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RESEARCH ARTICLE

Visceral adiposity and the prevalence of glucose intolerance: A predictive cut-off value.

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Abstract

Background: The Visceral Adiposity Index (VAI) is a sex-specific mathematical index indirectly expressing visceral adipose function and insulin sensitivity. Our aim was to find the optimal cut-off points of VAI identifying a visceral adipose dysfunction (VAD) associated with glucose intolerance.

Materials and Methods: This was a cross-sectional research that carried out on the 508 subjects (212 males and 296 females) using random collection sampling technique. FBG was measured in the morning after a 12-hour fast and the examination included also a 75-g oral glucose tolerance test and anthropometric measurements. Receiver operating characteristic curve and area under curve were applied to compare the ability of identifying impaired glucose tolerance (IGT) and diabetes risk and VAI.

Results: As whole, the mean of VAI in subjects with abnormal glucose (2.5 ± 0.94 mg/dl) was higher than in subjects with normal glucose tolerance tests (1.65 ± 0.56 mg/dl). Also, the mean of VAI in DM was higher than in IGT (2.94 ± 0.94 versus 2.79 ± 0.96). There were positively correlation between VAI and fasting and postprandial glucose (P=<0.001 for both). The cut-off points of VAI for screening and diagnosis of glucose intolerance are 1.7677 and 2.5579, respectively.

Conclusion: Greater visceral adiposity increases the risk of IGT and DM. Also, our study suggests that among our subjects there is clear cut-off points of VAI able to identify a VAD strongly associated with glucose intolerance. VAI is useable as a predictor of glucose intolerance and type 2 DM risk among adults.

INTRODUCTION

Obesity is major public health issue with a rapidly increasing prevalence [1]. Obesity, genetic susceptibility, aging, and male sex were found to be associated with increased visceral fat accumulation [2]. Despite having lower average body mass index (BMI) than whites, Asian women have a higher degree of central adiposity for a given BMI [3], which confers an increased risk for metabolic syndrome, type 2 diabetes, and cardiovascular diseases [4]. A central pattern of body fat distribution is now generally considered to play an important role in the insulin resistance syndrome, which is the cluster of obesity, insulin resistance, hyperinsulinemia, dyslipidemias, glucose intolerance, and hypertension [5]. In particular, visceral adiposity has been reported to play a key role in these diseases compared with other measurements of regional or generalized obesity [6].

To identify visceral obesity, the clinical parameter most commonly used today is Waist Circumference (WC). Nevertheless, WC alone does not help in distinguishing between subcutaneous and visceral (both omental and mesenteric) fat mass [7]. This is particularly significant given that differences in insulin sensitivity, lipolytic activity and adipocytokines production play a fundamental role in the genesis of cardiovascular sequelae [8-10]. Magnetic resonance imaging (MRI) and computed tomography (CT) are now considered the gold standard for the quantitative evaluation of Visceral Adipose Tissue (VAT) and Subcutaneous Adipose Tissue (SAT) [11]. Since these two methods are extremely expensive and complicated to perform, they cannot be recommended in routinely clinical practice. Furthermore, in order to predict VAT-associated cardiometabolic risk, it would be highly desirable to perform routine evaluation of "visceral adipose dysfunction" (VAD) by adipocytokine assessment. This approach, however, is also unfeasible because of the complexity of the 'adipose endocrine organ' function [12], and again for the high costs involved.

In the light of limitations and lack of exciting methods and the recognition that more reliable measure of visceral adiposity are needed. Amato et al. [13] developed the Visceral Adiposity Index (VAI), a mathematical model that uses both anthropometric (BMI and WC) and functional (triglycerides [TG] and high-density lipoprotein [HDL] cholesterol) simple parameters. To correct Model Of Adipose Distribution (MOAD) for fat function, TG and HDL lipoprotein levels were introduced in the formula. This was defined as VAI:

$$Males: VAI = \left(\frac{WC}{39.68 + (1.88\ X\ BMI)}\right) X \left(\frac{TG}{1.03}\right) X \left(\frac{1.31}{HDL}\right)$$

$$Females: VAI = \left(\frac{WC}{36.58 + (1.89\ X\ BMI)}\right) X \left(\frac{TG}{0.81}\right) X \left(\frac{1.52}{HDL}\right)$$

This index, which could be considered a simple surrogate marker of VAD, showed a strong association with both the rate of peripheral glucose utilization (M value) during the Euglycemic-hyperinsulinemic Clamp and with VAT measured with MRI. Furthermore, it showed a strong independent association with both cardiovascular and cerebrovascular events [13] and showed better predictive power for incident diabetes events than its individual components (WC, BMI, TG and HDL) [14].

The prevalence of Type 2 diabetes (hereafter diabetes) is undergoing a rapid progression [15], largely as a consequence of the epidemic proportions reached by obesity in various populations of the world [16]. "However, physicians have been puzzled by the heterogeneity of obesity as not every obese patient develops chronic complications." In this regard, visceral adiposity has been found to be associated with an increased risk of a cluster of diabetogenic, atherogenic, prothrombotic and inflammatory metabolic abnormalities increasing the risk of diabetes [17]. Visceral obesity [18] is associated with deterioration of insulin sensitivity [19], increased risk of developing diabetes, and "high-TGs/low-HDL-C dyslipidemia [13]." The identification of a routinely applicable indicator for the evaluation of visceral adipose function, with higher sensitivity and specificity than classical parameters such as WC, BMI, and lipids, could be useful for cardiometabolic risk assessment. Visceral adiposity is so strongly linked to the type 2 diabetes, that some experts have recently suggested the new term called "Diabesity" [20].

Therefore, using this cross sectional study we examined: first, if VAI could provide as much information as is expected to be obtained from original modeling of its components. Second, if VAI could outperform Metabolic Syndrome in predicting incident diabetes. Third, if VAI could add to the predictive ability of simple anthropometric measures of adiposity. Finally, we determined the VAI level corresponding to the threshold of risk for incident diabetes.

