Bratisl Lek Listy 2010; 111 (4)
200 – 204

CLINICAL STUDY

Evaluation of the relationship between insulin resistance and plasma tumor necrosis factor-alpha, interleukin-6 and C-reactive protein levels in obese women

Yusuf Bal[1], Mine Adas[2], Aysen Helvaci[3]

Second Internal Medicine Clinic; Okmeydani Training and Research Hospital, Istanbul, Turkey.
mineadas@yahoo.com

Abstract: *Objective:* To investigate the relationship between insulin resistance and tumor necrosis (TNF)-α, interleukin (IL)-6, C-reactive protein (CRP) in obese women.
Background: Obesity and type 2 diabetes are associated with insulin resistance, the mechanisms of which remain poorly understood.
Materials and μethods: Forty obese (35.8±9.6 years) and 20 non-obese women (31.1±7.7) were recruited between June 2002 and February 2003 at the Okmeydaný Training and Research Hospital, Istanbul, Turkey. The obese group was equally divided into two according ?to their WHR (>0.8 and 0.8). Subjects with blood pressure values higher than 140/90 mmHg, pathological findings on standard 12-lead ECG and leukocytosis and glucose levels >100 mg/dl were excluded.
Results: Plasma insulin ($p<0.0001$) and fasting glucose levels ($p<0.0001$), and HOMA values ($p<0.0001$) in the obese group were higher than in the controls. Serum triglyceride and VLDL levels were higher in the obese group ($p<0.0001$ in both), whereas HDL cholesterol levels were higher in the lean control group ($p<0.0001$). However, no difference was observed between two groups in terms of total cholesterol and LDL-cholesterol levels. The serum levels of both TNF-α, IL-6 and CRP were found elevated in the obese group ($p<0.05$, $p<0.05$, $p<0.01$, respectively). In the subgroup analysis, only the HOMA values and TNF-α levels were found higher in the android obese group ($p<0.05$ and $p<0.0001$, respectively).
Conclusion: Insulin resistance seems to be one of the major causes of obesity-related complications due to increased secretion of TNF-α, IL-6 and CRP together with android obesity *(Tab. 5, Ref. 33)*. Full Text (Free, PDF) *www.bmj.sk.*
Key words: insulin, obesity, tumor necrosis-α, interleukin-6, C-reactive protein.

Obesity and type 2 diabetes are associated with insulin resistance, the mechanisms of which remain poorly understood. Obesity represents an expansion of adipose tissue mass, and one explanation for obesity-related insulin resistance is the production of certain factors by adipose tissue including tumor necrosis factor (TNF)-α, interleukin (IL-6), C-reactive protein (CRP) that render some subjects more insulin resistant than others (1, 2).

TNF-α has been suggested to cause insulin resistance by impairing the insulin receptor signalization, inhibiting the lipoprotein lipase and thus triggering the lipolysis in adipose tissue (3, 4). Lipolysis in turn increases the levels of non-esterified fatty acids and thus induces the insulin insensitivity in liver and muscle via the glucose-fatty acid (Randle) cycle (5).

Approximately 25–30 % of serum IL-6 originates from adipose tissue, and the secretion of IL-6 from subcutaneous fat is in proportion to fat mass (6). Omental fat cells secrete approximately 2–3 times more IL-6 as compared to subcutaneous adipocytes (7). Plasma IL-6 levels have been found to be significantly and inversely related with insulin sensitivity (1). Current knowledge indicates that IL-6 is the major circulating component associated with insulin resistance. These two cytokines, TNF-α and mainly IL-6, are also responsible for the elevated C-reactive protein (CRP) levels (8, 9) which have been found to have a positive correlation with body mass index (BMI) (10, 11).

Mild inflammation or elevated CRP itself may contribute to insulin resistance. According to the Third National Health and Nutrition Examination Survey (NHANES III) CRP may indirectly reflect the association between factors such as TNF-α and IL-6, and BMI. CRP has a positive relation with BMI, insulin, glucose, glycosylated hemoglobin and diabetes and the demonstration of increased CRP levels in overweight and obese individuals is considered to be a risk factor for elevated morbidity and mortality (12).

