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The Role of Diet in the Pathogenesis of Cholesterol Gallstones

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Abstract

Cholesterol gallstone disease is a major health problem in Westernized countries and depends on a complex interplay between genetic factors, lifestyle and diet, acting on specific pathogenic mechanisms. Overweigh, obesity, dyslipidemia, insulin resistance and altered cholesterol homeostasis have been linked to increased gallstone occurrence, and several studies point to a number of specific nutrients as risk- or protective factors with respect to gallstone formation in humans. There is a rising interest in the identification of common and modifiable dietetic factors that put the patients at risk of gallstones or that are able to prevent gallstone formation and growth. In particular, dietary models characterized by increased energy intake with highly refined sugars and sweet foods, high fructose intake, low fiber contents, high fat, consumption of fast food and low vitamin C intake increase the risk of gallstone formation. On the other hand, high intake of monounsaturated fats and fiber, olive oil and fish (ω−3 fatty acids) consumption, vegetable protein intake, fruit, coffee, moderate alcohol consumption and vitamin C supplementation exert a protective role.

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CONFLICT OF INTEREST

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The effect of some confounding factors (e.g., physical activity) cannot be ruled out, but general recommendations about the multiple beneficial effects of diet on cholesterol gallstones must be kept in mind, in particular in groups at high risk of gallstone formation.

Keywords

Caloric intake; diet; fibers; macronutrients; obesity; weight loss

1. INTRODUCTION

Gallstone disease (GSD) is a major health problem in developed countries [1–5] and this trend includes Europe as well [6]. The prevalence of gallstones ranges from 10 to 20% in the adult populations [2, 7–9], which renders cholelithiasis a very common disease. It is estimated that about 6.3 million men and 14.2 million women aged 20 to 74 years suffer from gallbladder disease in the USA [8], and such scenario requires high costs for treating gallstones (about $4–6.2 billion [9, 10]), particularly if surgical complications occur [11].

Pathogenic factors include excessive and fast mobilization of body cholesterol into bile through the liver (with subsequent supersaturation of bile with cholesterol), increased cholesterol crystallization in gallbladder bile, hypersecretion of biliary mucin, and decreased gallbladder motility [12–23]. Genetic factors are certainly of major importance in the risk of cholesterol gallstones, and a series of genes have been identified, which are able to promote gallstone formation and growth [24]. However, the analysis of twin pairs showed that genetic factors are estimated to account for only about 25% of gallstone risk [25], underlying the importance of environmentally related modifiable factors. Several observations have found that a complex genetic basis could play a key role in determining individual predisposition to develop cholesterol gallstones in response to environmental stimuli [26–29], including diet. Dietary habits control quality and quantity of energy intake and play a key role in the onset and further development of metabolic disorders.

In Westernized countries the 75% of gallstones are composed of cholesterol [30–33], and their origin has common pathogenic links with broad metabolic abnormalities characterized by altered cholesterol homeostasis, such as obesity, dyslipidemia, type 2 diabetes [2, 34], and the metabolic syndrome [35–40]. In fact, the majority of components of the metabolic syndrome (visceral adiposity, insulin resistance/diabetes mellitus, dyslipidemia [41–43]) Fig. (1) have been associated with an elevated occurrence of cholesterol gallstones and liver steatosis, which have been recognized as “fellow travelers” with this syndrome [41, 44].

Increased body size (*i.e.* BMI equal or greater than 25 kg/m^2) due to excessive energy intake could double the risk of symptomatic gallstones, as compared to a BMI of less than 25 kg/m^2[45], and obesity (*i.e.* a BMI equal or greater than 30 kg/m^2) strongly predisposes to gallstone formation [46] and increases the rate of cholecystectomy by increasing the risk of symptomatic gallstones [21, 23, 47–55].

Besides the amount of energy intake and metabolic alterations, it is difficult to adequately estimate the exact role played by specific nutrients in large population-based, long-term,

prospective epidemiological studies, since gallstone formation is a slow and complex multifactorial process requiring years, and dietary habits are difficult to be described with precision over such a long time span [56]. However, several studies pointed to a number of specific nutrients as risk- or protective factors with respect to gallstone formation in humans (Table 1). This list of factors supports the enormous rising interest in the identification of common and modifiable dietetic factors that put the patients at risk of gallstones or that are able to prevent gallstone formation and growth, particularly in specific high-risk groups [57].

2. DIET AS A RISK FACTOR FOR GALLSTONE OCCURRENCE

It has been observed that the typical Westernized diet (hypercaloric, with highly refined sugars, low content of fiber, high-lipid) increases the likelihood of gallstone disease [58].

2.1. Energy Intake, Obesity

A nested case-control study by questionnaires showed that increased risks for gallstone disease were associated with high intakes of energy, total fat and saturated and monounsaturated fatty acids [59]. This finding partially confirms previous results from a large cohort study *i.e.* the Nurses' Health Study involving 88,837 women aged between 34 to 59 years. The risk of symptomatic gallstones was greater in the highest (1960 kcal/day) than in the lower quintile (1130 kcal/day) of energy intake, and the overall risk of 1.5 increased to 2.1 in lean women [48]. Similar findings have been obtained in a French study showing that the risk of gallstone disease increased in men consuming more than 2500 Kcal per day [60] and in a Spanish study where gallstone patients had a greater consumption of total calories and fats, spent less time walking and slept more than healthy controls [61].

Increased BMI *per se* acts as a well known risk factor for gallstone disease (particularly in women [62]), with a 7% [62] to 8% [45] rise in the occurrence of symptomatic gallstones with each BMI unit. The risk was 17% in genetically determined BMI [62] and increased with a high waist circumference and central adiposity [45], both factors frequently associated with dyslipidemia (particularly hypertriglyceridemia and low high-density lipoprotein (HDL) concentrations [63]).