Materials and Methods

This observational prospective study was carried out at the internal medicine, faculty of medicine, Zagazig University from Jan 2013 till September 2014. This study protocol was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Institutional Review Board of our faculty of medicine. Informed consent was obtained from all patients. Eligible subjects were previously untreated adults who are healthy and are undiagnosed glucose intolerance or incident type 2 DM. The current analysis included 508 subjects aged 17 to 67 years. Upon enrollment, data were resumed as follows: height, weight, BMI (kg/m^2), WC, personal and family history, and ongoing therapies. Exclusion criteria were as follows: previously known type 1 DM and untreated or treated type 2 DM; hormone treatments; suspected thyroid diseases; patients with very high fasting triglycerides ($\geq$7.7 mmol/L, Third Report of the National Cholesterol Education Program [21]); any therapy capable of influencing our data, chronic kidney disease, liver cirrhosis and other liver diseases, gastroenteropancreatic disturbances, and autoimmune disorders.

Glucose metabolism was assessed by fasting plasma glucose and insulin; oral glucose tolerance test (OGTT) for glucose; and glycated haemoglobin (HbA1c). Lipid analysis included total-cholesterol (t-CHO), HDL-cholesterol (HDL-CHO), low density lipoprotein-cholesterol (LDL-CHO) and triglycerides levels. ADA recommendations [22] were used for the definition of glucose metabolism and type 2 DM, as follows: normal fasting plasma glucose (FPG) if < 100 mg/dl (5.6 mmol/l); impaired FPG(IFG) if FPG was 100–125 mg/dl (6.9 mmol/l); impaired glucose tolerance (IGT) if 2-h post-OGTT plasma glucose was 140–199 mg/dl (7.8-11.0 mmol/l); type 2 DM if FPG was ≥ 126 mg/dl (≥7 mmol/l) on two days apart, or if 2-h post-OGTT plasma glucose was ≥ 200 mg/dl (≥11.1 mmol/l). HbA1c values of 5.7 and 6.5% were considered as the threshold of normal glucose metabolism and type 2 DM, respectively. Insulin resistance was calculated by the homeostatic model of insulin resistance (HOMA-IR) as fasting insulin (μU/m) × [fasting PG (mmol/l)/22.5].

Anthropometric and body fat assessment

The following anthropometric measurements were obtained: Weight was assessed by a balance-beam scale while the participant was wearing lightweight clothing. Standing height was assessed by a stadiometer. BMI was calculated by the Quetlet index: weight in kilograms/height in meters squared (kg/m^2) [23]. WC was measured by use of a metal tape measure at the maximum WC between the lower rib and the iliac crest. Participants were asked to stand with their weight equally distributed on both feet, with arms hanging at their sides and head facing straight ahead, relaxing their abdomen and breathing normally. The abdominal circumference was measured at eye level directly over bare skin, and the measurement was made at the end of a normal expiration to the nearest 0.1 cm. The measurement was taken twice. The final abdominal circumference value used was the mean of the 2 recorded values.

Biochemical tests

Blood chemistry analyses were performed in Zagazig University laboratories. Venous blood samples were collected after fasting for 14 hour and 2 hours after the ingestion of 75 gram glucose. Plasma glucose was assayed by an automated glucose oxidase method. HbA1c were measured by enzymatic methods (Roche Molecular Biochemicals, Mannheim, Germany). Fasting plasma insulin was measured by radioimmunoassay. Insulin sensitivity was estimated by using homeostasis model assessment for insulin resistance (HOMA-IR; (fasting glucose [measured in millimoles per liter])(fasting insulin [measured in microunits per milliliter])/22.5) [24]. Tests for triglyceride were performed on Hitachi Chemistry analyzers with Roche chemistry reagents; settings were as specified by the manufacturer. HDL cholesterol was determined by precipitation with phosphotungstic acid, Sigma Chemical Reagent for in vitro diagnosis. Glomerular Filtration Rate (GFR) was estimated from serum creatinine using the MDRD formula and was expressed as ml/min/1.73 m^2 [25]. VAI score was calculated as described [13; 26] using the following sex-specific equations, where TG is Triglycerides levels expressed in mmol/l and HDL is HDL-Cholesterol levels expressed in mmol/l:

$$Males: VAI = \left(\frac{WC}{39.68 + (1.88\ X\ BMI)}\right) \times \left(\frac{TG}{1.03}\right) \times \left(\frac{1.31}{HDL}\right)$$

$$Females: VAI = \left(\frac{WC}{36.58 + (1.89\ X\ BMI)}\right) \times \left(\frac{TG}{0.81}\right) \times \left(\frac{1.52}{HDL}\right)$$

Statistical analysis

The Statistical Packages for Social Sciences SPSS version 17 (SPSS Inc, Chicago, IL) was used for data analysis. Baseline characteristics were presented as mean ± Standard Deviation (SD) for continuous variables; rates and proportions were calculated for categorical data. Receiver-operating characteristic (ROC) curve analyses were performed to determine appropriate cut-off points of VAI in identifying subjects with glucose abnormalities. Differences between groups in univariate analysis were detected by the unpaired Student's t test for continuous variables and by the c2-test and Fisher's exact test (when appropriate) for categorical variables. To show associations with VAI Pearson's correlation coefficients were presented. A P value of <0.05 was considered statistically significant.

Results

A total of 508 subjects aged 17 to 67 years participated in this study. The main characteristics of the study population are presented in Table 1. Ranking the participants based on their glucose tolerance status resulted in 49.6% of the studied subjects had normal glucose tolerance tests (NGT) and 50.4% had abnormal results. Of the patients with abnormal results, 7.9% had impaired fasting glucose (IFG), 9.5% had impaired post-prandial glucose

(IPG), 26% had impaired fasting and post-prandial glucose (IGT), and 7% had type 2-diabetes which was previously unknown. Table 2 and 3 shows the results of these groups.

