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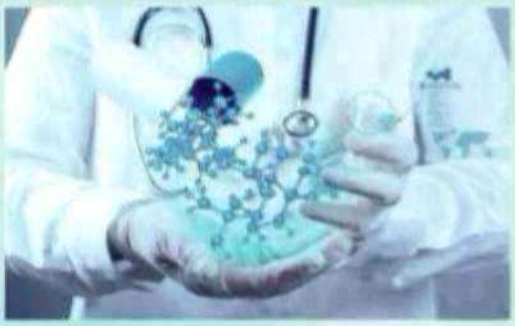

AVICENNA-MED.UZ

ISSN 2181-712X.
EiSSN 2181-2187

12 (86) 2025

ТИББИЁТДА ЯНГИ КУН
НОВЫЙ ДЕНЬ В МЕДИЦИНЕ
NEW DAY IN MEDICINE

Илмий-рефератив, маънавий-маърифий журнал
Научно-реферативный,
духовно-просветительский журнал

УЧРЕДИТЕЛИ:

БУХАРСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ ИНСТИТУТ
ООО «ТИББИЁТДА ЯНГИ КУН»

Национальный медицинский исследовательский центр хирургии имени А.В. Вишневского является генеральным научно-практическим консультантом редакции

Журнал был включен в список журнальных изданий, рецензируемых Высшей Аттестационной Комиссией Республики Узбекистан (Протокол № 201/03 от 30.12.2013 г.)

12 (86)

2025
декабрь

www.bsmi.uz
https://newdaymedicine.com E:
ndmuz@mail.ru
Тел: +99890 8061882

Received: 20.11.2025, Accepted: 06.12.2025, Published: 10.12.2025

UDC 616.366-089.87:616.36-003.826

CHOLECYSTECTOMY AS A RISK FACTOR FOR NON-ALCOHOLIC FATTY LIVER DISEASE DEVELOPMENT

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✓ ***Resume***

Cholecystectomy, the surgical removal of the gallbladder, is commonly performed for gallstones or cholecystitis. Recent evidence suggests that it may contribute to the development of non-alcoholic fatty liver disease (NAFLD). The gallbladder plays a key role in regulating bile acid release, which is important for lipid and glucose metabolism. After cholecystectomy, continuous bile flow can disrupt bile acid signaling, potentially leading to hepatic fat accumulation and insulin resistance. Additionally, gallbladder removal can alter gut microbiota and exacerbate metabolic risk factors such as obesity, diabetes, and hyperlipidemia, further increasing NAFLD risk.

Observational studies report higher rates of NAFLD in post-cholecystectomy patients, especially those with pre-existing metabolic syndrome. Clinically, monitoring liver function and promoting lifestyle interventions, including weight management, diet, and physical activity, are recommended to reduce NAFLD risk in these patients.

Cohort and retrospective studies have shown that patients who undergo cholecystectomy have a higher incidence of NAFLD compared to the general population. mSome studies suggest that risk is particularly significant in patients with pre-existing metabolic syndrome, and NAFLD can develop within a few years post-surgery. Meta-analyses indicate that cholecystectomy may be an independent risk factor for NAFLD, although the exact causal relationship is still under investigation.

Key words: non-alcoholic fatty liver disease, metabolic syndrome, atherosclerosis.

XOLETSISTEKTOMIYA NOALKOGOLIK YO‘G‘LI JIGAR KASALLIGINING RIVOJLANISHI UCHUN XAVF OMILI SIFATIDA

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✓ ***Rezyume***

Xolesistektomiya, ya’ni o't pufagining jarrohlik yo‘li bilan olib tashlanishi, odatda o‘tkir yoki surunkali o't toshlari va xolecistit sababli amalga oshiriladi. Yaqinda olib borilgan tadqiqotlar shuni ko‘rsatadiki, u alkogol iste’mol qilinmaydigan yog‘li jigar kasalligi (YJK) rivojlanishiga hissa qo‘shishi mumkin. O‘t pufagi jigar uchun muhim bo‘lgan xol kislotasi ajralishini tartibga solishda asosiy rol o‘ynaydi, bu esa lipid va glyukoza almashinuvi uchun zarurdir. Xolecistektomiya amalga oshirilgach, xol kislotasining uzluksiz oqishi uning signalizatsiyasini buzishi mumkin, natijada gepatotsitlarda yog‘ to‘planishi va insulin qarshiligi yuzaga kelishi ehtimoli mavjud. Shuningdek, o't pufagining olib tashlanishi ichak mikrobiotasini o‘zgartirishi va semizlik, qandli diabet, giperlipidemiyaga o‘xshash metabolik xavf omillarini kuchaytirishi mumkin, bu esa YJK rivojlanish xavfini oshiradi.

