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ASSESSMENT OF CLINICAL AND MOLECULAR-GENETIC RISK FACTORS FOR THE DEVELOPMENT OF GALLSTONE DISEASE AND POSTOPERATIVE RECURRENCE OF CHOLELITHIASIS IN PATIENTS WITH OBESITY

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Abstract: Gallstone disease is one of the most common disorders of the hepatobiliary system and is closely associated with obesity, insulin resistance, dyslipidemia and disturbances of cholesterol and bile acid metabolism. The purpose of this thesis is to evaluate, based on published scientific literature, the principal clinical and molecular-genetic factors associated with the development of gallstone disease and the recurrence of biliary stones after surgical or endoscopic treatment in patients with obesity. Particular attention is paid to the potential roles of the ADIPOQ and UGT2B15 genes. The work is a narrative literature review and does not contain original experimental or clinical data. Obesity promotes cholesterol supersaturation of bile, gallbladder hypomotility, chronic low-grade inflammation and changes in enterohepatic bile acid circulation. After cholecystectomy, true recurrence of gallbladder stones is anatomically impossible; therefore, postoperative recurrence generally refers to newly formed or recurrent common bile duct or intrahepatic stones after previous complete stone clearance. The ADIPOQ gene may influence lithogenic risk through adiponectin-mediated regulation of insulin sensitivity, lipid oxidation and inflammatory activity. UGT2B15 may be considered a candidate modifier because it participates in hepatic glucuronidation and steroid hormone metabolism. However, a direct association between UGT2B15 variants and gallstone recurrence has not yet been confirmed. Integrated assessment of obesity-related metabolic abnormalities, biliary anatomy and genetic predisposition may improve individual risk stratification and postoperative monitoring.

Keywords: obesity, gallstone disease, cholelithiasis recurrence, ADIPOQ, UGT2B15, adiponectin, bile acids.

Annotatsiya:O‘t-tosh kasalligi gepatobiliar tizimning eng ko‘p uchraydigan kasalliklaridan biri bo‘lib, semizlik, insulin rezistentligi, dislipidemiya hamda xolesterin va o‘t kislotalari almashinuvining buzilishi bilan chambarchas bog‘liq. Ushbu tezisning maqsadi ilmiy adabiyotlar asosida semizlik bilan og‘rigan bemorlarda o‘t-tosh kasalligi rivojlanishi hamda jarrohlik yoki endoskopik davolashdan keyin biliar toshlarning qaytalanishiga olib keluvchi asosiy klinik va molekulyar-genetik xavf omillarini baholashdan iborat. Ishda ADIPOQ va UGT2B15 genlarining ehtimoliy ahamiyatiga alohida e’tibor qaratilgan. Mazkur ish adabiyotlar tahliliga asoslangan bo‘lib, unda original tajriba yoki klinik tadqiqot natijalari keltirilmagan. Semizlik o‘t suyuqligining xolesterin bilan to‘yinishi, o‘t pufagi qisqaruvchanligining pasayishi, surunkali past darajali yallig‘lanish va o‘t kislotalarining enterohepatik aylanishi buzilishiga sabab bo‘ladi. Xoletsistektomiyadan keyin o‘t pufagida toshning qayta paydo bo‘lishi anatomik jihatdan mumkin emas. Shu sababli operatsiyadan keyingi qaytalanish deganda, odatda, toshlar to‘liq olib tashlanganidan keyin umumiy o‘t yo‘li yoki jigar ichki o‘t yo‘llarida yangi toshlarning shakllanishi tushuniladi. ADIPOQ geni adiponektin orqali insulin sezgirligi, lipidlar oksidlanishi va yallig‘lanish jarayonlarini boshqarib, litogen xavfga ta’sir ko‘rsatishi mumkin. UGT2B15 geni esa glyukuronidlanish va steroid gormonlar almashinuvidagi ishtiroki sababli kandidat-gen sifatida baholanishi mumkin. Biroq uning o‘t-tosh kasalligi qaytalanishi bilan bevosita bog‘liqligi hozircha yetarli darajada isbotlanmagan.