Table 1: Clinical and metabolic characteristics of the total studied population

Characteristic	Average ± STDEV (min to max)
Number (M to F)	508 (212 to 296)
Age (years)	39.024 ± 12.65 (17 - 67)
Weight (Kilograms)	84.811 ± 19.29 (45 - 136)
Height (meters)	1.64 ± 0.083 (1.46 – 1.86)
BMI (Wt/ht^2)	31.68 ± 7.64 (16.73 – 52.3)
WC (centimeters)	98.47 ± 16.86 (60 – 140)
HDL (mmol/L)	1.216 ± 0.197 (0.518 – 1.994)
Triglyceride (mmol/L)	1.503 ± 0.51 (0.814 – 3.79)
VAI	2.086 ± 0.888 (0.751 – 5.22)
Fasting blood glucose (mg/dl)	102.92 ± 30.9 (67 - 270)
Fasting blood glucose (mmol/L)	5.72 ± 1.72 (3.7 - 15)
Post prandial blood glucose (mg/dl)	145.39 ± 49.72 (94 - 377)
HbA1c (%)	6.012 ± 1.47 (4 – 12.3)
Fasting insulin (microunit/ml)	10.26 ± 8.56 (1 - 39)
HOMA-IR	3.084 + 3.59 (0.19 – 18.44)

At first, we formed a group included all subjects with any form of glucose intolerance or DM and named it subjects with abnormal glucose to compare it to subjects with NGT (table 2). The subjects with abnormal glucose had a higher VAI score compared to NGT subjects (2.5 ± 0.94 versus 1.65 ± 0.56, P = <0.001). Also, all variables indicated insulin resistance were elevated and there were highly significant difference between the two groups (HbA1c, fasting insulin, and HOMA-IR; P = < 0.001). This group was subdivided into subjects with IFG, IPG, IGT, and DM to show the relation between VAI and variable forms of glucose abnormalities (table 3). The VAI scores tend to be very high in subjects diagnosed with DM and IGT in comparison to NGT and IPG subjects (mean ± SD = 2.94 ± 0.94, 2.79 ± 0.96, 1.65 ± 0.56, and 1.72 + 0.54; respectively). The VAI score was moderately high in subjects with IFG in comparison to NGT (2.17 ± 0.64; P = 0.05).

Table 2: Clinical and metabolic characteristics of the healthy subjects in comparison to all patients with abnormal glucose

Characteristic	NGT (49.6%)	Subjects with Abnormal glucose (50.4%)	t	P
Number (M to F)	252 (100 to 152)	256 (116 to 140)		0.849
Age (years)	34.75 ± 11.94 (17—66)	43.23 ± 11.98 (19—67)	4.04	0.000
Weight (Kilograms)	76.23 ± 18.71 (45—130)	93.26 ± 15.92 (65—136)	5.65	0.000
Height (meters)	1.64 ± 0.084 (1.47—1.86)	1.64 ± 0.08 (1.46—1.82)	0.25	0.800
BMI (Wt/ht^2)	28.47 ± 7.263 (16.73—51.4)	34.83 ± 6.66 (21.3—52.3)	5.38	0.000
WC (centimeters)	90.59 ± 16.2 (60—135)	106.22 ± 13.67 (76—140)	6.01	0.000
HDL (mmol/L)	1.27 ± 0.17 (0.88—1.99)	1.16 ± 0.21 (0.52—1.66)	-3.66	0.001
Triglyceride (mmol/L)	1.29 ± 0.37 (0.81—3)	1.71 ± 0.55 (0.85—3.79)	5.05	0.000
VAI	1.65 ± 0.56 (0.76—3.71)	2.513 ± 0.944 (0.75—5.22)	5.91	0.000
Fasting blood glucose (mg/dl)	84.87 ± 8.31 (67—100)	120.7 ± 34.57 (71—270)	8.35	0.000
Fasting blood glucose (mmol/L)	4.71 ± 0.47 (3.7—5.6)	6.71 ± 1.92 (3.9—15)	8.35	0.000

Post prandial blood glucose (mg/dl)	111.44 ± 10.55 (94—140)	174.86 ± 55.27 (110—377)	8.84	0.000
HbA1c (%)	5.05 ± 0.44 (4—6.4)	6.96 ± 1.5 (4.5—12.3)	9.77	0.000
Fasting insulin (microunit/ml)	4.94 ± 2.49 (1—12)	15.5 ± 9.17 (2—39)	8.61	0.000
HOMA-IR	1.05 ± 0.56 (0.19—2.56)	5.1 ± 4.14 (0.44—18.44)	7.91	0.000

We found subjects with abnormal glucose were more likely to have higher VAI than normal glycemic subjects (2.513 ± 0.944 versus 1.65 ± 0.56) and also have higher BMI, WC, and triglycerides (34.83 ± 6.66 versus 28.47 ± 7.263; 106.22 ± 13.67 versus 90.59 ± 16.2; and 1.71 ± 0.55 versus 1.29 ± 0.37, respectively).

