Changes in Subcutaneous Fat Cell Volume and Insulin Sensitivity After Weight Loss

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Daniel P. Andersson,[1] Daniel Eriksson Hogling,[1] Anders Thorell,[2] Eva Toft,[3] Veronica Qvisth,[3] Erik Näslund,[4] Anders Thörne,[5] Mikael Wirén,[6] Patrik Löfgren,[1] Johan Hoffstedt,[1] Ingrid Dahlman,[1] Niklas Mejhert,[1] Mikael Rydén,[1] Erik Arner,[1] and Peter Arner[1]

OBJECTIVE

Large subcutaneous fat cells associate with insulin resistance and high risk of developing type 2 diabetes. We investigated if changes in fat cell volume and fat mass correlate with improvements in the metabolic risk profile after bariatric surgery in obese patients.

RESEARCH DESIGN AND METHODS

Fat cell volume and number were measured in abdominal subcutaneous adipose tissue in 62 obese women before and 2 years after Roux-en-Y gastric bypass (RYGB). Regional body fat mass by dual-energy X-ray absorptiometry; insulin sensitivity by hyperinsulinemic-euglycemic clamp; and plasma glucose, insulin, and lipid profile were assessed.

RESULTS

RYGB decreased body weight by 33%, which was accompanied by decreased adipocyte volume but not number. Fat mass in the measured regions decreased and all metabolic parameters were improved after RYGB ($P < 0.0001$). Whereas reduced subcutaneous fat cell size correlated strongly with improved insulin sensitivity ($P = 0.0057$), regional changes in fat mass did not, except for a weak correlation between changes in visceral fat mass and insulin sensitivity and triglycerides. The curve-linear relationship between fat cell size and fat mass was altered after weight loss ($P = 0.03$).

CONCLUSIONS

After bariatric surgery in obese women, a reduction in subcutaneous fat cell volume associates more strongly with improvement of insulin sensitivity than fat mass reduction per se. An altered relationship between adipocyte size and fat mass may be important for improving insulin sensitivity after weight loss. Fat cell size reduction could constitute a target to improve insulin sensitivity.

Obesity is associated with insulin resistance and dyslipidemia and also with a very high risk of developing type 2 diabetes. Interestingly, studies of bariatric surgery (i.e., techniques that reduce or bypass the stomach in order to achieve weight reduction) show, first, that there is no clear quantitative relationship between the weight loss induced by various surgical procedures and the degree of normalization in insulin sensitivity and other metabolic parameters and, second, that metabolism is markedly improved before any significant weight loss is achieved (1,2). In a hallmark study by Klein et al. (3), a large amount of subcutaneous abdominal adipose tissue was removed from obese subjects by liposuction. This was not accompanied by

[1]Department of Medicine, Karolinska Institutet, Stockholm, Sweden
[2]Department of Surgery, Karolinska Institutet, Ersta Hospital, Stockholm, Sweden
[3]Department of Medicine, Karolinska Institutet, Ersta Hospital, Stockholm, Sweden
[4]Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden
[5]Department of Surgery, Södertälje Hospital, Södertälje, Sweden
[6]Department of Surgery, Karolinska Institutet, Stockholm, Sweden

Corresponding author: Peter Arner, peter.arner@ki.se.

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any metabolic improvement at short- (10–12 weeks) (3) or long-term (82–208 weeks) follow-up (4). However, the regional distribution of adipose tissue could play a role since visceral fat mass displays a much stronger association with insulin resistance than the quantitatively much larger mass of subcutaneous adipose tissue (reviewed in Lebovitz and Banerji [5]). Furthermore, a study of weight loss induced by diet/lifestyle intervention showed that a reduction in visceral but not subcutaneous fat mass correlated with metabolic improvement (6). On the other hand, several studies have shown that removal of a subset of visceral adipose tissue (the greater omentum) in connection with bariatric surgery does not cause additional improvements in the metabolic profile (7–9).

