publicados nos últimos 05 anos foram incluídos nesta revisão. Foram identificados 31 estudos, dos quais 10 foram excluídos por não realizarem avaliação pós-operatória e 08 por não conterem os critérios metodológicos; ao total, 13 estudos incluídos nesta revisão. A literatura atual apresenta dados sugestivos da associação entre cirurgia bariátrica e regressão da DHGNA, entretanto, os estudos observados apresentam grandes variações nas aplicações metodológicas e amostras com perfis heterogêneos, o que dificulta a generalização dos resultados. Desse modo, mais estudos são necessários para que seja possível documentar com maior evidência e reprodutibilidade a ação dos diferentes tipos de cirurgia bariátrica sobre a taxa de regressão da DHGNA.

Palavras-chave: Hepatopatia gordurosa não alcoólica; Cirurgia bariátrica; Técnicas de diagnóstico e procedimentos; Doenças do sistema digestório.

Resumen

En este documento, el objetivo fue demostrar los resultados del impacto de la cirugía bariátrica en EHGNA a través de fuentes secundarias disponibles en la literatura. Se realizó una revisión de la literatura con los descriptores "Fatty Liver" OR "NAFLD" AND "Bariatric Surgery"; "Doença Hepática Gordurosa não Alcoólica" OR "DHGNA" AND "Bariatric Surgery" en las bases de datos: Literatura de Ciencias de la Salud de América Latina y el Caribe, a través de la Biblioteca Virtual en Salud, y Sistema de Análisis y Recuperación de Literatura Médica en Línea (Medline), a través de PubMed. En esta revisión se incluyeron los estudios de tipo cohorte que abordaron los efectos de la cirugía bariátrica en la EHGNA publicados en los últimos 5 años. Se identificaron 31 estudios, de los cuales 10 fueron excluidos por no realizar evaluación postoperatoria y 8 fueron excluidos por no contener los criterios metodológicos, totalizando 13 estudios. La literatura actual presenta datos sugestivos de la asociación entre cirugía bariátrica y regresión de EHGNA, sin embargo, los estudios observados presentan amplias variaciones en las aplicaciones metodológicas y muestras con perfiles heterogéneos, lo que dificulta la generalización de los resultados. Por tanto, se necesitan más estudios para que sea posible documentar con mayor evidencia y reproducibilidad la acción de diferentes tipos de cirugía bariátrica sobre la tasa de regresión de la EHGNA.

Palabras clave: Enfermedad del hígado graso no alcohólico; Cirugía bariátrica; Técnicas y procedimientos diagnósticos; Enfermedades del sistema digestivo.

1. Introduction

Non-alcoholic Fatty Liver Disease (NAFLD) is defined as an excessive accumulation of fat in the liver, regardless of excessive alcohol consumption or any other secondary cause (Milić, Lulić & Štimac, 2014). It is characterized by an increase in intrahepatic lipid content (steatosis) with or without inflammation and fibrosis (steatohepatitis) (Fabbrini, Sullivan & Klein, 2010). Thus, it comprises a wide spectrum of histological characteristics ranging from simple steatosis to steatohepatitis, fibrosis, and cirrhosis (Milić, Lulić & Štimac, 2014). Once cirrhosis is established, patients are at high risk of developing hepatocellular carcinoma (HCC), which is related to an increase in mortality due to liver causes (Bhala, Younes & Bugianesi, 2013).

NAFLD is considered the most common liver disease worldwide (Milić, Lulić & Štimac, 2014), with percentages ranging from 25 to 30% in the general population (Bhala, Younes & Bugianesi, 2013). It is commonly considered the hepatic manifestation of metabolic syndrome (MS), grouping with obesity and diabetes, for it reflects shared pathogenic factors (Bugianesi, McCullough & Marchesini, 2005). Given the close association with MS, the entire spectrum of NAFLD occurs mainly in patients with obesity (60-95%), type 2 diabetes mellitus (DM2) (28-55%) and hyperlipidemia (27-92%) (Bugianesi, McCullough & Marchesini, 2005). Among populations with obesity, MS and DM2, the prevalence of NAFLD is much higher, ranging from about 50% to 90%. Considering that the prevalence of obesity and overweight has increased to epidemic levels

over the last decades, NAFLD has become one of the greatest challenges for public health (Cazzo, Pareja & Chaim, 2017).

The classical pathogenic pathway leading to NAFLD has been described as the "two-hit hypothesis". This theory states that damage to liver tissue begins with lipid accumulation, a consequence of a sedentary lifestyle, high-fat diet and obesity – first hit. This lipid accumulation works as a sensitization factor for the activation of inflammatory mediators and fibrogenesis – second hit. Secondary aggressions would lead to steatohepatitis and fibrosis (Day & James, 1998). However, the several molecular and metabolic changes that occur in NAFLD cannot be fully explained by the "two-hit hypothesis".

Therefore, the "multiple-hit hypothesis" was then considered to explain the pathogenesis of NAFLD. This hypothesis considers multiple factors that, together, act in genetically predisposed individuals to induce the development of the disease. The hypothesis includes nutritional factors, hormones secreted by adipose tissue, existence of insulin resistance, changes in the intestinal microbiota, and influence of genetic and epigenetic factors.

