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Effect of Abdominal Obesity on Insulin Resistance and the Components of the Metabolic Syndrome: Evidence Supporting Obesity as the Central Feature

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Background: Metabolic syndrome includes abdominal obesity, diabetes type 2, hypertension, dyslipidemia, derangements of fibrinolysis, and atherosclerosis. Since abdominal obesity is one of the major components of the insulin resistance syndrome (IRS), an attempt was made to evaluate the interrelationships between the magnitude of obesity and the components of the syndrome.

Methods: A cross-sectional study of 123 subjects with type 2 diabetes, of whom 31 were normal body weight and 92 had varying degrees of obesity was conducted. The participants were investigated in terms of clinical and laboratory findings of IRS. Fasting and 30-min (early) plasma glucose and serum insulin excursions in response to oral glucose challenge (75 g) were determined. The peripheral and hepatic insulin resistance (insensitivity) was calculated by homeostasis model assessment (HOMA).

Results: Clinical and biochemical findings were compared with the components of the IRS, and demonstrated that a rise in fasting as well as 30-min insulin secretion increases as abdominal body fat (obesity) increases. There was also a significant and proportional correlation between the magnitude of abdominal obesity and the components of metabolic syndrome.

Conclusion: Abdominal adiposity appears to have a pivotal role in the development of IRS.

Key words: Obesity, hyperinsulinemia, insulin resistance, macro- and microangiopathy, metabolic syndrome, diabetes type 2, morbid obesity

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Introduction

Several studies have demonstrated that atherosclerotic cardiovascular disorders are still the leading cause of death in middle-aged and elderly patients with obesity and type 2 diabetes.[1,2] Type 2 diabetes associated with obesity may be accepted as "a visible part of an iceberg" of the insulin resistance syndrome (IRS). Zimmet[3] describes this peculiar pathology as "The New World Syndrome". As a growing health problem, the components of metabolic syndrome, coupled with cigarette smoking, sedentary life, and a diet with high lipid and carbohydrate content (ie. fast-food habits) cause atherosclerotic vascular disorders in many countries as well as in Turkey.[4] In this cross-sectional study, the effects of graded obesity on insulin resistance and the interrelationships between the adiposity and clinical and biochemical components of metabolic syndrome were delineated.

Materials and Methods

A total of 123 type 2 diabetic patients with varying body weights and who have been treated with regular sulfonylureas (tolbutamide, glipizide, glyburide) and/or biguanides (metformin) were recruited from

the Clinics of Florence Nightingale Hospital, Istanbul. Diabetic subjects who were treated with insulin, were taking drugs causing glucose intolerance, and who had any endocrinologic, metabolic, hepatic and renal disorders were excluded, except the early phase of diabetic nephropathy without renal insufficiency. All medications were stopped 2 days before the study, for a washout period.[5] This study was conducted in accordance with the 1964 Declaration of Helsinki and The French Guidelines and Recommendations for Good Clinical Practice in type 2 diabetes,[6] and the participants gave informed consent.

Fasting blood samples were taken after an overnight fast (12 h) for determination of plasma glucose, serum insulin levels, lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides), BUN, creatinine, and uric acid concentrations. A 75-g oral glucose dose was ingested after an overnight fasting (12 h) period. Plasma glucose and serum insulin concentrations of the blood samples obtained at 10 minutes before, 0 point and 30 minutes after oral glucose challenge were determined. The mean values of fasting plasma glucose and serum insulin that are necessary for the calculation of HOMA were the arithmetical mean of –10 and 0 times values of blood samples.[7] The diagnosis of type 2 diabetes was based on the criteria of the World Health Organization of 1999.[8] For evaluation of arterial blood pressure, the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[9] was used Serum LDL-cholesterol and triglyceride levels >100 mg/dl and >200 mg/dl (2.3 mmol/liter), respectively, and HDL-cholesterol <40.0 mg/dl were accepted for the diagnosis of dyslipidemia.[10] Obesity was graded according to Garrow's criteria,[11] based on body mass index (BMI). The ratio of waist-to-hip circumference (WHR) was used as body fat distribution. For the definition of metabolic syndrome, the criteria of the provisional WHO reports of Alberti and Zimmet were used.[12]

