Review Article

Physical Activity is Beneficial for Gallbladder Disease

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1. Abstract

Physical activity brings several beneficial effects on cardiovascular disease and in various metabolic disorders. The gallbladder is the dynamic reservoir of concentrated bile containing cholesterol, bile acids, and phospholipids as micelles and vesicles. Such lipid carriers depend on hepatic synthesis and play a key role in digestion and absorption of intestinal nutrients and cholesterol, in concert with intestinal motility. Bile acids also act as metabolically active hormones through interaction with small intestinal farnesoid-X receptor and GPBAR-1 receptor across the enterohepatic circulation. The gallbladder, however, can become the "fellow traveller" with several metabolic disorders (obesity, diabetes, insulin resistance, dyslipidaemia, nonalcoholic liver steatosis) and metabolic syndrome. In this context, aggregation and growth of excess biliary cholesterol into microcrystals and then macro-cholesterol gallstones may occur in the gallbladder. Notably, physical activity supports also benefits on the hepatobiliary tract, and via activation of bile acids acting as signalling molecules. Researchers should know that initial training condition, volume, age, intensity, aerobic capacity, body weight, and percent of body fat appear to interact with exercise-related health consequences. Thus, the overall beneficial effects of physical activity extend beyond the cardiovascular health, and involve the hepatobiliary health.

2. Keywords: Bile acids; Gallbladder disease; Physical activity

3. Abbreviations: BA; Bile acid; CVD; Cardiovascular disease; T2D; Type 2 diabetes

4. Introduction

Chronic diseases affect the vast majority of the elderly populations, and sedentary life contributes to the raising trend of chronic disease epidemics. This detrimental effect starts already during childhood and adolescence. Sedentary lifestyle brings negative effects on the cardiovascular system and overall health [1]. Little to no physical activity contributes to the onset of Type 2 Diabetes (T2D), Cardiovascular Disease (CVD) and premature mortality in the long-term [2]. Regular physical activity, by contrast, has beneficial effects on several chronic diseases [2], the cardiovascular system, and decreases the risk of CVD and mortality by all causes [3]. Obesity and hyperlipidaemia, as well as T2D, are components of the metabolic syndrome, a complex aggregation of conditions further complicated by cholesterol cholelithiasis [4, 6]. The effects of physical activity, within the policy of healthier lifestyles, might also extend beyond the simple benefits on CVD, involving the hepatobiliary tract (and vice-versa).

Here, we discuss the mechanisms relating physical activity to gallbladder disease and the hepatobiliary tract.

5. General Aspects of Exercise

Evidences show that unfit individuals have increased risk to die (2-3 times more) at follow-up when compared with their more fit counterparts. This worrisome trend occurs regardless of body habitus, or the presence of CVD. At variance with the unmodifiable genetic, age and gender factors, physical inactivity is a modifiable risk factor. Clinicians can properly assess and prescribe -virtually to all subjects- physical activity within a structured lifestyle program.

Table 1 depicts the exact terminology and purpose of different types of exercise. Determination of intensity of exercise allows tailoring high-intensity or moderate-intensity activities. This step requires the calculation of specific parameters. For example, Metabolic Equivalents (MET) compare the VO2 produced during a certain activity with resting VO2 (1 MET=3.5 mL per kg b.w./min) [7, 8]. In this context, the intensity of aerobic activity is grouped into light (2-3 METs), moderate (4-6 METs), vigorous (8-12 METs), and near maximal (14-20 METs) [9]. Notably, even moderate-intensity exercise brings significant health benefits [8]. Current guidelines in the USA, Canada, Australia and Europe for adults recommend at least 150 min/week of moderate-intensity exercise such as brisk walking) [10-14].

Table 1: Terminologies adopted for exercise

Type / Definition	Examples / Purpose
Physical activity	Jogging, walking, dancing, swimming gardening, heavy physical labor, car washing, etc.
Sustained body movement / Increased energy expenditure [8]	
Exercise Planned, regularly repeated, intentional physical exercise	Maintains health and fitness [8, 114]
• Aerobic (endurance) exercises	Walking, running
	Increased CV and respiratory fitness
• Strength (resistance) exercises	
	Weight lifting or bodyweight resistance
	Increased muscular strength
• Balance exercises	
	Tai chi, heel-toe walking Improved balance,
	proprioception Prevention of falls
• Mobility (flexibility) exercises	Yoga, stretching Maintenance or improved joint motions Muscle lengthening
Physical fittness	- Heath-related (CV, muscular endurance, mobility, muscular strength, body composition)
- Regular activity allowing vigorous tasks without undue fatigue	- Skill-related (balance, agility, power, coordination, reaction time)

