The transient hypercholesterolemia of major weight loss[1-3]

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ABSTRACT Serum lipoproteins, body composition, and adipose cholesterol contents of six obese women were studied during and after major weight loss by very-low-calorie diets (VLCDs). Subjects started at 168 ± 11% of ideal body weight, lost 30.3 ± 3.7 kg in 5–7 mo, followed by 2+ mo in weight maintenance. Serum cholesterol fell from a prediet (baseline) value of 5.49 ± 0.32 to 3.62 ± 0.31 mmol/L ($P < 0.01$) after 1–2 mo of VLCDs (nadir), after which it rose to 5.95 ± 0.36 mmol/L (peak, $P < 0.01$ compared with nadir and baseline) as weight loss continued. With weight maintenance, serum cholesterol fell to 4.92 ± 0.34 mmol/L ($P < 0.05$ compared with peak). Adipose cholesterol content did not change in peripheral (arm and leg) biopsy sites but rose significantly in abdominal adipose tissue with weight loss. We conclude that major weight loss was associated with a late rise in serum cholesterol, possibly from mobilization of adipose cholesterol stores, which resolved when weight loss ceased. *Am J Clin Nutr* 1991;53:1404–10.

KEY WORDS Very-low-calorie diets, serum cholesterol, adipose cholesterol

Introduction

Both elevated serum cholesterol concentration and obesity are well-established risk factors for atherosclerosis (1, 2). There is now reasonable evidence that reduction in serum cholesterol is directly linked to a reduction in coronary risk (3, 4). To act on this information, the National Institutes of Health have undertaken a campaign to promote serum cholesterol screening, combined with a major effort to educate physicians and the general public in the appropriate therapeutic steps to intervene for serum concentrations > 5.17 mmol/L (5).

The first therapeutic step recommended for the overweight patient with hypercholesterolemia (defined as > 5.17 mmol/L) is a diet to normalize body weight (6). The expected result of the weight-loss regimen is a progressive reduction in serum cholesterol as the person's excess weight is lost. Although the correlation between excess weight and elevated serum cholesterol is well-established (7), the mechanism for a relationship between excess adipose tissue and hypercholesterolemia remains unclear. Because people who are overweight are not necessarily overeaters, this is not simply an issue of dietary fat and cholesterol overconsumption by obese people (8).

There is also evidence that the response of serum cholesterol to weight loss is anything but uniform and that the individual patient's response to therapy may not follow expectations based upon epidemiologic data. For example, serum cholesterol was shown to rise in humans subjected to short periods of total starvation (9). Further, a tendency for a late rise in serum cholesterol was observed in patients undergoing therapeutic weight loss with very-low-calorie diets (VLCDs) (10–12). Although weight loss by either dieting or exercise was shown to reduce serum total cholesterol and raise high-density-lipoprotein (HDL) cholesterol (13), this is not a uniform response in all patient groups studied (14). This variability could be due to differences in methodology between these studies, such as diet composition, amount of weight lost, and timing of sample acquisition, but the underlying etiology of this variability has not been explained.

A particularly intriguing variability in serum cholesterol is the rise seen when VLCDs are taken for > 3 mo. In the course of other outpatient research, we observed that 88% of 44 adult patients experienced a diet-induced fall in cholesterol within 2 mo, 73% showed a late rise > 0.5 mmol/L, and 36% had serum cholesterol concentrations rise above prediet values while they were still losing weight.

To explore more carefully the dynamics of serum cholesterol and its subfractions during major weight loss, we obtained serum, adipose tissue, and body composition data from six moderately obese women during and after major weight loss induced by a VLCD administered in a multidisciplinary outpatient weight-management clinic.

Subjects and methods

Subjects

This outpatient study comprises data from six obese female volunteers aged 27–42 y who were recruited for the study in response to newspaper advertisements. All were ≥ 25 kg in excess of ideal body weight [IBW; taken as the median value of the medium-frame range from the Metropolitan Life Insurance Tables (15)]. Prediet studies included physical exam, electrocardiogram, and routine blood hematological and biochemical studies to exclude cardiac, hepatic, renal, or pancreatic β-cell dysfunction. All subjects were weight stable in a 3-kg range for the month before beginning the study.

