https://doi.org/10.22416/1382-4376-2023-33-1-7-14
UDC 616.366-003.7-084:612.766.1

Physical Activity and Gallstone Disease

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Aim: to present data of Russian and foreign studies about association between physical activity (PA) and gallstone disease (GSD).
Key point. A low PA level is one of the four major risk factors for chronic non-infectiuos diseases. The frequency of low PA in men and women of the Russian Federation (according to the medical examination in 2016) is 19 %. The global prevalence of GSD is up to 20 % among adults. Many systematic reviews and meta-analyses have confirmed an inverse association between GSD and PA in the world, regardless of potential risk factors for GSD, with a clear dose-dependent effect — the relative risk (RR) of GSD was 0.87 (95 % CI 0.83–0.92) per 20 metabolic equivalents (MET) of PA per week. According to our results of an epidemiological survey in the framework of the WHO MONICA program in Novosibirsk (n = 870) among women aged 25–64 with low total PA (less than 800 MET/min/week), as well as with the first class of PA in leisure-time, GSD occurred much more often (class 1 — 33 %, classes 2–4 — 8.7–11.0 %, $p < 0.01$). PA favorably affects almost all mechanisms of gallstone formation: improves cholesterol metabolism in bile, increases serum HDL cholesterol, bile acid synthesis, stimulates the release of cholecystokinin, reduces mucin hypersecretion, increases the diversity and richness of the intestinal microbiota. Daily PA serves as a preventive measure for GSD: the risk of GSD is reduced by 66 % (95 % CI 0.18–0.86).
Conclusion. EASL has recognized PA as a protective agent against gallstone formation.
Keywords: physical activity, gallstone disease, mechanisms
Conflict of interest: The work was carried out according to the state assignment within the framework of the budget topic "Epidemiological monitoring of the state of public health and the study of molecular genetic and molecular biological mechanisms for the development of common therapeutic diseases in Siberia to improve approaches to their diagnosis, prevention and treatment" No. AAAA-A17-117112850280-2.

For citation: Grigor'eva I.N., Notova T.E., Romanova T.I. Physical Activity and Gallstone Disease. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2023;33(1):7–14. https://doi. org/10.22416/1382-4376-2023-33-1-7-14

Физическая активность и желчнокаменная болезнь

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Цель обзора: представить данные отечественных и зарубежных исследований об ассоциации физической активности (ФА) и желчнокаменной болезни (ЖКБ).
Основные положения. Низкая ФА является одним из четырех основных факторов риска развития хронических неинфекционных заболеваний (ХНИЗ). Частота низкой ФА у мужчин и женщин РФ (по данным диспансеризации 2016 г.) составляет 19 %. Глобальная распространенность ЖКБ составляет до 20 % среди взрослых. Во многих систематических обзорах и метаанализах подтверждена обратная ассоциация между ЖКБ и ФА в мире независимо от потенциальных факторов риска ЖКБ, при этом наблюдался четкий дозозависимый эффект — относительный риск (RR) ЖКБ составлял 0,87 (95 % ДИ 0,83–0,92) на 20 метаболических эквивалентов (МЕТ) ФА в неделю. По нашим результатам эпидемиологического обследования в рамках программы ВОЗ "MONICA" в г. Новосибирске (n = 870 чел.) среди женщин 25–64 лет с низкой общей ФА (менее 800 МЕТ-мин/нед), а также при наличии первого класса ФА в свободное время ЖКБ встречалась значительно чаще (1-й класс — 33 %, 2–4-й классы — 8,7–11,0 %, $p < 0,01$). ФА благоприятно влияет практически на все механизмы желчекамнеобразования: улучшает метаболизм холестерина в желчи, повышает сывороточный ХС ЛВП, синтез желчных кислот, стимулирует выброс холецистокинина, снижает гиперсекрецию муцина, увеличивает разнообразие и богатство кишечной микробиоты. Ежедневная ФА служит мерой профилактики ЖКБ: риск ЖКБ снижается на 66 % (95 % ДИ; 0,18–0,86).
Заключение. ФА признана защитным агентом против образования камней в желчном пузыре.

