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PAPER

Changes in abdominal subcutaneous fat water content with rapid weight loss and long-term weight maintenance in abdominally obese men and women

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OBJECTIVE: Insulin resistance decreases blood flow and volume in fat tissue. We hypothesised that fat tissue nutritive blood flow and volume, and thereby water content, would increase during weight loss and weight maintenance in obese persons.
DESIGN: Longitudinal clinical intervention with a 9-week very-low-calorie diet (VLCD) followed by one year of weight maintenance.
SUBJECTS: Obese men ($n=13$) and women ($n=14$) with the metabolic syndrome.
MEASUREMENTS: Water content of abdominal subcutaneous fat tissue as estimated by a sensor on the skin surface measuring the dielectric constant at 300 MHz. Anthropometric measures of fatness and fat distribution. Biochemical measures related to insulin resistance.
RESULTS: Subjects lost 14.5 ± 3.4% of body weight during the VLCD, and generally sustained this weight loss during weight maintenance. Insulin sensitivity as estimated by an index (qualitative insulin sensitivity check index) increased during the VLCD, and remained increased throughout weight maintenance. The dielectric constant increased from 23.3 ± 2.3 to 25.0 ± 2.1 ($P<0.001$) during the VLCD, and further to 27.8 ± 1.9 ($P<0.001$) during weight maintenance, indicating an increase in the water content of subcutaneous fat. The increase in subcutaneous fat water content did not correlate with weight loss and other measures of adiposity during the VLCD, but there was an inverse correlation that strengthened in significance from baseline to 6, 9 and 12 mo ($r=-0.32$ to -0.64, $P=0.079$–0.002). Increases in subcutaneous fat water content also correlated with improvements in insulin sensitivity at 6, 9 and 12 months of weight maintenance ($r=0.34$–0.54, $P=0.094$–0.006).
CONCLUSIONS: Water content of abdominal subcutaneous adipose tissue increases with weight loss in obese persons with the metabolic syndrome, and may reflect increased subcutaneous fat tissue nutritive blood flow. The increase in water content correlates with the increase in insulin sensitivity, suggesting that weight loss and consequent improved insulin sensitivity could mediate the increase in abdominal subcutaneous fat hydration.
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Keywords: Insulin resistance; Metabolic syndrome; Subcutaneous fat tissue; Very-low-calorie diet; Weight maintenance

Introduction

Insulin plays a key regulatory role in many major physiological functions related not only to lipids and glucose, but also to blood flow and fat tissue metabolism. [1–6] Disturbances in the regulatory functions of insulin are a hallmark of the metabolic syndrome and type II diabetes mellitus.

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Decreased subcutaneous adipose tissue blood flow has been found in obesity.[7–9] In obesity, the insulin-stimulated increase in skeletal muscle and adipose tissue blood flow[2,4] also appears to be blunted.[2] These findings suggest that the decrease in basal and postprandial adipose and skeletal muscle blood flow[9] is because of insulin resistance. Decreased adipose tissue blood flow affects metabolism by decreasing delivery of glucose, fatty acids and hormones to adipose tissue, and by decreasing release of lipolysis products and peptides from fat tissue into the general circulation. The coupling of insulin-mediated glucose uptake and blood flow has been demonstrated in skeletal muscle, although not yet in fat tissue.[10] Tissue blood volume reflects

nutritive blood flow.[11–13] Similarly, both skeletal muscle basal and insulin-stimulated blood flow and blood volume have been shown to be decreased in hypertension, a condition characterised by insulin resistance.[5] The effect of insulin on interstitial tissue fluid volume has been less well described, but insulin also has been shown to increase acutely interstitial fluid volume, which partly explained the increase in muscle glucose uptake.[14]

The metabolic syndrome is characterised by abdominal obesity, insulin resistance, dyslipidaemia, disturbed glucose metabolism and hypertension.[1] The amount of both visceral and subcutaneous abdominal fat is strongly associated with insulin resistance.[15,16] Weight loss improves insulin sensitivity and most of the metabolic risk factors associated with the insulin-resistance syndrome.[17] Weight loss in response to a hypocaloric and to a very-low-calorie diet (VLCD) has been shown to enhance nutritive subcutaneous abdominal fat blood flow in the short term.[3,18] There have been no studies on the effects of long-term weight loss and weight maintenance on subcutaneous abdominal fat tissue blood flow or fluid volume, nor have there specifically been studies on the effects of weight loss on fat tissue blood flow or fluid volume in obese patients with the metabolic syndrome.

