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# Natural History and Treatment with Ursodiol of Gallstones Formed During Rapid Loss of Weight in Man

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Cholesterol gallstones form frequently among obese patients during rapid loss of weight. The aims of the present study were to determine the short-term natural history of these gallstones and the efficacy of ursodiol for their dissolution. Twenty-two patients whose gallstones had formed during rapid loss of weight were randomized in double-masked fashion to either ursodiol, 1200 mg/day, or placebo for nine months. Ultrasonography of the gallbladder was performed after three and nine months of treatment. All patients without disappearance of their gallstones after nine months received open-label ursodiol for an additional nine months with ultrasonography after three and nine months. Among the patients completing three months of masked treatment, disappearance of gallstones was seen in five of 11 patients who received placebo and four of seven patients who received ursodiol. Only one additional patient of six continuing placebo for nine months experienced disappearance. Neither of two patients continuing ursodiol for nine months had disappearance of gallstones. None of the five patients treated with open-label ursodiol for nine months had disappearance of gallstones. Thus, half of the gallstones that form during rapid loss of weight disappear rapidly once loss of weight ceases; ursodiol may not increase the frequency or rapidity of their disappearance.

**KEY WORDS:** gallstones; weight loss; ursodiol.

Gallstones form rapidly and frequently during rapid loss of weight induced by either dietary (1, 2) or surgical (3) means. The gallstones frequently cause symptoms and require treatment, yet many disappear (dissolve or pass) without causing symptoms (1, 2). Thus, clinical decisions regarding management of these gallstones is not straightforward.

Ursodiol can prevent the gallstones induced by very low calorie diets (1). Nevertheless, since only 25% of patients receiving very low calorie diets form gallstones, only 25% of the patients who form gallstones develop symptoms, and many of the gallstones disappear without causing symptoms, prophylaxis of all patients receiving very low calorie diets may not be reasonable (1). Furthermore, attempts to identify subgroups of dieters most appropriate for prophylactic treatment, ie, at highest risk for forming gallstones, have met with limited success (4).

While prophylaxis may be preferable, a second option for management is treatment with bile acids of the gallstones after they form or, alternatively, when they begin causing symptoms. The efficacy of bile acids for dissolution of gallstones, in general, however, is only 20–70% (5–7). Nevertheless, because gallstones that form during loss of weight are small (8) and high in cholesterol (1, 2), the efficacy of bile acids in these patients may be high (7).

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In order to assist with therapeutic clinical decisions, the aims of the present study were: (1) to obtain additional data on the short-term natural history (ie, tendencies to cause symptoms or disappear) of gallstones formed during very low calorie diets and (2) to determine the efficacy of the bile acid ursodiol for dissolving the gallstones.

## MATERIALS AND METHODS

All but two patients participating in this study had participated in a previously reported study of the incidence of gallstone formation during a very low calorie diet [520 kcal; Health Management Resources (HMR), Boston, Massachusetts] (4). Two patients had participated in an even earlier study (1). They all had an ultrasonogram of the gallbladder that was normal when they began the diet but an ultrasonogram showing gallstones during the 16th week of the diet. During the present study, few patients continued to receive the very low calorie diet for more than several weeks. Most resumed a "normal" diet that resulted in maintenance of weight or an increase in weight.

All patients who agreed to enter the present study were randomized in double-masked fashion to receive ursodiol, 600 mg twice a day, or an identical-appearing placebo. All but two patients were randomized within four weeks of the ultrasonogram showing gallstones (the 16th week of the diet). These two patients were randomized 19 and 22 months after their ultrasonograms showed gallstones. Ultrasonograms in both of these patients at the time of randomization showed persistence of the gallstones.

An ultrasonogram was obtained three months after treatment began. If gallstones still were present at three months, treatment was continued until nine months, when an ultrasonogram again was obtained. If gallstones no longer were present at the time of the three- or nine-month ultrasonogram, treatment was continued for three additional months, the absence of the gallstones was confirmed by another ultrasonogram, and masked treatment was discontinued.

