ORIGINAL RESEARCH

Relationship Between Changes in Fat and Lean Depots Following Weight Loss and Changes in Cardiovascular Disease Risk Markers

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Background—Gluteofemoral fat mass has been associated with improved cardiovascular disease risk factors. It is not clear if loss of this protective fat during weight loss partially negates the effect of loss of visceral fat. The aim of this study was to examine regional fat loss in a large weight-loss cohort from one center and to determine if fat loss in the leg and total lean tissue loss is harmful.

Methods and Results—We combined the data from 7 of our previously published 3-month weight-loss studies and examined the relationship between regional fat and lean tissue loss and changes in cardiovascular disease risk factors in 399 participants. At baseline, leg fat was positively associated with high-density lipoprotein cholesterol in women and inversely with fasting triglyceride level in both sexes. Abdominal lean tissue was also related to systolic blood pressure in men. Changes in regional fat and lean tissue were positively associated with changes in glucose, insulin, total cholesterol, triglycerides, low-density lipoprotein cholesterol and systolic and diastolic blood pressure (r=0.11–0.22, P<0.05) with leg fat and arm lean tissue dominating in multivariate regression. After adjustment for total weight or total fat change, these relationships disappeared except for a positive relationship between arm and lean leg mass loss and changes in triglycerides and systolic blood pressure.

Conclusions—Loss of leg fat and leg lean tissue was directly associated with beneficial changes in cardiovascular disease risk markers. Loss of lean tissue may not have an adverse effect on cardiovascular disease risk, and measures to retain lean tissue during weight loss may not be necessary. **(*J Am Heart Assoc*. 2018;7:e008675. DOI: 10.1161/JAHA.118.008675.)**

Key Words: caloric restriction • cardiovascular disease risk factors • obesity

There is a clear positive cross-sectional relationship between visceral adipose tissue and cardiovascular disease (CVD) risk factors and insulin resistance, while large subcutaneous lower body adipose tissue depots have been associated with protective effects in many studies on insulin, glucose, and lipids and arterial disease.[1–11]

Gluteofemoral fat, as measured by thigh circumference, hip circumference, or leg adipose tissue mass, is independently associated with lower total and low-density lipoprotein (LDL) cholesterol and triglyceride (TG) levels, and increased high-density lipoprotein (HDL) cholesterol levels.[1–4,9–11] Gluteofemoral fat mass is associated with lower aortic calcification and arterial stiffness[4,7,8] and decreased progression of aortic calcification.[12] Lower-body fat is inversely associated with fasting insulin levels and insulin levels after an oral glucose load, and positively associated with insulin sensitivity.[3,6,9–11] In healthy overweight and obese women, hip circumference and thigh adipose tissue mass are associated with a lower HbA_{1c}.[13] In the AusDiab study, a larger hip circumference was associated with a lower prevalence of undiagnosed diabetes mellitus and dyslipidemia.[14] The INTERHEART study established an independent association between larger hip circumference and lower risk for myocardial infarction.[15] In the European Prospective Investigation into Cancer and Nutrition–Norfolk study, larger hip circumference was associated with a lower hazard ratio for coronary heart disease.[16]

During weight loss, it is not clear if loss of these apparently protective depots weakens the beneficial effects of visceral fat loss. In the Look AHEAD (Action for Health in Diabetes) study,[17] in 92 volunteers with type 2 diabetes mellitus, all metabolic variables except LDL cholesterol were positively associated with changes in all adipose tissue depots; that is, leg fat loss was not apparently harmful. After adjusting for total weight loss, arm fat loss was still positively associated

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Clinical Perspective

What Is New?

- Loss of fat and lean tissue in any region is associated with a reduction in cardiovascular risk factors.
- Even after adjustment for total fat or total weight loss, reduction in leg and arm lean tissue was associated with reductions in triglycerides and systolic blood pressure.

What Are the Clinical Implications?