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The subjects were selected from a large pool of applicants, 10 of whom were randomly assigned into two groups of 5 and prescribed different VLCD regimens. Four of the subjects did not complete the study. The characteristics of the six subjects completing the protocol are included in **Table 1.** The study protocol was approved by the University of California at Davis Human Subjects Committee, and written informed consent was obtained from each subject before participation.

Diets

Because of the length of this protocol (> 6 mo), all prescribed diets were administered on an outpatient basis and monitored by intermittent food records. For 2 wk before beginning the weight-loss protocol, during which baseline studies were performed, all subjects were advised to follow their usual dietary habits. For the first 2 wk of weight loss, they were prescribed a diet providing 4.2 MJ/d (1000 kcal/d) containing 90 g protein. Starting in the third week of the weight-loss protocol, the two patient groups were then assigned different diets. Diet 1 (food VLCD) consisted of three daily portions of lean meat, low-fat fish, or poultry providing 1.5 g protein/kg IBW in 1.9–2.5 MJ/d (450–600 kcal/d). The lipid content of this diet consisted of those fats inherent in the foods selected and was judged by diet history to contain 15–20 g triglyceride/d and 150–250 mg cholesterol/d. This diet was supplemented daily with 25 mmol potassium bicarbonate (K-Lyte; Bristol Labs, Evansville, IL), four tablets of a calcium-magnesium antacid (Calcitrel; Sterling, New York) providing 800 mg Ca and 200 mg Mg and a multivitamin with minerals (Centrum; Lederle, Wayne, NJ). In total, the food portions plus supplements provided ≥ 100% of the National Research Council's recommended dietary allowance (RDA) for the major and trace minerals and vitamins (16).

Diet 2 (formula VLCD) was a commercial product (Optifast; Sandoz, Minneapolis) providing a daily intake of 1.8 MJ (420 kcal) with 70 g protein and 30 g carbohydrate. The protein source for this formula was pasteurized egg albumin and casein. It provided 2 g fat/d as hydrogenated soybean oil and was cholesterol free. The mineral and vitamin content of the formula met or exceeded the RDA for minerals, trace minerals, and vitamins. Sodium intake for both VLCDs was supplemented with bouillon up to a total intake of 4 g/d to prevent symptoms of weakness or fatigue (17).

Subjects were encouraged to continue with their assigned VLCDs for a total weight loss of 25–35 kg. During the VLCD they participated in weekly outpatient group sessions for support and education in weight-management topics. Subjects were requested to maintain their normal physical-activity patterns during the VLCD phase of the study. On completing their weight loss, they were advised to follow a high-carbohydrate, low-fat maintenance diet patterned after the American Heart Association Level II diet (18).

Monitoring

Blood pressure, pulse, body weight, and breath acetone (by gas chromatography; Caldetect Inc, Richmond, CA) were determined once weekly during early-morning outpatient visits. The weight and breath-acetone values were used as indicators of subject adherence to the prescribed diets. Resting electrocardiograms were done monthly. Fasting blood was drawn monthly by venipuncture with minimal hemostasis. Analyses by routine semiautomated techniques included complete blood count, glucose, serum electrolytes, calcium, phosphorus, magnesium, urea nitrogen, creatinine, uric acid, albumin, aspartate aminotransferase (AST), and alkaline phosphatase.

Analyses

Serum lipid analysis. Serum was obtained monthly, after an overnight fast. Total cholesterol was measured directly in the serum by an enzymatic method (Ciba-Corning reagent, Oberlin, OH) with a Gilford 400E clinical analyzer (Gilford Instruments, Oberlin, OH) in a laboratory that is a participant in the Lipid Standardization Program (CDC, Atlanta). HDL cholesterol was determined by the same method after precipitating low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) from the serum with dextran sulfate and magnesium sulfate. The serum triglyceride (TG) was similarly quantitated enzymatically by using the same instrument with Ciba-Corning TG(GPO) reagent. The LDL-cholesterol concentration was cal-