These alterations can influence the key steps involved in the pathogenesis of cholesterol gallstones, such as increased biliary cholesterol concentrations [64–66] and hypertriglyceridemia-induced secretion of gallbladder mucin [67]. Furthermore, subjects with overweight and obesity often display larger fasting gallbladder volumes and decreased postprandial gallbladder emptying, *i.e.* two conditions implying gallbladder stasis, which is a well-established promoting factor for gallstones [68–72]. Altered gallbladder motility is already present in obese children and pre-adolescents, and further deteriorates in obese adults [68, 73], leading to a high risk for gallstones. This trend is similar to other metabolic abnormalities linking childhood to adult obesity [74].

An increased risk of gallstone formation also exists in obese patients during rapid weight loss achieved by very-low-calorie diets containing less than 800 kcal per day [12, 14, 16, 75, 76] or undergoing bariatric surgery (*i.e.* currently the Roux-en-Y gastric bypass (RYGB) procedure [15, 17, 77–83]. This risk of gallstones is less with low-calorie diet (instead of

very-low-calorie diet) [76] because body weight loss is slower, *i.e.* max. 1.5 kg weekly [84–86].

2.2. Fast food, Westernized Diets, Fructose

The risk of gallstone disease appears to be also dependent on specific dietary components: consumption of fast food, at least once per week [62] and meat consumption [58, 61] have been identified as additional risk factors for symptomatic gallstones. In addition, high intake of refined sugars and sweet foods might represent risk factors for gallstone disease [87] in both genders [53, 61, 88–95]. The mechanism involves increased insulin levels, increased hepatic cholesterol synthesis and hypersecretion of cholesterol into bile [96, 97] leading to increased biliary cholesterol saturation [98]. These are key pathogenic mechanisms involved in cholesterol gallstone formation (1).

Moreover, insulin levels act as independent risk factor for gallstone formations, as shown in a large study on Italian subjects without diabetes. Serum insulin levels were associated with gallstones in multiple logistic regression analysis, when controlling for confounders (sex, age, body mass index and serum glucose concentrations) [99]. Of note, the risk of gallstones was more than doubled (2.66, 95%CI 1.04–6.72) in subjects falling in the highest quintile of serum insulin [99]. Insulin resistance has an independent effect on the risk of gallstone formation: in a large cohort of non-diabetic subjects the prevalence of elevated HOMA index was higher in patients with gallstones as compared to those without stones; only age and HOMA were independent predictors of gallstones, regardless of obesity by multiple logistic regression analysis [100].

The effects of a high carbohydrate and fructose intake on gallstone risk have been confirmed by a large ultrasonographic study in pregnant women [101]. Women were assessed for dietary habits and the risk of incident biliary sludge/gallstones during pregnancy was significantly higher among women in the highest quartile of total carbohydrate intake versus women in the lowest quartile. High intake of fructose (but not sucrose, lactose or galactose) was associated with an increased risk of incident sludge/gallstones, and this association was independent from total carbohydrate intake [101]. The lithogenic effect of fructose appears to depend from several concurrent mechanisms, as induction of insulin resistance, visceral adiposity, metabolic syndrome [102–111], fatty liver secondary to accumulation of triglycerides [106, 112], and gallbladder stasis [87]. The deleterious effects of excess fructose consumption can cause gastrointestinal symptoms due to intolerance and intestinal fermentation by resident intestinal microbiota [113], and can affect several liver metabolic pathways (*i.e.* gluconeogenesis, synthesis of glycerol which is the backbone of triglycerides, and *de novo* lipogenesis, where fatty acids are provided for triglyceride assembly [64]) Fig. (2).

2.3. Low Fiber, Trans-Fats, Low Vitamin C

Gallstone patients consume less fiber than controls [61], and low fiber intake might increase the risk of cholesterol gallstones. The mechanism involves a negative effect on colonic motility, and increased production of secondary (lithogenic) bile acids, *i.e.* deoxycholic acid and lithocholic acid [114, 115] Fig. (3). A negative effect is also attributed to the

consumption of fats of animal origin. Eating all visible fat on the meat and using butter were positively associated with cholelithiasis [116]. In French patients, a direct relationship between total and saturated fat intake and gallstone disease has been described [60].

An high intake of saturated fats and refined sugars has been also documented in subjects from Southern Italy with incident gallstones (detected by ultrasound) as compared to controls [91]. It has been reported that diet with high content of trans fatty acids might increase the cardiovascular risk [117, 118] and might also predispose to the formation of cholesterol gallstones [119].

Dietary vitamin C might also play a key role, since vitamin C modulates the hepatic and biliary pathways of cholesterol homeostasis by promoting the conversion of cholesterol into bile acids through liver 7α-hydroxylation [120, 121]. A deficiency of vitamin C has been associated with an increased risk of cholesterol gallstone formation [122]. Vitamin C deficiency promotes gallstone formation while vitamin C supplementation prevents lithogenesis in the animal model [123–126]. Clinical surveys found a positive relation between low vitamin C consumption and risk of gallstone formation, gallbladder disease [122, 127, 128], and cholecystectomy [129]. The supplementation of diet with vitamin C (2 g per day over 2 weeks) in humans prolongs the cholesterol crystallization time due to qualitative changes of bile acid composition and increased phospholipid concentrations in bile [130]. An observational study by ultrasonography showed that gallstone prevalence was half in subjects with regular intake of vitamin C (powder, tablets or capsules) as compared to those not taking the vitamin [131].

2.4. High Legume Intake

Some populations such as Amerindians Mapuche and Pima Indians consume a diet based on high legume intake (beans) which represents a risk factor for cholesterol gallstones [56, 132, 133]. The mechanism implies the decrease of total and very low density lipoprotein cholesterol concentrations in serum, and a high biliary cholesterol output [134]. Beans, in fact, contain the plant steroids saponins, which are able to increase biliary cholesterol secretion and crystallization [135].

