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ScienceDirect
Metabolism Clinical and Experimental 58 (2009) 995 – 1001
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Men develop more intraabdominal obesity and signs of the metabolic syndrome after hyperalimentation than women

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Received 18 October 2008; accepted 3 February 2009

Abstract

We prospectively studied the effects of fast food–based hyperalimentation on insulin sensitivity and components of the metabolic syndrome and analyzed this with respect to sex. Twelve nonobese men and 6 nonobese women (26 ± 6.6 years old), and an age-matched control group were recruited. Subjects in the intervention group aimed for 5% to 15% weight increase by doubling their regular caloric intake based on at least 2 fast food meals a day while also adopting a sedentary lifestyle for 4 weeks (<5000 steps a day). Weight of subjects in the intervention group increased from 67.6 ± 9.1 to 74.0 ± 11 kg ($P < .001$), with no sex difference with regard to this or with respect to changes of total abdominal fat volumes or waist circumferences. Fasting insulin (men: before, 3.8 ± 1.7 μU/mL; after, 7.4 ± 3.1 μU/mL; $P = .004$; women: before, 4.9 ± 2.3 μU/mL; after, 5.9 ± 2.8 μU/mL; $P = .17$), systolic blood pressure (men: before, 117 ± 13 mm Hg; after, 127 ± 9.1 mm Hg; $P = .002$; women: before, 102 ± 5.1 mm Hg; after, 98 ± 5.4 mm Hg; $P = .39$), serum low-density lipoprotein cholesterol, and apolipoprotein B increased only in the men of the intervention group. The sex differences in the metabolic responses to the intervention were linked to a considerable difference in the fat accumulation pattern; 41.4% ± 9.2% of the increase of the fat volume in the abdominal region was accumulated intraabdominally in men and 22.7 ± 6.5% in women ($P < .0001$). This study thus showed that women are protected, compared with men, against developing intraabdominal obesity when adopting a standardized obesity-provoking lifestyle. Our findings suggest that it is not different lifestyles and/or behaviors that underlie the fact that men have a higher cardiovascular risk at the same level of percentage of body fat than women.

1. Introduction

The prevalence of obesity has tripled in many European countries during the last 3 decades, and the number of people affected keeps rising. It is generally held that the increased prevalence of obesity is caused by a sedentary lifestyle and unfavorable food habits. In particular, energy-dense fast foods are often pointed out as important contributors to the increased incidence of obesity and hence to the increased prevalence of type 2 diabetes mellitus.

Obesity, in particular of the male abdominal pattern, is the main cause of insulin resistance and subsequently also of other components of the metabolic syndrome such as high blood pressure, dyslipidemia, and elevated plasma glucose levels. The adipose tissue releases free fatty acids, hormones, and proinflammatory cytokines that modulate the metabolism [1-3]. Human omental fat cells display a particularly high number of β-adrenergic receptors compared with subcutaneous fat cells, and these cells release large amounts of fatty acids [4]. The fatty acids from the fat tissue within

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doi:10.1016/j.metabol.2009.02.028

the abdominal cavity is drained via the hepatic vein that eventually subjects the liver to particularly high concentrations of fatty acids during hydrolysis of stored triglycerides [5]. This can affect liver metabolism to cause dyslipidemia and also indirectly lead to an increased production of glucose. Prospective studies in humans have demonstrated the importance of the intraabdominal fat volume for insulin sensitivity. Indeed, removal of the omentum in morbidly obese subjects has been shown to increase the sensitivity to insulin despite the fact that the omental fat mass corresponded to only 0.8% of total body fat [6]. On the other hand, surgical removal of 18% to 19% of total fat mass taken from the subcutaneous depot has been shown to be without effect on insulin sensitivity in humans [7]. Indeed, an abdominal fat distribution pattern constitutes a significant risk factor for insulin resistance even in subjects considered nonobese based on body mass index (BMI) [8,9].

There is a marked sex difference in fat distribution in humans according to cross-sectional studies. In men, most fat is stored in the upper body; and a large proportion of this is visceral fat, whereas in women, a greater amount of fat is stored in the gluteal region [10]. These sex differences are likely at least partially mediated by sex steroids because the fat distribution pattern shifts toward a more male-like pattern after menopause in women [11]. Although many earlier studies have provided crucial keys to the understanding of obesity and insulin resistance, very few have been prospective and interventional. This makes it difficult to fully clarify whether the sex differences with regard to cardiovascular risk markers and the related fat accumulation pattern are caused by differing behaviors or habits, for example, regarding exercise or food consumption.

