METHODS

# Correction of Hyperlipidemia in Patients with Cholelithiasis as a Means of Improving the Results of Extracorporeal Lithotripsy

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UDC 616.366-003.7-06:616.153.915-008.61]-085

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 118, № 11, pp. 555-558, November, 1994
Original article submitted March 9, 1994

The results of treatment of patients with uncomplicated cholelithiasis by extracorporeal lithotripsy are analyzed. Clinical evidence confirming the relationship between hyperlipidemia and cholelithiasis is presented. The number of recurrences is foudn to decrease considerably after extracorporeal lithotripsy for judicious correction of hyperlipoproteinemia.

**Key Words:** *hyperlipoproteinemia; cholelithiasis; extracorporeal lithotripsy*

The search for various ways of diagnosing, treating, and preventing cholelithiasis has been prompted by a marked increase in the occurrence of this disease during the last decade [1]. The use of new noninvasive methods for the treatment of cholelithiasis (CHL), for example, extracorporeal lithotripsy (ELT), has allowed clinicians to treat more patients but at the same time has led to a number of problems associated with a timely diagnosis and, even more important, with the prevention of CHL recurrences. According to published data, the recurrence rate of CHL within 8-12 months after ELT is 9-46% [6]. This cannot be blamed on inadequate ELT, since in most cases ultrasound examination confirms complete elimination of concrement fragments from the gallbladder. What, then, is the cause of cholelithiasis recurrence?

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It is known that normal bile contains only 8% cholesterol (72% bile acids and 20% phospholipids). These compounds form micelles which preserve their structure and solubility in the bile. An increase in the bile cholesterol content promotes the gradual formation of concrements. It should be emphasized that the bile cholesterol concentration positively correlates with the plasma cholesterol concentration. Therefore, a disturbance of the lipid metabolism, specifically, a rise in the blood cholesterol level (and, consequently, a rise of the level in the bile) induces a pathological process, CHL being one of its manifestations.

In removing concrements from the gallbladder, the surgeon eliminates the sequela but not the cause of CHL, which may result in the a recurrence of th disease.

There are no published clinical studies that prove the effect of hyperlipidemia on CHL reccurence after ELT or provide pathogenetic substantiation for the correction of lipid metabolism disorders

0007-4888/94/0011-1253$12.50 

as a means of prevention of CHL recurrence. The aim of this study was to examine the effect of hyperlipidemia and the relationship between hyperlipidemia and the frequency of CHL recurrences after ELT and to find a way to prevent them.

## MATERIALS AND METHODS

The study included 80 patients with uncomplicated CHL and isolated concrements with a diameter of up to 30 mm in a functioning gallbladder. Together with ultrasound diagnostics prior to ELP, the following parameters of lipid metabolism were evaluated in an Express-550 automatic biochemical analyzer (Ciba-Corning): the total contents of plasma cholesterol, triglycerides, and high-density and low-density lipoproteins (HDL and LDL). The coefficient of dyslipoproteinemia, which integrally reflects the ratio between plasma lipoprotein fractions, was calculated according to A. N. Klimov [3]. The lipid metabolism parameters were monitored throughout the period of lithotripsy in parallel with the control ultrasound investigation.

Extracorporeal lithotripsy was performed using a SONO-LIT 3000 apparatus (France) with an ultrasound targeting. The focal pressure gradient was 900-1100 bar/μsec at a voltage range of 14-15.8 kV. The number of sessions depended on the degree of fragmentation: it varied from 1 to 3, and the pulse number per min varied from 800 to 3200. The attainment of concrement fragments of less than 5 mm was considered as complete therapeutic fragmentation. In all patients the efficacy of ELT was periodically assessed during a one-year period of follow-up. Concrements detected in the gallbladder during this period indicated a CHL recurrence.