Table 3: Clinical and metabolic characteristics of the studied groups

Characteristic	NGT (49.6%)	IFG (7.9%)	IPG (9.5%)	IGT (26%)	DM (7%)	P
Number (M to F)	252 (100 to 152)	40 (24 to 16)	48 (28 to 20)	132 (48 to 84)	36 (16 to 20)	*P1=0.849 P2=0.339 P3=0.254 P4=0.681
Age (years)	34.75 ± 11.94 (17—66)	42.8 ± 12.91 (20—67)	39.25 + 16.65 (19—65)	43.73 ± 10.32 (26—62)	47.22 ± 9.62 (26—57)	P1=0.362 P2=0.92 P3=0.001 P4=0.008
Weight (Kilograms)	76.23 ± 18.71 (45—130)	86.1 ± 12.54 (70—109)	89.42 + 15.68 (65—110)	99.99 ± 15.56 (77.5—136)	81.67 ± 9.33 (66—93)	P1=0.688 P2=0.685 P3=0.000 P4=0.507
Height (meters)	1.64 ± 0.084 (1.47—1.86)	1.66 ± 0.08 (1.54—1.76)	1.67 + 0.09 (1.52—1.82)	1.64 ± 0.081 (1.46—1.8)	1.62 ± 0.083 (1.48—1.76)	P1=0.266 P2=0.475 P3=0.288 P4=1
BMI (Wt/ht^2)	28.47 ± 7.263 (16.73—51.4)	31.47 ± 4.58 (26.5—42.05)	32.23 + 5.7 (23.5—40.86)	37.7 ± 6.69 (27.8—52.3)	31.62 ± 5.67 (21.3—40.6)	P1=0.625 P2=0.984 P3=0.000 P4=0.778
WC (centimeters)	90.59 ± 16.2 (60—135)	100.4 ± 10.44 (86—117)	101.25 + 13.75 (76—120)	111.58 ± 13.47 (92—140)	99.67 ± 10.83 (79—117)	P1=0.963 P2=0.941 P3=0.000 P4=0.906
HDL (mmol/L)	1.27 ± 0.17 (0.88—1.99)	1.13 ± 0.28 (0.52—1.5)	1.2 ± 0.2 (0.91—1.55)	1.15 ± 0.19 (0.86—1.66)	1.18 ± 0.23 (0.91—1.66)	P1=0.114 P2=0.826 P3=0.036 P4=0.615
Triglyceride (mmol/L)	1.29 ± 0.37 (0.81—3)	1.48 ± 0.35 (0.85—2.13)	1.3 ± 0.26 (0.88—1.55)	1.83 ± 0.59 (1.07—3.79)	2.06 ± 0.45 (1.3—2.6)	P1=0.867 P2=0.213 P3=0.000 P4=0.096
VAI	1.65 ± 0.56 (0.76—3.71)	2.17 ± 0.64 (1.47—3.48)	1.72 ± 0.54 (75—2.78)	2.79 ± 0.96 (1.53—5.22)	2.94 ± 0.94 (1.48—4.57)	P1=0.05 P2=0.000 P3=0.000 P4=0.002
Fasting blood glucose (mg/dl)	84.87 ± 8.31 (67—100)	105.8 ± 6.16 (101—119)	93.75 ± 8.85 (71—100)	115.55 ± 10.04 (101—141)	192 ± 40.73 (144—270)	P1=0.000 P2=0.039 P3=0.000 P4=0.000

Fasting blood glucose (mmol/L)	4.71 ± 0.47 (3.7—5.6)	5.88 ± 0.34 (5.6—6.6)	5.2 ± 0.5 (3.9—5.6)	6.42 ± 0.56 (5.6—7.8)	10.7 ± 2.27 (8—15)	P1=0.000 P2=0.039 P3=0.000 P4=0.000
Post prandial blood glucose (mg/dl)	111.44 ± 10.55 (94—140)	130.9 ± 11.73 (110—140)	150.42 ± 18.67 (141—207)	164.43 ± 17.99 (141—201)	294.6 ± 47.44 (248—377)	P1=0.011 P2=0.000 P3=0.000 P4=0.000
HbA1c (%)	5.05 ± 0.44 (4—6.4)	5.63 ± 0.45 (5—6.3)	6.05 ± 0.63 (4.5—6.9)	6.87 ± 0.71 (5.4—8.3)	10 ± 1.08 (8.6—12.3)	P1=0.020 P2=0.000 P3=0.000 P4=0.000
Fasting insulin (microunit/ml)	4.94 ± 2.49 (1—12)	9.7 ± 4.57 (3—17)	6.3 ± 3.96 (2—15)	17.55 ± 7.73 (4—33)	26.7 ± 7.3 (17—39)	P1=0.101 P2=0.629 P3=0.000 P4=0.000
HOMA	1.05 ± 0.56 (0.19—2.56)	2.58 ± 1.33 (0.75—4.84)	1.5 ± 1.02 (0.44—3.73)	5.1 ± 2.44 (1.01—10.71)	12.62 ± 4.13 (7.03—18.44)	P1=0.037 P2=0.370 P3=0.000 P4=0.000

* P1 means comparison of NGT with IFG; P2 means comparison of NGT with IPG; P3 means comparison of NGT with IGT; and P4 means comparison of NGT with DM group.

The VAI was highly positively correlated with fasting plasma glucose, postprandial plasma glucose, fasting plasma insulin, and HOMA (P = < 0.001), but the correlation between HDL and these metabolic parameters were not significant or of smaller magnitude (Table 4). The correlations of these metabolic variables with triglycerides were highly significant.

Table 4: Correlations among Clinical and metabolic characteristics of the studied subjects

Parameters		**Parameters**											
		Wt	**Ht**	**BMI**	**WC**	**HDL**	**Tri**	**VAI**	**Fs**	**PPs**	**Hb**	**In**	**Homa**
Age	**r**	0.34**	-0.07	0.36	0.45	-0.1	0.19*	0.2	0.32	0.3	0.3	0.3	0.25
	P	0.000	0.439	0.000	0.000	0.248	0.033	0.022	0.000	0.001	0.000	0.002	0.004
Weight	**r**	1	0.11	0.9	0.93	-0.16	0.41	0.474	0.24	0.23	0.284	0.37	0.26
	P	1	0.206	0.000	0.000	0.07	0.000	0.000	0.01	0.009	0.001	0.000	0.003
Height	**r**		1	-0.32	-0.124	-0.11	0.11	-0.156	-0.13	-0.1	-0.12	-0.08	-0.11
	P		1	0.000	0.163	0.234	0.22	0.081	0.14	0.282	0.162	0.354	0.21
BMI	**r**			1	0.934	-0.118	0.346	0.521	0.3	0.274	0.335	0.394	0.312
	P			1	0.000	0.187	0.000	0.000	0.001	0.002	0.000	0.000	0.000
WC	**r**				1	-0.176	0.358	0.517	0.3	0.295	0.352	0.408	0.329
	P				1	0.048	0.000	0.000	0.000	0.001	0.000	0.000	0.000
HDL	**r**					1	-	-0.42	-0.11	-	-	-	-0.18

