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Original Article

EXPLORING VISCERAL ADIPOSITY INDEX AS A PREDICTOR OF VISCERAL ADIPOSITY DYSFUNCTION AND EVALUATING ITS PERFORMANCE IN PREDICTING HEPATIC INSULIN RESISTANCE IN INDIAN TYPE 2 DIABETICS

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ABSTRACT

Objective: Visceral adiposity index (VAI) is a simple clinical algorithm developed as a surrogate marker for characterizing visceral adiposity dysfunction (VAD). This study aimed to explore an optimal VAI cut off value for predicting VAD as reflected quantitatively by magnetic resonance imaging (MRI) and to evaluate its merit in predicting the severity of the cardiometabolic risk (CMR) in type 2 diabetic patients of India.

Methods: Data was collected from 81 diabetics and 48 healthy participants, who underwent metabolic assessments. VAI derived using BMI, waist circumference (WC), triglycerides (TG) and HDLc, was studied against visceral fat area measuring ≥130 cm^2 by MRI as it is associated with higher CMR through raised VAD. Optimal VAI cutoff was determined using the area under the receiver operator characteristic curve (AUROC). Diabetic participants were divided into VAD absent, and VAD present groups based on derived VAI cut off to study associated difference in their metabolic profile.

Results: Diabetic group had significantly deranged metabolic profile compared to the healthy control group. Most of the diabetic group participants had a visceral fat area between 101 and 200 cm^2. From the ROC curve analysis (AUROC = 0.761), VAI cut-off of 2.0 predicted VAD with sensitivity and specificity of 73.21% and 71.23% respectively. Diabetic participants with VAI values more than 2, had significantly ($p<0.05$) higher WC, visceral fat, fasting insulin, HOMA-IR (Homeostatic model assessment for insulin resistance), TG ($p<0.01$), non-HDLc and apolipoprotein B/A1 ratio values. Age adjusted partial correlation analysis showed a significant ($p<0.01$) positive correlation between VAI and HOMA-IR.

Conclusion: VAI was useful in predicting VAD and identifying the severity of CMR within type 2 diabetics. VAI can replace imaging procedures with the advantages of reduced economic burden and can be used as screening tool for surveillance of CMR in Indian population.

Keywords: Cardiometabolic risk, Magnetic resonance imaging, Receiver operating curve

INTRODUCTION

Metabolic diseases such as diabetes and cardiovascular disease (CVD) are extremely prevalent in obese patients than among normal-weight individuals. Obesity is a remarkably heterogeneous condition, and not every obese patient is characterized by co-morbidities. In this regard, increased accumulation of visceral fat leading to visceral adipose dysfunction (VAD) is a major link with a cluster of diabetogenic, atherogenic, prothrombic and pro-inflammatory metabolic abnormalities [1]. VAD causes release of various cytokines and hormones, such as adiponectin, leptin, tumor necrosis factor, resistin and interleukin 6. Due to its anatomic location and peculiar metabolic, hyperlipolytic activity, the expanded visceral adipose depot is considered to be an independent component of cardiometabolic risk (CMR) [1]. It is well established that type 2 diabetes significantly increases the risk of CVD and that merely treating hyperglycemia do not eliminate all the excess cardiovascular risk [2]. Gastaldelli *et al.* explored metabolic effects of visceral fat accumulation in type 2 diabetes using two specialized techniques viz. magnetic resonance imaging (MRI) and euglycemic insulin clamp and reported that visceral fat had a significant negative impact over glycemic control through a decrease in peripheral insulin sensitivity and an enhancement of gluconeogenesis. Further, while ethnicity, gender, age, duration of diabetes, and obesity (as body mass index) together explained only 25% of HbA1c variability; the inclusion of visceral fat in the model raised the explicable HbA1c variability to 45%. According to this model, HbA1c is predicted to be 0.8% higher for each 50-cm^2 increment in the visceral fat area. Thus, an accurate measurement of visceral fat is an important part of clinical phenotyping and has rather direct consequences for the metabolic control of patients with type 2 diabetes [3]. Since then, with advancement in imaging techniques such as computed tomography (CT) and MRI, it is clearly demonstrated that obese diabetic patients with raised metabolic abnormalities like high insulin resistance and atherogenic dyslipidemia associated with an excess visceral adiposity are predisposed to higher CVD risk [4].

