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Gallbladder motility and gallstone formation in obese patients following very low calorie diets. Use it (fat) to lose it (well)

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OBJECTIVE: Dieting obese subjects are at risk of developing gallstones. A gallbladder motor dysfunction could have a pathogenetic role. The principal aim of this study was to evaluate the long term effects of two very low calorie diets differing in fat content on gallbladder emptying and gallstone formation in obese subjects.
DESIGN AND SUBJECTS: Gallbladder emptying in response to meals (breakfast, lunch and dinner) in two different diet regimens (3.0 *vs* 12.2 g of fat/d) was evaluated by ultrasonography in 32 gallstone-free obese patients on different days, before and during (at 45 d intervals) one or two 6-month weight reduction diets (for the first three months: 2.24 MJ (535.2 kcal), 3.0 g fat/d *vs* 2.415 MJ (577.0 kcal), 12.2 g fat/d; for the second three months, the same low calorie diet of 4.194 MJ (1002 kcal)/d for both groups). In 10 subjects, bile analysis was also performed.
RESULTS: Twenty-two (69%) subjects concluded the study, eleven in each group, and a significant weight loss was achieved by all subjects. Gallstones (asymptomatic) developed in 6/11 (54.5%) ($P < 0.01$) of subjects following the lower fat diet, but in none with the higher fat regimen. In the dieters during the first three months (very low calorie phase) the higher fat meals always induced a significantly greater gallbladder emptying than the lower fat meals. The cholesterol saturation index initially increased significantly and then decreased, without difference between the two groups.
CONCLUSION: In the obese during rapid weight loss from a very low calorie diet, a relatively high fat intake could prevent gallstone formation, probably by maintaining an adequate gallbladder emptying, which could counterbalance lithogenic mechanisms acting during weight loss.

Keywords: weight loss; dietary programs; ultrasonography; biliary cholesterol; bile acids

Introduction

Clinical[1–3] and epidemiological[4–6] data show that obesity is significantly associated with cholesterol gallstone disease; this risk is even higher during rapid weight loss, whether achieved by bariatric surgery[7–11] or adherence to a very-low-calorie diet (VLCD).[12,13] This increase in risk has been attributed to several pathogenetic mechanisms, including increased biliary cholesterol output, increased gallbladder secretion of mucin and calcium, as well as increased presence of E2 prostaglandins and arachidonic acid.[14–18]

A pathogenetic role for gallbladder stasis, as a consequence of reduced gallbladder stimulation by the low fat content of VLCDs, has also been suggested.[19,20]

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We explored this possibility in a preliminary[21] study on obese subjects during weight reduction, using a VLCD similar to those[12,13] associated with increased gallstone formation in terms of energy (2.176 MJ or 520 kcal), but differing in relation to fat content (12.2 g/d *vs* 1 g/d) and food type (liquid formula plus conventional foods *vs* liquid formula), but we found no alterations in gallbladder emptying or gallstone formation. These results and those of a more recent paper[22] support the hypothesis that low fat intake, and consequent gallbladder stasis, in some measure favors the increased risk for gallstones in dieting obese subjects.

The principal aim of the present work was to verify this hypothesis by comparing the effects of two VLCDs of different fat content (3 g *vs* 12.2 g/d) on gallstone formation and gallbladder emptying in the dieting obese.

As a secondary aim, in a subgroup of subjects we comparatively evaluated the effects of the two VLCDs on biliary lipid composition and cholesterol saturation index. Finally, in an adjunctive pre-diet study, we compared the effects of meals of different fat content on gallbladder emptying in healthy controls *vs* obese subjects.

Methods

Patients

Thirty-two obese (body mass index, BMI: $41.6 \pm 1.4\,kg/m^2$) patients (12 male, 20 female; mean age 40.5 y, range 17–54 y) and 32 normal weight, healthy control subjects, matched for gender and age were studied. The controls participated only in the pre-diet baseline study of gallbladder emptying. All patients and controls were determined to be gallstone-free by ultrasonography (US); none of the obese subjects had cardiovascular, gastrointestinal or hepatobiliary diseases, diabetes, hypothyroidism or Cushing's syndrome. None of the patients were taking medications that could potentially influence gallstone formation, such as sex hormones, nonsteroidal anti-inflammatory drugs, lipid-lowering agents, anticholinergics or cholelitholytic bile acids. After they were informed about the possible risk of developing gallstones by adherence to a VLCD,[19] all patients gave written informed consent to participate in the study, which was carried out according to the Helsinki Declaration and was approved by the Ethics Committees of our Institutions.