				0.09			0.12	0.13	0.23	
	P		1	0.318	0.000	0.21	0.16	0.144	0.008	0.038
Trigly	**r**			1	0.822	0.42	0.471	0.494	0.662	0.577
	P			1	0.000	0.000	0.000	0.000	0.000	0.000
VAI	**r**				1	0.548	0.448	0.525	0.739	0.645
	P				1	0.000	0.000	0.000	0.000	0.000
F.Bl.Gl.	**r**					0.934	0.936	0.734	0.889	
	P					0.000	0.000	0.000	0.000	
PP.Bl.Gl.	**r**					1	0.952	0.734	0.883	
	P					1	0.000	0.000	0.000	
HbA1c	**r**						1	0.761	0.873	
	P						1	0.000	0.000	
F.Insulin	**r**							1	0.937	
	P							1	0.000	

* Correlation is significant at the 0.05 level; ** Correlation is significant at the 0.01 level

Table 5: VAI Cut-off values predicting the glucose abnormalities

	VAI versus FBS		**VAI versus PP-BS**		**VAI versus FBS-PPBS**		**VAI versus DM**		**VAI versus any glucose abnormalities**	
Cut-off point	1.744	2.5724	1.744	2.5	1.8234	2.666	1.8898	2.9	1.7677	2.5579
Area under the curve	0.846	0.5	0.815	0.5	0.881	0.5	0.889	0.556	0.811	0.5
P value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.004	0.004	0.000	0.000
Sensitivity	84.6%	50%	81.5%	50%	88.1%	50%	88.9%	55.6%	81.1%	50%
Specificity	61.3%	94.7%	60.3%	89%	62.4%	95.3%	53.4%	86.4%	60.8%	93.9%
Positive predictive value	92.3.1%	90.4%	90%	82%	92.6%	91.4%	93.8%	83.6%	89.9%	89%
Negative predictive value	42%	65.5%	42.6%	64%	41.5%	65.6%	37.5%	61%	42.9%	65%

For example, consider cutoff 1.744 for detection of abnormal fasting glucose. Using this criterion, assay results of higher values are classified as abnormal, which leads to a sensitivity of 0.846 and 1-specificity of 0.387 Thus, approximately 84.6% of all samples with high fasting glucose samples would be correctly identified as such, and 38.7% of all samples with normal fasting glucose would be incorrectly identified as positive.

The distance from the top left corner of the ROC curve of VAI for diagnosis of IFG are depicted in Figure 1. In all studied subjects, VAI ranged from 0.751 to 5.22. The cut-off 1.744 is the best threshold for abnormal fasting glucose; it minimized the distance on the ROC curve (sensitivity = 84.6%, specificity = 61.3%, area under the curve = 0.846). Using more distant one on the curve will improve the specificity. For example, area 0.5 will correspond to cut-off value 2.5724 with less sensitivity (50%) but higher specificity (94.7%). The others cut-off values for IPG and IGT are shown in table 5. In diabetic individuals, the optimal cut-off of VAI for diabetes diagnosis in this group was 1.8898 (sensitivity = 88.9%, specificity = 53.4%, area under the curve = 0.889). Any values above this one will improve the specificity at the expense of the sensitivity. For example, cut-off 2.9 will be more specific less sensitive (sensitivity = 55.6%, specificity = 86.4%, area under the curve = 0.556). Finally, from the ROC curve in figure 5, we can use two cut-off values of VAI for any glucose abnormalities. The first one with high sensitivity (81.1%) and acceptable specificity (60.8%) for early detection of glucose abnormalities is 1.7677. The other one with less sensitivity (50%) and very high specificity (93.9%) for very high suspicion of any form glucose abnormalities or even DM is 2.5579.

According to the optimal cut-off of VAI suggested by us, we subdivided the subjects with NGT into three groups: NGT subjects with VAI < 1.7, NGT subjects with VAI $\geq$ 1.7, and NGT subjects with VAI > 2.5. We found significant differences between NGT with VAI < 1.7 and NGT with VAI $\geq$ 1.7 in fasting insulin level and HOMA-IR (P = 0.004) (table 6). These results mean that it may be early detector of insulin resistance before actual glucose intolerance in subjects with NGT and high VAI. This early detection may prevent the progression of the case and the associated complication by early reduction of weight and modification of life-styles.

Table 6: Clinical and metabolic characteristics of the NGT group after subdividing it according to the suggested VAI cut-off values