A novel open-ended coaxial probe allowing noninvasive measurement of subcutaneous tissue water content without the use of radioisotopes has recently been developed.[19] The dielectric constant of biological tissue at 300 MHz is a measure of tissue water content.[20–22] We have validated dielectric measurements with human skin using an experimental three-layer setup including a movable acrylic piston that simulated subcutaneous fat with a low concentration of water.[23] Using the dielectric model that we developed the dielectric constant of the acrylic piston could be determined with an accuracy of $\pm 5\%$ in situations where the thicknesses of upper layers (representing stratum corneum, epidermis and dermis) were changed. This technique has also been applied to the measurement of changes in subcutaneous fat tissue in breast cancer patients undergoing radiation therapy.[23]

We hypothesised that the water content of subcutaneous abdominal adipose tissue as assessed by this probe would increase following rapid weight loss and extended weight maintenance in abdominally obese men and women with the metabolic syndrome. We also assessed the correlation of changes in abdominal subcutaneous fat hydration with changes in body weight, insulin sensitivity and other measures associated with the metabolic syndrome.

Methods

Subjects

Subjects were recruited into the study after giving informed written consent. In all, 27 subjects (14 women and 13 men) for whom measurements of subcutaneous fat hydration were made before and after the VLCD are included in this study (Table 1). All 27 subjects completed the 1-y weight maintenance phase. This is a substudy of a still ongoing multicentre randomised controlled double blind trial on the effects of the lipase inhibitor orlistat on weight maintenance after a VLCD in the abdominally obese with the metabolic syndrome. The inclusion criteria were (1) a body mass index (BMI) between 30 and 45 kg/m^2 and waist circumference greater than 102 cm for men and 90 cm for women; and (2) diabetes mellitus (plasma glucose concentrations at least 7.0 mmol/l[24]) treated by diet only or two of the three following metabolic abnormalities: impaired fasting glycaemia[24] (fasting plasma glucose concentration between 6.1 and 6.9 mmol/l), high-density lipoprotein (HDL) cholesterol level <1.0 for men and 1.2 for women, or triglyceride levels between 2.0 and 10.0 mmol/l. All had the metabolic syndrome as defined by the National Cholesterol Education Program criteria[25]. Exclusion criteria included poorly controlled diabetes (HbA1c at least 10%), uncontrolled hypertension (blood pressure $\geq 180/120$), ischaemic heart disease, significant psychiatric illnesses or psychiatric medications and significant kidney disease. The Research Ethics Committee of Kuopio University Hospital approved the study.

Table 1 Clinical characteristics of the 27 men and women with abdominal obesity and the metabolic syndrome

Age (y)	49.0 (range 32–61)
Sex	13 men, 14 women
Body mass index (kg/m^2)	35.8 ± 3.4
Smokers, *n* (%)	6 (22%)
Hypertension, *n* (%)	20 (74%)
Antihypertensive medication, *n* (%)	10 (37%)
Diabetes, *n* (%)	4 (14.8%)
Impaired fasting glycaemia, *n* (%)	5 (18.5%)
Serum total cholesterol (mmol/l)	5.9 ± 1.1
LDL cholesterol (mmol/l)	3.7 ± 1.1

Data are means (range), $\pm$s.d., or ordinal numbers (%).
LDL, low-density lipoprotein.

Usual blood pressure medication was maintained during the study, except for two for whom blood pressure medication was decreased, and one for whom medication was started. Exclusion of these individuals from analyses had no qualitative effect on the results.

VLCD

A VLCD of 3350 kJ/day (800 kcal/day) using Nutrilet VLCD products (Leiras Co., Espoo, Finland) was carried out for 9 weeks. Subjects were instructed to supplement the Nutrilet products with low-calorie vegetables as desired.

