Visceral Fat Volume is a Better Predictor for Insulin Resistance than Abdominal Wall Fat Index in Patients with Prediabetes and Type 2 Diabetes Mellitus

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Abstract

Objective: Relationship between Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and visceral adiposity that was assessed by ultrasonographic measurements of abdominal wall fat index (AFI) and visceral fat volume (VFV), was evaluated in our study.

Methods: A total of 150 patients (50 type 2 diabetes mellitus (DM) patients, 50 prediabetes (IFG+IGT) patients and 50 controls) were enrolled in the study. The diagnoses of type 2 DM and of prediabetes were established according to the American Diabetes Association 2010 criteria. AFI and VFV measurements were done by ultrasonography. HOMA-IR was calculated. Serum lipid profile and glucose were measured.

Results: The mean ages were 57.2 ± 9.2, 55.0 ± 11.3 and 52.8 ± 10.9 years for the type 2 DM, prediabetes and control groups, respectively. Groups were similar according to age and sex. There were significant differences between groups with respect to body mass index (BMI), waist circumference, hip circumference, and waist to hip ratio ($p<0.05$, $p<0.05$, $p<0.05$, and $p<0.05$, respectively). According to our results, there was a statistically significant positive correlation between VFV and HOMA-IR (rho=0.366, $p<0.05$), but no significant positive correlation between AFI and HOMA-IR (rho=0.153 and p=0.062).

Conclusion: Visceral fat volume is a better predictor for HOMA-IR than abdominal wall fat index in patients with prediabetes and type 2 diabetes mellitus.

Keywords: Visceral fat volume; Abdominal wall fat index; HOMA-IR; Ultrasonography

Introduction

Diabetes mellitus (DM), prediabetes and insulin resistance (IR) are important causes of morbidity and mortality, particularly due to their cardiovascular complications [1]. IR can be defined as the impairment of glucose transportation stimulated with insulin in tissues sensitive to insulin (muscle and fat tissues); however, it also results in atherosclerosis and endothelial dysfunction because of its clinical outcomes [2]. The homeostasis model assessment for insulin resistance (HOMA-IR) was used to measure of insulin resistance that only requires assessment of basal glucose and insulin concentrations [3].

The close relationship between metabolic disorders and body fat distribution has been reported [4,5]. Measurement of intra-abdominal visceral fat accumulation is an important step for the assessment of atherosclerosis risk [6].

Abdominal computed tomography (CT) is the most commonly used method for assessment of VF [7]. But we would suggest referring to the limitations of CT scanning, because of radiation dose, expensive, time-consuming and equipment that requires. Magnetic resonance imaging [MRI] has also been used for VF measurement [8,9], but MRI carries the same challenges with CT outside of radiation exposure [7]. Dual-Energy X-Ray Absorptiometry (DEXA) is also used for evaluation of VF measurement [7,10] and compared with ultrasonography, DEXA has some disadvantages such as radiation exposure, expensive and attainability.

Ultrasonography, alternatively to computerized tomography (CT) and magnetic resonance imaging (MRI) methods, can be used for determining visceral fat volume (VFV). CT and MRI methods may perform a better level of assessment; however, exposure to high levels of radiation, high costs and technical difficulties are among their disadvantages [6,11,12]. Another study showed that Visceral Adipose Tissue (VAT) measured by ultrasonography is better than Waist Circumference (WC) in predicting the presence of subclinical carotid atherosclerosis [13]. The measurement of the visceral fat volume using US also provided results as effectively as CT, and it was proven to be a useful method [14]. The purpose of our study was to evaluate the relationship between IR and visceral fat accumulation. IR was determined utilizing the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) in three groups (type 2 DM, prediabetes and controls), and the relationship between IR and abdominal wall fat index (AFI) and VFV, which were measured by ultrasonography, was evaluated.