6. Gallstone Disease

Cholelithiasis (either asymptomatic or symptomatic with or without the gallbladder *in situ* after cholecystectomy, with or without complications) [15, 16] is a highly prevalent condition, and one of the most expensive digestive diseases worldwide. Almost 20 million Americans (10-15% of adults in Europe and the USA) suffer from gallbladder disease [17, 18], and the raising incidence rate is 0.60-1.39% yearly [19]. The prevalence of gallstones is rising because of the increasing obesity worldwide [20, 21], metabolic syndrome [6, 22, 23], T2D [24-27] and insulin resistance [27, 28]. Additional factors include reduced high density lipoproteins (HDL) and hypertriglyceridemia [29], sedentary lifestyles [30, 31], hormone replacement therapy [30] and fast food consumption [30]. The risk of developing symptomatic gallstones prone to cholecystectomy also increases with obesity [32-38]. As the prevalence of cholelithiasis increases worldwide (mainly because of metabolic epidemics), the chance that biliary symptoms without or with complications will develop also increases (**Table 2**).

In westernized countries, about 75% of stones consist of aggregated monohydrate cholesterol crystals, and the pathogenesis is closely related to metabolic abnormalities [17, 22]. Black pigment stones represent about 20%, and brown pigment stones only about 5% [39-42]. The most important pathogenic factors for cholesterol gallstones include (**Figure 2**):

- Genetic factors which involve lithogenic (*LITH)* genes [43, 44]

- Hepatic hypersecretion of cholesterol leading to a sustained supersaturated gallbladder bile [45]

- Rapid phase transitions of excess biliary cholesterol which results in precipitation and aggregation of solid cholesterol crystals [46, 47] (**Figure 3**)

- Defective gallbladder motility (gallbladder stasis) [48-53] with hypersecretion and luminal accumulation of mucin gel secreted by the gallbladder epithelium which is exposed to an immune-mediated inflammation [54]

- Intestinal factors involving increased absorption of cholesterol in the small intestine, slow intestinal motility, and altered gut microbiota [15, 16, 55].

Table 2: Clinical manifestations of gallstones

Asymptomatic gallstones
Symptomatic uncomplicated gallstones
Biliary colic
Symptomatic gallstones with complication
Acute cholecystitis*
Acute biliary pancreatitis*
Acute cholangitis*
Acute acalculous cholecystitis*
Biliary enteric fistula and gallstone ileus*
Choledocholithiasis
Cholestatic jaundice*
Cholesterolosis and gallbladder polyps
Chronic cholecystitis
Gallbladder carcinoma and porcelain gallbladder
Recurrent pyogenic cholangitis*

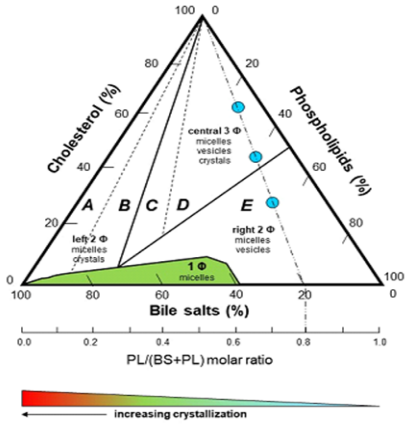

Figure 1: The ternary equilibrium cholesterol-taurocholate-phosphatidylcholine phase diagram as originally depicted by Wang et al. [47].

Components appear as mole percent. The one-phase (φ) (micellar) zone is at the bottom, on the left is the two-phase zone (containing micelles and solid cholesterol crystals), then a central three-phase zone (containing micelles, liquid crystals and solid cholesterol crystals), and a right two-phase zone (containing micelles and liquid crystals). At the bottom, phospholipids (bile salts + phospholipids) molar ratios are also given, which is abbreviated as PL/(BS+PL). Interrupted lines indicate identical PL/(BS+PL) molar ratios, as in the case of the 3 model bile systems plotting on the line (in this case ratio of 0.2). Adapted from Portincasa P, van Erpecum KJ, Di Ciaula A, Wang DQ. The physical presence of gallstone modulates ex vivo cholesterol crystallization pathways of human bile. *Gastroenterol Rep (Oxf)* 2019; **7**: 32-41 [116].