Changes in the intestinal microbiota, as observed in obesity and insulin resistance, have consequences for both energy homeostasis and systemic inflammation secondary to endotoxemia. At the hepatic level, high levels of free fatty acids can result in stress in the endoplasmic reticulum and mitochondrial dysfunction with consequent activation of inflammatory responses. In addition, genetic factors may explain more progressive courses of the disease in some individuals, comparatively. Herewith, it is understood that several parallel processes contribute to the development of steatosis and hepatic inflammation (Buzzetti, Pinzani & Tsochatzis, 2016).

Liver biopsy is currently the gold standard for the diagnosis of NAFLD (Chalasani et al, 2018). When at least 5% of hepatocytes have steatosis, patients can be defined as having NAFLD – in an appropriate clinical context. When, in addition, there is lobular inflammation and ballooning of liver cells, the lesion is usually defined as steatohepatitis (Milić, Lulić & Štimac, 2014). The analysis of samples collected by biopsy are commonly evaluated using the Non-Alcoholic Liver Disease Activity Score (NAS), which takes into account histological investigation of steatosis, lobular inflammation, and hepatocellular ballooning (Kleiner et al, 2005). The identification of the histological stage is crucial for the long-term prognosis because the population with NAFLD is associated with a significantly higher mortality, compared to the general population, mainly due to cardiovascular and hepatic complication (Cazzo, Pareja & Chaim, 2017).

The enzymes dosage of liver parenchyma may also reflect the severity of the disease. Steatosis correlates directly with liver function tests, especially aspartate transaminase (AST) and alanine transaminase (ALT) values (Ruiz-Tovar, Alsina & Alpera, 2017). Still regarding the non-invasive methods of NAFLD evaluation, the development of scores to evaluate liver diseases are an important tool for the analysis of laboratory and clinical variables of patients (Cazzo, Pareja & Chaim, 2017). Currently, the Non-Alcoholic Liver Disease Fibrosis Score (NAFLD-FS) is the most widely used score and can be easily calculated based on six available variables: age, body mass index (BMI), hyperglycaemia, platelet count, albumin, and AST/ALT1 ratio (Angulo et al, 2007). Nevertheless, although they do not cause morbidity and are easily evaluated by means of clinical and laboratory variables routine, the results of this score do not replace the diagnostic value of liver biopsy. The NAFLD-FS, then, has been adequate for population-based studies and for clinical screening and follow-up (Simo et al, 2014), especially in populations known to be more exposed to this disease, such as patients with MS, diabetes, dyslipidaemias, and obesity (Ruiz-Tovar, Alsina & Alpera, 2017).

Clinically, obesity reflects a generalized pro-inflammatory state with a high risk of metabolic comorbidities, such as NAFLD, which are highly influenced by the distribution of adipose tissue. Evidence suggests that visceral adipose tissue is directly associated with the development and progression of NAFLD. The most important pathological mechanisms involve increased secretion by visceral adipose tissue of pro-inflammatory cytokines, adipokines, and release of free fatty acids in the portal system and systemic circulation, causing dyslipidaemia and insulin resistance (Milić, Lulić & Štimac, 2014). Along with

insulin resistance, obesity contributes significantly to the initial accumulation of fat in the hepatocyte and to the progression of simple steatosis to non-alcoholic steatohepatitis, cirrhosis related to steatohepatitis, and hepatocellular carcinoma. From the clinical point of view, obesity increases morbidity and mortality when associated with NAFLD, due to cardiovascular and hepatic mortality (Polyzos, Kountouras & Mantzoros, 2017). Furthermore, the disease is an additional risk factor for this group of patients, especially for the possibility of progression to severe forms of hepatic fibrosis and hepatocellular carcinoma (Ruiz-Tovar, Alsina & Alpera, 2017). There is an established association between obesity and the incidence of NAFLD, as well as increased severity (Polyzos, Kountouras & Mantzoros, 2017).

In therapeutic aspects, weight loss is considered the main factor in the prevention and treatment of obesity and NAFLD (Polyzos, Kountouras & Mantzoros, 2017). In this context, bariatric surgery is recognized as an effective strategy in the induction and maintenance of weight loss in patients eligible for the procedure. Individuals with DM2, BMI between 30 Kg/m² and 35 Kg/m², and no response to clinical treatment may have indication for bariatric surgery. Similarly, patients with BMI higher than 35 Kg/m², with diseases associated with obesity or those with BMI higher than 40 Kg/m² – considered morbid obesity – are also eligible for surgery (Abeso, 2016). This intervention plays a significant role in the natural history of NAFLD and usually leads to rapid changes in its clinical progression (Ruiz-Tovar, Alsina & Alpera, 2017). The procedure has the potential to induce great weight loss and improve MS and DM2 characteristics. Additionally, the mechanisms involved in improving obesity and DM2 after bariatric surgery probably play important roles in the resolution of metabolic and inflammatory lipid abnormalities present in the pathophysiology of NAFLD.

Bariatric surgery promotes changes in three crucial metabolic areas that influence the spectrum of NAFLD: i) improvement of glucose homeostasis; ii) improvement of lipid metabolism; and iii) reduction of inflammatory activity. Therefore, bariatric surgery can reverse pathological changes in those patients' liver (Laursen et al, 2019). In addition, the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) states that bariatric surgery induces significant reversal or improvement of NAFLD. Considering the overall impact of bariatric surgery on obesity and related comorbidities, this option of treatment should be offered to the group of individuals who meet the current indication criteria, as a potentially effective therapy to minimize the risks of the disease. However, IFSO also concluded that, despite the solid evidence available, complementary studies to reach final conclusions about the real effect of bariatric surgery as a therapeutic option for patients with obesity and NAFLD are still required (De Luca et al, 2016).

