Cholesterol gallstones: from epidemiology to prevention

M Acalovschi

Gallstones are a major public health problem in all developed countries. Many epidemiological studies have been performed with the aim of establishing gallstone prevalence and incidence rates, and of defining risk factors, amenable to prevention. Cholesterol gallstones constitute more than 80% of stones in the Western world.

Epidemiology

The data usually employed in assessing gallstone prevalence were derived until recently from selected series of patients (necropsies, surgery, etc), which may not represent the general population. Suffice to say that the reported 0% prevalence of gallstones in the Masai population was deduced from surgical experience in that area, which is far from being an ideal way to collect epidemiological data.

Necropsy studies are subject to selection bias, which can be reduced by adjusting the data by standardisation. Necropsy studies have shown that, even after standardisation for age and sex, there are major differences between different countries (table 1). The available necropsy data, scrutinising longer intervals of time, decades1–2 or even a century,3 have revealed a trend of increasing gallstone prevalence.

Cholecystectomy rates, which fluctuate considerably (as much as fivefold) between countries and periods of time, have little relation to the prevalence rates. Oral cholecystography has been used by several researchers to assess gallstone prevalence, but no satisfactory evaluation on the prevalence of silent gallstones in the population was achieved.

Table 1 Age standardised necropsy prevalence of gallstones (see p 228 for list of references)

<table>
<thead>
<tr>
<th>Country (reference)</th>
<th>Gallstone prevalence (%)</th>
<th>Females</th>
<th>Males</th>
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<tbody>
<tr>
<td>Chile (Marinovic et al, 1972)</td>
<td>42.0</td>
<td>16.7</td>
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<tr>
<td>Germany (Balzer et al, 1986)</td>
<td>33.7</td>
<td>13.1</td>
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<tr>
<td>Czechoslovakia (Zahor et al, 1975)</td>
<td>23.3</td>
<td>13.2</td>
<td></td>
</tr>
<tr>
<td>Sweden (Lindström, 1977)</td>
<td>22.4</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>Scotland (Bateson and Bouchier, 1975)</td>
<td>21.7</td>
<td>9.9</td>
<td></td>
</tr>
<tr>
<td>England (Barker et al, 1979)</td>
<td>20.6</td>
<td>12.2</td>
<td></td>
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<tr>
<td>Mexico (Mendez-Sánchez et al, 1993)</td>
<td>16.2</td>
<td>5.6</td>
<td></td>
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<tr>
<td>Finland (Homeloff et al, 1984)</td>
<td>15.9</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>New Zealand (Douss and Castleden, 1973)</td>
<td>14.2</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>USA (Lieber, 1952)</td>
<td>14.1</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Australia (Cleland, 1953)</td>
<td>13.0</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Japan (Newman and Northup, 1959)</td>
<td>13.0</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Ireland (Hogan et al, 1977)</td>
<td>12.4</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Norway (Torkild and Hoivik, 1960)</td>
<td>10.4</td>
<td>3.3</td>
<td></td>
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<tr>
<td>Romania (Acalovschi et al, 1987)</td>
<td>8.4</td>
<td>5.0</td>
<td></td>
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<tr>
<td>Greece (Kalos et al, 1975)</td>
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<td>3.5</td>
<td></td>
</tr>
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<td>Singapore (Swang, 1970)</td>
<td>6.6</td>
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<td></td>
</tr>
<tr>
<td>Thailand (Stimimmankarn, 1960)</td>
<td>4.2</td>
<td>2.3</td>
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</table>

Currently, most studies have used real time ultrasonography as a screening method in randomly selected populations. Ultrasonography does not only allow the assessment of prevalence, but it is also suitable for follow up in order to establish gallstone incidence and to define risk factors for gallstone disease.

