Visceral Obesity and Hemostatic Profile in Patients with Type 2 Diabetes: the Effect of Gender and Metabolic Compensation

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■ Abstract

BACKGROUND: Type 2 diabetes (T2DM) patients are characterized by a very high risk of cardiovascular diseases. Among the factors that are responsible for this phenomenon are abdominal obesity and hemostatic abnormalities. **AIM OF THE STUDY:** To examine the association of the markers of coagulation and fibrinolysis with the parameters of abdominal obesity and metabolic compensation in T2DM patients. **METHODS:** 46 T2DM patients participated in the study: 24 men (mean age 61.1 ± 7.9 years) and 22 postmenopausal women (mean age 62.6 ± 8.7 years). In each patient the content and distribution of fatty tissue was measured by a dual energy X-ray absorptiometry method (DEXA). The central abdominal fat/gynoid hip fat (CAF/GF) ratio was calculated. The following hemostatic parameters were measured: fibrinogen (Fb), factor VII (fVII), antithrombin III (ATIII), C protein (pC), tissue plasminogen activator inhibitor (PAI-1) and alpha 2 antiplasmin (alpha2 AP). In addition, the biochemical indices of metabolic compensation were measured: HbA1c, glucose levels and lipids. **RESULTS:** Patients of both genders were divided according to median CAF/GF ratio. The activity of PAI-1 was significantly higher in women with CAF/GF ratio ≥ 0.88 as compared to those with CAF/GF < 0.88 (2.64 ± 1.28 vs. 1.61 ± 0.27 U/ml, $p < 0.05$). The activity of ATIII was significantly

lower in men with CAF/GF ratio ≥ 1.17 , as compared to those with CAF/GF < 1.17 (105.10 ± 10.02 vs. 113.42 ± 10.72 %, $p < 0.05$). There was a significant correlation between the CAF/GF ratio and the activity of PAI-1 in women ($r = 0.30$, $p < 0.05$). In addition, in men the CAF/GF ratio was negatively correlated with ATIII activity ($r = -0.44$, $p < 0.05$). Multiple stepwise regression analysis demonstrated independent association between the CAF/GF ratio and the activity of PAI-1 ($p < 0.001$), and between the CAF/GF ratio and the activity of alpha2 AP ($p < 0.01$). There was an independent association between the concentration of HbA1c and the concentration of Fb ($p < 0.001$) and between triglycerides and the activity of fVII ($p < 0.01$). **CONCLUSIONS:** The results of our study show that the patients with T2DM and with higher markers of abdominal obesity measured by DEXA show fibrinolysis impairment and thrombinogenesis elevation compared to those with lower abdominal obesity markers. Independent factors determining hypercoagulation also include metabolic control and lipids. Hemostatic disorders place subjects with diabetes and abdominal obesity at risk of developing vascular complications.

Keywords: hemostasis · type 2 diabetes mellitus · visceral obesity · dual energy X-ray absorptiometry

Introduction

Abdominal (android) obesity was first proposed to be a risk factor for the development of atherosclerosis and type 2 diabetes mellitus (T2DM) over 40 years ago [1]. Metabolic alterations accompanying the

visceral distribution of fat lead to arterial hypertension, dyslipidemia, insulin resistance and subsequently to T2DM [2-6]. This phenomenon is associated not only with classical atherosclerotic risk factors but also with coagulation and fibrinolysis abnormalities [7, 8]. Hypercoagulation in abdominal obesity is thought to be caused primarily by the synthesis of factors activating