Characteristic	NGT (63.5%) With VAI < 1.7	NGT (36.5%) With VAI $\geq$ 1.7	NGT (8%) With VAI $\geq$ 2.5	P
Number (M to F)	160 (88 to 72)	92 (20 to 72)	20 (8 to 12)	
Age (years)	33.5 $\pm$ 13.07	36.9 $\pm$ 9.6	36.4 $\pm$ 8.3	* P1=0.003 P2=0.212 P3=0.456
Weight (Kilograms)	70.7 $\pm$ 17.2	85.9 $\pm$ 17.6	88.6 $\pm$ 22.4	P1=0.003 P2=0.152 P3=0.742
Height (meters)	1.65 $\pm$ 0.08	1.616 $\pm$ 0.09	1.67 $\pm$ 0.14	P1=0.117 P2=0.981 P3=0.062
BMI (Wt/ht^2)	25.9 $\pm$ 6.3	32.9 $\pm$ 6.8	31.02 $\pm$ 4.19	P1=0.000 P2=0.06 P3=0.133
WC (centimeters)	84.4 $\pm$ 14.4	101.4 $\pm$ 13.5	101.2 $\pm$ 12.03	P1=0.000 P2=0.065 P3=0.529
HDL (mmol/L)	1.31 $\pm$ 0.166	1.2 $\pm$ 0.155	1.08 $\pm$ 0.16	P1=0.079 P2=0.042 P3=0.486
Triglyceride (mmol/L)	1.15 $\pm$ 0.21	1.55 $\pm$ 0.45	1.916 $\pm$ 0.74	P1=0.000 P2=0.089 P3=0.071
VAI	1.313 $\pm$ 0.261	2.243 $\pm$ 0.446	2.88 $\pm$ 0.51	P1=0.000 P2=0.002 P3=0.046
Fasting blood glucose (mg/dl)	83.9 $\pm$ 8.26	86.5 $\pm$ 8.3	84.4 $\pm$ 8.23	P1=0.164 P2=0.776 P3=0.541
Post prandial blood glucose (mg/dl)	113.1 $\pm$ 8.7	119.6 $\pm$ 12.3	113.6 $\pm$ 13.4	P1=0.75 P2=0.953

				P3=0.734
HbA1c (%)	4.98 ± 0.39	5.15 ± 0.51	4.9 ± 0.37	P1=0.556 P2=0.805 P3=0.938
Fasting insulin (microunit/ml)	4.3 ± 2.13	6.04 ± 2.74	7.8 ± 3.03	P1=0.004 P2=0.099 P3=0.091
HOMA-IR	0.907 ± 0.485	1.29 ± 0.59	1.64 ± 0.65	P1=0.004 P2=0.169 P3=0.129

* P1 means comparison of NGT with VAI < 1.7 group versus NGT with VAI ≥ 1.7 group; P2 means comparison of NGT with VAI < 1.7 group versus NGT with VAI > 2.5 group; P3 means comparison of NGT with VAI ≥ 1.7 group versus NGT with VAI > 2.5 group.

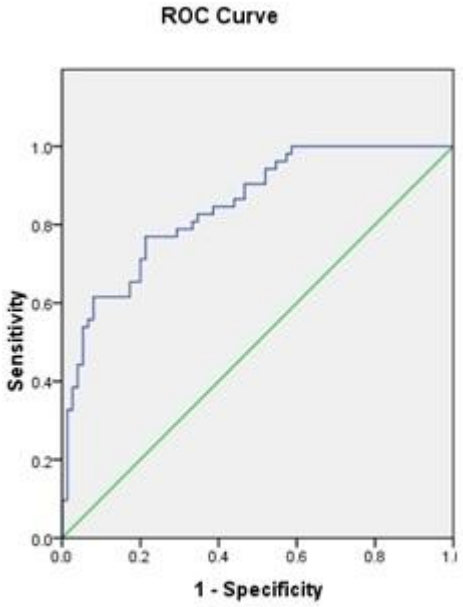

Figure 1: The ROC curve for the visceral adiposity index to detect glucose intolerance in fasting glucose.

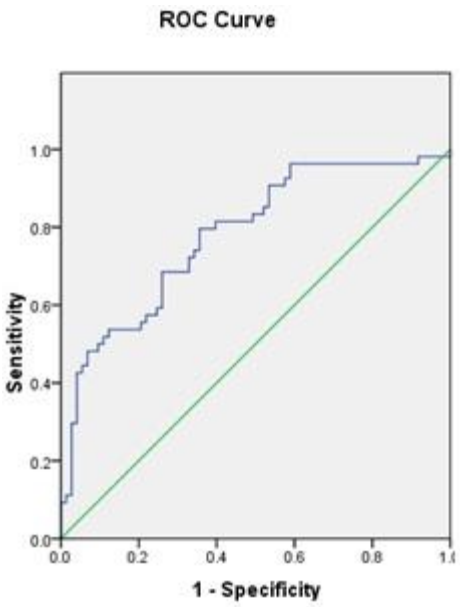

Figure 2: The ROC curve for the visceral adiposity index to detect glucose intolerance in post-prandial glucose.

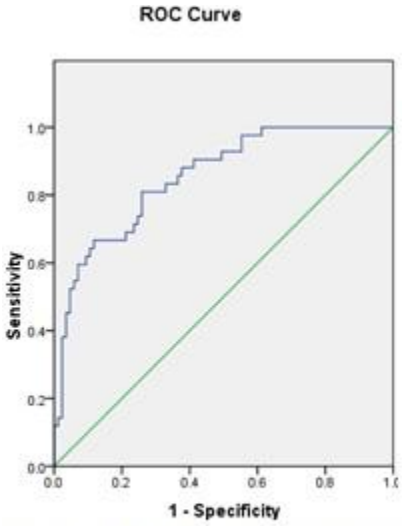

Figure 3: The ROC curve for the visceral adiposity index to detect glucose intolerance in subjects with IGT.

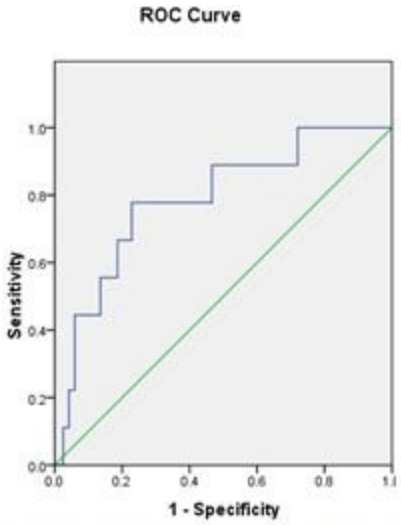

Figure4: The ROC curve for the visceral adiposity index to detect glucose intolerance in subjects with DM.