3. DIET AS A PROTECTIVE FACTOR FOR GALLSTONE OCCURRENCE

3.1. Meal Patterns

Frequent meals and avoidance of prolonged fasting periods act as protective factors against the formation of gallstones [90]. A regular gallbladder emptying follows meal stimulation and this physiological neurohormonal response decreases prolonged gallbladder stasis (a key factor involved in gallstone pathogenesis [136]).

3.2. Fats, Fish Oil, n-3 PUFA

High intake of monounsaturated fats and fibers from cellulose is inversely associated with the risk of gallstone formation [91]. Long-term intake of cisunsaturated and monounsaturated fats had a protective effect in men studied in a prospective population-based study [137]. Nuts can also be protective against gallstone disease [138, 139].

Monounsaturated fat appear to increase gallbladder motility avoiding bile stasis in the gallbladder [140]. The mechanism might involve the fat-dependent stimulation of galbladder contraction, since an appropriate content of fat (at least 7–10 g per day) in a very-low-calorie diet is able to improve gallbladder motility and prevent bile stasis [76, 141–143]. Regular consumption of olive oil which is enriched with monounsaturated plus polyunsaturated omega-6 fatty acids appears also to protect against gallstones [116]. In a small study from Spain, dietary supplementation with virgin olive oil (40 g per day of monounsaturated fat in 9 gallstone patients) or sunflower oil (20 g per day of polyunsaturated fat in 9 gallstone patients) for one month did not affect cholesterol saturation or bile acid species in the gallbladder bile. However, the cholesterol saturation index of hepatic bile decreased significantly in the postprandial period in patients given the olive oil diet but not in the group supplemented with sunflower oil, suggesting that type of dietary fat can influence bile composition in humans [144].

Low HDL cholesterol and high triglyceride concentrations have been associated with a high incidence of gallstones either in both genders [145] or in men only [146]. Dietary habits promoting an increase in serum HDL levels can therefore protect against gallstones, since they are able to increase the hepatic synthesis of primary bile salts (*i.e.*, cholic acid and chenodeoxycholic acid) and, in turn, to ameliorate biliary cholesterol solubilization [147, 148].

Impaired gallbladder emptying is found in patients with hypertriglyceridemia, likely due to decreased sensitivity to the endogenous gastrointestinal hormone cholecystokinin [149] (Fig. (4) Fish consumption might be inversely correlated with the occurrence of cholesterol gallstones [127, 150, 151], although not all studies are consistent [152]. In a study from Netherlands, fish oil supplementation was given to patients with hypertriglyceridemia for seven weeks (total 5 g per day ω−3 fatty acids mainly as 1.9 g of eicosapentaenoic acid C20:5 and 1.1 g of docosahexaenoic acid C22:6) (Fig. (5). Fish oil treatment decreased hypertriglyceridemia and was associated with improved gallbladder motility in response to exogenous infusion of cholecystokin and postprandially, without adversely affecting biliary cholesterol saturation. The results of this study suggest amelioration of gallbladder sensitivity to cholecystokinin upon fish oil supplementation [149]. Biliary enrichment in phospholipids and (less hydrophobic) ω−3 fatty acids might also play a role [153]. In fact, dietary supplementation with 1.5 g ω−3 fatty acids per day over six weeks decreases biliary cholesterol saturation and lithogenicity, without modifying phospholipid and bile acid composition. A similar effect was noted in gallstone patients supplemented with dietary fish oil n-3 polyunsaturated fatty acids (PUFA), in spite of unchanged cholesterol crystallization time [154]. Furthermore, oral supplementation with 11 g n-3 PUFA per day for 6 weeks has been demonstrated to ameliorate bile composition and to maintain cholesterol saturation index and cholesterol crystallization time of women undergoing rapid weight loss on hypocaloric diet (1,200 kcal per day) [155]. The beneficial effects of n-3 PUFA might involve fatty acid composition in bile and enrichment with the above mentioned eicosapentaenoic acid- and docosahexaenoic acid-containing phospholipids at the expenses of linoleic- and arachidonic acid-containing species. A fat-dependent effect on gallbladder contraction is also likely [155].

3.3. Vegetables, Vegetarian Diets

Vegetable protein intake might also be beneficial: the Women's Health Initiative was a large observational study in postmenopausal women and showed that subjects in the highest quintile of energy-adjusted vegetable protein intake (>24 g/d) had a lower risk of gallbladder disease, as compared with those in the lowest quintile (<16.3g/d) [156]. The Nurses' Health Study reported a decreased risk for cholecystectomy for fruits and vegetables in general as well as for individual groups of green leafy vegetables, citrus fruit and vitamin C-rich fruits and vegetables [157]. The vegetarian diets might also be beneficial because of a secondary effect inducing a lower BMI [158]. Previous studies in different populations, however, showed either protective [159–163] or no effect of vegetarian diets on gallstones [133, 152, 164]. A recent study reported an 8% prevalence of gallstone disease in 1,721 Taiwanese vegetarians of both sexes. Risk factors predicting gallstone disease in vegetarians were age and total bilirubin level in men, and age, BMI, and alcohol consumption in women. Thus, many previously identified risk factors for general population does arecthe observation that dietary fiber supplementation in obese patients undergoing diet-induced weight loss is able to prevent gallstone formation [166]. On the other hand, a reduced intake of fiber has been identified as a risk factor during weight loss in a study with 171 obese patients undergoing bariatric surgery, not taking ursodeoxycholic acid and monitored for 180 days. After surgery, patients who developed gallstones had a significantly ($P<0.001$) lower consumption of fiber (4.8 ± 3.2 g/day), as compared with gallstone-free subjects (6.9 ± 3.4 g/day) [167].

