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ScienceDirect
Metabolism Clinical and Experimental 60 (2011) 531 – 536
Metabolism
Clinical and Experimental
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Body fat changes and activity of tumor necrosis factor α system—a 5-year follow-up study

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Received 13 January 2010; accepted 26 April 2010

Abstract

Obesity is associated with subclinical, chronic, and systemic immune activation characterized by increased serum concentration of proinflammatory cytokines released by adipose tissue. The aim of the present study was to determine the relationship between stage of development of obesity and changes in activity of tumor necrosis factor (TNF) system during 5-year follow-up observation. One hundred fifty-four women—102 obese, 24 overweight, and 28 lean—without concomitant diseases were examined for the first time from 2000 to 2001. After 5 years, 57 obese, 12 overweight, and 14 lean subjects were reexamined. In addition to anthropometric measurements, body composition was determined by the bioimpedance method; and serum concentrations of glucose, lipids, insulin, TNF-α, and soluble TNF receptors (sTNFRs) were measured. Only reexamined subjects were included in the analysis. After 5 years, fat mass increased significantly in 46 (66.7%) overweight or obese women and in all lean subjects (39.0 ± 12.3 vs 47.3 ± 13.6 kg, $P < .001$; 14.8 ± 3.7 vs 20.6 ± 5.4 kg, $P < .01$, respectively), whereas it decreased in 23 (33.3%) overweight or obese subjects (41.3 ± 12.5 vs 37.2 ± 14.0 kg, $P < .005$). The TNF-α levels increased significantly only in lean women (3.1 ± 3.0 vs 5.6 ± 2.0 pg/mL, $P < .005$), but remained unchanged in overweight and obese subjects regardless of fat mass changes. Serum concentrations of sTNFR1 and sTNFR2 decreased by 71% and 25% in obese, by 104% and 21% in overweight, and by 31% and 32% in lean group, respectively. The increase of plasma TNF-α level is an early event in abdominal fat accumulation. It seems that further fat mass gain does not enhance circulating TNF-α levels.

1. Introduction

It is well known that adipose tissue is not only a simple reservoir of energy substrates but also the largest endocrine organ producing a variety of peptides and cytokines with auto-, para-, and endocrine properties [1].

White adipose tissue, besides adipocytes, is composed of stromal cells, vasculature, nervous fibers, and macrophages [2]. Secretion activity was demonstrated either for adipocytes or for other components of adipose tissue [3]. In obesity, the adipose tissue is infiltrated by macrophages [4]; and those become the major source of proinflammatory cytokines, such as tumor necrosis factor (TNF) α. However, it has recently been shown that adipocytes are also releasing TNF-α; and its production and secretion enhance along with increasing adipocyte volume [5]. There is a hypothesis that increased immune activation in obesity reflects some similar properties of adipocytes and macrophages and their mutual interaction in secretion of lipids and cytokines [6]. There is also a high similarity of gene expression profiles in both cell types [7]. Adipocytes and macrophages also have some common functional features. Macrophages are able to store lipids, whereas preadipocytes can phagocytose and kill bacteria via an oxygen-dependent mechanism and transdifferentiate into macrophages [8]. Another recently conceived hypothesis links increased immune activation in obesity with hypoxia of enlarged adipocytes with distant location from the vasculature [9].

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0026-0495/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2010.04.023

Potential mechanisms described above make obesity-associated immune activation very complex.

From the clinical point of view, it is important that obesity is associated with subclinical, chronic, and systemic immune activation (microinflammation) characterized by increased serum concentration of proinflammatory cytokines. An increased serum concentration of TNF-α was repeatedly reported in obesity [10,11], whereas weight loss was followed by a decrease of its serum concentration but increase of soluble TNF receptors (sTNRFs) levels [10,12,13]. Recently Vilarrasa et al [14] reported a decrease of serum concentration of sTNFR2 but not of sTNFR1 after massive weight loss 1 year after gastric bypass. However, data concerning the long-term influence of weight gain on systemic immune activation including changes in TNF-α and their soluble receptor are missing. Therefore, the aim of the present study was to determine relationship between stage of development of obesity and changes in activity of TNF system during 5-year follow-up observation.