Although the overall impact of bariatric surgery on NAFLD is positive, the ideal surgical technique still needs to be determined, as well as the long-term effects and ways to maintain the benefits achieved (Ruiz-Tovar, Alsina & Alpera, 2017). Recently, Vertical Sleeve Gastrectomy (VSG) and Roux-en-Y Gastric Bypass (RYGB) have been the most commonly performed bariatric procedures worldwide, leading to a significant, sustainable weight loss and improvement of metabolic comorbidities (Khorgami et al, 2017). Some authors state that, although both RYGB and VGS are effective in restoring liver function and structure in obese patients with NAFLD, the RYGB approach demonstrated an advantage over VGS in the disease regression (Froylich et al, 2016). On the other hand, some authors advocate equality among the several methods and state that, in patients with NAFLD and biopsy-proven non-alcoholic steatohepatitis, preoperative abnormal liver function tests are normalized in the vast majority of VGS and RYGB patients at the end of the first year after surgery, providing evidence that both procedures are equally effective in improving liver function (Cherla et al, 2020).

Considering the growing worldwide epidemic of obesity and the fact that this population represents a risk group for NAFLD and to develop advanced stages of liver disease and cardio metabolic disease, the therapeutic approach of these patients is an important priority for health care and clinical research. Notably, bariatric surgery is recognized as an effective strategy in the induction and maintenance of weight loss. Although there is no formal indication of this procedure for the

treatment of this liver disease, weight reduction is considered the main factor in the prevention and treatment of NAFLD. Therefore, this review aims to evaluate studies on the impact of bariatric surgery on NAFLD, through secondary sources available in the scientific literature.

2. Methods

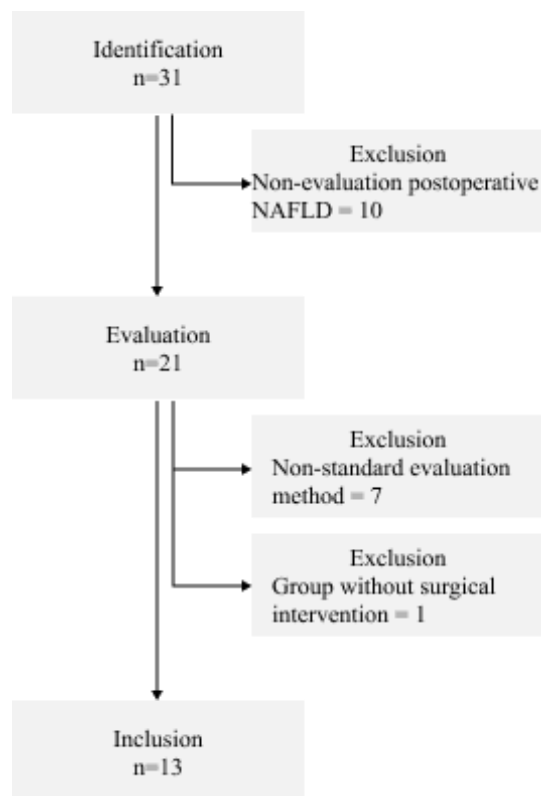
The integrative review is an important method for Evidence-Based Practice. The following steps were performed: elaboration of the guide question, research in the literature, data collection, critical analysis of the included studies, discussion of the results and the integrative review (Whittemore & Knafl, 2005; Souza & Silva, 2010). For the literature review, the following descriptors were considered: "fatty liver"[All Fields] OR "NAFLD"[All Fields] AND "bariatric surgery"[All Fields]; "Non-alcoholic fatty liver disease" OR "NAFLD" and "bariatric surgery". The research was conducted in the database of Latin American and Caribbean Literature on Health Sciences (LILACS), through the Virtual Health Library (VHL) and Medical Literature Analysis and Retrieval System (Medline), via PubMed. Cohort studies addressing the effects of bariatric surgery on NAFLD published in the last 5 years (2017-2021) were included in this review. Additionally, studies that did not perform standardized techniques for NAFLD evaluation, studies with groups of patients not submitted to bariatric surgery, and also studies that did not perform the reassessment of patients by the same method in the pre and postoperative periods were excluded.

The studies were classified as for the chosen bariatric surgery technique, the evaluation of NAFLD and had the level of evidence stratified by the Oxford classification. The regression analysis of the parameters observed by each study was based on the mean value of the indicators between patients in two moments M1 and M2: i) M1 corresponding to the preoperative, in non-invasive evaluation and intraoperatively studies and in studies that analysed NAFLD by liver biopsy; ii) M2 corresponds to the postoperative period of patient evaluation. Finally, the access to the full text of the selected studies to be reviewed was possible through the Coordination for the Improvement of Higher Education Personnel (CAPES) of the Ministry of Education. Other papers were used for the contextualization of the present study.

3. Literature Review: Studies and Observed Results

We identified 31 studies through this literature review. All of them were carefully analysed and 18 were excluded because they met at least one of the exclusion criteria, resulting in 13 studies that comprised the integrative review (Figure 1). Of this total, ten were prospective and three retrospective cohort studies.

