Editorial

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NON-ALCOHOLIC FATTY LIVER DISEASE AND BARIATRIC SURGERY: WHERE ARE WE NOW?

Gastroenterology

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ABSTRACT

Non-alcoholic fatty liver disease prevalence has been increasing globally. This has been linked to an increase in the incidence of hepatocellular carcinoma with and without cirrhosis and of the need for liver transplantation in this group of patients. This translates into a considerable increase in costs in treatment for this condition. Bariatric surgery has been largely demonstrated to treat this disease with a high cost-benefit. Although, it is not currently recommended as co-morbidity for indication of surgery in patients with body mass index 35 to 39 Kg/m². The authors suggest in this editorial that non-alcoholic fatty liver disease with fibrosis should be considered for inclusion as co-morbidity for indication of bariatric surgery.

KEYWORDS

Bariatric surgery; non-alcoholic fatty liver disease; Liver Cirrhosis; Hepatocellular carcinoma.

Non-alcoholic fatty liver disease (NAFLD) prevalence has been increasing globally, as Western diet patterns are becoming more common in the East, and it is believed to be currently similar in both the West and the East[1, 2]. Some of these patients will be diagnosed with a benign form of the disease, non-alcoholic fatty liver (NAFL) or a more severe form of the disease, which can lead to fibrosis and cirrhosis, known as non-alcoholic steato-hepatitis (NASH)[3]. This has been linked to an increase in the incidence of hepatocellular carcinoma with and without cirrhosis[4] and of the need for liver transplantation in this group of patients, which might impact prognosis[5-8].

For example, in a cohort of obese patients in Japan undergoing bariatric surgery, 77.5% of patients were diagnosed with NASH in intra-operative liver biopsies[9]. Even in adolescents, a group of patients that generally have lower NASH prevalence since they reach a body mass index (BMI) that justifies bariatric surgery prior to developing NASH[10], the prevalence of NAFLD was 59%, of NASH 34% and of fibrosis 18%[11,12]. This is particularly troublesome, hence no score or laboratorial test has been shown to be highly accurate in predicting prognosis or NASH and fibrosis in patients before bariatric surgery[13-16]. This metabolic health obese phenotype eventually will evolve to a complication, ratifying a need for a better evaluation[17].

NASH also has a pivotal role in the metabolic syndrome[18-20] rising the risk of cardiovascular disease[21,22] and associated co-morbidities[23]. It seems to be associated to a higher mortality overall[24] and to a higher mortality even 10 years after bariatric surgery[25]. Among NAFLD patients, the histological stage is essential for long-term prognosis. NASH can lead to cirrhosis more often than NAFL, around 10.8% in a 15-years follow up against 0.7%, with a liver related mortality of 7.3% against 0.9%[26].

In a systematic review, the prevalence of NASH in routine liver biopsy performed during bariatric surgery was 25%, with an anecdotal complication rate[27]. Also, many cases of cryptogenic cirrhosis seem to be actually cases of misdiagnosed NAFLD-related cirrhosis, until 63.3% which underwent liver transplantation[28].

The prevalence of fibrosis in obese patients which undergo bariatric surgery varies from 6% to 74.4% and of NASH from 26% to 55% in many studies[29-33]. The diagnosis of NASH, therefore, is sometimes elusive, although it is paramount for the definition of prognosis of the disease[34]. Other methods, although clinically useful, are not actually very accurate. Due to the importance, accuracy and low risk of intra-operative liver biopsy, the authors recommend that it should be done routinely during bariatric surgery.

BARIATRIC SURGERY AS TREATMENT FOR NON-ALCOHOLIC FATTY LIVER DISEASE

Currently, no clinical treatment has been shown to very effective for the treatment of NASH. It has been well demonstrated that weight loss equal or superior to 7 to 10% of total body weight is associated to a significant improvement of histological remission in NASH patients and even to regression of fibrosis, especially in patients who underwent bariatric surgery[13,35].

There are some medications which have been shown to improve histology and lead to regression of fibrosis. Caffeine consumption has been shown to slow NASH progression[36,37]. The PIVENS trial has shown efficacy of vitamin E and of pioglitazone for non-diabetics[38] and diabetic patients[39]. Some novel promising therapies are in phase 3 studies, such as liraglutide[40], elafibranor[41], emricasan[42] and obeticholic acid[43]. Although metformin has shown improvement in some laboratorial parameters of the disease, no clinical trial has shown histological improvement so far[44-46].