3.4. Coffee

The effect of caffeine is still controversial, since some [77, 151, 168–171] but not all [150, 164, 172] studies suggest a potentially protective effect on gallstone formation. The effect is mainly mediated by the decreased hepatic synthesis and secretion of cholesterol [173, 174] and a positive effect on gallbladder [175, 176] and intestinal [177] motility. Contradictory results, however, might be related to different drinking patterns of coffee and other caffeinated soft drinks in different countries. A sex hormone-related effect is also possible, since a prospective study in a large cohort of Swedish subjects demonstrated an inverse association between coffee consumption and the risk of cholecystectomy in premenopausal women and in women who used hormone replacement therapy, but neither in other women nor in men [178].

3.5. Alcohol

Alcohol intake influences cholesterol homeostasis and beneficial effect on the risk of cholesterol gallstones are possible. Alcohol inhibits the cholesteryl ester transfer protein (CETP)-mediated conversion of HDL into low-density lipoprotein (LDL)-cholesterol [179]. This step is followed by increased HDL cholesterol concentrations [147, 180, 181] which are inversely correlated with biliary cholesterol saturation [147, 148]. Small doses of alcohol also stimulate gallbladder contractility through increased cholecystokinin release [182, 183].

Such general pathophysiological effect of alcohol on biliary function need clinical confirmation. The Nurses' Health Study cohort [48] suggests that regular alcohol consumption (as compared with abstention) might have a protective effect on gallstones; indeed an alcohol intake larger than 5 g per day was associated with decreased incidence of

symptomatic gallstones. Later studies demonstrated an inverse relation between consumption of different alcoholic beverages (wine, beer, liquors) and the risk of cholecystectomy (76), while a prospective study found that frequent and moderate alcohol intake reduces the risk for symptomatic gallstones, as compared to infrequent or episodic alcohol intake (194). Furthermore, a protective effect of small doses of alcohol (particularly in men) was documented in the cohort from the European Prospective Investigation into Cancer-Norfolk (EPIC-Norfolk). In this study, every unit of alcohol consumed per week decreased the risk of symptomatic gallstones by 3% [45].

Findings from the EMIL study also showed a protective effect, starting from a consumption of 21–40 g alcohol per day [164]. The topic, however, is controversial in many respects: not all studies have confirmed the protective effect of alcohol on gallstone disease [160, 172, 184], while others find some protection with elevated doses of alcohol consumption [139, 164, 185]. Excessive alcohol consumption, by contrast, increases the risk of chronic liver injury and cirrhosis, a condition associated with an increased risk of (pigment) gallstones [186, 187].

CONCLUSION

The formation of cholesterol gallstones derives from a complex interplay of genetic factors with environmental stimuli, through well-known pathogenic mechanisms. The role of genes, however, seem to be of lower epidemiologic importance, as compared with modifiable environmental factors affecting potentially modifiable mechanisms as cholesterol synthesis by the liver and secretion into bile, bile composition, cholesterol aggregation in the gallbladder, fasting and postprandial gallbladder motility. Lifestyle and dietary factors, in particular, might either indirectly (*e.g.*, inducing overweight, obesity, insulin resistance and the metabolic syndrome) or directly (*e.g.* dietary content in fiber and specific macronutrients, vitamin C) interfere with the pathogenesis of cholesterol gallstones acting on common pathogenic pathways (Fig. 6).

Factors linking dietary habits to gallstone disease have been broadly investigated and open the way to interventions acting on modifiable factors able to prevent gallstone formation, particularly in risk groups. Maintenance of ideal body weight by adequate energy intake and lifestyle interventions, appropriate weight loss among overweight and obese individuals and possible selection of specific nutrients might significantly lower the risk of gallstone disease also in the general population.

The ultimate efficacy of single dietary components or specific dietary regimens is prone to the effect of a number of confounding factors (*i.e.* genetic factors, physical activity, extra-dietary environmental influences). Thus, further studies are needed in order to better explore the role of diet as a whole, of dietary single components and on the role of gene/environmental interaction in the multifactorial pathogenesis of cholesterol gallstones. However, recommendations on beneficial effects of diet should be considered, particularly in high-risk groups and considering that cholesterol cholelithiasis is often part of the broader scenario linked with the metabolic syndrome [44].

ABBREVIATIONS

GSD	Gallstone disease
BMI	Body mass index
HDL	High-density lipoprotein

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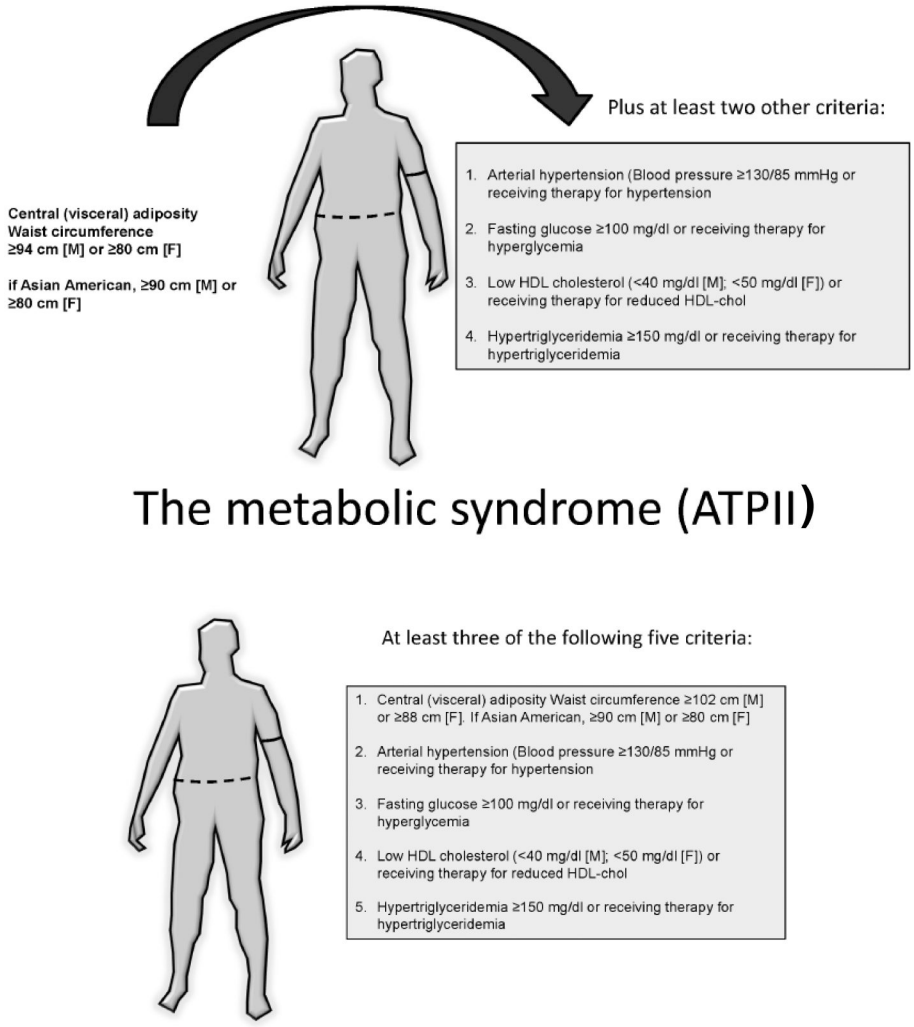