Accurate data for local gallstone prevalence and incidence rates are not yet available for every country. The largest number of sonographic studies have been performed in Western Europe (table 2). The median prevalence rate ranges from 5.9% to 21.9%, with the highest rates seen in Bergen, Norway and Schwedt, Germany and the lowest in Chianciano and Sirmione, Italy.4 The gallstone incidence evaluated in 10–11 year follow ups in Europe ranges between 0.63 and 0.93/100 persons/year.5

The highest prevalence of gallstones was found in Pima Indians from Arizona, USA by oral cholecystography screenings.7 Almost all ultrasound surveys in the Americas were conducted on Latin American populations. The prevalence rates in Hispanics were higher than those reported in European populations. A large ultrasound survey just completed (NHANES III) indicated an age standardised prevalence of gallstones higher in Mexican Americans than in non-Hispanic whites, with the lowest prevalence in non-Hispanic blacks.8 In South America, a very high gallstone prevalence was found in Chile. In Chilean women, gallstone incidence was 1.2/100 women/year.9 The lowest gallstone prevalence rates were found in Asian and African countries.

In almost all populations in which the necessary data were provided, gallstones were more frequent in women than in men and the majority of persons with gallstone disease had not had a cholecystectomy and were unaware of having gallstones.

Pathogenesis

Gallstone pathogenesis must be briefly considered to facilitate the presentation of risk factors. Cholesterol gallstones, composed predominantly of cholesterol crystals, result from abnormalities in cholesterol metabolism.

Three types of abnormalities have been considered to be responsible for cholesterol gallstone formation. The first and essential requirement is bile supersaturation in cholesterol. The per cent saturation of the cholesterol in bile is determined by the molar ratio of the three major biliary lipids: cholesterol, bile acids, and phospholipids. Cholesterol super-

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saturation, the essential requirement for cholesterol gallstone formation, might occur via excessive cholesterol biosynthesis (increased 3-hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) reductase activity), which is the main lithogenic mechanism (that is, in obese persons) (fig 1). A reduced acyl-CoA cholesterol acyltransferase (ACAT) activity, inhibiting cholesterol esterification, leads to an increased excretion of free cholesterol into the bile. In the non-obese, excessive cholesterol secretion could result from defective conversion of cholesterol to bile acids, due to a low or relatively low activity of cholesterol 7α hydroxylase, the rate limiting enzyme for bile acid biosynthesis (and cholesterol elimination). Finally, interruption of the enterohepatic circulation of bile acids could increase bile saturation. Temporary interruption of the enterohepatic bile acid circulation during overnight fasting leads to a higher cholesterol/phospholipid ratio in the vesicles secreted by the liver.

The second abnormality is enhanced nucleation of cholesterol crystals. Mucin and its congeners, the major proteins, act as matrix molecules to hold cholesterol crystal agglomerates together to form a stone.

There also must be sufficient time for nucleation to occur, for crystals to form and grow to microliths, and for microliths to aggregate to form gallstones, hence gallbladder stasis is a contributing factor to gallstone formation. During overnight fasting, the gallbladder does not empty so that hours of storage occur in all individuals.

It should be the sum of these three factors that determines when gallstones form. If bile is highly supersaturated, hypernucleation and stasis might be modest. Conversely, if bile were only slightly supersaturated, hypernucleation or prolonged stasis might result in gallstone formation.

Intestinal hypomotility has been recently recognised as a fourth primary factor in cholesterol lithogenesis (box 1). Having a longer exposure to intestinal micro-organisms, primary bile salts are in greater proportion deconjugated and dehydroxylated to more hydrophobic secondary bile salts. An increased proportion of the secondary bile acid deoxycholate, a potent down regulator of the rate limiting enzyme for bile acid biosynthesis, enhances cholesterol hypersecretion into bile.

Risk factors
Gallstone formation is multifactorial, both constitutional (unmodifiable) (box 2) and environmental (modifiable) (box 3) risk factors competing to lithogenesis.