TABLE 1
Characteristics of the subjects completing the protocol

Subject	Diet*	Age	Height	Weight	Percent IBW†	BMI‡	Weight loss§		
							At C	At D	Maximum
		y	*cm*	*kg*	*%*			*kg*	
1	Opti	41	166	115.5	203	41.9	41.5	43.2	45.7
2	MFP	27	163	83.5	152	31.4	31.9	29.6	38.0
3	Opti	32	168	104.2	180	36.9	22.2	19.9	22.2
4	Opti	39	168	114.1	197	40.4	31.4	27.5	31.4
5	Opti	41	170	88.8	148	30.7	22.5	22.0	22.5
6	MFP	42	163	80.3	146	30.2	21.3	19.0	21.8
$\bar{x}$		37	166	97.7	168	35.2	28.5	26.9	30.3
SEM		2	1	5.8	11	2.1	3.0	3.4	3.7

* Opti, Optifast 70, Sandoz, Minneapolis. MFP, meat-fish-poultry VLCD.
† Ideal body weight (15).
‡ Body mass index (weight in kg divided by height in meters squared).
§ Point C, point of maximum late rise in cholesterol; point D, weight stability after refeeding to calorie maintenance.

culated according to the Friedewald formula with 0.20 used for the ratio of cholesterol to TG in VLDL (19). All determinations were done in duplicate.

Serum apolipoproteins A-I and B (apo A-I and apo B) were quantitated by radioimmunoassay (RIA; Ventrex Labs, Portland, ME). The apo A-I RIA method utilized a monoclonal antibody and radiolabeled apo A-I. The apo B RIA employed a polyclonal antibody and radiolabeled LDL. All samples were run in duplicate and the apolipoprotein concentrations were calculated from standard curves fitted by logistic-regression analysis.

Adipose-tissue cholesterol analysis. Subcutaneous adipose tissue was obtained from three body sites (triceps, abdomen, and quadriceps–lateral thigh) by needle biopsy before dieting and then twice during weight loss: after 12–15 kg loss and again after 22–35 kg loss. The tissue was obtained via suction through a 14-gauge needle, floated on saline, and stored at −20 °C until analysis. After careful washing, 10 mg tissue was digested in 1 mL 20 g KOH/L ethanol-water (9:1, by vol) containing 20 μg of 5-β-cholestan-3a-ol. The capped tube was incubated in a 70 °C water bath for 90 min. Two milliliters hexane and 1 mL water were then added, mixed thoroughly, and centrifuged for 10 min at 500 × *g*, after which 0.6 mL of the hexane phase was removed and blown to dryness under nitrogen gas, mixed with 0.1 mL silylating mixture [4 vol BSTFA (Sigma, St Louis) and 5 vol dry pyridine] and incubated in a capped tube for 60 min at 37 °C.

The samples were analyzed by gas chromatography on an HP 5890 instrument equipped with an Ultra-1 12.5-m capillary column (Hewlett-Packard, Palo Alto, CA) run at 275 °C with a split ratio of 100:1 with helium carrier and a flame-ionization detector. Output data were integrated with an HP 3396A recorder, and the cholesterol content of the tissue was calculated from the ratio of the internal standard to the cholesterol peak. Each sample was run in triplicate. Both peaks and their relative response factors were established with authentic standards.

The TG content of the tissue was determined by measuring the glycerol content of the adipose digestion aqueous layer with a commercial assay kit for TG (Gilford GPO triglyceride). The aqueous phase volume was quantitated and a sample was analyzed as described above for serum TG analysis.

Data for recovery and reproducibility of the TG and cholesterol values were determined by using known lipid mixtures (Sigma) or multiple samples derived from a single tissue (pig omental adipose tissue). The procedure showed a recovery of TG and cholesterol of 95% (n = 6) and a reproducibility of ±10% (n = 5).

Body-composition analysis. Body fat content was quantitated by densitometry three times for each subject at the same times that adipose biopsies were done. All studies were done after an overnight fast. A continuous weight reading for the fully submerged subjects was obtained for a 3–5 s interval after maximal exhalation. The residual lung volume was measured concurrently by nitrogen washout. This procedure was repeated several times until three consistent weights were obtained. The Siri equation was used for the calculation of percent body fat (20).

Statistical analysis

Data analysis was performed by using the *PC-SAS* package on a microcomputer (21). The results for the serum lipoprotein fractions, adipose cholesterol content, and body composition were assessed over time by analysis of variance (ANOVA), and tests for individual differences between times were done by using the least-significant-differences test. The threshold for significance was taken as $P < 0.05$. Data in the text and tables are expressed as the mean ± SEM. For comparisons of serum samples chosen at selected times (A, baseline; B, nadir; C, peak total cholesterol late in weight loss; D, maintenance), the absolute values were used for statistical analysis rather than the normalized values shown in the figures.