The plasma glucose concentration was measured by the glucose oxidase method using the kit of Biotrol on Bayer/opeRA Analyser. Serum insulin determination was made by the electrochemilumiscence immunoassay "ECL" on the Roche Elecsys 1010 and 2010 immunoassay analyzer without cross-reactivity with proinsulin or split-proinsulin products. Serum total cholesterol was measured using the commercial kit of Biotrol. HDL-cholesterol was measured using commercial Randox's kit. LDL-cholesterol was calculated by the formula of Friedewald. Triglyceride determination was made by the method of lipase/glycerol kinase UV endpoint on an opeRA Analyser. Urinary microalbumin concentration was measured by an immunoassay method. Serum total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride concentrations were measured by enzymatic assays on opeRA analyser. For the serum BUN, creatinine, and uric acid determinations an opeRA otoanalyser was used.

BMI was calculated as weight (kg) divided by height (m) squared (kg/m^2), as an index of overall obesity. Garrow's criteria were based on BMI; namely, non-obese patients were considered to be those of BMI were 20.0-24.9; obese patients were divided into three grades according to their BMI: grade I obesity, 25.0-29.9; grade II obesity, 30.0-39.9; grade III obesity, >40.0.[11] The amount of body fat tissue was calculated by the formula depicted by Hume.[13] The rate of insulin resistance and hepatic insulin sensitivity were evaluated by the homeostatic model assessment (HOMA) of Matthews et al,[7] and for their calculations the formula of Bonora et al[14] and Matsuda and DeFronzo[15] were utilized, respectively. The 30-min serum insulin and glucose excursion from the basal value (absolute increments) and their ratio (insulinogenic index of early insulin secretion ($\Delta I^{30\text{-}F}/\Delta G^{30\text{-}F}$) were considered as early responses of insulin secretion to the oral glucose challenge, and the values obtained from the patients with normal body weight were compared with that of graded obese patients.

Statistical analyses were conducted using Unistat 5.1 software. Clinical characteristics were compared among type 2 diabetic patients separately for each obesity grade. These analyses were compared using analysis of variance (one-way ANOVA). The fasting insulin, fasting glucose, first 30 min insulin excursion and first 30 min insulinogenic index were compared for each obesity grade with normal weight diabetics with one-way ANOVA and Dunnett test. Data are expressed as means ± SE. For categorical variables, χ^2 testing was used to assess differences in proportions (or Fisher's exact test when cell frequencies were small). *P*-values <0.05 were consid-

ered statistically significant.

Results

The clinical and metabolic parameters of the participants are given in Table 1. The amounts of body fat, and the measures of BMI and WHR of obese participants were significantly and proportionally different from that of the patients with normal body weight ($P<0.001$). The abdominal localization of body fat was observed in all obese participants with varying degree. The HOMA scores of peripheral insulin resistance and hepatic insulin sensitivity of graded obese diabetic subjects were also different, with different significance from that of the patients with normal body weight (Table 1). Although lipid profiles of the study groups indicate that there is a manifest dyslipidemia (LDL>100 mg/dl, HDL<40.0 and triglyceride ≥200 mg/dl), a difference was not found between the study groups. Furthermore, the levels of BUN and creatinine were normal, indicating that there was no renal dysfunction in the study patients, except microalbuminuria.

The fasting insulin values and the first 30-min absolute insulin excursion ($\Delta I^{30\text{-}F}$) and insulinogenic index ($\Delta I^{30\text{-}F}/\Delta G^{30\text{-}F}$), as the measures of early insulin-secretion response to glucose, and statistical analysis in the participants who have different body weights are presented in Table 2. Fasting insulin levels as well as the first 30-min insulin increments of graded obese diabetics were found to be significantly different from that of normal body weight (Figure 1). The first 30-min insulinogenic index ($\Delta I^{30\text{-}F}/\Delta G^{30\text{-}F}$) levels were also significantly higher in grade-III obese subjects compared with normal body weight diabetics (Figure 2).

Table 3 indicates the frequencies of the components of metabolic syndrome in the patients with normal and different body weights. It was found that there is a significant difference between the obese groups and the patients with normal body weight in terms of frequencies of hypertension ($P<0.05$), dyslipidemia ($P<0.001$), macroangiopathy ($P<0.001$) and diabetic microangiopathy ($P<0.01$).

Discussion

The results of the study suggest that central obesity *per se* may be a consistent clinical feature of the metabolic syndrome as a principal causative factor.