Associations between the risk of gallstones and demographic characteristics have been sought from epidemiological studies. Most of these studies have looked for differences between people with gallstones and people who are stone-free (case-control studies). Unmodifiable risk factors such as age and gender have been first established, and then controlled in the search for other factors. Usually, this is

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**Table 2** Prevalence of gallstones in the largest sonographic surveys, which included persons from all age groups (see p 228 for list of references)

<table>
<thead>
<tr>
<th>City (country)</th>
<th>Reference</th>
<th>No of participants</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirmonne, Italy</td>
<td>Barbara et al, 1987</td>
<td>1 911</td>
<td>6.7</td>
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<tr>
<td>Copenhagen, Denmark</td>
<td>Jorgensen, 1987</td>
<td>3 608</td>
<td>5.6</td>
</tr>
<tr>
<td>Bergen, Norway</td>
<td>Glambek et al, 1987</td>
<td>1 371</td>
<td>20.3</td>
</tr>
<tr>
<td>Timisoara, Romania</td>
<td>Sporea et al, 1993</td>
<td>1 323</td>
<td>6.1</td>
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<tr>
<td>Chianciano, Italy</td>
<td>Loria et al, 1994</td>
<td>1 804</td>
<td>3.7</td>
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<tr>
<td>Castellana, Italy</td>
<td>Misciagna et al, 1994</td>
<td>2 461</td>
<td>6.4</td>
</tr>
<tr>
<td>Stockholm, Sweden</td>
<td>Muhrhbeck and Ahlberg, 1995</td>
<td>556</td>
<td>11</td>
</tr>
<tr>
<td>10 regions, Italy</td>
<td>Astil et al, 1995</td>
<td>29 739</td>
<td>9.5</td>
</tr>
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<td>Bristol, England</td>
<td>Heaton et al, 1991</td>
<td>1 896</td>
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<tr>
<td>lung, Germany</td>
<td>Berndt</td>
<td>10 133</td>
<td>8.2</td>
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<tr>
<td>Pampas de San Juan, Peru</td>
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<td>6.8</td>
</tr>
</tbody>
</table>

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**Box 1: Pathogenetic mechanisms of cholesterol gallstone formation**

- Supersaturation of bile in cholesterol.
- Enhanced nucleation of cholesterol crystals.
- Impaired gallbladder emptying with stasis.
- Intestinal hypomotility.

**Box 2: Unmodifiable risk factors for cholesterol gallstones**

- Female gender.
- Increasing age.
- Genetic factors: ethnicity, family.

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**Figure 1** Metabolic pathways in cholesterol and bile acid homoeostasis (ACAT = acyl-CoA cholesterol acyltransferase; HMGCoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low density lipoprotein).
Box 3: Modifiable (environmental) risk factors for cholesterol gallstones

- Obesity.
- Rapid weight loss.
- Hypertriglyceridaemia.
- Drugs lowering serum cholesterol.
- Slow intestinal transit.
- Gallbladder stasis.
- High caloric diet.
- Highly absorbable sugars.
- Low fibre diet.
- Low calcium low vitamin C diet.
- Alcohol abstinence.
- Smoking.
- Sedentary behaviour.

done by multiple regression analysis. The case-control approach can be used to look for differences in lifestyle, such as eating and drinking habits, etc. But most of the published case-control studies suffer from inadequate sample size or various types of selection bias which confound the results. Small studies might yield false negative results (that is, fail to reveal a genuine difference). Selection bias might also create non-existing differences (false positive results). The most reliable data come from studies of asymptomatic cases identified by population screening, and those have increased in number in the last decade.

GENDER, PARITY, AND ORAL CONTRACEPTIVES

In all populations of the world, regardless of overall gallstone prevalence, women are almost twice as likely as men to experience cholecystitis. Gender is one of the most powerful influences on gallstones, which are more common in females during their fertile years as in males. This preponderance persists to a lesser extent into the postmenopausal period, but the sex difference narrows with increasing age. Among persons younger than 40, the female/male prevalence ratio varies from 1.2 in Bergen, Norway, to 9.9 among Pima Indians. For ages 60 and older, the female/male ratio varies from 0.96 in Okinawa, Japan, to 2.9 among Mexican Americans in the south western USA. Women with gallstones are more likely to have had a cholecystectomy than men with gallstones.