Weight maintenance

Persons having lost at least 5% of their initial body weight at the end of the VLCD were randomised to receive orlistat 120 mg or placebo three times daily with meals for the

weight maintenance phase of the study. All were prescribed mildly hypocaloric low-fat (<30 E%) diets of at least 5.020 kJ/day (1200 kcal/day), individualised to allow a 2512 kJ (600 kcal) deficit from the estimated daily caloric expenditure.

Measurements of adiposity

BMI was computed as the ratio of weight (kg) to the square of height (m). Waist circumference was taken as the average of two measurements at the midpoint between the lowest rib and the iliac crest.

Measurement of percent body fat

Percent body fat was determined using bioelectrical impedance analysis (BioElectrical Impedance Analyzer System, RJL Systems, Detroit, MI, USA).

Biochemical determinations

Subjects were asked to fast for 12 h before blood sampling. They were also asked to refrain from smoking for 12 h and from consuming alcohol for 3 days before blood was drawn.

Glucose and insulin determinations

Fasting plasma glucose levels were measured using a glucose dehydrogenase method after precipitation of proteins by trichloroacetic acid. The serum samples for insulin determination were stored at -20°C. Serum insulin was determined with a radioimmunoassay kit (Pharmacia Diagnostics, Uppsala, Sweden).

Insulin sensitivity

The so-called qualitative insulin sensitivity check index (QUICKI)[26] was calculated ($[\log(\text{glucose})+\log(\text{insulin})]^{-1}$. This index has been previously validated and has been shown to correlate closely with insulin sensitivity as measured by the euglycaemic hyperinsulinaemic clamp ($r=0.78$)[26].

C-peptide

The serum samples for C-peptide determination were stored at -20°C. C-peptide concentrations were determined with an ELISA kit (Dako A/S, Santa Barbara, CA, USA).

Lipoprotein and triglyceride determinations

Fractions of low-density lipoprotein (LDL) and HDL cholesterol were separated from fresh serum by combined ultracentrifugation and precipitation. The cholesterol contents of lipoprotein fractions and serum triglycerides were measured enzymatically.

Blood pressure

Casual office blood pressure was measured with an automatic digital sphygmomanometer (Omron HEM-907, Omron Corporation, Tokyo, Japan). The average of two measurements with the subject at a sitting position were taken at a 2- to 3-min interval after resting for at least 15 min. Hypertension was defined by use of hypertensive medication or casual office blood pressure $\geq 140/90$[27]. The 24-h blood measurements were conducted using a digital ambulatory blood pressure system (SpaceLabs 90207, SpaceLabs Medical, Inc., Redmond, WA, USA). The blood pressure measurements were performed at 15-min intervals except at night, when the interval was 30 min.

Dielectric probes for measurement of tissue water content

Open-ended coaxial probes were used to measure the dielectric constants of skin and subcutaneous fat.[23] The information measured by a 10 mm probe is principally from the skin while that of the 30 mm probe is mainly from the subcutaneous fat. The applied frequency of the electromagnetic field was 300 MHz. The coefficient of variation (CV) for a single measurement estimated from 10 consecutive measurements was 2.0%. The long-term CV over 8 weeks was 5.0%.

Statistical analysis

Normally distributed data are presented as means $\pm$ s.d. Skewed data are presented as medians (lower quarter, upper quarter), but are analysed after natural log transformation. Repeated-measures ANOVA was used to analyse changes of variables during the study. Pearson and partial correlation analysis was carried out to assess the association between changes of selected baseline measures during weight loss and weight maintenance. $P<0.05$ was considered to be statistically significant.

Results

Weight loss and changes in adiposity

Subjects lost 15.6 kg of weight (15.2%) during the VLCD. Body weight was still 14.3 kg (14.0%) lower than baseline after 1 y of weight maintenance (Table 2). The corresponding decreases in percent body fat and waist girth during the VLCD were well maintained throughout the weight maintenance period.