Kalit so‘zlar:semizlik, o‘t-tosh kasalligi, xolelitiaz qaytalanishi, ADIPOQ, UGT2B15, adiponektin, o‘t kislotalari.

Аннотация:Желчнокаменная болезнь является одним из наиболее распространённых заболеваний гепатобилиарной системы и тесно связана с ожирением, инсулинорезистентностью, дислипидемией, а также нарушениями обмена холестерина и желчных кислот. Целью настоящего тезиса является оценка на основании научной литературы основных клинических и молекулярно-генетических факторов риска развития желчнокаменной болезни и рецидива камнеобразования после хирургического или эндоскопического лечения у пациентов с ожирением. Особое внимание уделено потенциальной роли генов ADIPOQ и UGT2B15. Работа представляет собой обзор литературы и не содержит результатов собственных экспериментальных или клинических исследований. Ожирение способствует перенасыщению желчи холестерином, снижению сократительной функции желчного пузыря, развитию хронического низкоинтенсивного воспаления и нарушению энтерогепатической циркуляции желчных кислот. После холецистэктомии истинный рецидив камней в желчном пузыре анатомически невозможен. Поэтому под послеоперационным рецидивом обычно понимают повторное образование камней в общем желчном протоке или внутрипечёночных желчных протоках после их первоначального полного удаления. Ген ADIPOQ может влиять на литогенный риск посредством регуляции чувствительности к инсулину, окисления липидов и воспалительных реакций. Ген UGT2B15 может рассматриваться как кандидатный модификатор риска благодаря его участию в глюкуронировании и метаболизме стероидных гормонов. Однако прямая связь вариантов UGT2B15 с рецидивом желчнокаменной болезни в настоящее время не доказана.

Ключевые слова: ожирение, желчнокаменная болезнь, рецидив холелитиаза, ADIPOQ, UGT2B15, адипонектин, желчные кислоты.

Introduction

Gallstone disease is a multifactorial metabolic and hepatobiliary disorder characterized by the formation of cholesterol, pigment or mixed stones in the gallbladder and biliary tract. Cholesterol stones constitute the predominant type in many populations. Their formation is based on the interaction of cholesterol supersaturation of bile, accelerated nucleation of cholesterol crystals, impaired gallbladder emptying and increased intestinal absorption or hepatic secretion of cholesterol. Modern clinical guidelines identify obesity, female sex, increasing age, high-calorie diets, dyslipidemia, rapid weight loss, prolonged fasting and previous gastrointestinal or bariatric surgery as important risk factors for cholesterol gallstones [1–4].

The relationship between obesity and gallstone disease is not limited to the presence of metabolic syndrome. In a prospective cohort study involving 58,862 adults without gallstones at baseline, metabolically healthy obesity was also associated with an increased risk of developing gallstones. The risk increased in parallel with body mass index and waist circumference, indicating that excessive adiposity itself may promote lithogenesis even before clinically apparent metabolic complications develop [6].The pathogenesis of gallstone disease also has a genetic component. Twin studies and genome-wide investigations indicate that inherited factors contribute significantly to individual susceptibility. Large-scale genome-wide association analyses have identified variants in genes related to cholesterol secretion, phospholipid transport, bile acid circulation, hepatic metabolism and intestinal bile acid reabsorption. Nevertheless, gallstone disease cannot be explained by a single gene. It

develops through interactions between multiple genetic variants, obesity, dietary patterns, hormonal status, intestinal microbiota and biliary motility [5,7].

The aim of this thesis is to analyse the principal clinical and molecular-genetic risk factors for gallstone formation and postoperative recurrence of biliary stones in patients with obesity, with particular emphasis on the possible contribution of ADIPOQ and UGT2B15. The thesis is based on a narrative analysis of Uzbek and international textbooks, clinical guidelines, cohort studies and molecular-genetic reviews. No original biological samples, genotyping procedures, clinical interventions or experimental investigations were performed.