coagulation and inhibiting fibrinolysis (for example factor VII activator and the fibrinolytic inhibitor PAI-1) in adipose tissue [9, 10]. Hemostatic abnormalities may also result from the synthesis in adipose tissue of cytokines that are mediators of inflammation and insulin resistance, such as interleukin 6 and TNF- α [7]. In addition to this direct effect, the metabolic and lipid alterations that accompany obesity and T2DM are likely to indirectly influence coagulation properties in these patients. Other factors that may be implicated in the generation of hypercoagulation state in visceral obesity and T2DM are endothelial injury and dysfunction [9]. Computerized tomography and magnetic resonance imaging are the most specific and accurate methods for measuring fat distribution and diagnosing abdominal obesity. In recent years dual energy X-ray absorptiometry (DEXA) has also been used as a standard technique for analyzing body composition and fat distribution [6, 11-18]. It was found that the assessment of adipose tissue at L1-L4 might be an indicator of glucose intolerance and lipid abnormalities [16]. Comparative studies by DEXA, computerized tomography and magnetic resonance imaging demonstrated the concordance of both techniques in the assessment of fat distribution [6, 12, 15, 17]. As shown by magnetic resonance imaging, L2-L4 is the region of the highest intra-abdominal fat and the lowest subcutaneous fat [6, 17]. The DEXA technique allows for the assessment of fat distribution and, on this basis, provides information on insulin resistance and metabolic disorders [6, 14, 15, 16].

The purpose of the present study was the assessment of the relationship of hemostatic factors with fat content and distribution as measured by the DEXA method and with parameters of metabolic compensation in patients with T2DM.

Material and Methods

Study population

46 T2DM patients participated in this study: 24 men (mean age at examination 61.1 ± 7.9 years, mean diabetes duration 11.3 ± 5.9 years) and 22 postmenopausal women (mean age 62.6 ± 8.7 years, mean diabetes duration 14.2 ± 8.7 years). All individuals with diseases that might influence the parameters of the coagulation system (liver diseases, diabetic nephropathy and renal failure, with clinically overt coronary artery disease, peripheral and cerebral vascular diseases, severe nonproliferative and proliferative diabetic retinopathy,

acute and chronic infections, ketosis and ketone acidosis) were excluded from the study. Similarly, patients receiving antiplatelet agents, anticoagulants, heparin, glycosaminoglycans, glucocorticoids and hypolipemic drugs and women receiving hormone replacement therapy were not eligible. Subjects abusing alcohol were also banned from the study. Diabetes was treated as follows: 19 of the women and 17 of the men were treated with a fixed diet and insulin, 3 of the women and 7 of the men were treated with a fixed diet and sulphonylurea (gliclazide or glipizide). Each patient underwent a standard clinical examination with blood pressure measurement and an analysis of diabetic complications. Ophthalmological work-up included a full ophthalmological examination and eye fundus photography. Peripheral neuropathy was diagnosed from clinical examination with assessment of sensation and vibration. Diabetic nephropathy was assessed on the basis of screening tests for the ratio of urine albumin to creatinine levels.

Blood samples for the study of hemostatic factors were taken from the antecubital vein without clamping in the fasting state between 7 a.m. and 8 a.m. A tube containing 1 ml of 3.8% trisodium citrate and 9 ml of blood was immediately centrifuged at 4°C. Plasma was frozen at -40°C and stored for later use. Blood for HbA1c measurement was collected in a tube with EDTA as an anticoagulant. Blood was also sampled for measurement of glucose, lipids, creatinine and hepatic enzymes.

Biochemical measurements

Fibrinogen concentration was measured using a modified Clauss method on a Fibrintimer (Behringwerke). Each measurement was repeated twice and a mean was calculated. Variation coefficients were as follows: the coefficient of variation intra-assay and inter-assay 3-6%. The activity of factor VII, ATIII, C protein, PAI-1 and alpha2 AP was measured using a ChromoTimeSystem (Behringwerke) twice and then a mean was calculated. The factor VII coefficient of variation: intra-assay and inter-assay was 4%, the AT III coefficient of variation intra-assay was 2.5-7.5%, the coefficient of variation inter-assay 5.8-8.1%, the C protein coefficient of variation intra-assay and inter-assay < 0.4%, the PAI-1 coefficient of variation intra-assay < 4%, the coefficient of variation inter-assay 3-6%, the alpha2 AP coefficient of variation intra-assay 3.2-8.5%, and the coefficient of variation inter-assay 2.9-8.8%. Concentration of HbA1c was measured by