India is a global leader in diabetes, currently with second largest pool of diabetes in the world. Asian Indian phenotype is uniquely predisposed to develop diabetes and represents the population with increased abdominal adiposity (especially visceral adiposity) predisposing them to higher CMR compared to Caucasians at the same levels of BMI [5]. Excess of fat in the abdominal region is reported to be a better predictor of risk factors (dyslipidemia, glucose intolerance, and hyperinsulinemia) than the total amount of adipose tissue [6]. Indian diabetes federation (IDF) recommends CT and MRI for assessing visceral fat accumulation, where MRI is considered to be the gold standard in estimating visceral fat values non-invasively [7,8]. The association between CMR factors and visceral fat values measured using these techniques is stronger than the associations observed with waist to hip ratio and waist circumference [6].

Using CT and MRI techniques, diagnostic thresholds have been established. Presently, the visceral fat threshold is 100 cm^2 below which disturbances of glucose, insulin and lipid metabolism are uncommon. Secondly, a level of 130 cm^2 often detects the metabolic abnormalities representing an increased risk group [9-11].

Although CT or MRI is precise, they have certain limitations. CT imaging exposes the subject to ionizing radiation while MRI is not done routinely in clinical practice as the setup is not available at all centers and further high cost involved in scan acquisition, and analysis restricts its use in research setting. However, MRI is a safe, accurate and precise imaging modality for measuring visceral

adipose tissue, making it a favorable alternative to CT for quantification of visceral fat values [12].

Recently, to identify a routinely applicable indicator of VAD having higher sensitivity and specificity than classical parameters (such as waist circumference, BMI and lipids), Amato *et al.* came up with visceral adiposity index (VAI). It is a gender-specific mathematical index based on simple anthropometric [BMI and waist circumference (WC)] and metabolic [triglycerides (TG) and HDLc] parameters. It is a surrogate marker of adipose tissue function and distribution, independently linked to insulin sensitivity and CMR in the general population [13-15].

Although VAI was modeled in Caucasian population, several studies have been carried out in different races (Chinese, Sicilian, Japanese and Caucasians) to explore and validate VAI cut offs in determining metabolic risk [16, 17]. To our knowledge, no such study is done in context to the Indian population. Therefore, the aim of this present study was to evaluate whether VAI could become a surrogate marker for abdominal MRI scanning and predict the severity of metabolic abnormalities and insulin resistance in Indian type 2 diabetic subjects.

MATERIALS AND METHODS

Participants

We analysed data from participants recruited for human metabolic studies from primary and secondary care hospitals. For the study, all participants gave written informed consent, and ethical approval was obtained from the respective local ethics committee. Data was obtained for healthy controls and individuals with diabetes being overweight/obese (BMI 23-35 kg/m^2), with a waist circumference ≥80 cm in females and≥90 cm in males . For diabetes group, the participants selected were either newly diagnosed or diagnosed case of diabetes, not on any antidyslipidemic medications.

We excluded data for participants with a history of type 1 diabetes mellitus, pregnancy, any significant history of endocrine, cardiovascular, renal or hepatic disease and standard MR contraindications. Similarly, data for other causes of chronic liver disease were excluded by taking a careful alcohol and drug history and performing hepatitis serology. Moreover, data for participants with alcohol intake>20 ml/day ethanol and any individuals with a history of alcohol excess were not considered.

Anthropometric assessments

BMI was calculated in kg/m^2; waist circumference was measured midway between the lower rib margin and the iliac crest.

Biochemical assessments

Biochemical assessments included estimation of glycemic parameters (fasting glucose, fasting insulin, glycosylated hemoglobin) and lipid parameters (total cholesterol, TG, LDLc, HDLc, non-HDLc, apolipoprotein B, apolipoprotein A1). Routine laboratory markers were measured from venous blood samples using standard methods in the central research laboratory.

Estimation of abdominal fat by MRI

Abdominal fat (visceral and subcutaneous) measurement was done by using single slice axial measurement at the Level of L4-L5 using 3-Tesla MRI. The images were converted into files compatible with commercial image analysis software (SliceOmatic). Abdominal fat segmentation was done based on intensity histogram. The fat segment was further divided into subcutaneous and visceral compartments by drawing the contours. The visceral adipose tissue was then quantified. Visceral fat content (cm^2) was quantified but also coded ordinal as no VAD (<130 cm^2) or present (≥130 cm ^{2}). Between visceral fat area of 100 cm^2 and 130 cm^2, the latter was chosen as a representative of further cardio-metabolic disturbances in type 2 diabetic patients.