Subjects and Methods

Patients

A total of 150 subjects (50 type 2 DM patients, 50 prediabetes (impared fasting glucose (IFG)(28)+impared glucose tolerance (IGT) (22) patients and 50 controls), who were admitted to the second department of internal medicine outpatient clinic and check-up outpatient clinic for the control group at Diskapi Yildirim Beyazit Education and Research Hospital were enrolled in this study. All subjects provided written informed consent forms before enrolling in the study. The study protocol was approved by the Local Ethical Committee.The diagnosis of prediabetes (IFG+IGT) and type 2 DM were established by using the American Diabetes Association (ADA) 2010 criteria [15]. Prediabetes includes Impared Fasting Glucose (IFG) and Impared Glucose Tolerance (IGT). IFG is that fasting plasma glucose should be 100-125 mg/dl. If post- prandial blood glucose of outpatients were 140-199 mg/dl, we performed 75-g oral glucose tolerance test for these patients. Then, IGT was that 2-hr plasma glucose after 75-g oral glucose tolerance test should be 140-199 mg/dl. The protocol was approved by the local ethics committee. Consecutive patients with type 2 DM and prediabets who were seen at a outpatient clinic were evaluated for eligibility. The control group was selected from among consecutive individuals with no history of any disease or drug usage, based upon medical history, physical examination and complete blood chemistry.

Each patient determined suitable for inclusion in the study underwent a physical examination, and detailed medical histories were recorded. Exclusion criteria were as follows: previous abdominal surgery, renal failure, hyperthyroidism, acromegaly, pheochromocytoma, any drug use for obesity, history of alcohol consumption, current smokers, history of participation in any fitness or diet program, history of another severe systemic disorder, liver cirrhosis, history of cancer, and pregnancy, current breastfeeding, or possibility of becoming pregnant.

Information including sex, age, height, body weight, body mass index (BMI), waist circumference, hip circumference, waist-hip ratio (WHR), systolic and diastolic blood pressure, triglyceride (TG) level, low-density lipoprotein (LDL), hemoglobin (Hb)A1C, insulin, and fasting plasma glucose values were collected for each patient. The height (cm) and weight (kg) of the patients were measured and BMI (kg/m²) was calculated. Waist circumference measurement was performed while the patient was in standing position and after expiration, between the edge of the lower ribs and iliac process. Hip circumference (cm) was measured parallel to the ground between the spina ischiadica majors and WHR was determined. Blood pressure was measured in all patients with conventional sphygmomanometer after 10 minutes of rest; two measurements from both arms were performed with a 15–minute interval, and the average of these values was recorded.

Biochemical study

Venous blood samples were taken after 12 hours of fasting. Biochemical assays were done in P800 Roche Hitachi and Olympus AU 5200 devices. Complete blood count was done with ROUCHE Sysmex SE 9000 automatic blood count devices. Glucose was assayed with original kits on the Synchron LX 20 device (Beckman Coulter). HbA1C measurements were established with Cobas Integra 700 autoanalyzer by using immunoturbidimetric method (Roche,

Indianapolis, USA). Insulin was assayed by original kits in DPC Immulite 2000 device (Bio DPC). Total cholesterol, high-density lipoprotein (HDL)-cholesterol and TG levels were assayed with original kits in Synchron LX 20 device (Beckman Coulter). LDL-cholesterol was calculated from total cholesterol, HDL-cholesterol and TG levels by Friedewald formula [LDL-chol = (total chol) - (HDL-chol) - (TG/5)]. IR was determined by the HOMA-IR formula [fasting plasma glucose (mg/dl) X fasting plasma insulin (mu/mL)/405] [16]. In a study with healthy volunteers showed that HOMA value above 1.8 in females and 2.12 in males was described as IR [17].

Ultrasonography

All ultrasonographic measurements were done in our hospital by the same physician was using by LOGIQ-7 GE ultrasound device and the physician has not known the group's knowledge. Thus, it was prevented possible errors due to measurement differences by different physicians. Ultrasonographic assessments were made using by 7.5 MHz linear type B mode probe within 2 days of performing biochemical analyses. AFI was assessed in the supine position by proportioning maximum preperitoneal (Pmax) fat tissue thickness to minimum subcutaneous (Smin) fat tissue thickness in the median line from the xiphoid process to the umbilicus by positioning the probe vertically to the skin, anterior to the liver and epigastrium: AFI: Pmax (mm)/Smin (mm) [18]. VFV was calculated as: 1- length between interior of abdominal muscle and splenic vein (SPLEEN) (mm); 2- Length between interior of abdominal muscle and posterior wall of abdominal aorta (AORTA) (mm); and 3- Fat thickness of posterior right renal wall (PARARENAL) (mm) [18]. VFV= - 9.008+ (1.191 x length between interior of abdominal muscle and splenic vein (mm)) + (0.987 x length between interior of abdominal muscle and posterior wall of abdominal aorta (mm)) + (3.644 x fat thickness of posterior right renal wall (mm)) [14].