Results

Six subjects completed the full protocol including repeated serum samples, adipose biopsies, and body-composition studies. Two of these were assigned the food VLCD and four, the formula VCLD. These subjects' weights are shown in **Figure 1.** The upper panel shows the plot of weekly values starting with the hypocaloric diets beginning at month 0. The subjects' weights, although different at the start, follow parallel lines for the first 4 mo when all subjects were prescribed weight-loss regimens. The lower panel in this figure shows the subjects' weights calculated as percent loss from initial weight and illustrates the remarkably similar responses of these subjects to the two VLCDs in the outpatient setting. Presented in this way, the data indicate both the uniformity of weight loss among subjects and also the quality of adherence to the diets by the individual subjects. This figure also shows the different durations of the VLCDs (some subjects

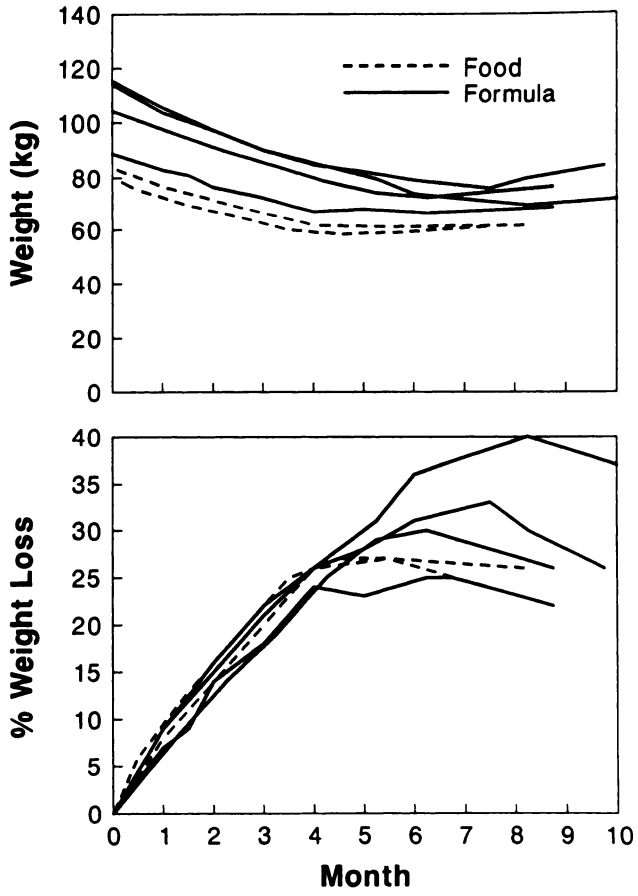

FIG 1. Weight loss for six subjects as kilogram over time and as percent weight lost. Month 0 begins with the start of weight-loss dieting.

chose to continue weight loss after the third set of studies). Table 1 provides initial weight, height, and diet-group information for the six subjects completing the protocol and also indicates the weights at which the peak cholesterol (At C) and maintenance cholesterol (At D) concentrations were obtained. On the basis of serum-chemistry results, there were no disturbances in liver or kidney function or mineral nutriture during either the weight-loss or maintenance phases.

Figure 2 shows the monthly fasting serum cholesterol values for each of the six subjects. Three started > 5.17 mmol/L and the other three were below this value. Although they varied in this initial value and the magnitude of the subsequent changes, all subjects showed the same pattern of an initial reduction to nadir after 1–2 mo of dieting, a slow progressive rise as the weight loss continued, and finally a decline with weight stabilization after refeeding to maintenance calories. By comparing Figures 1 and 2, it can be seen that all subjects had experienced a rise in serum total cholesterol by month 4, at which time the weight-loss data in the bottom panel of Figure 1 show continued uniform rates of loss.

Subjects showed the same pattern of serum cholesterol changes over time regardless of VLCD used. However, the sample size (two food VLCD, four formula VLCD) was too small to determine if there was a difference in the magnitude of these changes between the two diets. Thus, because of the uniformity of the response pattern among all subjects and the small sample size, subsequent data are grouped independently of the VLCD used.