The influence of the female sex hormones has been studied in normal females, during pregnancy, and in women using oral contraceptives. The risk of gallstones is greater in younger women, and is influenced by parity. A critical review of the literature indicates that parity is associated with gallstones only in younger females. This risk seems to apply to both the number and age of pregnancies. For example, a woman who has four pregnancies before the age of 25 has a fourfold to 12-fold increased risk of cholesterol gallstones compared with an age matched, weight matched nulliparous woman. Pregnancy favours gallstone formation through the hormonal influences on bile composition (increased biliary cholesterol secretion, decreased and unbalanced bile acid pool). Oestrogens induce an increased input to the hepatic free cholesterol pool by up-regulating the low density lipoprotein receptor. Decreased gallbladder motility during the third trimester of pregnancy and an altered function of gallbladder mucosa may favour nucleation and growth of stones. The occurrence of sludge increases steadily during pregnancy (30%–35%), but gallstones develop at a lesser frequency (2%–3%). Biliary sludge and most gallstones will disappear spontaneously within a few weeks after delivery.

Several studies have confirmed an association between gallstones and use of exogenous oestrogens, whether as oral contraceptives, postmenopausal oestrogen replacement, or oestrogen administration in men. The current evidence indicates that the modern contraceptives, containing a medium/low (less than 50 μg) daily dose of oestrogen, do not increase the risk of forming gallstones, but may accelerate the performance of cholecystectomy. Sex steroids given by other routes, such as transdermal or vaginal, are less lithogenic, probably by avoiding the first pass effect in the liver.

AGE

Gallstones are generally uncommon in infants and children. The recently reported increasing number of cholecystectomies in this population refers mainly to girls aged over 16 years, obese, parous, and/or of Mexican-American origin.

All epidemiological studies showed that increasing age was associated with an increased prevalence of gallstones. Gallstones are four to 10 times more frequent in older than younger subjects. Biliary cholesterol saturation increases with age, due to a decline in the activity of cholesterol 7α-hydroxylase, the rate limiting enzyme for bile acid synthesis. In the elderly, bile acid synthesis is reduced, biliary cholesterol output is increased and cholesterol saturation of bile increases, and that is true both in men and women. Deoxycholic acid proportion in bile increases with age through enhanced 7α-dehydroxylation of the primary bile acids by the intestinal bacteria. In addition, increasing age allows the cumulative lithogenic action of more risk factors.

GENETIC FACTORS

Both necropsy and population studies have clearly shown the existence of racial differences that can not completely be explained by environmental factors. Cholesterol gallstone prevalence varies widely, from extremely low (<5%) in Asian and African populations, to intermediate (10%–30%) in European and Northern American populations, and to extremely high (30%–70%) in populations of Native American ancestry (Pima Indians in Arizona, Mapuche Indians in Chile).

The Pima tribe of Arizona has the highest gallstone prevalence in the world: more than 70% of Pima women older than 25 had gallstones or a history of cholecystectomy. High rates of gallstone prevalence have been also reported in other North American Indian tribes, including the Chipewyas, Navajo, Micmacs, and Cree-Ojibwas. A high mortality from gallbladder cancer, a disease intimately linked
to gallstones, was found in Native Americans living in Alaska, Minnesota, Oklahoma, New Mexico, and Bolivia. That these high prevalence rates are observed in native people throughout North and South America, who differ markedly in local environment, culture, and diet argues for a common, genetically determined predisposition to gallstone formation.

Certain Hispanic populations in the USA are above average risk for gallbladder disease. Some studies strongly support the existence of Amerindian lithogenic genes in Mexican-Americans. The NHANES III survey confirms the higher prevalence of gallstones among Mexican-American than non-Hispanic whites. As not all Hispanic populations living among Mexican-American than non-Hispanic firms the higher prevalence of gallstones markedly in local environment, culture, V throughout North and South America, who prevalence rates are observed in native people

The NHANES III survey also confirmed the low gallstone prevalence among American blacks compared with whites, mentioned by several epidemiological surveys. An ultrasound survey of South African black women older than 55 has shown a 10% prevalence of stones, lower than in South African white women.