high performance liquid chromatography (Variant, BioRad). The concentrations of cholesterol and triglycerides were measured using enzymatic methods, with HDL cholesterol (HDL-ch) measured after precipitation of VLDL. The concentration of LDL cholesterol (LDL-ch) was calculated using the Friedewald formula. The level of glucose was measured using an enzymatic method.

Densitometric studies of fatty tissue

In each patient the body composition and distribution of fatty tissue was measured by dual energy X-ray absorptiometry (DEXA; Lunar DPX). The total content of adipose and soft tissue was determined. The adipose tissue in the abdominal region (central abdominal adipose tissue) was measured from the upper border of L2 to the lower border of L4. The adipose tissue of the hip region (gynoid adipose tissue) was measured as adipose tissue content between the superior iliac spines and sciatic tubers [11]. The following ratios were calculated: total fat/soft tissue (TF/ST -%), and central abdominal fat/gynoid hip fat ratio (CAF/GF).

Statistical analysis

Statistical analysis included the Students' t-test, Mann-Whitney U-test, Pearson and Spearman correlation analysis and multiple stepwise regression analysis. A $p < 0.05$ was considered as significant. Statistical analysis was carried out using the SAS package.

Results

The clinical characteristics of the study group are summarized in Table 1. The mean fasting glucose concentration was significantly higher in women than in men ($p < 0.05$). There was no difference between genders in respect to HbA1c level. However, women had a significantly higher total cholesterol level ($p < 0.05$) and LDL-ch ($p < 0.05$) compared to men. In women, the total fat content and the TF/ST ratio was significantly higher than in men ($p < 0.001$ for both parameters), while the CAF/GF ratio was significantly higher in men than in women ($p < 0.001$ for both parameters).

Table 1. Characteristics of the study groups

Parameter	Women (n = 22)	Men (n = 24)	p
Age (yr)	62.60 ± 8.70	61.10 ± 7.90	n.s.
Diabetes duration (yr)	14.20 ± 8.20	11.30 ± 5.90	n.s.
Glucose (mmol/l)	10.00 ± 4.10	7.70 ± 1.90	$p < 0.05$
HbA1c (%)	8.00 ± 1.70	7.30 ± 1.10	n.s.
BMI (kg/m ²)	30.80 ± 3.10	29.10 ± 4.70	n.s.
Total cholesterol (mmol/l)	5.98 ± 0.88	5.31 ± 1.10	$p < 0.05$
HDL-cholesterol (mmol/l)	1.47 ± 0.37	1.31 ± 0.42	n.s.
Triglycerides (mmol/l)	1.79 ± 1.18	2.17 ± 2.07	n.s.
LDL-cholesterol (mmol/l)	3.70 ± 0.93	3.10 ± 0.82	$p < 0.05$
Hypertension/ACEI treatment (n)	17 / 16	20 / 19	
Insulin/gliclazide/glipizide (n)	19 / 3 / 0	17 / 4 / 3	
Smoking (n)	3	5	
Non-proliferative retinopathy (n)	7	10	
Peripheral neuropathy (n)	12	15	
TF (%)	40.78 ± 4.13	24.00 ± 5.73	$p < 0.01$
TF/ST (%)	42.23 ± 4.23	24.94 ± 5.86	$p < 0.01$
CAF/GF	0.86 ± 0.19	1.13 ± 0.21	$p < 0.01$

Legend: Data are means ± SD. BMI: body mass index. ACEI: angiotensin converting enzyme inhibitor. TF (%): total fat share. TF/ST: total fat to soft tissue ratio. CAF/GF: central abdominal fat to gynoid hip fat ratio. n: number of patients.