Overall, the fact that overweight and obese individuals yield an increase in serum levels of CRP, IL-6 and TNF-α, which are known markers of inflammation, strongly suggests that obesity is a low-grade systemic inflammatory disease (10). Recent data

[1]Second Internal Medicine Clinic; Okmeydani Training and Research Hospital, Istanbul, Turkey, [2]Endocrinology Clinic; Okmeydani Training and Research Hospital, Istanbul, Turkey, and [3]Cardiology Clinic; Okmeydani Training and Research Hospital, Istanbul, Turkey

Address for correspondence: Mine Adas, MD, Istinye Hillpark Evleri, Balandere Cad. 47. Parsel A-4, Sariyer, Istanbul, Turkey.
Phone: +90.532.4157339

suggest that inflammation is involved in atherogenesis and that insulin resistance syndrome is accompanied by an increase in acute--phase response (13, 14). Obesity, insulin resistance syndrome, and atherosclerotic disease are closely linked and the increased acute-phase response may be a common denominator in all.

It is well known that body fat distribution generally differs between men and women. Men often have abdominal obesity, whereas peripheral obesity is the most common form among women. Waist-hip ratio (WHR) is a well known determinant of abdominal obesity and compared to BMI a better, albeit indirect, marker of visceral fat mass. Since the calculation of WHR is totally for free and at the same time it gives a good idea about the ratio of intra-abdominal fat, the incorporation of WHR into the clinical markers of obesity would render it precious in the application of preventative medicine.

In summary, obesity which is considered a low-grade systemic inflammatory disease is characterized by a reduction in insulin sensitivity. Cytokines produced by adipose tissue including TNF-α and IL-6, and CRP seem to play a role in obesity-related insulin resistance. In this study, we aimed to investigate the relationship between insulin resistance, TNF-α, IL-6, and CRP in obese women, and to see whether there is any difference in waist-to-hip ratio.

Materials and methods

Study population

Forty otherwise healthy and physically active obese women (mean age: 35.8±9.6 years) and 20 non-obese women (mean age: 31.1±7.7 years) were recruited between June 2002 and February 2003 at the S.B. Okmeydani Training and Research Hospital. Subjects with blood pressure values higher than 140/90 mmHg, pathological findings on standard 12-lead ECG and leukocytosis and plasma fasting glucose levels >100 mg/dl were excluded from the study.

Study procedures

Height, weight as well as waist and hip circumferences were measured while the subjects were in their indoor clothes and without shoes. BMI (weight divided by the square of height) and waist-to-hip ratios (WHR) were calculated. Blood pressures, 12-lead standard ECGs were obtained, and laboratory examinations were performed to determine the conformity of subjects to exclusion criteria. Venous blood samples were drawn from each subject after an overnight fasting at 08:00. Hemograms were assessed with Coulter and biochemical parameters including glucose, total cholesterol, triglyceride, HDL-, LDL- and VLDL-cholesterol) with Olympus AU 5200 autoanalyser. Serum insulin was determined with Roche Elecsys 2010 autoanalyser. Serum samples were centrifuged and stored at -20 °C to be used for the measurement of TNF-α, IL-6, CRP levels. TNF-α and IL-6 were measured with Immulite 1000 autoanalyser, and CRP was measured with Turbitimer device by Behring using the commercially available kits. Insulin resistance was calculated according to the formula of the homeostasis model assessment method (HOMA) (15):

$$\text{HOMA} = \frac{\text{Fasting insulin (pU/ml) X Fasting glucose (mmol/L)}}{22.5}$$

The obese subjects were then divided into two groups according to their WHR. All study parameters were also compared between these two subgroups consisting of 20 obese women with WHR >0.8 and 20 obese women with WHR 0.8.

Statistical analysis

Data are presented as mean ±+ standard deviation (SD). Statistical analyses were performed with GraphPad Prism V.3 software. Independent t-test was used for the paired group comparisons and Chi-square test for the analyses of qualitative data. TNF-α, IL-6, CRP and HOMA parameters with skewed distributions were log-transformed and geometric means were used in the analyses. Results were evaluated with a 95 % confidence interval and a p value <0.05 was regarded significant.

Results

Mean age was 31.1±7.7 years in the study group and 35.8±9.6 years in the control group and there was no statistically significant difference between the groups (p>0.05). The height also did not differ between these two groups (162.5±4.6 cm and 160.1±6.9 cm in the study and control groups, respectively; p>0.05). On the contrary, weight, waist circumference, hip, BMI and WHR values were significantly higher in the study group compared to control (p<0.0001). Demographic features of the study population are presented in Table 1.

