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Influence of dietary components on the risk of gallstone formation

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Abstract

Gallbladder disease is a common condition in the population that has a negative impact on quality of life. The development of gallstones is influenced by both non-modifiable factors such as genetics, age, gender and modifiable risk factors including physical activity, body weight, diet. Dietary factors affecting the occurrence of the disease are difficult to capture in clinical studies, but the effect of certain substances on the development of gallstones has been proven. Positive risk factors include a high-calorie diet, obesity, increased intake of carbohydrates, saturated fatty acids, small amounts of fiber ingested. Moderate alcohol consumption reduces the risk of gallstones. Coffee may reduce the risk of the disease, but results are inconclusive. Inverse risk factors include consumption of monounsaturated fatty acids, consumption of nuts, olive oil, n-3 PUFA found in fish oil, vitamin C supplementation. No clear effect of consuming large amounts of dietary cholesterol can be established. The type of protein consumed also matters - vegetable protein reduces the risk of gallstones, animal protein has no such effect. Better understanding of dietary risks of cholelithiasis may help in future disease prevention.

Key words: **“**diet”, “gallbladder disease”, “gallstones”, “risk factors”, “cholelithiasis”

Introduction

Gallstones are a common condition in the population of developed countries [1, 2, 3]. Symptomatic cholelithiasis reduces quality of life, forces patients to visit health care facilities more often and increases costs to the health care system [4, 5]. These factors create a demand for a better understanding of this disease and its risk factors. Multifactorial etiology and pathophysiology depends on the presence of many factors such as obesity [6], increased dietary cholesterol supply, age, gender, physical activity [7]. The purpose of this work is to evaluate the current state of knowledge regarding dietary factors affecting gallstone formation. Dietary risk factors are more difficult to determine, as gallstones are a disease that develops over years, and dietary habits are difficult to observe and describe over such a long period of time [8]. However, research points to several specific substances that have the effect of promoting or preventing gallstone formation. These factors are modifiable and changes to the everyday diet may help prevent stone formation, especially in patients at high risk for gallstones [9].

Epidemiology

The problem of gallstones affects about 10-15% of the adult population of Europe and the United States [10], making it one of the major health problems in Western countries. In the U.S. population, according to the study, about 6.3 million men and 14.2 million women aged 20-74 years have been diagnosed with gallbladder stones [11]. Possible genetic factors that increase the incidence of gallstones have also been identified [12].

Pathophysiology

The main pathogenetic factor in the development of cholelithiasis is the rapid increased secretion of hepatic cholesterol from liver into bile, the excessive secretion of bile mucin and bile stasis resulting from decreased gallbladder motility [13, 14, 15]. These processes lead to supersaturation of bile with cholesterol and crystallization of cholesterol in bile. Genetic factors play a major role in the risk of lithiasis [16]. However, one of the biggest risk factors remains modifiable environmental factors, including diet. Diet plays a significant role in the onset and development of gallstones. In Western cultures, more than 75% of gallstones are composed of cholesterol [15], and their formation is associated with impaired cholesterol metabolism caused by conditions such as obesity [6], dyslipidemia, type 2 diabetes, and metabolic syndrome [17, 18]. Increased body weight due to excessive caloric intake can double the risk of developing symptomatic gallstones [19], and obesity by increasing the incidence of hypercholesterolemia predisposes to gallstones [20].

Methods

In this paper, we review the current knowledge on the influence of dietary components on the risk of occurrence of gallstones. We selected articles with an unlimited search period in several databases, including PubMed, Google Scholar, and Web of Science. In the review we only included articles written in English and with full text available. No restrictions were made based on article type.

Energy intake, obesity

Case-control studies have confirmed the increased risk of gallstones associated with a high-calorie [21], increased fat intake, and saturated and monounsaturated fatty acids [22]. This was also confirmed by the Nurses' Health Study [23], which included a large number of women aged 34 to 59. It showed that a high-calorie diet increases the risk of symptomatic lithiasis compared to a low-calorie diet. Similar data was obtained from a French study of men who took

in more than 2,500 kcal per day [24]. A similar Spanish study showed increased caloric intake in men with gallstones compared to a healthy control group [25].