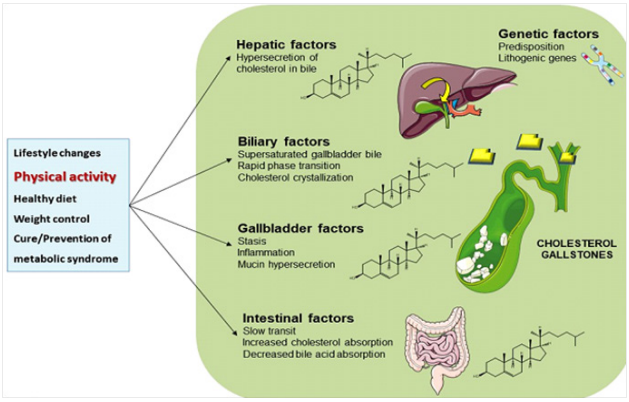

Figure 2: Role of physical activity appears together with lifestyle opportunities on pathogenic factors involved in the formation of cholesterol gallstones. Therapeutic interventions include also general lifestyle recommendations, dietary changes, regular physical activity, and cure and prevention of metabolic abnormalities. Excess cholesterol plays a key role at different places as solubilized molecule or solid (anhydrous, monohydrate) crystals or stones [15, 16, 45, 63, 115-117]. Adapted from: Di Ciaula A, Portincasa P. Recent advances in understanding and managing cholesterol gallstones. F1000Res 2018; 7: 1529.[62]

Table 3: Benefits of physical activity on gallbladder diseases

Author(s)	Publication type	Exercise Intervention	Main Results
Figuereido et al., 2017 [88]	Clinical Study	Vigorous physical activity	Vigorous physical activity: inverse association with risk of gallbladder disease
Li et al., 2017 [89]	Clinical Study	Aerobic capacity level	Progressively increasing aerobic capacity level: lower prevalence of gallbladder disease
Talseth et al., 2016 [90]	Clinical Study	Vigorous physical activity	Increasing the load of physical activity: reduced risk for cholecystectomy
Henao-Moran et al., 2014 [91]	Clinical Study	General physical activity	Increasing the load of physical activity: protection against asymptomatic gallstones
Banim et al., 2010 [68]	Clinical Study	General physical activity	Highest level of physical activity: reduction of 70% in the risk of symptomatic gallstones
Williams, 2008 [92]	Clinical Study	Aerobic capacity level	Higher aerobic capacity level and speed: less risk of gallbladder disease
Shabanzadeh, 2018 [93]	Review	General physical activity	Sedentary physical activity associated with hospital admission for gallbladder disease
Aune et al., 2016 [95]	Review	General physical activity	Higher levels of physical activity inversely related to gallbladder disease
Shephard, 2015 [96]	Review	General physical activity	Potential decrease of gallstones and gallbladder cancer

7. Physical Activity and Gallbladder Disease

Physical activity affects gallbladder function, while decreasing the risk of gallstone disease and gallbladder disease. Mechanisms involved, however, require further elucidations with respect to cholesterol absorption, synthesis and secretion, gallbladder and intestinal motility, and neuro-hormonal aspects [56]. American Indians have a high risk of metabolic disorders and cholesterol gallstones. A previous ultrasonographic study found that physical activity related significantly and inversely to the development of gallbladder disease in a population at high risk for gallbladder disease (N=3143 subjects of both sexes, from 13 American Indian communities examined at baseline in 1989-92 and at follow-up in 1993-95). Results persisted irrespective of potential confounders (body mass index), sex, and in individuals without diabetes (not in those with diabetes) [57]. We recently reviewed the topic of lifestyles in the guidelines by the European Association for the Study of the Liver (EASL). The protective effect of physical activity on cholesterol gallstone formation is evident [20, 31, 58-61]. About 20% of gallstone patients (irrespective of the type of gallstones, i.e. cholesterol or pigment) will develop biliary symptoms, a condition which requires either medical attention or cholecystectomy [15-17, 62, 63]. In this context, questionnaire-based surveys found that physical activity is able to decrease the risk of symptomatic gallstones by one-third [31, 57, 58, 64, 65]. Two factors leading to CVD risk, such as physical inactivity and overnutrition, are precursors to increased body mass index and hepatic cholesterol synthesis rate [66]. Deposition of metabolically active visceral fat, moreover, increases gastrointestinal morbidity and mortality (due to gallstone disease, tumors, and endoscopy

complications) [67].