Changes in insulin sensitivity and fasting blood glucose levels with weight loss and weight maintenance

Insulin sensitivity as estimated by the insulin sensitivity index increased markedly during the VLCD. The improvement in insulin sensitivity persisted throughout the weight

Table 2 Changes from baseline in measures of adiposity; insulin, glucose and lipid metabolism; blood pressure; and subcutaneous abdominal fat and skin water content as estimated by the dielectric constant at 300 MHz during the 9-week very-low-calorie diet and weight maintenance (6, 9 and 12 months).

	Rapid weight loss		*Weight maintenance*			
	Baseline	*9 week*	*6 months*	*9 months*	*12 months*	P
Weight (kg)	102.5±12.8	86.9±10.4	86.2±11.3	87.7±10.8	88.2±12.4	<0.001
Percent body fat	33.7±6.4	28.3±7.5	26.4±8.9		29.8±9.4	< 0.001
Waist girth (cm)	115±8	103±8	102±9	102±9	103±10	< 0.001
Insulin sensitivity (QUICKI)	0.32±0.03	0.36±0.03	0.35±0.02	0.35±0.03	0.35±0.04	< 0.001
Fasting plasma glucose (mmol/l)	6.2±1.8	5.5±0.6	5.4±0.5	5.4±0.6	5.3±0.8	< 0.001
Fasting C-peptide (nmol/l)	0.89±0.37	0.64±0.32	0.67±0.22	0.63±0.26	0.72±0.34	< 0.001
Fasting serum HDL (mmol/l)	1.09±0.18	1.17±0.22	1.17±0.22	1.33±0.33	1.22±0.26	< 0.001
Fasting serum TG (mmol/l)	2.2 (1.6, 2.8)	1.0 (0.8, 1.4)	1.6 (1.1, 2.2)	1.6 (1.2, 2.3)	1.4 (1.2, 1.8)	< 0.001
Ambulatory SBP (mmHg)	129.4±8.6	119.9±8.4	125.2±8.5		126.5±8.5	< 0.001
Ambulatory DBP (mmHg)	79.4±5.9	74.4±5.6	77.3±5.6		77.8±6.8	< 0.001
SAF dielectric constant	23.3±2.3	25.0±2.1	24.3±2.4	27.5±2.0	27.8±1.9	< 0.001
Skin dielectric constant	28.4±4.5	26.4±4.6	26.6±4.7	28.9±9.2	30.4±6.4	0.012

P in the right-hand column represents the statistical significance of the overall changes during the study (repeated-measures ANOVA).
Data are means±s.d. or medians (lower quartile, upper quartile). HDL, high-density lipoprotein cholesterol; TG, triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure; SAF, subcutaneous abdominal fat.

maintenance period (Table 2). Fasting plasma glucose levels also decreased during the VLCD and weight maintenance.

Changes in serum HDL cholesterol and triglycerides with weight loss and weight maintenance

Fasting serum HDL increased and triglyceride levels decreased during the VLCD (Table 2). The changes were maintained during weight maintenance.

Changes in 24-h ambulatory blood pressure

Twenty-four-h ambulatory blood pressure decreased markedly during the VLCD (Table 2). The decrease in blood pressure was largely transient, however, and approached baseline levels at the end of weight maintenance.

Changes in abdominal subcutaneous fat water content with weight loss and weight maintenance

Subcutaneous fat water content increased during the VLCD and weight maintenance (Table 2). Cutaneous water content changed less markedly, and appeared to increase from baseline only at the end of weight maintenance.

Correlations of the changes in the subcutaneous abdominal water content with changes in adiposity and insulin, glucose and lipid metabolism during weight loss and weight maintenance.