We performed a study in which healthy nonobese men and women were instructed to double their calculated required caloric intake and to combine this with adoption of a sedentary behavior for 4 weeks. The aims of the study were to prospectively analyze the impact on components of the metabolic syndrome, in particular of the fat accumulation pattern, and to determine the impact of sex under these standardized obesity-provoking circumstances.

2. Methods

2.1. Subjects

We recruited 12 men and 6 women, by local advertising, as volunteers for the study. All participants had to be willing to accept a 2-fold increase in the daily caloric consumption until the goal of gaining 5% to 15% of weight was reached. To accomplish this, the participants in the intervention group were asked to eat at least 2 fast food–based meals a day, preferably at well-known fast food restaurants such as McDonald's and Burger King. Physical activity was not to exceed approximately 5000 steps per day; and bus tickets were issued to avoid walking or even using bicycles, as necessary. If a study subject reached a weight gain of 15%, he or she terminated the study as soon as possible by reperforming the same study investigations as were done at baseline. The participants were all free from current diseases as judged by medical checkup and medical history. Dieticians helped the participants to plan the hyperalimentation. During the course of the study, the dieticians were readily available as consultants to help the subjects reach the daily caloric intake and to make this as close as possible to constitute, or correspond to, that of fast food, that is, a diet rich in protein and animal fat. The receipts for food consumed were collected on a weekly basis for reimbursement. These receipts also formed the basis for the calculation of the total amount of calories consumed during the study period. The detailed composition of the diet (ie, including analysis of specific fatty acids, type of carbohydrates, and intake of fiber [12]) was based on reports from 3 days before the study and another two 3-day periods at the end of the first and third weeks (or a week earlier in the 1 subject who ended the trial after 2 weeks). In most cases, exact food composition given by the corresponding fast food restaurant could be used as source of information; but when such information was incomplete, we used food composition charts instead. For food bought at groceries, the manufacturer's information was used in a corresponding manner. If no such information was available, the foodstuff was equilibrated with a similar item in the Swedish National Food Administrations database. The total caloric intake per day of macronutrients (fat, carbohydrates, and proteins) during the hyperalimentation was based on all receipts and on interviews performed after the intervention period. The objective of the interviews was to clarify potential uncertainties about which particular goods the receipts declared and also to reduce other possible sources of error such as lost receipts, food consumed without receipts, and foodstuffs that had not completely been consumed. To achieve good compliance, the interviews were conducted under the context that foodstuffs added or subtracted would not affect the amount of reimbursement that the participants had received.

2.2. Control group

An age- and sex-matched control group was recruited to allow discrimination of changes of metabolic risk factors induced by the intervention from random fluctuations. The control group underwent the laboratory investigations and anthropometric measurements at baseline and after 4 weeks, as well as measurement of basal metabolic rate.

2.3. Laboratory tests

Blood samples were drawn in the fasting state at baseline, that is, before starting on the extra caloric intake, after 2 weeks on the fast food based diet, and at the end of the study, that is, either at the end of fourth week or earlier, if prematurely terminated. Blood was also drawn in the nonfasting state at the end of the first and the third study

weeks to monitor safety parameters, that is, changes in liver enzyme concentrations, as reported [12]. Serum insulin and C-peptide were assayed using immunoassay methods (AutoDelfia; Perkin Elmer, Linköping, Sweden). Apolipoproteins A-1 and B were analyzed by turbidimetry after an immunochemical reaction (Dako, Glostrup, Denmark). Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were determined by colorimetric analyses (Siemens, Liederbach, Germany); and low-density lipoprotein (LDL) cholesterol was calculated according to Friedewald (total cholesterol − HDL cholesterol − 0.456 × total triglyceride concentration). Glucose was determined by the hexokinase method (Siemens).