Regarding dietary patterns, some trials have suggested that low-carb diets, such as the Mediterranean diet, could have some additional benefit over low-fat diets[47-50]. Exercise has been shown to improve NASH, whether associated to weight loss or not[51,52], even contributing to a reduction in insulin resistance[53].

This translates into a considerable increase in costs in treatment for this condition. Although diet and exercise can be somewhat inexpensive, the new drugs under development for treatment of NASH do not look so powerful, except for the Acetyl-CoA carboxylase inhibitors[54,55], which are yet to begin phase 2. So, we might get in the short term a group of effective but no so powerful drugs, for such a common and rising condition[56].

Bariatric surgery, in the form of the two most common procedures currently, Sleeve Gastrectomy (SG) or Roux-en-Y Gastric Bypass (RYGB), has been shown to be highly effective for the treatment of NAFLD. For the treatment of obesity itself, it has been shown to be highly effective and cost-benefit, with total costs increasing with the delay in surgery[57]. SG has been even shown to be safe in cirrhotic patients Child-Pugh A[58]. This has been ratified by a recent systematic review that has shown an extremely high rate of resolution of NASH in patients who underwent bariatric surgery[59].

Although bariatric surgery has been largely demonstrated to treat NASH with a high cost-benefit[60,61], it is not recommended as a co-morbidity indication for surgery in patients with body mass index 35 to 39 Kg/m². Both SG and RYGB have been shown to be safe and highly effective, even in the long term, improving quality of life and histological disease[59,62-65].

SHOULD NON-ALCOHOLIC FATTY LIVER DISEASE BECOME A CO-MORBITY INDICATION FOR BARIATRIC SURGERY?

Although data from large randomized trials are still much needed, the mounting clinical[19,59,66-70] and physiological evidence[71-73] of the

efficacy of RYGB and SG in the treatment of NASH is very thorough. Given the available evidence reviewed, the authors defend in this editorial that NAFLD, especially in the form of NASH, should be considered for inclusion as co-morbidity for patients with BMI 35 to 39 Kg/m^2.

REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, et al. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73-84. [doi:10.1002/hep.28431] [PMID: 26707365]
2. Malik VS, Willett WC, Hu FB. Global obesity: trends, risk factors and policy implications. Nat Rev Endocrinol 2013;9:13-27. [doi:10.1038/nrendo.2012.199] [PMID: 23165161]
3. LaBrecque DR, Abbas Z, Anania F, Ferenci P, Khan AG, Goh KL, Hamid SS, Isakov V, Lizarzabal M, Peñaranda MM, Ramos JF, Sarin S, Stimac D, Thomson AB, Umar M, Krabshuis J, LeMair A; World Gastroenterology Organisation. World Gastroenterology Organisation global guidelines: Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. J Clin Gastroenterol. 2014;48:467-73. [doi:10.1097/MCG.0000000000000116] [PMID: 24921212]
4. Onzi G, Moretti F, Balbinot SS, Balbinot RA, Soldera J. Hepatocellular carcinoma in non-alcoholic fatty liver disease with and without cirrhosis. Hepatoma Res 2019;5:7. [doi:10.20517/2394-5079.2018.114]
5. Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, Eguchi Y, Wong VW, Negro F, Yilmaz Y, Romero-Gomez M, George J, Ahmed A, Wong R, Younossi I, Ziayee M, Afendy A; Global Nonalcoholic Steatohepatitis Council. Nonalcoholic Steatohepatitis Is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates. Clin Gastroenterol Hepatol. 2019;17:748-55. [doi:10.1016/j.cgh.2018.05.057] [PMID: 29908364]
6. Chedid MF. Nonalcoholic Steatohepatitis: The Second Leading Indication for Liver Transplantation in the USA. Dig Dis Sci. 2017;62:2621-22. [doi:10.1007/s10620-017-4724-6] [PMID: 28840385]
7. Soldera J, Camazzola F, Rodríguez S, Brandão A. Dobutamine stress echocardiography, myocardial perfusion scintigraphy, invasive coronary angiography, and post-liver transplantation events: Systematic review and meta-analysis. Clin Transplant. 2018;32:e13222. [doi:10.1111/ctr.13222] [PMID: 29436036]
8. Soldera J, Camazzola F, Rodríguez S, Brandão A. Cardiac stress testing and coronary artery disease in liver transplantation candidates: Meta-analysis. World J Hepatol. 2018;10:877-86. [doi:10.4254/wjh.v10.i11.877] [PMID: 30533188] [PMCID: PMC6280161]
9. Seki Y, Kakizaki S, Horiguchi N, Hashizume H, Tojima H, Yamazaki Y, Sato K, Kusano M, Yamada M, Kasama K. Prevalence of nonalcoholic steatohepatitis in Japanese patients with morbid obesity undergoing bariatric surgery. J Gastroenterol. 2016;51:281-9. [doi:10.1007/s00535-015-1114-8] [PMID: 26314837]
10. Manco M, Mosca A, De Peppo F, Caccamo R, Cutrera R, Giordano U, De Stefanis C, Alisi A, Baumann U, Silecchia G, Nobili V. The Benefit of Sleeve Gastrectomy in Obese Adolescents on Nonalcoholic Steatohepatitis and Hepatic Fibrosis. J Pediatr. 2017;180:31-37. [doi:10.1016/j.jpeds.2016.08.101] [PMID: 27697327]
11. Xanthakos SA, Jenkins TM, Kleiner DE, Boyce TW, Mourya R, Karns R, Brandt ML, Harmon CM, Helmrath MA, Michalsky MP, Courcoulas AP, Zeller MH, Inge TH; Teen-LABS Consortium. High Prevalence of Nonalcoholic Fatty Liver Disease in Adolescents Undergoing Bariatric Surgery. Gastroenterology. 2015;149:623-34. [doi:10.1053/j.gastro.2015.05.039] [PMID: 26026390] [PMCID: PMC4654456]
12. Corey KE, Stanley TL, Misdraji J, Scirica C, Pratt J, Hoppin A, Misra M. Prevalence and outcome of non-alcoholic fatty liver disease in adolescents and young adults undergoing weight loss surgery. Pediatr Obes. 2014;9:e91-3. [doi:10.1111/j.2047-6310.2014.219.x] [PMID: 24677740] [PMCID: PMC4163105]