- It appears that worrying about the inevitable loss of lean tissue with weight loss is misplaced and special efforts to minimize lean tissue loss are not required.

with changes in TG and systolic blood pressure (SBP) and diastolic blood pressure (DBP), while leg fat was positively associated with changes in DBP. No negative effect of fat loss in these regions was seen.

Opposite findings occurred in a short-term study by Okura et al,[18] who found leg adipose tissue mass change after a 14-week intervention study with diet and exercise in 128 healthy obese women was inversely associated with DBP, LDL cholesterol levels, and the number of coronary heart disease risk factors even after adjustment for total fat and lean tissue loss.

Thus, there is no agreement in whether regional fat changes with weight loss are positively or negatively related to changes in CVD risk markers, and there has been no comprehensive review of this area. The aim of this study is to assess whether loss of peripheral fat or peripheral lean tissue, particularly in the leg, has adverse effects after diet-induced weight loss. We hypothesize that loss of leg fat and lean tissue will reduce the improvement in CVD risk factors seen with visceral fat loss and that sex may influence the outcome seen.

Methods

Seven published weight-loss studies from our research group,[19–25] which had a total body dual-energy x-ray absorptiometry scan at baseline and 12 weeks and had a minimum of measures of glucose and lipids at each time point, were combined electronically for analysis. All studies followed a similar protocol, with variations in the amount of protein, carbohydrate, and fat, and had similar amounts of weight loss. All studies were approved by the Commonwealth Scientific and Industrial Research Organization Human Ethics Committee, and all subjects gave written, informed consent. All interventions were tightly energy controlled, with a reduction in energy intake of about 30% with dietitian visits every 2 weeks and a target weight loss of 0.5 to 1 kg/week. Protein intake varied from 15% to 30% of energy with matching differences in either carbohydrate or fat but not both. Women predominated in the data set, which was composed entirely of Anglo-Saxon individuals. One study in people with type 2 diabetes mellitus in which 25 managed their diabetes mellitus by diet alone, 26 required oral hypoglycemic medications (19 on metformin, 15 on sulfonylureas alone or combination), and 4 required insulin. Four subjects with fasting plasma glucose of 4–6 mmol/L were asked to cease medications before commencement of the diet to allay possible hypoglycemic episodes with weight loss. Volunteers were requested not to change their medication for lipids and blood pressure, but the exact number on these medications was not recorded in the papers. Many volunteers (157) had impaired fasting glucose (5.6–7.0 mmol/L). The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Statistical Analysis

Unpaired *t* test, one-way ANOVA, Pearson correlation coefficients, and backward linear regression were performed using SPSS 22 (IBM). Data shown are mean and standard deviation, and $P<0.05$ is accepted as being statistically significant. CVD risk factors were correlated with absolute total and regional fat and lean masses separately in men and women at baseline. Changes in total and regional fat and lean tissues were computed separately in men and women and assessed using paired *t* tests within each sex and one-way ANOVA between sexes with adjustment for diabetes mellitus. Overall absolute regional fat changes were correlated with absolute changes in CVD risk factors after adjustment for sex by partial Pearson correlations (SPPS 22). No adjustment was made for multiple comparisons.

Multiple linear regression with backward selection was conducted examining 3 predictor areas—abdomen, arms and legs, both fat and lean—and relating them to changes in CVD risk markers before and after adjustment for changes in all regions together and total weight and total fat change. Diabetes mellitus, sex, and study were included as predictors but were not forced into the equations if they were not significant. Collinearity was assessed by the variance inflation factor. Changes in fat and lean regions were also assessed using *Z* scores and percentage change in each region.