Genetic influence in gallstone formation is also suggested by familial clustering within populations. An increased frequency of gallstones was found among the relatives of gallstone patients as compared with families of controls. Familial dietary habits are not likely to offer an explanation of the increased familial incidence of gallstones, in view of the negative findings in spouses. Patients who are young when gallstones develop are more likely to have affected relatives, because an early age onset of gallstone disease would reflect a greater polygenic predisposition. The finding that gallstones are more frequent in monozigotic than in dizygotic twins strongly supported the genetic contribution to gallstone formation. A higher saturation in cholesterol of the bile and a higher correlation of the cholic acid contents were found in the monozygotic as compared with dizygotic twins.

Using inbred strains of mice, two genes have been identified that confer susceptibility to gallstones in an autosomal dominant pattern: Lith1 (the bile salt export pump, Bsep), and Lith2 (the canalicular multiorganic anion transporter, cMoat). Mice with overexpression of Lith1 gene appear unable to down-regulate the activity of HMGCoA reductase, and thus, cholesterol synthesis when fed a lithogenic diet. The activity of cholesterol 7α hydroxylase and sterol 27 hydroxylase is also downregulated. Up-regulation of cMoat induces cholesterol lithogenicity from bile salt-lecithin decoupling due to bile salt-anion binding. No human homologue of this gene has yet been found.

A genetic factor in humans, polymorphism of the apolipoprotein E locus, has recently been identified. Apolipoprotein E plays a part in dietary lipid absorption, transport, and distribution to the liver and peripheral tissues and exists as three different alleles: apoE2, apoE3, and apoE4. ApoE4 genotype is associated with biliary cholesterol supersaturation, rapid nucleation, an increased cholesterol content of gallstones, a rapid clearance of gallstones by lithotripsy and a high risk of recurrence after treatments that leave the gallbladder in situ. This allele might affect hepatocyte uptake and biliary secretion of lipids, or might act as a promoter in the bile.

OBESITY AND BODY FAT DISTRIBUTION

Ultrasonographic and cohort studies in selected populations have confirmed the clinical impression that gallstones are more frequent among obese than non-obese persons. Obesity is an important risk factor for gallstone disease, more so for women than for men. It raises the risk of cholesterol gallstones by increasing biliary secretion of cholesterol, as a result of an increase in HMGCoA reductase activity. Epidemiological studies have found that the lithogenic risk of obesity is strongest in young women and that slimness protects against cholelithiasis.

In a follow up study of 90,000 women, a striking monotonic increase in gallstone risk with obesity was observed. Women with a body mass index (BMI) greater than 45 kg/m² had a sevenfold excess risk as compared with those with a BMI less than 24 kg/m². The annual gallstone incidence rose parallel with the BMI, up to 2/100/year in morbidly obese. The risk seemed greater when obesity developed early in life (obesity present by the age of 18 and subsequently maintained). The intentional, long term, moderate weight changes over a 16 year period progressively increased the risk of cholecystectomy in women, from light (2.3–4.1 kg (5–9 lb) of weight loss and gain) to moderate and to severe cyclers (≥9.0 kg (≥20 lb) of weight loss and gain), compared with weight maintainers.

In most studies, obesity in men as expressed by BMI, was not related to an increased gallstone formation. As abdominal or central obesity is associated in both men and women with hypertriglyceridaemia, low plasma high density lipoprotein (HDL) concentrations, impaired glucose tolerance, hyperinsulinaemia etc, all metabolic abnormalities linked with gallstones, one might expect an association between gallstones and abdominal obesity. A significant stepwise relationship of gallstones with waist/hip circumference ratio was found in men aged 40–69 years, although there was no association between BMI and
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...gallstones in this population. Further studies confirmed that men's chances of having gallstones are increased by having an abdomi-
nal distribution of body fat, leading to the conclusion that obesity represents a risk for
gallstones both through total body fat mass and through fat regional distribution.