Obese subjects show increased cholesterol secretion into the bile, resulting in a cholesterol-saturated bile and subsequent crystallization of cholesterol, which aggregates into increasingly large clusters until macroscopic stones are formed [26]. It has been estimated that each excessive kilogram of body weight contributes to the production of an additional 20 mg of cholesterol [27]. A BMI above normal (i.e., >25 kg/m2) is a known promoter of lithiasis, especially in women [28] - an increase of 7% in the risk of symptomatic lithiasis has been shown [29]. Abdominal obesity compared to gluteal-femoral obesity increases the risk of lithiasis.

Obesity is also associated with hypertriglyceridemia and this predisposes to lithiasis because of increased mucin secretion [30]. In addition, subjects who are overweight or obese are more likely to present with increased gallbladder volume and decreased postprandial gallbladder emptying rate, which further promotes lithiasis [31]. Abnormal bladder motility is already present in children and adolescents with elevated BMI and is exacerbated in obese adults [31].

Typically, reducing body weight reduces the risk of gallstones, but there is an increased risk of gallstones in obese patients who reduce weight rapidly by changing their diet to a very low-calorie (<800 kcal/day) [32, 33] and patients undergoing bariatric surgery [34, 35]. Studies show that the risk is lower when eating a low-calorie diet compared to a very low-calorie diet as it slows weight loss [36].

Carbohydrates

Increased intake of refined sugars (derived from plants such as beets, sugar cane, corn) may be a risk factor for lithiasis in both men and women [37]. This occurs by increasing insulin secretion in response to increased levels of glucose from consumed carbohydrates, which in turn causes increased cholesterol synthesis in the liver and secretion of increased amounts of cholesterol into the bile, consequently increasing the saturation of bile with cholesterol and leading to the formation of gallstones [38, 39]. On the other hand, reducing the supply of high-calorie foods, especially those rich in carbohydrates, has a beneficial effect on body weight and reduces the risk of gallstones.

A study conducted on Italian non-diabetic patients additionally showed that increased insulin levels are a distinct factor in the occurrence of gallstones [40]. It showed a more than twofold increase in risk in those with serum insulin levels in the highest quintile [40]. In addition, insulin

resistance increases the risk of lithiasis. Elevated HOMA was more common in those with gallstones than in those without gallstones [41]. Another ultrasound-utilizing study conducted with pregnant women found an increased risk of lithiasis due to high carbohydrate intake [42]. Carbohydrate consumption decreases the volume of the gallbladder and increases the mass of the cholesterol crystals [37].

High fructose intake influences stone formation probably through the formation of insulin resistance, visceral obesity and metabolic syndrome [43, 44]. Fructose intake also contributes in formation of hepatic steatosis, as a result of increased triglycerides, and bile stasis in the gallbladder. These factors increase the risk of bile sludge and gallstones, and this association occurs independently of total dietary carbohydrate intake [42]. Other sources claim that fructose only in very high concentrations affects lipid changes in plasma, liver and bile [45]. The differences in study results appear to be due to genetic differences and, as a result, different metabolic responses to fructose concentrations [46]. Studies also often do not take into account the dose of fructose that causes metabolic effects [47].

Elevated serum triglycerides are often found in patients with obesity and elevated BMI. Hypertriglyceridemia reduces sensitivity to cholecystokinin, which can slow gallbladder emptying. Hypertriglyceridemia and reduced HDL levels increase the incidence of cholelithiasis in men and women [55]. A diet aimed at increasing serum HDL concentrations may have a protective effect by increasing hepatic synthesis of cholic acid and chenodeoxycholic acid, which increase the solubility of cholesterol in bile [56, 57].

