UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO

FACULTAD DE MEDICINA

# CHOLESTEROLOSIS IS NOT ASSOCIATED WITH HIGH CHOLESTEROL LEVELS IN PATIENTS WITH AND WITHOUT GALLSTONE DISEASE

TRABAJO QUE PARA OBTENER EL DIPLOMA DE ESPECIALISTA EN GASTROENTEROLOGÍA

PRESENTA

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# Cholesterolosis Is Not Associated With High Cholesterol Levels in Patients With and Without Gallstone Disease

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High levels of cholesterol have been associated with certain gallbladder disorders such as cholesterolosis and gallstone disease. Furthermore, obesity is considered the main risk factor for cholesterol gallstone disease. We investigated the incidence of cholesterolosis in patients with and patients without gallbladder stones (GS). We reviewed the clinical records of patients with gallstone disease and other gallbladder disorders who had consecutive cholecystectomy during a 5-year period. We recorded demographic data, sex, age, serum cholesterol levels, and body mass index. The diagnosis of cholesterolosis was made macroscopically and microscopically. A total of 636 patients were included in this study: 446 with and 190 without GS. Cholesterolosis was more frequent in patients without GS ($p < 0.01$). However, hypercholesterolemia occurred more frequently in patients with GS ($p < 0.001$). Obese patients with GS had higher percentages of cholesterolosis and hypercholesterolemia than did eutrophic patients ($p < 0.01$ and $p < 0.05$, respectively). We suggest that cholesterolosis in the human gallbladder is not necessarily associated with gallstone disease and high plasma cholesterol levels.

**Key Words:** Cholesterolosis—Cholesterol—Obesity—Cholelithiasis.

The gallbladder's primary function is to remove water and inorganic electrolytes from the body, thereby concentrating the organic solute molecules. In addition, the mucosa of the gallbladder absorbs many lipid-soluble compounds, such as unsaturated fatty acids, lecithin, lysolecithin, and even free cholesterol (1). Although the gallbladder may be important in the pathogenesis of cholesterol gallstones, any such role is poorly understood in the case of cholesterolosis. Patients with cholesterol gallstones have gallbladder dysmotility characterized mainly by increased fasting and residual volumes (2), with the degree of impairment of gallbladder emptying increasing with the cholesterol content of gallbladder bile, even in healthy persons who have no stones (3).

Cholesterolosis is usually present in the human gallbladder with or without cholesterol stones, suggesting that increased amounts of cholesterol molecules may play an important role in the pathogenesis of both cholesterol gallstones and cholesterolosis. In patients with normal serum lipid levels, Sahlin et al.(4) found that cholesterolosis is associated with a fivefold increase in esterified cholesterol and a normal content of free cholesterol in the gallbladder mucosa.

On the other hand, epidemiologic studies around the world, mostly in Western countries (5–7), have identified obesity as the main risk factor for cholesterol gallstone disease (8). The Mexican-American population has greater overall adiposity and an unfavorable body fat distribution, of the centripetal variety that has been associated with an increased risk for clinical gallstone disease (7). A study in Mexico City reported a high prevalence of obesity: The crude prevalence was 36.8% in men and 60% in women (9). Because this condition might increase the production of cholesterol in obese persons (10), we examined the incidence of cholesterolosis in patients of healthy weight and those who were obese with gallstone disease.

