Association between visceral adiposity index, hirsutism and cardio-metabolic risk factors in women with polycystic ovarian syndrome: A cross-sectional study

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(Index words: adipocyte dysfunction, cardio-metabolic risk factors, hirsutism, polycystic ovarian disease, visceral adiposity index)

Abstract

Introduction Visceral adiposity index (VAI) is a mathematical index derived from the body mass index (BMI), waist circumference (WC), serum fasting triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C). It reflects visceral adipocyte dysfunction (VAD) and is associated with cardiometabolic risk. Women with polycystic ovarian syndrome (PCOS) have adipocyte dysfunction, which is associated with metabolic disorders. Hirsutism in PCOS is considered to be due to high insulin levels which enhances androgen activity at the pilosebaceous unit.

Objectives To determine the association between VAI, hirsutism and cardiometabolic risk factors in patients with PCOS.

Methods A total of 99 patients aged 18-40 years with PCOS diagnosed by the Rotterdam consensus criteria-2003 and a hirsutism score of 8 or more according to the Ferriman-Gallway Score (FGS) were studied. BMI, WC, fasting lipid profile, serum leptin, insulin, sex hormone binding globulin (SHBG), free-androgen index (FAI), fasting blood glucose (FBG) and oral glucose tolerance test (OGTT) were determined. Homeostasis model assessment (HOMA)-beta, HOMA-insulin resistance (IR) and VAI were calculated. Diameter and rate of hair growth at sideburns and chin; density of hair at sideburns were measured. Data were analyzed by SPSS-22.0.

Results There was no significant association between parameters of hirsutism and VAI. There was a significant association between VAI and OGTT, FAI, systolic and diastolic blood pressure: but not between VAI and other metabolic parameters.

Conclusion Visceral adipocyte dysfunction is closely linked to glucose intolerance and blood pressure in women with PCOS. However, hirsutism is unlikely to be due to adipocyte dysfunction.

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Introduction

Background and rationale

Visceral adipose tissue surrounds the intraabdominal organs. High visceral adipose tissue is associated with visceral adipocyte dysfunction which is characterized by an altered insulin sensitivity, lipolytic activity, a pro-inflammatory state and release of adipocytokines [1, 2]. They play a major role in cardiometabolic disease as it has been shown to be associated with diabetes, hypertension, lipid abnormalities and a high mortality rate [3]. Visceral

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adipocyte dysfunction leads to a rise in adipocytokines such as leptin, adiponectin, tumor necrosis factor-alpha and resistin [4]. This provides an objective index of the extent of adipose tissue dysfunction [5]. This index further predicts the conversion of metabolically healthy obesity to metabolically unhealthy obesity [6]. The quantitative analysis of visceral and cutaneous fat is carried out via MRI (Magnetic Resonance Imaging) or CT (Computed Tomography) and remain the gold standard for assessment of visceral adipose tissue though rather expensive and not routinely used in clinical practice [7].

The gender specific empirical mathematical model visceral adipose tissue index (VAI) is a surrogate marker of adipose tissue function [8]. It is estimated by the use of simple anthropometric (body mass index and waist circumference) and biochemical (triglycerides and high-density lipoprotein cholesterol) parameters [7].

The equation for VAI for females is as follows

$$VAI = \left(\frac{Waist\ Circumference}{36.58 + 1.89 \times BMI}\right) \times \left(\frac{Triglcerides}{0.81}\right) \times \left(\frac{1.52}{High\ Density\ Lipid\text{-}Cholesterol}\right)$$

The measurement of this value predicts the cardiometabolic risk of an individual early as it is indicative of insulin resistance and it is positively correlated with CT assessment of adipose tissue, the visceral to subcutaneous fat ratio and peripheral glucose utilization. It is a convenient index that can be easily used to assess the extent of adipocyte dysfunction in patients. Based on the above, age and gender specific quartiles have been calculated in order to classify the metabolic risk in these patients [7].

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder characterized by a diverse collection of reproductive and metabolic abnormalities and part of the clinical spectrum of metabolic syndrome. It is characterized by hyperandrogenemia and chronic anovulation. In patients with PCOS VAI increases in relation to the severity of anovulation, insulin resistance and inflammation [4]. It predicts the cardio-metabolic risk of oligomenorrheic phenotype of PCOS. It enables to distinguish between metabolically healthy and metabolically unhealthy PCOS (9).