Because the duration of the VLCD varied for subjects, diet-induced changes in serum lipids could not be compared on an absolute time scale. To normalize the data for the various periods of dieting, four serum cholesterol values were selected for each subject: the initial preweight loss level (A), the early nadir at month 1–2 of the VLCD (B), the peak value late in the weight-loss phase (C), and the maintenance value once weight loss had ceased for 1–2 mo (D). In addition, the serum cholesterol values at points B, C, and D were expressed as percent of the initial value at A for each subject. These data are shown in the top panel of **Figure 3.** By repeated-measures ANOVA (using the absolute values), the changes in serum total cholesterol over time were highly significant ($P < 0.0001$). The mean value at B was lower than at A, C, and D ($P < 0.01$, $P < 0.01$, and $P < 0.05$, respectively) and the final value at D differed from C ($P < 0.05$). The mean serum cholesterol at maintenance (D) did not differ from the preweight-loss value (A) although four subjects had maintenance values below their preweight loss values.

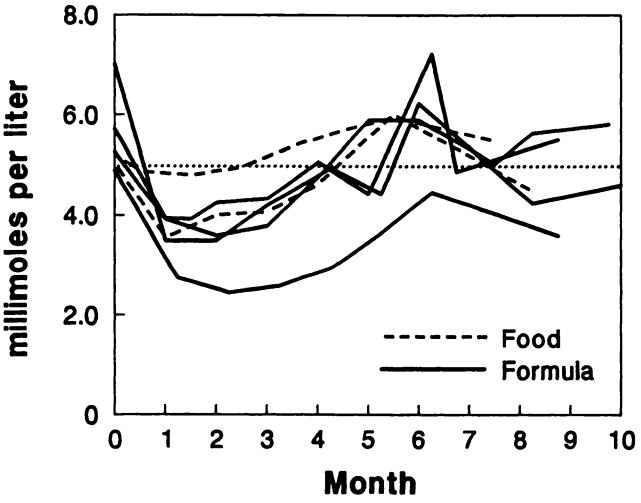

FIG 2. Serum total cholesterol, monthly values for each subject. The dotted line at 5.17 mmol/L represents the acceptable upper limit according to current guidelines (6).

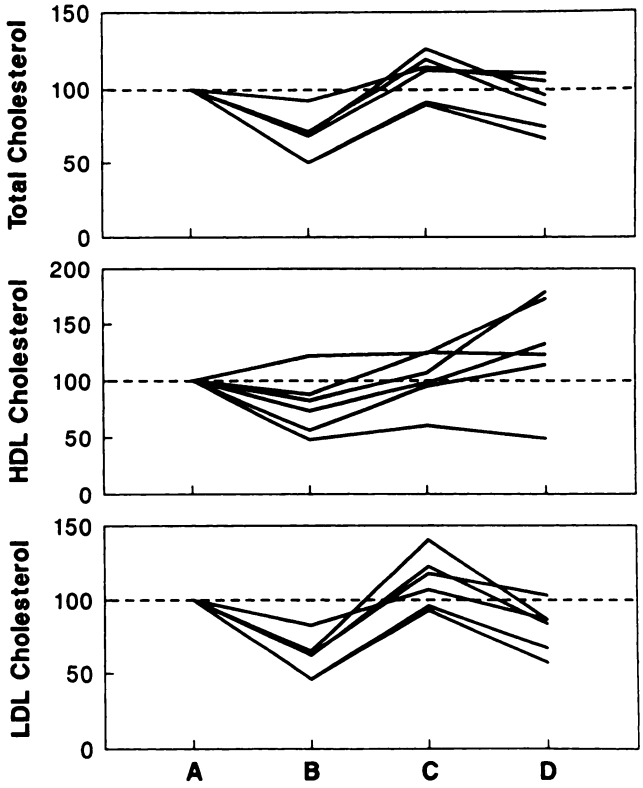

FIG 3. Serum total, HDL, and LDL cholesterol. Selected values were taken for each subject at baseline (A), at total cholesterol nadir (B), at total cholesterol peak (C), and in postweight-loss maintenance (D). All values are normalized as percent of the baseline value A.