The study group which consisted of obese individuals with BMI>30 kg/m^2, was further divided into two subgroups according to WHR and demographic features of these subgroups did not differ significantly (p>0.05) except for the waist circumference (98.85±10.40 cm vs 107.15±9.71 cm; p<0.05). Demographic features of the study subgroups are presented in Table 2.

Tab. 1. Demographic features of the control and study groups.

	Control group (n=20)	Study group (n=40)	p
Age (year)	31.10 ± 7.67	35.78 ± 9.57	>0.05
Height (cm)	162.50 ± 4.62	160.15 ± 6.87	>0.05
Weight (kg)	56.75 ± 4.42	93.05 ± 14.27	<0.0001
Waist (cm)	68.55 ± 4.72	103.00 ± 10.78	<0.0001
Hip (cm)	92.80 ± 4.10	125.33 ± 12.95	<0.0001
BMI (kg/m^2)	21.70 ± 1.50	36.19 ± 4.49	<0.0001
WHR	0.73 ± 0.04	0.82 ± 0.06	<0.0001

BMI – Body mass index; WHR – Waist to hip ratio

Tab. 2. Demographic features of the obese women according to their waist to hip ratio (WHR).

	WHR≤0.8 (n=20)	WHR> 0.8 (n=20)	p
Age (year)	33.90 ± 8.78	37.65 ± 10.16	>0.05
Height (cm)	161.10 ± 5.70	159.20 ± 7.90	>0.05
Weight (kg)	94.50 ± 15.47	91.60 ± 13.20	>0.05
Waist (cm)	98.85 ± 10.40	107.15 ± 9.71	<0.05
Hip (cm)	128.75 ± 13.91	121.90 ± 11.22	>0.05
BMI (kg/m^2)	36.28 ± 5.54	36.10 ± 3.28	>0.05

BMI - Body mass index

Tab. 3. Plasma fasting insulin, glucose levels and HOME values of the control and study groups.

	Control group (n=20)	Study group (n=40)	p
Insulin levels (mU/ml)	7.15 ± 3.57	16.19 ± 8.28	<0.0001
Glucose levels (mg/dl)	80.0 ± 4.87	97.47 ± 8.34	<0.0001
HOMA	3.44	1.29	<0.0001

Serum fasting insulin levels

Serum fasting insulin levels were found to be significantly higher in the study group compared to control (Tab. 3). However, no statistically significant difference was determined in subgroup comparisons (15.32±5.65 mU/ml vs 17.11±10.46 mU/ml in the WHR ≤0.8 and >0.8 groups, respectively; p>0.05).

Serum fasting glucose levels

As shown in Table 3, serum fasting glucose levels were significantly higher in the study group compared to control. However, no statistically significant difference was determined in subgroup comparisons (97.93±8.40 mg/dl vs 97.00±8.49 mg/dl in the WHR ≤0.8 and >0.8 groups, respectively; p>0.05).

Evaluation of insulin resistance

The geometric mean (G.M.) of HOMA, an indicator of insulin resistance, was found to be significantly lower in the study group than in the control group (Tab. 4). When compared between the subgroups, however, HOMA did not differ between groups with WHR ≤0.8 and WHR>0.8 (3.436 vs 3.453, respectively; p>0.05).

Serum TNF-α and IL-6 levels

As given in Table 4, mean serum TNF-α level were significantly higher in the control group in comparison to the study group. The significance in serum TNF-α levels was even higher when compared to study subgroups (0.66 pg/ml vs 1.03 pg/ml in the WHR ≤0.8 and >0.8 groups, respectively; p>0.0001). TNF-α level did not show significant correlations with any of HOMA, BMI, WHR indices (Tab. 5).

Similarly, mean serum IL-6 levels were found to be higher in the study group than in the control group (Tab. 4). However study subgroups did not differ significantly in terms of serum IL-6 levels (0.84 pg/ml vs 0.97 pg/ml in the WHR ≤0.8 and >0.8 groups, respectively; p>0.05). IL-6 levels did not correlate with any of HOMA, BMI, and WHR indices (Tab. 5).

Serum CRP levels

Similarly, serum CRP levels were significantly higher in the study group compared to the control group (Tab. 4). Study subgroups did not show statistically significant difference in terms of serum IL-6 levels (1.04±1.43 mg/dl vs 0.84±0.48 mg/dl in the WHR ≤0.8 and >0.8 groups, respectively; p>0.05). While CRP correlated with HOMA (r=0.31; p<0.05), no such correlation was determined with BMI and WHR indices (Tab. 5).

