Nutritional Factors associated with Gallstones

Rakesh K Tandon, MD, PhD*; Sudeep Khanna, MD, DM

Abstract
Several epidemiological studies have shown that high intake of calories in the form of refined sugars and fiber depleted diets promote gallstone formation. Consumption of high total fat, high cholesterol and specific types of fat have only a limited role in the formation of gallstones. Prolonged periods of fasting as well as drastic dieting increase the lithogenicity of bile. Alcohol, coffee consumption and ascorbic acid have a protective role against the formation of gallstones.

Introduction
Cholesterol gallstones are a multifactorial disease influenced by a complex interaction of environmental and genetic factors that determine the precipitation of cholesterol in gallbladder bile. The most important pathophysiological mechanism involved in gallstone formation is an increased biliary secretion of cholesterol from the liver producing cholesterol-supersaturated bile. Diet not only increases the serum cholesterol but also increases biliary cholesterol secretion in association with genetic predisposition. Thus, the need to look at dietary factors influencing gallstone disease.

I. Role of increased calorie intake.
Sarles et al., first observed that calorie intake was significantly more in gallstone patients as compared with controls. Subsequently, we as well as others confirmed this association of increased calorie intake with gallstones.

Furthermore, at least two groups, ours and Scragg et al.'s observed that this association was more significant in younger patients than older patients with gallstone disease. The mechanism thought to be responsible for increased gallstones in patients with increased calorie intake is an increase in hepatic cholesterol secretion. Jorgensen et al. however, found no such association. Smith et al. and workers of a recent study of 152 patients gallstone disease from France showed a negative correlation between energy intake and presence of gallstones.

These discrepancies highlight the difficulties in assessing any dietary associations with a disease of long standing such as gallstone disease, as the intake prior to the onset of the disease is difficult to assess. Nor is it possible to know when exactly the disease started.

Role of Refined Carbohydrates: Most authors agree that over consumption of carbohydrates is a risk for cholelithiasis and the increased calories in patients with gallstone disease are due to excessive intake of refined sugars. Israeli population has a higher incidence of cholelithiasis as compared to Palestinians and this has been attributed to high consumption of sugar and dietary products by the Israeli population. Scragg et al. reported a doubling of risk of symptomatic gallstones if an equivalent of 40 gram of sugar per day was consumed from diet containing sucrose.

* Rakesh K Tandon; Professor and Head Department Of Gastroenterology, All India Institute of Medical Sciences, Ansari nagar, New Delhi-110029
Phone: 011-6594425,6867912
Fax: 011-68967912
E-mail: rakesh tandon@hotmail.com
By contrast, the amount of sugar originating from other nutrients was similar in patients with or without cholelithiasis. In a recent study from France\(^2\) a significant risk of cholelithiasis was observed in individuals with excessive consumption of carbohydrates (>55 grams/day). Paradoxically, consumption below 12 grams/day was also found to increase significantly the risk of cholelithiasis. It was postulated that the single most important factor associated with gallstone formation was the high intake of refined carbohydrates. A positive association between intake of refined carbohydrates and risk of gallstone formation has been reported consistently\(^5,6\).

Tandon et al\(^1\), reported a high consumption of refined carbohydrates in their female patients with gallstones as compared to the controls. Refined sugar increases cholesterol saturation and lithogenicity of bile\(^9\).

2. Role of dieting and fasting.

The benefits of limited periods of fasting and a regulated decrease in dietary intake are healthy habits and have beneficial effect on an individual's health. Prolonged fasting and drastic reduction in calorie intake however, predisposes to gallstone formation. In a recent study from USA\(^1\), consisting of more than 4500 women with gallstones disease, dieting was associated significantly with increased risk of gallstone formation disease. A Danish population based study\(^5\) of ultrasonographically diagnosed gallstone disease, found a history of "slimming treatments" associated with gallstones in men but not in women. A study from Germany\(^12\) showed no correlation between the number of daily meals and the prevalence of gallbladder stone disease. Long periods of fasting and dieting diminish gallbladder motility and increase the saturation of bile with cholesterol.