Fats, fish oil, n-3 PUFA

Monounsaturated fats reduce the risk of gallstones [48, 49]. It is possible that their positive effect is the action of increasing the mobility of the gallbladder, which prevents bile stasis [50]. Nuts also may have a protective effect on the incidence of gallstones [51]. Consuming nuts five or more times a week for men reduced the risk of lithiasis by about 30% [52].

Regular consumption of olive oil can be prophylactic [53]. In a Spanish study, a diet enriched with extra-virgin olive oil or sunflower oil for one month showed no effect on cholesterol saturation, which may be due to the pre-existence of stones before the study began. People with gallstones taking olive oil, but not sunflower oil, showed a decrease in postprandial bile cholesterol saturation [54]. This result suggests that the type of fat consumed matters regarding bile composition.

Reduced bile cholesterol saturation and reduced lithogenicity were observed in patients with gallstones who were given n-3 polyunsaturated fatty acids (PUFA) from fish oil. Supplementation with 11 grams of n-3 PUFA per day for 6 weeks was shown to improve bile composition in women undergoing weight reduction [58]. Supplementation with n-3 PUFA had a beneficial effect on bile cholesterol saturation, but did not affect cholesterol crystallization time [59]. Fish oil supplementation reduced hypertriglyceridemia and improved gallbladder motility without a negative effect on biliary cholesterol saturation. Improvements in vesicle motility were observed after exogenous cholecystokinin infusion and postprandially. This suggests an improvement in follicle sensitivity to cholestyramine after fish oil supplementation [60].

Fats of animal origin, or saturated fats, are associated with a higher risk of gallstones and symptomatic cholelithiasis [61, 62]. Similar conclusions were reached in a study detecting lithiasis by ultrasonography [63], in which patients with lithiasis had a documented high intake of saturated fats compared to a control group.

The results of studies targeting the correlation of high dietary cholesterol intake and gallstone risk remain inconclusive. High cholesterol intake is thought to increase the risk of gallstones [64], but at the same time, exposure to low cholesterol intake may lead to increased cholesterol synthesis and secretion into the bile, causing it to become saturated with cholesterol and increasing the risk of cholesterol stones [65]. These differences may be due to genetic predisposition and diet composition.

Low Fiber

Reduced dietary fiber intake has a negative effect on colonic motility and increases the production of secondary fatty acids, which have been shown to promote gallstone formation. Fiber has a greater impact on the risk of gallstones in overweight and obese people compared to people of normal weight [66]. Patients with gallstones consume less fiber, which may increase the risk of gallstone disease [67]. Many of the components contained in vegetables and fruits can reduce the risk of gallstones [68]. High fiber intake is recommended to reduce the risk of symptomatic cholelithiasis requiring cholecystectomy [69].

Vitamin C

Vitamin C regulates hepatic cholesterol metabolism by promoting the conversion of cholesterol to bile acids through hepatic 7alpha-hydroxylation. Vitamin C deficiency increases the risk of

stone formation and vitamin C supplementation prevents stone formation in animal studies [70, 71]. Clinical surveys also indicate an association of vitamin C deficiency with increased risk of stones [72, 73] and required cholecystectomy [74]. Dietary vitamin C supplementation of 2 g per day for 2 weeks in animal model prolongs cholesterol crystallization, affecting the qualitative composition of bile and increases the concentration of phospholipids [75].

Meal Patterns

Meal patterns are of importance in the risk of gallstone formation. Frequent meals and avoidance of extended periods of fasting reduces the risk of stone formation [76]. This is associated with regular emptying of the gallbladder after meals, which reduces the periods with bile stasis in the gallbladder. Bile stasis is one of the main pathogenetic processes leading to stone formation.

