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Special Article: Gallstones (Cholelithiasis)

Cholesterol Gallstones and Cholecystectomy are both associated with Non-Alcoholic Fatty Liver Disease

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Abstract

Gallstone Disease (GD) has a 10-20% incidence rate among adults. Non-Alcoholic-Fatty Liver (NAFLD) is a frequent health problem, affecting about 1 in 4 adults globally. Research on the pathogenesis of gallstones in patients with NAFLD, as well of strategies for primary prevention of gallstones have been recommended by the EASL Clinical practice guidelines on the prevention, diagnosis and treatment of gallstones (2016). We present here the association of GD with NAFLD, and the strategies for GD primary prevention.

An increase in the body mass index has been demonstrated worldwide with great variations among continents. Obesity is the main risk factor for GD in patients with known gallstone heredity, and also in the general population. Besides age and family history of gallstones, early onset of obesity, hyperlipoproteinemia type 4, diabetes mellitus, reduced gallbladder motility and sedentary style of life, are the most risk factors for GD. The frequent association between GD and obesity is part of the Metabolic Syndrome (MetS, or Insulin Resistance Syndrome). The more the components of MetS, the higher the prevalence of GD in both males and females.

Non-alcoholic fatty liver disease has numerous metabolic risk factors that are common for GD. A positive concurrent and bidirectional relationship between NAFLD and GD were demonstrated by many epdemiological studies. It is difficult to establish which of the two diseases was the first one, as the studies performed show contradictory results. But which ever comes first, should make the physician to look for the other one. Awareness of this association may result in an earlier diagnosis for both diseases.

Observational studies have recently found that the MetS prevalence was significantly higher in subjects with a history of cholecystectomy. It was suggested that cholecystectomy itself increases the NAFLD risk. Explanation is that removal of the gallbladder will affect its role in bile acid homeostasis as well as in the metabolic / hormonal activity regulated by the gallbladder mucosa. The decreased FGF-19 (fibroblast growth factor) after removing the gallbladder may increase the hepatic triglyceride content, thus favoring the development of NAFLD.

A diet poor in sugars and fat, and reach in vegetable fibers, a regular eating pattern, as well as regular physical activity seem to protect against gallstone formation, and also against the metabolic disorders linking liver steatosis and GD.

Introduction

Gallstone disease and NAFLD share similar risk factors, therefore, the diagnosis of each one should prompt the clinician to look for the other condition. An increase of both GD and NAFLD prevalence rates is to be expected, which will parallel the aging populations. Lifestyle interventions for prevention of both GD and NAFLD should focus on ideal weight maintenance, recommending weight loss among overweight and obese individuals in the general population.

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Research on the pathogenesis of Gallstone Disease (GD) in patients with Non-Alcoholic Fatty Liver Disease (NAFLD) and on their prevention have been recommended by the most recent *EASL Clinical practice guidelines on the prevention, diagnosis and treatment of gallstones* with the aim to implement both genetic and exogenous lithogenic risk factors in novel prevention strategies of GD [1].

Cholesterol GD is a complex disease, characterized by the interaction of a genetic (polygenic) predisposition to develop gallstones associated with an important environmental influence. Gallstone disease is a common pathology of the digestive system, with a 10-20% incidence rate among adults. Prevalence of GD is rising in the industrialized countries in Europe and North America, and also in the Asia-Pacific countries. Given the high incidence at advanced age, the longer life expectancy of the population and the high costs of cholecystectomy, GD represents a significant burden for these societies. Sustained efforts are presently directed to elucidate the etiology of this common disease, with the goal of preventing gallstone formation. Non-Alcoholic Fatty Liver Disease (NAFLD) is an increasingly common chronic liver disease around the world, and has some common metabolic risk factors with GD. It is an important public health problem, as it affects about 1 in 4 adults globally.

Most recommendations for prevention these diseases derive from epidemiological information. Prevention could be addressed for the entire population with recommendations for a healthy life, but could be more productively focused on subjects with increased risk [1].