Main Part

Obesity affects bile composition through several interconnected mechanisms. Increased hepatic synthesis and secretion of cholesterol result in bile that contains more cholesterol than can be solubilized by bile acids and phospholipids. Cholesterol subsequently precipitates as solid crystals, which aggregate and form stones. Hyperinsulinemia and insulin resistance can stimulate hepatic cholesterol production and alter the activity of enzymes and transport proteins involved in biliary lipid secretion. Abdominal obesity is particularly important because visceral adipose tissue is metabolically active and produces adipokines, free fatty acids and pro-inflammatory mediators that directly affect hepatic metabolism.Gallbladder hypomotility is another important mechanism. In patients with obesity, the gallbladder may have an increased fasting volume and reduced contractile response to food. Incomplete emptying causes prolonged retention of concentrated bile and creates favourable conditions for crystal nucleation and stone growth. Diets rich in animal fats, refined carbohydrates and excessive calories may further increase cholesterol secretion into bile. Low physical activity, irregular food intake and long periods of fasting can aggravate biliary stasis. Conversely, extremely rapid weight loss is also lithogenic because mobilization of adipose tissue markedly increases the amount of cholesterol transported to the liver and secreted into bile [3,4,6].

The clinical risk profile of an obese patient should therefore include body mass index, waist circumference, duration of obesity, rate of recent weight change, dietary habits and physical activity. Laboratory assessment should include fasting glucose, glycated haemoglobin, total cholesterol, low-density and high-density lipoprotein cholesterol, triglycerides, liver enzymes and markers of cholestasis. Type 2 diabetes mellitus, metabolic dysfunction-associated steatotic liver disease, hypertriglyceridemia and reduced high-density lipoprotein cholesterol may strengthen the lithogenic effect of obesity. Female sex, pregnancy, use of oestrogen-containing medicines, increasing age and a positive family history should also be considered [3–6].The term postoperative recurrence requires clarification. Following complete removal of the gallbladder, recurrent formation of stones inside the gallbladder is impossible. Postoperative recurrence generally refers to common bile duct or intrahepatic stones detected after a period during which complete biliary clearance had been documented. Stones found shortly after treatment may be residual stones that were overlooked during the initial procedure, whereas stones appearing after a longer stone-free interval are more likely to have formed de novo.

Clinical and anatomical risk factors for recurrent common bile duct stones include persistent common bile duct dilatation, impaired bile drainage, periampullary duodenal diverticulum, biliary strictures, marked angulation of the common bile duct, pneumobilia, bacterial colonization, previous endoscopic sphincterotomy and repeated endoscopic interventions. Large or multiple stones, difficult stone extraction and incomplete clearance of biliary sludge may also increase recurrence risk. In patients who have undergone cholecystectomy, sustained common bile duct dilatation and periampullary diverticulum are among the most consistently described predictors of recurrence [10].

Obesity may contribute to postoperative recurrence by maintaining a lithogenic metabolic environment after the initial operation. Cholecystectomy removes the organ in which most cholesterol stones originate, but it does not directly eliminate insulin resistance, dyslipidemia, hepatic cholesterol

hypersecretion or altered bile acid metabolism. Therefore, an obese patient may continue to produce bile with an unfavourable cholesterol-to-bile-acid ratio. Nevertheless, evidence supporting obesity as an independent predictor of recurrent common bile duct stones is less consistent than the evidence linking obesity to primary gallstone formation. Anatomical abnormalities and biliary stasis frequently have a stronger direct influence on recurrence.