Statistical analysis

Data entry and analysis were performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 11.5 program. Shapiro-Wilk test was used to test the normality of the continuous variables, and the mean is shown as ± standard deviation or median (min-max). One-way ANOVA test was used for comparisons of means of the groups, and Kruskal-Wallis test was used to make median value comparisons. When significant differences were detected, post-hoc tests, Tukey or multiple comparison tests were used to identify the significant differences among the groups. Nominal variables were evaluated with Pearson's chi-square test or with Fisher's exact test. The degree of the relationship between continuous variables was calculated with Spearman's "rho" correlation coefficient. Multiple linear regression analyses were used to determine the indicator affecting the HOMA-IR. Coefficient of regression and 95% Confidence Intervals (CIs) were calculated for all independent variables. Logarithmic transformations were applied for all linear regression analyses, which had non-normal distributions. Results having a p value lower than 0.05 were accepted as significant.

Results

The mean ages of the patients were 57.2 ± 9.2, 55.0 ± 11.3 and 52.8 ± 10.9 years for the type 2 DM, prediabetes and control groups, respectively. The mean ages were similar (p=0.600). Sixty-six percent of the patients were female. Gender distribution was similar between groups (p=0.700) (Table 1).

Variables	Control	Prediabetes	Type 2 DM	P
Age (years)	52.8 ± 10.9	55.0 ± 11.3	57.2 ± 9.2	0.600a
Gender F/M	31 / 19	35 / 15	33 / 17	0.700b
BMI (kg/m²)	27.0 ± 3.6	32.6 ± 7.2*	30.6 ± 4.9*	<0.05c
Waist circumference (cm)	87.7 ± 10.1	106.1 ± 13.7*	102.1 ± 10.3*	<0.05c
Hip circumference (cm)	102.7 ± 11.6	113.7 ± 13.1*	112.7 ± 9.6*	<0.05c
Waist-hip ratio (cm)	0.84 ± 0.09	0.92 ± 0.05*	0.90 ± 0.06*	<0.05c
History of hypertension (n/%)	-	22 (44.0%)	22 (44.0%)	-
History of dyslipidemia (n/%)	-	15 (30.0%)	17 (34.0%)	-
Family history of coronary artery disease (CAD) (n/%)	-	-	10 (20.0%)	<0.05b
History of CAD (n/%)	-	-	4 (8.0%)	0.117d

DM: Diabetes Mellitus; BMI: Body mass index; F: Female; M: Male; CAD: Coronary artery disease; a- One-way ANOVA; b- Pearson chi-square test; c- Kruskal-Wallis test; d- Fisher's exact test; *p < 0.05 versus controls

Table 1: Demographic and Clinical Features.

Forty-four percent of the patients in the prediabetes and type 2 DM groups had hypertension. Dyslipidemia was present in 30% and 34% of the patients in prediabetes and type 2 DM groups, respectively. 8% of the patients with type 2 DM had CAD and 20% of the patients with type 2 DM had a family history of CAD. Laboratory Parameters were shown at (Table 2).

Variables	Control	Pre-diabetes	Type 2 DM	P
Triglyceride (mg/dl)	121(35-211)	156.5 (58-336) c	146 (55-398) c	<0.05b
Total Cholesterol (mg/dl)	185 (115-252)	214 (147-299) c	184 (123-295) d	<0.05 b
LDL-C (mg/dl)	111(62-155)	120.5 (70- 199) c	113 (74-185)	<0.05b
HDL-C (mg/dl)	45.8 ± 9.5	45.3 ± 9.3	41.4 ± 10.2	0.063ᵃ
Hb A1c (%)	5.2 (2.2-5.5)	6 (5.5-6.0)	7.1 (5.5-11.7) c, d	<0.05 b
Insulin (mu/ml)	4.4 (2.5-12.6)	10.5 (2.5-84) c	9.7 (1.9-85) c	<0.05 b
Fasting Glucose (mg/dl)	96.5 (78-109)	116.5 (111-125) c	135 (88-423) c, d	<0.05 b

a One-way ANOVA; b Kruskal-Wallis test; c The difference between control group was statistically significant (p<0.05); d The difference between pre-diabetes group was statistically significant (p<0.05).