Fig. (1).

a) Definition of the metabolic syndrome according to the International Diabetes Federation (IDF) [42, 191]. b) Definition of the metabolic syndrome according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) [36].

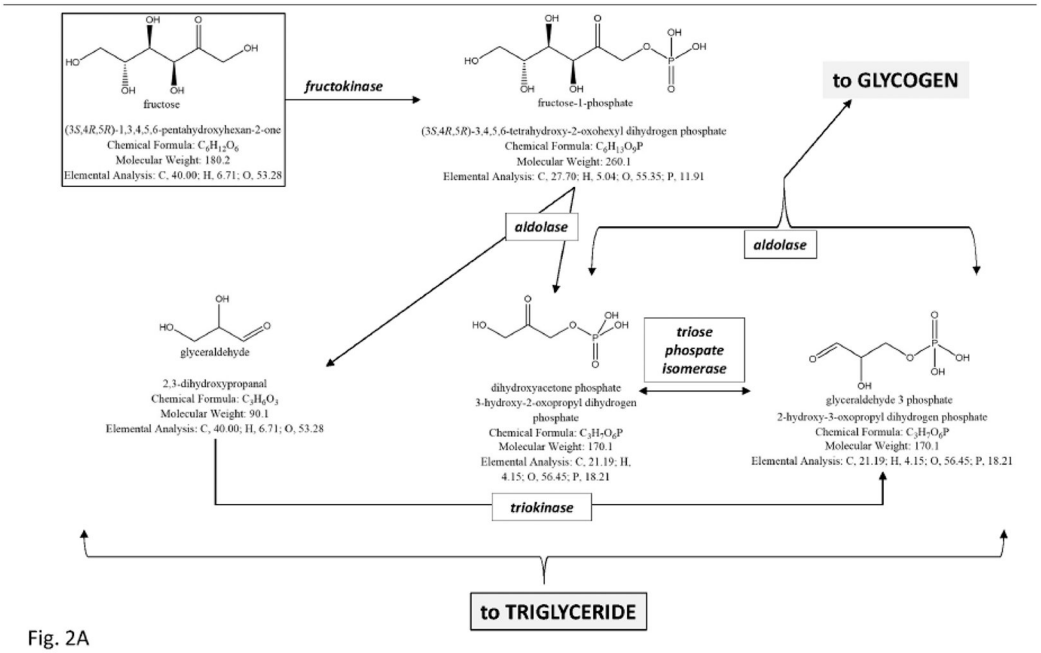

Fig. 2A

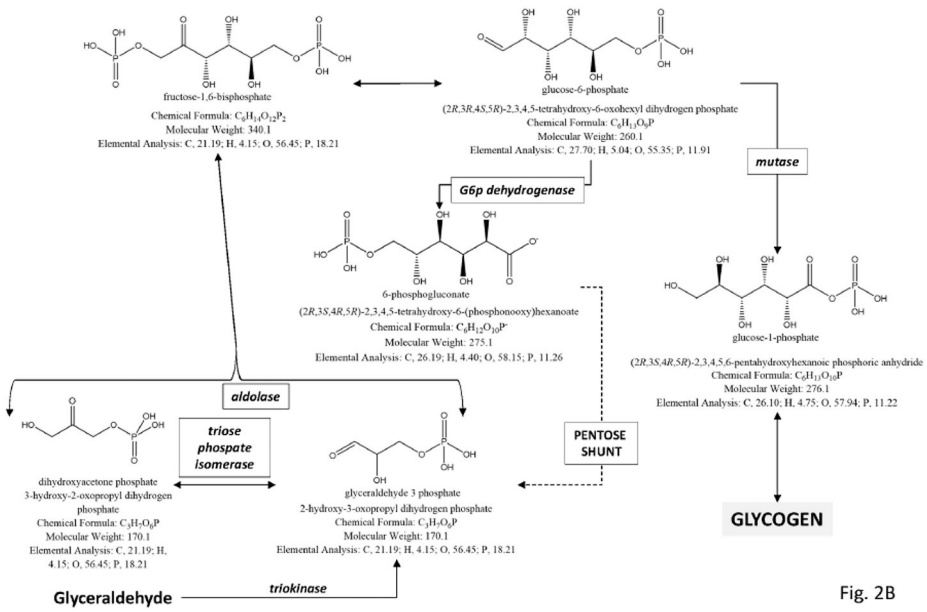

Fig. 2B

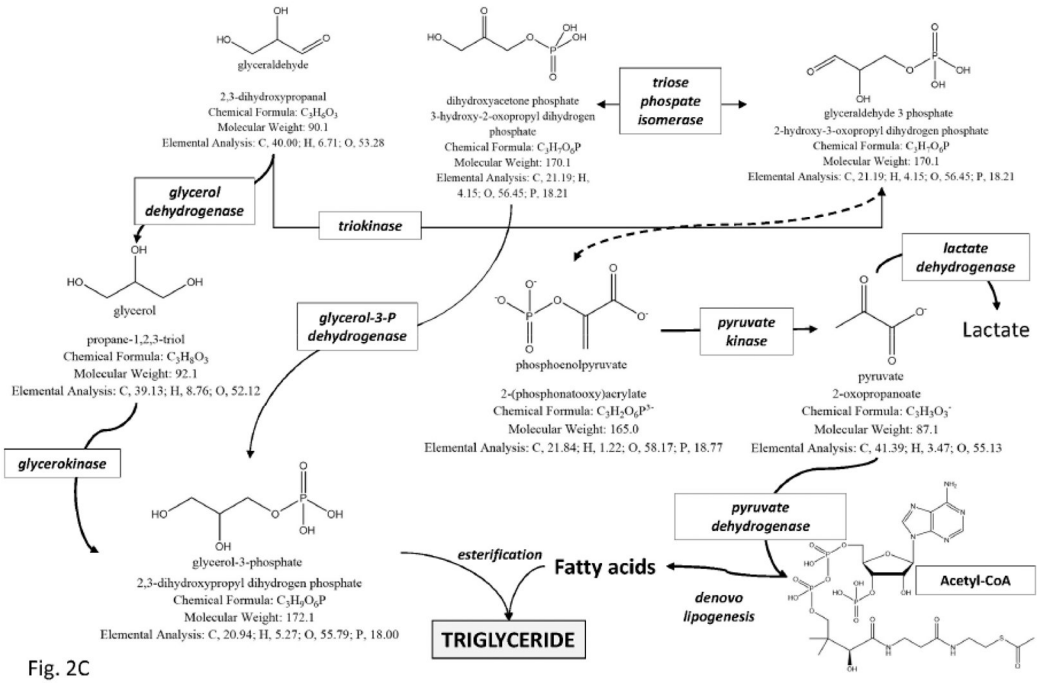

Fig. (2).

The potential deleterious metabolic effects of excess fructose consumption in diet are shown by the study of metabolic pathways of fructose in the liver. a) A first step is the conversion of fructose to fructose-1-phosphate and then to glyceraldehyde, dihydroxyacetone phosphate, and glyceraldehyde-3-phosphate. This first important step paves the way to the synthesis of glycogen and the synthesis of triglycerides, this latter pathway, a potential risk for liver steatosis. b) The conversion of fructose to glycogen is shown in the liver, anticipated by gluconeogenic precursors. Once liver glycogen is accumulated, the following pathway re-direct the fructose intermediates towards the synthesis of triglyceride. c) Conversion of fructose to triglyceride in the liver. Especially in the presence of excess fructose intake, the steps leading to glycerol synthesis and pyruvate synthesis are followed by construction of the backbone of triglyceride.