Observatsion tadqiqotlar xolecistektomiya o‘tkazilgan bemorlarda, ayniqsa oldindan metabolik sindrom mavjud bo‘lganlarda, YJK holatlari ko‘proq uchrashini ko‘rsatadi. Klinik amaliyotda jigar funksiyasini kuzatish va bemorlarning vaznini nazorat qilish, to‘g‘ri ovqatlanish hamda jismoniy faoliyatni rag‘batlantirish kabi hayot tarzi o‘zgarishlari YJK rivojlanish xavfini kamaytirishda tavsiya etiladi.

Kohort va retrospektiv tadqiqotlar xolecistektomiya o‘tkazilgan bemorlarda YJK rivojlanish ehtimoli umumiy aholiga nisbatan yuqoriligini ko‘rsatgan. Ba’zi tadqiqotlar shuni bildiradiki, xavf ayniqsa oldindan metabolik sindromi mavjud bemorlarda sezilarli bo‘lib, YJK jarrohlikdan keyingi bir necha yil ichida rivojlanishi mumkin. Meta-tahlillar xolecistektomiya YJK uchun mustaqil xavf omili bo‘lishi mumkinligini ko‘rsatadi, ammo uning aniq sababiy aloqasi hali tadqiq qilinmoqda.

Kalit so‘zlar: alkogolsiz yog‘li jigar kasalligi, metabolik sindrom, ateroskleroz.

ХОЛЕЦИСТЭКТОМИЯ КАК ФАКТОР РИСКА РАЗВИТИЯ НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ

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✓ ***Резюме***

Холецистэктомия, то есть хирургическое удаление желчного пузыря, обычно выполняется при наличии желчных камней или холецистита. Недавние исследования показывают, что эта операция может способствовать развитию неалкогольной жировой болезни печени (НАЖБП). Желчный пузырь играет ключевую роль в регулировании выделения желчных кислот, которые важны для обмена липидов и глюкозы. После холецистэктомии непрерывный поток желчи может нарушать сигнальные пути желчных кислот, что потенциально приводит к накоплению жира в печени и развитию инсулинорезистентности. Кроме того, удаление желчного пузыря может изменять микробиоту кишечника и усиливать метаболические факторы риска, такие как ожирение, диабет и гиперлипидемия, дополнительно увеличивая риск НАЖБП.

Наблюдательные исследования показывают более высокие показатели НАЖБП у пациентов после холецистэктомии, особенно у тех, у кого уже был метаболический синдром. В клинической практике рекомендуется мониторинг функции печени и внедрение изменений образа жизни, включая контроль массы тела, рацион питания и физическую активность, чтобы снизить риск НАЖБП у этих пациентов.

Когортные и ретроспективные исследования показали, что пациенты, перенесшие холецистэктомию, имеют более высокую заболеваемость НАЖБП по сравнению с общей популяцией. Некоторые исследования указывают, что риск особенно высок у пациентов с уже существующим метаболическим синдромом, и НАЖБП может развиться в течение нескольких лет после операции. Метаанализы показывают, что холецистэктомия может быть независимым фактором риска НАЖБП, хотя точная причинно-следственная связь пока изучается.

Ключевые слова: неалкогольная жировая болезнь печени, метаболический синдром, атеросклероз.

Relevance

Non-alcoholic fatty liver disease (NAFLD) refers to liver fat accumulation, which exceeds 5–10% of the organ total weight, without the cause being chronic alcohol consumption. The disease includes a broad spectrum of liver conditions ranging from pure fatty liver (simple steatosis), usually a benign and non-progressive condition, to non-alcoholic steatohepatitis, which may eventually progress to cirrhosis and hepatocellular carcinoma [1]. The pathophysiology and natural evolution are still under study and are inconclusive; however, approximately 10% of NAFLD carriers will evolve to steatohepatitis, and 20–25% of these patients will develop fibrosis that will evolve to cirrhosis and 5% to hepatocarcinoma[2]. NAFLD is observed worldwide and is the most common hepatic disorder in western industrialized countries, with one or more risk factors: central obesity, systemic hypertension, dyslipidemia, insulin resistance (IR), metabolic syndrome and type 2 diabetes mellitus (T2D). The number of patients with NAFLD is increasing globally, with a prevalence in the adult population of approximately 30% [3,4]. NAFLD definition is about the infiltration of fat in the liver on radiological examination or biopsy, without significant alcohol intake (≤210 g/week for males and ≤140 g/week for females), medication intake causing fatty liver, or other causes (eg, autoimmune hepatitis, or hepatitis B antigen or hepatitis C virus antibody positivity) [5]. In the USA, NAFLD prevalence has increased over time, as evidenced by the National Survey of Health and Nutrition Examination three-cycle comparison, which shows that in 1988 and 1994, NAFLD prevalence was 5.5%, between 1999 and 2004 it was 9.8% and between 2005 and 2008 it was 11%, representing an increment of 47, 63 and 75%