2. Material and methods

One hundred fifty-four women (102 obese, 24 overweight, and 28 lean) without any concomitant disease who were examined between the years 2000 and 2001 were invited for reexamination after 5 years. The characteristics of the initial study groups were published previously [11]. Fifty-seven obese, 12 overweight, and 14 lean women accepted the invitation for checkup (performed in 2005 and 2006). Only the reexamined subjects were included in the statistical analysis. The study was approved by the local Ethical Committee, and informed consent was obtained from all participants.

All obese and overweight subjects included in the study were diagnosed as having simple obesity without concomitant diseases. The exclusion criteria included evidence of present or recent (last 3 months) infectious disease, cigarette smoking, and any medication. Medical history, physical examination, anthropometric measurements (body mass, height, and waist circumference), body composition assessment, and blood pressure measurement were performed during the initial and follow-up checkup. The characteristics of the analyzed group are given in Table 1.

Body mass index (BMI) was calculated with the standard formula. The BMI intervals were defined as 18.5 to 24.9 kg/m^2 (lean subjects), 25.0 to 29.9 kg/m^2 (overweight group), and greater than 30.0 kg/m^2 (obese group). Body composition was determined by the bioimpedance method using the Bodystat 1500 analyzer (Douglas, Isle of Man).

Samples (6-8 mL) of venous blood were collected in the morning, after an overnight fast. The blood samples were collected according to the recommendations of the manufacturer of kits. The blood for measurements of TNF-α and sTNFRs was collected into the Lavender Vacutainer tubes that contain EDTA (BD, Plymouth, UK). Subsequently, the blood was transferred to centrifuge tubes containing aprotinin (0.6 trypsin inhibitor units per milliliter of blood). After centrifugation at 4°C, plasma samples were frozen and stored at −80°C until the time of assessment.

Plasma concentrations of TNF-α and sTNFRs were measured using a commercially available highly sensitive enzyme-linked immunosorbent assay kit (R&D System, Minnesota, MN). The sensitivity of the TNF-α assays is typically less than 0.18 pg/mL. Mean intraassay coefficient of variance was less than 14.4%, and mean interassay coefficient of variance was less than 18.7%. The sensitivity of the sTNFR1 and sTNFR2 assays is typically less than 0.77 and 0.6 pg/mL, respectively. Mean intraassay coefficients of variances were less than 3.6% and 2.6%, respectively; and mean interassay coefficients of variances were less than 3.7% and 3.5%, respectively. Insulin was assessed by radioimmunometric method (DPC Diagnostic Products, Los Angeles, CA) with a lower limit of sensitivity of 1.2 μIU/mL and intra- and interassay coefficients of

Table 1
Patient characteristics and changes in anthropometric measurements and blood pressure during a 5-year observation