RAPID WEIGHT LOSS
Weight reduction in obesity is associated with gallstone formation risk. Different studies in the
morbidly obese presenting for gastric bypass surgery or after a very low calorie diet
showed the occurrence of sludge and gallstones in 10% to 25% of patients in a few weeks after
slimming procedures. During weight loss, bile
lithogenicity is further enhanced by increased
excretion of cholesterol due to the decrease in
the synthesis and pool size of bile acids, and to
the rapid mobilisation of cholesterol from adipose
tissue stores. In the case of severely fat
restricted diets, gallstone formation is also
favored by gallbladder stasis. Enhancing gall-
bladder emptying by inclusion of a small
amount of dietary fat inhibits gallstone forma-
tion in patients undergoing rapid weight loss.

The effect of weight loss on bile lithogenicity
is dependent on the initial body weight, on the
calorie and fat content of the diet and on the
rate of weight loss. A dramatically increasing
risk for gallstone formation was found at rates
of weight loss above 1.5 kg/week.

HYPERTRIGLYCERIDAEMIA
Most biliary stones are made of cholesterol;
lipoprotein lipids are precursors of biliary
lipids; synthesis, uptake, and degradation of
plasma lipoproteins occur in the liver; choles-
terol and bile acids in bile are the only means of
eliminating cholesterol from the body. Yet, even
in the largest clinical series, no definite associ-
ation trends between serum lipoproteins occur
in patients with injury above the T7 through
T10 level, the site of the emergence of the sym-
pathetic innervation for the gallbladder. Litho-
genic risk is due to gallbladder and intestinal
hypomotility.

SPINAL CORD INJURY
Necropsy studies first revealed an increased
prevalence of gallstones in subjects with spinal
cord injury. This was subsequently confirmed
in patients with injury above the T7 through
T10 level, the site of the emergence of the sym-
pathetic innervation for the gallbladder. Litho-
genic risk is due to gallbladder and intestinal
hypomotility.

DIET
One of the main environmental exposures con-
tributing to gallstone formation is the nutri-
tional exposure. The progressive increase in
the prevalence rate of gallstones during this
century supports the role of lifestyle and
dietary factors in gallstone pathogenesis. In
Japan, postwar westernisation has provided an
example for the interplay between environment
and disease. Since the late 40s, the prevalence
of gallstones in Tokyo has more than doubled.
Moreover, there has been a change from
pigment to cholesterol gallstones and the sex
ratio has changed in favour of females. This
increase in gallstone incidence was associated
with an increased fat intake and a decreased
fibre content of the diet and consequently was
attributed to the westernisation of the Japanese
diet.

Studies in France have observed a higher
caloric intake in subjects with gallstones than in
controls. Refined carbohydrates cause obes-
ity, raise plasma triglyceride and fasting plasma
insulin level, and lower plasma HDL chole-
terol. Most cholesterol is endogenously synthe-
sised, so dietary cholesterol has only a limited
impact on cholesterol saturation. Studies on
the influence of various fats on gallstone
formation offered contradictory results, most
finding no association at all with animal fats
and proteins with gallstone formation. For vege-
table fats and protein, an inverse association
with gallstones was found in some studies, but
not confirmed in others.

A high fibre intake in the form of wheat bran
lowers the cholesterol saturation of bile. Fibres
have a protective effect against cholesterol gall-
stones by accelerating intestinal transit and
hence decreasing the deoxycholate in bile. An

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A shorter overnight fasting is protective against sludge and eventually gallstone formation. Younger women with gallstones were shown to be more prone to skip breakfast than controls. A shorter overnight fasting is protective against gallstones in both sexes.38

ALCOHOL CONSUMPTION

Some experimental studies have suggested the protective effect of alcohol against gallstone formation. Alcohol intake has been shown to reduce bile lithogenicity in humans.73-75 The protective effect of alcohol may occur via the liver, by increasing the conversion of cholesterol to bile acids or by altering the enterohepatic circulation of bile acids, including deoxycholic acid. Moderate alcohol consumption also raises plasma HDL cholesterol concentrations.