The European Prospective Investigation into Cancer (EPIC-Norfolk study) [68], using a validated questionnaire, investigated 25,639 volunteers (aged 40–74 years) monitored for symptomatic gallstones. Four groups of increasing physical activity were examined after 5 and 14 years. The highest level of physical activity (equivalent to exercising for 1 h a day in a sedentary job, or 30 min a day in a standing job, or heavy manual job without any additional activity) was associated with a 70% decreased risk of symptomatic gallstones in both sexes. Physical exercise appears to influence key pathogenic mechanisms of gallstone disease. Regular exercise decreases insulin levels [69] as well as insulin resistance [70]. By contrast, hyperinsulinemia promotes hepatic cholesterol uptake [71] and this situation, in turn, increases the secretion of biliary cholesterol [72], while decreasing the secretion of bile acids [73]. Notably, both conditions predispose to the accumulation of cholesterol in bile, making the environment supersaturated with excess cholesterol [62, 63]. Physical exercise has also several effects on lipid metabolism: reduces serum cholesterol and triglycerides, as shown by a large meta-analysis [74], and increases serum HDL levels [75, 76]. This effect is important since serum HDL represents a marker of reverse cholesterol transport to the liver [77], and is the precursor of bile acid synthesis [78]. In turn, this HDL-mediated pathway would participate in mechanisms leading to decreased biliary cholesterol saturation [55]. In line with this possibility, studies found that serum HDL levels are inversely related to gallstone prevalence [79]. The beneficial effects of physical exercise might also extend to the control of the fatty acid-dependent hypersecretion of gallbladder mucin [80, 81], which is another event playing a role in the pathogenesis of cholesterol cholelithiasis [17, 66, 82].

Physical activity has a prokinetic effect on the intestine [83] and appears to stimulate hormonal mechanisms, such as the cholecystokinin-dependent gallbladder contraction [84]. While keeping the ideal weight and losing excess weight is part of healthy lifestyles to prevent gallstone disease and metabolic disorders [7, 85, 86], rapid weight loss can lead to opposite effects. In fact, rapid mobilization of body cholesterol and increased secretion in bile increase the risk of gallstones formation in almost one third of the subjects [66]. Thus, the degree of obesity as well as rapidity of weight loss are crucial in developing gallstones [87].

A detailed list of benefits of physical activity performance on the gallbladder is depicted in **Table 3**. Vigorous physical activity was inversely associated with risk of gallstone disease [88]. Aerobic capacity related to prevalence of gallbladder disease; an increase in aerobic capacity by one metabolic equivalent task (MET) reduced the odd of suffering from gallbladder disease by 8% and 13%, in men and women respectively [89]. Increasing the load of vigorous physical activity was also associated with reduced risk for cholecystectomy [90], and in another study in adult women it protected against gallstones formation [91]. Similarly, higher levels of physical activity might be associated with a 70% reduction of risk for symptomatic gallstones, as reported in a five-year long study [68]. Vigorous aerobic exercise, as measured by aerobic capacity, was also inversely associated with gallbladder disease risk [92]. Hospital admission for gallbladder disease appears to be inversely associated to physical activity as well [93, 94]. Further benefits are evident by increasing the intensity of physical activity in patients with gallbladder disease, as seen for vigorous vs. non-vigorous physical activity [95]. Notably, regular aerobic exercise may favorably influence the progression of both gallstones formation and gallbladder cancer [96].

One of the main pro-kinetic effects of physical activity affecting gastrointestinal function relies on the release of cholecystokinin (CCK) [97, 98]. Not only gastrointestinal function, but also hunger has been influenced by this gastrointestinal hormone, as shown in a study involving acute exercise (from 30 to 120 min), which resulted in suppression of hunger [99]. Improvement of smooth muscle contractility by physical activity might also reinforce gallbladder emptying and refilling processes, two factors involved in the pathogenesis of gallbladder disease [52, 100]. The exact confirmation of the role of any physical activity in gallbladder disease deserves further attention. To achieve this goal fully, measurements that are more objective would be required (such as accelerometers) [57].

8. Bile Acid Metabolism and Physical Activity

Bile acids (BAs) are soluble amphiphiles and constitute the main lipid component of bile. BAs are synthetized from cholesterol and stored in the gallbladder particularly during fasting.

The enterohepatic circulation of BAs consists of few steps [101-103]:

- Hepatic synthesis of "primary" BAs (colic acid, CA; chenodeoxycholic acid, CDCA) from cholesterol. The essential enzymes are the rate-limiting microsomal enzyme cholesterol 7-α-hydroxylase (CYP7A1), the sterol 12-α-hydroxylase (CYP8B1) at a later step (the "classical pathway"), the sterol 27-hydroxylase (CYP27A1) (the "alternative pathway"). The synthesized BAs, after conjugation with taurine or glycine to increase their solubility, are secreted into bile and enter the gallbladder.