Table 2: Laboratory Parameters.

A statistically significant difference was detected between all groups for AFI (p<0.05). There was a significant difference between control group and the type 2 DM group for AFI (p<0.05); however, there were not statistically significant differences between prediabetes and control groups and between prediabetes and type 2 DM groups for AFI (p=0.060 and p=0.099, respectively).

There was a significant difference between control group and type 2 DM group and between control group and prediabetes group for VFV (p<0.05 and p<0.05, respectively); however, there was not statistically significant difference between prediabetes and type 2 DM groups for VFV (p=0.750).

There was no statistically significant correlation (r=0.153 and p=0.062) between AFI and HOMA-IR. There was a statistically significant positive correlation between VFV and HOMA-IR (r=0.366, p<0.05) (Table 3).

Variables	Control	Prediabetes	Type 2 DM	P
HOMA-IR	1.1 ± 1.2	2.9 ± 2.8 c	3.2 ± 3.0 c	<0.05b
AFI	0.7 ± 1.1	1.0 ± 0.71	1.1 ± 1.04 c	<0.05b
Smin (mm)	11.6 ± 5.5	15.0 ± 7.17 c	13.6 ± 5.98 d	<0.05b
Pmax (mm)	8.2 ± 5.14	16.2 ± 5.27 c	16.6 ± 5.46 c	<0.05b
VFV	140.8 ± 20.4	161.3 ± 33.2 c	157.3 ± 27.4 c	<0.05a
AORTA (mm)	70.9 ± 12.38	74.4 ± 15.09	70.7 ± 13.95	0.412b
SPLEEN (mm)	31.6 ± 7.4	39.0 ± 12.0 c	39.6 ± 11.3 c	<0.05a
PARARENAL(mm)	7.02 ± 1.67	9.5 ± 3.05 c	8.3 ± 2.9 c, d	<0.05b

DM: Diabetes Mellitus; HOMA-IR: Homeostasis model of insulin resistance; AFI: Abdominal wall fat index; VFV: Visceral fat volume; Smin: minimum subcutaneous fat tissue thickness;

Pmax: maximum preperitoneal fat tissue thickness; AORTA: Length between interior of abdominal muscle and posterior wall of abdominal aorta; SPLEEN: length between interior of abdominal muscle and splenic vein; PARARENAL: Fat thickness of posterior right renal wall; a- One-way ANOVA; b- Kruskal-Wallis test; c- The difference between control group was statistically significant (p<0.05); d The difference between pre-diabetes group was statistically significant (p<0.05).

Table 3: Insulin Resistance and Visceral Fat Volume.

A statistically significant positive correlation was detected between BMI and HOMA-IR (r=0.281, p<0.05). There were statistically significant positive correlation between waist circumference and HOMA-IR (r=0.325, p<0.05). Also, there were no statistically significant correlations between total cholesterol, triglyceride, LDL, HDL and HOMA-IR (p=0.170, p=0.362, p=0.127 and p=0.124 respectively) (Table 4).

Variables	HOMA-IR	
	rho	p
BMI	0.281	<0.05
WC	0.325	<0.05
Total cholesterol	0.113	0.170

Triglyceride	0.075	0.362
LDL-C	0.125	0.127
HDL-C	-0.126	0.124
AFI	0.153	0.062
VFV	0.366	<0.05

Tablo 4: Relationship between HOMA-IR and clinical parameters.