Patients were divided according to median CAF/GF ratio (Table 2). In women whose CAF/GF ratio was ≥ 0.88 the activity of PAI-1 was significantly higher than in the group with CAF/GF ratio < 0.88 ($p < 0.05$). In men whose CAF/GF ratio was ≥ 1.17 the activity of ATIII was significantly lower than in the group with CAF/GH ratio < 1.17 ($p < 0.05$). In women there was a positive correlation between the TF and alpha2 AP ($r = 0.43$, $p < 0.05$), between the TF/ST ratio and alpha2 AP ($r = 0.44$, $p < 0.05$) and between the CAF/GF ratio and PAI-1 ($r = 0.30$, $p < 0.05$). Furthermore, C protein and alpha2 AP were negatively correlated with the activity of PAI-1 ($r = -0.31$, $r = -0.36$, $p < 0.05$ in both cases) and there was a negative correlation between diabetes duration and

ATIII ($r = -0.48$, $p < 0.05$) and positive correlation between diabetes duration and PAI-1 ($r = 0.48$, $p < 0.05$). In men there was a significant negative correlation between the CAF/GF ratio and ATIII ($r = -0.44$, $p < 0.05$), a positive correlation between HbA1c and fibrinogen ($r = 0.57$, $p < 0.05$) and a negative correlation between HDL-ch and fibrinogen ($r = -0.45$, $p < 0.05$). Furthermore, there was a negative correlation between HDL-ch and alpha2 AP ($r = -0.51$, $p < 0.05$) and a positive correlation between triglycerides and factor VII ($r = 0.64$, $p < 0.01$). There was no relationship between diabetes treatment (insulin/sulphonylureas) and hemostatic factors, lipids and fat distribution parameters. Smoking had no effect, either.

Table 2. Coagulation and fibrinolysis parameters and lipids for women and men divided according to median central abdominal fat/gynoid hip fat ratio

Parameter	Women		Men	
	CAF/GF $< 0.88\%$ (n = 11)	CAF/GF $\geq 0.88\%$ (n = 11)	CAF/GF < 1.17 (n = 12)	CAF/GF ≥ 1.17 (n = 12)
CAF/GF	0.71 $\pm$ 0.13 ^a	1.02 $\pm$ 0.10 ^a	0.96 $\pm$ 0.11 ^a	1.29 $\pm$ 0.13 ^a
TF (%)	42.33 $\pm$ 1.12	39.22 $\pm$ 3.67	23.75 $\pm$ 6.62	24.22 $\pm$ 5.08
TF/ST (%)	43.86 $\pm$ 4.18	40.60 $\pm$ 3.78	24.71 $\pm$ 6.75	25.15 $\pm$ 5.20
BMI (kg/m ²)	31.67 $\pm$ 3.90	30.02 $\pm$ 2.13	29.98 $\pm$ 5.78	28.30 $\pm$ 3.59
Total cholesterol (mmol/l)	5.76 $\pm$ 0.74	6.20 $\pm$ 0.99	5.12 $\pm$ 1.05	5.49 $\pm$ 1.15
HDL-cholesterol (mmol/l)	1.59 $\pm$ 0.41	1.35 $\pm$ 0.28	1.30 $\pm$ 0.50	1.30 $\pm$ 0.20
Triglycerides (mmol/l)	1.65 $\pm$ 0.73	1.92 $\pm$ 0.85	2.60 $\pm$ 2.80	1.70 $\pm$ 0.90
LDL-cholesterol (mmol/l)	3.41 $\pm$ 0.84	3.97 $\pm$ 0.96	2.88 $\pm$ 0.72	3.27 $\pm$ 0.87
Fb (g/l)	3.12 $\pm$ 0.50	3.17 $\pm$ 0.67	2.98 $\pm$ 0.78	2.68 $\pm$ 0.88
f VII (%)	134.54 $\pm$ 34.63	130.72 $\pm$ 19.48	124.22 $\pm$ 26.86	122.19 $\pm$ 24.12
AT III (%)	105.16 $\pm$ 15.23	108.63 $\pm$ 13.16	113.42 $\pm$ 10.72 ^b	105.10 $\pm$ 10.02 ^b
pC (%)	112.68 $\pm$ 19.77	107.09 $\pm$ 11.97	105.89 $\pm$ 22.22	105.18 $\pm$ 25.48
PAI-1 (U/ml)	1.61 $\pm$ 0.27 ^b	2.64 $\pm$ 1.28 ^b	1.93 $\pm$ 0.65	2.16 $\pm$ 0.89
alpha 2 AP (%)	87.88 $\pm$ 11.85	78.71 $\pm$ 10.62	83.89 $\pm$ 10.74	73.96 $\pm$ 14.21