This review presents the association of GD with common diseases, mainly with NAFLD, and describes the strategies for GD primary prevention, i.e. the inhibition of gallstone formation in the subjects who have not previously had gallstones.

Cholesterol Gallstones and Obesity

An association of obesity with GD has been mentioned already in1892 by Osler. Most studies have confirmed this association in the last decades. Obesity is the main risk factor for GD in patients with a known heredity of GD and also in the general population. Obesity increases the risk of symptoms, especially in women [2-4], with each BMI unit [5], with waist circumference, serum triglycerides and the molar concentration of biliary cholesterol [6] and also with obesity onset early in life [7,8]. In a 2-6-yr follow-up, we found that the risk factors associated with GS formation in moderately obese women were age, family history of GD, early obesity onset, and hyperlipoproteinemia type IV [8]. The same risk factors have been found in most epidemiological studies, and a high risk class was identified among obese women, offering a most realistic approach for the primary prevention of gallstones.

Additional obesity-associated factors that increase the risk of GD are insulin resistance / diabetes mellitus type 2 (prevalence of diabetes mellitus has doubled in the last three decades), sedentary lifestyle, severe weight cycling [9]. and rapid weight loss (>1.5 kg/week) [10]. Obese subjects also display abnormal gallbladder and gastric motility patterns. An age-related decline of motility is probably secondary to excessive fat and insulin-resistance [11].

The rapidly increasing prevalence of obesity is very alarming and has been demonstrated worldwide with great variations among continents. The most dramatic epidemic obesity has been observed in the USA [12].

As in North America and Europe, in China and affluent Asia-Pacific countries prosperity and lifestyle, cheap processed foods and reduced physical activity have created an epidemic of overnutrition resulting in overweight/obesity. "Indigenous Australians, once the leanest and fittest humans, now have exceedingly high rates of obesity and type 2 diabetes, contributing to shorter life expectancy" [13].

Cholesterol Gallstones and the Metabolic Syndrome (MetS)

Higher insulinemia à jeun in patients with gallstones, independent from other factors [14] has been observed even before Reaven described the Metabolic Syndrome (MetS) in 1988 [15]. We now recognize the association between GS and obesity as part of the more complex MetS (Insulin Resistance Syndrome).

Insulin Resistance (IR) is associated with GD, independently from the presence of diabetes mellitus [16,17], hypertriglyceridemia [18], obesity [19,20] and gallbladder hypomotility [21].

Hepatic IR is associated with gallstones even in non-diabetic, non-obese individuals. An experimental model was recently developed in mice with specifically ablated insulin receptors in hepatocytes. Studies in these LIRKO (Liver Insulin Receptor KnockOut) mice showed that they are susceptible to cholesterol gallstone formation due to at least two distinct mechanisms: an increased expression of the biliary cholesterol transporters Abcg5 and Abcg8, that stimulates biliary cholesterol secretion and a decreased expression of the bile acid synthetic enzymes, leading to a lithogenic bile salt profile [22].

Gallstone disease is strongly associated with MetS, and the more the MetS components, the higher the prevalence of gallstones in both males and females [23].

Cholesterol Gallstones and NAFLD

Non-Alcoholic Fatty Liver Disease (NAFLD), recently renamed as metabolic-associated fatty liver disease, MAFLD [24,25], is an increasingly common chronic liver disease around the world, with a diverse histopathological spectrum ranging from Simple Steatosis (SS) without significant inflammation to steatohepatitis (NASH) with varying stages of fibrosis.

It is already well-known that NAFLD occurs more frequently in obese and diabetics. Gallstone disease and NAFLD are both present in patients with MetS [26-28].

Gallbladder dysfunction and increase in gallbladder wall thickness were observed even in NAFLD patients without asymptomatic without stone/sludge in the gallbladder, indicating that evaluation of these variables in NAFLD patients might be useful in identifying those at higher risk for GD [29].

The association between GSD and MetS was also found in elderly people with NAFLD, in relation with reduced HDL-cholesterol and elevated fasting plasma glucose [30].