Still, factors other than fat mass could play a role for the beneficial effects of weight loss. Adipose tissue can expand by increasing the number and/or volume of its fat cells, causing distinct adipose morphologies termed hyperplasia (many small fat cells), hypertrophy (few large fat cells), or an intermediate of the two, as previously reviewed (10). Fat morphology can be estimated by comparing body fat mass with average fat cell size. When this is performed in a large set of individuals with a broad range in fat mass, this results in a curve-linear relationship (11). Values for adipocyte size and total fat mass from an individual are then plotted into the graph, and values above the mean curve fit indicate hypertrophy and those below suggest hyperplasia (11). It is well established that large subcutaneous fat cells are associated with a pernicious metabolic profile (12), and more recent studies demonstrate that enlarged fat cell size increases the future risk of developing type 2 diabetes (13,14). Regional variations in adipocyte size may have different pathophysiological impact; thus, enlarged fat cells in the visceral and subcutaneous depots associate with dyslipidemia and insulin resistance, respectively (15,16). It should be emphasized that although it is well established that weight loss is accompanied by a decrease in fat cell size, fat cell number is not influenced by (even pronounced) weight loss (17).

In this study, we aimed to investigate the long-term effects of changes in fat cell size and fat mass in different regions on insulin sensitivity and other metabolic parameters after weight loss induced by Roux-en-Y gastric bypass surgery (RYGB). Many obese patients undergoing RYGB have concomitant type 2 diabetes. Since insulin sensitivity is a continuous variable and our aim was to study improvements in insulin resistance rather than impact on diabetes prevention, subjects with type 2 diabetes were also enrolled.

RESEARCH DESIGN AND METHODS

Subjects

Sixty-two women undergoing surgical treatment for obesity were included (cohort 1). Patients with type 2 diabetes who were not on insulin therapy were included. The subjects had not been instructed to follow any hypocaloric diet prior to the first examination and all had been weight stable (weight change <2 kg) for at least 1 year before their first visit. After RYGB, subjects reported their actual body weight every 6 months postoperatively and were reexamined when they reached a new weight-stable level, which occurred on average after 24 months (14–54 months). To obtain a sufficiently reliable relationship between fat mass and fat cell volume, particularly for the baseline estimates, inclusion of 62 subjects with a large interindividual variation in BMI (20–62 kg/m^2) was required (cohort 2). All of these additionally added women were otherwise healthy and free of continuous medication and none had undergone any important weight reduction.

Examinations and Calculations

The women reported to the laboratory in the morning after an overnight fast. Height and weight were determined for assessment of BMI. Systolic and diastolic blood pressure were determined in the supine position after 15 min of rest with a fully automatic device (Omron M10-IT; Omron Healthcare, Hoofddorp, the Netherlands). A venous blood sample was obtained, and plasma levels of insulin, glucose, triglycerides, cholesterol, and HDL cholesterol were determined as previously described (15). Low-density cholesterol was calculated with the Friedewald formula (18). Total body fat, abdominal (android) fat, hip (gynoid) fat, and android/gynoid fat ratio were measured by dual-energy X-ray absorptiometry (DEXA) using a GE Lunar iDXA with the software enCORE (version 14.10.022) provided by the manufacturer (GE Healthcare, Madison, WI) (19). The software was also used to calculate estimated visceral fat (EVAT) in the android region from the following formula: total adipose fat mass in the android region = EVAT + estimated subcutaneous adipose tissue (ESAT) in the android region, as previously described (20). Determination of EVAT with this method shows a strong correlation ($r^2 \geq 0.95$) with measures using computed tomography (20). Assessment of android fat mass by DEXA is widely used and well accepted as a valid measure. Since total android fat mass and EVAT are used to determine ESAT and both are valid measures, it follows that the calculation of ESAT should also be valid. Estimated subcutaneous adipose tissue in the android region (ESAT) was therefore calculated as total android fat minus EVAT.