Figure 1 - Flowchart of the integrative literature review.



Source: Authors.

The main characteristics and results of the cohort studies analysed were summarized in Table 1. Altogether, they counted a sample of 507 patients, with a mean of 50.7, median of 41.5 and standard deviation of ± 28.19 . The study with higher number of patients was composed of a sample of 100 patients, and the lowest with 25. NAFLD evaluation was performed by invasive methods, by intraoperative biopsy (5 studies) and non-invasive methods, by enzymatic evaluation through standardized scores (5 studies). The Vertical Sleeve Gastrectomy technique was performed in 7 studies; in 3, its results were compared with those obtained in patients who underwent surgery performed with Roux-en-Y Gastric Bypass technique, which was used in isolation in 2 other studies. There is also one study that evaluated intragastric balloon and endoscopic sleeve gastropasty techniques. All studies were classified with evidence level 2B, following the parameters established by the Oxford classification. The mean regression rate of NAFLD among the studies was 66.49%, with a standard deviation of ± 22.48 and median of 68.30. The maximum value in the regression rate was 94.2% and the minimum was 12%.

Table 1 - Data from studies evaluating the effect of bariatric surgery on Non-alcoholic fatty liver disease (NAFLD) in the last 5 years.

Reference	N	Follow-up (months)	Evidence level	Evaluation	Evaluation method	Surgical technique	Regression percentage (%)
Praveen et al. ²⁶	30	6	2b	Biopsy	NAS	VSG/RYGB	80,9
von Schonfels et al. ³⁰	46	6	2b	Biopsy	NAS	VSG/RYGB	50,2
Cazzo et al. ⁶	63	12	2b	Enzymes	NAFLD FS	RYGB	94,2
Froylich et al. ¹⁶	25	18	2b	Biopsy	NAS	VSG/RYGB	66,7
Chaim et al. ⁸	30	22	2b	Biopsy	AASLG/EA SL	VSG	68,0
Ruiz-Tovar et al. ²⁸	100	12	2b	Enzymes	NAFLD FS	VSG	76,7
Esquivel et al. ¹⁴	43	12	2b	Biopsy	Brunt	VSG	81,6
Nickel et al. ²⁴	100	12,5	2b	Enzymes	NAFLD FS	VSG	66,0
Coll et al. ¹¹	30	12	2b	Enzymes	NAFLD FS	IB/ ESG	12,0
Nascimento et al. ²³	40	12	2b	Enzymes	NAFLD FS	RYGB	68,6

N=Number of patients; NAS= Non Alcoholic fatty liver disease activity score; NAFLD FS= Non Alcoholic fatty liver disease fibrosis score; AASLD= American Association for the study of Liver Disease; EASL= European Association for the Study of the Liver; VSG= Vertical Sleeve Gastrectomy; RYGB= Roux-en-Y Gastric Bypass; IB= intragastric balloon; ESG= Endoscopic Sleeve Gastroplasty; Stratification of the level of evidence of the studies analysed based on the Oxford classification (1a. Systematic reviews with homogeneity of randomized controlled trials; 1b. Randomized controlled trials and narrow confidence interval; 1c. Non-randomized controlled clinical trials; 2a. Systematic reviews of cohort studies; 2b. Low-quality randomized cohort studies or trials (e.g. <80% follow-up); 2c. Ecological studies; 3a. Systematic reviews of case-control studies; 3b: Case-control studies; 4. Case series (cohort or low-quality case-control; 5. Expert opinion). Regression rate calculated based on the results presented by the studies in the evaluations performed in the pre and postoperative periods, in the respective evaluation methods.

Source: Authors.

Additionally, samples collected through liver biopsy were evaluated in most studies (3) using the Non-Alcoholic Fatty Liver Disease Activity Score (NAS). Other methods were also used, such as the Brunt classification (1) and the evaluation parameters established by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL).

Among the non-invasive evaluation methods identified, the Non-Alcoholic Liver Disease Fibrosis Score (NAFLD-FS) was used in all studies, being combined with other parameters, including ALT/AST ratio, APRI, BARD score, FLI, HSI and FIB-4. Table 2 shows the mean scans of the NAFLD FS values obtained before and after bariatric surgery in the various studies.

Table 2 - NAFLD FS pre and post bariatric surgery mean.

Reference	N	NAFLD Fibrosis Score				
		Preoperative	SD	Postoperative	SD	
Cazzo et al. ⁶	63	1,142	1,26	0,066	1,03	
Ruiz-Tovar et al. ²⁸	100	3,000	1,30	0,700	1,10	
Nickel et al. ²⁴	100	-1,030	1,51	-1,710	1,30	
Coll et al. ¹¹	30	-2,900	1,02	-3,250	0,71	
Nascimento et al. ²³	Public Health System	14	-0,684	2,17	-1,689	1,91
	Private Health System	26	-2,121	1,65	- 3,040	0,93

N=Number of patients; SD= Standard Deviation; NAFLD= Non Alcoholic fatty liver disease; NAFLD Score < -1.455 = F0-F2 (with no advanced fibrosis), NAFLD Score -1.455 – 0.675S = undetermined score, NAFLD Score > 0.675 = F3-F4 (with advanced fibrosis).

Source: Authors.