Table 1. Clinical and metabolic parameters of the NIDDM patients on the basis of body mass index

	Normal-Weight Diabetics (n=31)	Grade I obese (n=42)	Grade II obese (n=25)	Grade III obese (n=25)
Age (years)	48.1 ± 2.54	51.5 ± 1.79	48.7 ± 2.62	46.4 ± 3.01
Weight (kg)	69.4 ± 1.61	80.1 ± 1.63	87.1 ± 1.75	106.6 ± 1.99[a]
Height (cm)	170.9 ± 1.69	167.4 ± 10.6	165.6 ± 8.76	161.3 ± 9.95[b]
BMI (kg/m^2)	24 ± 0.25	28.6 ± 0.20[b]	32.6 ± 0.23[b]	41.7 ± 0.78[b]
WHR	73.2 ± 1.18	103.1 ± 1.10[b]	103.9 ± 0.71[b]	117.9 ±1.03[b]
Fat tissue (kg)	20.6 ± 1.36	28.3 ± 0.58[b]	35.5 ± 0.59[b]	49.1 ± 2.29[b]
IR	7.27 ± 1.06	11.2 ± 1.11	11.7± 1.27	17.6 ± 2.22[b]
HIS	0.19 ± 0.11	0.14 ± 0.09[c]	0.11 ± 0.05[a]	0.08 ± 0.05[b]
Cholesterol (mg/dl)	254.7 ± 16.7	245.7 ± 11.1	240.6 ± 6.31	230.7 ± 7.36
HDL-Chol (mg/dl)	41.3 ± 2.15	40 ± 1.45	36 ± 2.41	42.5 ± 2.32
LDL-Chol (mg/dl)	161.5 ± 10.7	145.1 ± 6.04	154.1± 10.6	148.8 ± 9.73
Triglyceride (mg/dl)	239.58 ± 22.6	380 ± 106.9	318.1 ± 34.3	271.9 ± 20.9
BUN (mg/dl)	17.22 ± 1.19	15.61 ± 0.95	14.64 ± 1.34	17.11 ± 2.29
Creatinine (mg/dl)	0.96 ± 0.05	0.96 ± 0.05	1.03 ± 0.07	1.04 ± 0.07
Uric acid (mg/dl)	5.60 ± 0.65	5.83 ± 0.54	6.11 ± 0.44	5.94 ± 0.39

Values are presented as means ± SE.
[a]$P<0.01$ vs normal weight diabetics; [b]$P<0.001$ vs normal weight diabetics; [c]$P<0.05$ vs normal weight diabetics.

Table 2. The comparison between fasting serum insulin, plasma glucose, first 30 min insulin excursion ($\Delta I^{30\text{-}F}$) and first 30-min insulinogenic index ($\Delta I^{30\text{-}F}/\Delta G^{30\text{-}F}$) after 75 g oral glucose challenge

	Normal-Weight Diabetics (n)	Grade I (n)	Grade II (n)	Grade III (n)
Fasting glucose (mg /dl)	121.2 ± 7.94 (31)	139.8 ± 8.61 (42)	132.4 ± 11.1 (25)	143.2 ± 13.2 (25)
30-min glucose (mg /dl)	191.5 ± 11.5 (22)	200.4 ± 9.02 (31)	201 ± 19.9 (17)	193.4 ± 10.9 (18)
Fasting insulin (μU/ml)	23.6 ±1.22 (31)	33.9 ± 2.85[c] (42)	36.3 ± 3.29 (25)	50.3 ± 5.72[b] (25)
30 min insulin (μU/ml)	64.9 ± 1.83 (21)	109.6 ± 9.4[a] (28)	136.3 ± 15.6[b] (17)	163 ± 14.8[b] (18)
$\Delta I^{30\text{-}F}$	38.2 ± 1.71 (21)	70.5 ± 1.44 (28)	98.8 ± 3.86[d] (17)	110 ± 3.91[b] (18)
$\Delta I^{30\text{-}F}/\Delta G^{30\text{-}F}$	0.56 ± 0.11 (21)	1.46± 0.19 (28)	1.56 ± 0.30 (17)	2.76 ± 0.61[a] (18)

Values are presented as mean ± SE.
[a]$P<0.05$ vs normal weight diabetics; [b]$P<0.001$ vs normal weight diabetics; [c]$P<0.01$ vs Grade III;
[d]$P<0.01$ vs normal weight diabetics.