3. Role of specific dietary factors.

Role of Cholesterol: The role of dietary cholesterol in formation of gallstones is till date debatable with various studies showing conflicting results. It is not surprising because dietary cholesterol is poorly absorbed in humans and the absorption mechanism is often saturated even with normal load of exogenous cholesterol. Only in one study with human subjects maintained on a formula diet, it was found that consumption of 750 grams of cholesterol per day led to significant increases in biliary cholesterol saturation as well as the plasma cholesterol levels\(^15\). On a more standard diet, however, the intake of large amounts of cholesterol does not increase biliary cholesterol level\(^14\).

Role of Total Fat: It was initially thought that high fat content in the diet may lead to increased loss of bile acids in the faeces and decreased bile acid pool per day led to significant increases in biliary cholesterol saturation as well as the plasma cholesterol levels\(^11\). On a more standard diet, however, the intake of large amounts of cholesterol does not increase biliary cholesterol level\(^14\).

Role of Total Fat: It was initially thought that high fat content in the diet may lead to increased loss of bile acids in the faeces and decreased bile acid pool promoting supersaturation of bile. Indeed, Sarles et al\(^3\), found a significant correlation between consumption of total lipids (more than 125 grams/day) and cholelithiasis and this was confirmed in a recent epidemiological study from France\(^8\). However, in the MICOL study\(^15\) there was no association found between total fat intake and gallstones. The studies in Danish population by Jorgensen et al\(^9\) and the study of Pixley and Mann\(^16\) from England also did not detect any correlation between cholelithiasis and consumption of total lipids. In fact, the diets used to induce cholesterol gallstones in animal models have either minimal or no fat at all.

Role of Saturated and Unsaturated Fats: The Framingham study showed that the population given increased amounts of polyunsaturated fats developed coronary artery disease much less often than expected but suffered a two-fold increase in the occurrence of gallstones\(^13\).

In the MICOL study\(^15\), no association between gallstone disease and intake of saturated, monounsaturated or polyunsaturated fat was found. The French study by Bosc et al\(^3\), did not find any protective effect of mono-unsaturated fatty acids, including olive oil, which is the richest mono-unsaturated fatty oil. Another study from Italy\(^18\) did not find any evidence of a link between poly-unsaturated fats and risk of gallstones. Mono-unsaturated fats, like all fats have been shown to have powerful effect on the rate of gallbladder emptying. However, the effect is different from that of saturated fats because mono-unsaturated fats increase the ratio of HDL to LDL cholesterol and therefore may have important protective effect against gallstone formation.

Role of Dietary Fibre: Fibre depleted diets are epidemiologically associated with a high prevalence of gallstones. In the MICOL study\(^15\) a small protective effect of fibre intake was observed in females but not males. Sama et al\(^18\) and Smith et al\(^7\) also found the protective effect of dietary fibre.

The protective role of dietary fibre has been attributed to various factors, the most important of them being decreased intestinal transit time. As a result there is less time for colonic bacteria to produce secondary
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**Role of Different Proteins:** Experimental evidence suggests that animal proteins in the diet are more lithogenic than vegetable proteins. Hamsters fed a lithogenic diet comprising of casein (animal protein) developed stones more often than those that were fed the same diet but with substitution of casein by soybean protein or buck wheat protein.

Protein intake has not been found to be significantly different in patients with cholelithiasis as compared to controls \textsuperscript{25}, though, Fiona et al\textsuperscript{23} did describe a lower intake of protein of plant origin in non-vegetarians who were at an increased risk of developing gallstones.

**4. Role of alcohol.**

Alcohol has been shown to have a protective effect against gallstones. Because ethanol exerts a profound effect on membrane transport properties, it is possible that ethanol prevents cholelithiasis by decreasing the absorption of water and electrolytes by the gallbladder mucosa.