Cardiometabolic risk is the overall risk of developing type 2 diabetes and cardiovascular diseases. The key risk factors which are known to be associated with enhanced cardio-metabolic risk include increased waist girth, elevated blood pressure, low HDL cholesterol, high triglycerides and impaired fasting glucose [10]. Abdominal visceral fat is a better determinant of cardiometabolic risk factors such as hypertension, type 2 diabetes, and dyslipidaemia than abdominal subcutaneous fat. Visceral adipocyte dysfunction is associated with a high cardiometabolic risk [7].

Hirsutism is the excessive growth of terminal hair in androgen dependent areas in women. It is a common feature seen in PCOS and is part of the diagnostic criteria; further, it gives rise to considerable anguish to women. It is caused by ovarian derived androgen excess and individual sensitivity of the pilosebaceous unit to androgen which supposedly mediated by high insulin levels [10]. Most patients with high insulin levels tend to have hirsutism as has been found to be associated with insulin resistance [11].

Most of the data available is for Caucasian patients aged 18 to 83 years and patients of South East Asian descent [7, 12]. Hence a lack of data for South Asians means caution needs to be exercised, when extrapolating these data to other ethnic groups.

Since hyperinsulinemia levels are attributed to be a causative mechanism for high androgenic activity at the pilosebaceous unit we postulated a probable correlation between the VAI and hirsutism in patients with PCOS and carried out this study to find, whether there is an association between VAI and hirsutism as well as cardiometabolic risk factors.

Objectives

Method

This is the baseline data from a clinical trial to assess the "effectiveness of ethinyl estradiol /cyproterone acetate and ethinyl estradiol/desogestrel with or without low-dose metformin on patients with polycystic ovary syndrome: A randomised, double-blind, placebo-controlled study". Data was collected from 99 female patients diagnosed to have PCOS. The inclusion criteria included females aged 18 to 40 years, diagnosed to have PCOS according to the Rotterdam consensus criteria and a hirsutism score of 8 or more according to the modified Ferriman-Gallway score. The patients who did not consent were excluded from the study. Patients with secondary causes of hirsutism such as idiopathic hirsutism, Cushing's syndrome, hyper-thecosis, androgen secreting tumor etc.

The study was conducted at the Pharmacology Department, Faculty of Medicine, University of Peradeniya. The patients were recruited from the Gynecology and Obstetrics Unit of Teaching Hospital Peradeniya and Teaching Hospital, Kandy.

The basic demographic data such as name, age, marital status was collected from the patient. The weight, height, waist circumference, hip circumference, systolic and diastolic blood pressure was measured by a standard technique. The BMI (Body Mass Index) was calculated in these patients by the equation weight (in kg)/ height (in m)^2.

Venous blood samples were drawn from the patients after a 10-hour fasting duration. The Triglyceride (TG) and High-Density Lipid-Cholesterol (HDL-C) value were obtained from the lipid profile.

Further biochemical parameters such as leptin, sex hormone binding globulin, insulin, fasting blood glucose, oral glucose tolerance test (OGTT) and testosterone levels were measured and the free androgen index, homeostasis model assessment of insulin resistance (HOMA-IR), homeostasis model assessment of β cell function (HOMA-β) and the area under the curve (AUC) for OGTT were derived.

The BMI, waist circumference, TG and HDL-C were used to calculate the gender specific-VAI and categorized according to the degree of visceral adipocyte dysfunction.

Hirsutism was assessed by determining the modified Ferriman-Gallway score, hair diameter and hair growth rate in chin and sideburns and hair density in sideburns. Hair density was measured by marking a 2cm × 2cm square in front of the tragus and the number of hairs was counted using a digital photograph and Microsoft Paint software. Diameter of the hair was assessed by taking the average diameter of 5 strands of hair plucked measured from each site using Olympus B53 microscope (Olympus, Hamburg, Germany) and the software CellSense Entry (Olympus, Japan). The rate of hair growth was assessed by taking the average length of 5 hair strands plucked from each site and measured by Vernier calipers and recording the last date of shaving [13].

Baseline characteristics were presented as mean ± Standard Deviation (SD) for continuous variables; rates and proportions were calculated for categorical data. Normality of distribution for quantitative data was assessed by the Kolmogorov-Smirnov test. The variables that did not show a normal distribution were log-transformed. The categorical data was analyzed by the Man-Whitney U test.