	Obese n = 57			Overweight n = 12			Lean n = 14		
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ
Age (y)	43.8 ± 10.8	48.8 ± 10.8	5.0 ± 0.0	33.3 ± 12.0	38.3 ± 11.9	5.0 ± 0.0	36.4 ± 8.0	41.4 ± 8.0	5.0 ± 0.0
Weight (kg)	95.2 ± 14.8	96.9 ± 17.2	1.7 ± 7.0	77.4 ± 7.6	76.5 ± 10.4	−0.9 ± 9.3	59.8 ± 7.0	61.9 ± 7.2	2.1 ± 5.2
BMI (kg/m^2)	36.2 ± 4.6	36.9 ± 5.4	0.7 ± 2.6	28.2 ± 1.7	27.7 ± 2.9	−0.5 ± 3.2	22.3 ± 2.1	23.1 ± 2.7	0.8 ± 1.9
Fat-free mass (kg)	52.9 ± 7.1	49.6 ± 7.0†	−.3.3 ± 6.4	49.7 ± 5.5	48.4 ± 5.2	−1.3 ± 3.1	45.1 ± 4.7	41.4 ± 3.2†	−3.7 ± 3.7
Fat–free mass (%)	56.2 ± 6.9	51.9 ± 6.8‡	−4.3 ± 6.7§	64.3 ± 4.7	63.6 ± 4.5	−0.7 ± 5.5¶	75.5 ± 4.4	67.3 ± 5.6†	−8.3 ± 4.3
Body fat (kg)	42.3 ± 11.9	47.3 ± 13.4‡	5.0 ± 7.8	27.7 ± 4.9	28.1 ± 6.5	0.4 ± 4.5	14.8 ± 3.7	20.6 ± 5.4†	5.8 ± 3.9
Body fat (%)	43.9 ± 6.9	48.1 ± 6.8‡	4.3 ± 6.6§	35.7 ± 4.7	36.4 ± 4.5	0.7 ± 5.5¶	24.5 ± 4.4	32.7 ± 5.6†	8.3 ± 4.3
WC (cm)	107.8 ± 11.7	110.7 ± 13.6†	3.0 ± 7.3§	90.8 ± 10.0	90.0 ± 8.4	−0.8 ± 9.9¶	69.9 ± 6.3	78.4 ± 9.6*	8.5 ± 7.3
SBP (mm Hg)	130.5 ± 10.4	137.4 ± 10.4‡	6.8 ± 10.9	119.6 ± 13.6	128.3 ± 9.1*	8.8 ± 7.7$^{\|}$	120.7 ± 10.5	124.6 ± 7.7	3.9 ± 6.6
DBP (mm Hg)	80.4 ± 7.0	85.3 ± 7.2†	4.8 ± 8.7	79.2 ± 7.0	86.3 ± 7.4†	7.1 ± 4.5$^{\|}$	77.9 ± 7.0	81.5 ± 6.6*	3.6 ± 5.0

WC indicates waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure.
*$P < .05$, $^{\dagger}P < .001$, and $^{\ddagger}P < .0001$: follow-up vs baseline.
$^{\S}P < .0001$: obese vs lean.
$^{\|}P < .05$ and $^{\P}P < .0001$: overweight vs lean.

Table 2
Characteristics of subgroups A and B

	Subgroup A n = 46			Subgroup B n = 23			Lean n = 14		
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ
Age (y)	42.2 ± 11.0	47.2 ± 11.0	5.0 ± 0.0	41.7 ± 13.0	46.7 ± 13.0	5.0 ± 0.0	36.4 ± 8.0	41.4 ± 8.0	5.0 ± 0.0
Weight (kg)	92.4 ± 14.9	96.89 ± 17.2§	4.4 ± 6.1$^{\|}$	91.6 ± 16.5	86.5 ± 17.7†	−5.1 ± 5.5**	59.8 ± 7.0	61.9 ± 7.2	2.1 ± 5.2
BMI (kg/m^2)	35.0 ± 5.0	36.6 ± 5.5§	1.6 ± 2.3$^{\|}$	34.5 ± 5.8	32.7 ± 6.6†	−1.9 ± 2.0	22.3 ± 2.1	23.1 ± 2.7	0.8 ± 1.9
Fat-free mass (kg)	53.4 ± 7.3	49.5 ± 6.8‡	−3.9 ± 6.3$^{\|}$	50.3 ± 5.5	49.3 ± 6.6	−1.0 ± 4.9**	45.1 ± 4.7	41.4 ± 3.2†	−3.7 ± 3.7
Fat–free mass (%)	58.5 ± 7.7	51.8 ± 6.8§	−6.7 ± 5.2$^{\|}$	55.8 ± 6.1	58.2 ± 8.2	2.4 ± 4.6**	75.5 ± 4.4	67.3 ± 5.6†	−8.3 ± 4.3
Body fat (kg)	39.0 ± 12.3	47.3 ± 13.6§	8.3 ± 5.8$^{\|}$	41.3 ± 12.5	37.2 ± 14.0‡	−4.1 ± 4.4**	14.8 ± 3.7	20.6 ± 5.4†	5.8 ± 3.9
Body fat (%)	41.5 ± 7.7	48.2 ± 6.8§	6.7 ± 5.2$^{\|}$	44.2 ± 6.1	41.8 ± 8.2	−2.4 ± 4.5**	24.5 ± 4.4	32.7 ± 5.6†	8.3 ± 4.3
WC (cm)	104.5 ± 12.1	109.9 ± 13.6§	5.4 ± 6.7$^{\|\#}$	105.5 ± 15.1	101.5 ± 16.3*	−4.0 ± 6.2**	69.9 ± 6.3	78.4 ± 9.6*	8.5 ± 7.3
SBP (mm Hg)	128.7 ± 10.9	136.6 ± 9.1§	7.9 ± 10.1¶	129.6 ± 12.9	135.2 ± 13.4	5.7 ± 11.0	120.7 ± 10.5	124.6 ± 7.7	3.9 ± 6.6
DBP (mm Hg)	80.1 ± 6.8	85.9 ± 6.8‡	5.8 ± 7.9	81.1 ± 7.7	85.0 ± 7.5	3.9 ± 8.9	77.9 ± 7.0	81.5 ± 6.6*	3.6 ± 5.0