A subcutaneous fat biopsy was obtained from the abdominal wall at the same level as the measured ESAT. Fat cell weight and volume of fat cells were determined as previously described (15). In brief, fat cells were isolated, and the diameter of 100 cells was measured. Using established formulas (21), the mean fat cell volume and weight were determined. The number of fat cells in the ESAT region was determined by dividing ESAT weight with mean fat cell weight. After 45 min of rest, the women underwent a hyperinsulinemic-euglycemic clamp as previously described (15). In brief, after an intravenous bolus dose of insulin (1.6 units/m^2 body surface area) (11,100 pmol/m^2), insulin was infused intravenously at 0.12 units/m^2/min (830 pmol/m^2/min) for 2 h, and a variable intravenous infusion of glucose (200 mg/mL) was used to maintain euglycemia between 4.5 and 5.5 mmol/L (81–99 mg/dL). The infusion rate of glucose during the last 60 min of the clamp, when insulin levels are in a steady state, was used to calculate whole-body glucose disposal rates (M value). The average values of blood glucose and insulin at steady state during clamp were 5.05 $\pm$ 0.19 mmol/L and 1,680 $\pm$ 530 pmol/L at baseline and 5.10 $\pm$ 0.18 mmol/L and 1,170 $\pm$ 290 pmol/L at follow-up. The two insulin levels differed significantly ($P < 0.001$ by paired Student

Table 1—Characterization of obese women before and after surgery

Measures	Before surgery	After surgery	*P* value
Age (years)	(62) 43 ± 9	(62) 45 ± 9	<0.0001
Waist circumference (cm)	(62) 130 ± 10	(62) 97 ± 12	<0.0001
Total body fat, kg	(61) 60 ± 10	(62) 30 ± 11	<0.0001
Android fat, kg	(61) 6.1 ± 1.3	(62) 2.5 ± 1.3	<0.0001
Gynoid fat, kg	(61) 9.3 ± 2.0	(62) 5.1 ± 1.7	<0.0001
Android fat mass/gynoid fat mass ratio	(61) 1.16 ± 0.11	(62) 0.92 ± 0.19	<0.0001
EVAT, kg	(60) 2.4 ± 0.9	(62) 0.7 ± 0.4	<0.0001
ESAT, kg	(60) 3.8 ± 1.0	(62) 1.8 ± 0.9	<0.0001
Fat cell volume, pL	(62) 972 ± 177	(61) 450 ± 179	<0.0001
ESAT fat cell number × 10^9	(60) 4.3 ± 1.5	(61) 4.2 ± 1.5	0.39
M value, mg/kg/min	(57) 3.9 ± 1.5	(54) 6.6 ± 1.5	<0.0001
P-insulin, pmol/L	(62) 108 ± 59	(55) 32 ± 63	<0.0001
P-glucose, mmol/L	(62) 5.6 ± 1.3	(57) 4.8 ± 0.6	<0.0001
P-cholesterol (mmol/L)	(62) 4.9 ± 0.9	(62) 4.1 ± 0.8	<0.0001
P-HDL cholesterol (mmol/L)	(62) 1.1 ± 0.3	(62) 1.5 ± 0.4	<0.0001
P-LDL cholesterol (mmol/L)	(61) 3.4 ± 0.9	(62) 2.4 ± 0.7	<0.0001
P-triglycerides mmol/L	(61) 1.5 ± 0.7	(62) 0.9 ± 0.4	<0.0001
P-apo B (g/L)	(62) 1.0 ± 0.2	(62) 0.8 ± 0.2	<0.0001
P-apo A1 (g/L)	(62) 1.2 ± 0.2	(62) 1.4 ± 0.3	<0.0001
Systolic blood pressure (mmHg)	(62) 135 ± 17	(62) 124 ± 15	<0.0001
Diastolic blood pressure (mmHg)	(62) 84 ± 8	(62) 75 ± 10	<0.0001
Patients treated with antihypertensive medication	20	13	
Patients treated with metformin/metformin and sulfonylureas	3/1	0/0	
Patients treated with statins	3	1	