Calculation

VAI score was calculated using the following sex-specific equations, where TG levels expressed in mmol/l and HDLc levels expressed in mmol/l [13]:

Males: VAI = (WC/39.68+(1.88 × BMI)) X (TG/1.03) X (1.31/HDL)

Females: VAI = (WC/36.58+(1.89 × BMI)) X (TG/0.81) X (1.52/HDL)

Statistical analysis

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL) software. Data is presented as mean±SD for continuous variables following a normal distribution, median (interquartile range) for non-normally distributed data and as proportions for categorical variables. To assess the ability of a variable to discriminate between patients with and without VAD, receiver operator characteristic (ROC) curves were constructed for VAI. In addition, for VAI, a number of other diagnostic statistics such as sensitivity, specificity, positive likelihood ratio and negative likelihood ratio at various cut-points were measured. Statistical comparisons of patients with and without VAD were taken for all demographic variables, unpaired t-test or Mann–Whitney U test was used for continuous variables, depending on whether relevant distributional assumptions were met. Linear regression analysis was performed to evaluate the merit of VAI cut point in predicting hepatic insulin resistance. A two-tailed P value<0.05 was considered statistically significant.

RESULTS

Characteristics of the participants

Clinical, biochemical and anthropometric characteristics of the participants are given in table 1. Participants were subdivided into two groups, healthy controls (35 males and 13 females) and overweight/obese type 2 diabetics (46 males and 35 females).

Table 1: Baseline, clinical, anthropometric and biochemical characteristics of participants

Parameters	Controls N = 48 (M: F 35:13)	Diabetics N = 81 (M: F 46:35)	P-value
Age (years)	34.5 (31, 41.5)	52.0 (45.5, 57)	<0.01
BMI (Kg/m^2)	21.8 (20.3, 22.6)	27.5 (25.4, 30.5)	<0.01
Waist circumference (cm)	80.6 (6.2)	97.5 (9.4)	<0.01
Visceral fat (cm^2)	70.2 (50.3)	148.6 (50)	<0.01
Fasting glucose (mg/dl)	93.9 (84.8, 108.6)	132.1 (105.8, 172.7)	<0.01
HbA1C (%)	5.5 (5.2, 5.7)	7.4 (6.5, 8.5)	<0.01
Fasting insulin (µU/ml)	7.3 (4.3, 10.7)	17.3 (10.2, 40.2)	<0.01
HOMA-IR	1.67 (0.94, 2.6)	5.4 (2.61, 14.9)	<0.01
Total cholesterol (mg/dl)	163 (38.50)	195.4 (40.5)	<0.01
TG (mg/dl)	81.2 (60.6, 100.6)	177.2 (114.3, 242.6)	<0.01
LDLc (mg/dl)	98.5 (30.3)	108.7 (29.8)	0.067
HDLc (mg/dl)	41 (33.9, 46.5)	40.8 (35.4, 47.3)	0.886
Non-HDLc (mg/dl)	120.9 (35.0)	152.9 (39.9)	<0.01
Apolipoprotein B (mg/dl)	75.1 (55, 99.6)	83.6 (69.6, 107.8)	<0.05
Apolipoprotein A1 (mg/dl)	118.3 (29.7)	132.6 (23.4)	<0.05
Apolipoprotein B/A1 ratio	0.70 (0.49, 0.86)	0.62 (0.53, 0.85)	0.918
Visceral adiposity index (VAI)	1.13 (0.87, 1.8)	3.1 (1.7, 4.5)	<0.01

Data distributed normally are shown as mean (SD), whereas non-normally distributed data are shown as median (25% percentile, 75% percentile). Continuous variable compared using the unpaired t-tests or Mann-Whitney U tests depending on whether data met the relevant distributional assumptions.

Participants in the diabetes group had significantly higher BMI and waist circumference than the healthy controls. Pathophysiologically, diabetes group demonstrated higher fasting glucose and fasting insulin levels. Consecutively, they were significantly insulin resistant with HOMA-IR of 5.4 (IQR = 2.61, 14.9) in the diabetes group vs 1.67 (IQR = 0.94, 2.6) in healthy controls. In addition to being overweight/obese and insulin resistant, participants in the diabetes group demonstrated multiple CMR factors with significantly high TG, i.e. 177.2 mg/dl (IQR = 114.3, 242.6) vs 81.2 mg/dl (IQR = 60.6, 100.6) in healthy controls, total cholesterol concentration, i.e. 195.4 mg/dl (SD = 40.5) vs 163 mg/dl (SD = 38.50) in healthy controls and non-HDLc, i.e. 152.9 mg/dl (SD = 39.9) vs 120.9 mg/dl (SD = 35.0) in the healthy control group (table 1). Dyslipidemic diabetes group also showed significant deranged lipoprotein levels with higher apolipoprotein B value of 83.6 mg/dl (IQR = 69.6, 107.8) vs 75.1 mg/dl (IQR = 55, 99.6) in the control group.