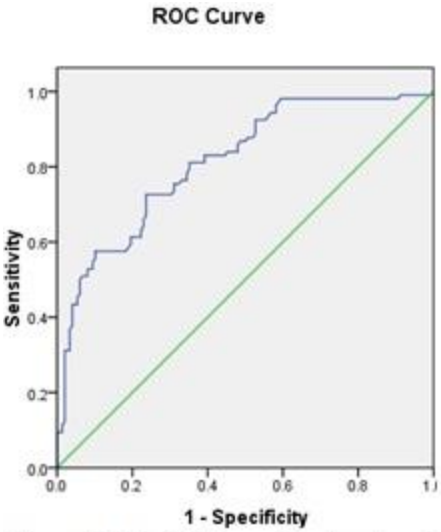

Figure 5: The ROC curve for the visceral adiposity index to detect glucose abnormalities in the total studied

Discussion

Although the metabolic dysfunctions that are traditionally related to obesity are determined by several factors, it should be emphasized that two of them may be particularly important. *First*, the regional distribution and metabolism of adipose tissue are crucial factors that determine the existence/absence of a dysmetabolic state. *Second*, differentiation of preadipocytes into mature adipocytes is a key process contributing to the biology of adipose tissue. Therefore, if the differentiation of preadipocytes is hampered in the context of a positive energy balance, it will promote, at some stage, the formation of larger, dysfunctional adipocytes. As a result, these hypertrophied adipocytes with large triglyceride stores will have a high lipolytic rate; they will produce more leptin

and less adiponectin, two important adipokines that influence inflammation and overall carbohydrate and lipid metabolism. These processes also contribute to systemic inflammation and insulin resistance [27]. Moreover, it has been calculated that the onset of type 2 diabetes occurs approximately 10 years before clinical diagnosis [28]. Retinopathy and proteinuria are present at the time of diagnosis in as many as 29% and 37% of these patients, respectively [29]. Early diagnosis, anticipating treatment, could delay or even prevent the onset of the debilitating complications of the disease [30]. Therefore, an appropriate screening for diabetes mellitus should be performed in all patients risky for it, so we accomplished our study.

In our cross sectional study, we estimated the prevalence of glucose intolerance in randomly selected sample of apparent healthy subjects. We found that 50.4% of subjects affected by glucose intolerance or even DM (22.8% male and 27.6% female). This percentage was distributed as follow: 7.9% IFG, 9.5% IPG, 26% IGT, and 7% DM. Hayashi et al. [4] found that the overall incidence of IGT was 44.5% in Japanese Americans with normal glucose tolerance at entry during the 10- to 11-year follow-up period. This seemingly high rate might not be unexpected in the third-generation of their study because they previously reported that in the second-generation of Japanese Americans IGT incidence was 54% for women and 37% for men over the 5-year follow-up interval [31]. These results agree with our percentage of 43.4% of impaired glucose tolerance in large randomly sample but the difference in that they selected NGT subjects to detect the percentage of IGT during a known follow up period.

All subjects with abnormal glucose had higher anthropometric measures in comparison to subjects with NGT (weight = 93.26 $\pm$ 15.92 in comparison to 76.23 $\pm$ 18.71; BMI = 34.83 $\pm$ 6.66 in comparison to 28.47 $\pm$ 7.26; and WC = 106.22 $\pm$ 13.67 in comparison to 90.59 $\pm$ 16.2, $P < 0.001$ for all). Also this group had higher triglycerides, Fasting insulin level, and HOMA-IR score when compared to NGT group (triglycerides = 1.71 $\pm$ 0.55 in comparison to 1.29 $\pm$ 0.37; Fasting insulin level = 15.5 + 9.17 in comparison to 4.94 $\pm$ 2.49; and HOMA-IR = 1.05 $\pm$ 0.56 in comparison to 5.1 $\pm$ 4.14, $P < 0.001$ for all). A few previous studies have shown that insulin resistance and abnormal insulin secretion are both risk factors for the development of IGT [32; 33; 4]. Haffner et al. [33] showed in the San Antonio Heart Study that decreased insulin secretion, assessed by low insulinogenic index using OGTT data, and increased insulin resistance, assessed by fasting serum insulin, and predicted the development of IGT. Hayashi et al. [4] showed in an analysis of prospective OGTT data from the Japanese American Community Diabetes Study that both HOMA-IR and insulinogenic index were independent risk factors for incident IGT, even after adjusting for visceral adiposity as measured by computed tomography. Faerch et al. [32] reported that prospective data from the Inter 99 Study showed reduced insulin secretion was present before the development of IFG and low insulin sensitivity was present before the development of IGT. However, there was no adjustment for BMI, insulin secretion, insulin sensitivity and other factors. Onishi Y. et al. [34] had provided evidence that lower insulinogenic index or HOMA-beta and higher HOMA-IR are significant risk factors for the future development of prediabetes among Japanese with NGT in prospective assessed by using only a fasting measurement, to incident IGT and/or IFG study.