Data are presented as (number of subjects) value ± SD. Values are fasting values mean ± SD. The groups were compared at baseline level and after gastric bypass by paired Student *t* test. To convert insulin to mU/L, divide by 6.9. To convert triglycerides to mg/dL, multiply by 88.49. To convert glucose to mg/dL, multiply by 18.0. Apo, apolipoprotein; P, fasting plasma.

t test), which probably was due to the body surface area (used to estimate insulin dosage) decreasing after RYGB. Changes in insulin clearance after RYGB could also be involved (22). Glycerol levels were measured before and during steady state and were suppressed to a similar degree, by 55 ± 11% at baseline and 59 ± 17% at follow-up.

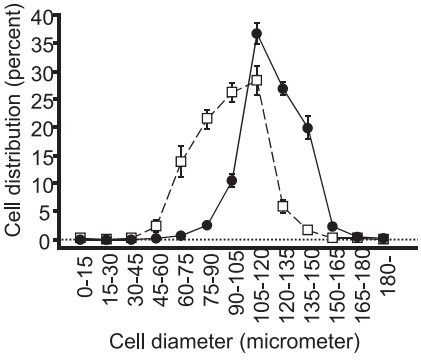

Figure 1—Distribution of fat cell diameter before and after gastric bypass of obese women. Black circles, before surgery; white squares, after surgery.

The relationship between fat mass and fat cell volume was determined as follows: a curve fit of the relationship between ESAT adipocyte volume and ESAT mass was performed as previously described (11,17). The relationship is $V = (a \times m)/(1 + b \times m)$, where V is mean fat cell volume, m is the amount of adipose tissue, and a and b are variables that are obtained by fitting the formula to subject data. The difference between measured fat cell volume and the expected fat cell volume obtained from the mean curve fit at the corresponding fat mass is indicative of adipose morphology, as previously discussed in detail (11). If the measured fat cell volume is larger than expected, adipose hypertrophy prevails, whereas the opposite is valid for hyperplasia. One curve fit was made from the two cohorts of women when examined in a non–weight-reduced state, and a separate curve fit was made for the 62 women who were subjected to weight reduction by RYGB.

Statistics

Group values are mean ± SD in text and Table 1 and ± SEM in Fig. 1. Results were compared by paired Student *t* test or ANCOVA and Fisher post hoc test. Differences in adipose and metabolic parameters between baseline and reexamination were calculated and compared using Spearman correlation and multiple regression analyses. Differences between curve-linear relationships were tested using Student *t* test as described in the supplement of a previous study (17). A *P* value <0.05 was considered to be statistically significant in all analyses.

RESULTS

Sixty-two obese women were included in the study comparing results before and after weight reduction, and the clinical characteristics at baseline and at follow-up are shown in Table 1. Six women had type 2 diabetes; two were treated with lifestyle intervention only, three with metformin, and one with metformin plus glibenclamide. At the follow-up

Table 2—Relationship between changes in adipose and metabolic parameters after bariatric surgery

Adipose variable	Metabolic variable						
Values after-before	*M* value	Insulin	Glucose	Triglycerides	Total cholesterol	HDL cholesterol	LDL cholesterol
Subcutaneous fat cell volume	0.0057	0.430	0.389	0.072	0.025	0.085	0.0021
ESAT	0.313	0.398	0.554	0.855	0.311	0.233	0.180
Android fat mass	0.060	0.411	0.701	0.11	0.152	0.666	0.063
Gynoid fat mass	0.372	0.138	0.752	0.791	0.021	0.497	0.0074
Android fat/gynoid fat ratio	0.091	0.038	0.648	0.121	0.0073	0.697	0.0013
EVAT	0.0154	0.525	0.438	0.033	0.085	0.299	0.027
Total fat mass	0.061	0.151	0.733	0.186	0.044	0.710	0.010