If gallstones still were present at the time of the nine-month ultrasonogram, patients were placed on open-label ursodiol, 600 mg twice a day, without unmasking their prior treatment. Ultrasonograms were obtained after three and nine months of treatment with open-label ursodiol. If either ultrasonogram showed disappearance of the gallstones, treatment was continued for another three months, at which time disappearance was confirmed by another ultrasonogram.

All ultrasonograms were read individually by a single ultrasonographer who was masked to the identity of the patient, the timing of the ultrasonogram, and the treatment. Upon completion of the study by each patient, the ultrasonogram showing gallstones (16th week of the diet) and the final ultrasonogram were read side-by-side in masked fashion to confirm the reading of disappearance or nondisappearance. (All initial readings were confirmed by the side-by-side readings.)

TABLE 1. TREATMENT OF GALLSTONES FORMED DURING RAPID LOSS OF WEIGHT WITH PLACEBO OR URSODIOL

| | *Placebo* | | *Ursodiol* |
|---|---|---|---|
| Randomized (*N*) | 12 | | 10 |
| Gender, male/female (*N*) | 4/8 | NS | 4/6 |
| Age (years ± SD) | 46 ± 12 | NS | 41 ± 13 |
| Weight (kg ± SD) | 82.1 ± 18.4* | NS | 89.3 ± 25.2 |
| Completing 3 months of treatment, stone-free/stones (*N*) | 5/6 | | 4/3 |
| Completing 9 months of treatment, stone-free/stones (*N*) | 1/5 | | 0/2 |
| Completing 9 months of open-label ursodiol, stone-free/stones (*N*) | 0/4 | | 0/1 |

*$N = 11$.

The study was approved by the Human Subjects Committee of Cedars-Sinai Medical Center, and all patients gave informed consent before entering the study.

## RESULTS

Twenty-seven of 253 patients (10%) who completed 16 weeks of the HMR diet developed gallstones. Seven patients (three of them symptomatic) did not agree to participate in the present study. Twenty patients (all asymptomatic) agreed to participate and were randomized to treatment along with the two additional patients who had formed gallstones 19 and 22 months previously in an earlier study. (One of these two patients received placebo and the other ursodiol.) The majority of patients in both groups had gallstones that were multiple and less than 1 cm in diameter.

When patients forming gallstones ($N = 29$) were compared with patients to whom treatment was randomized ($N = 22$), there were no significant differences ($P > 0.05$) in gender, age, or weight. The placebo- and ursodiol-treated groups also were similar with respect to gender, age, and weight when they began treatment (Table 1).

Among the 20 patients randomized to treatment within four weeks of the ultrasound examination first showing gallstones, two patients in the placebo-treated group and one in the ursodiol-treated group had biliary-type pain (episodic, upper abdominal, constant, and lasting less than several hours) two weeks to six months after starting treatment.

In the placebo-treated group 11 of 12 patients completed three months of treatment, and five of the 11 had disappearance of their gallstones (Table 1). One of six patients completing nine months of placebo had disappearance of gallstones. In the

ursodiol-treated group, seven of 10 patients completed three months of treatment, and four of the seven had disappearance of their gallstones. Neither of two patients who completed nine months of therapy with ursodiol had disappearance of their gallstones. Gallstones did not disappear after nine months of treatment in either of the two patients whose gallstones had formed 19 and 22 months previously.

Only two patients randomized to ursodiol received open-label ursodiol, and only one of these completed nine months of therapy (without disappearance of gallstones). Among the five patients randomized to placebo who then received open-label ursodiol, none had disappearance of gallstones (including the one patient whose gallstones had formed 19 months previously). Duodenal biliary drainage in four of the five patients not experiencing disappearance of their gallstones during treatment with open-label ursodiol revealed relative ursodiol concentrations (as percentage of total bile acids) of 34%, 34%, 39%, and 29% with cholesterol saturation indices of 0.94, 0.90, 1.30, and 1.31, respectively.

## DISCUSSION

Three of the 27 patients who were eligible to participate in the study (excluding the two patients whose gallstones had formed 19 and 22 months prior to randomization) experienced biliary pain prior to randomization and chose not to enter the study. Three patients developed biliary symptoms within 10 months of entering the study. Thus, six patients became symptomatic within six months of beginning the diet (6/27 or 22%). This is similar to the incidence of symptoms reported by others (2, 3). Nevertheless, this may be an underestimate since seven patients were lost to follow-up following formation of their gallstones.