13. Hannah WN Jr, Harrison SA. Effect of Weight Loss, Diet, Exercise, and Bariatric Surgery on Nonalcoholic Fatty Liver Disease. Clin Liver Dis. 2016;20:339-50. [doi:10.1016/j.cld.2015.10.008] [PMID: 27063273]
14. Reha JL, Lee S, Hofmann LJ. Prevalence and predictors of nonalcoholic steatohepatitis in obese patients undergoing bariatric surgery: a Department of Defense experience. Am Surg. 2014;80:595-9. [PMID: 24887798]
15. Petrick A, Benotti P, Wood GC, Still CD, Strodel WE, Gabrielsen J, Rolston D, Chu X, Argyropoulos G, Ibele A, Gerhard GS. Utility of Ultrasound, Transaminases, and Visual Inspection to Assess Nonalcoholic Fatty Liver Disease in Bariatric Surgery Patients. Obes Surg. 2015;25:2368-75. [doi:10.1007/s11695-015-1707-6] [PMID: 26003548] [PMCID: PMC4917009]
16. Hagström H, Nasr P, Ekstedt M, Stål P, Hultcrantz R, Kechagias S. Accuracy of Noninvasive Scoring Systems in Assessing Risk of Death and Liver-Related Endpoints in Patients With Nonalcoholic Fatty Liver Disease. Clin Gastroenterol Hepatol. 2019;17(6):1148-56. [doi:10.1016/j.cgh.2018.11.030] [PMID: 30471458]
17. Caleyachetty R, Thomas GN, Toulis KA, Mohammed N, Gokhale KM, Balachandran K, Nirantharakumar K. Metabolically Healthy Obese and Incident Cardiovascular Disease Events Among 3.5 Million Men and Women. J Am Coll Cardiol. 2017;70:1429-37. [doi:10.1016/j.jacc.2017.07.763] [PMID: 28911506]
18. Cazzo E, Pareja JC, Chaim EA. Nonalcoholic fatty liver disease and bariatric surgery: a comprehensive review. Sao Paulo Med J. 2017;135(3):277-95. [doi:10.1590/1516-3180.2016.0306311216] [PMID: 28562737]
19. Mummadi RR, Kasturi KS, Chennareddygari S, Sood GK. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2008;6:1396-402. [doi:10.1016/j.cgh.2008.08.012] [PMID: 18986848]
20. Lonardo A, Ballestri S, Marchesini G, Angulo P, Loria P. Nonalcoholic fatty liver disease: a precursor of the metabolic syndrome. Dig Liver Dis. 2015;47:181-90. [doi:10.1016/j.dld.2014.09.020] [PMID: 25739820]
21. Wu S, Wu F, Ding Y, Hou J, Bi J, Zhang Z. Association of non-alcoholic fatty liver disease with major adverse cardiovascular events: A systematic review and meta-analysis. Sci Rep. 2016;6:33386. [doi:10.1038/srep33386] [PMID: 27633274] [PMCID: PMC5026028]
22. Hagström H, Nasr P, Ekstedt M, Hammar U, Stål P, Askling J, Hultcrantz R, Kechagias S. Cardiovascular risk factors in non-alcoholic fatty liver disease. Liver Int. 2019;39:197-204. [doi:10.1111/liv.13973] [PMID: 30253056]
23. Bang KB, Cho YK. Comorbidities and Metabolic Derangement of NAFLD. J Lifestyle Med. 2015;5(1):7-13. [doi:10.15280/jlm.2015.5.1.7] [PMID: 26528424] [PMCID: PMC4608226]
24. Duseja A, Chalasani N. Epidemiology and risk factors of nonalcoholic fatty liver disease (NAFLD). Hepatol Int. 2013;7 Suppl 2:755-64. [doi:10.1007/s12072-013-9480-x] [PMID: 26202291]
25. Goossens N, Hoshida Y, Song WM, Jung M, Morel P, Nakagawa S, Zhang B, Frossard JL, Spahr L, Friedman SL, Negro F, Rubbia-Brandt L, Giostra E. Nonalcoholic Steatohepatitis Is Associated With Increased Mortality in Obese Patients Undergoing Bariatric Surgery. Clin Gastroenterol Hepatol. 2016;14(11):1619-28. [doi:10.1016/j.cgh.2015.10.010] [PMID: 26492845] [PMCID: PMC4838546]
26. Angulo P. Long-term mortality in nonalcoholic fatty liver disease: is liver histology of any prognostic significance? Hepatology. 2010;51:373-5. [doi:10.1002/hep.23521] [PMID: 20101746] [PMCID: PMC2945376]
27. Barbois S, Arvieux C, Leroy V, Reche F, Stürm N, Borel AL. Benefit-risk of intraoperative liver biopsy during bariatric surgery: review and perspectives. Surg Obes Relat Dis. 2017;13(10):1780-6. [doi:10.1016/j.soard.2017.07.032] [PMID: 28935200]