Results

Baseline Characteristics

In this study population (Table 1), there were 88 men and 311 women with an average age of 53 and 49 years ($P=0.009$) and a body mass index of 33.7, with 18 men and 35 women with

Table 1. Baseline Characteristics of Volunteers in Included Studies

	Age, y*	Sex	BMI	Weight	Glucose*	Insulin*
Diabetes mellitus (n=53)	61.2±9.5	18 M, 35 W	33.7	93.7±17.6	8.1±1.7	16.1±7.3
No Diabetes mellitus (n=346)	48.3±10.4	70 M, 276 W	33.7	92.2±14.4	6.5±2.2	11.8±6.8
Total 399	50.0±11.2	88 M, 311 W	33.7±4.3	92.4±14.9	6.7±2.2	12.4 7.0

BMI indicates body mass index; M, men; W, women.
*P<0.05 for differences between groups by unpaired t test.

type 2 diabetes mellitus. The 53 people with diabetes mellitus were older than the people without diabetes mellitus (61 years versus 48 years, P<0.01) while BMI was the same. Fasting insulin and glucose were higher in the diabetes mellitus group (P<0.01). Baseline dual-energy x-ray absorptiometry and after 12 weeks' weight loss and corresponding CVD risk markers are shown in Table 2. Men had greater abdominal fat but lower total, arm, and leg fat than women (all P<0.001). Men had greater lean tissue in all regions (all P<0.001). There was limited and weak evidence of protection from elevated CVD risk factors from specific fat and lean regions, with leg fat associated with a greater HDL cholesterol in women and lower TG in both sexes, before and after adjustment for diabetes mellitus status (Table 3). Thus, from these baseline data one could hypothesis that a greater loss of leg fat relative to other regions might adversely influence HDL cholesterol and TG after weight loss.

Changes in Fat and Lean Tissue With Weight Loss

Over 12 weeks men lost 9.5 kg (9.1%) and women 7.2 kg (8.1%; P<0.001 for difference between sexes). Men lost more total, abdominal, and leg fat as a percentage of fat in that region than did women (24% versus 15% [P<0.001], 22%

Table 2. Baseline Weight and Regional Fat and Lean Depots and CVD Risk Factors and Changes With Weight Loss Separated by Sex

		Baseline			Change		
Variable	N	M	W	Range	M	W	Range
Weight	399	104.2±14	89.0±13.4	62.3–140.9	9.5±5.3	7.2±3.5†	31.0–2.1
Total fat	399	9.7	42.2±9.2	17.3–75.4	6.2±3.6	5.3±3.48	19.6–4.5
Total lean	399	64.4±8.1	43.6±6.9	26.9–83.3	2.7±2.7	1.5±1.8†	11.6–4.1
Leg fat	399	9.9±3	13.1±3.5	5.3–28.7	1.5±1	1.5±1.3	12.3–2.6
Leg lean	399	21.7±3	14.9±2.6	1.2–17.8	1.0±1.2	0.7±1.1*	13.4–1.7
Arm fat	399	5.5±2.5	8.6±3.1	2.3–19.4	1.0±1.1	1.3±1.3*	7.2–2.2
Arm lean	399	8.2±1.5	5.5±1.3	3–11.8	0.5±0.9	0.3±0.6*	5.4–1.9
Abdo fat	399	9.0±2.3	7.3±3.7	5.5–1.5	1.9±1.3	1.1±1.0†	5.5–1.5
Abdo lean	399	12.0±4.2	6.6±3.9	3.0–11.8	0.5±1.2	0.1±0.7†	4.8–3.3
Insulin	372	15.0±8.9	11.6±6.1	2.8–50.4	4.7±8.6	2.8±5.4	43–39
Glucose	396	6.9±2.5	6.7±2.4	3.3–21.9	0.5±1.3	0.5±1.4	7–1.5
TC	399	5.4±1	5.7±1	2.9–10.1	0.6±0.7	0.4±6.4	3.3–1.1
TG	399	2.0±0.9	1.7±0.8*	0.4–6.4	0.6±0.4	0.4±0.6	4.1–2.0
HDL	399	0.9±0.2	1.2±0.3*	0.5–2.3	−0.1±0.1	0±1.6	0.5–0.6
LDL	399	3.5±0.9	3.8±1	0.8–8.2	0.4±0.6	0.2±0.6	2.4–2.4
SBP	252	134±15	130±15	100–180	6±13	7±12	50–29
DBP	252	78±11	73±9	5–113	3±9	3±8	28–23
CRP	152	4.5±4.5	6.4±5.3	0.4–39	−0.4±10.9	0.6±6.2	17–89

All weights are in kilograms; serum variables except insulin in millimoles per liter; insulin milli–international units per liter. Abdo indicates abdomen; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; M, men; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; W, women.
*P<0.05 by one-way ANOVA between sexes after adjustment for diabetes mellitus.
†P<0.001 by one-way ANOVA between sexes after adjustment for diabetes mellitus.