Ключевые слова: физическая активность, желчнокаменная болезнь, механизмы
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов. Работа выполнена по государственному заданию в рамках бюджетной темы «Эпидемиологический мониторинг состояния здоровья населения и изучение молекулярно-генетических и молекулярно-биологических механизмов развития распространенных терапевтических заболеваний в Сибири для совершенствования подходов к их диагностике, профилактике и лечению» No AAAA-A17-117112850280-2.

Для цитирования: Григорьева И.Н., Нотова Т.Е., Романова Т.И. Физическая активность и желчнокаменная болезнь. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2023;33(1):7–14. https://doi.org/10.22416/1382-4376-2023-33-1-7-14

Introduction

According to the WHO definition (2010), physical activity (PA) is any bodily movement produced by skeletal muscle that results in energy expenditure [1]. PA in every forth adult worldwide does not meet the internationally recommended PA levels, which is projected to cause 5.3 million of the 57 million deaths worldwide, accounting 9 % of premature deaths and 6–10 % of all deaths from major noncommunicable diseases [2]. Lack of PA is the fourth most important risk factor for global mortality [1]. Low PA or its absence is a recognized modifiable risk factor for cardiovascular disease and a number of other chronic diseases [3]: 30 % of the risk of coronary artery disease, 27 % of the risk of diabetes, 21–25 % of the risk of breast and colorectal cancer are associated with low PA, as well as a 15–20 % risk of hip fractures in the elderly [4]. Adults aged 18–64 years are recommended to do at least 150–300 min per week of moderate-intensity aerobic exercise (e.g., brisk walking) or at least 75–150 minutes of high-intensity aerobic exercise, such as weightlifting, per week [1]. The frequency of low PA in men and women of the Russian Federation (according to the medical examination in 2016) is 19 % [5].

Total PA activity is estimated by multiplying the intensity of each activity by its duration. The metabolic equivalent tasks (METs) is a construct that is commonly used to quantify PA as well as exercise performance. 'One MET' is equal to a resting oxygen uptake of 3.5 ml O_2 per kg body weight x min (mL/kg/min) [4]. According to the degree of energy costs, PA is divided into 3 levels: light-intensity activities are defined as 1.1 to 2.9 METs; moderate-intensity activities are defined as 3.0 to 5.9 METs; vigorous-intensity activities are defined as 6.0 METs or more [4].

Gallstone disease (GSD)

Liver and biliary tract diseases are one of the leading causes of death and morbidity, accounting for 2.4 million deaths worldwide in 2017 [6]. The global prevalence of GSD is up to 20 % among adults [7]. In 2015, US annual health care costs for biliary tract disease amounted to $10.3 billion; in Germany, more than 175,000 cholecystectomies for GSD are performed annually [8].

Gallstones in 90 % of cases consist mainly of cholesterol (the remaining 10 % are black and brown pigmented stones) and are often associated with systemic metabolic disorders, such as metabolic syndrome [9]. Five primary defects work together to enhance cholesterol cholelithogenesis, which include 1) *Lith* genes and genetic factors; 2) hepatic hypersecretion of biliary cholesterol, inducing cholesterol-supersaturated gallbladder bile; 3) rapid cholesterol nucleation and crystallization and accelerated growth of solid cholesterol crystals; 4) dysfunctional gallbladder motility, leading to impaired gallbladder emptying and refilling with mucin hypersecretion and gel formation, ultimately promoting the development of biliary sludge, i.e., the precursor of gallstones; 5) intestinal factors, including increased delivery of the cholesterol absorbed from the small intestine to the liver for biliary hypersecretion, alterations in gut microbiota, and sluggish intestinal transit [10].

The risk of gallstone formation is associated with a combination of non-modifiable (female sex, age, genetic characteristics, such as *ABCG8* gene polymorphism) and modifiable (environment/lifestyle) factors. The latter includes a combination of obesity, lipid metabolism disorders, parity, diabetes, lack of PA and high-calorie diet [8, 11], and there are also rarer risk factors for GSD — total parenteral nutrition, rapid weight loss, celiac disease, hemolytic anaemia, taking fibrates, oral contraceptives and conjugated estrogens, etc. [10].