28. Nayak NC, Vasdev N, Saigal S, Soin AS. End-stage nonalcoholic fatty liver disease: evaluation of pathomorphologic features and relationship to cryptogenic cirrhosis from study of explant livers in a living donor liver transplant program. Hum Pathol. 2010;41(3):425-30. [doi:10.1016/j.humpath.2009.06.021] [PMID: 19954815]
29. Abrams GA, Kunde SS, Lazenby AJ, Clements RH. Portal fibrosis and hepatic steatosis in morbidly obese subjects: A spectrum of nonalcoholic fatty liver disease. Hepatology. 2004;40:475-83. [doi:10.1002/hep.20323] [PMID: 15368453]
30. Guajardo-Salinas GE, Hilmy A. Prevalence of nonalcoholic fatty liver disease (NAFLD) and utility of FIBROspect II to detect liver fibrosis in morbidly obese Hispano-American patients undergoing gastric bypass. Obes Surg. 2010;20:1647-53. [doi:10.1007/s11695-009-0027-0] [PMID: 19957049]
31. Boza C, Riquelme A, Ibañez L, Duarte I, Norero E, Viviani P, Soza A, Fernandez JI, Raddatz A, Guzman S, Arrese M. Predictors of nonalcoholic steatohepatitis (NASH) in obese patients undergoing gastric bypass. Obes Surg. 2005;15:1148-53. [doi:10.1381/0960892055002347] [PMID: 16197788]
32. Kashyap SR, Diab DL, Baker AR, Yerian L, Bajaj H, Gray-McGuire C, Schauer PR, Gupta M, Feldstein AE, Hazen SL, Stein CM. Triglyceride levels and not adipokine concentrations are closely related to severity of nonalcoholic fatty liver disease in an obesity surgery cohort. Obesity (Silver Spring). 2009;17(9):1696-701. [doi:10.1038/oby.2009.89] [PMID: 19360015] [PMCID: PMC2829436]
33. Cazzo E, de Felice Gallo F, Pareja JC, Chaim EA. Nonalcoholic fatty liver disease in morbidly obese subjects: correlation among histopathologic findings, biochemical features, and ultrasound evaluation. Obes Surg. 2014;24(4):666-8. [doi:10.1007/s11695-014-1183-4] [PMID: 24415281]
34. Kleiner DE, Berk PD, Hsu JY, Courcoulas AP, Flum D, Khandelwal S, Pender J, Pomp A, Roerig J, Machado LL, Wolfe BM, Belle SH; LABS Consortium. Hepatic pathology among patients without known liver disease undergoing bariatric surgery: observations and a perspective from the longitudinal assessment of bariatric surgery (LABS) study. Semin Liver Dis. 2014;34(1):98-107. [doi:10.1055/s-0034-1371083] [PMID: 24782263] [PMCID: PMC4139971]
35. Glass LM, Dickson RC, Anderson JC, Suriawinata AA, Putra J, Berk BS, Toor A. Total body weight loss of ≥ 10 % is associated with improved hepatic fibrosis in patients with nonalcoholic steatohepatitis. Dig Dis Sci. 2015;60:1024-30. [doi:10.1007/s10620-014-3380-3] [PMID: 25354830]
36. Barros RK, Cotrim HP, Daltro C, Alves E, de Freitas LA, Daltro C, Oliveira Y. Nonalcoholic steatohepatitis in morbid obese patients: coffee consumption vs. disease severity. Ann Hepatol. 2016;15(3):350-5. [doi:10.5604/16652681.1198804] [PMID: 27049488]
37. Wijarnpreecha K, Thongprayoon C, Ungprasert P. Coffee consumption and risk of nonalcoholic fatty liver disease: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2017;29:e8-e12. [doi:10.1097/MEG.0000000000000776] [PMID: 27824642]
38. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010;362(18):1675-85. [doi:10.1056/NEJMoa0907929] [PMID: 20427778] [PMCID: PMC2928471]
39. Bril F, Kalavalapalli S, Clark VC, Lomonaco R, Soldevila-Pico C, Liu IC, Orsak B, Tio F, Cusi K. Response to Pioglitazone in Patients With Nonalcoholic Steatohepatitis With vs Without Type 2 Diabetes. Clin Gastroenterol Hepatol. 2018;16(4):558-66. [doi:10.1016/j.cgh.2017.12.001] [PMID: 29223443]
40. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, Hazlehurst JM, Guo K; LEAN trial team, Abouda G, Aldersley MA, Stocken D, Gough SC, Tomlinson JW, Brown RM, Hübscher SG, Newsome PN. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016;387(10019):679-90. [doi:10.1016/S0140-6736(15)00803-X] [PMID: 26608256]
41. Ratziu V, Harrison SA, Francque S, Bedossa P, Lehert P, Serfaty L, Romero-Gomez M, Boursier J, Abdelmalek M, Caldwell S, Drenth J, Anstee QM, Hum D, Hanf R, Roudot A, Megnien S, Staels B, Sanyal A; GOLDEN-505 Investigator Study Group. Elafibranor, an Agonist of the Peroxisome Proliferator-Activated Receptor-α and -δ, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening. Gastroenterology. 2016;150(5):1147-59. [doi:10.1053/j.gastro.2016.01.038] [PMID: 26874076]
42. Frenette CT, Morelli G, Shiffman ML, Frederick RT, Rubin RA, Fallon MB, Cheng JT, Cave M, Khaderi SA, Massoud O, Pyrsopoulos N, Park JS, Robinson JM, Yamashita M, Spada AP, Chan JL, Hagerty DT. Emricasan Improves Liver Function in Patients With Cirrhosis and High Model for End-Stage Liver Disease Scores Compared With Placebo. Clin Gastroenterol Hepatol. 2019;17(4):774-83. [doi:10.1016/j.cgh.2018.06.012] [PMID: 29913280]
43. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, Chalasani N, Dasarathy S, Diehl AM, Hameed B, Kowdley KV, McCullough A, Terrault N, Clark JM, Tonascia J, Brunt EM, Kleiner DE, Doo E; NASH Clinical Research Network. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet. 2015;385(9972):956-65. [doi:10.1016/S0140-6736(14)61933-4] [PMID: 25468160] [PMCID: PMC4447192]
44. Li Y, Liu L, Wang B, Wang J, Chen D. Metformin in non-alcoholic fatty liver disease: A systematic review and meta-analysis. Biomed Rep. 2013;1(1):57-64. [doi:10.3892/br.2012.18] [PMID: 24648894] [PMCID: PMC3956897
45. Loomba R, Lutchman G, Kleiner DE, Ricks M, Feld JJ, Borg BB, Modi A, Nagabhyru P, Sumner AE, Liang TJ, Hoofnagle JH. Clinical trial: pilot study of metformin for the treatment of non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2009;29(2):172-82. [doi:10.1111/j.1365-2036.2008.03869.x] [PMID: 18945255] [PMCID: PMC2990687]
46. Sturm N, Bronowicki JP, Maynard-Muet M, Tran A, Heluwaert F, Plages A, Zarski JP. Metformin plus pentoxifylline versus prescriptive diet in non-alcoholic steatohepatitis (NASH): a randomized controlled pilot trial. Gastroenterol Clin Biol. 2009;33(10-11):984-6. [doi:10.1016/j.gcb.2009.05.010] [PMID: 19646832]
47. Properzi C, O'Sullivan TA, Sherriff JL, Ching HL, Jeffrey GP, Buckley RF, Tibballs J, MacQuillan GC, Garas G, Adams LA. Ad Libitum Mediterranean and Low-Fat Diets Both Significantly Reduce Hepatic Steatosis: A Randomized Controlled Trial. Hepatology. 2018;68(5):1741-54. [doi:10.1002/hep.30076] [PMID: 29729189]
48. Katsagoni CN, Papatheodoridis GV, Ioannidou P, Deutsch M, Alexopoulou A, Papadopoulos N, Papageorgiou MV, Fragopoulou E, Kontogianni MD. Improvements in clinical characteristics of patients with non-alcoholic fatty liver disease, after an intervention based on the Mediterranean lifestyle: a randomised controlled clinical trial. Br J Nutr. 2018;120(2):164-75. [doi:10.1017/S000711451800137X] [PMID: 29947322]
49. Anania C, Perla FM, Olivero F, Pacifico L, Chiesa C. Mediterranean diet and nonalcoholic fatty liver disease. World J Gastroenterol. 2018;24(19):2083-94. [doi:10.3748/wjg.v24.i19.2083] [PMID: 29785077] [PMCID: PMC5960814]
50. Abenavoli L, Milic N, Peta V, Alfieri F, De Lorenzo A, Bellentani S. Alimentary regimen