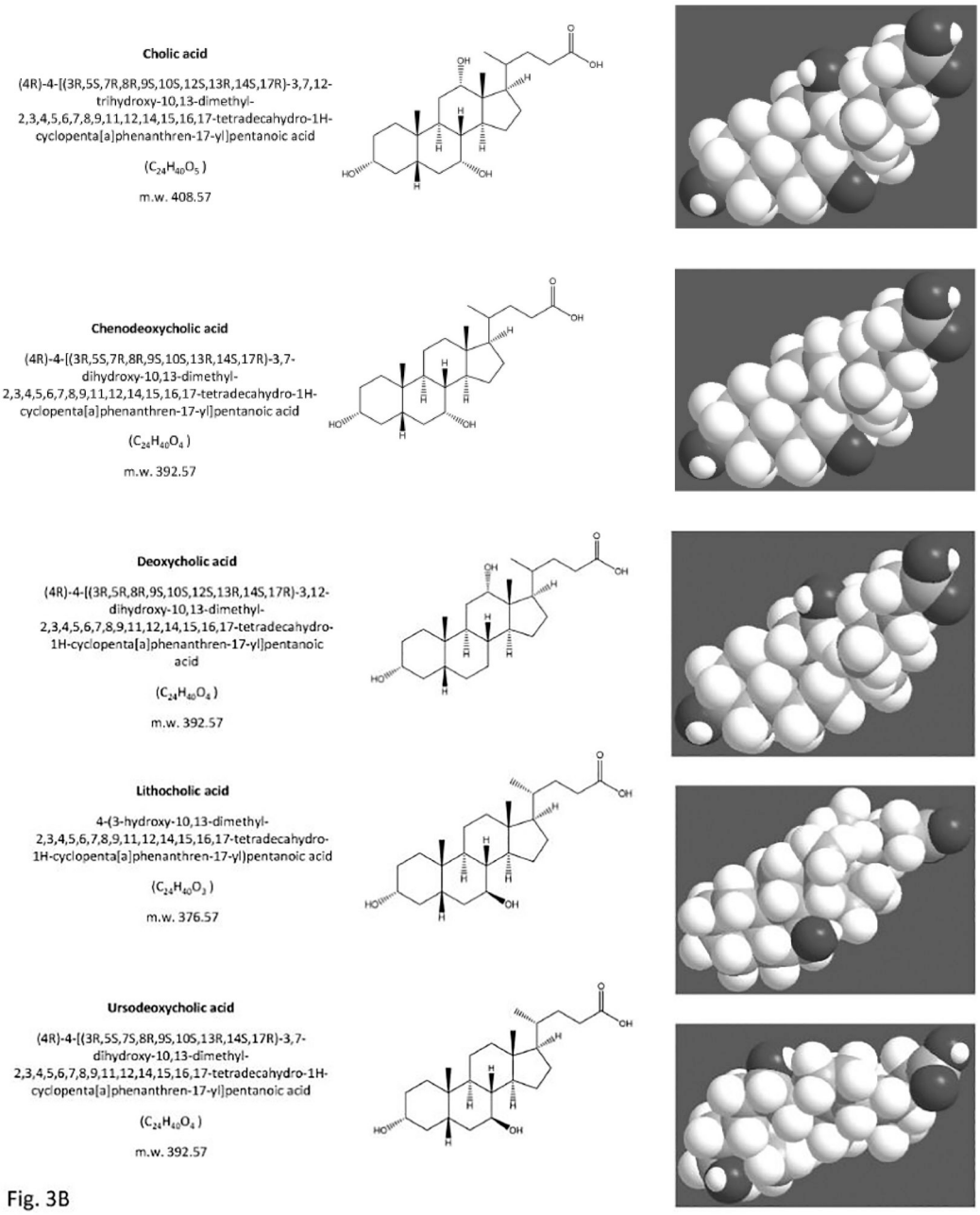

Fig. (3).

The structure of the primary bile acids, secondary bile acids and “tertiary” bile acid ursodeoxycholic acid. Bile acids are synthesized from cholesterol in the liver as soluble amphiphiles. The biliary bile acid pool in humans is mainly made of the primary bile acids, i.e. the 3,7,12-trihydroxy cholic acid and the 3,7-dihydroxy chenodeoxyholic acid. After being secreted in bile and entering the recirculation in the intestine, the primary bile acids are biotransformed by colonic bacteria into secondary bile acids, i.e. the 3,12-dihydroxy deoxycholic acid (from cholic acid) and the3- monohydroxy lithocholic acid (from chenodeoxycholic acid). “Tertiary” bile acids are the result of modification of secondary bile acids by intestinal flora or hepatocytes. These are the sulfate ester of lithocholic acid and the