Table 3. Correlation Matrix With Specific Fat and Lean Depots and CVD Variables at Baseline Separated by Sex

	Glucose	Insulin	TC	TG	HDL	LDL	SBP	DBP	CRP
Weight									
M		0.35							0.35
W		0.18	−0.11						0.21
BMI									
M	0.22	0.38							0.32
W									
Abdo fat									
M	0.27								0.34
W	0.31	0.15		0.13	−0.16		0.19		0.20
Abdo lean									0.23
M	0.21						−0.23		
W	0.37	0.16		0.14	−0.15		0.16		
Arm fat									
M								0.13	0.25
W									0.21
Arm lean					…				
M									
W									0.20
Leg fat									
M				−0.14					0.24
W				−0.13	0.17				
Leg lean									
M									
W		0.17							
Total fat									
M		0.30							0.32
W		0.15					0.15		0.23
Total lean									
M		0.25							
W	0.13	0.22			−0.13				0.13

All values shown are $P<0.05$ by Pearson correlation coefficients. Insignificant values are not shown. No adjustment is made for multiple comparisons. Regional fat/lean correlations are not adjusted for total weight or total fat and lean. Abdo indicates abdomen; BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

versus 17% [$P=0.002$], and 15% versus 11% [$P=0.001$], respectively), while arm fat (16% versus 14%) and lean tissue losses were not different, with the latter varying from 2% to 5% of initial mass. In absolute terms, women lost more arm fat and men more total and abdominal fat and total, leg, arm, and abdominal lean tissue. In men, when expressed as a percentage of baseline fat, total and abdominal fat changes were greater than leg and arm fat changes. In women, leg fat loss was lower than in the other depots and arm fat loss was only a little less than total and abdominal fat loss. As a percentage of total fat loss, abdominal fat loss in men was more than twice as great as arm fat loss (30% versus 11%; $P<0.001$), whereas in women these regions were the same (17% versus 22%), with leg fat loss exceeding arm loss (29% versus 22%; $P=0.006$). Men had a greater percentage of total fat lost as abdominal fat compared with women (30% versus 22%; $P=0.034$), but the other regions were the same.

Changes in CVD Risk Markers

All variables were significantly different between baseline and week 12 except for glucose, HDL, and C-reactive

Table 4. Correlation Matrix of Changes in CVD Risk Variables

	Glucose	Insulin	TC	TG	HDL	LDL	SBP	DBP	CRP	GGT	ALT
Glucose		0.17		0.1				0.14			
Insulin	0.17		0.13	0.33							
TC				0.34		0.9					
TG					−0.32						
HDL		−0.11	0.10								
LDL									−0.11		
SBP								0.69			
DBP	0.28										
CRP											
GGT	0.28		0.25		0.24						
ALT				0.20	−0.23					0.20	

All values shown are $P<0.05$ by Pearson correlation coefficients. Abdo indicates abdomen; ALT, alanine aminotransferase; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

protein (CRP). Changes in TG were positively related to changes in glucose, insulin, alanine aminotransferase and inversely with changes in HDL (Table 4). Changes in insulin were positively related to changes in glucose and inversely with changes in HDL, while changes in glucose were positively related to changes in DBP and gamma-glutamyl transferase.

Correlation Between Fat and Lean Tissue Changes and Changes in CVD Risk Markers

All variables except HDL cholesterol and CRP were positively related to changes in weight and fat, with most being positively related to abdominal fat and arm fat changes (glucose, insulin, total cholesterol, LDL, TG, SBP, and DBP) and about one half being positively related to leg fat changes (TC, TG and LDL; Table 5). Lean tissue changes were similar but not as common. No negative relations were observed.