In the multiple linear regression analysis, it was demonstrated that while VFV has a statistically significant effect on the HOMA-IR, AFI does not. In the multiple linear regression analysis, dependent variable HOMA-IR and independent variables prediabetes, type 2 DM, female gender, BMI, waist circumference, AFI, and VFV were included in the model. VFV in the prediabetes and type 2 DM groups (as compared to the control group) were shown as independent indicators for HOMA-IR determination (95%CI=0.004-0.014, p<0.05) (Table 5).

Dependent Variable	Coefficient of Regression (B)	p value	95% CI for (B)	
Independent Variables			Lower	Upper
HOMA-IR				
Pre DM	0.724	<0.05	0.357	1.09
Type 2 DM	0.781	<0.05	0.433	1.129
Female Factor	-0.069	0.64	-0.362	0.223
BMI	-0.001	0.955	-0.038	0.035
Waist Circumference	-0.006	0.413	-0.022	0.009
AFI	-0.026	0.698	-0.16	0.108
VFV	0.009	<0.05	0.004	0.014

Table 5: Multiple Linear Regression Analysis Results.

Discussion

Throughout the world, type 2 DM and also obesity incidence and prevalence are increasing dramatically. As an important factor in type 2 DM pathogenesis, IR is an independent risk factor for type 2 DM as well as hypertension, stroke, and coronary artery disease, and it carries high mortality and morbidity such as in metabolic syndrome [14].

A close association between metabolic disorders and body fat distribution was demonstrated in various articles [19-23]. Necropsy studies, ultrasonography, CT, magnetic resonance imaging (MRI), and Dual-Energy X-ray Absorptiometry (DEXA) are used for body fat distribution and in particular visceral fat determination. The anthropometric measurements for determination of abdominal obesity are conicity index, sagittal waist measurement, WHR, and transverse waist circumference measurement (16). Following experts' consensus, waist circumference (WC) is the best anthropometric obesity index. In a study showed that volumes of visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (SAT) were obtained using MRI. Their studies were included blood pressure, plasma lipids, glucose, and homeostasis model (HOMA index). The authors showed that each WC had a stronger correlation with SAT than with VAT and

suggested that WC is predominantly an index of abdominal subcutaneous fat [24].

We showed that in our study, there is no significant difference between WC and HOMA-IR in linear regression analyses (beta:-0.006, %95CI:-0.022-0.009, p: 0.413). This may be due to the fact that WC is associated with subcutaneous fat tissue. In our study, we show that while AFI was not related with HOMA-IR (95%CI=-0.160-0.108, p=0.698), there was a statistical significant relationship between VFV and HOMA-IR (95%CI=0.004-0.014, p<0.05).

There is a lot of method for measurement of visceral adiposity. In other study, in which VFV was measured at the umbilicus level by CT, two types of obesity were demonstrated: visceral fat type - fat accumulation in the abdominal area predominantly and subcutaneous fat type – fat accumulation in subcutaneous tissue [16,25]. Fujioka et al. demonstrated that the ratio of visceral fat area to subcutaneous fat area was related to plasma glucose, serum TG, total cholesterol, and atherosclerosis severity [26]. In a study in which VFV was assessed by CT, the VFV value was found significantly higher in non-obese new-onset type 2 DM patients as compared to healthy controls. VFV was claimed as an important indicator for IR as measured by CT [27].

There has been no readily available method to quantify VF. The authors in a study were showed that, the measurements such as BMI, waist circumference, and the waist-to-hip ratio have been used to obtain an assessment of metabolic and cardiovascular risk were not reflected VF in a reliable manner and, importantly, SF has no significant relation with VF by using DEXA. Dual-energy X-ray absorptiometry (DEXA) can accurately measure body composition with high-precision, low X-ray exposure, and short-scanning time [7,28,29].

In recent study was evaluated the association between intermuscular AT (IMAT) in the abdominal skeletal muscles (total, paraspinal and psoas) and fasting serum glucose, insulin, and homeostasis model assessment of insulin resistance (HOMA-IR). Abdominal IMAT, visceral and subcutaneous AT (cm^3) were measured by quantitative computed tomography at the L4-L5 intervertebral space. It was shown that independent association between abdominal myosteatosis and hyperinsulinemia and insulin resistance among older Caucasian men in this study [30].