A systematic review and meta-analysis of the published studies confirms that GD is significantly associated with NAFLD [31]. Awareness of this association may result in an earlier diagnosis. Giving the positive concurrent and bidirectional relationships between NAFLD and GD, the study concluded that clinicians may alert the possibility of NAFLD in patients with GD and vice versa.

Cholelithiasis, an independent risk factor for NAFLD, together with metabolic risk factors could be regarded as an additional risk factor of liver damage in patients with NAFLD.

Most recent studies confirmed the significant association between cholesterol gallstones and NAFLD, indicating the growing interest for this subject [32,33]. Further research is needed to evaluate if the presence of GD in association with NAFLD increases the risk of liver fibrosis, and if therapy of NAFLD might impact the incidence of GD**.** Analysis of five large databases also supported the positive concurrent and bidirectional relationships between NAFLD and GD [34].

There are no firm recommendations regarding the screening of NAFLD in patients at risk. A study which aimed to assess the prevalence and the factors associated with NAFLD in a cohort of patients operated for symptomatic GD and to evaluate the usefulness of routine liver biopsy, concluded that the high prevalence of NAFLD in patients with GD may justify routine liver biopsy during cholecystectomy in order to establish the diagnosis, stage, and possible direct therapy [26].

At the question *Which one comes first?* of the two diseases [35], studies performed on liver biopsy in cholecystectomized pts with NAFLD or NASH showed that GD was more frequently present in the advanced stages of NASH [36], that 55% of the patients with GD had already NASH on liver histology [37] and, on the contrary, presence of GD does not predict liver histology in NAFLD [38].

It is thus difficult to estimate the chronology of the two diseases. Is advanced stage of liver disease a risk factor for gallstone formation? Or does longstanding GD favor an increase in the severity of the fatty liver diseases? Or do none of the two diseases adversely influence the outcome of the other one? Anyway, whichever comes first should make the physician to look for the other.

Not solely Cholesterol Gallstones, but also Cholecystectomy is associated with NAFLD

For many years, when analyzing gallstone prevalence, both gallstones and cholecystectomy were mentioned as GD. Cholecystectomy was considered as the proof for gallstones being symptomatic. Cholecystectomy is the mainstay of GD treatment.

Some epidemiological studies found that the MetS prevalence was significantly higher in subjects with a history of cholecystectomy than in those with GD and even than in those without GD [39,40]. The age-standardized prevalence of NAFLD was also higher in patients with cholecystectomy than in those with GD. A large cross sectional retrospective study conducted among US adults in the Third National Health and Nutrition Examination Survey (NHANES III) showed that after controlling for numerous factors associated with both NAFLD and GD, the multivariate-adjusted analysis confirmed the association of NAFLD with cholecystectomy. In that study, NAFLD was associated with cholecystectomy (OR 2.4) but not with gallstones (OR 1.1) [41].

If prevalence of NAFLD is higher in patients with cholecystectomy than in those with gallstones, *Is cholecystectomy itself a risk factor for NAFLD?* [40-42]. Does gallbladder removal have metabolic consequences?

The relationship between cholecystectomy and NAFLD was explained by the important role of the gallbladder in regulating bile acid homeostasis within the enterohepatic circulation. Removal of the gallbladder will affect both the gallbladder role in bile acid homeostasis ***(A)*** and the gallbladder mucosa role in regulating the metabolic / hormonal activity ***(B).***

A) Cholecystectomy alters bile acids circulation, and thus activation of the bile acid receptors FXR (farnesoid X Receptor) and TGR5 (the transmembrane G protein-coupled receptor 5). Bile acids are endogenous ligands for FXR and for TGR5. Gain- and loss-of-function studies have demonstrated that both FXR and TGR5 play important roles in regulating lipid and carbohydrate metabolism and inflammatory responses.The studies showing that FXR receptor plays an important role in regulating both lipid homeostasis and inflammation, thus maintaining cholesterol and bile acid homeostasis, and regulates many metabolic enzymes and transporters suggested that FXR may modulate the progression of NAFLD [43]. TGR5 has been well recognized not only for its role in bile acid homeostasis but also for its role in glucose and lipid homeostasis as well as energy expenditure. It regulates the expression of genes involved in inflammation and modulates plasma glucose and lipid levels [44].