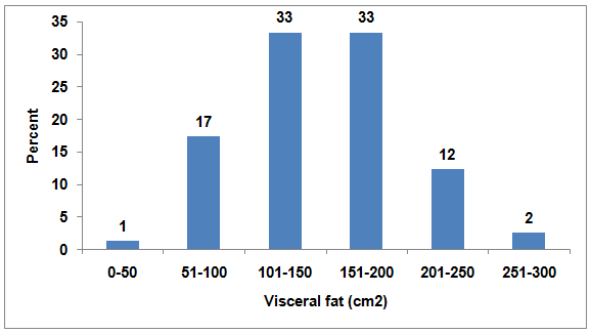

Fig. 1: Distribution of visceral fat (cm²) in diabetes group

The mean visceral fat value was significantly (p<0.001) lower in the healthy control group (70.2±50.3 cm²) as compared to the diabetes group (148.6±50 cm²). The distribution of visceral fat within the diabetes group is shown in fig. 1, which clearly indicates the predominance of high visceral fat among diabetics. Over 80% of the participants in diabetes group had visceral fat>100 cm². Thus, visceral fat cut-off of 130 cm² was chosen to explore the VAI value indicative of severity of metabolic disturbances (VAD) within diabetics predisposing them to higher CMR.

In concurrence with the above observations, participants in the diabetes group had significantly higher VAI, i.e. 3.1 (IQR = 1.7, 4.5) vs 1.13 (IQR = 0.87, 1.8) than the healthy controls.

ROC curve and cut off determining VAD

ROC curves were constructed and an area under the ROC curve (AUROC) with a measure of visceral fat area ≥130 cm² on MRI (fig. 2) representing higher CMR was estimated. VAI could discriminate participants with and without VAD. The AUROC for VAI was 0.761 at 95% CI 0.678 to 0.844.

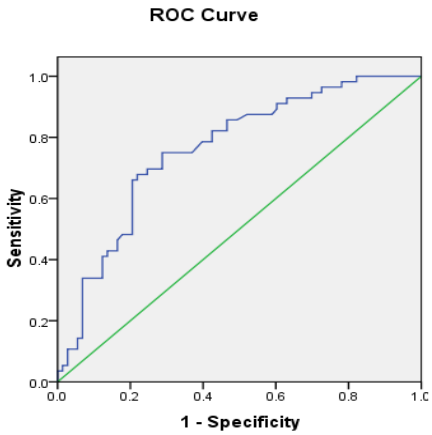

Fig. 2: Receiver operating characteristics (ROC) analysis of VAI to predict the absence or presence of VAD as defined by visceral fat value of ≥130 cm² on MRI

Table 2 gives the sensitivity, specificity, positive likelihood ratios and negative likelihood ratios for the range of 0.25 unit intervals for VAI. The optimal cutoff point to predict visceral adiposity was 2.0, which yielded a sensitivity of 73.21% with a negative likelihood ratio of 0.38 and specificity of 71.23% with a positive likelihood ratio of 2.55.

Table 2: Diagnostic accuracy of VAI at various cut points

VAI values	Se	Sp	+LHR	-LHR	PPV	NPV
≥ 0.50	100	2.74	1.03	0	44.09	100
≥ 0.75	100	15.07	1.18	0	47.46	100
≥ 1.00	94.64	30.14	1.35	0.18	50.96	88
≥ 1.25	91.07	38.36	1.48	0.23	53.12	84.85
≥ 1.50	85.71	50.68	1.74	0.28	57.14	82.22
≥ 1.75	78.57	60.27	1.98	0.36	60.27	78.57
≥ 2.00	73.21	71.23	2.55	0.38	66.13	77.61
≥ 2.25	69.64	75.34	2.82	0.4	68.42	76.39
≥ 2.50	66.07	79.45	3.22	0.43	71.15	75.32
≥ 2.75	58.93	79.45	2.87	0.52	68.75	71.6
≥ 3.00	48.21	79.45	2.35	0.65	64.29	66.67
≥ 3.25	42.86	83.56	2.61	0.68	66.67	65.59
≥ 3.50	42.86	86.3	3.13	0.66	70.59	66.32
≥ 3.75	37.5	87.67	3.04	0.71	70	64.65
≥ 4.00	33.93	90.41	3.54	0.73	73.08	64.08
≥ 4.25	30.36	93.15	4.43	0.75	77.27	63.55
≥ 4.50	26.79	93.15	3.91	0.79	75	62.39