Lipid profile

The comparison of triglyceride and VLDL levels revealed higher results in the obese group (p<0.0001 in both), whereas HDL cholesterol levels were found to be higher in the lean control group (p<0.0001) compared to the obese group. On the contrary, no difference was determined between the two groups in terms of total cholesterol and LDL-cholesterol levels (p>0.05). In the subgroup analysis none of the lipid parameters correlated significantly with WHR (p>0.05).

Tab. 4. Plasma TNF-a, IL-6 and CRP levels of the control and study groups.

	Control group (n=20)	Study group (n=40)	p
TNF-α (pg/ml)	0.662	0.831	<0.0001
IL-6 (pg/ml)	0.908	0.817	<0.05
CRP (mg/dl)	3.44	0.94 ± 1.06	<0.01

Tab. 5. Correlations of plasma TNF-a, IL-6 and CRP levels with BMI and WHR in the study group (n=40) and with HOMA values in the entire group (n=60).

	BMI	WHR	HOMA
TNF-α	r=0.04 p>0.05	r=0.296 p>0.05	r=0.10 p>0.05
IL-6	r=0.16 p>0.05	r=0.265 p>0.05	r=0.02 p>0.05
CRP	r=0.24 p>0.05	r=0.099 p>0.05	r=0.31 **p<0.05**

Discussion

Obesity defined as an increase in adipose tissue, is associated with insulin resistance. Its mechanism might be based on the fact that the increased adipose tissue secretes particular factors which render some people more insulin resistant than others (1).

Fasting insulin concentrations is often used as a rough measure of *in vivo* insulin resistance since hyperinsulinemia is generally associated with insulin resistance. This assumption is particularly valid in non-diabetic individuals with no impairment in their glucose tolerance. In our study, we found that both fasting insulin and HOMA levels were statistically significantly elevated in the obese group. Similarly, Kern et al (1) demonstrated a strong relationship between obesity and insulin resistance in both diabetic and non-diabetic individuals and suggested that the risk of diabetes might be 11 times higher when BMI increases from 20 to 30 (1). In the present study, HOMA levels were also noted to be significantly associated with BMI while this was a common finding in previous studies (1, 16, 17).

Our results regarding the relationship between WHR and HOMA showed that WHR, which is an index of visceral (android) obesity, correlates positively with HOMA levels. This translates into more insulin resistance in android obese women with higher WHR. Correspondingly, Bastard et al (16) have studied fasting insulin resistance index in diabetic and non-diabetic android obese women (WHR>0.90) in comparison to lean control group, and determined insulin resistance in the group of android obese women.

TNF-α has been shown to induce insulin resistance via endocrine and/or autocrine effects on adipose and muscle tissue, and to impair the effect of insulin by inhibiting the tyrosine kinase activity of insulin receptor (3). TNF-α levels in obese women were found to be significantly higher than in non-obese women. In addition, plasma TNF-α levels were seen to correlate positively with BMI. The study by Hotamisligil et al (18) also demonstrated the increased secretion of TNF-α from adipose tissue and suggested this as a possible explanation of insulin resistance in obesity. Similarly to our results, Bastard et al (16) reported significantly higher TNF-α levels in obese compared to lean women and added that TNF-α levels were markedly associated with BMI. Furthermore, Kern et al (1) compared lean and obese individuals and found a 7.5 times increase in TNF-α secretion and significantly higher plasma TNF-α levels in the obese group. Yudkin et al (19) also reported elevated plasma TNF-α levels in their obese group, suggesting an important role for TNF-α in obesity and insulin resistance. All these findings are in agreement with ours and suggest that plasma TNF-α levels, which have a role in insulin resistance, are elevated in obese individuals. Plasma TNF-α levels were also studied in our study subgroups and found to be significantly higher in the group with WHR>0.80 compared to the group with WHR<0.80. Parallel to our findings, Bastard et al (16) also found higher plasma TNF-α levels in both diabetic and non-diabetic android obese people. However, Yudkin et al (19) found no association between plasma TNF-α with WHR in android obese individuals.

The role of IL-6 in insulin resistance is a less known parameter compared to other parameters of obesity. Studies have shown that the subcutaneous adipose tissue secretes IL-6 and that this secretion is associated with BMI suggesting a role for IL-6 in insulin resistance due to obesity (6, 16). We also found higher levels of plasma IL-6 in obese compared to non-obese women and this was a statistically significant finding. Both Yudkin et al (19) and Kern et al (1) studied plasma IL-6 levels in obese individuals and found significantly higher levels suggesting a positive correlation with BMI. Our results complied with the results of both of these studies. However, we could not determine any relationship between IL-6 levels and WHR in the subgroup analysis.