Experimental design

The weight reduction diet commonly used at our Institutions is characterized by an initial three month period in which patients follow a VLCD of about 2.093 MJ (500 kcal/d) with 12 g/d of fat, consisting of liquid formula plus conventional foods (to facilitate patient compliance), and by a subsequent phase of another three months duration in which a low calorie diet (LCD) of about 4.186 MJ (1000 kcal/d) consisting of conventional foods is followed. This latter phase is aimed at maintaining the weight reduction obtained during the initial phase.

In the present study, for the initial three-month phase, obese subjects were randomized into one of two VLCDs (a low-fat VLCD or a high-fat VLCD) of similar total caloric intake but differing mainly in fat content, while for the second phase the same LCD was used for both groups of subjects.

As a pre-diet assessment, a three-day study of gallbladder emptying was performed in all obese subjects, before being randomized, and in 32 matched controls as follows: on day 1, gallbladder emptying was evaluated three times in response to each of the three daily meals (breakfast, lunch and dinner) comprising low-fat VLCD (low-fat VLCD test meals); on day 2, emptying was measured in response to each of the three daily meals comprising high-fat VLCD (high-fat VLCD test meals); and, on day 3, after the standard liquid test meal that we routinely use to induce maximal gallbladder emptying.[23] In obese subjects only, the same three-day study of gallbladder emptying was repeated during the weight reduction starting on day 45 and day 90 of the VLCDs, to investigate the long term effect of these diets and resultant weight loss on gallbladder emptying, and to exclude an adaptive gallbladder response to either of the VLCDs. This full gallbladder kinetics evaluation was also performed during this phase of the weight loss programs, since it has been demonstrated that the highest risk for gallstone formation occurs early in the course of a VLCD weight loss program.[19] Finally on day 135 and day 180 (during the LCD phase), gallbladder emptying was studied in response to the liquid test meal only. This complex experimental design was adopted in order to obtain a more complete picture of the differences in gallbladder emptying in response to the different VLCDs.

Throughout the six months, at each 45 day US examination, the presence of biliary sludge or gallstones was also sought. In addition, samples of gallbladder bile from 10 obese subjects were collected by duodenal intubation at day 0, day 45 and day 90 of the weight reduction diets.

Experimental procedure

Weight reduction diets. Phase One (VLCD). Obese patients were randomly assigned to one of two 90-day weight reduction dietary regimens, 1) Low-fat program or 2) High-fat program.

1) Low-fat program: In this program, subjects followed low-fat VLCD (2.24 MJ (535.2 kcal), obtained from 3.0 g fat, 44.4 g protein and 82.2 g carbohydrate), with the addition of vitamins, trace elements and mineral supplements, plus at least 2 l/d of non-caloric liquids. Low-fat VLCD was consumed in three meals per day as follows: for breakfast (08.00 h), 2 rusk toasts and a cup of unsweetened tea; lunch (13.00 h), half a unit dose of a powdered supplement (Precision BR, Sandoz Nutrition Company, Minneapolis, MN, USA) dissolved in 100 ml of water and 120 g of turkey breast and for dinner (18.00 h), half a unit dose of Precision BR and two helpings of lettuce.

2) High-fat program: In this program, subjects followed high-fat VLCD (2.415 MJ (577 kcal), obtained from 12.2 g fat, 55.0 g protein and 61.7 g carbohydrate), with the addition of vitamins, trace elements and mineral supplements, plus at least 2 l/d of non-caloric liquids. High-fat VLCD was consumed in three meals per day as follows: for breakfast (08.00 h), 2 rusk toasts and a cup of unsweetened tea; lunch (13.00 h), half a unit dose of a powdered supplement (Precision N, Sandoz Nutrition Company) dissolved in 100 ml water and 120 g turkey breast; and dinner (18.00 h), half a unit dose of precision N and two helpings of lettuce.

Phase two (LCD). After the first 90 d of the study, both groups of obese subjects (Low-fat and High-fat programs) followed a LCD of 4.194 MJ (1.002 kcal)/d, identical for both groups, for the remaining 90 d of the study. The regimen consisted of 50 g mixed proteins, 30 g fats and 133 g complex carbohydrates, supplied by conventional foods (no liquid formula meals); vitamins, trace elements and mineral supplements at least 2 l/d of non-caloric liquids were also given. All studied subjects were instructed to consume their food allowances in no more than three meals per day.