Se = sensitivity; Sp = specificity; +LHR = positive likelihood ratio; -LHR = negative likelihood ratio; PPV = positive predictive value; NPV = negative predictive value

Characteristics of diabetics based on VAI cut off

Using the VAI cut off 2.0, participants in the diabetes group were divided into two groups; VAI<2.0 (DM+VAD absent group) and other with VAI ≥2.0 (DM+VAD present group).

Both the groups did not differ significantly in age and BMI (as given in table 3). However, DM+VAD present group showed significantly (p<0.05) larger waist circumference, i.e. 96 cm (IQR = 93, 104.8) vs 92 cm (IQR = 87.5, 102) in DM+VAD absent group and high visceral fat area, i.e. 157.1±49.1 cm² vs 129.6±47.8 cm² in DM+VAD absent group.

Table 3: Baseline characteristics of DM+VAD absent and DM+VAD present patients

Parameters	Diabetes group		P-value
	VAI<2.0 (DM+VAD absent) N = 25 (M: F 16:9)	VAI ≥ 2.0 (DM+VAD present) N=56 (M: F 30:26)	
Age (years)	53.7 (6.6)	50 (8.5)	0.056
BMI (Kg/m^2)	26.4 (24.7, 29.4)	28.4 (25.8, 30.5)	0.121
Waist circumference (cm)	92 (87.5, 102)	96 (93, 104.8)	<0.05
Visceral fat area (cm^2)	129.6 (47.8)	157.1 (49.1)	<0.05
Fasting glucose (mg/dl)	124.8 (103.1, 138)	138.3 (104.7, 186.9)	0.56
HbA1C (%)	7.7 (6.8, 8.4)	7.3 (6.4, 8.6)	0.898
Fasting insulin (µU/ml)	10.8 (6.1, 31.1)	20.1 (11.5, 52.5)	<0.05
HOMA-IR	3.6 (1.7, 10.1)	7.8 (3.2, 19.1)	<0.05
Total cholesterol (mg/dl)	185.7 (40.3)	199.6 (40.3)	0.155
TG (mg/dl)	102.2 (78, 118.9)	215 (168.4, 269.4)	<0.01
LDLc (mg/dl)	101 (27.50)	112.1 (30.4)	0.122
HDLc (mg/dl)	51.4 (43.7, 57.2)	37.5 (34.8, 42)	<0.01
Non-HDLc (mg/dl)	134.9 (37.8)	160.9 (38.4)	<0.05
Apolipoprotein B (mg/dl)	78.4 (57.6, 86.6)	86.2 (74, 116.9)	0.154
Apolipoprotein A1 (mg/dl)	142 (24.3)	128.4 (21.9)	<0.05
Apolipoprotein B/A1 ratio	0.55 (0.37, 0.66)	0.69 (0.56, 0.910	<0.05
VAI	1.46 (0.9, 1.6)	3.9 (3.0, 5.6)	<0.01

Data distributed normally are shown as mean (SD), whereas non-normally distributed data are shown as median (25% percentile, 75% percentile). Continuous variable compared using the unpaired t-tests or Mann-Whitney U tests depending on whether data met the relevant distributional assumptions

Participants of both the groups were type 2 diabetics having raised HbA1C levels and fasting glucose levels, which did not differ significantly (refer table 3). However, VAI could divide the group (VAI ≥ 2.0) having statistical significant ($p<0.05$) difference in serum insulin, i.e. 20.1 µU/ml (IQR = 11.5, 52.5) vs 10.8 µU/ml (IQR = 6.1, 31.1) in DM+VAD absent group and HOMA-IR value of 7.8 (IQR = 3.2, 19.1) vs 3.6 (IQR = 1.7, 10.1) in DM+VAD absent group was observed.