Values are *P* values following Spearman correlation test.

examination, none of the women with diabetes were taking any antidiabetic drugs. At baseline, 20 women were treated with antihypertensive medication, and 7 additional patients had a systolic blood pressure ≥140 mmHg. At follow-up, 13 women were still on antihypertensive medication, and 8 who had preoperatively diagnosed hypertension still had a systolic blood pressure ≥140 mmHg. BMI decreased from an initial 42.7 ± 4.4 to 28.5 ± 4.2 kg/m^2, which corresponded to a total weight loss of 33 ± 9%. The fat mass in all examined regions (ESAT, EVAT, android, etc.) decreased markedly after RYGB. Subcutaneous fat cell volumes decreased markedly after surgery, whereas there was no significant change in the number of fat cells. Not surprisingly, there was a significant improvement of the metabolic risk profile (clinical chemistry and body fat distribution) after surgery.

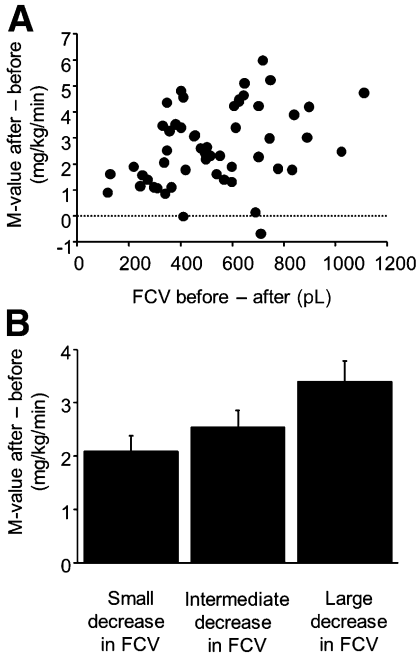

Figure 2—Relationship between changes in mean fat cell volume and insulin sensitivity (*M* values) after gastric bypass of obese women. *A*: The relationship between absolute values. *B*: The relationship when women were divided into tertiles based on fat cell volume (FCV) changes. See Table 2 and text for statistical results.

The distribution of fat cell volumes before and after RYGB is detailed in Fig. 1. Although a uniform distribution was observed at both examinations, the distribution curve at reexamination was markedly shifted to the left, indicating smaller cell volumes.

As expected, there was a strong relationship between the decrease in subcutaneous fat cell volume and the decrease in ESAT ($P = 0.0012$). The changes in adipose parameters were compared with changes in metabolic risk factor parameters (Table 2). Adipocyte volume reduction was significantly and strongly associated with an improvement in the *M* value ($P = 0.0057$ for relationship in Fig. 2*A*), whereas a decrease in ESAT or total fat mass was not ($P = 0.31$ and $P = 0.06$, respectively). Assuming that changes in adipose tissue and metabolic parameters were normally distributed, multiple regression was performed and showed a significant correlation between changes in subcutaneous fat cell volume and *M* value independently of the initial fat cell volume (partial $r = 0.38$; $P = 0.031$). Similar analyses with changes in *M* value as dependent factor and fat cell volume changes as one independent factor and fat mass changes in different depots (total fat, android, gynoid, EVAT, or ESAT) as a second independent factor only showed a significant correlation between changes in fat cell volume and *M* value (Table 3). We also subdivided the subjects into tertiles for changes in fat cell volume after RYGB (Fig. 2*B*). Changes in *M* values for the three groups were compared by ANCOVA using changes in ESAT as covariate. An overall effect of fat cell volume reduction was observed ($F = 4.0$; $P = 0.025$). The mean increase in *M* value after bariatric surgery between women in the lowest and highest tertile of fat cell volume change was 2.0 ± 1.1 mg glucose/kg body weight/min and 3.4 ± 1.7 mg glucose/kg body weight/min, respectively ($P = 0.0054$ by post hoc test). Similar results were obtained when changes in the other measured adipose tissue parameters were used as covariates in the ANCOVA instead of ESAT (values not shown).

