Non-alcoholic Fatty Liver Disease, Cholelithiasis, and Cholecystectomy: Insights on a Complex Association

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Non-alcoholic fatty liver disease and gallstones: An overview

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is one the most prevalent liver disorders worldwide. NAFLD refers to the significant fat accumulation of hepatocytes in the absence of excessive alcohol consumption or other causes of liver disease. NAFLD encompasses a wide spectrum of liver conditions which range from simple steatosis to steatohepatitis and cirrhosis. Available data suggests highly variable rates of NAFLD prevalence in the general population, with results ranging from 14% to 40%.[1,2]

NAFLD has been associated with an increased risk of death from malignancy or cardiovascular disease. When individuals present with the features of metabolic syndrome, such as overweight/obesity, hypertension, insulin resistance, and dyslipidemia, it is reasonable to envisage the possibility of NAFLD. In fact, NAFLD is considered the hepatic manifestation of metabolic syndrome. Additionally, ethnicity, obesity phenotype, reduced physical activity, and high-fat diets also act as significant risk factors for NAFLD (Box 1).[2,3]

Box 1: Risk factors for NAFLD

- Overweight/obesity
- Obesity phenotype
- Reduced physical activity
- High-fat diets
- Increased waist circumference
- Hypertension
- Insulin resistance
- Dyslipidemia
- Ethnicity

Adapted from: **1.** Shen SS, Gong JJ, Wang XW, *et al.* Promotional effect of nonalcoholic fatty liver disease on Gallstone disease: A systematic review and meta-analysis. *Turk J Gastroenterol.* 2017;28(1):31-39. **2.** Majumdar A, Misra P, Sharma S, *et al.* Prevalence of nonalcoholic fatty liver disease in an adult population in a rural community of Haryana, India. *Indian J Public Health.* 2016;60(1):26-33.

Burden of NAFLD in the Indian population

In the Indian population, the burden of NAFLD is shown to be around 9–32% based on the data extracted from various trials.[4] Majumdar et al,[3] in 2016, conducted a study to examine the prevalence of NAFLD among adults in India. The investigators also accounted the relationship of diet, physical activity, and other selected risk factors with NAFLD. Individuals ≥35 years of age were enrolled for this study. Altogether, a total of 176 participants were evaluated post ultrasonography of the liver, anthropometry, blood pressure recording, and blood sample collection.

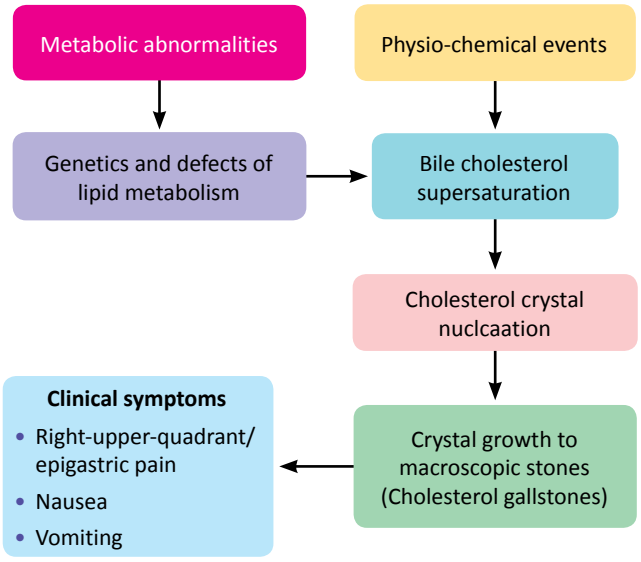
The prevalence of NAFLD was found to be 30.7%. There was no marked difference in the calorie intake and average total physical activity between participants with and without NAFLD. Hypertension and an increased waist circumference were independently associated with NAFLD. It was further observed that a normal high-density lipoprotein (HDL) level was protective against NAFLD. This study substantiated the alarming rates of NAFLD both in the urban as well as the rural parts of India. Urgent interventions are required to treat this disorder and also to prevent its future development by controlling the risk factors associated with it.[3]