Consecutively, VAI cut-off of 2.0 could distinguish the diabetic participants with adiposity related raised CMR. DM+VAD present group had significantly ($p<0.001$) raised TG value, i.e. 215 mg/dl (IQR = 168.4, 269.4) vs 102.2 mg/dl (IQR = 78, 118.9) and low HDLc, i.e. 37.5 mg/dl (IQR = 34.8, 42) vs 51.4 mg/dl (IQR = 43.7, 57.2) compared participants in DM+VAD absent group respectively. Furthermore, DM+VAD present group had significantly ($p<0.05$) higher non-HDLc levels, i.e. 160.9±38.4 vs 134.9±37.8 mg/dl and apolipoprotein B/A1 ratio, i.e. 0.69 (IQR = 0.56, 0.910) vs 0.55 (IQR = 0.37, 0.66) compared to DM+VAD absent group respectively.

Performance of VAI in predicting hepatic insulin resistance

The age-adjusted partial correlation coefficient of VAI, BMI and waist circumference with hepatic insulin resistance estimated using HOMA-IR was 0.32, 0.31 and 0.35 respectively. The correlation of these measures with insulin resistance was comparable and significant ($p<0.001$). Further, the results of logistic regression analysis for predicting hepatic insulin resistance using VAI had odds ratio of 5.6 (95% CI of 2.6–12.2).

DISCUSSION

In this study, the use of VAI to determine any given individual's probability of having visceral adiposity dysfunction, based on simple clinical parameters was explored. The VAI cut off was explored in a relatively large cohort of individuals with varying degrees of obesity (including both healthy and overweight/obese diabetic participants) with and without visceral adiposity dysfunction as defined using visceral fat area less than or greater than equal to 130 cm2 measured using MRI technique.

The study compared clinical indices between healthy controls and overweight/obese diabetic group. It is well established that type 2 diabetic patients are predisposed to high CMR, and obesity has been implicated in the pathogenesis of CMR [18, 19]. Our study results confirm this i.e. the baseline characteristics of dysglycemic, insulin resistant and hyperinsulinemic overweight/obese diabetic group had additional CV risk factors linked to atherogenic dyslipidemia i.e. raised total cholesterol, TG, non-HDLc, apolipoprotein B and apolipoprotein B/A1 ratio compared to participants in healthy controls. Further, diabetic group had significantly elevated visceral fat values, i.e. 148.6±50 vs 70.2±50.3 cm2 healthy controls and same was reflected in VAI values of 3.1 vs 1.13 in the healthy control group.

Although VAI is simple to derive and well correlated with visceral fat accumulation, there is no definite value which can reflect visceral fat values corresponding to visceral adiposity dysfunction. In this study, an optimal VAI cutoff point for visceral adiposity dysfunction (defined as VFA greater than 130 cm2 by MRI) is established and this value was 2.0.

One of the features of diabetes is abdominal obesity, and the visceral adiposity plays an important role in the progression of diabetes. VAI is strongly associated with incident diabetes. In this study, we found that DM+VAD present group was significantly more hyperinsulinemic and insulin resistant compared to diabetic group without VAD. DM+VAD present group also had more predominant components of metabolic syndrome as reflected by significantly high TG and low HDLc levels. Further, this group had significantly high non-HDLc and apolipoprotein B/A1 ratio. Collectively, DM+VAD present group was more insulin resistant, hyperinsulinemic, dyslipidemic group predisposed to cardiovascular risk as compared to DM+VAD absent group. Age adjusted partial correlation between VAI and HOMA-IR ($r = 0.32$) was found to be significant ($p<0.001$).

CONCLUSION

Metabolic parameters were deranged in overweight/obese diabetics than healthy controls. VAI as a simple indicator of visceral adipose dysfunction was strongly associated with the severity of obesity-related CMR. The optimal cutoff point of VAI for predicting VAD was found to be 2.0 having a sensitivity of 73.21% and specificity 71.23%. This cut-off point of VAI was useful in distinguishing diabetic patients with greater CMR. The VAI also showed good correlation with hepatic insulin resistance measured using HOMA-IR after adjusting the age. Thus, we suggest that the VAI would be an easy tool for the evaluation of the CMR in type 2 diabetes or in other populations, mainly in the absence of an overt metabolic syndrome. Further, this data also suggests that VAI can replace specialized imaging procedures with the advantages of a reduced economic burden and radiation hazard. However, it is necessary to identify the age-and sex-specific cutoff points in the general population for early diagnosis and individualized therapeutic programs in persons at risk for CVD, which is in progress.

CONFLICTS OF INTERESTS

All authors have none to declare

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