*$P < .05$, $^{\dagger}P < .01$, $^{\ddagger}P < .005$, and $^{\S}P < .0001$: follow-up vs baseline.
$^{\|}P < .0001$: group A vs B.
$^{\P}P < .05$ and $^{\#}P < .0001$: group A vs lean.
**$P < .0001$: group B vs lean.

variations of 5.2% and 5.8%, respectively. The kits for TNF system at the baseline and follow-up were produced by the R&D. The assessments were performed at the same analyzer. The plasma specimen were stored at a temperature of −80° for less than 6 months.

Plasma glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were determined using a commercially available test kit (Roche, Basel, Switzerland).

Insulin resistance was scored using the homeostasis model assessment of insulin resistance index (HOMA-IR) that was calculated according to the following formula: fasting plasma glucose concentration (millimoles per liter) × fasting plasma insulin concentration (micro–international units per milliliter)/22.5 (normal HOMA-IR range, <2.5).

3. Statistical analysis

All statistical analyses were performed with the use of Statistica 8.0 (Statsoft, Tulsa, OK) software. Results are presented as means ± SD. The follow-up results were tested with the use of analysis of variance with Newman-Keuls correction. Wilcoxon rank sum tests (for continuous and ordered variables) and Fisher exact tests (for discrete variables) were used to compare baseline and post–follow-up clinical/laboratory characteristics.

The correlation coefficients between changes in serum TNF-α, sTNFR1, and sTNFR2 levels and changes in body mass, body composition, and waist circumference were calculated according to Spearman. Multivariate stepwise analysis was performed for changes in serum TNF-α, sTNFR1, and sTNFR2 levels (also expressed as percentage changes) as the dependent variables and age and changes in body fat and waist circumference as the independent variables.

The results were considered as statistically significant with a P value < .05.

4. Results

After 5 years, mean body mass remained unchanged in all study groups, whereas mean fat mass and waist circumference increased significantly both in obese and in lean subjects. The decrease of percentage of free fat mass was significantly higher in lean subjects than in obese group. We also observed a greater increase of percentage of fat mass and waist circumference in lean subjects than in the obese group (Table 1). Arterial hypertension was diagnosed in 2 overweight and 22 obese subjects.

Based on changes in body composition during a 5-year follow-up, we divided overweight and obese subjects into 2 subgroups: with an increase of body fat: subgroup A (n = 46) and without any increase of body fat: subgroup B (n = 23) (Table 2). The increase of fat mass in subgroup A