Multiple Regression

Collinearity of predictors

Total fat loss was strongly related to change in arm fat (r=0.53), change in leg fat (r=0.73), and weakly to abdominal fat loss (r=0.21). Leg fat and arm fat changes were weakly correlated (r=0.29), whereas abdominal fat loss was more strongly correlated with leg fat loss (r=0.42) and very weakly with arm fat loss (r=0.11, P=0.007).

Total lean tissue loss was strongly related to change in arm lean tissue loss (r=0.41), leg lean tissue loss (r=0.78), and

Table 5. Correlation Matrix With Changes in Total Weight, Fat and Lean Mass, and Regional Fat and Lean and Changes in CVD Risk Markers After Adjustment for Sex

	Glucose	Insulin	TC	TG	HDL	LDL	SBP	DBP	CRP
Total weight	0.14	0.32	0.26	0.24		0.18	0.19	0.19	
Total fat	0.15	0.19	0.26	0.13		0.23	0.16	0.18	
Total lean		0.16	0.20	0.26			0.15		
Abdo fat		0.12	0.17	0.12		0.15		0.15	
Abdo lean		0.10							
Arm fat	0.15	0.14	0.13			0.11	0.19	0.16	
Arm lean		0.11	0.15	0.18			0.16		
Leg fat		0.12	0.22	0.17		0.21			
Leg lean	0.15	0.12		0.17					

All values shown are $P<0.05$ by Pearson partial correlation coefficients after adjustment for sex. No adjustment is made for multiple comparisons, and no adjustment is made for changes in total weight or total fat and lean mass. Abdo indicates abdomen; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 6. Multivariate Models

	Glucose	After Adjustment for Weight Change	Insulin	After Adjustment for Weight Change	TG	After Adjustment for Weight Change
Baseline value	0.636	0.643	0.673	0.672	0.701	0.683
Diabetes mellitus	0.132	0.103	0.187	0.130	0.133	0.110
Sex						
Study	−0.074	−0.063				
Weight		0.144		0.257		0.139
Abdo fat					0.102	0.067
Abdo lean						
Arm fat						
Arm lean					0.135	0.116
Leg fat	0.099	0.015	0.124	−0.024	0.095	0.02
Leg lean						
Adjusted I^2	0.38	0.41	0.45	0.54	0.52	0.53
ANOVA F	60	54	78	106	86	75

Standardized betas are shown. Abdo indicates abdomen; TG, triglyceride.

abdominal lean tissue loss (r=0.43). Leg lean and arm lean tissue losses were strongly correlated (r=0.41), whereas abdominal lean tissue loss was weakly related to arm lean tissue loss (r=0.19) and more strongly to leg lean tissue loss (r=0.36).

Regional fat and lean tissue losses were strongly related in the arm and abdomen (r=0.39–0.43) but weakly related in the leg (r=0.2). Total fat and total lean tissue losses were not correlated.

In the final regression models, the collinearity diagnostics were low, with a variance inflation factor of 1 to 1.2.

Insulin and glucose. Change in insulin over 12 weeks of weight loss was positively related to loss of leg fat (P=0.002) after adjustment for baseline insulin (P<0.001) and diabetes mellitus (P<0.001). Total variance accounted for was 45%, most of which was attributable to the relationship with baseline insulin. Adjustment for abdominal fat loss, abdominal lean tissue loss, and arm lean tissue loss had no effect on the total variance predicted, while addition of weight loss removed the significance of leg fat. Multivariate equations for insulin, glucose, and TG before and after adjustment for weight loss are shown in Table 6.

Change in glucose was predicted by change in leg fat (P=0.015) after adjustment for baseline glucose (P<0.001), diabetes mellitus status (P=0.002), and study (P=0.064), with a total of 38% of the variance accounted for. Addition of arm and abdominal fat and lean tissue loss and leg lean tissue loss together (P=0.02) had no effect on the significance of leg fat. Leg fat became insignificant after the addition of change in weight to the equation.