Legend: Data are means $\pm$ SD. CAF/GF: central abdominal fat to gynoid hip fat ratio. TF (%): total fat share. TF/ST: total fat to soft tissue ratio. BMI: body mass index. Fb: fibrinogen. f VII: factor VII. AT III: antithrombin III. pC: protein C. PAI-1: plasminogen activator inhibitor 1. alpha 2 AP: alpha 2 antiplasmin. ^a $p < 0.001$, ^b $p < 0.05$.

Multiple stepwise regression analysis included the following parameters: sex, age, duration of diabetes, metabolic control (HbA1c, lipids) and densitometric measurements of adipose tissue as independent variables and hemostatic parameters as dependent variables (Table 3). There was an independent relationship between fibrinogen level and HbA1c ($p < 0.001$) and

between triglycerides and the activity of factor VII ($p < 0.01$). The activity of PAI-1 was independently modified by the duration of diabetes ($p < 0.05$), the CAF/GF ratio ($p < 0.001$), total cholesterol ($p < 0.01$) and negatively by HDL-ch ($p < 0.001$). There was an independent relationship between the CAF/GF ratio and the activity of alpha2 AP ($p < 0.01$).

Table 3. Multiple stepwise regression analysis taking into account sex, age, duration of diabetes, metabolic control and densitometric measurements

Dependent variable	Independent variable	B	Standard error of B	p-level
Fibrinogen $R^2 = 0.26$ (Adjusted $R^2 = 0.24$)	HbA1c	0.24	0.06	0.0005
Factor VII $R^2 = 0.26$ (Adjusted $R^2 = 0.24$)	Triglycerides	13.40	4.70	0.006 0.04
Alpha 2 antiplasmin $R^2 = 0.26$ (Adjusted $R^2 = 0.24$)	CAF/GF	(-) 21.60	7.81	0.008
PAI-1 $R^2 = 0.26$ (Adjusted $R^2 = 0.24$)	Diabetes duration	0.03	0.01	0.02
	CAF/GF	4.04	0.69	0.0003
	HDL-cholesterol	(-) 8.99	2.23	0.0003
	Total cholesterol	7.58	2.21	0.001

Discussion

The present study demonstrated the relationships between hemostatic factors and abdominal adipose tissue parameters and metabolic control in patients with T2DM.

In this study, women with an increased abdominal obesity had a higher activity of PAI-1. Furthermore, there was a correlation between the CAF/GF ratio and PAI-1 in women, and multiple step-wise regression analysis showed an independent relationship between the CAF/GF ratio and the activity of PAI-1 in women and in men. PAI-1 is the main inhibitor of fibrinolysis, and its activity is correlated with cardiovascular diseases. It should be noted that the cardiovascular risk increases more in diabetic women than in men as compared to the healthy population of both genders. One of the possible explanations is hemostatic abnormalities. Furthermore, some prospective studies in postmenopausal women showed intra-abdominal fat accumulation and increased insulin resistance [19, 20]. In our study the indices of visceral obesity were significantly lower in women than in men, whereas PAI level was correlated with the degree of obesity in the female group. This could have been influenced by the lipid abnormalities that were more profound in women. It should be noticed that in multiple regression analysis they were correlated with PAI-1. A few previously published studies showed similar results. In obese women with T2DM, increased PAI-1 was described, and this was correlated with parameters of visceral obesity measured by DEXA [22]. PAI-1 has also been found to correlate with insulin resistance