2.4. Magnetic resonance imaging and quantification of intraabdominal fat volume

Images were acquired from the level of the diaphragm to the bottom of the pelvis using a 1.5-T Philips Achieva MR scanner (Philips Medical Systems, Best, the Netherlands). A 4-element sensitivity encoding body coil was used to obtain magnitude and phase images from 2 different stacks using a field of view of 290 × 410 × 200 mm^3, 5-mm slice thickness, and 2.14 × 2.16-mm^2 in-plane resolution. In cases when 2 stacks in the superior-inferior direction provided insufficient volume coverage, an extra image stack (50 mm) was acquired using the quadrature body coil (integrated in the bore). The images were obtained at 2 different echo times (TEs) using a dual-echo, multislice, spoiled, fast gradient echo pulse sequence. The first echo was obtained using TE1 = 2.3 milliseconds with the water and fat signals out of phase, and the second was obtained using TE2 = 4.6 milliseconds with the water and fat in phase. The repetition time was 286 milliseconds, and the flip angle was 80°. Data were collected using breath hold technique (28 seconds using the sensitivity encoding body coil and 8 seconds using the quadrature body coil) with constant level appearance reconstruction. The fat/water contents in each voxel were determined using a Dixon [13] reconstruction followed by phase unwrapping [14]. This results in a water image and a fat image. The images were then corrected for field inhomogeneities by interpolating between known fat voxels using normalized convolution [15]. The abdominal adipose tissue was then segmented into 3 different types—subcutaneous, intraabdominal, and retroperitoneal adipose tissue—by registering a manually defined general prototype to the data using the Morphon method [16]. This nonrigid registration process uses the water image that contains structures with less variability than the fat image. The registration was then used to classify each voxel containing fat into 1 of the 3 different types of adipose tissue. Finally, the volume of each adipose tissue was determined by integrating the fat image for the corresponding tissue type.

2.5. Ethics

The study was approved by the Regional Ethics Committee of Linkoping and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participating subjects.

2.6. Statistical analyses

Statistical analyses were done using SPSS 15.0 software (SPSS, Chicago, IL). The results were considered statistically significant at the 5% level ($P \leq .05$). Comparisons within and between groups were done with Student paired

Table 1
Anthropometric and laboratory data before and after weight gain after hyperalimentation and adoption of a sedentary behavior in the intervention group

	All			Men			Women		
Variable	Before	After	*P*	Before	After	*P*	Before	After	*P*
Age (y)	26 ± 6.6			26.4 ± 6.3			24.5 ± 7.6		
Weight (kg)	67.6 ± 9.1	74.0 ± 11	<.001	71.4 ± 8.0	78.5 ± 8.5	<.001	60.0 ± 6.3	64.8 ± 8.1	.006
BMI (kg/m^2)	21.9 ± 1.9	23.9 ± 2.2	<.001	21.8 ± 2.0	24.0 ± 2.2	<.001	22.0 ± 2.0	23.8 ± 2.4	.005
Abdominal sagittal diameter (cm)	18.4 ± 1.7	20.4 ± 1.6	<.001	18.6 ± 1.8	20.9 ± 1.3	<.001	18.0 ± 1.6	19.5 ± 1.9	.048
Waist circumference (cm)	76.4 ± 6.4	83.1 ± 7.9	<.001	78.1 ± 6.9	85.1 ± 7.8	.001	72.8 ± 3.4	79.2 ± 7.2	.022
Hip circumference (cm)	86.5 ± 7.1	90.4 ± 8.5	.028	87.4 ± 8.4	90.6 ± 8.9	.16	84.7 ± 3.2	90.0 ± 8.4	.09
Fasting plasma insulin (μU/mL)	4.2 ± 1.9	6.9 ± 3.0	.002	3.82 ± 1.7	7.4 ± 3.1	.004[a]	4.9 ± 2.3	5.9 ± 2.8	.17[a]
Fasting plasma glucose (mg/dL)	96 ± 9.7	104 ± 11	.011	96.3 ± 5.5	104.8 ± 12	.065	100 ± 3.2	103 ± 8.4	.43
HOMA	0.89 ± 0.42	1.6 ± 0.83	.002	0.80 ± 0.36	1.7 ± 0.91	.005	1.0 ± 0.52	1.3 ± 0.63	.16[a]
QUICKI	0.40 ± 0.041	0.36 ± 0.033	.001	0.40 ± 0.034	0.35 ± 0.026	.001	0.39 ± 0.056	0.37 ± 0.044	.29
Caloric intake (kcal/24 h)	2820 ± 440	4930 ± 1070	<.001	3050 ± 310	5340 ± 920	<.001	2350 ± 210	4100 ± 900	.004
Systolic BP (mm Hg)	112 ± 12	116 ± 16.8	.172	117 ± 13	127 ± 9.1	.002[a]	102 ± 5.1	98 ± 5.4	.39[a]
Diastolic BP (mm Hg)	67 ± 7.2	69 ± 4.8	.433	67 ± 7.2	69 ± 4.8	.57[a]	63 ± 5.0	59 ± 8.6	.088[a]
Triglycerides (mmol/L)	0.72 ± 0.2	0.85 ± 0.5	.3	0.72 ± 0.2	0.95 ± 0.58	.2	0.73 ± 0.2	0.65 ± 0.2	.4
Apo B (g/L)	0.74 ± 0.2	0.82 ± 0.2	.076	0.71 ± 0.2	0.82 ± 0.2	.03[a]	0.80 ± 0.05	0.77 ± 0.03	.5[a]
Apo A-1 (g/L)	1.64 ± 0.4	1.83 ± 0.4	.014	1.4 ± 0.3	1.6 ± 0.2	.009	1.90 ± 0.5	2.10 ± 0.4	.2
HDL cholesterol (mmol/L)	1.51 ± 0.4	1.62 ± 0.4	.031	1.4 ± 0.4	1.5 ± 0.4	.1	1.7 ± 0.4	1.8 ± 0.5	.2
LDL cholesterol (mmol/L)	2.29 ± 0.5	2.54 ± 0.6	.006	2.3 ± 0.6	2.6 ± 0.7	.025	2.3 ± 0.3	2.5 ± 0.3	.1