For both phases, no medications were allowed, while moderate physical activity was recommended. Clinical assessment and biochemical tests (liver function tests; serum total protein, lipid pattern, iron and electrolytes; red and white blood cell counts and urinary nitrogen excretion) were performed every 10 d during phase one and every 15 d during phase two. Subject compliance to the diet regimen was verified by monitoring urinary ketone bodies[24] using the Keto-Diabur Test 5000 (Boerhinger Mannheim, Mannheim, Germany). At the end of the study, a maintenance diet was established for each patient, based on the weight reduction achieved with the previous programs and on the specific metabolic requirements of each patient.

Gallbladder emptying before and during weight loss. In all obese patients (prior to starting the weight reduction program), and in a matched set of control subjects, gallbladder emptying was evaluated for three consecutive days, as described above. The same three-day study was subsequently performed in obese subjects starting on day 45 and day 90 of the VLCDs; whereas, on day 135 and day 180 (day 45 and day 90 of the LCD), gallbladder emptying was evaluated only in response to the ingestion of the standard liquid meal.

The standard liquid meal (Colecystotest, IMS, Milano, Italy) contains 1.57 MJ (375 kcal) derived from 17 g fats, 10.4 g proteins and 45 g carbohydrates.

Gallbladder volumes were measured as previously described,[23] using the ellipsoid method,[25] by which volume is given as 0.52 (WxHxL), where W is gallbladder width; H, height and L, axial length. Measurements were performed before, and every 10 min after, ingestion of the meals until 80% gallbladder refilling was reached. Results were expressed as: fasting gallbladder volume (FV, in ml), given as the mean of the four measurements obtained before meal ingestion; and percent gallbladder emptying (%E), given by (1.0, postprandial gallbladder volume/fasting gallbladder volume) $\times$ 100%. US was performed using a real-time instrument (Toshiba SS 90A, Tokyo, Japan) with 3.75 MHz linear and sector transducers. All of the measurements were obtained by three sonographers (DF, AC and MO) and inter and intraobserver variations of less than 8% were documented.

In the obese patients, the presence of biliary sludge or gallstones was also sought by US at the same 45 d intervals for the entire 6 months of the study.

The sonographers were blinded to the dieting status of the subjects.

Bile analysis. In 10 obese patients (five following Low-fat program, five High-fat program), biliary lipid composition, cholesterol saturation index and cholesterol crystals were evaluated in bile collected by duodenal intubation just before initiating the weight reduction diets, and on day 45 and day 90 of the programs.

Bile samples were collected after fasting, through a polyvinyl nasoduodenal tube positioned under fluoroscopic control in the second portion of the duodenum. To obtain gallbladder contraction, caerulein (2 ng/kg bw/min for 5 min) (Takus, Farmitalia-Carlo Erba, Milan, Italy) was slowly infused intravenously. One milliliter of dark duodenal juice was diluted 1:9 (vol./vol.) with isopropanol and the remainder was analyzed for cholesterol crystals. Each sample of diluted bile was analyzed for cholesterol,[26] phospholipids[27] and total bile acids (Sterognost 3 alpha, Nyegard and Co-Ass, Oslo, Norway) utilizing enzymatic spectrocalorimetric assays.

Statistics

The results were expressed as mean $\pm$ s.e.m. Student's *t* test was used to assess whether there was a statistically significant difference between the two groups for continuous variables. Fisher's exact test provided a statistical assessment of whether there was an association between two dichotomous variables.[28] Repeated-measurement Analysis of Variance was used. When interaction terms were significant, Fisher's least significant difference was used to simultaneously test valid simple effects.[29] Statistical significance was assigned if P was < 0.05. Statistical analysis was performed using the Statistical Analysis System (SAS) version of 6.04.[30]

Results

Weight reduction program

Patient compliance. Twenty-two of 32 patients (69%) concluded the study. Adherence to the diet program was confirmed for all subjects by verifying expected weight loss, and by detection of ketone bodies in the urine (during the first 90 d). The remaining 10 subjects (five each in the Low-fat and High-fat programs) stopped the diet, either because of excessive initial weight loss (two patients) or inability to adhere to the diet (eight patients). The drop-out group showed no differences in gender or age with respect to the group completing the study.

No clinical or biochemical abnormalities were observed in any patient during the six months of the study.

Weight loss. BMI and body weight significantly decreased throughout the six-month weight reduction diet in each group (Low-fat and High-fat programs, see Figure 1). Values for these parameters were statistically different from baseline at each timepoint; however, there was no difference between the two groups in this respect. Moreover, no difference in weight reduction rate was observed between the two groups of patients, nor was any difference found between subjects who formed gallstones and those who did not.

Six months after stopping the diet, the mean weight gain was 3.8 ± 1.9 kg for subjects who followed Low-fat program and 3.1 ± 1.5 kg for those in High-fat program.