Use of Z scores and percentage change of the regional depot improved the significance of the change in leg fat and added change in leg lean mass as a minor predictor, but for both glucose and insulin, change in leg fat was the major predictor, while for both, change in weight removed the significance of leg fat (data not shown).

TG, LDL, and HDL cholesterol. Changes in fasting TG were related to changes in abdominal fat loss (P<0.017), arm lean loss (P=0.001), diabetes mellitus status (P<0.001), and leg fat loss (P=0.02) after adjustment for baseline TG. After addition of change in arm fat loss, abdominal lean tissue loss, and leg lean tissue loss, the variance accounted for showed little change; all the predictor variables remained significant and change in leg lean mass was significant (P=0.046). After the addition of change in weight, only arm lean tissue loss persisted. Sex and study played no role.

Use of Z scores and percentage change of the regional depot did not change the results.

HDL cholesterol at 12 weeks was unrelated to change in regional fat or lean masses and was related only to baseline HDL cholesterol (P<0.001). Changes in LDL cholesterol were related to changes in leg fat (P<0.001) and abdominal lean (P=0.052) after adjustment for baseline LDL (P<0.001) and sex (P=0.009). These changes were not influenced by the addition of the other fat and lean regions. Use of Z scores and percentage change of the regional depot did not change the results.

Blood pressure. Change in SBP was predicted positively by change in arm fat (P=0.001) and leg lean mass (P=0.007), sex

(P=0.07), and diabetes mellitus status (P<0.001) after adjustment for baseline SBP. Arm fat persisted after adjustment for weight change (P=0.043) and all the other fat and lean regions but not fat change. However, leg lean mass (P=0.005) remained with total fat change in the equation. Exactly the same relationships were seen, with DBP accounting for 28% to 37% of the adjusted variance.

Inflammation. Change in CRP was predicted inversely by change in abdominal fat mass (P=0.06) and baseline CRP (P=0.002) but the variance in CRP changes accounted for was quite small at 3%. Change in other regions made change in abdominal fat loss nonsignificant. Change in ALT was inversely related to changes in arm fat (P=0.08) and baseline alanine aminotransferase (P<0.001), and addition of the other fat and lean regions improved the relationship (P=0.02) while gamma-glutamyl transferase changes were only related to baseline gamma-glutamyl transferase.

Discussion

We have shown in this cohort of mostly female overweight and obese middle-aged volunteers that leg fat was modestly protective at baseline, with increases in HDL cholesterol in women and lower TGs in both men and women, but leg fat accounted for only 1% to 2% of the baseline variance in these CVD risk variables. SBP was negatively related to abdominal lean tissue in men. In all other regions, both fat and lean tissue masses were related to a worse CVD profile, and leg fat in men was positively related to CRP.

Despite the apparent protective effect of leg fat before weight loss, loss of leg fat with weight loss was not harmful and was directly correlated with changes in insulin and glucose and TG before adjustment for weight loss, accounting for about 6% to 7% of the variance. Abdominal fat loss, despite being a major contributor to total fat loss in both men and women, was unrelated to changes in CVD risk factors with leg fat change in the regression model. This is in spite of the positive relationship between abdominal fat mass and glucose levels at baseline. The persistence of arm lean tissue loss as a positive predictor for change in TG after adjustment for weight or fat loss suggest that lean mass loss, at least in this region, is not harmful. Loss of lean mass in the leg was directly associated with reductions in SBP after full adjustment, suggesting that strategies to maintain lean mass during weight loss may not be required. This is completely opposite to the observations of Okura et al,[18] who found in a 14-week weight loss and exercise study in 128 overweight and obese women that fat tissue change in the legs correlated negatively with percentage changes in DBP, LDL-C, fasting plasma glucose, and the number of coronary heart disease risk factors per subject (r=−0.17, P<0.05 to −0.26, P<0.01) in response to weight reduction. Weight reduction was 12% with a fat mass reduction of 26%, which was similar in all depots with a small reduction of 3% in lean tissue, which varied from 2% to 7% depending on the region. Lean tissue changes in the legs correlated negatively with percentage changes in SBP, glucose, and the number of risk factors (r=−0.20 to −0.21, P<0.05). Truncal fat changes were correlated positively with changes in TG, LDL cholesterol, and glucose and the number of CVD risk factors. (r=0.17, P<0.05 to 0.25, P<0.01). All CVD risk markers were reduced significantly, varying from a 6% to 37% reduction. Our weight loss in women was only half of that seen in this study, but it is doubtful that this alone could account for the differences seen. In the Okura study,[18] they computed percentage changes in risk factors, whereas we adjusted for baseline levels. Exercise may account for some of the differences.