As indicated in Table 1, HOMA scores for insulin resistance (peripheral as well as hepatic) significantly and proportionately increase as the body weight increases. In comparison with the fasting and first 30-min insulin secretion patterns as well as 30-min insulinogenic index between the graded obese groups and that of normal body weight, an almost linear relationship between the early insulin secretion patterns and the magnitude of body weight may be assumed (Table 2 and Figures 1 and 2). These findings are consistent with the results of our previous study.[16] It has also been claimed that the hyper-responsiveness of the endocrine pancreas to various stimuli seems to be a secondary manifestation of insulin resistance that is a remarkable sign of the early stage of type 2 diabetes in the obese.[17] Although the major cause of hypersecretion of insulin is insulin resistance, other factors such as decreased hepatic clearance and/or uptake of insulin because of decreased hepatic insulin sensitivity may also play a role.[18]

As mentioned before, there is considerable evidence that obesity, particularly the abdominal type, is associated with hyperinsulinemia in the fasting as well as postprandial period due to insulin resistance.[17,19] DeFronzo and Ferrannini,[20] describing the clinical components of metabolic syndrome and the etio-pathogenic relationships between components, demonstrated that insulin resistance was a consequence of increased intra-abdominal adipose tissue mass. Castagneto et al[21] reported that insulin resistance was normalized after stable weight reduction

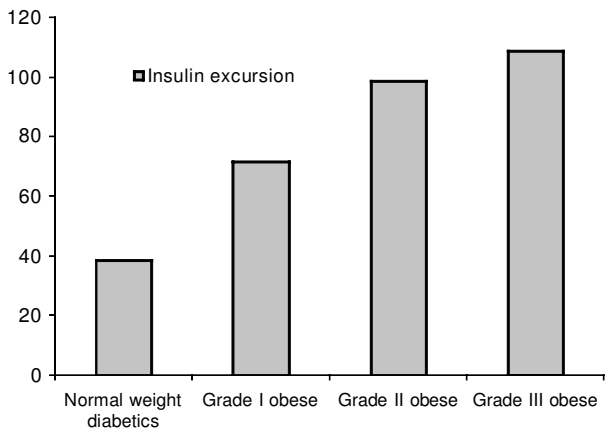

Figure 1. The results of the first 30-min absolute insulin excursion ($\Delta I^{30\text{-}F}$) in diabetic patients with different body weights.

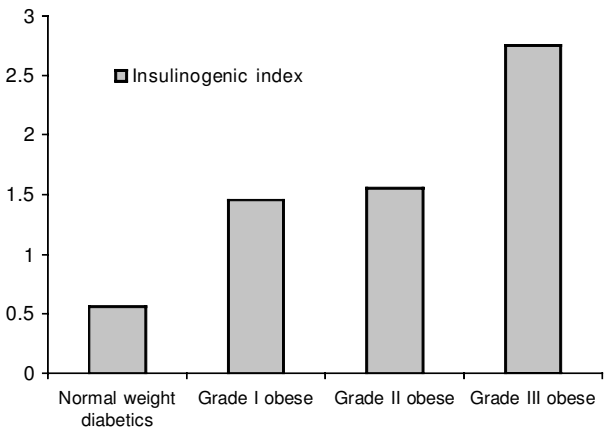

Figure 2. The results of first 30-min insulinogenic index ($\Delta I^{30\text{-}F}/\Delta G^{30\text{-}F}$) in diabetic patients with different body weights.

Table 3. Incidence of different obesity grades in terms of metabolic syndrome components. Frequencies were compared with Fisher's exact test

	Normal n(%)	Grade I n(%)	Grade II n(%)	Grade III n(%)	*P*
Hypertension					
Yes	13 (16)	31(38.3)	17 (21)	20 (24.7)	
No	18 (42.9)	11 (26.2)	8 (19)	5 (11.9)	p<0.05
Hyperlipidemia					
Yes	3 (4.2)	23 (32.4)	24 (33.8)	21 (29.6)	
No	28 (53.8)	19 (36.5)	1 (1.9)	4 (7.7)	p<0.001
Macroangiopathy*					
Yes	3 (7)	24 (53.5)	8 (18.6)	9 (20.9)	
No	22 (27.5)	32 (41.3)	14 (17.5)	11 (13.8)	p<0.001
Microangiopathy**					
Yes	-	8 (53.3)	7 (32)	6 (40)	
No	31 (28.7)	34 (31.5)	24 (22.2)	19 (17.6)	p<0.01