3,7-dihydroxy ursodeoxycholic acid (UDCA), and the 7β-epimer of chenodeoxycholic acid. Bile acids are highly soluble, detergent-like amphiphilic molecules; the hydrophilic (polar) areas of bile acids are the hydroxyl groups and conjugation side chain of either glycine or taurine and their hydrophobic (nonpolar) area is the ringed steroid nucleus [64, 192].

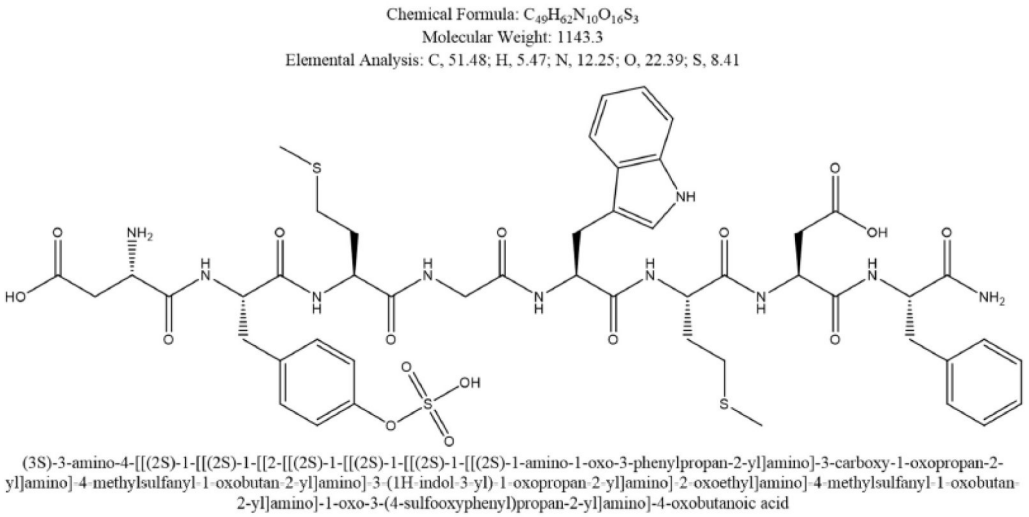

Fig. (4).

The structure of the potent gastrointestinal hormone cholecystokinin (CCK) acting on the smooth muscle contractility at the level of the gallbladder, upon fat stimulation in food [2, 193].The figure depicts the 8-amino acid C-terminal fragment of cholecystokinin, and also known as CCK-8. From National Center for Biotechnology Information. PubChem Compound Database; CID=9833444, https://pubchem.ncbi.nlm.nih.gov/compound/9833444 (accessed May 12, 2016).

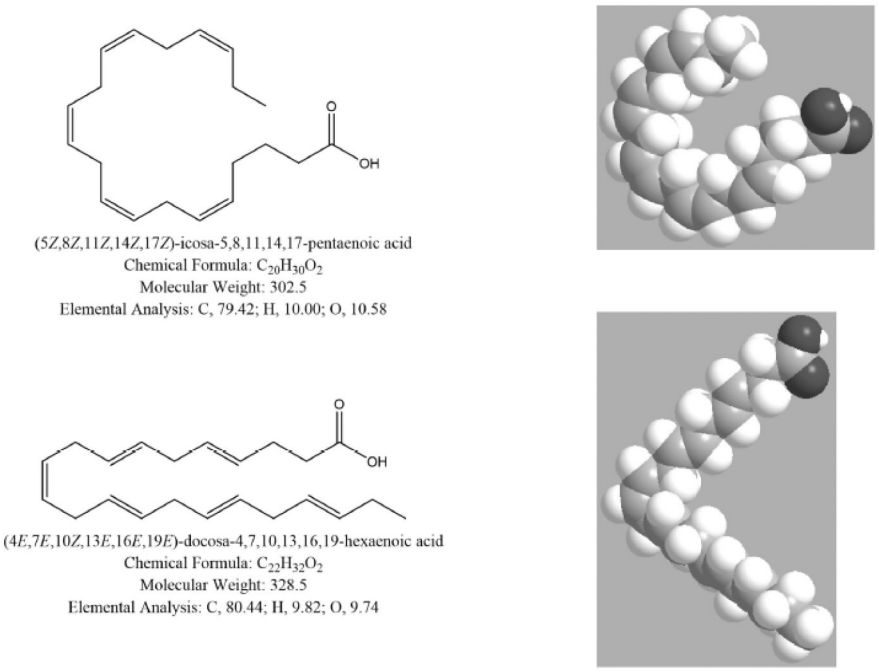

Fig. (5).