In another study was concluded that, independent of the individual's body type, visceral fat dominant accumulation as opposed to subcutaneous fat accumulation is associated with hepatic insulin resistance, whereas peripheral (muscle) insulin resistance is more closely related to general obesity (i.e. higher BMI and total fat mass, and increased abdominal SF and VF) in male patients with type 2 diabetes [31].

In a study showed that abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were both associated with adverse cardiometabolic risk factors, but VAT remains more strongly was associated with these risk factors. The results from this study suggested that relations with cardiometabolic risk factors were consistent with a pathogenic role of abdominal adiposity in participants of African ancestry [23].

In recent study showed that visceral, but not sc, abdominal adiposity was strongly related to cardiometabolic risk factors and to the prevalence of cardiovascular disease and might have been an important role of cardiometabolic risk in patients regardless of type 2 diabetes status [32]. Therefore, in a study suggested that increased

visceral fat was related to dyslipidemia and increased frequency of insulin resistance and might account for the increased prevalence of diabetes mellitus and cardiovascular disease in Asian Indians [33].

In another study, an ultrasonography and CT comparison was made, and ultrasonography was found as efficient as CT, while being easier to use, cheaper, and lacking radiation exposure; thus, it was highlighted that ultrasonography can be preferred over CT [11,14]. In another a cross-validation study showed that, intra-abdominal fat tissue measured by CT at L4-L5 was significantly correlated with Ultrasonography (US) for intra-abdominal thickness [14,34]. Ultrasonography is cheap, easy to use and achieve, and lack of radiation exposure. Therefore, ultrasonography should be first choice for assessment of visceral adiposity. In our study, the relationship between HOMA-IR and visceral fat accumulation is assessed. Visceral fat accumulation is determined by ultrasonography in two different methods: AFI and VFV. In present study, we showed that ultrasonographic measurement of visceral adiposity is significant for assessment of insulin resistance. VFV can be the routine ultrasonographic method for assessment of insulin resistance and visceral adiposity. In the literature, there is no study that is relationship between HOMA-IR and two different ultrasonographic determinations for visceral adiposity.

Suzuki et al. demonstrated previously that AFI could be used for the determination of VFV, which is known to be induced by IR [35]. In the study, following multiple regression analysis, an independent relation between VFV and blood pressure, TG level, HDL-cholesterol, fasting insulin, and HOMA score was indicated. Subcutaneous fat tissue is related independently to systolic blood pressure, fasting insulin and HOMA score. In this study, there was a relationship between cardiovascular risk factors with VFV and IR [35]. In the other hand, one study suggested that, compared with BMI, AFI might have been useful in identifying blood pressure-related abnormalities, which was represented an atherosclerotic risk in older Japanese women [36].

In another study, a statistically significant negative correlation was shown between AFI and HOMA-IR. In addition, a statistically significant positive correlation of Smin and Pmax with HOMA-IR was reported in the research, and Smin and Pmax were argued to be better indicators of HOMA-IR than AFI [37]. Therefore, AFI was claimed as not showing the IR level at all times. In the study of Soyama et al., HOMA-IR levels were detected to be statistically significantly higher in impaired fasting glucose+impaired glucose tolerance, impaired fasting glucose, and DM groups as compared to normal glucose tolerance [37]. In our study, there was a positive correlation in the prediabetes and type 2 DM groups as compared to the control group for HOMA-IR. The results of our study were in line with the literature.

In our study, there was no statistically significant linear correlation (r=0.153 and p=0.062) between AFI and HOMA-IR. Thus, our study supports the claim that AFI may not show the HOMA-IR completely (beta: -0.026, %95CI: -0.160-0.108, p: 0.698).

In conclusion, visceral adiposity had been demonstrated as an indicator of IR. Our study showed that the correlation between HOMA-IR and VFV and AFI. Additionally, we showed that VFV is a better indicator for detection of HOMA-IR than AFI. According to our study, AFI may not show the correlation with HOMA-IR at all times. However, we showed that VFV, BMI and waist circumference were positively correlated with HOMA-IR. VFV can be used to detect visceral obesity and IR. There were small number of patients in our study and this might be restrictive. Further studies of patients are needed to show the association between VFV and IR.

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