Results

Descriptive Statistics

A total of 99 subjects were included in the final analysis of the baseline data of patients who were part of the clinical trial. The VAI value was analyzed by quartiles to examine the relationship of the clinical and metabolic characteristics according to the VAI values. Anthropometric and clinical variables, biochemical variables and parameters of hirsutism according to VAI quartiles are stated in Table 1, 2 and 3 respectively.

Correlation between natural logarithms of clinical, biochemical variables and natural logarithms are shown in Table 4. Correlation between the natural logarithms of VAI and natural logarithms of parameters of hirsutism revealed hair growth on the left side r = -0.047 (0.646), right side r = -0.012 (0.904) and chin of -0.044 (0.664); density of hair growth r = -0.099 (0.33); diameter on the left side r = 0.015 (0.886), right side r = 0.079 (0.438) and chin r = 0.145(0.145) and FGS r =0.019 (0.854).

Table 1. Anthropometric and clinical variables according to VAI quartiles Mean (SD)

	Normal	*Mild*	*Moderate*	*Severe*
Number	62	6	3	27
Age	23.89 (5.53)	26.67 (6.74)	30.0 (8.66)	26.48 (8.11)
Height	155.92 (4.9)	150.58 (18.22)	155.5 (11.63)	154.0 (6.7)
Weight	64.74 (15.2)	71.28 (11.9)	63.1 (11.56)	70.14 (10.3)
Waist Circumference	80.93 (15.58)	88.5 (6.59)	94.67 (14.6)	90.9 (9.09)
Waist/Hip Ratio	0.803 (0.094)	0.862 (0.035)	0.86 (0.047)	0.88 (0.049)
BMI	26.7 (5.75)	28.22 (3.42)	25.89 (1.034)	29.13 (3.72)
Systolic Blood Pressure	115.56 (13.55)	118.67 (9.2)	118.67 (9.6)	124.7 (12.8)
Diastolic Blood Pressure	76 (10.2)	75 (11.1)	81 (11.5)	84.22 (8.3)

Table 2. Biochemical variables according to VAI quartiles Mean (SD)

	Normal	*Mild*	*Moderate*	*Severe*
Number	62	6	3	27
Total Cholesterol (TC)	184.93 (41.44)	217.5 (29.14)	181.33 (41.36)	202.26 (28.56)
Triglyceride	92.03 (25.15)	118.8 (23.8)	143.67 (29.5)	204.56 (78.1)
LDL 120.67(35.18)	154.4 (32.4)	110.9 (45.6)	124.4 (21.8)	
HDL 47.8(17.09)	38.83 (5.46)	41.67 (6.35)	37.16 (10.45)	
TC/HDL-C ratio	5.59 (10.93)	5.71 (1.18)	4.46 (1.42)	5.41 (1.07)
Leptin 23.4(24.1)	19.18 (17.9)	35.1 (14.7)	26.15 (17.1)	
Testosterone	8.6 (51.0)	4.67 (3.78)	5.37 (3.95)	2.79 (2.33)
Free Androgen Index	4.57 (5.7)	9.36 (14.9)	1.66 (1.56)	5.25 (4.2)
SHBG 97.24(79.95)	74.1 (53.9)	85.21 (94.9)	78.48 (61.6)	
Insulin 8.01(12.8)	12.82 (22.8)	2.9 (2.95)	6.32 (10.71)	6.4 (11.14)
HOMA-B	105.9 (314.6)	32.9 (56.5)	17.66 (28.9)	154.19 (413.4)
FBS 83.9(19.5)	80.17 (8.52)	69.66 (9.5)	87.15 (18.1)	
OGTT (2-hour value)	106.3 (19.3)	111.67 (25.1)	112.33 (24.1)	117.15 (24.5)
OGTT(AUC)	212.5 (33.1)	202.3 (30.3)	212.0 (48.9)	235.3 (81.4)

Table 3. Parameters of hirsutism according to VAI quartiles Mean (SD)