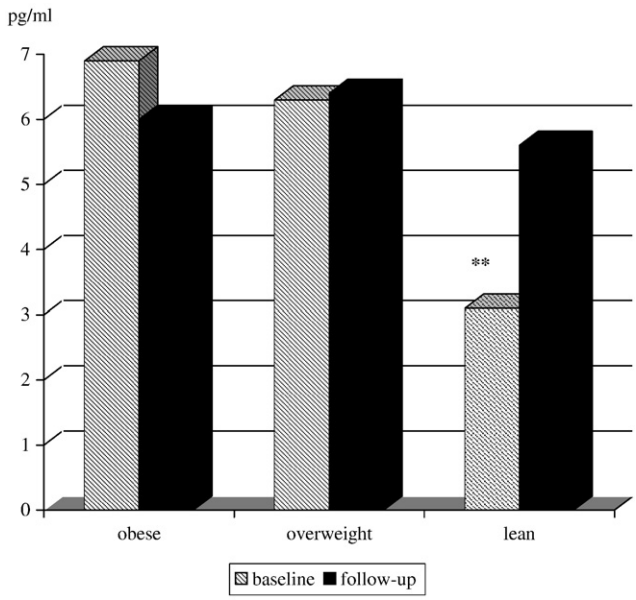

Fig. 1. The changes in plasma TNF-α levels during 5 years of observation.

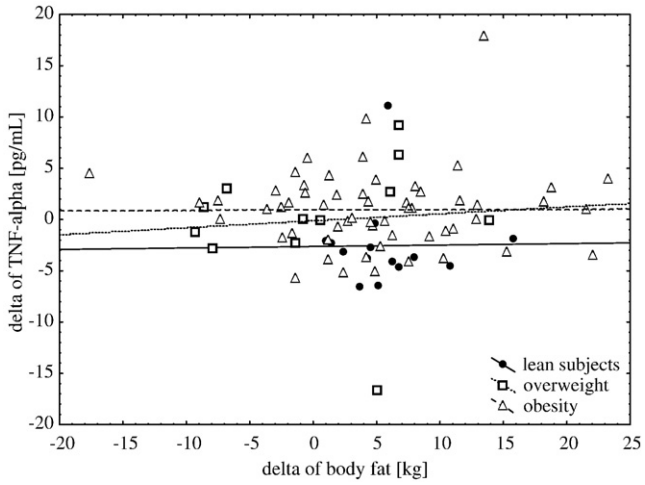

Fig. 2. The changes in body fat and plasma TNF-α levels during 5 years of follow-up.

(8.3 kg) was comparable to that in lean subjects (5.8 kg). However, the increase of waist circumference in lean subjects was significantly higher than that in subgroup A (8.5 vs 5.4 cm). In subgroup B, fat mass and waist circumference decreased during the 5-year follow-up by 1.0 kg and by 4.0 cm, respectively.

4.1. Glucose, lipids, and insulin

At the beginning of the study, serum glucose and lipid levels were within reference ranges in all groups. During reevaluation, lipid disturbances were found in 3 overweight and 16 obese women. Serum insulin levels were higher in obese and overweight women than in lean subjects. In obese and overweight groups, mean HOMA-IR values were higher than those in lean subjects (3.9 ± 2.1, 3.1 ± 1.4, and 1.9 ± 0.9, respectively), indicating insulin resistance. No significant changes in these parameters were found after 5 years of follow-up in all study groups (data not shown). One overweight and 3 obese patients developed diabetes during 5-year follow-up. In subgroup B, mean HOMA-IR value significantly decreased (3.6 ± 2.4 vs 2.2 ± 1.5, $P < .05$).

4.2. TNF-α and sTNRFs

Plasma concentration of TNF-α increased significantly only in lean women (3.1 ± 3.0 vs 5.6 ± 2.0 pg/mL, $P < .005$), whereas they did not change in overweight and obese groups during the 5-year follow-up observation (Fig. 1). There were also no alterations in plasma TNF-α levels in the separate analysis of the A and B subgroups (Table 4). Changes in body fat and plasma TNF-α level are presented in Fig. 2.

Serum sTNFR1 and sTNFR2 levels significantly declined by 71% and 25% in obese, by 104% and 21% in overweight, and by 31% and 32% in the lean subjects, respectively (Table 3). The increase in plasma sTNFR1 level was significantly higher in the overweight and obese groups than in lean subjects. On the other hand, changes in plasma sTNFR2 levels were similar in all study groups and subgroups.

Comparable increases of sTNFR1 (by 75% and 80%) and sTNFR2 (by 22% and 34%) were observed in subgroups A and B. The increases in plasma sTNFR1 levels in both subgroups (A and B) were significantly higher than in the lean subjects (Table 4).