respectively. Also, in these same three periods, obesity, T2D and high blood pressure increased [6]. Another study estimated that the prevalence of NAFLD between 2011 and 2012 was 30% with ultrasound, taking into account fasting insulin and triglyceride concentrations, body mass index, sex and gamma-glutamyl transferase activity [7]. Patients diagnosed with NAFLD have a higher risk of death compared to the general population, and increasing rates of obesity and T2D will be directly associated with NAFLD mortality escalation in the next years [8]. IR produces relevant changes in lipid metabolism, including increased peripheral lipolysis, hepatic fatty acid uptake, and triglyceride synthesis, which contributes to fatty acid β oxidation, the accumulation of lipids in the liver and therefore oxidative stress.[9] On the other hand, liver iron, leptin, antioxidant deficiency, and intestinal bacteria have been proposed as possible oxidative stressors, improving insulin sensitivity and reducing iron-mediated oxidative stress, which decreases hepatocyte substrate burden, lipid peroxidation, hepatocellular injury and serum ALT activity. Although it is speculative, some studies support that diminished iron chelation and increased iron load decrease oxidative stress and lipid peroxidation, improving NAFLD [10]. As well, increased bacteria growth in the small intestine and hence intestinal permeability markers are closely related to NAFLD [11].

Adiponectin is a hormone secreted exclusively by adipose tissue that produces beneficial effects on lipid metabolism, but also has direct anti-inflammatory effects that suppress tumor necrosis alpha factor production in the liver. Therefore, low serum adiponectin levels are associated with metabolic syndrome, which correlate with NAFLD presence and liver fibrosis [12]. Besides, NAFLD is a complex disorder that involves environmental and genetic factors. Studies in twins have shown an active hereditary component (approximately 50 percent) in both liver fat content and liver fibrosis. Different PNPLA3 genetic variants, studied in homozygous twins are responsible for coding the proteins that regulate lipid metabolism in the liver, which are associated with NAFLD development and progression. On the other hand, in Western societies, cholesterol gallstones account for 80–90% of the gallstones found at cholecystectomy. Excess cholesterol precipitation in bile as solid crystals is a prerequisite for cholesterol gallstone formation; these gallstones are composed mainly of cholesterol crystals (70%) held together in a glycoproteins organic matrix, calcium salts, and bile pigments. Several risk factors are involved in gallstone formation, such as having given birth, estrogen replacement therapy, oral contraceptive use, and rapid weight loss. Similar to atherosclerosis, the risk of gallstone disease (GSD) increases with age, obesity, T2D, dyslipidemia, hypertriglyceridemia, poor high-density lipoprotein (HDL), elevated serum cholesterol, hyperinsulinemia, and sedentary lifestyle. All these conditions are risk factors for metabolic syndrome, with cholesterol gallstones being another complication [13]. If biliary cholesterol concentration increases or bile salt and phosphatidylcholine concentrations drop, cholesterol supersaturation occurs, and cholesterol crystals and stones precipitate. The most common severe mutation p.E342K (‘PiZ’) might interfere with hepatic lipid metabolism and contribute to fatty liver disease, and promote cholesterol crystallization in bile. GSD is a complex trait resulting from an interaction between genetic predisposition and environmental risk factors. In recent years, large cohorts of patient's analyses, using different approaches, have helped to detect the predisposing variants that might increase or decrease gallstones development risk. The first genome-wide association study for a hepatobiliary disease, identified the hepatic cholesterol transporter ABCG8 as a susceptibility gene for human GSD. NAFLD and cholelithiasis are chronic diseases with a multifactorial evolution that involve alterations in genetic and epigenetic regulation. During the last decade, the role of epigenetic mechanisms in NAFLD pathogenesis has become relevant, although they have not yet been fully described; several studies suggest that epigenetic regulation, mainly by microRNAs is mediated by post-transcriptional modifications that can alter cell signaling pathways by modifying physiological functions without changes in the DNA sequence. Although NAFLD treatment is mainly based on promoting lifestyle changes with relatively poor results due to the patient's low adherence, the best and most effective approach for GSD is cholecystectomy, which is the most frequent surgical procedure worldwide.