B) The epithelial cells of gallbladder mucosa and intestine secrete the fibroblast growth factor 19 (FGF 19), which regulates gallbladder refilling acting on receptors in the liver and gallbladder [45]. FGF 19 regulates bile acid synthesis and glucose metabolism and has an inhibitory effect on hepatic fatty acid synthesis and a favorable effect on MetS. The decreased FGF-19 levels after cholecystectomy may increase the hepatic triglyceride content, thus favoring NAFLD development. Lower serum levels of FGF19 were found in patients with NAFLD [46,47].

Prevention of GD and of NAFLD

Occurrence of cholelithiasis is related to modifiable risk factors, mainly metabolic diseases – obesity, diabetes mellitus type 2, hypertriglyceridemia, MetS, diabetes, NAFLD, and some other diseases.

In obese persons, decreased gallbladder motility has been heterogeneously reported as a consequence of the different types of meals used to induce gallbladder contraction, characteristics of the population studied, technique used, and proportion of patients with hyperinsulinaemia.

The most important environmental risk factors for GD are diet and lifestyle.

Although the link is certain, the effect of diet is difficult to evaluate. Except for the diet rich in refined sugars and fat, and poor in vegetable fibers, other components of the diet have a controverse effect on lithogenesis [68]. Eating patern: fasting / decreased meal frequency [49] and fast-food consumption [50] were also mentioned as risk factors.

Gallbladder motility in obesity has been attributed to various factors, such as underlying autonomic neuropathy, reduced gallbladder sensitivity to cholecystokinin and/or reduced number of cholecystokinin receptors on the gallbladder wall [51]. Prospective studies have confirmes the relationship between physical activity and gallbladder motility.

Exercise may affect gallbladder motility via neural or hormonal mechanisms. The effects of aerobic exercise on gallbladder motility were evaluated in a group of obese women without gallstones and showed that exercise decreased late-phase postprandial gallbladder volume and increased late-phase postprandial gallbladder motility in these obese women [52].

Physical activity seems to protect against gallstone formation [18,52] and to reduce the risk of symptomatic stones by about 30% [53-56]. The EPIC-Norfolk prospective study [5] showed that the highest level of physical activity reduced by 70% the

risk of symptomatic gallstones in both sexes after 5 years if exercising for 1h a day in a sedentary job / 30 min a day in a standing job / heavy manual job without any additional activity. Regular exercise reduces insulinemia, insulin resistance, triglyceride levels and increases HDL-cholesterol level (as a marker of increased reverse cholesterol transport), and also stimulates intestinal and gallbladder motility. Thus, it helps maintain a normal body weight, all of which, therefore, might be protective against gallstone formation. Several beneficial effects of physical activity are anticipated regarding metabolic disorders linking liver steatosis, GD, gut motility, enterohepatic circulation of signalling bile acids in relation to intestinal microbiota and inflammatory changes [56,57].

Conclusions

Gallstone disease and NAFLD share similar risk factors, therefore, the diagnosis of each one should prompt the clinician to look for the other condition.

An increase of GD and NAFLD prevalence rates is to be expected, which will parallel the aging populations in these countries.

Prevention is advisable whenever possible in the general population, and especially in specific high-risk groups *(EASL CP Guidelines 2016)* [1].

Lifestyle interventions for prevention of both GD and NAFLD should focus on ideal weight maintenance, recommending weight loss among overweight and obese individuals in the general population. As prevention is mainly based on promoting lifestyle changes, it still has relatively poor results owing to the low levels of patient adherence.