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## MATERIALS AND METHODS

We reviewed the clinical records of patients who had cholecystectomy for gallbladder stones or other disorders, such as polyps and cholesterolosis, between 1 January 1989 and 31 December 1994 who were registered at the Departmento de Patologia of the Instituto Nacional de la Nutrición "Salvador Zubirán." This hospital is a 200-bed medical facility that provides care primarily for moderate income patients (80%), but with some participants from other socieconomic strata, such as persons who do not have social security (low income) and others who can pay directly for their treatments (high income). On the other hand, approximately 60% of the patients are from Mexico City and 40% from other Mexican states, including rural areas, and they lack all types of medical insurance. Patients were excluded from the study if cholecystectomy was due to acute acalculous cholecystitis or trauma. The diagnosis of GS was based on the presence of gallstones during the surgical and pathologic examination. The diagnosis of cholesterolosis was based on macroscopic and microscopic criteria. From each clinical record we recorded patient sex, age, and serum cholesterol level. Patients were classified according to body mass index as eutrophic or obese. Body mass index was calculated according to the formula weight (measured in kilograms)/height$^2$ (measured in meters). Obesity was defined as body mass index > 25. Serum cholesterol levels were considered abnormal when they were ≥ 220 mg/dl. This estimation was based on the recommendations of the American Medical Association and was standardized according to our hospital population. Ethical aspects of the study were approved by the ethics committee at our institution. Results were analyzed using Student's $t$ and chi-squared tests. Probability values $< 0.05$ were considered significant.

## RESULTS

Table 1 shows the clinical characteristics of patients with and without GS. Distribution by sex and mean age were similar in both groups. We found a difference between the two groups in the percentage of patients with cholesterolosis, which occurred more frequently in those without GS ($p = 0.01$) and hypercholesterolemia, which was more frequent in patients with GS ($p < 0.001$). We observed no differences in the number of patients who were obese in either group. The analysis of patients with GS according to body mass index showed that the percentage of patients with cholesterolosis and hypercholesterolemia was higher in the group of obese than in the normal-weight patients ($p < 0.01$ and $p < 0.05$, respectively; Table 2). However, we found no differences in the percentage of cholesterolosis and hypercholesterolemia in the group of patients without GS, as shown in Table 3. Finally, the frequency of obesity and hypercholesterolemia in patients with cholesterolosis was similar in both groups of patients with and without GS (Table 4).

TABLE 1. *Characteristics of patients with and without gallbladder stones*

| Characteristic | With GS | Without GS | p |
|---|---|---|---|
| n | 446 | 190 | |
| Sex (M/F) | 121/325 | 60/230 | NS |
| Age (yr) | 50.7 ± 16.6 | 53.0 ± 16.6 | NS |
| Obesity | 259 | 100 | NS |
| Eutrophic | 187 | 90 | NS |
| Cholesterolosis | 53 | 37 | 0.01 |
| Hypercholesterolemia | 191 | 54 | 0.001 |

GS, gallbladder stones; NS, not significant.

## DISCUSSION

The frequency of obesity was similar in both groups of patients with and without GS. Although we found more patients with cholesterolosis without GS, hypercholesterolemia occurred more frequently in patients with GS.

Of particular interest is a high percentage of patients with GS who had higher plasma cholesterol levels than did patients without GS. An association between gallstones and plasma lipids is well recognized (11–17), and obesity is a well-known risk factor for cholesterol gallstones, especially in Western countries and in Mexican-American and Mexican populations. However, in our study the percentage of obese patients in both groups was similar, 58% in patients with and 52% in those without GS. Because both groups had the same risk for GS, how can we explain why some patients develop gallstones and others do not? The answer is not easy, because many factors are involved in the pathogenesis of cholesterol gallstones. The percentage of patients with hypercholesterolemia was higher in those with GS (43%) than in those without GS (28%), which could explain, at least in part, our results. In addition, some disturbances in cholesterol metabolism, such as increased 3-hydroxy-3-methylglutaryl coenzyme A reductase activity, decreased cholesterol 7α-hydroxylase activity, and decreased acyl coenzyme A: cholesterol acyltransferase (ACAT) activity have already been found in patients with cholesterol gallstones (18–22).