A brief about cholelithiasis

Gallbladder disease is one of the highly prevalent gastrointestinal disorders. Diseases of the gallbladder commonly manifest as cholelithiasis, which is also known as gallstones. The manner of living of the individuals, especially eating habits and sedentary lifestyle has increased the probability of gallstone disease. Gallstones affect 10-15% of the adult population and cause major affliction in the society, constituting a significant health problem across the globe.[5,6] Although gallstone disease has a low mortality rate of 0.6%, gallstones are frequent emergencies reported in clinics affecting patients with sudden epigastric pain, nausea, vomiting, abdominal pain and loss of appetite. Meanwhile, since the 1980s, its financial burden has increased by more than 20%, thus representing a significant health problem.[2,5,6]

There are two major gallstone subtypes with regard to the chemical composition: cholesterol type and pigment type. Cholesterol gallstones represent the major type of gallstones in developed nations.[7] In India, the prevalence as well as subtypes of gallstone disease has been found to vary with different regions, with individuals in the North having predominantly the cholesterol type gallstone while those in the South having mostly the pigment type gallstones.[8,9] The overall prevalence of

Figure 1: Pathogenesis of cholesterol gallstones



Adapted from: Tazuma S. Bile Acids and Gallstones: Epidemiology, Pathogenesis, Diagnosis, and Management. In: Tazuma S., Takikawa H. (eds) Bile Acids in Gastroenterology. Tokyo: Springer; 2017. 93-107.

gallstones in India ranges from 6-9% in the adult population, with the North Indians having an increased prevalence followed by the South Indians and those in the coastal regions. Females are more vulnerable to gallstone disease as compared to men.[10,11]

Pathogenesis of gallstones

Majority (almost 80%) of the gallstones are composed primarily of cholesterol; either pure or mixed with bilirubin, and calcium salts, with smaller amounts of protein and other materials.[12,13] The pathogenesis of cholesterol gallstones is known to be complex, and is processed by two major steps; metabolic abnormalities, such as genetics and defects of lipid metabolism, and physico-chemical events that include bile cholesterol supersaturation, cholesterol crystal nucleation, and crystal growth to macroscopic stones (Figure 1). The gallbladder and intestines play an important role in these processes.[14]

Several risk factors for gallstone formation have been identified. Certain risk factors for gallstones are immutable, that include female gender, increasing age and ethnicity. Whereas, others are modifiable, such as obesity, metabolic syndrome, rapid weight loss, certain diseases (cirrhosis, Crohn's disease) and gallbladder stasis.[2,15,16] Sex hormones are most likely to be responsible for the increased risk. Estrogen increases biliary cholesterol secretion causing cholesterol supersaturation of bile (Box 2).[12-17]

Non-alcoholic fatty liver disease and gallstones: Exploring the correlation

Gallstones and NAFLD are commonly found to coexist in the general population and both conditions are associated with

Box 2: Risk factors for gallstones

Non-modifiable

- Female gender
- Increasing age
- Ethnicity

Modifiable

- Obesity
- Metabolic syndrome
- Rapid weight loss
- Cirrhosis
- Crohn's disease
- Gallbladder stasis
- Hypertriglyceridemia
- High calorie diet

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several similar risk factors including age, ethnicity, metabolic factors, obesity, insulin resistance, type 2 diabetes, and high dietary cholesterol intake.[18-21] In addition, both conditions are associated with high risk of cardiovascular disease and mortality. These common factors account for the higher prevalence of cholesterol gallstones in patients with NAFLD. Evidence also suggests that the risk of gallstone disease increases with the severity of liver disease, with the highest prevalence of gallstones being found in the more advanced stages of fibrosis in patients with NAFLD.[7,20]

Various studies have attempted to understand the association between the two conditions. Some of these studies evaluated the prevalence of gallstone disease in patients with NAFLD and others evaluated the frequency of NAFLD in patients with gallstone disease.[20-23] However, it remains unclear whether NAFLD is a precursor of gallstone disease or if the presence of gallstone disease possibly indicates the presence of long-standing features of metabolic syndrome, which accelerates the progression of NAFLD.[2]