PA and GSD: pros and cons

Pro. There are a number of studies in the literature, including systematic reviews and meta-analyses, confirming the inverse association between GSD and PA [8, 12–38]. Reduced PA is a risk factor for GSD in Germany [8], Canada [12, 29], Japan [13], Poland [14], India [15], Italy [16, 36], USA [17–23, 32], China [24, 37], Great Britain [25, 30], Mexico [26, 40], Turkey [27], Iran [28], Norway [31], Korea [35], in Russia [38], as well

as in multiethnic cohorts [33, 34]. In prospective cohort studies, M.F. Leitzmann et al. showed that after adjustment for multiple confounders, increased PA was inversely related to risk for GSD and cholecystectomy (a relative risk (RR) of GSD of 0.63 in men and 0.69 in women) [17, 18]. A meta-analysis of 260,000 participants shows an inverse relationship between PA and GSD (when comparing the highest and lowest levels groups) as in men (OR = 0.76 (95 % CI 0.60–0.97), and in women (OR = 0.77; 95 % CI 0.66–0.91); in a dose-response analysis, RR of GSD was 0.87 (95 % CI 0.83–0.92; I = 1.0 %) for 20 MET-hour of recreational PA per week [34]. The protective ability of aerobic capacity was noted in both asymptomatic [26] and symptomatic GSD, as well as in gallbladder disease [30]. Frequent aerobic exercise can have a beneficial preventive effect on gallstones formation [29]. Vigorous PA (activities that expend at least six-fold the energy equivalent of being at rest [1]) was inversely related to the age-adjusted risk for gallstones in both men and women [33, 46] and reduces the risk of cholecystectomy [31].

According to the Russian study, it was also revealed that among women aged 25–64 years with low total FA (TPA) (less than 800 MET/min/week), as well as in the presence of the first class of PA in the leisure-time (LTPA), i.e. minimal LTPA, in contrast to the average, intense and maximum LTPA in 2, 3, 4 classes of LTPA, GSD occurred much more often, which was accompanied by a significant increase in the triglyceride levels in the blood serum [38]. In 1994–1995 within the framework of the WHO "MONICA" program, a representative sample of 870 women (aged 25–64 years) living in Novosibirsk, Western Siberia, was screened for the presence of gallstones by gallbladder ultrasound [38]. PA was evaluated by self-administered questionnaire (WHO-MONICA Optional Study of Physical Activity – MOSPA) [39]. The prevalence of GSD was inversely related to PA ($p < 0.01$), there was also a significant increase in the incidence of GSD (by 1.9 times, $p < 0.05$) in the absence of occupational PA (OPA) compared with that in the presence of an average level of OPA. In women with mild-intensity of the leisure-time PA (LTPA), GSD was more common (33.3 %) than LTPA of moderate- and heavy-intensity (8.7 and 11.0 %, respectively, $p < 0.01$). In women with GSD no association was found between PA and diet, coronary heart disease, hypertension or diabetes [38].

A prospective population-based study including 460,937 participants aged 30–79 years from 10 different regions of China found that total PA was inversely associated with GSD (hazard ratio (HR) comparing top vs bottom quintile: 0.86, 95 % CI 0.81–0.90); for LTPA, there was an inverse trend for GSD (HR comparing ≥7.5 MET-hours/day with none: 0.82, 95 % CI 0.66–1.01) [37]. Among Mexican women, an inverse relationship was also noted between LTPA and the risk of asymptomatic GSD (odds ratio (OR) = 0.76; 95 % CI 0.61–0.95; $p = 0.02$) [26]. Sedentary behaviour was positively related to risk for symptomatic GSD [18]. In symptomatic gallstone patients, exercise may reduce pain perception [19].