in non-alcoholic fatty liver disease: Mediterranean diet. World J Gastroenterol. 2014;20(45):16831-40. [doi:10.3748/wjg.v20.i45.16831] [PMID: 25492997] [PMCID: PMC4258553]
51. Houghton D, Thoma C, Hallsworth K, Cassidy S, Hardy T, Burt AD, Tiniakos D, Hollingsworth KG, Taylor R, Day CP, McPherson S, Anstee QM, Trenell MI. Exercise Reduces Liver Lipids and Visceral Adiposity in Patients With Nonalcoholic Steatohepatitis in a Randomized Controlled Trial. Clin Gastroenterol Hepatol.2017;15:96-102. [doi:10.1016/j.cgh.2016.07.031] [PMID: 27521509] [PMCID: PMC5196006]
52. Fealy CE, Haus JM, Solomon TP, Pagadala M, Flask CA, McCullough AJ, Kirwan JP. Short-term exercise reduces markers of hepatocyte apoptosis in nonalcoholic fatty liver disease. J Appl Physiol (1985). 2012;113(1):1-6. [doi:10.1152/ japplphysiol. 00127.2012] [PMID: 22582214] [PMCID: PMC3404833]
53. Zou TT, Zhang C, Zhou YF, Han YJ, Xiong JJ, Wu XX, Chen YP, Zheng MH. Lifestyle interventions for patients with nonalcoholic fatty liver disease: a network meta-analysis. Eur J Gastroenterol Hepatol. 2018;30(7):747-55. [doi:10.1097/ MEG. 0000000000001135] [PMID: 29683979]
54. Loomba R, Kayali Z, Noureddin M, Ruane P, Lawitz EJ, Bennett M, Wang L, Harting E, Tarrant JM, McColgan BJ, Chung C, Ray AS, Subramanian GM, Myers RP, Middleton MS, Lai M, Charlton M, Harrison SA. GS-0976 Reduces Hepatic Steatosis and Fibrosis Markers in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology. 2018;155:1463-73. [doi:10.1053/j.gastro.2018.07.027] [PMID: 30059671] [PMCID: PMC6318218]
55. Stiede K, Miao W, Blanchette HS, Beysen C, Harriman G, Harwood HJ Jr, Kelley H, Kapeller R, Schmalbach T, Westlin WF. Acetyl-coenzyme A carboxylase inhibition reduces de novo lipogenesis in overweight male subjects: A randomized, double-blind, crossover study. Hepatology. 2017;66:324-34. [doi:10.1002/hep.29246] [PMID: 28470676] [PMCID: PMC5599970]
56. Connolly JJ, Ooka K, Lim JK. Future Pharmacotherapy for Non-alcoholic Steatohepatitis (NASH): Review of Phase 2 and 3 Trials. J Clin Transl Hepatol. 2018;6:264-75. [doi:10.14218/JCTH.2017.00056] [PMID: 30271738] [PMCID: PMC6160309]
57. Cohen RV, Luque A, Junqueira S, Ribeiro RA, Le Roux CW. What is the impact on the healthcare system if access to bariatric surgery is delayed? Surg Obes Relat Dis. 2017;13:1619-27. [doi:10.1016/j.soard.2017.03.025] [PMID: 28499887]
58. Rebibo L, Gerin O, Verhaeghe P, Dhahri A, Cosse C, Regimbeau JM. Laparoscopic sleeve gastrectomy in patients with NASH-related cirrhosis: a case-matched study. Surg Obes Relat Dis. 2014;10(3):405-10. [doi:10.1016/j.soard.2013.09.015] [PMID: 24355322]
59. Lee Y, Doumouras AG, Yu J, Brar K, Banfield L, Gmora S, Anvari M, Hong D. Complete Resolution of Nonalcoholic Fatty Liver Disease After Bariatric Surgery: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2019;17:1040-60. [doi:10.1016/j.cgh.2018.10.017] [PMID: 30326299]
60. Klebanoff MJ, Corey KE, Chhatwal J, Kaplan LM, Chung RT, Hur C. Bariatric surgery for nonalcoholic steatohepatitis: A clinical and cost-effectiveness analysis. Hepatology. 2017;65(4):1156-64. [doi:10.1002/hep.28958] [PMID: 27880977]
61. Klebanoff MJ, Corey KE, Samur S, Choi JG, Kaplan LM, Chhatwal J, Hur C. Cost-effectiveness Analysis of Bariatric Surgery for Patients With Nonalcoholic Steatohepatitis Cirrhosis. JAMA Netw Open. 2019;2(2):e190047. [doi:10.1001/jamanetworkopen.2019.0047] [PMID: 30794300]