Gallstones. Six (4 female and 2 male) of the 11 patients (54.5%) who followed the Low-fat program, but none from High-fat program, developed gallstones during phase one (the first 90 days) of the weight reduction program ($P < 0.01$ by Fisher's exact test). All six patients were asymptomatic. No further gallstone development was apparent in either group of patients during phase two (LCD), but all six patients still had gallstones, detected by US, at the end of the study period.

No difference in initial BMI, weight reduction rate or pre-diet serum levels of triglycerides were documented between subjects who developed gallstones and those who remained gallstone-free throughout the six months.

At an additional follow-up US examination performed six months after the end of the study, no additional gallstones were detected in any subject.

Biliary lipid composition and cholesterol saturation index. The biliary lipid composition and cholesterol saturation index of both groups of dieters during the first three-month study period are shown in Figure 2. In both groups, cholesterol molar percentage was significantly increased on day 45, but was significantly decreased with respect to basal values on day 90.

No differences were observed in either bile acid or phospholipid molar percentages during phase one of the diet. The cholesterol saturation index initially increased significantly and later decreased with respect to basal values. No differences were observed

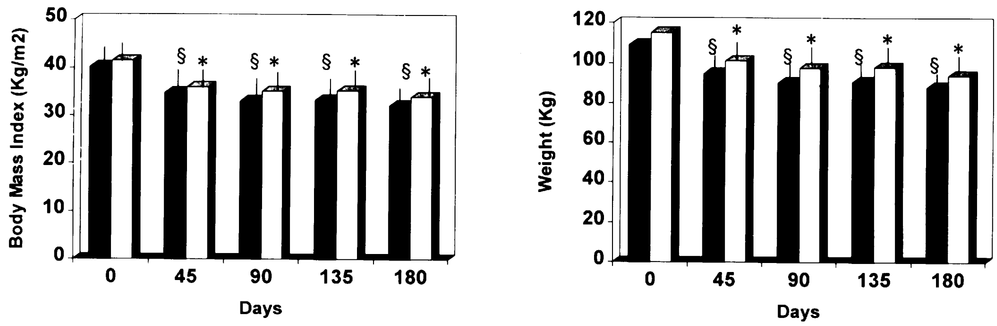

Figure 1 Body mass index (BMI) (on the left) and body weight (on the right) during weight reduction diets in obese subjects following Low-fat program (■, $n = 11$) and High-fat program (□, $n = 11$). Mean ± s.e.m., § $P < 0.05$ *vs* Day 0, * $P < 0.05$ *vs* Day 0.

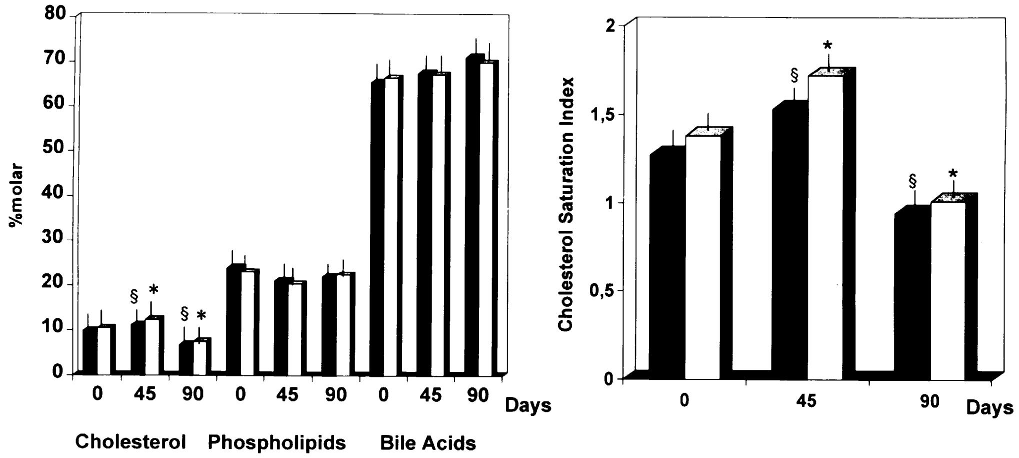

Figure 2 Biliary lipid composition (on the left) and cholesterol saturation index (on the right) in obese subjects following weight reduction Low-fat program (■, $n = 5$) and High-fat program (□, $n = 5$). Mean ± s.e.m., § $P < 0.05$ *vs* Day 0, * $P < 0.05$ *vs* Day 0.

between the two groups of dieters in terms of biliary lipid composition or cholesterol saturation index. Cholesterol crystals were found in the bile of four patients at the beginning of the diet, two each from the Low-fat and High-fat programs, and these were still present at day 45 and day 90; a third patient following the Low-fat program showed cholesterol crystals on day 45 that were still present on day 90.