Subjects with abnormal glucose had higher VAI than those with NGT (2.513 $\pm$ 0.944 versus 1.65 $\pm$ 0.56; $P < 0.001$). Also this group had higher weight, BMI, WC, and triglycerides than NGT subjects (93 $\pm$ 15.92 versus 76.23 $\pm$ 18.71; 34.83 $\pm$ 6.66 versus 28.47 $\pm$ 7.26; 106.22 $\pm$ 13.67 versus 90.59 $\pm$ 16.2; and 1.71 $\pm$ 0.55 vesus1.29 $\pm$ 0.37, respectively; P = < 0.001 for all). We will note that some subjects in the NGT group had high BMI and WC (overweight and obese). And also, by subdividing the subjects with abnormal glucose into IFG, IPG, IGT, and those with DM, we found that no significant difference between the subjects with NGT and IFG in weight, BMI, WC, and triglycerides (P = 0.688, P = 0.625, 0.963, and P = 0.867, respectively). Also, no significant difference between the subjects with NGT and IPG in weight, BMI, WC, and triglycerides (P = 0.685, P = 0.984, 0.941, and P = 0.213, respectively). And also, no significant difference between the subjects with NGT and DM in weight, BMI, WC, and triglycerides (P = 0.507, P = 0.78, 0.906, and P = 0.096, respectively). This means that weight, BMI, WC, and triglycerides alone is not good to predict the risk of glucose intolerance or DM. By comparison of VAI of NGT subjects to IFG, IPD, IGT, and DM subjects we found very high significant difference between them (1.65 $\pm$ 0.56 versus 2.17 $\pm$ 0.64; 1.72 $\pm$ 0.54; 2.94 $\pm$ 0.94; and 2.94 $\pm$ 0.94, respectively; p = 0.05, <0.001, < 0.001, 0.002, respectively). We found also the increase of VAI was positively associated with fasting plasma glucose, postprandial glucose, fasting plasma insulin, and HOMA-IR (diabetes risk) with clear dose–response relationships. Compared to other body fatness indices, VAI was observed to be better in identifying the risk of glucose intolerance and diabetes than weight, BMI, WC and triglycerides alone. We also noted that the VAI increases more in patients with IGT (2.79 $\pm$ 0.96) than those with IFG (2.17 $\pm$ 0.64) only or IPG (1.72 $\pm$ 0.54) and in those with DM (2.94 $\pm$ 0.94) than those with IGT (2.79 $\pm$ 0.96).

The strong relationship between obesity and diabetes has been reported by many studies. Some researchers even use the term “diabesity” to describe their close associations [35]. Yang SL et al. [36] found that people with large WC has 3.79-fold risk of diabetes than those whose WC were normal. Yang SL et al. [36] reported that the prevalence

of diabetes in overweight group was 43% higher than that of normal people, and about 70% diabetes patients whose BMI were more than 25 kg/m2. Clinical trials showed that even 5% weight loss was sufficient to prevent most obese subjects from impaired glucose tolerance and developing diabetes [37], especially for abdominal obesity. The main harm caused by obesity is visceral adipose accumulation [38]. He HB et al. [39] found that among men with normal WC, the incidence of metabolic syndrome (MS) in visceral obese people was significantly higher than that of normal group. Fox et al. [40] reported that both SAT and VAT were associated with increased odds ratio (OR) of MS. In women, the OR for VAT (OR = 4.7) was stronger than that for SAT (OR = 3.0); similar difference was shown for men (OR for VAT = 4.2; OR for SAT = 2.5). The molecular mechanism underlying this is unclear yet. It has been suggested that compared with subcutaneous fat, high visceral fat produces more free fatty acid, thus will increase the risk of IR and diabetes [40-41]. Fontana et al. [38] reported that visceral adipose can secrete a large number of inflammatory cytokines, cells and adipokines, which may play important roles in the occurrence of IR and diabetes. Liu J. et al. [42] observed that visfatin, an adipokine which mainly produced by visceral adipose had the insulin-like effect, and has been proved to aggravate IR. Moreover, as Masuzaki et al. [43] found in transgenic animals experiments, when 11 beta hydroxysteroid dehydrogenase type 1 (11βHSD-1) excessively expressed in fat cells, it would cause visceral adiposity and a series of metabolic disorders, which indicates that 11βHSD- 1 enzyme may have the same molecular basis with visceral obesity and metabolic disorders. However, the mechanism between visceral adiposity and metabolic disorders still needs to be further elucidated.

Recently reported by Al-Daghri et al. [44], VAI was negatively related with adiponectin value, this was the first report for the direct relations of VAI with adipose tissue secretion. Some researchers have proved that VAI could be used to predictive individual risk of IR, MS, acromegaly, cardiovascular disease and diabetes [14; 45; 46; 47]. Chen et al. [48] also indicated that VAI is a useful surrogate marker to identify the risk of diabetes; individuals with high VAI were accompanied with increased risk of metabolic disorders and diabetes. The risk of getting diabetes at the highest VAI group was 2.55 folds higher as compared to the lowest VAI group.

We demonstrated that the risk of glucose abnormalities increased with rising VAI values. The optimal cut-off point of VAI for the diagnosis of any glucose abnormalities in our studied subjects was estimated to be 1.77. Different cut-off points might be selected to optimize sensitivity versus specificity depending on the purpose. A screening test requires high sensitivity and moderate specificity, so the cut-off 1.77 is the preferred one (81.1% sensitivity and 60.8% specificity), whereas a diagnostic test requires a much higher specificity, so the cut-off 2.56 is the best (50% sensitivity and 93.9% specificity).

Measurement of visceral adiposity during a routine clinical follow up might improve the performance of screening for glucose intolerance. Moreover, identifying subjects at high risk for IGT and DM because of elevated visceral adiposity could lead to either earlier screening or earlier dietary and lifestyle modifications. Clearly, this opens up a new avenue for research. Long period of follow up was needed to elucidate the relation between these cut-off values and the changes in glucose tolerance, this can be considered as a limitation of our study and is to be addressed in future work.

Conclusion

In conclusion, this work presents a simple and reliable tool for expecting glucose intolerance. We showed that risk for glucose intolerance increases with increasing VAI. The optimal cut-off point of VAI for glucose intolerance screening is 1.7677 and 2.5579 for glucose intolerance diagnosis in non-diabetics subjects. Further prospective studies are warranted to elucidate the performance of these cut-offs in predicting incident diabetes or its vascular complications and its role in prevention of the disease by maintaining it below this cut-off value in our country.

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Conflict of interest The authors who have taken part in this study declare that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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