In fact, the complex association between gall stones and NAFLD is considered to be bidirectional.[20] A prospective, large-scale cohort study of young and middle-aged individuals by Chang et al[21] demonstrated a bidirectional association between NAFLD and gallstone disease. In one direction, NAFLD was associated with an increased risk of developing gallstone disease, and in the other direction, gallstone and cholecystectomy were associated with an increased risk of incident NAFLD. Using the non-invasive fibrosis markers, individuals with NAFLD and intermediate or high NAFLD fibrosis score (NFS) had the highest incidence of gallstones, but even with a low probability of hepatic fibrosis based on fibrosis markers, NAFLD was significantly associated with the development of gallstones. These findings suggest that the conditions may affect each other, requiring further studies to elucidate the potential mechanisms underlying this association.

Likewise, in a systematic review and meta-analysis conducted by Jaruvongvanich et al,[22] the pooled odds ratio (OR) of NAFLD in patients who had gallstone disease was 1.55. The statistical between-studies heterogeneity was 64%. The association remained significant when limited to cohort studies with pooled OR 1.33. This meta-analysis demonstrated a significant association between gallstone disease and NAFLD.

In another study by Lee et al,[23] a considerable difference was observed in the severity of NAFLD between subjects with and without gallstone disease. Based on logistic regression, age ≥65 versus <40 years, 40-64.9 versus <40 years, female, current alcohol drinking, diabetes, hypertension, HDL-C level and moderate to severe NAFLD, but not mild NAFLD, were the independently associated risk factors of gallstone disease . This study suggested that moderate to severe, but not mild, NAFLD was associated with an increased risk of gallstone disease, independent of the traditional cardio-metabolic risk factor. Age, female, diabetes, and hypertension were also associated with a higher risk of gallstone disease, but HDL-C level and moderate alcohol drinking showed a lower risk.

In a nutshell, available data suggest that NAFLD and gallstone disease are significantly associated in a bidirectional fashion. Thus, although NAFLD appears to be an independent risk factor for gallstone disease, the latter also represents an independent risk factor for NAFLD with gallstone disease potentially being linked to greater disease severity.[20]

Potential mechanism of association between non-alcoholic fatty liver disease and gallstone disease

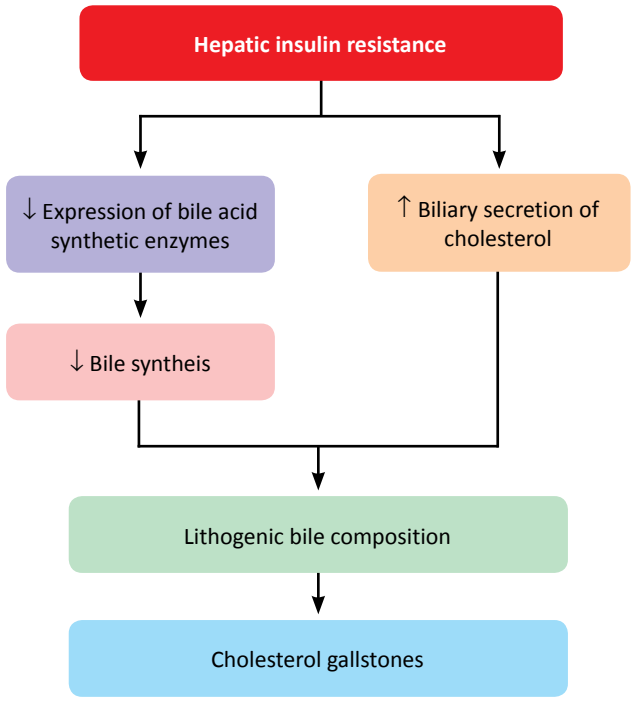
The complex and bidirectional association between NAFLD and gallstone disease is partially explained by a number of common pathogenic links but the precise underlying mechanisms of the association of gallstone disease and NAFLD remains to be elucidated. In this context, recent findings unveiling new aspects of gallbladder physiology and endocrine actions of bile acids seems promising in expounding this complex association.[20]