62. Tan CH, Al-Kalifah N, Ser KH, Lee YC, Chen JC, Lee WJ. Long-term effect of bariatric surgery on resolution of nonalcoholic steatohepatitis (NASH): An external validation and application of a clinical NASH score. Surg Obes Relat Dis. 2018;14(10):1600-6. [doi:10.1016/j.soard.2018.05.024] [PMID: 30077664]
63. von Schönfels W, Beckmann JH, Ahrens M, Hendricks A, Röcken C, Szymczak S, Hampe J, Schafmayer C. Histologic improvement of NAFLD in patients with obesity after bariatric surgery based on standardized NAS (NAFLD activity score). Surg Obes Relat Dis. 2018;14:1607-16. [doi:10.1016/j.soard.2018.07.012] [PMID: 30146425]
64. Kalinowski P, Paluszkiewicz R, Ziarkiewicz-Wróblewska B, Wróblewski T, Remiszewski P, Grodzicki M, Krawczyk M. 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. Ann Surg. 2017;266(5):738-45. [doi:10.1097/SLA.0000000000002397] [PMID: 28767558]
65. Billeter AT, Senft J, Gotthardt D, Knefeli P, Nickel F, Schulte T, Fischer L, Nawroth PP, Büchler MW, Müller-Stich BP. Combined Non-alcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus: Sleeve Gastrectomy or Gastric Bypass?-a Controlled Matched Pair Study of 34 Patients. Obes Surg. 2016;26:1867-74. [doi:10.1007/s11695-015-2006-y] [PMID: 26660688]
66. Schwarz AC, Billeter AT, Scheurlen KM, Blüher M, Müller-Stich BP. Comorbidities as an Indication for Metabolic Surgery. Visc Med. 2018;34(5):381-7. [doi:10.1159/000493291] [PMID: 30498706] [PMCID: PMC6257097]
67. Caravatto PP, Cohen R. The Role of Metabolic Surgery in Non-alcoholic Steatohepatitis Improvement. Curr Atheroscler Rep. 2017;19(11):45. [doi:10.1007/s11883-017-0681-y] [PMID: 28986720]
68. Jirapinyo P, Thompson CC. Treatment of NASH with Gastric Bypass. Curr Gastroenterol Rep. 2018;20(10):49. [doi:10.1007/s11894-018-0653-6] [PMID: 30244334]
69. Bedossa P, Tordjman J, Aron-Wisnewsky J, Poitou C, Oppert JM, Torcivia A, Bouillot JL, Paradis V, Ratziu V, Clément K. Systematic review of bariatric surgery liver biopsies clarifies the natural history of liver disease in patients with severe obesity. Gut. 2017;66:1688-96. [doi:10.1136/gutjnl-2016-312238] [PMID: 27884920]
70. Sasaki A, Nitta H, Otsuka K, Umemura A, Baba S, Obuchi T, Wakabayashi G. Bariatric surgery and non-alcoholic Fatty liver disease: current and potential future treatments. Front Endocrinol (Lausanne). 2014;5:164. [doi:10.3389/fendo.2014.00164] [PMID: 25386164] [PMCID: PMC4209858]
71. Laursen TL, Hagemann CA, Wei C, Kazankov K, Thomsen KL, Knop FK, Grønbæk H. Bariatric surgery in patients with non-alcoholic fatty liver disease - from pathophysiology to clinical effects. World J Hepatol. 2019;11:138-49. [doi:10.4254/wjh.v11.i2.138] [PMID: 30820265] [PMCID: PMC6393715]
72. Verbeek J, Lannoo M, Pirinen E, Ryu D, Spincemaille P, Vander Elst I, Windmolders P, Thevissen K, Cammue BP, van Pelt J, Fransis S, Van Eyken P, Ceuterick-De Groote C, Van Veldhoven PP, Bedossa P, Nevens F, Auwerx J, Cassiman D. Roux-en-y gastric bypass attenuates hepatic mitochondrial dysfunction in mice with non-alcoholic steatohepatitis. Gut. 2015;64:673-83. [doi:10.1136/gutjnl-2014-306748] [PMID: 24917551]
73. Clanton J, Subichin M. The Effects of Metabolic Surgery on Fatty Liver Disease and Nonalcoholic Steatohepatitis. Surg Clin North Am. 2016;96:703-15. [doi:10.1016/j.suc.2016.03.008] [PMID: 27473796]