BP indicates blood pressure; QUICKI, quantitative insulin sensitivity check index.

[a] Significant sex difference for the change induced by the intervention.

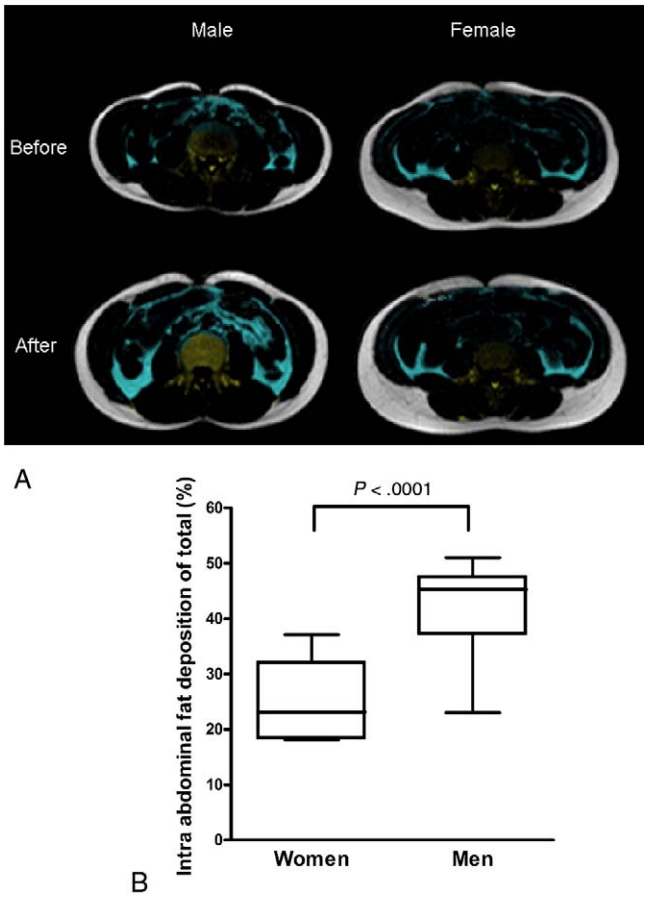

Fig. 1. A, Example of accumulation of subcutaneous and intraabdominal fat volume in 1 man and 1 woman after fast food–based hyperalimentation and adoption of a sedentary behavior for 4 weeks. The different fat compartments are shown using blue color for intraabdominal, yellow for retroperitoneal, and white for subcutaneous adipose tissues. Note that only 1 slice of the complete 3-dimensional volume, at the umbilical level, is shown and that image intensity corresponds to fat signal strength. B, Proportion of the volume of fat accumulated in the intraabdominal region, as percentage of the total increase in abdominal fat volume, after fast food–based hyperalimentation and adoption of a sedentary behavior for 4 weeks in nonobese subjects (6 women and 12 men). Men accumulated 41.4% ± 9.2% of the increase of the total abdominal fat volume intraabdominally, whereas the corresponding figure for women was 22.7% ± 6.5% ($P < .0001$).