In the 33-year prospective US study "Aerobics Center Longitudinal Study (ACLS)" ($n = 54,734$) the results of the test of maximum physical activity on the treadmill, corresponding to the maximum aerobic power (similar to the maximum oxygen consumption), were obtained; test scores of a particular patient are classified from 0 to 20 % as low fit, i.e. fitness, the next 20–40 % (as a moderate fit, and above 40 %) as a high fit in accordance with the data of the surveyed ACLS cohort [32]. When compared with low cardiorespiratory fitness (CRF), adjusted ORs for gallbladder disease for those with moderate and high CRF were: 0.74 (0.55–0.99) and 0.59 (0.42–0.82), respectively when adjusted for all the potential confounders [32]. Each one MET increment of CRF was associated with 10 % lower odds of gallbladder disease in all participants (P for trend <0.001), 13 % lower in women (P for trend <0.001), and 8 % lower in men (P for trend = 0.08) [32]. Similar results were presented in a systematic review of 218,204 participants: the pooled RR for the highest and lowest PA was 0.75 (95 % CI 0.69–0.81, I^2 heterogeneity = 0 %), which confirms the protective effect of PA for gallbladder diseases [30].

Regular PA and an appropriate diet are recognized as the most important measures for the prevention of GSD [8]. An Iranian cross-sectional study of 1522 men and women aged ≥30 years showed that daily PA reduced the risk of GSD by 66 % (95 % CI 0.18–0.86) [28]. Intensive PA also serves as a preventive factor for the cholelithogenesis [33] and has a negative (protective) relationship with cholecystectomy, which was proved in a large population-based cohort study conducted in Norway [31].

Contra. However, some researchers have not found a relationship between GSD and PA [41–47]. In a randomized study in the Danish female and male population, no association was found between GSD and PA [41]. In Japanese men, PA was not measurably related to either gallstones or postcholecystectomy [44]. Intervention to increase PA from moderate to high did not reduce the incidence of sludge or gallstones during

pregnancy [47]. In a 50-year prospective study of 16,785 alumni of Harvard University, PA did not predict either the risk of gallbladder disease, hypertension, or diabetes mellitus [45], which contradicts the generally accepted opinion about the risk factors for GSD [8–11, 37].

Mechanisms of associations between PA and GSD

The main mechanism of the effect of PA in GSD may be associated with the release of the hormone of the upper gastrointestinal tract, cholecystokinin (CCK), with a prokinetic effect. In response to dietary fats and proteins, CCK triggers a variety of physiological processes, including cholecystokinetic (contraction of the gallbladder, relaxation of the sphincter of Oddi, increased bile flow and accelerated transit through the small intestine), pancreozimic effects [48], as well as inhibition of gastric emptying and acid secretion, slowing colonic motility and satiety regulation — all this is mediated by the CCK A receptor (CCKAR) signaling cascade. The CCKAR gene has been identified as a critical gallstone gene, named *Lith13*, which is associated with an increased prevalence of cholesterol GSD in humans [10]. CCK release increases immediately after exercise independently of feeding [49]. Acute PA, i.e. short term intense exercise, can increase gallbladder emptying in individuals with biliary pathology, including GSD, by stimulating CCK release [29]. Hunger suppression was also associated with an increase in CCK levels after acute exercise [50]. In addition, activation of smooth muscles through CCK receptors enhances the processes of emptying and filling of the gallbladder, which affect the pathogenesis of cholesterol gallstones [51]. However, other authors do not find a relationship between PA and the CCK level [52].

There are other potential mechanisms for association of PA with a lower risk of GSD [3, 37]. Higher PA is associated with a reduced risk of obesity, hyperinsulinemia and diabetes mellitus [53], hypertension [54], hyperlipidemia, including hypertriglyceridemia, and low levels of HDL cholesterol [13, 17, 55]. It is these diseases that are recognized as risk factors for GSD [8, 9, 11, 56]. Serum high-density lipoprotein cholesterol (HDL-C), as a marker of reverse cholesterol transport to the liver, acts as a precursor of bile acid [57], which contribute to decreased biliary cholesterol saturation. So an increase in the HDL-C levels is inversely proportional to the prevalence of gallstones [56]. Low serum HDL-C levels have been shown to increase with PA even in the presence of GSD [58]. In addition, PA accelerates fat oxidation in the body [59], and also favorably affects mucin hypersecretion by the gallbladder epithelium, mediated by free fatty acids: mucin is a known factor that pronucleates cholesterol crystals in bile [60].