References

1. Acalovschi M, Ercolani G, van Erpecum K, Gurusamy KS, van Laarhoven K, Portincasa P. European Association for the Study of the Liver (EASL) Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones. Lammert F (chairman). J Hepatol. 2016; 65: 146-81.
2. Petitti DB, Sidney S. Obesity and cholecystectomy among women: implications for prevention. Am J Prev Med. 1988; 4: 327-30.
3. Stampfer MJ, Maclure KM, Colditz GA, Manson JE, Willett WC. Risk of symptomatic gallstones in women with severe obesity. Am J Clin Nutr. 1992; 55: 652-8.
4. Stender S, Nordestgaard BG, Tybjaerg-Hansen A. Elevated body mass index as a causal risk factor for symptomatic gallstone disease: a Mendelian randomization study. Hepatology. 2013; 58: 2133-41.
5. Banim PJ, Luben RN, Bulluck H, Sharp SJ, Wareham NJ, Khaw KT, et al. The aetiology of symptomatic gallstones quantification of the effects of obesity, alcohol and serum lipids on risk. Epidemiological and biomarker data from a UK prospective cohort study (EPIC-Norfolk). Eur J Gastroenterol Hepatol. 2011; 23: 733-40.
6. Acalovschi M, Suciu A, Florea M, Dumitrascu D, Grigorescu M. Lipides biliairres majeurs et lipides plasmatiques. Acta Gastroenterol Belg. 1984; 47: 381-6.
7. Maclure KM, Hayes KC, Colditz GA, Stampfer MJ, Speizer FE, Willett WC. Weight, diet, and the risk of symptomatic gallstones in middle-aged women. N Engl J Med. 1989; 321: 563-9.
8. Acalovschi MV, Blendea D, Pascu M, Georoceanu A, Badea RI, Prelipceanu M. Risk of asymptomatic and symptomatic gallstones in moderately obese women: a longitudinal follow-up study. Am J Gastroenterol. 1997; 92: 127-31.
9. Syngal S, Coakley EH, Willett WC, Byers T, Williamson DF, Colditz GA. Long-term weight patterns and risk for cholecystectomy in women. Ann Intern Med. 1999; 130: 471-7.
10. Erlinger S. Gallstones in obesity and weight loss. Eur J Gastroenterol Hepatol. 2000; 12: 1347-52.
11. Di Ciaula A, Wang DQ, Portincasa P. Gallbladder and gastric motility in obese newborns, pre-adolescents and adults. J Gastroenterol Hepatol. 2012; 27: 1298-305.
12. Obesity trends among U.S. Adults. Behav Risk Factor Surveill Syst CDC. 1990; 2000: 2010.
13. Farrell GC. The liver and the waistline: fifty years of growth. J Gastroenterol Hepatol. 2009; 24:S105-18.
14. Scragg RK, Calvert GD, Oliver JR. Plasma lipids and insulin in gall stone disease: a case-control study. Br Med J (Clin Res Ed). 1984; 289: 521-5.
15. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988; 37: 1595-607.
16. Heaton KW, Braddon FE, Mountford RA, Hughes AO, Emmett PM. Symptomatic and silent gall stones in the community. Gut. 1991; 32: 316-20.
17. Ruhl CE, Everhart JE. Gallstone disease is associated with increased mortality in the United States. Gastroenterology. 2011; 140: 508-16.
18. Misciagna G, Guerra V, Di Leo A, Correale M, Trevisan M. Insulin and gallstones: a population case control study in southern Italy. Gut. 2000; 47: 144-7.
19. Chang YC, Liu PH, Lee WJ, Chang TJ, Jiang YD, Li HY, et al. Common variation in the fat mass and obesity-associated (FTO) gene confers risk of obesity and modulates BMI in the Chinese population. Diabetes. 2008; 57: 2245-52.
20. Grundy SM. Cholesterol gallstones: a fellow traveler with metabolic syndrome? Am J Clin Nutr. 2004; 80: 1-2.
21. Nakeeb A, Comuzzie AG, Al-Azzawi H, Sonnenberg GE, Kissebah AH, Pitt HA. Insulin resistance causes human gallbladder dysmotility. J Gastrointest Surg. 2006; 10: 940-8.
22. Biddinger SB, Haas JT, Yu BB, Bezy O, Jing E, Zhang W, et al. Hepatic insulin resistance directly promotes formation of cholesterol gallstones. Nat Med. 2008; 14: 778-82.
23. Chen LY, Qiao QH, Zhang SC, Chen YH, Chao GQ, Fang LZ. Metabolic syndrome and gallstone disease. World J Gastroenterol. 2012; 18: 4215-20.
24. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol. 2020; 73: 202-9.
25. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. NAFLD Nomenclature consensus group. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol. 2023; 24: S0168-8278(23)00418-X.
26. García-Monzón C, Vargas-Castrillón J, Porrero JL, Alonso MT, Bonachía O, Castillo MJ et al. Prevalence and risk factors for biopsy-proven non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in a prospective cohort of adult patients with gallstones. Liver Int. 2015; 35: 1983-91.
27. Ramos-De la Medina A, Remes-Troche JM, Roesch-Dietlen FB, Pérez-Morales AG, Martinez S, Cid-Juarez S. Routine liver biopsy to screen for nonalcoholic fatty liver disease (NAFLD) during cholecystectomy for gallstone disease: is it justified? J Gastrointest Surg. 2008; 12: 2097-102.