SMOKING

Data related to smoking as a risk factor for gallstones are inconsistent. Some authors found a linear relationship between amount smoked and gallstone risk,53 while other studies found no relation between smoking and gallstones. Smoking is associated with low plasma HDL cholesterol concentrations, a risk factor for gallstones. It also depresses prostanoid synthesis and mucus production in the gallbladder.

SOCIOECONOMIC STATUS

Diehl et al analysed the socioeconomic status in Mexican Americans as compared with non-Hispanic whites and observed that those living in affluent neighbourhoods, with high occupational status, high family incomes, and high educational attainment had lower rates of gallstones than those lower on the social scale.55

Interestingly, at high levels of socioeconomic status, the ethnic differences in gallbladder disease prevalence narrowed or even reversed. As other studies failed to find an association, the relation between socioeconomic status and gallstone disease is still controversial.

Box 4: Strategy and measures for cholesterol gallstone prevention

(1) Prevention of bile supersaturation in cholesterol

- Reduce BMI in the obese by gradual weight loss; avoid weight cycling.
- Lower serum triglyceride concentration.
- Increase hydrophylic bile acid content of bile (chenodeoxycholic acid, ursodeoxycholic acid).
- Lower hydrophobic bile acid content of bile (high fibre high calcium diet, normal intestinal transit, antibiotics, etc).
- Practice regular physical exercise.

(2) Prevention of accelerated nucleation and mucus secretion

- Take anti-inflammatory non-steroidal: aspirin (?)

(3) Prevention of gallbladder stasis

- Keep a regular eating pattern, avoid long periods between meals.
- Eat small fatty meals (or administer cholecystokinin) during rapid weight loss.

(4) Prevention of intestinal hypomotility

- Stimulate intestinal transit (high fibre high calcium diet, cisapride).
- Lower intestinal pH (lactulose).

PHYSICAL ACTIVITY

The potential role of physical activity in preventing cholesterol gallstone formation is largely unknown. Regular exercise, in addition to facilitating weight control, alone or in combination with dieting, improves several metabolic abnormalities related to both obesity and cholesterol gallstones. In a prospective study in 60 290 women, increased physical activity was associated with a significant reduction in the risk of cholecystectomy. Not only vigorous physical activity, but also moderate forms of exercise, such as brisk walking, were associated with a reduced risk of cholecystectomy. In contrast, sedentary behaviour, as assessed by time spent sitting, was positively associated with the risk of cholecystectomy.52

Cholesterol gallstone prevention

Gallstones are highly prevalent in most Western countries. Although symptomatic and complicated stones represent less than 20% of all gallstones, they lead to important morbidity and complications, and to high costs of medical care, making gallstone prevention highly desirable. Based on the present epidemiological knowledge, we are now in the position to do something about cholesterol gallstone prevention.

Primary prevention would be the inhibition of formation of stones in subjects who have not previously had gallstones. It could address the entire population with recommendations for a healthy lifestyle, but could be most productively focused on subjects at increased risk, that is obese women, with many pregnancies and positive family history, etc. The strategy for...
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preventing cholesterol gallstone formation should be targeted to the main pathogenetic mechanisms: supersaturation of bile in cholesterol accelerated nucleation; impaired gallbladder emptying and intestinal hypomotility (box 4).