With placebo, gallstones disappeared in approximately half the patients during the first three months of treatment, while between the third and ninth month gallstones disappeared in only one of the six remaining patients. Although additional patients might have experienced disappearance of their gallstones if followed for longer than nine months, these data suggest that at least half of all patients will have their gallstones disappear spontaneously and rapidly once loss of weight ceases.

There are two potential explanations for the frequent and rapid disappearance of the gallstones. The first is that the gallstones passed spontaneously through the biliary ducts and into the intestine. This seems unlikely since the rate of spontaneous disappearance of gallstones, in general, is much lower than what we observed (8). The second explanation is that the gallstones dissolved within the gallbladder. This is a more reasonable explanation since: (1) it has been shown that when the weight of obese individuals decreases and stabilizes, bile becomes less saturated with cholesterol, a change that would favor dissolution (9), and (2) the biliary cholesterol-saturating effects of weight loss (1) would be expected to cease once weight loss ceased. Nevertheless, the rapidity of dissolution was extraordinary since even the gallstones of patients treated with ursodiol, an agent that cholesterol-unsaturates bile, usually require more than three months of treatment to dissolve (6). This suggests that there is something unique about many of the gallstones that form during rapid loss of weight, eg, a very high concentration of cholesterol, that makes the gallstones unusually susceptible to spontaneous dissolution.

Three months of treatment with ursodiol did not increase the frequency of disappearance of gallstones. It is possible, however, that ursodiol hastened the disappearance of the gallstones within the first three months of treatment and that this would have been detected if ultrasonography had been done prior to three months. Nevertheless, this hastening of dissolution would have limited clinical relevance since only a small percentage of symptoms potentially would be prevented.

Six of nine patients whose gallstones had not disappeared after three months of treatment with either placebo or ursodiol received nine months of ursodiol, and none experienced disappearance of gallstones. Neither of the two patients who were randomized 19 and 22 months after their gallstones were first seen, and none of four patients who received nine months of placebo followed by nine months of open-label ursodiol experienced disappearance of their gallstones. It is possible that the delay in treatment of nine or more months resulted in resistance of the gallstones (10).

The bile of four patients receiving open-label ursodiol for nine months contained substantial amounts of ursodiol, suggesting compliance with treatment. Two of the four patients had cholesterol-saturated bile despite receiving 15 and 20 mg/kg/day of ursodiol. This is consistent with the previously reported resistance of some obese patients to bile

acid therapy (11). The lack of dissolution of gallstones in the two patients with cholesterol-unsaturated bile suggests that at least some gallstones, in fact, are resistant to the biliary cholesterol-unsaturating effects of ursodiol.

Despite the limitations of small numbers of patients and a high loss of randomized patients, what conclusions might be drawn from this study regarding gallstones that form during rapid loss of weight and their treatment with ursodiol? The first conclusion is that many of the gallstones (22%) become symptomatic early (within weeks or months) after their formation. Second, there is a high frequency (approximately 50%) of spontaneous and rapid (less than three months) disappearance of the gallstones. Third, ursodiol for three months at 600 mg twice a day may be ineffective at promoting disappearance of gallstones. Even if ursodiol were to hasten disappearance of gallstones, the effect of short-term treatment (three months) would probably be of little clinical benefit because of the high frequency of spontaneous, rapid disappearance of gallstones. Fourth, at least some gallstones do not dissolve rapidly (by nine months) with ursodiol treatment. Finally, when treating obese patients, it may be prudent to determine if adequate doses of ursodiol (as reflected by biliary cholesterol saturation) are being given.

Before ursodiol can be considered further for treatment of gallstones that form during rapid loss of weight, additional studies with ursodiol should be carried out to: (1) predict formation and disappearance of gallstones and development of biliary symptoms, (2) assess longer duration, higher dose or delayed initiation of treatment, and, if warranted by these studies, (3) compare treatment and prophylaxis.

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