Recent data indicate that an increase in acute-phase response commonly accompanies the insulin resistance syndrome (12). Serum CRP levels were shown to be associated with obesity as well as fasting plasma insulin levels (20–22). In addition, high serum CRP concentrations are associated with insulin resistance and cardiovascular diseases, and CRP is a marker used in establishing the risk of cardiovascular diseases (20, 23). In our study, we found significantly higher plasma CRP levels in the group of obese women. This suggests that obesity affects the serum CRP levels, which has also been shown to be proportional with the measurements of body adipose tissue (21, 24). Correspondingly, McLaughlin et al (25) have shown elevated serum CRP levels in insulin-resistant obese people. Authors have also observed a reduction in serum CRP levels and an improvement in insulin resistance in response to weight loss (26).

Studies in the literature have shown that plasma HDL-cholesterol levels are decreased in android obese people (27–30), the mechanism of which might be based on reduced lipoprotein lipase levels that convert HDL 3 to HDL 2 in android obesity (31). Although we determined significantly lower HDL levels in obese women, we were unable to study the HDL 2 and 3 levels. Further studies should focus on these two parameters in android obesity. On the other hand, our findings of plasma total cholesterol and LDL-cholesterol levels suggest no significant difference between obese and lean people and thus comply with literature data in this respect (32).

On the other hand, no significant difference was observed in terms of CRP in the subgroup analysis for android obesity. Contrary to BMI, serum CRP levels were not associated with WHR of the whole group. Similarly, Linonen et al (33) determined no relationship between WHR and serum CRP levels but did suggest a strong correlation of CRP levels with BMI and waist circumference. BMI and CRP were also found to be positively associated in NHANES III where the lowest CRP levels were determined in individuals with BMI <18.5 kg/m^2 (12). In the present study, serum CRP levels demonstrated a significant relationship only with HOMA, not with plasma IL-6 and TNF-α levels. The positive association of CRP with fasting plasma insulin levels was also common in the study of Bastard et al (16).

In conclusion, we hereby demonstrated that insulin resistance develops in individuals with BMI>30 kg/m^2. Correspondingly, plasma insulin levels, HOMA values, TNF-α, IL-6 and CRP concentrations increase in proportion to BMI and WHR, the marker of android obesity. It can thus be concluded that insulin resistance develops in obese people due to increased levels of TNF-α, IL-6 and CRP and together with android obesity it is the major

cause of complications (including diabetes, hypertension, cardiovascular diseases and gall bladder diseases) seen in obesity.

References

1. Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance Am J Physiol Endocrinol Metab 2001; 280: E745—E751.

2. McCarty MF. Interleukin-6 as a central mediator of cardiovascular risk associated with chronic inflammation, smoking, diabetes, and visceral obesity: down-regulation with essential fatty acids, ethanol and pentoxyphylline (In Process Citation). Med Hypotheses 1999; 52: 465—467.

3. Hotamisligil GS, Budavari A, Murray D, Spiegelman BM. Reduced tyrosine kinase activity of the insulin receptor in obesity-diabetes. Central role of tumor necrosis factor-•. J Clin Invest 1994; 94: 1543—1549.

4.Patton JS, Shepard HM, Wilking H, Lewis G, Aggarwal BB, Eesalu TE, Gavin LA, Grunfeld C. Interferons and tumor necrosis factors have similiar catabolic effects on 3T3-L1 cells. Proc Natl Acad Sci USA 1986; 83: 8313—8317.

5. Randle PJ, Garland PB, Hales CN, Newsholme CA. The glucose fatty acids cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963; 1: 785—789.

6. Mohamed-Ali V, Goodrick S, Rawesh A, Miles JM, Katz DR, Yudkin JS, Coppack SW. Human subcutaneous adipose tissue releasesIL-6 but not TNF-á in vivo J Clin Endocrinol Metab 1997; 82: 4196—4200.

7. Lang CH, Dobrescu C. Sepsis-induced changes in in vivo insulin action in diabetic rats Am J Physiol 1989; 257: E301—308.

8. Varren RS, Starnes HF Jr, Gabrilove JL, Oettgen HF, Brennan MF. The acute metabolic effects of tumor necrosis factor administration in humans. Arch Surg 1987; 122: 1396—1400.