ADIPOQ is located on chromosome 3 and encodes adiponectin, an adipose tissue-derived protein involved in glucose regulation, fatty acid oxidation, insulin sensitivity and inflammatory control. Unlike several other adipokines, circulating adiponectin concentrations generally decrease as visceral adiposity increases. Reduced adiponectin activity is associated with insulin resistance, increased triglycerides, lower high-density lipoprotein cholesterol, hepatic fat accumulation and chronic low-grade inflammation.Adiponectin activates AMP-activated protein kinase and peroxisome proliferator-activated receptor alpha signalling pathways. Through these mechanisms, it stimulates fatty acid oxidation, decreases hepatic glucose production and improves insulin sensitivity. Adiponectin also inhibits pro-inflammatory mediators, including tumour necrosis factor alpha, interleukin-6 and nuclear factor kappa B. Consequently, genetically determined or obesity-related reductions in adiponectin may indirectly increase lithogenic risk by worsening hepatic lipid metabolism, insulin resistance and inflammation [8].

Several ADIPOQ single-nucleotide variants, including rs266729, rs2241766 and rs1501299, have been studied in relation to circulating adiponectin concentrations, obesity, dyslipidemia and metabolic syndrome. Their effects may differ among ethnic populations because allele frequencies, environmental exposures and patterns of linkage disequilibrium are not identical. At present, ADIPOQ should be considered a biologically plausible candidate gene for gallstone susceptibility rather than an independently validated diagnostic marker of gallstone disease or postoperative recurrence. Its strongest probable contribution is mediated through obesity-related metabolic phenotypes.In a future clinical-genetic study, ADIPOQ genotyping could be combined with measurements of serum adiponectin, insulin resistance, lipid profile, body mass index and waist circumference. Such an approach would make it possible to determine whether ADIPOQ variants add predictive value beyond routine clinical and biochemical indicators. Separate comparison of obese patients without gallstones, obese patients with primary gallstones and patients with recurrent bile duct stones would be particularly informative.

UGT2B15 encodes an enzyme belonging to the uridine diphosphate glucuronosyltransferase family. The enzyme participates in glucuronidation, a phase II metabolic process that increases the water solubility of endogenous compounds and xenobiotics and facilitates their elimination. UGT2B15 is expressed in the liver and other tissues and is particularly important in the metabolism and inactivation of steroid hormones, including androgen metabolites [9]. NCBI expression data also indicate substantial expression in hepatic and gallbladder tissues.

The possible relationship between UGT2B15 and gallstone disease is indirect and remains hypothetical. Steroid hormones influence hepatic cholesterol metabolism and gallbladder motility, while glucuronidation pathways contribute to the metabolism of hormones, medicines and endogenous lipophilic compounds. Functional variation in UGT2B15 could theoretically modify hormonal exposure or hepatic metabolic responses and thereby influence lithogenic susceptibility. This hypothesis may be especially relevant in women, individuals receiving hormonal treatment and patients with obesity-associated endocrine disturbances.However, UGT2B15 is not currently recognized as an established gallstone gene. Large genome-wide studies have identified strong associations for genes such as ABCG5, ABCG8, ABCB4, SLC10A2, HNF4A and several loci involved in lipid and bile acid metabolism, but they have not demonstrated a definitive association between UGT2B15 variants and gallstone disease [7]. Therefore, the inclusion of UGT2B15 in a

molecular-genetic assessment should be regarded as exploratory. Any association detected in a future study would require replication in independent populations and functional confirmation.

A comprehensive risk assessment model for obese patients should integrate clinical, biochemical, imaging and genetic parameters. The clinical component should include age, sex, body mass index, waist circumference, duration of obesity, weight-loss rate, diabetes, dietary pattern and family history. The biochemical component should include glucose metabolism, serum lipids, hepatic enzymes, bilirubin and, where possible, adiponectin. Ultrasonography and magnetic resonance cholangiopancreatography can assess bile duct diameter, residual stones, biliary sludge, strictures and anatomical abnormalities. The molecular component may include ADIPOQ as a metabolically relevant candidate gene and UGT2B15 as an exploratory glucuronidation-related candidate.