In the study by Bosc et al from France\textsuperscript{9}, a protective effect of alcohol was detected. In the multivariate as well as univariate analysis, this protective effect was significant with higher pure alcohol consumption, i.e. 20-40 grams/day. Other epidemiological studies, including the MICOL study\textsuperscript{22}, and the study by Schwersing et al\textsuperscript{24} have shown a positive effect of alcohol consumption in the prevention of gallstones. These studies also support the hypothesis that alcohol protects against gallstone formation by increasing serum HDL cholesterol levels \textsuperscript{15,21}. Other mechanisms may also underlie this beneficial effect.

Recent studies from Germany\textsuperscript{25} and India\textsuperscript{26} did not show any association between gallstones and alcohol consumption.

**5. Role of smoking.**

The possible consequences of nicotine intake with regard to the etiology of cholelithiasis remain controversial. Jorgensen et al\textsuperscript{23} suggested that the consumption of nicotine increased slightly the prevalence of gallstones. Similar results were shown also in other studies \textsuperscript{24,25}. However the Ulm gallstone study from Germany\textsuperscript{12} did not show any positive correlation between the history of smoking and presence of gallstones. Singh et al\textsuperscript{27} found no correlation between smoking and gallstones in the study from India.

An explanation of these contradictory findings may lie in the dose-dependent effect of nicotine. Experiments in mice have shown that low doses of nicotine are associated with the pronounced increase in bile acid secretion as compared to the high dose group and the control group\textsuperscript{11}.

**6. Role of vitamins.**

One of the causes of biliary supersaturation is decreased cholesterol catabolism resulting from a low rate of cholesterol 7-alpha hydroxylase, the rate-limiting step in the catabolism of cholesterol to bile acids. In experimental models it has been shown that deficiency of ascorbic acid increases the incidence of gallstones.

On analysis of data of 9000 people from the Second National Health and Nutrition Survey (NHANES II)\textsuperscript{28} an inverted U shaped relationship between serum ascorbic acid level and prevalence of clinical gallbladder disease among women was found. Low levels and high levels of ascorbic acid were associated with lowest prevalence of gallstone disease. Low levels of ascorbic acid are associated with decreased hepatic cholesterol synthesis and low blood cholesterol levels. This can explain the low prevalence of gallstone disease in women with low ascorbic acid levels.

**7. Role of coffee consumption.**

Coffee and various individual coffee constituents affect various metabolic processes that are involved in cholesterol lithogenicity. Coffee stimulates cholecystokinin release, increases gallbladder motility, and possibly enhances large bowel motility\textsuperscript{27}. Caffeine inhibits biliary cholesterol crystallization, decreases gall bladder fluid absorption, and increases hepatic bile flow\textsuperscript{27}.

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In the Health Professional Follow-up Study, a prospective cohort study, more than 1000 men reported symptomatic gallstone disease. After adjusting for other known or suspected risk factors, compared with men who did not consume regular coffee, a significant difference in the relative risk for gallstone disease was found. All coffee brewing methods showed a decreased risk. In contrast, decaffeinated coffee was not associated with a decreased risk. In analysis of the NHANES III, no relation of total gallbladder disease and coffee was found. But when the analysis was restricted to previously diagnosed gallbladder disease a protective effect of coffee consumption was found. The Danish study and the German study did not find any correlation between coffee consumption and the prevalence of gallstones.

**Conclusion**

Several epidemiological studies have shown that high intake of calories in the form of refined sugars and fibre depleted diets help in the formation of gallstones. High total fat, high cholesterol and type of fat have only a limited role in the etiology of gallstones.

Prolonged periods of fasting increases the lithogenicity of bile as does drastic dieting. Alcohol, coffee consumption and ascorbic acid have a protective role against the formation of gallstones.

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