parameters, BMI, and visceral fat [23, 24, 25]. However, the study by Cho did not confirm the correlation between fibrinolytic activity and obesity [26]. Martens *et al.* show that visceral fat is more significant than BMI or total body fat in the determination of PAI-1 levels [27]. The results by Cigolini suggest that abdominal accumulation of visceral fat is an independent predictor of plasma PAI-1 activity in healthy men [28]. In patients with visceral obesity and diabetes mellitus, fibrinolytic disorders may play a key role in atherogenesis and may be a cardiovascular risk factor.

In the present study, men with abdominal obesity had a lower activity of coagulation inhibitors ATIII which correlated with abdominal obesity indices. ATIII is an inhibitor of thrombin and factor X. In patients with obesity and diabetes, decreased ATIII activity may be a marker of thrombinogenesis and its depletion may result in inactive thrombin. It may also be related to protein inactivation in the process of non-enzymatic glycation [29]. In the present study there was no relationship between HbA1c and ATIII, only diabetes duration was significantly negatively correlated with ATIII.

Data on the relationship between C protein and obesity and diabetes is scarce and controversial [30, 31]. The study by Vegilo did not show the relationship between BMI and the activity of C protein, nor did diabetes treatment affect its activity [31]. In the present study there was no correlation between C protein activity and fat distribution parameters.

We did not find the relationship between abdominal obesity and fibrinogen concentration, whereas the concentration of Fb showed a negative correlation

with HDL-ch. In another study in patients with the metabolic syndrome, there was a correlation between Fb and BMI, WHR, triglycerides, LDL-ch and HDL-ch (32, 33, 34). In the present study, the concentration of fibrinogen correlated significantly with the level of HbA1c. There was an independent relationship between the level of HbA1c and the concentration of fibrinogen, which indicates an important effect of metabolic control on hemostatic parameters. Previously Ceriello found a relationship between the level of HbA1c and Fb in diabetes patients [35].

The present study also confirms the effect of lipids and lipoproteins on the parameters of coagulation and fibrinolysis. We found an independent relationship between triglycerides and factor VII. There was no increased activity of factor VII depending on abdominal fat distribution. Previous studies in patients with obesity measured by BMI, WHR, and DEXA show an increased activity of factor VII [22, 36, 37, 38]. A BMI-independent effect of triglycerides on factor VII was also demonstrated in individuals with hyperlipoproteinemia [37].

In our study, there was a negative relationship between abdominal obesity parameters and the activity

of alpha2 AP, and a positive correlation between total fat and alpha2 AP. Alpha2 antiplasmin is the main plasma inhibitor of plasmin and a negative relationship between visceral obesity and alpha2 AP may indirectly argue in favor of increased inactivation of plasmin and inhibition of fibrinolysis. Plasmin generation is also affected by increased PAI-1 activity; the significance of this phenomenon is indirectly confirmed by the correlation between PAI-1 and alpha2 AP. Epidemiological studies show a negative correlation between the concentration of the plasmin-alpha2 AP complex and BMI, insulin, and the development of atherosclerosis; however, in patients with diabetes, the concentration of this complex was found to be increased [39, 40].

In summary, in our study, patients with T2DM and higher markers of abdominal obesity measured by DEXA showed fibrinolysis impairment and thrombinogenesis elevation compared to those with lower abdominal obesity markers. Independent factors determining hypercoagulation also include metabolic control and lipids. Hemostatic disorders place subjects with diabetes and abdominal obesity at risk of developing vascular complications.

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