Changes in fat cell volume after RYGB were also significantly related to changes in plasma total and LDL cholesterol (Table 2). Some fat mass and fat cell volume measures correlated with individual values or blood pressure, but the associations were not consistent for any of the fat parameters (values not shown). As several patients were on antihypertensive treatment or used lipid-lowering drugs, the findings on blood pressure and different cholesterol measures were not further analyzed. In order to estimate the influence of multiple testing in Table 2, Bonferroni correction of *P* values was performed (*P* multiplied with 7, which was the number of dependent variables for each independent variable). Only subcutaneous fat cell volume versus *M* value remained statistically significant ($P = 0.04$).

The relationship between mean fat cell volume and fat mass in ESAT is depicted in Fig. 3. In subjects who had not been subjected to weight reduction ($n = 124$ including cohort 1 at baseline and cohort 2), a curve-linear relationship between the two parameters was observed. In the women who were reexamined after

Table 3—Correlation between changes in *M* value (dependent) and changes in subcutaneous fat cell volume and other variables tested with multiple regression analyses

	Subcutaneous fat cell size		Covariable	
Covariable	Partial *r*	*P* value	Partial *r*	*P* value
ESAT	0.32	0.04	−0.003	0.99
Android fat mass	0.38	0.03	−0.05	0.79
Gynoid fat mass	0.40	0.01	−0.10	0.53
Android fat/gynoid fat ratio	0.36	0.04	−0.01	0.95
EVAT	0.28	0.07	0.09	0.54
Total fat mass	0.33	0.07	0.04	0.85

RYGB (n = 62), the relationship was still curve linear but the position of the curve was markedly different from the one prior to surgery (P = 0.03 by Student t test). The fitted fat cell volume at a particular fat mass was much smaller in the weight-reduced subjects than in the whole group of non–weight-reduced subjects. This suggests that the relationship between fat mass and fat cell volume was altered after weight reduction.

CONCLUSIONS

In this prospective study, we show that marked weight reduction is associated with a decrease in fat cell volume (but not number) in subcutaneous adipose tissue, which is significantly associated with improvements in insulin sensitivity. Furthermore, our present study confirms earlier observations (6) that decreased visceral, but not subcutaneous fat mass, correlated significantly with improvements in metabolic risk factors, including insulin sensitivity and plasma triglycerides. A similar lack of associations was observed for android and gynoid fat (mostly composed of subcutaneous fat) as for ESAT, further supporting the notion that a decrease in subcutaneous fat mass per se has little impact on improvements in insulin sensitivity. Unfortunately, we cannot say if a decrease in visceral fat cell volume may also be important since this measure could not, for obvious ethical reasons, be obtained after weight reduction. It is of interest to note that when the present prospective cohort was investigated at baseline, subcutaneous fat cell volume correlated more strongly than visceral fat cell volume with insulin sensitivity (15). This suggests that for subcutaneous adipose tissue, fat cell size may be of greater importance than fat mass. It is possible that the lack of effect of liposuction on the metabolic profile (3,4) is dependent on the fact that such an intervention does not alter the size of fat cells in the remaining subcutaneous adipose tissue. A decrease in subcutaneous fat cell size rather than a decrease in subcutaneous adipose mass per se may therefore be of greater importance for improvement of insulin sensitivity after weight loss. At present we cannot identify which functional aspects related to fat cell size play a causal role in the reversal of insulin resistance after weight loss. Alterations in adipocyte turnover resulting in adipose remodeling could play a role. This notion is based on the observation that when the mean curve fit for ESAT versus fat cell volume was determined, the curve for women investigated at baseline was significantly different from that obtained with women examined after RYGB. According to previously published estimates of human adipocyte turnover data, ~20% of all fat cells are renewed after 2 years (17), which was the mean difference in time between the first and second examination. It could be speculated that these new fat cells, developed during at least a period of caloric restriction, may have a different size than the fat cells they replaced.