Gallbladder motility

Pre-diet study. The response of gallbladder volume to low-fat VLCD test meals on day 1, high-fat VLCD test meals on day 2 and the standard liquid meal on day 3 for both obese and control subjects is shown in Table 1. Significantly greater gallbladder emptying (%E) occurred at both lunch and dinner for the high-fat VLCD test meal with respect to low-fat VLCD test meal. At breakfast, which was identical for both VLCDs, no difference in %E was noted.

Comparison between obese and control subjects showed that obese subjects had a significantly larger FV and reduced %E, and this was true for both low-fat and high-fat VLCD test meals, as well as for the standard liquid meal (Table 1).

During weight reduction. The results of the gallbladder motility studies performed on day 45 and day 90 of both programs in obese subjects, indicated that a significant reduction in FV occurred during both dietary regimens (Figure 3). A significant increase in %E was only present in subjects given the high-fat VLCD test meals (Figure 4). Furthermore, when VLCD test meals were comparatively tested within each group of subjects, the high-fat VLCD test meal always induced a significantly greater %E than the low-fat VLCD test meal for both lunch and dinner (Figure 4). At breakfast, which was identical for both VLCDs, no difference was found between VLCD test meals, or between programs. (In subjects on the Low-fat program, %E in response to breakfast on the low-fat VLCD test meal day was 26 ± 2.2% at pre-diet evaluation, 28.9 ± 1.9% at day 45, 27.2 ± 1.5% at day 90 and in response to breakfast on the high-fat VLCD test meal day, 27.1 ± 2.3% at pre-diet evaluation, 28 ± 2.5% at day 45 and 27.4 ± 1.8% at day 90. In subjects on the High-fat program %E in response to breakfast on the high-fat VLCD test meal day was 24.2 ± 1.2% at pre-diet evaluation, 26.3 ± 1.8% at day 45 and 25.8 ± 1.3% at day 90 and in response to breakfast on the low-fat VLCD test meal day 25 ± 2.3% at pre-diet evaluation, 27 ± 1.3% at day 45 and 24.6 ± 1.1% at day 90.)

The results of gallbladder motility evaluations, in response to the administration of the standard liquid meal, performed during the entire six month study period in the two groups of subjects, are shown in

Table 1 Fasting gallbladder volumes and gallbladder emptying in response to diets of different fat content and to a standard test meal in obese and control subjects (pre-diet three day study). (mean ± s.e.m.)

	Low-fat VLCD test meals						High-fat VLCD test meals							
	Breakfast		Lunch		Dinner		Breakfast		Lunch		Dinner		Test meal	
Subjects	*FV (ml)*	*%E*	*FV (ml)*	*%E*	*FV (ml)*	*%E*	*FV (ml)*	*%E*	*FV (ml)*	*%E*	*FV (ml)*	*%E*	*FV (ml)*	*%E*
Obese (*n* = 32)	34.7 ± 2.7*	24.8 ± 1.4*	34.7 ± 2.6*	41.2 ± 2.5*	32.5 ± 2.6*	41.1 ± 1.8*	36.4 ± 3*	26.2 ± 1.4*	34.5 ± 2.8*	61.6 ± 2.7*,**	32.7 ± 2.9	62.2 ± 2.2*,**	34.4 ± 2.7*	57.6 ± 2.5*
Control (*n* = 32)	19.2 ± 1.9	32.3 ± 1.9	18.2 ± 1.5	50.2 ± 1.6	19.5 ± 3.1	49.5 ± 1.4	19.4 ± 1.9	33.7 ± 3.8	18.9 ± 3.9	78.2 ± 1.8**	18.4 ± 2.2	81.2 ± 2.9**	18.5 ± 2.0	76.2 ± 2.8

VLCD = very low calorie diet; FV = fasting gallbladder volume; %E = percent gallbladder emptying.
* $P < 0.05$ *vs* controls.
** $P < 0.05$ *vs* Low-fat VLCD test meals.