Correlations of the changes in subcutaneous abdominal water content with changes in body weight were statistically most significant after 9 and 12 months of weight maintenance (Table 3). The correlations of the changes in water content and percent body fat became significant already at 6 months of weight maintenance after rapid weight loss. The changes of subcutaneous abdominal fat water content and insulin sensitivity as estimated by the insulin sensitivity

Table 3 Correlations of the changes in the subcutaneous abdominal fat water content as estimated by the dielectric constant at 300 MHz with changes in measures of adiposity, blood pressure and insulin, glucose and lipid metabolism during the VLCD (9 weeks) and weight maintenance (6, 9 and 12 months

	Change from baseline in the subcutaneous fat dielectric constant (%)			
	VLCD	*Weight maintenance*		
	9 weeks	*6 months*	*9 months*	*12 months*
Change from baseline (%)				
Weight	0.20	−0.32	−0.55 **	−0.64 ***
Percent body fat	0.20	−0.39 *		−0.40 *
Waist girth	0.30	0.01	−0.33	−0.50 **
Insulin sensitivity index	0.07	0.47 *	0.54 **	0.34
C-peptide	−0.08	−0.45 *	−0.61 **	−0.44 *
Fasting plasma glucose	−0.06	0.29	−0.13	0.06
Serum HDL cholesterol	0.18	0.07	0.09	0.47 **
Serum triglycerides	0.09	−0.54 *	−0.29	−0.36
Ambulatory DBP	−0.06	−0.35		−0.11

VLCD, very-low-calorie diet; for Other abbreviations see Table 2.
*$P<0.05$, **$P<0.01$, ***$P<0.001$.

index were correlated especially at 6 and 9 months of weight maintenance, but became weaker thereafter. The associations of changes in subcutaneous abdominal fat water content with triglycerides and HDL cholesterol levels were less consistent. No association with ambulatory blood pressure was seen (Table 3). Changes in skin water content as estimated with the 10 mm dielectric probe did not consistently correlate with changes in body weight or changes in characteristics related to insulin resistance (not shown). Adjusting for the change in the cutaneous water content had no qualitative effect on the correlations of changes in subcutaneous abdominal fat water content with changes in indices of body fat and insulin sensitivity (not shown).

Adjustment for changes in insulin sensitivity somewhat weakened the association between changes in subcutaneous fat water content and changes in body weight during weight maintenance, especially at 6 months (6 months, $r=-0.18$, $P=0.38$; 9 months, $r=-0.39$, $P=0.062$; 12 months, $r=-0.58$, $P=0.003$). Controlling for weight change attenuated the association between the changes in subcutaneous fat water content and changes in insulin sensitivity during weight maintenance especially at 12 months (six months $r=0.40$, $P=0.045$; 9 months $r=0.38$, $P=0.068$; 12 months $r=0.02$, $P=0.91$).

Discussion

The water content of subcutaneous abdominal fat as estimated by a novel coaxial probe measuring the adipose tissue dielectric constant increased during a 9-week VLCD and remained so throughout the 1-y weight maintenance period. Changes in abdominal fat tissue hydration correlated with changes in body weight and insulin sensitivity.

The increase in subcutaneous abdominal fat water volume as estimated by changes in the fat dielectric constant indicates an increase in the intravascular or extravascular extracellular fluid volume. The methodology does not distinguish between these two fluid compartments. An increase in subcutaneous fat intravascular volume would reflect increased nutritive blood flow.[5,11,12] An increase in overall subcutaneous abdominal blood flow as measured by xenon washout[3] and in nutritive subcutaneous abdominal fat blood flow as measured by the microdialysis technique[18] has also been shown previously in obese subjects after a 4-week VLCD. Extravascular or interstitial fluid volume changes in response to weight loss have not been previously reported. We found no evidence of attenuation of the increased subcutaneous fat water content as estimated by degree of hydration during 1 y of successful weight maintenance. To our knowledge, this is the first report on the changes of adipose tissue fluid volume during extended weight maintenance after weight loss.

The increase in abdominal subcutaneous water content as measured by the coaxial probe in this study most probably results from a weight-loss-induced and possibly insulin-mediated augmentation of nutritive blood flow or interstitial fluid volume. Insulin acutely increases adipose tissue blood flow, but in insulin resistant states such as obesity, blood flow is decreased.[2,4] Other studies have shown that weight loss improves not only insulin sensitivity, but also increases adipose tissue blood flow.[3,18] Extravascular or interstitial fluid volume in relation to insulin physiology has not been well studied, but muscle interstitial fluid volume appeared to increase acutely in response to insulin, and was related to the increase in glucose uptake.[14] Skin water content or blood flow does not influence the results, because skin hydration changed little during the study. Furthermore, controlling for changes in the skin water content did not qualitatively alter correlations between changes in subcutaneous fat water content and changes in measures of adiposity or insulin sensitivity.