PA also contributes to the reduction of systemic inflammation indicators due to changes in pro- and antiinflammatory factors (C-reactive protein, adiponectin and interleukin-6) [61], as well as activation of G-protein bile acid receptor 1 (GPBAR-1), mediating the subsequent activation of other immune cells, such as macrophages, monocytes and dendritic cells [62]. It is possible that PA can influence the risk of gallbladder disease by modulating gallbladder mobility by increasing vagal tone [63], which affects both contraction (muscarinic receptors M1) and relaxation of the gallbladder (muscarinic receptors M2) [64]. The opinion is expressed about the mechanical effect of PA on the motility of the gastrointestinal tract in the form of vibration and "bouncing" of the intestine during exercise [65], while a decrease in the motility of the gallbladder and colon are links in the pathogenesis of GSD [10]. In GSD, there is usually a deficiency of bile acids in the bile (bile acids are lipid-solubilising molecules, which also regulate metabolic processes as signalling factors), therefore among bile acids, ursodeoxycholic acid is the drug of choice for the treatment of cholesterol gallstones [66]. In obese women with insulin resistance, bile acid synthesis increased after 14 weeks of exercises and diet [67]. The serum concentration of total bile acids was found to be significantly reduced by 46 % after middle distance running [68]. Physical exercise restores negative feedback in enterohepatic metabolism of bile acids, lowering their content in serum, promotes the synthesis of more bile acids by the liver into bile [68]. An increase in biliary bile acid secretion (68 %, $p = 0.007$) was shown in physically active running mice compared to remaining sedentary controls [69]. Moderate long-term PA improves the secretion of not only biliary bile salts, but also biliary phospholipids in rats [70]. A possible mechanism for the protective effect of PA on gallstone formation is the lowering of biliary cholesterol levels, thereby preventing cholesterol from precipitating in the bile [21]. In mice, exercise promotes almost doubled changes in several hepatic gene expression that increase cholesterol uptake by the liver (low-density lipoprotein receptor (*LDLr*), scavenger receptor class B type 1 (*SRB1*), and sterol 27 hydroxylase (*Cyp27*) genes) but simultaneously increase cholesterol catabolism to bile acids, effectively reducing bile cholesterol saturation, suggesting an effect of endurance exercise on inhibition of gallstone formation [71].

PA and microbiota

It has been proven that intestinal dysbiosis makes a significant contribution to the development

of not only GSD itself, but also to the development of many disorders that are risk factors for GSD, including obesity, diabetes, etc. [72–74]. Most studies have recognized the beneficial impact of exercise on gut microbiota composition [75–78], including an increase in the diversity and richness of the microbiota in physically active individuals, among them health-promoting bacteria *Faecalibacterium prausnitzii*, *Roseburia hominis*, *Akkermansia muciniphila* [79], *Veillo-nella* [80], etc. *V. atypica* enhances athletic performance via its metabolic conversion of exercise-induced lactate into propionate [80]. PA can significantly accelerate whole bowel transit time [81], which also modulates the composition of the intestinal microbiota. Obese individuals — and patients with GSD — are known to have a higher *Firmicutes/Bacteroidetes* ratio [73], and PA may improve this ratio by increasing *Bacteroides* [77]. In the intestine, bacteria produce short-chain fatty acids (SCFA), which play an important role in maintaining intestinal and immune homeostasis, as well as in the regulating metabolism, inflammation and disease, — endurance exercise increased fecal concentrations of SCFAs [82], while SCFAs may contribute to physical performance of the host [83]. Certain microorganisms own the potency to increase host PA and performance [78]. The relationship between PA and gut microbiota composition is complex and apparently bidirectional.

Conclusion

Numerous studies have recognized PA as a protective agent against gallstone formation, which was emphasized by the recommendations of the European Association for the Study of the Liver (EASL) [85]. To increase the PA of the world's population, there is a program "WHO Global Action Plan to increase physical activity for 2018-2030: increasing the level of activity of people to improve health in the world" [86], since increasing the level of PA in adults and the elderly reduces all-cause mortality and is one of the most effective strategies for improving primary, secondary, and tertiary disease prevention and management in various global settings [87].

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Поступила: 09.03.2022 Принята: 25.08.2022 Опубликована: 27.02.2023
Submitted: 09.03.2022 Accepted: 25.08.2022 Published: 27.02.2023

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