9. Baumann H, Gauldie J. Regulation of hepatic acute phase plasma protein genes by hepatocyte stimulating factors and other mediators of inflammation. Mol Biol Med 1990; 7: 147—159.

10. Das UN. Is obesity an ýnflammatory condition? Nutrition 2001; 17: 953—966.

11. Mendall MA, Patel P, Ballam M, Strachan D, Nortfield TC. C-reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. BMJ 1996; 312: 1061—1065.

12. Cook DG, Mendall MA et al. C-reactive protein concentration in children: relationship to adiposity and other cardiovascular risk factors. Atherosclerosis 2000; 149: 139—150.

13. Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. Diabetologia 1997; 40: 1286—1292.

14. Yudkin JS, Stenodwer CDA, Emeis JJ, Coppack SW. Insulin resistance syndrome and endothelial damage: role of adipose tissue derived proinflammatory cytokines. Arterioscler Thromb Vasc Biol

15. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and ß-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412—419.

16. Bastard JP, Jardel C, Bruckert E, Blondy P, Capeau J, Laville M, Vidal H, Hainque B. Elevated levels of interleukin-6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. J Clin Endocrinol Metab 2000; 85: 3338—3342.

17. Bastard JP, Jardel C, Delattre J, Hainque B, Bruckert E, Oberlin F. Evidence for a link between adipose tissue interleukin-6 content and serum-C reactive protein concentrations in obese subjects. Circulation 1999; 99: 2221—2222.

18. Hotamisligil GS, Shaegill NS, Spiegelman BM. Adipose expression of tumor-necrosis factor-•: direct role in obesity-linked insulin resistance. Science 1993; 259: 87—91.

19. Yudkin JS, Yajnik CS, Mohamed-Ali V, Bulmer K. High levels of circulating proinflammatory cytokines and leptin in urban, but not rural Indians. A potential explanation for increased risk of diabetes and coronary heart disease [letter]. Diabetes Care 1999; 22: 363—364.

20. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity,insulin resistance and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 1999; 19: 972—978.

21. Bastard JP, Grimaldi A, Jardel C, Porquet D, Bruckert E, Hainque B. A simple index of insulin resistance. Diabetes Metab 1997; 23: 87—88.

22. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? Atherosclerosis 2000; 148: 209—214.

23. Lemieux I, Pascot A et al. Elevated C-reactive protein, another component of the atherothrombotic profile of abdominal obesity. Arterioscler Thromb Vasc Biol 2001; 21: 961—967.

24. Ridker P. High sensitivity C-reactive protein. Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001; 103: 1813—1818.

25. McLaughlin T, Abbasi F, Lamendola C et al. Differentiation between obesity and insulin resistance in the association with C-reactive protein. Circulation 2002; 106: 2908—2912.

26. Heilbronn LK, Noakes M, Clifton PM. Energy restriction and weight loss on very-low fat diets reduce C-reactive protein concentration in obese, healthy women. Arterioscler Thromb Vasc Biol 2001; 21-968—970.

27. Gaal VL, Rillaets E, Creten W, De Leeuw I. Relationship of body fat distribution pattern to atherogenic risk factors in NIDDM. Diabetes Care 1998; 11: 103—106.

28. Haffner SM, Stern MP, Hazuda HP, Pugh J, Patterson JK. Do upper body and centralized adiposity measure different aspects of regional body fat distribution, relationship to NIDDM, lipids and lipoproteins. Diabetes 1987; 36: 43—51.

29. Kissebah AH, Vydelingum N, Murray E, Evans DJ et al. Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab 1982; 54: 254—260.

30. Peiris AN, Sothmann MS, Hoffman RG, Hennes MI et al. Adiposity, fat distribution and cardiovascular risk. Ann Intern Med 1989; 110: 867—872..

31. Despres JP. Dyslipidemia and obesity. J Clin Endocrinol Metab 194; 8: 629—660.

32. Despres JP, Moorjani S, Lupien PJ, Trembley A. Regional distribution of body fat, plasma, lipoproteins and cardiovascular disease. Arteriosclerosis 1990; 10: 497—511.

33. Linonen E, Hurt-Camejo E, Wiclund O et al. Insulin resistance and adiposity correlate with acute-phase reaction and soluble cell adhesion molecules in type 2 diabetes. Atherosclerosis. 2003; 166—387—394.

Received April 20, 2009.
Accepted January 17, 2010.