4.3. Correlations between changes in study parameters

Changes in plasma levels of sTNFR1 were in significant positive correlations with changes in plasma sTNFR2 levels ($R = 0.22$, $P < .05$).

There was no correlation between changes in body mass and changes in plasma concentrations of TNF-α, sTNFR1, and sTNFR2 ($R = 0.11$, $P = .34$; $R = 0.01$, $P = .96$; and $R = 0.05$, $P = .63$, respectively).

A multivariate stepwise regression revealed that 5.0% of TNF-α changes variability could be explained by changes in waist circumference ($\beta = -0.23$, $P = .046$) but not by changes in fat mass.

5. Discussion

It is the first study assessing the influence of long-term changes in body fat content and waist circumference on the activity of TNF-α system. Numerous recent studies revealed increased plasma levels of TNF-α and sTNFRs in obese subjects; however, these studies examined either single levels [11] or their changes after weight reduction therapy [10,12-16]. It is of interest to find out at what stage of development of obesity the increase of systemic inflammation appears.

Table 3
Changes in plasma levels of TNF-α and sTNFRs in obese, overweight, and lean subjects

	Obese n = 57			Overweight n = 12			Lean n = 14		
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ
TNF-α (pg/mL)	6.9 ± 2.9	6.0 ± 2.4	−0.9 ± 3.9**	6.3 ± 3.0	6.4 ± 4.9	0.1 ± 6.3§	3.1 ± 3.0	5.6 ± 2.0†	2.5 ± 4.3
sTNFR1 (pg/mL)	1264 ± 202	2103 ± 564‡	839 ± 612#	1156 ± 145	2333 ± 477†	1177 ± 493¶	1141 ± 99	1502 ± 468*	361 ± 454
sTNFR2 (pg/mL)	1911 ± 563	2223 ± 455*	312 ± 684	1899 ± 581	2242 ± 505*	343 ± 846	1695 ± 377	2123 ± 437*	428 ± 618

*$P < .05$, † $P < .005$, and ‡$P < .0001$: follow-up vs baseline.
§$P < .05$, ‖$P < .005$, and ¶$P < .0001$: overweight vs lean.
#$P < .005$ and**$P < .0001$: obese vs lean.

Table 4
Changes in plasma levels of TNF-α and sTNFRs in obese, overweight, and lean subjects in subgroups A and B

	Subgroup A n = 46			Subgroup B n = 23			Lean n = 14		
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ
TNF-α (pg/mL)	7.1 ± 3.4	6.4 ± 3.3	−0.7 ± 5.0[§]	6.2 ± 1.6	5.3 ± 1.7	−0.9 ± 2.7[#]	3.1 ± 3.0	5.6 ± 2.0[†]	2.5 ± 4.3
sTNFR1 (pg/mL)	1247 ± 178	2134 ± 587[‡]	886 ± 641[‖]	1240 ± 235	2162 ± 492[‡]	921 ± 536[¶]	1141 ± 99	1502 ± 468*	361 ± 454
sTNFR2 (pg/mL)	1941 ± 547	2196 ± 415	255 ± 709	1845 ± 598	2287 ± 544*	442 ± 705	1695 ± 377	2123 ± 437*	428 ± 618

*$P < .05$, [†]$P < .01$, and [‡]$P < .0001$: follow-up vs baseline.
[§]$P < .05$ and [‖]$P < .01$: group A vs lean.
[¶]$P < .01$ and [#]$P < .0001$: group B vs lean.
**$P < .05$: group A vs B.

It is well known that body fat mass, particularly deposit of visceral fat, increases along with aging. In this study, during the 5-year follow-up, the increase of body fat mass accompanied by enlargement of waist circumference was observed in 66.7% of the studied overweight and obese women and in all lean subjects. The increase of body fat mass appeared in lean healthy premenopausal women despite the stable body weight. The only manifestation of these changes was the enlargement of waist circumference.