28. Koller T, Kollerova J, Hlavaty T, Huorka M, Payer J. Cholelithiasis and markers of nonalcoholic fatty liver disease in patients with metabolic risk factors. Scand J Gastroenterol. 2012; 47: 197-203.

29. Colak Y, Bozbey G, Erim T, Caklili OT, Ulasoglu C, Senates E, et al. Impaired gallbladder motility and increased gallbladder wall thickness in patients with Nonalcoholic Fatty Liver Disease. J Neurogastroenterol Motil. 2016; 22: 470-6.

30. Hung MC, Chen CF, Tsou MT, Lin HH, Hwang LC, Hsu CP. Relationship between gallstone disease and cardiometabolic risk factors in elderly people with Non-Alcoholic Fatty Liver Disease. Diabetes Metab Syndr Obes. 2020; 13: 3579-85.

31. Jaruvongvanich V, Sanguankeo A, Upala S. Significant association between gallstone disease and Nonalcoholic Fatty Liver Disease: A systematic review and meta-analysis. Dig Dis Sci. 2016; 61: 2389-96.

32. Yi M, Peng W, Feng X, Teng F, Tang Y, Kong Q, et al. Extrahepatic morbidities and mortality of NAFLD: an umbrella review of meta-analyses. Aliment Pharmacol Ther. 2022; 56: 1119-30.

33. Konyn P, Alshuwaykh O, Dennis BB, Cholankeril G, Ahmed A, Kim D. Gallstone Disease and its association with Nonalcoholic Fatty Liver Disease, All-cause and cause-specific mortality. Clin Gastroenterol Hepatol. 2023; 21: 940-948.e2.

34. Gu S, Hu S, Wang S, Qi C, Shi C, Fan G. Bidirectional association between NAFLD and gallstone disease: a systematic review and meta-analysis of observational studies. Expert Rev Gastroenterol Hepatol. 2023; 17: 283-93.

35. Ahmed MH, Ali A. Nonalcoholic fatty liver disease and cholesterol gallstones: which comes first? Scand J Gastroenterol. 2014; 49: 521-7.

36. Fracanzani AL, Valenti L, Russello M, Miele L, Bertelli C, Bellia A, et al. Gallstone disease is associated with more severe liver damage in patients with non-alcoholic fatty liver disease. PLOS ONE. 2012; 7: e41183.

37. Yener O, Aksoy F, Demır M, Özçelık A, Erengül C. Gallstones associated with nonalcoholic steatohepatitis (NASH) and metabolic syndrome. Turk J Gastroenterol. 2010; 21: 411-5.

38. Yilmaz Y, Younossi ZM. Obesity-associated nonalcoholic fatty liver disease. Clin Liver Dis. 2014; 18: 19-31.

39. Shen C, Wu X, Xu C, Yu C, Chen P, Li Y. Association of cholecystectomy with metabolic syndrome in a Chinese population. PLOS ONE. 2014; 9: e88189.

40. Ruhl CE, Everhart JE. Relationship of non-alcoholic fatty liver disease with cholecystectomy in the US population. Am J Gastroenterol. 2013; 108: 952-8.