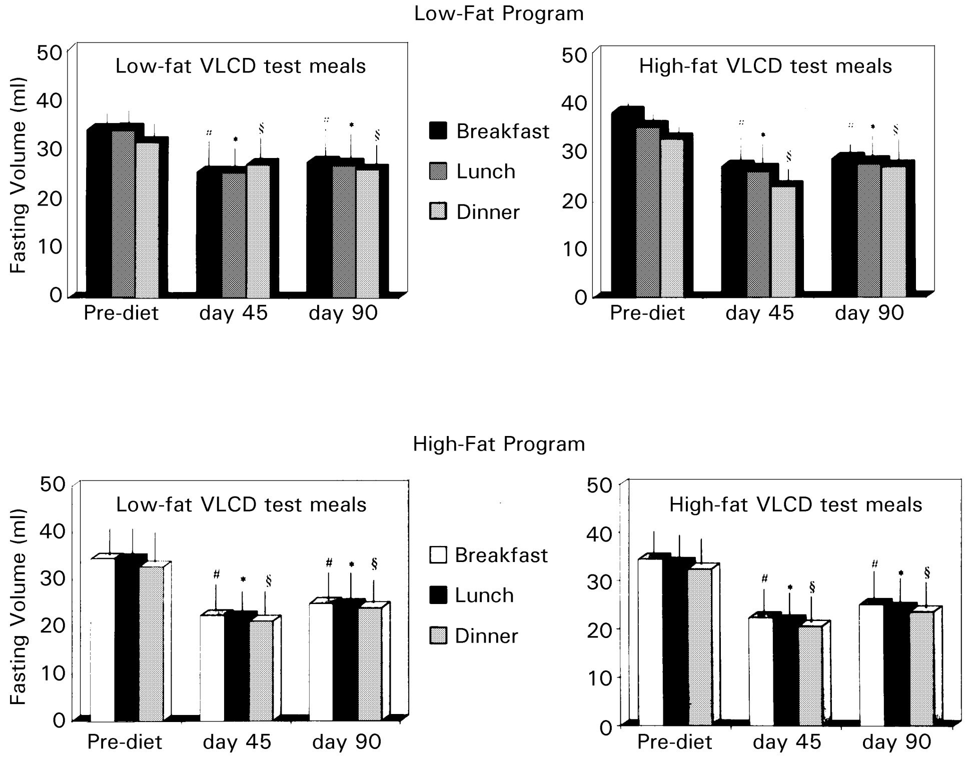

Figure 3 Fasting gallbladder volumes in obese subjects during weight reduction induced by Low-fat program ($n = 11$) (top) and High-fat program ($n = 11$) (bottom). A significant reduction in fasting volumes was documented at breakfast, lunch and dinner of day 45 and day 90 in both groups of patients when either low-fat very low calorie diet (VLCD) test meals and high-fat VLCD test meals were tested as stimuli to evaluate gallbladder motility. Mean ± s.e.m. # $P < 0.01$ *vs* Day 0, * $P < 0.01$ *vs* Day 0, § $P < 0.01$ *vs* Day 0.