3.1 Liver biopsy in the evaluation of NAFLD

Praveen et al. (2015) conducted a study (n = 30) in which intraoperative biopsy was performed after 6 to 8 months of bariatric surgery. NAFLD was timed by the NAS score. In the intraoperative biopsy, all patients had steatosis. In the second biopsy, 19 had resolution of steatosis. In 11 of them, there was a reduction in the degree of steatosis with significant statistical differences. Additionally, the NAS biopsy score performed 6-8 months after bariatric surgery showed a statistically significant reduction in relation to intraoperative biopsy. Regarding the surgical techniques employed, both (RYGB and VSG) showed reductions in NAS score, with no statistically significant relationship between the reduction of NAS score and the surgical technique employed.

In another study, Von Schonfer et al. (2018) conducted a retrospective cohort and assessed the evolution of NAFLD in 53 patients after bariatric surgery, comparing the two main surgical methods used (RYGB and VSG). In intraoperative biopsy, a positive and statistically significant relationship was observed between the NAS score and the presence of MS. After surgery, the patients presented a significant reduction in weight and BMI, but no significant differences were found between the techniques performed and the percentage of weight loss. There was a resolution for metabolic syndrome in 83% of patients, with a statistically significant reduction and no difference between the methods. In the histological analysis, there was a significant improvement in the NAS score, which showed an average improvement of -2. In the first biopsy, 21% of the patients presented in the most severe stages of NAFLD, with NAS between 5 and 8; after surgery, only 2% continued in these stages. This improvement was not related to the method of surgery, the sex of the patient or liver enzymes when these variables were analysed individually.

Froylich et al. (2016) retrospectively analysed intra and postoperative biopsies of 23 patients. Weight loss was expressive in both groups. However, when comparing the surgical techniques employed (RYGB and VSG), RYGB was superior. Regarding NAFLD, all patients submitted to RYGB showed significant improvement in NAS score components; among VSG patients, there was improvement in all NAS components, but only the evolution of fibrosis was statistically significant. When taking both methods into account, the mean NAS value went from 3.6 ± 1.8 to 1.2 ± 1.5 . In absolute values, surgery by RYGB presented better results than VSG, but without statistical differences.

Chaim et al. (2020) conducted a prospective study with 30 patients. With regard to NAFLD, in the intraoperative biopsy, a prevalence of 50% was found: 33.33% of steatohepatitis and 16.67% of steatosis. When analysing postoperative biopsy, only 16.67% of the patients had NAFLD, 10% had steatohepatitis and 6.67% had steatosis. When comparing both biopsies, a significant reduction was observed in the values of ALT, total protein, triglycerides, plasmatic albumin, total cholesterol, and gammaglutamyl transferase (GGT). In addition, BMI decreased significantly from an average of 37.9 ± 2.21 to 25.69 ± 3.79 kg/m².

In a retrospective cohort study, Esquivel et al. (2018) analysed the biopsy of 43 patients at the time of surgery using the VSG method and a year after the procedure. Importantly, all subjects presented statistically significant reduction in the degree of NAFLD. There was also a significant decrease in liver enzymes, BMI, glycemia, LDL-c, and total cholesterol. However, no significant increase in HDL-c was found.

Kalinowski et al. (2017) conducted a randomized clinical trial with 66 patients, analysing the evolution of liver status through NAS and liver function tests. In this study, 53% of the patients had steatohepatitis at the time of surgery, and 100% had some degree of NAFLD. A significant relationship was found between NAS value and age, female gender, and serum concentrations of AST and ferritin. Conversely, in the evaluation after one year, there was a significant decrease in weight. ALT, AST, and GGT decreased significantly only in patients who underwent VGS. Albumin, though, reduced significantly only in RYGB patients.

3.2 Non-invasive evaluation of NAFLD

In a retrospective cohort study, Ledoux et al. (2019) evaluated NAFLD in 554 patients before and after one year of bariatric surgery, through metabolic and ultrasound parameters. Interestingly, weight loss was significantly higher in patients who were operated using the RYBG method in relation to the VGS method. RYBG surgery showed better evolution in relation to fasting glycemia, LDL-c, and C-reactive protein inflammation marker (CRP). On the other hand, in liver function tests, such as alkaline phosphatase and transaminases, there was a greater reduction in patients operated by VGS. The gamma-glutamyl transferase values showed a reduction in both VSG and RYBG, with no significant differences between the methods. Abdominal US showed a reduction in the number of patients with hepatic steatosis, but without significant differences between the VSG and RYBG methods.

In another study, Cazzo, Jimenez, Pareja e Chaim (2015) evaluated NAFLD at the time and one year after bariatric surgery, in a sample of 63 patients. To determine the efficiency of non-invasive methods for diagnosing NAFLD, the researchers performed an intraoperative biopsy and compared it to the NAFLD fibrosis score. They observed an overall accuracy of 87.3% for the non-invasive method as a diagnosis, with sensitivity of 97% and specificity of 75.9%. Compared to the evaluation after one year of the procedure, there was a significant decrease (p -value <0.05) of the NAFLD fibrosis score, which decreased from an average of $1,142 \pm 1,261$ to $0.006 \pm 1,027$. In addition, surgery led to a resolution of NAFLD in 55% of patients. This result had a significant association with female gender, percentage of weight lost, post-surgical BMI, platelets after surgery, and resolution of DM2.