The serum HDL- and LDL-cholesterol fractions are also shown in Figure 3, with the values taken at the same times as the serum total cholesterol (as indicated above) and normalized against each subject's initial value. By ANOVA there were significant changes in both fractions over time (HDL, $P < 0.05$; LDL, $P < 0.0001$). The mean serum HDL cholesterol at D was significantly greater than the value at B ($P < 0.01$), and five of six subjects ended with HDL-cholesterol concentrations above their starting values. The serum LDL cholesterol at B was lower than at A, C, and D ($P < 0.01$ for all) and the maintenance value at D was lower than at C ($P < 0.01$). There were no significant differences between A and either C or D, but again, five of six subjects had lower serum LDL-cholesterol concentrations after weight loss compared with before.

The ratios of HDL cholesterol to LDL cholesterol were 0.25, 0.35, 0.26, and 0.44 at the points A, B, C, and D, respectively. By ANOVA there was significant change over time ($P = 0.01$) and the final value at D was significantly higher than either A or C ($P < 0.01$ for both).

The serum values for the apo A-I and apo B (shown in **Fig 4**) were taken at the same times as those for the serum cholesterol shown in Figure 3. There were significant changes over time for

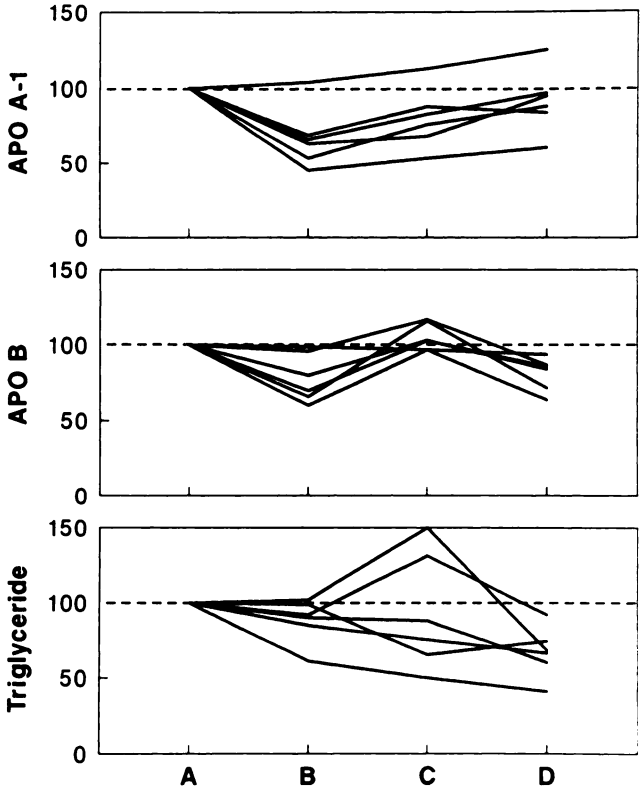

FIG 4. Serum apolipoproteins A-I and B and triglycerides. Selected values for each subject were taken at the same time points as in Figure 3. All values are normalized as percent of the baseline value A.

both apo A-I and apo B (by ANOVA, $P < 0.02$ and $P < 0.005$, respectively). For apo A-I times B and C differed from the initial value at A ($P < 0.01$ and $P < 0.05$, respectively) and the maintenance value at D differed from that at B ($P < 0.05$). The changes in apo B were parallel to those of the LDL cholesterol, with the value at B less than at A and C ($P < 0.05$ and 0.01, respectively), the value at C greater than at D ($P < 0.01$), and the value at D less than at A ($P < 0.05$). The serum TG values are shown at the same times at the bottom of Figure 4. There were no significant changes by ANOVA in TGs despite a downward trend across weight loss although all six subjects were numerically lower at the end of the study.

The cholesterol content of adipose tissue at three separate anatomical biopsy sites and at three different times during weight loss are shown in **Figure 5.** There were no significant changes in the cholesterol-TG ratio with weight loss at the triceps and quadriceps biopsy sites. The abdominal adipose tissue taken after a weight loss of 22–35 kg had a higher cholesterol-TG ratio than did either the baseline sample or the biopsy taken midway through the diet ($P < 0.05$ for both).