	Normal	*Mild*	*Moderate*	*Severe*
Number	62	6	3	27
Hair Growth Rate-Left sideburns	1.43 (0.84)	1.61 (0.97)	1.14 (0.55)	1.28 (0.55)
Hair Growth Rate-Right sideburns	1.32 (0.57)	1.25 (0.67)	1.17 (0.72)	1.37 (0.6)
Hair Growth Rate-Chin	0.29 (0.17)	0.32 (0.19)	0.23 (0.11)	0.26 (0.11)
Density of Hair Growth	100.23 (61.7)	73.44 (43.8)	69.33 (44.5)	106.76 (67.56)
Diameter of Hair-Left sideburns	65.37 (29.44)	72.53 (22.24)	95.7 (34.4)	66.39 (22.86)
Diameter of Hair-Right sideburns	63.41 (24.4)	77.89 (21.5)	76.57 (10.9)	69.89 (22.86)
Hair Growth Rate-Chin	70.19 (31.3)	84.5 (30.7)	90.98 (26.2)	78.61 (26.86)
Total FGS	19.44 (5.77)	24.0 (5.8)	20.0 (6.00)	18.89 (5.8)

Table 4. Correlation between natural logarithms of clinical, biochemical variables and natural logarithms of VAI

	VAI correlation (p value)
Leptin	0.166 (0.104)
Testosterone	0.123 (0.22)
Free Androgen Index	0.250 (0.014)
SHBG	-0.133 (0.199)
Insulin	-0.021 (0.84)
HOMA-IR	-0.101 (0.338)
HOMA-B	0.081 (0.444)
FBS	0.013 (0.898)
OGTT (2-hour value)	0.194 (0.054)
OGTT (AUC)	0.122 (0.228)
Systolic Blood Pressure	0.346 (<0.05)
Diastolic Blood Pressure	0.321 (<0.05)

Correlation between the free androgen index and parameters of hirsutism revealed hair growth on the left side r = 0.021 (p=0.841), right side r = 0.003 (p=0.976) and chin of 0.022 (p=0.828); density of hair growth r = -0.195 (p=0.055); diameter on the left side r = 0.181(p=0.077), right side r = 0.136 (p=0.183) and chin r= 0.059 (p=0.569) and FGS r =0.060 (p=0.559).

Correlation between the testosterone and parameters of hirsutism revealed hair growth on the left side r = -0.063 (p=0.536), right side r = -0.108 (p=0.286) and chin of -0.060 (p=0.560); density of hair growth r = -0.133 (p=0.190); diameter on the left side r = -0.067 (p=0.510), right side r = -0.059 (p=0.559) and chin r= -0.066 (p=0.517) and FGS r =-0.199 (p<0.05).

Correlation between the insulin and parameters of hirsutism revealed hair growth on the left side r = -0.062 (p=0.544), right side r = -0.119 (p=0.242) and chin of -0.067 (p=0.512); density of hair growth r = -0.071 (p=0.484); diameter on the left side r = 0.132 (p=0.193), right side r = 0.030 (p=0.768) and chin r= 0.092 (p=0.363) and FGS r =0.038 (p=0.708).

Correlation between the SHBG and parameters of hirsutism revealed hair growth on the left side r = 0.035 (0.734), right side r = 0.060 (0.560) and chin of 0.033 (0.747); density of hair growth r = -0.104(0.308); diameter on the left side r = -0.128 (0.210), right side r = -0.126 (0.210) and chin r= -0.060 (0.56) and FGS r =-0.010 (0.921).

Adiposity index demonstrates a skewed distribution with a kurtosis of 6.274. The patients were divided into two categories based on the VAI as metabolically unhealthy and healthy (Table 5). The VAI cut-off value for severe visceral adipocyte dysfunction was used to differentiate between metabolically healthy and unhealthy. Since most variables showed a non-normal distribution, as well as the difference of the number of subjects between the two groups Mann-Whitney U test was carried out.

Table 5. Difference of the clinical, biochemical variables and parameters of hirsutism in between the two groups