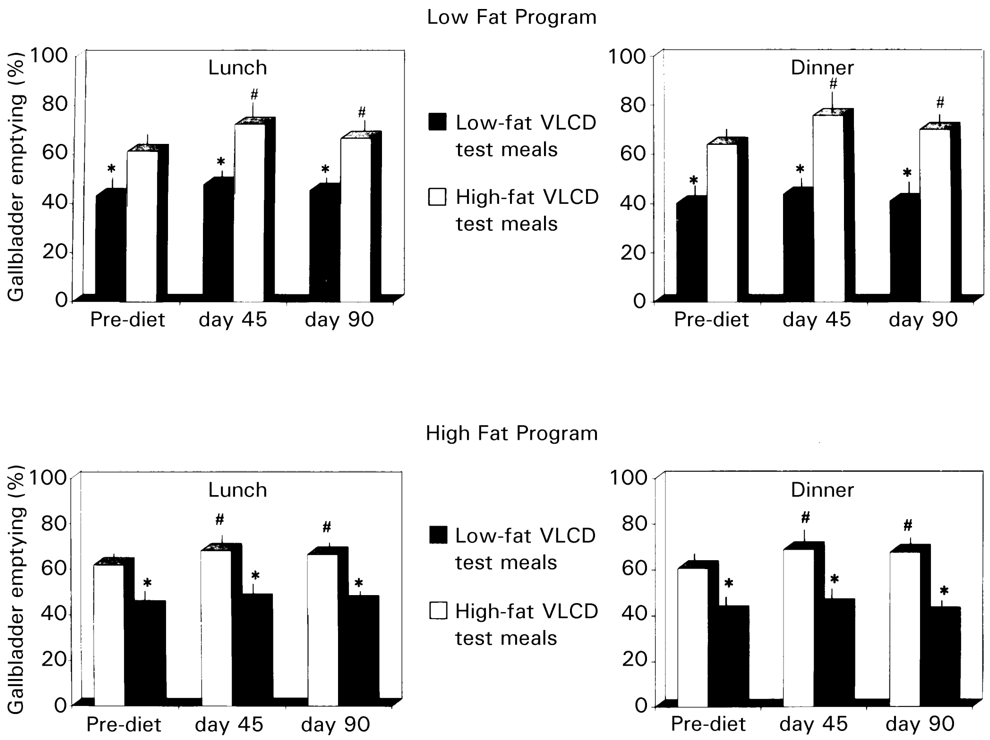

Figure 4 Percent gallbladder emptying in response to low-fat very low calorie diet (VLCD) test meals (■) and to high-fat VLCD test meals (□) tested as stimuli to evaluate gallbladder motility in the obese subjects who followed the Low-fat program (top) ($n = 11$) and in those who followed the High-fat program (bottom) ($n = 11$) for weight reduction. When the high-fat VLCD test meals were tested in subjects following the Low-fat program, a greater percentage emptying was obtained at both lunch and dinner, in relation to that induced by the low-fat VLCD test meals. The same trend was present in subjects following the High-fat program, in which a lower percentage emptying was observed when the low fat VLCD test meals were tested against the high-fat VLCD test meals. Mean ± s.e.m., * $P < 0.05$ *vs* high-fat VLCD; # $P < 0.01$ *vs* Day 0.

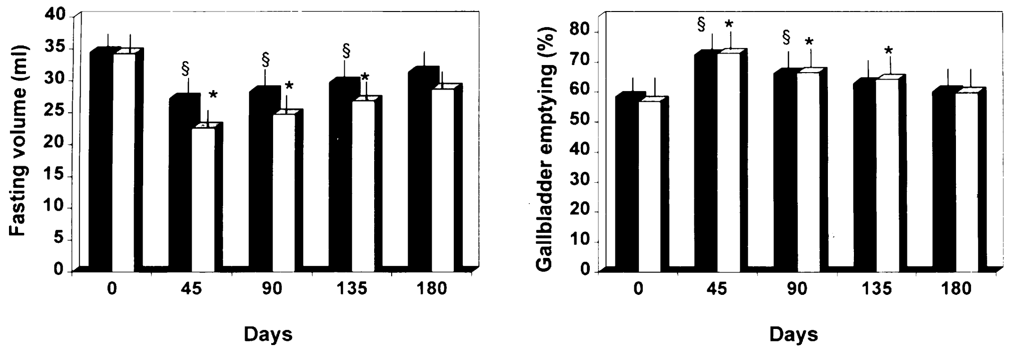

Figure 5 Fasting gallbladder volume (on the left) and percent gallbladder emptying (on the right) in response to a standard liquid meal evaluated for the entire six month study period in the obese subjects who followed the Low-fat program (■, $n=11$) and in those who followed the High-fat program (□, $n=11$) for weight reduction. Mean ± s.e.m., § $P<0.05$ *vs* Day 0; * $P<0.01$ *vs* Day 0.

Figure 5. A significant reduction in FV was observed at each repeated study until day 135 in both Low-fat and High-fat programs. %E increased in both groups of subjects, but this increase was significant only until day 90 in subjects who followed the Low-fat program and until day 135 in those who followed the High-fat program (Figure 5). There were no differences at any time between Low-fat and High-fat programs as far as FV and %E responses to the standard meal were concerned.

In phase one and phase two of both programs, no correlation was found between FV and indices of body size, BMI, body surface area, weight or height.

Furthermore, no significant differences were found in FV and %E between subjects who developed gallstones and those who remained gallstone-free.

Discussion

Bile cholesterol supersaturation, cholesterol crystal nucleation and gallbladder motor dysfunction are considered the main pathogenetic mechanisms involved in gallstone formation.[31] There is general agreement that, in the obese, supersaturation of bile due to an absolute increase in biliary cholesterol secretion is likely to be present,[14–16] and so may explain some of their propensity for forming gallstones.[19] Whether an impairment of motor activity is present in this population, however, remains controversial. Both reduced[32–34] and unmodified[35–37] gallbladder emptying have been reported and, regarding fasting gallbladder volume, although there is wide accord that obese subjects have enlarged fasting volumes, for some authors this increase is correlated with body size,[34,38] but for others it is not.[33]

In our study, the obese subjects showed a larger FV and reduced %E with respect to controls, supporting the proposition that at least some of the increased risk for gallstone formation in the obese, as for gallstone patients in general,[23,39,40] can be attributed to defective gallbladder tone and emptying.