Body composition done by hydrostatic weighing before, at the midpoint, and after 22–35 kg weight loss indicated that body fat was reduced progressively from 44.4 ± 2.8% to 24.2 ± 2.5% by dieting. This translates into 82% of the weight loss from adipose tissue and a 46% reduction in adipose-tissue mass occurring between the first and last biopsies in this protocol.

Discussion

Previous studies of serum cholesterol with caloric restriction in humans have yielded highly variable results. Those reports showed reductions in serum cholesterol after minor to moderate weight loss (13, 14, 22–25), early hypercholesterolemia with total starvation (9, 26), and a late rise in serum cholesterol after major weight loss (10–12). Our results indicate that much of this variability is due to the timing of sampling and the rate of cholesterol release from tissue. Thus, rapid weight reduction by very-low-calorie dieting causes a non–steady-state that can have dramatic but transient effects on serum total cholesterol and its lipoprotein distribution.

This pattern of a late rise in serum cholesterol was seen in both normal and moderately hypercholesterolemic subjects who achieved major weight loss by close adherence to VLCDs and is a cause for concern relative to current treatment guidelines (6). The most pronounced effect was observed 6 mo into the weight-loss effort. With further follow-up, however, we observed that this diet-induced rise in serum total cholesterol was transient, resolving when the weight loss ceased. Most patients showed a modest improvement in the serum total cholesterol concentrations and the lipoprotein distribution pattern (as evidenced by an increased HDL-LDL ratio) as the net effect of major weight loss. However the timing of this phenomenon is such that the current therapeutic guidelines (indicating pharmacologic intervention after 6 mo if dietary therapy fails to resolve hypercholesterolemia) should be modified to specify that patients achieve weight stability after successful dieting before drug treatment is initiated.

With 40–50 kg adipose tissue containing ~2 mg cholesterol/g, our subjects entered the weight-loss protocol with adipose cholesterol stores in the range of 100 g. The lack of a significant rise in the adipose cholesterol content from two of three biopsy sites despite a 46% reduction in adipose-tissue mass indicates that these adipose cholesterol stores were being mobilized (although the retention of cholesterol by abdominal adipose tissue makes quantitation of its mobilization difficult). This mobilization of existing cholesterol contained in the shrinking peripheral adipocytes may make a significant contribution to the late rise in serum cholesterol. If so, it appears from the changes in serum lipoproteins to be carried predominantly in the LDL fraction associated with apo B. This interpretation fits with our observation that the serum total cholesterol declined significantly during refeeding to weight maintenance, at which time net adipose TG (and along with it adipose cholesterol) mobilization would stop. However, another factor that could contribute to the lowered LDL cholesterol after weight loss would be the low-fat, high-carbohydrate maintenance diet that our subjects were encouraged to follow (18).

The serum apo B concentrations reflect the balance between synthesis and degradation, which are affected by the packaging of dietary constituents into lipoproteins by both liver and small intestine. The initial decline to the cholesterol nadir (B) presumably reflects the change in dietary intake of calories and fat and hence the decline in dietary constituents that are packaged into intestinal-origin lipoproteins. The subsequent rise in serum total cholesterol, LDL cholesterol, and apo B concentrations (C) could be due to liver synthesis of VLDL and accelerated conversion to LDL, resulting from hepatic repackaging of lipids derived from the lipolysis of adipose tissues. This rapid conversion of VLDL to LDL would be mediated via the increase in lipoprotein lipase activity that has been reported in response to caloric deprivation (27). The 1–2-mo delay for the LDL rise may reflect the similar delay seen for adaptation of other metabolic variables

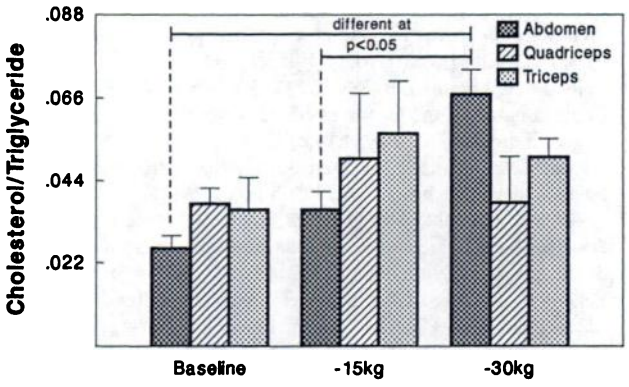

FIG 5. Cholesterol-triglyceride ratio (expressed in moles) from adipose-tissue biopsies. Samples were taken at baseline and after 12–15 and 22–35 kg weight loss from each of three anatomical sites. $\bar{x} \pm$ SEM.

after the onset of nutritional ketosis (28, 29). However, these rises in serum apo B and cholesterol are most likely the result of continued adipocyte cholesterol mobilization and a decline in degradation of LDL via the apo B receptor. Hepatic Apo B receptors were shown to control the serum concentrations of LDL cholesterol (30), and changes in diet were reported to alter the hepatic LDL-receptor number (31).