Our findings are in agreement with the Look AHEAD Study,[17] where in a small subset of 54 women and 38 men there were no negative effects observed of leg subcutaneous fat loss measured using magnetic resonance imaging. There were positive relationships with CVD risk markers and arm and leg fat losses despite adjustment for total weight loss, whereas only relationships with arm lean mass losses and changes in TG survived adjustment for weight change. Because they did not adjust for initial levels of the risk factors, the relationship with change in fat mass is probably overstated, as often there will be a positive relationship between the marker and the fat mass region at baseline and this is not completely eliminated by adjustment for change in weight. They found the regression coefficients for visceral adipose tissue loss and leg fat loss were similar for cholesterol, glucose, HbA_{1c}, HDL cholesterol (in women only). Only with TG and SBP were changes in leg fat found to be unrelated.

As in the Look AHEAD study, we found that men lost more abdominal fat than women as both a proportion of total fat loss (22% versus 17%) and a proportion of the fat in that region (30% versus 17%). Hallgreen and Hall[26] proposed the change of visceral adipose tissue (VAT) to the change of fat mass (FM) is proportional to the initial ratio of VAT to total FM, that is, $dVAT/dFM=k\times VAT/FM$, where k is a constant. With a constant of 1.3, the model appeared to fit a variety of weight-loss interventions in both sexes. In our study, k was 1.8 for men and 0.8 for women, who thus had less VAT loss than expected from this equation. The weight loss in the Look AHEAD study at 1 year was similar to our 3-month weight loss.

It is claimed that the benefit of energy restriction without exercise may be limited by loss of lean body mass,[27] but there is little evidence available to support this statement. A trial using testosterone supplementation after a very low calorie diet–induced weight loss in obese middle-aged men produced

a difference in fat-free mass of 3.4 kg compared with placebo at the end of 12 months, but no differences were seen in blood pressure, homeostatic model assessment of insulin resistance, HDL cholesterol, or TG.[28] In our study, loss of lean mass did not adversely influence the beneficial effects of weight loss, and changes in lean mass were positively related to changes in CVD risk factors. An issue that we could not examine in this data set was whether excessive loss of lean tissue predisposes to weight regain and that the weight regain is proportionally more fat than lean tissue, contributing to sarcopenia. There appears to be little evidence that lean tissue loss differs between those with weight stability and those with weight regain after energy-restriction–induced weight loss.[29] In the 8-year follow-up of the Look AHEAD study, the education group suffered both fat and lean tissue loss throughout this time, whereas in the intervention group the lean tissue loss, which was maximal at the end of 1 year, became indistinguishable with weight regain from the education group.[30] Thus, the failure to regain lean tissue in the same proportion as fat tissue seen in some studies[31] would be less significant if compared to an age-matched control group.

Limitations of the current analysis include its short-term nature, the predominance of women, and the small number of people with type 2 diabetes mellitus.

In conclusion, loss of fat or lean tissue from the leg, which appears to be protective in prospective epidemiology, is associated with benefit in terms of CVD risk factors. Loss of lean tissue from any region does not appear to be harmful, so worrying about minimizing lean tissue loss may be unnecessary.

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Disclosures

None.

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