The structure of ω−3 fatty acids eicosapentaenoic acid (top) and docosahexaenoic acid (bottom).

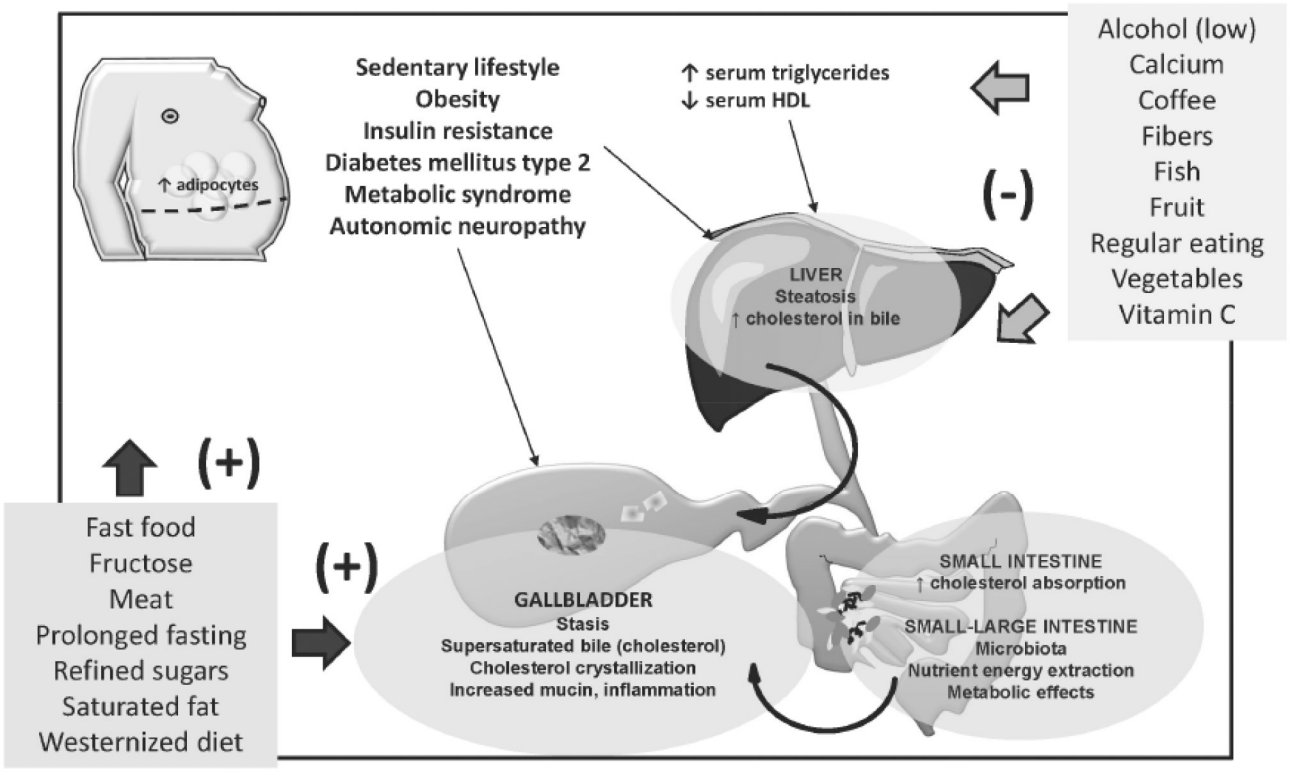

Fig. (6).

Dietary factors and lifestyles may act as risk factors (+) or protective factors (−) on typical pathogenic factors of cholesterol cholelithiasis, involving the liver, the intestine and the gallbladder.

Table 1.

Studies identifying dietary factors potentially able to promote or to prevent the formation of cholesterol gallstone in humans

PROMOTING FACTORS
Fast food [62]
Meat consumption, saturated fat [91, 127]
Hypercaloric diet [58, 91]
Prolonged fasting [90]
Refined sugars, high dietary carbohydrates* [53, 61, 88–95]
Low fiber intake [114, 115]
Very low calorie diets [12, 14, 16, 75, 76]
High fructose intake [87, 101]
High bean intake [132, 133]
Low vitamin C [61, 122, 128, 129, 131]
PREVENTING FACTORS
Monounsaturated fats, Polyunsaturated fats, Fiber from cellulose, Nuts [91, 137–140, 155, 188]
High-fiber and high-calcium diet [136]
Vegetables, fruit [62, 157, 189]
Moderate alcohol consumption* [45, 139, 152, 190]
Coffee, caffeine* [77, 151, 168–171]
Vitamin C supplement [91, 122–126, 130]
Regular eating pattern [90, 136]
Vegetarian diet* [158–163]
Sufficient fat in very-low calorie diet (7–10 g per day) [76, 141–143]
Fish, fish oil (PUFA)* [120, 141, 142, 145, 147[127, 150, 151, 153, 155]
Monounsaturated fats, Polyunsaturated fats, Fiber from cellulose, Nuts [91, 137–140, 155, 188]

Asterisk (*) indicates the existence of controversial studies; PUFA, polyunsaturated fatty acids