To this effect, insulin resistance has been shown to provide a crucial link between NAFLD and increased susceptibility to gallstone disease. Thus, although insulin resistance is a key phenomenon in NAFLD development and progression, hepatic insulin resistance has been pointed as a key determinant for cholesterol gallstones formation by itself.[20]

It has been shown that insulin resistance plays an important role in gallstone formation through regulation of bile acid synthesis. Mechanistically, hepatic insulin resistance directly increases biliary secretion of cholesterol and decreases the expression of the bile acid synthetic enzymes, particularly Cyp7b1, and produces partial resistance to the farnesoid X receptor (FXR), thus leading to a lithogenic bile salt profile; it thus promotes cholesterol gallstone formation (Figure 2).[20,24]

Therefore, hepatic insulin resistance links the hyperglycemia, dyslipidemia and gallstone formation of the metabolic syndrome. These findings also suggest that therapies that improve hepatic insulin resistance and decrease the activity of forkhead transcription factor FoxO1 might prevent formation of cholesterol gallstones, in addition to having beneficial effects on glucose homeostasis.[24]

Figure 2: Hepatic insulin resistance and gallstone formation



Adapted from: 1. Arrese M, Cortés V, Barrera F, et al. Nonalcoholic fatty liver disease, cholesterol gallstones, and cholecystectomy: new insights on a complex relationship. *Curr Opin Gastroenterol.* 2018;34(2):90-96. **2.** Biddinger SB, Haas JT, Yu BB, et al. Hepatic insulin resistance directly promotes formation of cholesterol gallstones. *Nat Med.* 2008;14(7):778–782.

Cholecystectomy and non-alcoholic fatty liver disease

Besides the data showing association between NAFLD and gallstone disease, recent evidence has also demonstrated that cholecystectomy may itself be a risk factor for NAFLD development. Pathogenesis of NAFLD and gallbladder disease secondary to cholesterol gallstones is complex, yet both conditions share similar associated risk factors, most of them related to the metabolic syndrome. Cholecystectomy is considered the best treatment for gallstone disease and it is one of the most performed abdominal surgeries worldwide.[20,25]

However, recent studies evaluating patients with cholecystectomy as a separate group have found an independent association with NAFLD, which is even stronger than that reported for gallstone disease.[20] In two studies from different populations, the risk of NAFLD and hepatic steatosis was also markedly increased in patients who had undergone cholecystectomy compared to those with gallstone disease with their gallbladder in situ and control individuals.[26,27]

Likewise, Ruhl and Everhart,[28] using data from the Third United States National Health and Nutrition Examination Survey (1988-1994), demonstrated that NAFLD is associated with cholecystectomy (OR, 2.4), but not with gallstones (OR, 1.1). Thus, cholecystectomy may not be innocuous and the association of NAFLD with cholecystectomy, but not with gallstone disease in these studies suggest that cholecystectomy may itself be a risk factor for the progression of NAFLD.[20,25,28]

Conclusion

Non-alcoholic fatty liver disease and gallstones are commonly found to coexist in the general population and both conditions are associated with several similar risk factors. A large pool of studies has addressed the association between NAFLD and gallstone disease underscoring that NAFLD is an independent risk factor for gallstone disease. On the other hand, gallstone disease has also been found to be an independent risk factor for NAFLD with gallstone disease potentially being associated with greater disease severity. Besides the association between NAFLD and gallstone disease, recent evidence has also demonstrated that cholecystectomy may itself be a risk factor for the development and progression of NAFLD. The complex and bidirectional relationship between these diseases is partially explained by several common pathogenic links. In particular, the central role of hepatic insulin resistance and the FXR-regulated pathways in both diseases may provide a prospect for interventions using insulin sensitizers and/or FXR agonists.

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