	Metabolically Healthy (Mean Rank)	*Metabolically Unhealthy (Mean Rank)*	*Test statistic*	*P value*
Weight	47.05	57.04	759.5	0.095
Age	46.69	58.83	733.5	0.06
Waist Circumference	45.31	62.52	634	0.008
Waist-Hip Ratio	42.62	69.69	440.5	<0.05
BMI	46.4	59.59	713	0.042
Systolic Blood Pressure	44.67	64.2	588.5	0.003
Diastolic Blood Pressure	43.49	67.35	503.5	<0.05
Leptin	46.37	56.17	736.5	0.129
SHBG	49.98	48.24	924.5	0.787
Testosterone	49.05	52.54	903.5	0.59
Androgen Index	46.07	56.59	747	0.099
Insulin	50.63	48.31	926.5	0.721
HOMA-IR	50.16	47.76	911.5	0.709
HOMA-B	47.39	55.64	809	0.234
FBS	49.01	52.65	900.5	0.574
OGTT-2-hour value	46.29	59.89	705	<0.05
OGTT-AUC	47.74	56.04	809	0.2
Triglyceride	37.95	82.13	104.5	<0.05
LDL	49.59	51.09	942.5	0.817
HDL	56.14	33.63	530	0.001
TC/HDL-C ratio	42.69	69.8	445.5	<0.05
Hair Growth Rate-Left sideburns	50.37	49.02	945.5	0.835
Hair Growth Rate-Right sideburns	49.54	51.22	939	0.795
Hair Growth Rate-Chin	50.33	49.13	948.5	0.853
Density of Hair Growth	49.31	51.83	922.5	0.697
Diameter of Hair-Left sideburns	50.01	49.98	971.5	0.997
Diameter of Hair-Right sideburns	48.89	52.96	892	0.53
Hair Growth Rate-Chin	48.26	54.65	845.5	0.324
Ferriman-Gallway Score	50.7	48.13	921.5	0.691

Discussion

The main findings in this study are that about 30% of the patients have the metabolically-unhealthy variant of PCOD, there is no correlation between parameters of hirsutism and the visceral adiposity index and VAI is associated with an elevated cardio-metabolic risk.

Visceral adiposity index predicts transition from metabolically healthy to unhealthy status; hence almost 30% of our patients were metabolically unhealthy which places them at a higher risk of cardiovascular morbidity and mortality, hence it is prudent to follow up these patients to detect adverse cardiovascular outcomes in the future [6].

Majority of the patients were overweight, with an increased waist circumference, increased waist to hip ratio, impaired glucose tolerance and high systolic and diastolic blood pressure readings which places them in the category of metabolic syndrome which is a predictor of adverse cardiovascular outcome. They are at high risk of conversion to a state of metabolic ill health in the future even despite of normal visceral adipose dysfunction at the moment [1].

Although about 30% of our patients had severe VAD they did not have higher fasting insulin levels than the patients with normal VAD. Our findings do not support the hypothesis of hyperinsulinaemia as a contributory factor for hirsutism.

OGTT 2-hour value was higher among the metabolically unhealthy than the metabolically healthy patients but the AUC for OGTT did not demonstrate a significant difference between the two groups. Though very few patients had overt diabetes within our population there was evidence of glucose intolerance which correlated with the VAD.

There was an overall increase in the parameters on the lipid profile. Triglyceride and HDL-C were elevated in the metabolically unhealthy patients compared to metabolically healthy patients whereas the reverse was observed with regard to HDL levels. Triglyceride levels in particular have been associated with VAD and poor metabolic health.

The hair growth rate, hair diameter, hair density and modified FGS has not been previously studied in Sri Lankan individuals thus, it is difficult to make a comparison of the values observed in these women. There is lack of both normative data and hirsutism indices in our population [14]. Testosterone, insulin and free androgen index were elevated but there was no significant correlation between them and visceral adipocyte dysfunction or parameters of hirsutism [2].

SHBG, HOMA-IR, HOMA-β, insulin and leptin levels were elevated in our population compared to age stratified cut-off values but no difference was observed between metabolically healthy and unhealthy patients and do not appear to be correlated with the VAI which is both an index of VAD and insulin resistance [15]. Systolic and diastolic blood pressures significantly correlated with the VAI and this could possibly be related to endothelial dysfunction [16]. However, since this was a cross-sectional study the probability of a subsequent development of hypertension could not be predicted.

Since this was the baseline data obtained from a clinical trial the major limitation of the study was the inadequacy of the sample size which may be a reason for the lack of detection of associations which have been observed in prior studies.

Conclusions

Visceral adipocyte dysfunction (as measured by VAI) is closely linked to impaired glucose tolerance and blood pressure in women with PCOS. Hirsutism is unlikely to be related to adipocyte dysfunction in these women. A larger sample size may be required to discern the presence of an association between the above-mentioned variables in PCOS.

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Availability of data

The data of findings of this study is available from the corresponding author (SF) on request.

Conflict of interests

No conflicts of interest have been declared.

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