All the patients were assigned to 3 groups. Group I consisted of CHL patients ($n$=16) with essentially normal lipid metabolism parameters prior to ELT. Group II (control) contained 31 CHL patients in whom hyperlipidemia was not corected after ELT. These were the patients treated in our clinic between 1989 and 1991, a time when methods of hyperlipidemia correction had not yet been developed. The 33 patients who comprised group III were divided into 2 subgroups according to the severity of lipid metabolism disorders. Patients from subgroup IIIA ($n$=16) had the following lipid metabolism parameters: serum cholesterol <250 mg/dl (6.5 mmol/liter), triglycerides <200 mg/dl (2.3 mmol/liter), and a dyslipoproteinemia coefficient <3.5. Subgroup IIIB included patients ($n$=17) with pronounced alterations in lipid metabolism: cholesterol >250-300 mg/dl (6.5-7.8 mmol/liter), triglycerides >200 mg/dl (2.3 mmol/liter), and a dyslipoproteinemia coefficient >3.5.

For correction of hyperlipoproteinemia the patients of subgroup IIIA were put on the low-cholesterol diet recommended by WHO with our modifications [2]. Subgroup IIIB patients and patients from subgroup IIIA who did not respond positively to the diet were treated with Mevacor (a hydroxy methyl-glutaryl CoA reductase inhibitor), which was administered in a dose of 40-80 mg/day over a 30-day period depending on the severity of hyperlipidemia. After normalization of the lipid metabolism, they were maintained on the low-cholesterol diet. In addition, after ELT all patients were prescribed choleretics and cholekine-

**TABLE 1.** Lipid Metabolism Parameters before and after Extracorporeal Lithotripsy

| Patients, periods of investigation | Parameter | | | | |
|---|---|---|---|---|---|
| | cholesterol | triglycerides | HDL cholesterol | LDL cholesterol | dyslipoproteinemia coefficient |
| Healthy | 209.38±6.87 | 109.17±7.47 | 51.52±3.29 | up to 130.0 | up to 3.0 |
| Group I ($n$=16) | | | | | |
| without hyperlipidemia, baseline | 172.4±16.5 | 95.7±10.8 | 49.3±5.2 | 103.4±19.7 | 2.51±0.16 |
| after 8–12 months | 164.5±9.4 | 101.9±16.8 | 52.3±8.2 | 112.4±12.6 | 2.33±0.21 |
| Group II ($n$=14) | | | | | |
| without correction of hyperlipidemia, baseline | 272.5±16.0* | 192.2±13.2* | 47.8±4.7 | 187.9±17.2* | 4.78±0.49* |
| after 8–12 months | 297.1±19.4* | 196.2±12.2* | 57.3±6.2 | 155.5±8.8* | 4.67±0.51* |
| Subgroup IIIA ($n$=16) | | | | | |
| diet therapy, baseline | 255.5±7.1* | 139.9±13.1 | 61.2±4.0 | 166.2±5.7* | 3.2±0.23* |
| after 8–12 months | 230.8±8.3** | 102.0±9.4** | 57.3±3.0 | 147.6±2.2** | 3.15±0.24 |
| Subgroup IIIB ($n$=17) | | | | | |
| Mevacor, baseline | 291.2±12.3* | 188.1±20.6* | 60.9±3.9 | 187.6±11.2* | 3.73±0.26* |
| after 8–12 months | 223.7±13.4** | 100.0±8.6** | 61.1±3.8 | 142.4±7.6** | 3.1±0.21** |

**Note.** One asterisk indicates $p<0.05$ compared with the norm; two asterisks indicate $p<0.05$ compared with the baseline.

TABLE 2. Effect of Hyperlipidemia on the Frequency of Cholelithiasis Recurrences after Extracorporeal Lithotripsy

| Patients | Number of patients | Number of recurrences | % of recurrences |
|---|---|---|---|
| Group I (without hyperlipidemia) | 16 | 0 | 0 |
| Group II (control, noncorrected hyperlipidemia) | 31 | 24 | 77 |
| Group III (corrected hyperlipidemia) | 33 | 4 | 12 |
| Subgroup IIIA (correction with diet therapy) | 16 | 3 | 18 |
| Subgroup IIIB (correction with Mevacor) | 17 | 1 | 6 |

tics according to the conventional method of elimination of concrement fragments from the gallbladder [4].