The increase in abdominal subcutaneous fat water content relative to baseline was fairly consistently correlated with improvements in insulin sensitivity and with decreases in fasting C-peptide levels, especially at 6 and 9 months. Changes in abdominal subcutaneous fat water content were also inversely associated with changes in body weight and percent body fat during the weight maintenance period, particularly towards the end. These findings again suggest that the increase in subcutaneous abdominal fat water content is induced by weight loss and mediated by insulin sensitivity. There were inconsistent correlations between changes in subcutaneous fat water content and HDL cholesterol and triglycerides.

There was no correlation between changes in abdominal subcutaneous fat water content relative to baseline and changes in weight, insulin sensitivity or other characteristics related to the metabolic syndrome immediately after the VLCD, even though subcutaneous fat water volume as estimated by the coaxial probe increased. It should also be noted that the correlation of changes in weight loss or percent body fat with changes in insulin sensitivity immediately after the VLCD were also uncorrelated ($r=-0.09$–0.02, not shown). A VLCD acutely induces numerous changes in neurohumoral regulation, including salt balance, renin–aldosterone axis function and sympathetic nervous system function,[28] which may weaken the correlations between changes in fat tissue water content, weight loss and insulin sensitivity.

We used a novel open-ended coaxial probe that allows a noninvasive measurement of subcutaneous fat water content and thereby blood and extravascular water volume.[23] The dielectric technique applies a high-frequency electromagnetic field to estimate the water content of a biological tissue.[20–22] Measurement with the probe is simple and noninvasive, and does not require the use of radioisotopes. The probe cannot distinguish between tissue free and bound water, but it can be expected that fat tissue has less bound water per unit dry volume than tissues with high water content.[20]

The subjects of this study were abdominally obese, with evidence of disturbed lipid and glucose metabolism. All fulfilled the recently published NCEP criteria for the metabolic syndrome.[25] These individuals thus represent a relevant high-risk subgroup of obesity for the study of weight loss and weight maintenance on abdominal subcutaneous fat water content.

This is a substudy of a larger and still ongoing randomised controlled double blind trial on the effects of the lipase inhibitor orlistat on weight maintenance after VLCD in the abdominally obese with the metabolic syndrome. We do not know which patients have been randomised to orlistat, but this is unlikely to influence our results. Orlistat has been shown in large long-term clinical trials to be an effective weight-loss drug that also lowers LDL cholesterol.[29,30] Orlistat has not been shown in these large studies to have effects on other major cardiovascular or metabolic risk factors independently of weight loss. Furthermore, orlistat is only minimally absorbed into the blood stream.[31]

The noninvasive measurement of changes in water content of subcutaneous adipose tissue, although as yet not well characterised, may provide important insight on the metabolic changes that occur in subcutaneous fat tissue with weight loss and weight maintenance, and on the mechanisms that regulate those changes. The increased water content in abdominal subcutaneous fat tissue most probably indicates increased blood flow. Increased adipose blood flow could have implications not only for the storage and breakdown of triglycerides in fat tissue, but also in the regulation and release of numerous hormones and peptides, including leptin, resistin, adiponectin and tumour necrosis factor-α.

In what is to our knowledge the first study assessing the effects of weight loss and long-term weight maintenance on adipose tissue water content, subcutaneous abdominal fat water content as estimated by a novel dielectric probe increased after rapid weight loss and weight maintenance in abdominally obese persons with the metabolic syndrome. Changes in abdominal fat tissue water content furthermore correlated with changes in bodyweight and insulin sensitivity, suggesting that increased insulin sensitivity or other factors related to the metabolic syndrome may mediate the increase in subcutaneous fat nutritive blood flow that apparently occurs with weight loss and weight maintenance in the obese.

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