Genetic test results should not be interpreted separately from clinical data. The presence of a risk allele does not mean that gallstones or recurrence will inevitably occur, while the absence of a studied variant does not exclude disease. Obesity, diet, biliary anatomy and previous interventions may have effects that are as important as, or more important than, individual genetic variants. Molecular markers are most useful when they improve risk prediction beyond information already available from standard clinical assessment.Preventive management should focus on gradual and sustained weight reduction rather than rapid restrictive dieting, correction of hyperglycaemia and dyslipidemia, regular physical activity and avoidance of prolonged fasting. Patients undergoing bariatric procedures require specific assessment because rapid postoperative weight loss can substantially increase gallstone formation. After treatment for common bile duct stones, patients with duct dilatation, periampullary diverticulum, repeated biliary infection or previous recurrence may require prolonged clinical, biochemical and ultrasound monitoring.

Conclusion

Gallstone disease in patients with obesity develops through a complex interaction between excessive adiposity, hepatic cholesterol hypersecretion, insulin resistance, dyslipidemia, gallbladder hypomotility, inflammation, altered bile acid circulation and genetic predisposition. Even metabolically healthy obesity cannot be considered harmless with respect to gallstone formation.

Postoperative recurrence most commonly represents recurrent common bile duct or intrahepatic stone formation rather than recurrence inside the removed gallbladder. Persistent bile duct dilatation, periampullary diverticulum, impaired biliary drainage, infection, anatomical abnormalities and repeated endoscopic procedures are important clinical predictors. Obesity may maintain metabolic lithogenicity, although its independent role in postoperative recurrence requires further investigation.ADIPOQ is a biologically plausible molecular marker because adiponectin regulates insulin sensitivity, lipid oxidation and inflammation. ADIPOQ variants may influence gallstone susceptibility indirectly through obesity, metabolic syndrome and hepatic lipid disturbances. UGT2B15 may be considered an exploratory candidate gene due to its expression in the liver and gallbladder and its participation in glucuronidation and steroid hormone metabolism. Nevertheless, no sufficiently strong evidence currently supports its use as a validated marker of gallstone disease or postoperative recurrence.

Future prospective studies should combine anthropometric measurements, metabolic indicators, biliary imaging, serum adiponectin and ADIPOQ and UGT2B15 genotyping. Such studies may clarify gene-environment interactions and contribute to individualized prevention, postoperative surveillance and early identification of obese patients at high risk of recurrent biliary stone formation.

References :

1. Ergashev, U. Yu. (2023). Xirurgik kasalliklar. Tibbiyot nashriyoti matbaa uyi.
2. Jumayeva, M. M. (2025). O‘t-tosh kasalligida o‘t pufagining ultratovush tashxisoti va gistokimyoviy o‘zgarishlari to‘g‘risida. Buxoro tibbiyot instituti.

3. Xo‘jaboyev, S. T. (2025). Keksa yoshdagi bemorlarda o‘t-tosh kasalligini zamonaviy xirurgik davolash. Samarqand.
4. Министерство здравоохранения Российской Федерации. (2024). Желчнокаменная болезнь: Клинические рекомендации.
5. Научное общество гастроэнтерологов России. (2012). Рекомендации по диагностике и лечению желчнокаменной болезни. Экспериментальная и клиническая гастроэнтерология, 4, 114–123.
6. Щеголев, А. А. (Ред.). (2015). Желчекаменная болезнь (2-е изд.). РНИМУ им. Н. И. Пирогова.
7. Błażejewska, W., Dąbrowska, J., Michałowska, J., & Bogdański, P. (2025). The role of adiponectin and ADIPOQ variation in metabolic syndrome: A narrative review. Genes, 16(6), 699.
8. Gauthier-Landry, L., Bélanger, A., & Barbier, O. (2015). Multiple roles for UGT2B15 and UGT2B17 enzymes in androgen metabolism. Journal of Steroid Biochemistry and Molecular Biology, 145, 187–192.
9. Stokes, C. S., Krawczyk, M., & Lammert, F. (2011). Gallstones: Environment, lifestyle and genes. Digestive Diseases, 29(2), 191–201.
10. Wen, N., & Wang, Y. (2023). Risk factors for recurrent common bile duct stones: A systematic review and meta-analysis. Expert Review of Gastroenterology & Hepatology.