We observed some correlations between changes in fat cell size or fat mass parameters and various measures of cholesterol and blood pressure. These associations, although interesting, were not studied in detail due to possible effects of concomitant medications and the fact that the focus of this study was effects on insulin sensitivity.

Admittedly, our study has some caveats. We only studied fat cells from the subcutaneous umbilical region and we cannot extrapolate our findings to other subcutaneous fat depots. In fact, fat cell size differs slightly between abdominal and peripheral subcutaneous adipose regions (23,24), which may have an impact on the relationship between fat cell size and metabolic profile (23). We used DEXA instead of computed tomography or magnetic resonance imaging to estimate fat mass content in different adipose regions and we cannot exclude that this might have influenced the results. However, the DEXA method shows a very high concordance with computed tomography measurement also for determination of visceral fat mass (20). Moreover, we only studied women and cannot exclude the possibility that there may be sex-specific differences. Also, since treatment with pharmacological agents affecting metabolism is common in patients undergoing bariatric surgery, we cannot exclude the possibility that this could have affected our results. Finally, all women were treated with RYGB, which may also cause hormonal changes independent of weight loss (25). Although not likely, the outcome might have been different if gastric volume restriction surgery would have been used instead. Other factors not examined in this study might also contribute to metabolic improvements after weight loss. For example, nutritional factors and changes in physical activity

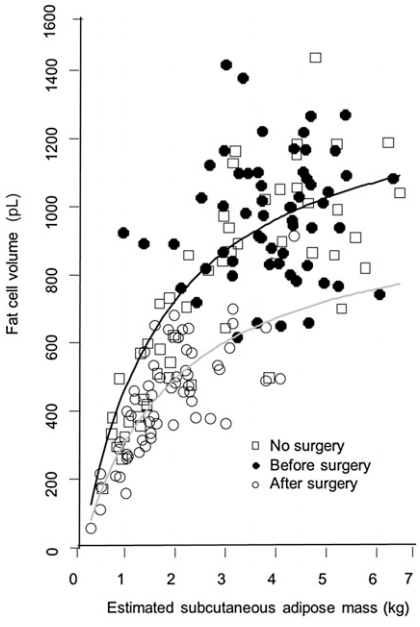

Figure 3—Relationship between mean fat cell volume and ESAT. Black line is the relationship for all subjects at a baseline non–weight-reduced state. Gray line is the relationship in subjects investigated after weight reduction. The curve-linear relationships between baseline and the weight-reduced state were significantly different (P = 0.03 with Student t test).

may have metabolic effects that are not related to adipose tissue when body weight is reduced by lifestyle factors (2,26–28).

Measuring fat cell size might have important implications. Degree of obesity is usually just defined by the amount and (sometimes) distribution of body fat. As recently discussed, other parameters are needed to better classify subtypes of obesity that have different impacts on the risk of developing type 2 diabetes and other obesity complications (29,30). One such parameter could be subcutaneous fat cell size, which is a measure of quality, rather than quantity, of fat. It is easy to obtain small subcutaneous fat biopsies, and the size of the fat cells can readily be determined histologically (10,12).

In conclusion, a decrease in subcutaneous fat cell volume rather than a decrease in subcutaneous adipose tissue mass is associated with improvements in insulin sensitivity after marked weight loss. An altered relationship between fat mass and fat cell volume (i.e., remodeling) may at least in part explain the findings.

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Author Contributions. D.P.A. and M.R. designed the study, recruited and examined the obese women, and wrote the first version of the manuscript. D.E.H., A.Thore., E.T., V.Q., E.N., A.Thörn., M.W., P.L., J.H., I.D., and N.M. recruited and examined the obese women. E.A. and P.A. designed the study and wrote the first version of the manuscript. P.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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