- With ingestion of food, cholecystokinin (CCK) plasma levels increase, as the consequence of fat-induced stimulation of upper enterocytes. CCK is a potent agonist of CCK receptors

(CCK-R) in the gallbladder smooth muscle and neurones. Activation of CCK-R stimulates gallbladder contraction and flow of bile and BAs into the duodenum (together with cholesterol and phospholipid, solubilized in 95% water as micelles and vesicles). These cholesterol carriers in bile help the intestinal digestion and absorption of lipids and fat-soluble vitamins [55, 101, 104].

- Secreted BAs undergo effective active reabsorption (>95%) in the terminal ileum into the portal vein [101]. The remaining BAs which enter the colon are transformed by the resident gut microbiome into "secondary" BAs (deoxycholic acid, DCA and litocholic acid, LCA), and "tertiary" BAs (ursodeoxycholic acid, UDCA), which are then passively reabsorbed.

- The continuous recirculation of BAs to the liver across the portal vein is such that only 5% of daily synthetized BAs are lost into feces, while 10-50% of peripheral reabsorbed BAs undergo spillover into systemic circulation [101]. BAs act as special "hormones" because they display additional metabolic effects involving the liver, the intestine, and other tissues. BAs in the terminal ileum activate the orphan farnesoid X receptor (FXR). FXR, in turn, increases the transcription of the enterokine fibroblast growth factor 19 (FGF19 in humans) [101], with gallbladder (relaxation, refilling with freshly synthetized hepatic bile) and liver effects involving BA synthesis. BAs also activate the ileal G protein-coupled receptor (GPBAR-1), and this step leads to the secretion of peptide YY (PYY), glucagon-like peptide 1 (GLP-1) and glucagon-like peptide 2 (GLP-2). BAs help modulating the epithelial cell proliferation, gene expression, and energy, glucose, lipid and lipoprotein metabolism via activation of intestinal foresaid X receptor (FXR) and G-protein-coupled bile acid receptor-1 (GPBAR-1), which are found in the intestine, brown adipose tissue and musculoskeletal muscle [6, 7, 101, 103, 105]. BAs also have antimicrobial and anti-inflammatory functions [101].

Physical activity could ameliorate BA metabolism by improving gastrointestinal motility (gallbladder, intestine). This aspect is still a matter of debate [106]. Previous studies in animals showed that moderate physical activity increases BA excretion [107-109]. As mentioned earlier, the recirculating FGF19 ultimately activates the hepatic FGF4 receptor/β-clotho and subsequent small heterodimer-mediated inhibition of BA synthesis [101]. In principle, by increasing intestinal motility, BA flow as well as FXR expression would increase. A recent study in mice, however, demonstrated that physical activity stimulates BA secretion and fecal output. This mechanism probably involves increased reverse cholesterol transport and independent upregulation of genes involved in BA synthesis, as well as FXR-FGF19 feedback [110]. Additional mechanisms include metabolic post-transcriptional pathways (increased fatty acid absorption). In the clinical setting, however, both fecal and serum BA concentrations decreased significantly in runners [111, 112], but the study did not investigate FXR function. It is still unknown whether physical activity might be able to produce additional BA/GPBAR-1-mediated mediated metabolic or anti-inflammatory effects, due to an apparent lack of translational results from clinical to animal studies.

9. Conclusion and Future Perspectives

In general, physical activity is the only valid scientific therapeutic approach to counteract sedentary dysfunctions as well as the increasing trends of several chronic diseases [2]. Physical activity should be an integral component of healthy lifestyles aimed at maintaining the ideal weight, to achieve the ideal weight or – in subjects unable to attain and maintain substantial weight reduction – to plan a modest weight loss (≤10%) [113]. Beside the numerous beneficial metabolic and cardiovascular effects, physical activity targets also the biliary tract. This aspect raises the possibility that physical activity (many possibilities investigated so far) would play a role as therapeutic tool in primary (and secondary) prevention of gallbladder disease (i.e. gallbladder hypomotility, gallstone disease, symptomatic gallstones and subsequent cholecystectomy). The benefits of physical activity might extend to the gastrointestinal function and the enterohepatic re-circulation of bile acids acting as hormone-like signaling agents and undergoing continuous enterohepatic recirculation. Further research should explore measurements that are more accurate, in order to dissect distinctive outcomes of each physical activity modality. Future studies should also explore the main beneficial and harmful effects of physical activity in cohorts exposed to different nutrition intake, weight changes, or initial physical condition of the individual.

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