## RESULTS

Table 1 summarizes the biochemical parameters characterizing lipid metabolism in the observed patients. In group I patients the initially normal blood lipid contents remained unchanged. In none of these patients did we detect any concrements in the gallbladder during a 12-month period after ELT. In group II patients (control) the cholesterol, triglyceride, and LDL cholesterol levels were significantly higher than in the norm and remained virtually unchanged during the 12-month period. In 24 patients (77%) newly formed concrements were detected in the gallbladder. Cholecystectomy was performed in 5 patients due to episodic recurrences of the disease.

Judging from the studied lipid metabolism parameters, the subgroup IIIB patients exhibited a more pronounced hyperlipidemia. Diet therapy and treatment with Mevacor induced unidirectional changes in these parameters. It should be stressed that in group IIIA patients (diet therapy) the cholesterol, triglyceride, and LDL cholesterol levels dropped 9.6, 27, and 11.2%, respectively, while in subgroup IIIB (Mevacor) the changes in these parameters were much more pronounced: 23.2, 47, and 23%, respectively. Detailed analysis showed that a hypolipidemic effect was not achieved in 3 out of 16 patients (18%) of subgroup IIIA. It is noteworthy that in these patients newly formed concrements were detected during the 12-month follow-up period. After repeated ELT these patients were given Mevacor to correct hyperlipidemia. After 6 months their lipid metabolism normalized, and there were no concrements in the gallbladder.

In group IIIB, treatment of hyperlipidemia with Mevacor resulted in a more dramatic - all the lipid metabolism parameters normalized and there were no CHL recurrences after ELT. Only in one female patient out of 17 persons (6%) did Mevacor (40 mg/day) fail to have an effect: her lipid metabolism parameters did not normalize, and newly formed concrements were detected in her gallbladder.

Thus, if the cases of refractory hyperlipidemia are excluded from the analysis, it is clear that against the background of appropriate therapy the probability of CHL recurrence is extremely low, and the results of ELT in such patients were practically the same as in patients without hyperlipidemia (group I).

This study shows that the results of ELT in the treatment of uncomplicated CHL may hinge not just on the selection of patients, the specific technicalities of treatment, and standard lithotripsy. There is a large group of patients, 47.5% according to our results, in whom CHL is a clinical manifestation of hyperlipidemia. The fulfillment of all ELT requirements and conditions, including complete removal of concrement fragments from the gallbladder, did not cure these patients. In patients with refractory CHL a recurrence will occur after a certain time. This is confirmed by the study of lithogenesis in hyperlipidemia, demonstrating a strong positive correlation between lithogenesis and plasma lipid levels [8,9]. Nilsell *et al.* showed that in hyperlipidemia the bile becomes lithogenic only in the gallbladder and attributed this to a toxic influence of solubilized bile acids on the gallbladder mucosa when the cholesterol concentration in the bile increases. These sites on the mucosa may serve as nucleation zones for repeated formation of concrements even in the absence of cholesterol crystals, concrement fragments, or any other matrix [7].

A prolonged cycle of enterohepatic circulation of bile acids due to impaired peristaltic function of the intestine is an additional pathogenetic link in cholelithiasis recurrence [5].

Our results confirm the experimental evidence on the relationship between hyperlipidemia and cholelithogenesis. The marked drop in the frequency of CHL recurrences after ELT is an additional indication of the importance of this pathogenetic link in CHL development. The choice of the mode of hyperlipidemia correction is determined by the disease severity and can be modi-

fied depending on the lipid spectrum of the patient's plasma. A prompt identification of lipid metabolism disorders in CHL patients paves the way for a clear prognosis for the chosen treatment as well as a pathogenetically substantiated cholesterol-lowering corrective therapy for the prevention of CHL recurrence after extracorporeal lithotripsy.

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