Ruiz-tovar e Zubiaga (2019) conducted a study with 100 patients and analysed blood samples before and one year after bariatric surgery. The authors analysed the following indexes: HSI, LFS, APRI, FIB-4, and NAFLD-FS. They also assessed imaging evaluation in both moments, by ultrasound and magnetic resonance imaging. The authors observed that the mean BMI went from $49.1 \pm 7.3 \text{ kg/m}^2$ to $28.3 \pm 3.7 \text{ kg/m}^2$; weight reduction was of $82.5\% \pm 17.8\%$. Among the patients who had DM2 preoperatively, 73.4% had remission; hypertension disappeared in 60.5% of patients. The HSI, LFS, and NAFLD-FS scores showed a statistically significant reduction (p -value <0.05) when comparing the values in the preoperative period with the values after one year of surgery. In preoperative US, 75% of the patients had degrees of steatosis: 20% level I, 30% level II, and 25% level III. While in the postoperative period, all patients who were in grade I had remission and the others had a reduction in the degree of hepatic steatosis. In the MRI evaluation, 33% of the patients did not present steatosis in the first evaluation; a year later, that percentage rose to 77%. Moreover, the mean percentage of fat in the liver decreased from 16.9 ± 6.4 to 4.4 ± 2.5 . When comparing imaging methods, there was a positive correlation between the results demonstrated by US and those demonstrated by MRI. Nevertheless, US has been shown to overvalue the degrees of NAFLD. When comparing biochemical methods with MRI, LFS was the only index to present statistically significant correlation.

In a prospective study with 100 patients, Nickel et al (2018) assessed the improvement in NAFLD after bariatric surgery through non-invasive methods, transient elastography and fibrosis scores (AST/ALT ratio; BRAD; APRI; NAFLD score). In the evaluation one year after surgery, and by elastography, 94% of patients had an improvement in the degree of NAFLD. The values observed in the examination significantly reduced (p -value <0.05) from an average of $12.9 \pm 10.4 \text{ kPa}$ to $7.1 \pm 3.7 \text{ kPa}$. Regarding laboratory parameters, both AST and ALT decreased significantly after one year (p -value <0.05). All scores analysed showed statistically significant decreases in the second evaluation. However, no relationship was found between the improvement in NAFLD and sex.

In another study, Coll et al. (2019) evaluated 30 patients relating endoscopic techniques (intra-gastric balloon and gastroplasty) with decreasing NAFLD. Total weight loss and reduction in abdominal circumference after one year was statistically significant (p -value <0.05) for both techniques analysed. Among the four fibrosis markers assessed, three (FLI,

HIS, and NAFLD-Fibrosis Score) showed a significant reduction (p -value <0.05), while FIB-4 did not present relevant alterations. There was also a significant reduction (p -value <0.05) in glucose and insulin values, but not in Hb1Ac. It was also important to highlight that 50% of patients who had DM2 were able to stop the medication after one year of the procedure.

Finally, Nascimento et al. (2015) conducted a study in which they compared the NAFLD score for fibrosis preoperatively and postoperatively, in six months and one year after bariatric surgery, in patients operated in the private and public health system. They also compared the results between the health systems. The authors observed that 95% of the patients presented a decrease in the absolute value of the evaluated score. Among those in the public system, the mean value increased from -0.6845 ± 2.17 to -1.6898 ± 1.91 , with statistical difference (p -value <0.05), one year after surgery. In the private system, the evolution went from -2.1212 ± 1.65 to -3.04 ± 0.93 , but with no statistical significance. The variation in BMI and weight before and after one year of surgery was significant for both groups, while there were no differences in changes in AST, ALT and albumin values.

4. Conclusions

The current literature presents data suggestive of the association between bariatric surgery and the regression of NAFLD and corroborating the potential of this surgical procedure as a formal indication for the control of this pathological process. Nonetheless, the studies present herein showed large variations in methodological applications and samples with heterogeneous profiles, which makes it difficult to generalize the results obtained.

Importantly, studies that quantify the reduction in NAFLD or its resolution after bariatric surgery, using invasive and non-invasive evaluation criteria, are scarce in the scientific literature. Therefore, this points to the need for further clinical studies, so that the evaluation and documentation of the action of different types of bariatric surgery on the regression rate of NAFLD, with greater evidence and reproducibility, might be possible.