41. Rodríguez-Antonio I, López-Sánchez GN, Garrido-Camacho VY, Uribe M, Chávez-Tapia NC, Nuño-Lámbarri N. Cholecystectomy as a risk factor for non-alcoholic fatty liver disease development. HPB (Oxford). 2020; 22: 1513-20.

42. Huh JH, Lee KJ, Cho YK, Moon S, Kim YJ, Han KD, et al. Cholecystectomy increases the risk of metabolic syndrome in the Korean population: a longitudinal cohort study. Hepatobiliary Surg Nutr. 2023; 12: 523-33.

43. Lefebvre P, Cariou B, Lien F, Kuipers F, Staels B. Role of bile acids and bile acid receptors in metabolic regulation. Physiol Rev. 2009; 89: 147-91.

44. Pols TW, Noriega LG, Nomura M, Auwerx J, Schoonjans K. The bile acid membrane receptor TGR5 as an emerging target in metabolism and inflammation. J Hepatol. 2011; 54: 1263-72.

45. Zweers SJLB, Booij KAC, Komuta M, Roskams T, Gouma DJ, Jansen PLM, et al. The human gallbladder secretes fibroblast growth factor 19 into bile: towards defining the role of fibroblast growth factor 19 in the enterobiliary tract. Hepatology. 2012; 55: 575-83.

46. Eren F, Kurt R, Ermis F, Atug O, Imeryuz N, Yilmaz Y. Preliminary evidence of a reduced serum level of fibroblast growth factor 19 in patients with biopsy-proven nonalcoholic fatty liver disease. Clin Biochem. 2012; 45: 655-8.

47. Barrera F, Azócar L, Molina H, Schalper KA, Ocares M, Liberona J, et al. Effect of cholecystectomy on bile acid synthesis and circulating levels of fibroblast growth factor 19. Ann Hepatol. 2015; 14: 710-21.

48. Sun H, Warren J, Yip J, Ji Y, Hao S, Han W, et al. Factors influencing gallstone formation: a review of the literature. Biomolecules. 2022; 12: 550.

49. Attili AF, Scafato E, Marchioli R, Marfisi RM, Festi D. Diet and gallstones in Italy: the cross-sectional MICOL results. Hepatology. 1998; 27: 1492-8.

50. Stender S, Dyerberg J, Astrup A. High levels of industrially produced trans fat in popular fast foods. N Engl J Med. 2006; 354: 1650-2.

51. Fraquelli M, Pagliarulo M, Colucci A, Paggi S, Conte D. Gallbladder motility in obesity, diabetes mellitus and coeliac disease. Dig Liver Dis. 2003; 35: S12-6.

52. Sari R, Balci N, Balci MK. Effects of exercise on gallbladder volume and motility in obese women. J Clin Ultrasound. 2005; 33: 218-22.

53. Leitzmann MF, Rimm EB, Willett WC, Spiegelman D, Grodstein F, Stampfer MJ, et al. Recreational physical activity and the risk of cholecystectomy in women. N Engl J Med. 1999; 341: 777-84.

54. Leitzmann MF, Giovannucci EL, Rimm EB, Stampfer MJ, Spiegelman D, Wing AL. The relation of physical activity to risk for symptomatic gallstone disease in men. Ann Intern Med. 1998; 128: 417-25.

55. Storti KL, Brach JS, FitzGerald SJ, Zmuda JM, Cauley JA, Kriska AM. Physical activity and decreased risk of clinical gallstone disease among post-menopausal women. Prev Med. 2005; 41: 772-7.

56. Molina-Molina E, Lunardi Baccetto R, Wang DQ, de Bari O, Krawczyk M, Portincasa P. Exercising the hepatobiliary-gut axis. The impact of physical activity performance. Eur J Clin Investig. 2018; 48: e12958.

57. Molina-Molina E, Furtado GE, Jones JG, Portincasa P, Vieira-Pedrosa A, Teixeira AM, et al. The advantages of physical exercise as a preventive strategy against NAFLD in postmenopausal women. Eur J Clin Investig. 2022; 52: e13731.