In recent decades, many efforts have been made to develop therapeutic strategies, based mainly on surgery or dietary regimens, for safe and effective weight reduction in obese patients.[41,42] An unexpected problem that has arisen with rapid weight loss in this group, is that the already elevated risk of gallstone formation is further increased, indeed, it has been reported that 11–36% of obese subjects who lose weight rapidly, form gallstones, 6% of whom undergo cholecystectomies for acutely symptomatic calculi.[19] Up to now, the only proven means of preventing gallstone formation during rapid weight loss induced by VLCDs[43,44] or surgical procedures[45,46] has been the administration of ursodeoxycholic acid, an agent known to reduce biliary cholesterol supersaturation.[47] The present results confirm our previous findings,[21] as well as those recently published by Gebhard *et al*[22] showing that modification of VLCD fat content, through an effect on gallbladder emptying, may be an effective alternative. In fact, in the present study, the %E was significantly lower in response to stimulation by the low-fat VLCD test meals with respect to those of the high-fat VLCD, at the initial pre-diet evaluation as well as during the diet; this was also demonstrated by Gebhard *et al*,[22] albeit with a different study design since these authors compared two liquid meals differing in calories and fat content (2.18 MJ (520 Kcal), < 2 g fat/d *vs* 3.77 MJ (900 kcal), 30 g fat/d). In our study, in addition to the persistence of a significant difference in %E between the two groups of obese subjects, we also saw an initial improved motor function within each group: indeed, a significant reduction from baseline values in FV in both groups and a significantly increased %E (only in the higher fat group) were still present after 45 and 90 days of dieting. Although these values tended to return towards baseline by the third month, they did not reach pre-diet size. It may be speculated that the reduction in FV could be related to the temporary decrease in bile acid pool size and secretion known to occur during weight loss.[14,15,48] As far as %E is concerned, the reduction in the bile acid pool could enhance cholecystokinin (CCK) release[49] and, hence increase gallbladder emptying, by a mechanism similar to that demonstrated during cholestyramine administration.[50]

Further confirmation of the key role played by the diet composition in stimulating gallbladder contraction, is provided by the repeated evaluations performed starting on day 45 and day 90 of the study, when the patients who had been following the low-fat VLCD (Low-fat program) were given the high-fat VLCD test meal, a higher %E resulted. On the contrary, when patients who had been following the high-fat VLCD (High-fat program) were given the low-fat VLCD test meals, a lower %E was seen. These comparisons also allowed indirect exclusion of a possible adaptive response of the gallbladder to a given diet.

In the present study, the two dieting groups (higher *vs* lower daily fat allowances) showed similar changes in biliary lipid composition, during the weight loss program. In both groups biliary cholesterol and cholesterol saturation index increased in phase one of the diet and then later decreased to levels significantly below baseline. These results accord with those of previous studies[12,14–17] showing increased cholesterol biliary output in patients following a weight reduction diet, particularly during the initial stages of weight loss.

Thus, the most likely explanation for the fact that gallstones tended to form in those who followed the lower fat diet but not in those adhering to the higher fat regimen is that, the former had chronic inadequate gallbladder stimulation, in addition to other pathogenetic factors, whereas in the latter, the effects of the other lithogenic mechanisms were at least partially counterbalanced by adequate gallbladder emptying.

Conclusion

Our results do not accord with those of Weinsier *et al*[51] who found that the risk of gallstone formation was correlated with the rate of weight loss or energy intake rather than with fat content of the diet. Our patients lost an average of 2.0 kg/week for the first four weeks of the diet and 1.4 kg/week for the remaining weeks; however, there was no difference in the rate of weight loss between those who did and those who did not develop gallstones. Thus, while we do not necessarily disagree with these authors' assertion that 1.5 kg/week represents the upper limit for medically safe weight loss, we do believe that adequate dietary fat content is essential for gallstone prevention.

Furthermore, the risk factors that have been reported for gallstone formation during rapid weight reduction in the obese,[52] (high absolute rate of weight loss, high initial BMI and elevated serum triglyceride concentrations) were not present in our subjects who developed gallstones.

Further studies are obviously needed to gain a more complete understanding of the pathogenetic mechanisms involved in the development of gallstones in obese subjects during weight loss. In our Departments we are currently studying the influence of manipulations of VLCD dietary content on other possible lithogenic factors such as nucleating agents, release of regulating hormones and intestinal transit time.

In conclusion, in obese subjects following a VLCD for rapid weight reduction, adequate fat content of the diet appears to have an important role in preventing gallstone formation, probably by maintaining adequate gallbladder motility. Assuring adequate fat intake may be a more physiological and economical approach to gallstone prevention than administration of a pharmacological agent.

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