Gallstones as a risk factor for NAFLD. GSD currently represents a significant public health problem that affects approximately 20% of the general population in Europe; Hispanics have the highest prevalence rates with more than 50%, mainly in Central and South America [17]. Cholesterol gallstone formation involves an abnormal bile composition, with supersaturated cholesterol high concentrations, coupled with proteins that promote cholesterol crystals nucleation, as well as gallbladder malfunction

due to decreased contractility and impaired epithelial secretion [12]. From 5 to 30% of the laparoscopic cholecystectomies performed annually are for acalculous vesicular disease diagnosis; however, this surgical procedure is recommended for gallbladder diseases, such as vesicular polyps, tumors, GSD, cholecystitis, and biliary dyskinesia [11]. This technique is currently one of the most frequently performed surgical procedures worldwide [10]. NAFLD as a risk factor for gallstones. NAFLD and GSD are diseases derived from cholesterol deposition, which are associated with increased mortality from chronic liver disease, cardiovascular disease, and cancer, representing a significant impact on public health. Both diseases have very high prevalence rates; similar in North and South America, as well as in Europe, which represent between 10 and 50% of the adult population. GSD and NAFLD often coexist, and their association is determined by the presence of shared risk factors such as age, ethnicity, obesity, IR, metabolic syndrome, atherosclerosis and cardiovascular disease risk. (Fig. 1).

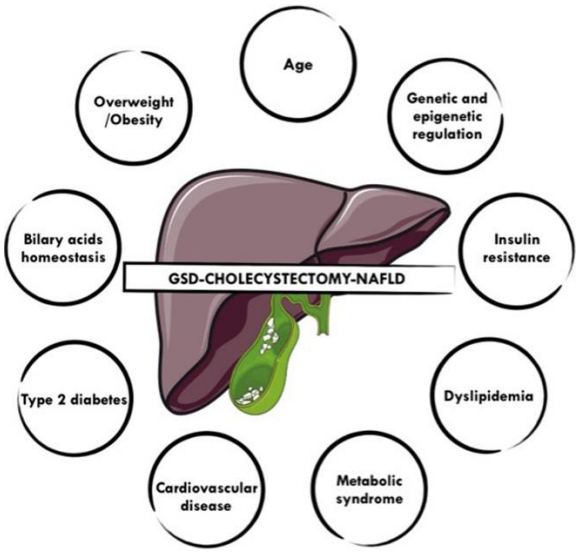

Figure 1 Associated risk factors in GSD-Cholecystectomy-NAFLD

There is convincing evidence based on retrospective epidemiological studies showing that cholecystectomy can be an independent risk factor in the progression of NAFLD and metabolic syndrome. This association is explained by metabolic alterations related to the gallbladder baseline physiological function, the recognition of bile acids (BAs) as key signaling molecules and endocrine imbalance, which support reciprocal influences between the trinomial disease gallstones-cholecystectomy-NAFLD. A recent study showed a significant relationship between NAFLD and GSD grade. Participants with GSD are more likely to have dyslipidemia, hyperglycemia, obesity, and metabolic syndrome that are also associated with NAFLD. Clinical studies and systematic reviews have supported the link between NAFLD and GSD, highlighting that NAFLD is an independent risk factor for developing GSD. Besides, cholecystectomy itself can be a metabolic risk factor for NAFLD progression, which forces us to analyze gallbladder ablation consequences. Koller *et al*. have evaluated the existing evidence between the GSD-cholecystectomy-NAFLD trinomial, founding a higher prevalence of GSD among patients with NAFLD versus those without NAFLD (47 vs. 26%, respectively; $P < 0.0001$) where NAFLD is an independent risk factor for developing cholelithiasis. The finding was also reported by Loria *et al*. in a cohort of 161 patients with NAFLD, defined by ultrasound, where GSD prevalence was higher than the reported in the general population. On the other hand, an Asian study with large-scale longitudinal cohort found NAFLD as an independent risk factor for GSD development, especially in women. The results of an adjusted multivariate analysis showed that NAFLD is associated with cholecystectomy (OR = 2.4; 95% CI 1.8–3.3), but not with gallstones (OR = 1.1; 95% CI 0.84–1.4). This study grouped subjects with cholecystectomy separated from patients with gallstones, showing a stronger association between NAFLD and cholecystectomized subjects compared to patients with gallstones; being stronger in men than in women, approximately two-thirds of cholecystectomized men had NAFLD. Therefore, cholecystectomy itself increases NAFLD risk, in addition to increasing other diseases associated with metabolic syndrome. The data available so far, only show association, not causality between NAFLD and GSD, which corresponds to a bidirectional association where NAFLD appears to be an independent risk factor for GSD and the latter represents an independent risk factor for NAFLD, the