Animal and vegetable protein

There is not much research pertaining to the effect of type and amount of protein on the development of gallstones. A lower incidence of lithiasis has been observed in people consuming a vegetarian diet [77, 78], but specific aspects of the vegetarian diets and their effect on the disease have not been studied. The results of studies on the effect of protein intake on lithiasis have varying conclusions. Prospective Nurses' Health Study have shown women with an increased vegetable protein supply had a reduced risk of symptomatic gallstones and a lower risk of cholecystectomy [79, 80]. In contrast, other studies [79, 81] found no association between protein intake and gallstones. A more recent study observed the effect of protein intake pattern on lithiasis, using a breakdown of protein by amount and type (animal or vegetable) among postmenopausal women [82]. Women with intake of >24 g/d of plant protein had a lower risk of lithiasis compared to women with intake of <16.3 g/d of plant protein. The conclusion of this study was that plant protein reduces the risk of lithiasis among postmenopausal women. Looking at the results of the studies described above, the origin of the protein (animal vs. plant) seems to matter more than the amount of protein intake.

Coffee

Some studies suggest a reduced risk of stone formation through caffeine consumption [84, 85, 86]. Other studies have found no clear effect of caffeine on gallstone formation [87, 88]. Caffeine's proposed action is to reduce hepatic cholesterol synthesis [89] and secretion and

increase motility [90]. One Swedish study found an association between coffee consumption and a reduction in the risk of cholecystectomy; however, the positive effect was only in premenopausal women and those on hormone replacement therapy, and did not occur in postmenopausal women or men [91]. The effect of coffee consumption on cholecystectomy appears to be dependent on the presence of female sex hormones. In view of inconsistent findings from various studies, the true effect of caffeine in cholecystolithiasis is not fully known. An additional difficulty in assessing the effect of caffeine is the different habits and amounts of caffeine consumed (both in coffee and in caffeinated drinks) depending on personal preferences but also on the culture of the countries concerned.

Alcohol

Alcohol consumption has an inhibitory effect on the conversion of HDL cholesterol to LDL cholesterol [92], this action results in increased HDL cholesterol [93, 94], which in turn leads to reduced cholesterol saturation in gallbladder bile [95]. Alcohol in small doses increases whole-gut transit time [96]. Alcohol may therefore reduce the risk of gallstones. The Nurses' Health Study found that compared with abstinence, regular alcohol consumption may have a protective effect on gallstone formation [23]. Another study showed a linear decrease in risk associated with consuming 28-40 grams of alcohol per day compared to consuming <28 grams of alcohol per day[97]. Not all studies support these findings [88, 98], and the very topic of alcohol consumption as a positive factor is controversial, as increased consumption of alcoholic substances increases the risk of chronic liver diseases, including cirrhosis, and cirrhosis is associated with an increased risk of pigment stones [99, 100].

Conclusions

Gallstones, as a common phenomenon in the population, are of a growing interest in this disease. Available information on the pathogenesis, epidemiology and cost to the health care system explains the importance of further understanding of risk factors and developing treatments for gallstones. The formation of gallstones is associated with a multitude of both modifiable and non-modifiable factors. Non-modifiable factors include among others individual anatomy, gender, age and genetic factors. Modifiable factors primarily involve lifestyle and environmental factors. Currently, cholelithiasis seems to be treated mainly when symptoms of the disease are present, and treatment is mostly surgical. However, attention can also be paid to primary prevention, such as dietary changes, lifestyle changes. These changes

in modifiable risk factors can reduce the incidence of gallstones and costs to the health care system. Lifestyle changes, including changes to the daily diet, should target factors that affect metabolic pathways that lead to gallstones. Substances that increase the risk of gallstone formation can be distinguished, such as a high-calorie diet, reduced dietary fiber intake, high carbohydrate and fat intake. There are also substances that have a protective effect on the risk of developing gallstones, for example, consumption of olive oil, consumption of monounsaturated fatty acids, fiber, vitamin C supplementation, frequent consumption of nuts and moderate consumption of alcohol. In order to guide proper beneficial dietary changes, patients should be thoroughly informed and educated about pathogenetic factors and the impact of specific nutrients on the development of gallstones. Continuing to learn about new risk factors and deeper analysis of the impact of already known factors will allow us to better understand, better treat gallstones and, above all, allow us to understand how to better prevent the disease.

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