and unpaired 2-tailed *t* test. Data were expressed as means ± SD. Linear correlations were calculated as given in the text. *Ratios* were defined as the level of the variable at study end divided by baseline level of the corresponding variable.

3. Results

The 18 (12 men and 6 women) subjects recruited for the intervention group were 26 ± 6.6 years old. All subjects except 1 were university students, most of which studied medicine. One of the participants had many years ago been diagnosed with celiac disease and underwent a duodenal biopsy at the end of the study that showed normal duodenal histology. The main results are shown in Table 1. The unexpected large increases in serum alanine aminotransferase, with no sex differences, after the intervention have previously been reported including that 1 male subject who was returned to his regular eating pattern at week 3 because of particularly high concentrations of alanine aminotransferase (450 U/L [12]). There were no sex differences with regard to the increase in weight, sagittal abdominal diameter, or waist circumference (Table 1). Systolic blood pressure increased in men, but no such increase was seen in the women; and this same sex difference with regard to cardiovascular risk factors was apparent also for apo B and LDL cholesterol, which increased in men but remained unchanged in women (Table 1). There were no sex differences with regard to the changes in HDL cholesterol levels or apo A-1, but the increase in apo A-1 was statistically significant only in men. Fasting plasma insulin and homeostasis model assessment (HOMA) [17] index of insulin resistance increased significantly in the men, whereas there was no such change in the women; correspondingly,

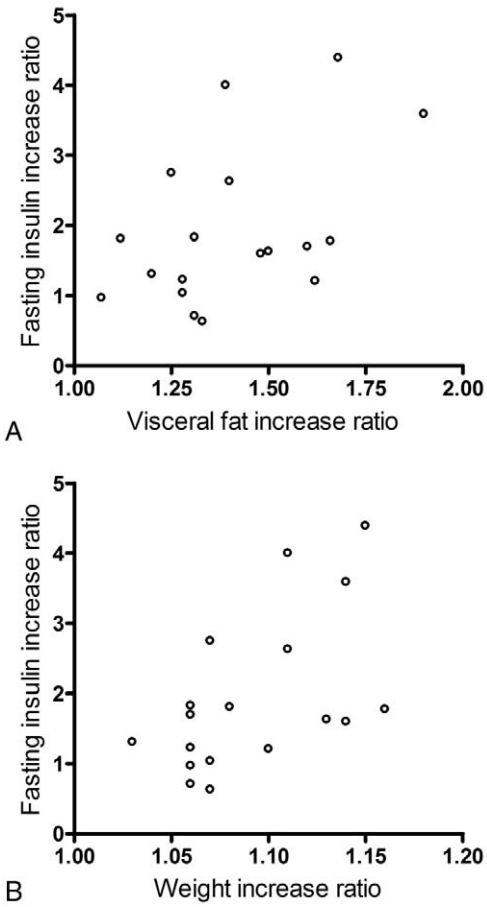

Fig. 2. A, Correlation between relative increase in visceral fat volume as determined by magnetic resonance imaging (visceral fat increase ratio = visceral fat volume at end of study/baseline visceral fat volume) and relative increase in fasting insulin in the intervention group; $r = 0.48$, $P = .04$, n = 18. B, Correlation between relative increase in weight (weight increase ratio = weight at end of study/baseline weight) and relative increase in fasting insulin in the intervention group; $r = 0.55$, $P = .02$, n = 18.