metabolic disorder commonly present in these two entities can be considered as the liver risk factor. **Cholecystectomy as a risk factor for NAFLD**. Most of the studies include patients with cholecystectomy and cholelithiasis within the same group, a relationship that seems logical because the vast majority of cholecystectomized patients have a GSD history. However, recent studies analyze groups with prior cholecystectomy, finding an independent association with NAFLD, which is even stronger than reported for the association with GSD. Two cross-sectional studies of different populations are the basis for establishing that NAFLD risk increases significantly with a cholecystectomy compared to patients with GSD who preserve the gallbladder and control patients, even after making adjustments in the shared metabolic risk factors. Therefore, this association was mainly attributable to a previous cholecystectomy history, not to gallstones presence, establishing cholecystectomy as a risk factor for NAFLD development. Recent information on the endocrine functions of the gallbladder makes it possible to assume that its ablation represents critical metabolic consequences in NAFLD.

Conclusion

Clinical studies and systematic reviews have demonstrated the association between GSD, cholecystectomy, and NAFLD, underlining that NAFLD is an independent risk factor for GSD, and conversely, when performing separation of GSD in gallstones in situ and previous history of cholecystectomy, it is confirmed that cholecystectomy but not gallstones appear as a risk factor for complications associated with metabolic syndrome, particularly NAFLD. Also, elective cholecystectomy increases the liver fat content index, HOMA-IR, and serum apoB concentration. These results support the idea that cholecystectomy is a risk factor for NAFLD and other conditions associated with IR. Cholecystectomy or gallbladder dysfunction increases the cycle of BAs through the liver and intestine, which has repercussions on metabolic regulation regarding the hepatic triglycerides' accumulation, favoring the appearance of NAFLD. The bidirectional relationship between NAFLD and GSD is summarized in the role of central and peripheral IR, the importance of endocrine pathways regulated by BAs with change in the expression of transcription factors LXR, FXR and TGR5, in addition of the physiological role of the gallbladder in the signaling of insulin through the secretion of FGF19, however more epidemiological and experimental studies should be complemented.

LIST OF REFERENCES:

1. Takahashi Y. Fukusato T. Histopathology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. //World J Gastroenterol. 2014;20:15539-15548
2. Díaz-Rosales, J. de D. · Enríquez-Dominguez, L. · Díaz-Torres, B. Archivos de Medicina. //Arch Med. 2016;16:98-108
3. Neuschwander-Tetri, B.A. Fatty liver and the metabolic syndrome. Curr Opin Gastroenterol. 2007;23:193-198
4. Marchesini G. Bugianesi, E. · Forlani, G. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome Hepatology. 2003;37:917-923
5. Kim Y.-K. Kwon, O.-S. · Her, K.H. The grade of nonalcoholic fatty liver disease is an independent risk factor for gallstone disease. //Medicine. 2019;98:e16018
6. Younossi Z.M., Stepanova M., Afendy, M. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clin Gastroenterol Hepatol. 2011; 9
7. Ruhl C.E., Everhart J.E. Fatty liver indices in the multiethnic United States National Health and Nutrition Examination Survey. //Aliment Pharmacol Therapeut. 2015; 41:65
8. Estes C., Razavi H., Loomba R. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease //Hepatology. 2018;67:123-133
9. Sanyal A.J. Campbell-Sargent C., Mirshahi F. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. Gastroenterology. 2001; 120:1183-1192
10. Facchini F.S., Hua N.W., Stoohs R.A. Effect of iron depletion in carbohydrate-intolerant patients with clinical evidence of nonalcoholic fatty liver disease. Gastroenterology. 2002; 122:931-939
11. Loomba R., Schork N., Chen C.H. Heritability of hepatic fibrosis and steatosis based on a prospective twin study //Gastroenterology. 2015;149:1784-1793
12. Xu A., Wang Y., Keshaw H. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. //J Clin Investig. 2003;112:91
13. Portincasa P., Moschetta A., Palasciano G. Cholesterol gallstone disease.

Entered 20.11.2025