We are limited in this interpretation of the lipoprotein distribution of mobilized adipose cholesterol because we do not have a direct measure of the flux through the various lipoprotein pools. The serum concentration of any lipoprotein is a function of both its appearance and clearance, and the observed mobilization of adipose cholesterol from two of the three biopsy sites mandates only a part of this balance for the accepting lipoprotein particle. Thus our observation of reduced LDL cholesterol and increased HDL cholesterol at weight maintenance, during which time we hypothesize that there is a reduction in adipose-tissue cholesterol mobilization, could be due to differential changes in particle clearance, altered rates of cholesterol exchange between particles, or effects of independent factors not controlled in this study (such as an increased level of physical activity facilitated by major weight loss).

Our observation of increased cholesterol concentration in abdominal adipose biopsies agrees in part with a recent report by Jimenez et al (32). They noted a significant rise in omental (but not subcutaneous) abdominal-adipocyte cholesterol in morbidly obese patients with major weight loss. Schaefer et al (33) obtained gluteal-adipose biopsies before and after a weight loss and observed an increase in the cholesterol-TG ratio with no change in the cholesterol content per cell. They concluded that cholesterol is not mobilized from adipose tissue across major weight loss. Although this is in agreement with our observations from the abdominal site, it differs from what we found at the peripheral sites (triceps and lateral thigh).

This observation of differences in adipose cholesterol mobilization between abdominal and peripheral (arm and leg) sites is a new and potentially important observation. For instance, it could explain in part the greater epidemiologic risk associated with central obesity (34–36). If, as suggested by Fong and Angel (37), the abdominal adipocyte is able to concentrate cholesterol more effectively than are other tissue sites, central adipose tissue may absorb cholesterol during periods of dietary excess (or, as in this study, cholesterol coming from mobilization of peripheral adipose tissue) and then slowly relinquish it to LDL particles (38). This process could lead to a prolonged elevation in serum LDL concentration over time and thus more risk of cholesterol deposition in other tissues. In this context, it is interesting to note that 25-y follow-up of the Western Electric Study participants by Hamm et al (39) showed that the greatest risk of coronary disease occurred in individuals who repeatedly experienced large fluctuations in weight as adults. A potential explanation is that weight loss redistributes tissue cholesterol, resulting in a temporary period of an atherogenic lipoprotein pattern. On a recurring basis this could measurably affect coronary risk.

The interpretation of our findings depends heavily on our subjects' close adherence to the prescribed VLCDs for periods > 4 mo. This is appropriately suspect in an outpatient study and may limit the interpretation of the findings of this study. However, two monitoring indices indicated the quality of our subjects' efforts. The first was the rate of weight loss during the VLCD, averaging the expected 1.5 kg/wk (40) and following remarkably uniform lines when expressed as percent weight loss (bottom panel of Fig 1). The second index was the breath-acetone determination (data not shown), which gave both the subject and investigator a weekly indicator of dietary adherence. In combination, these monitoring indices provided an objective basis that allowed us to use an outpatient protocol lasting > 7 mo in free-living patients.

In summary, we observed a dynamic process involving an initial fall in serum cholesterol with dieting, then a rise as continued weight loss induced a major reduction in adipose mass, and finally a resolution of this diet-induced hypercholesterolemia as weight loss was stopped by resumption of an eucaloric diet. This delayed rise in serum cholesterol during major weight loss reached a magnitude in some patients that could lead to pharmacologic intervention by current guidelines, when a return to a low-fat, maintenance energy intake would likely achieve the desired effect. The differences in cholesterol metabolism by adipose tissue from separate anatomic sites and its contribution to the variable cholesterol concentrations observed during weight loss invites further exploration.

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