*Includes coronary artery disease, cerebrovascular disease and peripheral atherosclerosis.
**Includes diabetic retinopathy, nephropathy and neuropathy.

with biliopancreatic diversion in morbidly obese patients. Carey and associates[22] measured regional adiposities, such as visceral-abdominal, subcutaneous-abdominal, and peripheral non-abdominal, and insulin sensitivity; they compared these measures in healthy obese women and found that abdominal obesity appears to be a major determinant of insulin resistance. Again, metabolic and cardiovascular risk factors greatly improved in obese patients after weight reduction by gastric banding.[23,24] Abdominal adipose tissue is highly responsive to lipolytic stimuli, and large amounts of free fatty acids drain into the portal vein in obese subjects, impairing both hepatic and peripheral insulin sensitivity in obese diabetics.[18] As indicated in Table 1, we found a close relationship between peripheral and hepatic insulin resistance and the magnitude of abdominal adiposity, assessed by BMI, body fat and WHR.

Visceral adipose tissue, as an endocrine organ,[25] also secretes cytokines such as tumor necrosis factor-α (TNF-α), and chemical messengers or hormones such as leptin, resistin, adiponectin, PAI-1, angiotensinogen. All these factors may act as modulators to equilibrate the metabolic, hormonal and hydraulic status of the *milieu intérieure*, and result in insulin resistance. For these reasons, Björntorp[26] put forward the concept of *portal adipose tissue* as an energy generator and causative factor for insulin resistance.

Since obesity is one of the important determining factors of hyperinsulinemia, and hyperinsulinemia and hyperglycemia in turn act as factors in the development of ischemic cardiovascular disorders, the interrelationship between the components of metabolic syndrome and the participants' body weight intrigued us. Our study supports a positive correlation between the magnitude of abdominal obesity and the frequencies of the components of metabolic syndrome, such as type 2 diabetes, hypertension, dyslipidemia, atherosclerosis, and microangiopathies (Table 3). In consideration of the pathophysiology of type 2 diabetes, one can focus on the respective role of adipose tissue together with islet, muscle tissues, and liver.[27] The primary disturbance in diabetes appears to be the insulin action; fasting and postprandial hyperglycemia ensue despite hyperinsulinemia, because of insulin resistance.[17,20] The link between visceral adiposity and type 2 diabetes is well established.[17,20] Fasting hyperinsulinemia due to insulin resistance has correlated with the elevation in blood pressure in subjects with obesity and diabetes.[21,28] It has also been found that hyperinsulinemia is linked with dyslipidemia in obese and insulin resistant diabetics.[29] Similarly, dyslipidemia observed in obese patients with insulin resistance creates an important risk factor for the development of atherosclerosis in both non-diabetic and type 2 diabetic obese individuals.[30]

Maison et al,[31] in a prospective population-based

cohort study at a 4.5-year interval, analyzed the principal components of the metabolic syndrome such as blood glucose, blood pressure, and lipidemia, and concluded that BMI was the central feature of the syndrome. Numerous clinical and experimental investigations may have shed light on the mechanisms of vascular injury caused by sustained hyperinsulinemia. In this context, prandial and postprandial hyperinsulinemia due to insulin resistance may result in a deleterious effect on the integrity of vascular tissue. Thus, insulin *per se* plays a major role in the development of atherosclerosis by increasing the formation and decreasing the regression of lipid plaques, causing proliferation of smooth muscle cells, stimulating connective tissue synthesis, enhancing cholesterol synthesis and increasing LDL-receptor activity and activating growth factors within the arterial wall.[32,33] In addition to the direct harmful effect of insulin, the other components of metabolic syndrome, such as hyperglycemia, hypertension and dyslipidemia independently and/or synergistically foster the development of coronary heart disease.

Our study has also disclosed that macroangiopathy coexists with microangiopathy (Table 3). The relation between two types of angiopathy may be a coincidence. However, the presence of many common factors, such as genetic backgrounds, hypertension, hyperglycemia, dyslipidemia, and probably hyperinsulinemia, that may play a role in the genesis of microangiopathy, should be taken into account.

In conclusion, our study demonstrates that central obesity plays a crucial role in the development of metabolic syndrome.

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