Table 2
Anthropometrics, basal metabolic rate, and HOMA of the control group in comparison with the intervention group

Variable	Baseline	*P* value for baseline levels in controls compared with intervention group	Control group after 4 wk	*P* value for levels at study end in controls compared with intervention group
Age (y)	25 ± 3.5	.3		
Sex (male/female)	12/6			
Weight (kg)	69.7 ± 8.4	.5	69.7 ± 8.7	.2
BMI (kg/m^2)	22.2 ± 2.1	.7	22.2 ± 2.2	.02
Abdominal sagittal diameter (cm)	17.8 ± 1.3	.3	17.8 ± 1.4	<.0001
Waist circumference (cm)	75.5 ± 5.8	.7	75.4 ± 6.0	.002
Hip circumference (cm)	89.0 ± 6.9	.3	89.8 ± 6.1	.8
Systolic BP[a] (mm Hg)	118 ± 6.7	.9	118 ± 8.5	.056
Diastolic BP[a] (mm Hg)	73 ± 4.8	.4	72 ± 7.8	.8
Basal metabolic rate (kcal/24 h)	1700 ± 243	.3	1712 ± 262	.3
HOMA	1.2 ± 0.86	.2	1.1 ± 0.53	.02

There were no statistically significant changes of the variables within the control group.

[a] Blood pressure in Table 1 in the intervention group was the mean value of recordings made at several of the investigations (only performed in the intervention group), whereas the value of the controls in this table was based on 1 measurement; the *P* value thus refers to measurements made at the same occasion for both groups.

quantitative insulin sensitivity check index [18] of insulin sensitivity was reduced only in men (Table 1).

There were no sex differences regarding the relative increase of calorie intake during the whole study period (men, +68.5% ± 31%; women, +74.3% ± 45%) or in the food composition regarding energy from fat, protein, and carbohydrates during the intervention (mean study values for men: 39% ± 4.0% energy percentage of total caloric intake from fat, 13% ± 1.5% from protein, and 48% ± 5.1% from carbohydrates; corresponding figures for women: 39% ± 2.9%, 11% ± 0.86%, and 50% ± 3.0%, respectively). There was no difference between sexes with regard to relative increase in basal metabolic rate (women: from 1325 ± 128 to 1483 ± 132 kcal/24 h, $P = .04$; men: from 1759 ± 205 to 1978 ± 262 kcal/24 h, $P = .006$; $P = .9$ for increase ratio between sexes).

Although there was no sex difference with regard to the increase in waist circumference (Table 1), this does not give information on whether the fat accumulation was subcutaneous or intraabdominal. The absolute increase in fat volume in the abdominal region (ie, subcutaneous, intraabdominal, and retroperitoneal fat) was similar in men and women (men: 4.53 ± 2.0 to 5.88 ± 1.9 L, ie, an increase in volume of 1.34 ± 0.71 L; women: 5.12 ± 1.4 to 6.47 ± 2.0 L, ie, an increase of 1.34 ± 0.72 L; $P = 1.0$ for comparison of sexes). However, determination of localization of the accumulated fat volume by magnetic resonance imaging showed a distinct sex difference. As depicted in an example in Fig. 1A, 41.4% ± 9.2% of the increase of the fat volume in the abdominal region was intraabdominal in men, whereas the corresponding figure for women was 22.7% ± 6.5% ($P < .0001$ for sex difference, Fig. 1B). Three subjects (1 woman and 2 men) were not whites. However, the sex difference in fat accumulation pattern was similar among these 3 subjects ($P = .047$) as in the remaining 15 whites ($P = .003$).

The increase in fasting insulin concentration correlated positively with intraabdominal fat increase ratio ($r = 0.48$, $P = .044$, Fig. 2A) and Δ ($r = 0.54$, $P = .02$). It was also positively related with the increase in body weight ratio ($r = 0.55$, $P = .02$, Fig. 2B) and tended to be related to the increase in energy intake ($r = 0.40$, $P = .1$). The sex differences regarding increase in systolic blood pressure or fasting insulin were no longer statistically significant when corrected for the proportional increase in intraabdominal adipose tissue and absolute fat volume increase in the abdominal region (blood pressure, $P = .1$; insulin, $P = .7$).

There were no differences between controls and subjects in the intervention group with regard to metabolic risk markers or basal metabolic rate at baseline, whereas BMI, sagittal abdominal diameter, waist circumference, and HOMA were higher in the intervention group compared with controls at the end of the study (Table 2) [12].