Another important finding of our study was that the percentage of cholesterolosis in patients without GS was higher than in those with GS. In contrast, these patients did not have higher serum cholesterol levels than did patients with GS. This fact seems to play an important role in the pathogenesis of cholesterol gallstones, but not for the development of cholesterolosis. But how can cholesterolosis develop in obese patients who have normal

TABLE 2. *Characteristics of patients with gallbladder stones according to BMI*

| | Obese | Eutrophic | p |
|---|---|---|---|
| n | 259 | 187 | |
| Sex (M/F) | 64/195 | 57/130 | NS |
| Cholesterolosis | 40 | 13 | 0.01 |
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BMI, body mass index.

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TABLE 3. *Characteristics of patients without gallbladder stones according to BMI*

| Characteristic | Obese | Eutrophic | p |
|---|---|---|---|
| n | 100 | 90 | |
| Sex (M/F) | 25/75 | 35/55 | NS |
| Cholesterolosis | 14 | 8 | NS |
| Hypercholesterolemia | 32 | 22 | NS |

BMI, body mass index.

TABLE 4. *Characteristics of patients with cholesterolosis*

| Characteristic | With GS | Without GS | p |
|---|---|---|---|
| n | 53 | 37 | NS |
| Sex (M/F) | 18/35 | 12/25 | NS |
| Obesity | 34 | 24 | NS |
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cholesterol levels? The gallbladder mucosa can absorb cholesterol from micelles of supersaturated bile efficiently (23). This step is important because, before cholesterol is absorbed, it is esterified by gallbladder ACAT. Because the gallbladder mucosa does not synthesize lipoproteins and virtually all of this lipid is esterified, the molecules that remain free dissolve in plasma and intracellular membranes, where they become intercalated with phospholipids and stiffen their molecules (24). Interestingly, there is an increase in ACAT activity in the gallbladder mucosa of patients with cholesterolosis but without stones (4).

To explain the possible mechanisms involved in the pathogenesis of cholesterolosis, we hypothesize that cholesterolosis in the gallbladder is probably produced by a larger pool of biliary cholesterol that stimulates ACAT activity. This increased amount of esterified cholesterol is probably deposited subsequently in the gallbladder mucosa, as has been suggested by Koga et al.(25), who also propose that cholesterol might be engulfed by macrophages, which become foamy cells. Furthermore, Feldman and Feldman (26) suggest that venous and lymphatic stasis may be etiologic factors causing disturbance in the absorptive or secretory mechanisms of the gallbladder mucosa. Another hypothesis has been proposed by Izeki et al.(27) and by Celoria et al.(28) in that the gallbladder epithelium of patients with cholesterol polyps is stimulated by cholesterol and transformed into papillary hyperplasia. This tissue would then adsorb more cholesterol and develop cholesterolosis.

In addition, impairment of gallbladder motility could be implicated in the pathogenesis of cholesterolosis (29). LaMont and Carey (24) postulated that absorption of molecular cholesterol from the gallbladder lumen is associated with muscle dysfunction. The current working scheme is that G proteins are not activated when cholecystokinin binds to its receptors on smooth muscle cells of a lithogenic gallbladder. One likely reason for this is stiffening of sarcoplasmal membranes secondary to increased content of membrane cholesterol.

Finally, similar percentages of patients with obesity and hypercholesterolemia were found among those with and without GS. In this regard, a previous report suggests that cholesterolosis is induced by hypercholesterolemia. Nevertheless, our study does not support that observation (30). Because cholesterolosis develops in many patients with GS, patients with cholesterolosis may have at least two defects in both enzymes involved in cholesterol homeostasis, 3-hydroxy-3-methylglutaryl coenzyme A, and ACAT. Furthermore, a higher polymorphism in the frequency of the X1X1 genotype of apolipoprotein BXbaI has been demonstrated in patients with cholesterolosis (with and without stones) than in those with gallstone disease (with or without cholesterol gallstones) (22).

In conclusion, we suggest that the development of cholesterolosis in the human gallbladder is not necessarily associated with gallstone disease, obesity, or high plasma cholesterol levels.

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4

TABLE 3. *Characteristics of patients without gallbladder stones according to BMI*

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