In 33.3% of overweight and obese subjects, during 5-year follow-up, body fat mass even decreased; and it should be emphasized that the reduction of each kilogram of fat mass was accompanied by diminution of waist circumference by 1 cm on average. Therefore, an assumption can be made that alteration of waist circumference is a good measure of changing deposits of visceral fat.

The increase of plasma TNF-α level during 5-year follow-up was found only in lean women with increased visceral adiposity. This observation was confirmed by the results of multivariate stepwise regression, which revealed that changes in serum TNF-α levels are more related to changes in waist circumference than changes in total body fat in the whole analyzed group. Similar results were obtained by Cartier et al in men [17]. They showed that visceral adipose tissue accumulation measured by computed tomography correlated positively with levels of inflammatory markers like TNF-α, interleukin-6, and C-reactive protein [17]. The same authors described lower plasma TNF-α levels in premenopausal women than in men, which were related to visceral fat deposits [18].

Potentially, plasma TNF-α levels could be affected by a diet or physical activity. However, the most recent studies demonstrated the lack of impact of low-carbohydrate and low-fat diet on TNF-α levels [19,20]. Moreover, only some [15,21] but not all studies [22] revealed the decrease of systemic inflammation and plasma TNF-α level as a result of taking up regular exercise by obese women. Therefore, it seems unlikely that the changes in plasma TNF-α levels observed in our study in lean women were significantly affected by the changes in diet or the level of physical activity. However, diet changes and decrease of physical activity might contribute to the increase of visceral fat depot and indirectly to the increase of systemic inflammation.

Experimental studies revealed that sTNFRs play a physiologic role in limiting body weight gain and adiposity by a modest intensification of metabolic rate, fatty acid oxidation, and activation of adipose tissue macrophages [23]. The present study showed a significant increase of both sTNFR1 and sTNFR2 levels during 5-year follow-up in obese, overweight, and lean women. The lowest increase of both soluble TNF-α receptors was found in lean women. The role of sTNFRs in human pathology is still largely unknown. There are some hypotheses assigning them a role in neutralization of circulating TNF-α, whereas others compromised them as a TNF-α reservoir. As TNF-α stimulates production of sTNFRs [24], one may hypothesize that increased levels of soluble receptors, similarly to TNF-α [25], may be one of the counterregulatory mechanisms preventing further weight gain in morbid obesity. On the other hand, experimental data revealed that TNF signaling through TNFR1 may decrease thermogenesis, inducing weight gain [26]. Moreover, in a population study (Framingham Offspring Study,) correlation between insulin resistance and circulating sTNFR2 was found [27]. It suggests that sTNFR2 may prevent the weight gain by decreasing accumulation of fatty acids in adipocytes [27]. Our results showing the increase of sTNFR2 may confirm this hypothesis. However, the larger simultaneous increase in plasma sTNFR1 than sTNFR2 levels observed in our study may suggest that sTNFR1 abolish those beneficial effects of sTNFR2. Our results do not confirm the observation of Cartier et al [28] showing a closer relation of plasma sTNFR2 levels with the accumulation of abdominal adipose tissue than with total body adiposity.

Surprisingly, the increase of plasma sTNFs levels was also found in the subgroup of obese and overweight women without increase of body fat content. These results are only partially in accordance with our previous studies, which revealed that body weight reduction is followed by an increase of plasma levels of sTNFR2 but decrease of sTNFR1 [11,13].

The main limitation of our study is the small size of the study population. Thus, larger longitudinal studies are necessary to confirm the impact of abdominal adipose tissue accumulation on the increase of TNF system activity of TNF-α in lean subject. It seems particularly important in metabolically obese subjects within the normal BMI range,

as increase of TNF-α production is involved in the development of insulin resistance. We also did not analyze fractions of sTNFR2, like described by Fernandez-Real et al [29]—differential splicing TNFR2 with antagonizing TNF-α biological activity. They revealed that plasma differential splicing TNFR2 concentration was significantly lower among patients with glucose intolerance and type 2 diabetes mellitus and that it was declining with the number of metabolic syndrome components.

In summary, our results suggest that the increase of plasma TNF-α level is an early event in abdominal fat accumulation. It seems that further fat mass gain does not enhance circulating TNF-α levels.

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