4. Discussion

The well-founded sex differences with regard to both cardiovascular risk factors and disease could theoretically be caused by inherited biological and hormonal differences, be consequences of differences of behavioral factors such as exercise habits, effects of stress, and/or differences with regard to diets and food intake, or be a combination of these factors. To our knowledge, our study is the first prospective evaluation of the effects of an obesity-provoking lifestyle composed of overconsumption of energy-dense food in combination with adoption of a sedentary behavior in nonobese subjects of both sexes. The participants were subjected to a fast food–based regimen because the consumption of this kind of food is often blamed for being a part of the worldwide obesity epidemic [19-21], in particular so if combined with a sedentary behavior [22]. Although the male and female participants gained a similar amount of weight and abdominal fat volume, we found a pronounced sex difference with regard to several cardiovascular risk factors,

such as blood pressure, insulin sensitivity, and plasma lipid concentrations. A striking sex difference indeed was the almost double relative amount of the increase in intraabdominal fat volume in men as compared with women, which to our knowledge has never been prospectively evaluated previously. Intraabdominal obesity is indeed linked more strongly to markers of the metabolic syndrome and cardiovascular disease than total amount of body fat [23]. Our study adds knowledge in this area of research because it demonstrates that, under similar conditions of increased food intake and sedentary lifestyle and similar relative increase of total fat volume in the abdominal area, almost twice as much fat accumulated intraabdominally in men compared with women. Indeed, when corrected for the differences in the proportion of intraabdominal fat accumulation, the sex differences in several components of the metabolic syndrome were no longer statistically significant.

The weaknesses in this study include the small number of female participants and the nonrandomized design. This was a consequence of the very demanding intervention in which all participants had to accept a considerable weight gain in combination with a limited period available for recruitment. To achieve the planned number of participants for the total study cohort, we allowed inclusion of more men than women because men were considerably easier to recruit. Furthermore, when gaining knowledge of the rather extreme changes in liver enzyme changes [12], an even more restricted inclusion pattern consisting of predominantly medical and nurse students was adopted to make communication of changes in laboratory tests with the participants more informative. The differences between sexes were consistent regarding several components of the metabolic syndrome such as blood pressure, insulin levels, and dyslipidemia. For ethical reasons, we only included nonobese subjects; and thus, our results may not be possible to extrapolate to the general population. The findings of sex differences in this study might also not be valid for postmenopausal women because earlier studies have suggested that sex differences for cardiovascular risk might be a consequence of hormonal differences at premenopausal age [24-26]. We can also not exclude the possibility that prolongation of the study period to more than a month would have affected our results. However, short periods of changes in lifestyle toward higher caloric intake and sedentary lifestyles are quite common in life, such as during vacation, which in Sweden typically lasts 4 to 5 weeks.

It is well known that obtaining complete information on actual food intake under freely living conditions is very difficult [27]. However, it is likely that the incentive to be reimbursed for food costs was favorable with respect to avoiding underreporting of the actual caloric intake in our study. Still, lost receipts, food bought or consumed without receipts, and receipts for food that was not consumed during the study were reported by some participants. These sources of errors were addressed by dedicated interviews, and the data were adjusted accordingly.

In summary, this study shows that, under similar obesity-provoking circumstances, men develop a more harmful cardiovascular risk profile, in particular signs of reduced insulin sensitivity, than women and that this was linked to a larger increase in the accumulation of intraabdominal fat volume. Thus, premenopausal nonobese women are protected compared with men against the metabolic risk after hyperalimentation and adoption of a similar sedentary lifestyle.

Acknowledgment

The contributions to the development of the image analyses by Andreas Johansson and Dr Joakim Rydell are gratefully acknowledged. In addition to the main authors of the manuscript, the Fast Food Study Group consisted of Preben Kjölhede, MD, PhD, Division of Obstetrics and Gynaecology; Anneli Sepa, PhD, Division of Pediatrics, both at Department of Molecular and Clinical Medicine; Prof Peter Strålfors, Department of Cell Biology, all 3 being at Faculty of Health Science Linkoping University; and Martin Carlsson, MD, PhD, Department of Internal Medicine, County Hospital of Kalmar. The study was supported by University Hospital of Linkoping Research Funds, Linkoping University, Gamla Tjänarinnor, the Diabetes Research Centre of Linkoping University, and Medical Research Council Grant 12661.

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