First and foremost, cholesterol supersaturation is a matter of obesity, hence it should be approached by reducing BMI in obese people and by lowering triglyceride serum concentrations. Rapid weight loss in the obese should be replaced by a gradual weight loss sustained over a long period. The long term numerous weight cycles should be avoided as each weight reduction regimen causes tissue cholesterol from the shrinking adipose tissue to be excreted in bile. Increased cholesterol saturation in the bile could be prevented by increasing the bile proportion of hydrophilic bile acids. Administration of chenodeoxycholic or ursodeoxycholic acids would be too expensive an approach to be recommended, except for small risk groups (that is, morbidly obese women during rapid weight loss). Reduction of the proportion of hydrophobic bile acids, that is, deoxycholic acid, could be reached by stimulating intestinal motility and by a high calcium high fibre diet in constipation cases. Antibiotics would diminish the number of bile acid metabolising anaerobes.

Accelerated nucleation and mucus secretion in the gallbladder might be diminished by prostaglandin inhibitors. Aspirin, in the dose of four tablets a day, was shown to prevent gallstone formation in rapid weight reduction patients. But it was not confirmed that persons regularly taking aspirin have a lower incidence of gallstones, making it questionable whether “one aspirin a day keeps the gallstone away”.

Gallbladder stasis should be approached by a regular eating pattern, avoiding long periods between meals, by a bedtime snack to reduce overnight fasting or by small fatty meals during rapid weight loss.

Stimulation of intestinal motility would decrease bacterial bile acid metabolism. Intestinal pH lowering might also lead to deoxycholate reduction in bile. A high calcium high fibre diet, as well as lactulose or prokinetics (cisapride) could thus prevent cholesterol gallstone formation in constipation.

Descriptive epidemiology suggests consistently that environmental factors characterising modern Western civilisation and urbanisation may be responsible for most cholesterol rich gallstones. All these factors are amenable to prevention. Habits (smoking, coffee, and alcohol consumption) and activities (physical load) can be changed, diets modified, and thus exposures limited.

People (particularly women) should limit their energy intake and especially readily absorbed carbohydrates and animal fats so as to maintain the ideal body weight. In addition, they should eat enough dietary fibre to avoid constipation, they should respect a regular eating pattern, and avoid a long overnight fasting. Of course, no one would ever suggest restricting the family size by modulating the number of pregnancies! A modest alcohol intake could be protective, but should not be recommended to non-drinkers. Cessation of smoking is advisable, as well as a sustained physical activity, even if limited to a 30 minute brisk walk daily for five days a week. In fact, the preventive measures for cholesterol gallstone formation reproduce those already recommended for cardiovascular disease prevention and they should be proposed at least in high risk individuals.

Questions (answers on p 229)

1. Name the populations with the highest prevalence of cholesterol gallstones.
2. Name the populations with the lowest prevalence of cholesterol gallstones.
3. Name the factors which support the intervention of the genetic control in cholesterol gallstone formation.
4. The contributive factors to cholesterol gallstone formation in obese women are:
   (A) Age of obesity onset.
   (B) Regular aspirin intake.
   (C) Avoidance of severe weight cycling.
   (D) Lactulose.
   (E) Ursodeoxycholic acid.
5. The current evidence supports the protective role of the following dietary components in cholesterol gallstone formation:
   (A) Refined carbohydrates.
   (B) Fibres.
   (C) Alcohol.
   (D) Animal proteins.
   (E) Vitamin C.
6. Bile supersaturation in cholesterol gallstone might be prevented by:
   (A) Regular physical exercise.
   (B) Regular aspirin intake.
   (C) Avoidance of severe weight cycling.
   (D) Lactulose.
   (E) Degree of weight cycling.

References

References for table 2


References for table 1


Answers

1. Pima Indians in Arizona, other Indian tribes in North America, Mapuche Indians, and Chilean Mestizos in Chile.


3. The facts are:
   - Racial/ethnic differences in gallstone prevalence.
   - Family clustering of gallstone carriers.
   - Higher prevalence in monozygotic vs dizygotic twins.
   - Lith1 and Lith2 genes in mice strains susceptible to form gallstones.
   - ApoE4 genotype in humans associated with increased gallstone formation.

4. (A), (B), (E).

5. (B), (C), (E).

6. (A), (C), (E).