References

- Angulo, P., Hui, J. M., Marchesini, G., Bugianesi, E., George, J., Farrell, G. C., Enders, F., Saksena, S., Burt, A. D., Bida, J. P., Lindor, K., Sanderson, S. O., Lenzi, M., Adams, L. A., Kench, J., Thorneau, T. M., & Day, C. P. (2007). The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology (Baltimore, Md.)*, *45*(4), 846–854. <https://doi.org/10.1002/hep.21496>
- Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica. Diretrizes Brasileiras de Obesidade. (4a ed.). <https://abeso.org.br/diretrizes/>.
- Bhala, N., Younes, R., & Bugianesi, E. (2013). Epidemiology and natural history of patients with NAFLD. *Current pharmaceutical design*, *19*(29), 5169–5176. <https://doi.org/10.2174/13816128113199990336>
- Bugianesi, E., McCullough, A. J., & Marchesini, G. (2005). Insulin resistance: a metabolic pathway to chronic liver disease. *Hepatology (Baltimore, Md.)*, *42*(5), 987–1000. <https://doi.org/10.1002/hep.20920>
- Buzzetti, E., Pinzani, M., & Tsochatzis, E. A. (2016). The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism: clinical and experimental*, *65*(8), 1038–1048. <https://doi.org/10.1016/j.metabol.2015.12.012>
- Cazzo, E., Jimenez, L. S., Pareja, J. C., & Chaim, E. A. (2015). Effect of Roux-en-Y gastric bypass on nonalcoholic fatty liver disease evaluated through NAFLD fibrosis score: a prospective study. *Obesity surgery*, *25*(6), 982–985. <https://doi.org/10.1007/s11695-014-1489-2>
- Cazzo, E., Pareja, J. C., & Chaim, E. A. (2017). Nonalcoholic fatty liver disease and bariatric surgery: a comprehensive review. *Sao Paulo medical journal = Revista paulista de medicina*, *135*(3), 277–295. <https://doi.org/10.1590/1516-3180.2016.0306311216>
- Chaim, F., Pascoal, L. B., Chaim, F., Palma, B. B., Damázio, T. A., da Costa, L., Carvalho, R., Cazzo, E., Gestic, M. A., Utrini, M. P., Milanski, M., Chaim, E. A., & Leal, R. F. (2020). Histological grading evaluation of non-alcoholic fatty liver disease after bariatric surgery: a retrospective and longitudinal observational cohort study. *Scientific reports*, *10*(1), 8496. <https://doi.org/10.1038/s41598-020-65556-2>
- Chalasan, N., Younossi, Z., Lavine, J. E., Charlton, M., Cusi, K., Rinella, M., Harrison, S. A., Brunt, E. M., & Sanyal, A. J. (2018). The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology (Baltimore, Md.)*, *67*(1), 328–357. <https://doi.org/10.1002/hep.29367>
- Cherla, D. V., Rodriguez, N. A., Vangoitsenhoven, R., Singh, T., Mehta, N., McCullough, A. J., Brethauer, S. A., Schauer, P. R., & Aminian, A. (2020). Impact of sleeve gastrectomy and Roux-en-Y gastric bypass on biopsy-proven non-alcoholic fatty liver disease. *Surgical endoscopy*, *34*(5), 2266–2272. <https://doi.org/10.1007/s00464-019-07017-0>

- Espinet Coll, E., Vila Lolo, C., Díaz Galán, P., Gómez Valero, J. A., Bacchiddu, S., Quintana Tomás, C., Irigoyen, D., Gunnard, K., & Juan-Creix Comamala, A. (2019). Bariatric and metabolic endoscopy in the handling of fatty liver disease. A new emerging approach? *Revista española de enfermedades digestivas: organo oficial de la Sociedad Española de Patología Digestiva*, *111*(4), 283–293. <https://doi.org/10.17235/reed.2019.5949/2018>
- Day, C. P., & James, O. F. (1998). Steatohepatitis: a tale of two "hits"? *Gastroenterology*, *114*(4), 842–845. [https://doi.org/10.1016/s0016-5085\(98\)70599-2](https://doi.org/10.1016/s0016-5085(98)70599-2)
- De Luca, M., Angrisani, L., Himpens, J., Busetto, L., Scopinaro, N., Weiner, R., Sartori, A., Stier, C., Lakdawala, M., Bhasker, A. G., Buchwald, H., Dixon, J., Chiappetta, S., Kolberg, H. C., Frühbeck, G., Sarwer, D. B., Suter, M., Soricelli, E., Blüher, M., Vilallonga, R., & Shikora, S. (2016). Indications for Surgery for Obesity and Weight-Related Diseases: Position Statements from the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO). *Obesity surgery*, *26*(8), 1659–1696. <https://doi.org/10.1007/s11695-016-2271-4>
- Esquivel, C. M., Garcia, M., Armando, L., Ortiz, G., Lascano, F. M., & Foscarini, J. M. (2018). Laparoscopic Sleeve Gastrectomy Resolves NAFLD: Another Formal Indication for Bariatric Surgery? *Obesity surgery*, *28*(12), 4022–4033. <https://doi.org/10.1007/s11695-018-3466-7>
- Fabbrini, E., Sullivan, S., & Klein, S. (2010). Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. *Hepatology (Baltimore, Md.)*, *51*(2), 679–689. <https://doi.org/10.1002/hep.23280>
- Froylich, D., Corcelles, R., Daigle, C., Boules, M., Brethauer, S., & Schauer, P. (2016). Effect of Roux-en-Y gastric bypass and sleeve gastrectomy on nonalcoholic fatty liver disease: a comparative study. *Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery*, *12*(1), 127–131. <https://doi.org/10.1016/j.soard.2015.04.004>
- Kalinowski, P., Paluszkiwicz, R., Ziarkiewicz-Wróblewska, B., Wróblewski, T., Remiszewski, P., Grodzicki, M., & Krawczyk, M. (2017). Liver Function in Patients With Nonalcoholic Fatty Liver Disease Randomized to Roux-en-Y Gastric Bypass Versus Sleeve Gastrectomy: A Secondary Analysis of a Randomized Clinical Trial. *Annals of surgery*, *266*(5), 738–745. <https://doi.org/10.1097/SLA.0000000000002397>
- Khorgami, Z., Shoar, S., Andalib, A., Aminian, A., Brethauer, S. A., & Schauer, P. R. (2017). Trends in utilization of bariatric surgery, 2010–2014: sleeve gastrectomy dominates. *Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery*, *13*(5), 774–778. <https://doi.org/10.1016/j.soard.2017.01.031>
- Kleiner, D. E., Brunt, E. M., Van Natta, M., Behling, C., Contos, M. J., Cummings, O. W., Ferrell, L. D., Liu, Y. C., Torbenson, M. S., Unalp-Arida, A., Yeh, M., McCullough, A. J., Sanyal, A. J., & Nonalcoholic Steatohepatitis Clinical Research Network (2005). Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology (Baltimore, Md.)*, *41*(6), 1313–1321. <https://doi.org/10.1002/hep.20701>
- Laursen, T. L., Hagemann, C. A., Wei, C., Kazankov, K., Thomsen, K. L., Knop, F. K., & Grønbaek, H. (2019). Bariatric surgery in patients with non-alcoholic fatty liver disease - from pathophysiology to clinical effects. *World journal of hepatology*, *11*(2), 138–149. <https://doi.org/10.4254/wjh.v11.i2.138>
- Ledoux, S., Sami, O., Calabrese, D., Le Gall, M., Flamant, M., & Coupaye, M. (2019). Gastric bypass specifically impairs liver parameters as compared with sleeve gastrectomy, independently of evolution of metabolic disorders. *Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery*, *15*(2), 220–226. <https://doi.org/10.1016/j.soard.2018.10.035>
- Milić, S., Lulić, D., & Štimac, D. (2014). Non-alcoholic fatty liver disease and obesity: biochemical, metabolic and clinical presentations. *World journal of gastroenterology*, *20*(28), 9330–9337. <https://doi.org/10.3748/wjg.v20.i28.9330>
- Nascimento, T. M., Alves-Júnior, A., Nunes, M. A., de Freitas, T. R., da Silva, M. A., & Alves, M. R. (2015). Comparison of hepatic profile in pre and postoperative of bariatric surgery: private vs public network. *Arquivos brasileiros de cirurgia digestiva: ABCD = Brazilian archives of digestive surgery*, *28*(4), 274–277. <https://doi.org/10.1590/S0102-6720201500040014>
- Nickel, F., Tapking, C., Benner, L., Sollors, J., Billeter, A. T., Kennigott, H. G., Bokhary, L., Schmid, M., von Frankenberg, M., Fischer, L., Mueller, S., & Müller-Stich, B. P. (2018). Bariatric Surgery as an Efficient Treatment for Non-Alcoholic Fatty Liver Disease in a Prospective Study with 1-Year Follow-up: BariScan Study. *Obesity surgery*, *28*(5), 1342–1350. <https://doi.org/10.1007/s11695-017-3012-z>
- Polyzos, S. A., Kountouras, J., & Mantzoros, C. S. (2017). Adipose tissue, obesity and non-alcoholic fatty liver disease. *Minerva endocrinologica*, *42*(2), 92–108. <https://doi.org/10.23736/S0391-1977.16.02563-3>
- Praveen Raj, P., Gomes, R. M., Kumar, S., Senthilnathan, P., Karthikeyan, P., Shankar, A., & Palanivelu, C. (2015). The effect of surgically induced weight loss on nonalcoholic fatty liver disease in morbidly obese Indians: "NASHOST" prospective observational trial. *Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery*, *11*(6), 1315–1322. <https://doi.org/10.1016/j.soard.2015.02.006>
- Ruiz-Tovar, J., Alsina, M. E., Alpera, M. R., & OBELCHE Group (2017). Improvement of nonalcoholic fatty liver disease in morbidly obese patients after sleeve gastrectomy: association of ultrasonographic findings with lipid profile and liver enzymes. *Acta chirurgica Belgica*, *117*(6), 363–369. <https://doi.org/10.1080/00015458.2017.1334858>
- Ruiz-Tovar, J., & Zubiaga, L. (2019). Validation of biochemical scores for liver steatosis before and 1 year after sleeve gastrectomy. *Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery*, *15*(9), 1447–1453. <https://doi.org/10.1016/j.soard.2019.05.004>
- Souza, M. T., Silva, M. D., & Carvalho, R. (2010). Revisão integrativa: o que é e como fazer. *einstein (São Paulo)*, *8*(1), 102–106. <https://doi.org/10.1590/s1679-45082010rw1134>
- Simo, K. A., McKillop, I. H., McMillan, M. T., Ahrens, W. A., Walters, A. L., Thompson, K. J., Kuwada, T. S., Martinie, J. B., Iannitti, D. A., Gersin, K. S., & Sindram, D. (2014). Does a calculated "NAFLD fibrosis score" reliably negate the need for liver biopsy in patients undergoing bariatric surgery? *Obesity surgery*, *24*(1), 15–21. <https://doi.org/10.1007/s11695-013-1044-6>
- Von Schönfels, W., Beckmann, J. H., Ahrens, M., Hendricks, A., Röcken, C., Szymczak, S., Hampe, J., & Schafmayer, C. (2018). Histologic improvement of NAFLD in patients with obesity after bariatric surgery based on standardized NAS (NAFLD activity score). *Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery*, *14*(10), 1607–1616. <https://doi.org/10.1016/j.soard.2018.07.012>
- Whittemore, R., & Knaf, K. (2005). The integrative review: Updated methodology. *Journal of Advanced Nursing*, *52*(5), 546–553. <https://doi.org/10.1111/j.1365-2648.2005.03621.x>