Abstract

Aim: To study visceral adiposity index (VAI) and its association with cardiometabolic risk in different phenotypes of polycystic ovary syndrome (PCOS). Materials and Methods: It is a case–control cross-sectional study where 100 reproductive age (18–35 years) women with PCOS were classified in different phenotypes as per Rotterdam criteria and compared with age and Body mass index (BMI) matched 50 eumenorrheic and nonhirsute women. Various anthropometric, clinical, biochemical, and hormonal parameters were measured in both women with PCOS and controls. VAI was calculated using waist circumference (WC), BMI, serum triglyceride, and High density lipoprotein (HDL) cholesterol levels in all the subjects and compared between cases and controls. Subsequently, women with PCOS were assessed for cardiometabolic risk according to androgen excess society statement 2010 as “at risk” and “at high risk.” Finally, risk was correlated with VAI for all the phenotypes of PCOS. Results: Mean VAI was significantly higher (P < 0.001) in cases than controls (2.07 vs. 1.27). Mean VAI in phenotype A (O+P+HA), B (O+HA), C (P+HA), and D (O+P) was 2.46, 2.48, 1.47, and 1.70, respectively. A total of 56% of women with PCOS were at risk and 12% at high risk for cardiometabolic disease. Metabolic syndrome was prevalent in 11% of cases and 1% had type 2 diabetes mellitus. Phenotypically, 88% of women with PCOS with phenotype A (O+P+HA), 67% of B (O+HA), 67% of C (P+HA), and 55% of D (O+P) were at increased risk. VAI was found to be positively correlated with WC (r, 0.550), waist to hip ratio (r, 0.295), Homeostasis model assessment of insulin resistance (HOMA IR) (r, 0.455), and cardiometabolic risk (r, 0.399). Also, it was the best factor associated with cardiometabolic risk (area under curve, 0.793). Conclusion: This study concluded that visceral adiposity index can be used as simple and effective tool for assessing the cardiometabolic risk in women with PCOS as higher VAI values were observed in those cases who were at high risk for developing cardiometabolic disorder in future.

Keywords: Cardiometabolic risk, PCOS, phenotypes, visceral adiposity index

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorder in reproductive age women, affecting 5–10% women worldwide. It is characterized by combination of hyperandrogenism (HA) (either clinical or biochemical), chronic anovulation, and polycystic ovaries. Also, it is frequently associated with insulin resistance and obesity and has possible adverse reproductive, metabolic as well as cardiovascular consequences.

According to androgen excess society (AES) consensus statement 2010, women with PCOS have increased risk of developing cardiometabolic disease in future. Insulin resistance is present in 70% of PCOS women, while prevalence of metabolic syndrome is 8–25% in classic PCOS. This statement also classifies cardiometabolic risk in women with PCOS as being “at risk” and “at high risk” depending on factors like cigarette smoking, obesity, and hypertension. Impaired glucose metabolism, dyslipidemia, presence or absence of metabolic syndrome, and type 2 diabetes mellitus. In various studies, this increased cardiometabolic risk has been mainly attributed to increased visceral fat as visceral fat is the main source of free fatty acids and inflammatory cytokines. About 50–60% of women with PCOS have central body fat distribution. Thus, in women with PCOS assessing visceral adipose dysfunction at a younger age should help
in preventing the future cardiometabolic complications by either lifestyle modification or medical treatment.

Visceral adipose dysfunction was traditionally assessed by BMI, waist to hip ratio (WHR) and waist circumference (WC) but now BMI is not considered a good marker as it does not include factors like gender, race, and hydration status. WC is a good marker and has good relation with visceral fat, but its only limitation is it cannot accurately distinguish between subcutaneous and visceral fat. Visceral fat is also assessed by Magnetic resonance imaging (MRI), Computed tomography (CT) scan, ultrasonography, and altered levels of adipocytokines but all these are neither easily available nor cost-effective.[7] Henceforth, this study evaluated a newer index visceral adiposity index (VAI) for assessment of visceral tissue dysfunction and its role in assessing cardiometabolic risk in PCOS.

**Visceral Adiposity Index**

VAI is a new gender-specific index, based on simple anthropometric (BMI and WC) and functional parameters [triglycerides (TGs) and HDL cholesterol], and indicative of fat distribution and function.[7] It is a based on linear relationship of BMI and WC in a healthy/normal weight population and correlated with visceral fat mass as determined by MRI. Then a Model of adipose distribution was created which was subsequently corrected for HDL cholesterol and TG levels, thus determining VAI.[7]

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\text{Females : } \text{VAI} = \frac{WC}{36.58 + (1.89 \times \text{BMI})} \times \frac{\text{TG}}{0.81} \times \frac{1.52}{\text{HDL}}
\]

where WC is expressed in cm, BMI in Kg/m², TG in mmol/L, and HDL in mmol/L.

The VAI has shown a strong positive correlation with peripheral glucose utilization during euglycemic hyperinsulinemic clamp studies and seems to be independently associated with cardiovascular events. In the recent years, there has been extensive research regarding the role of VAI in assessing visceral adipose dysfunction in metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, and in PCOS.[7-15]

**Materials and Methods**

It was a cross-sectional observational study including 100 reproductive age women (18–35 years) fulfilling Rotterdam criteria of PCOS and 50 women (18–35 years) who are eumenorrheic and nonhirsute with no family history of PCOS attending gynecology outpatient department at our hospital. For all the study subjects, a detailed clinical history including menstrual history (h/o of onset and duration of symptoms, duration of cycles, amount of flow, and treatment received), h/o acne, h/o of hair growth at abnormal sites like chin, upper lip, and breast, h/o weight gain or loss, h/o acanthosis nigricans, h/o galactorrhea, h/o thyroid dysfunction was taken followed by general, systemic, and local examination. This was followed by baseline clinical assessment and these parameters were recorded: Height, weight, BMI, WC, WHR, presence of acne and hirsutism. Systolic blood pressure and diastolic blood pressure were measured in a relaxed sitting position.

Endocrine assessment by measurement of levels of serum luteinizing hormone, serum follicle-stimulating hormone, thyroid-stimulating hormone, serum prolactin, serum total testosterone, sex hormone binding globulin was done on day 2 or 3 of the follicular phase. Serum progesterone levels between 20 and 24 days were determined to evaluate anovulation in women with regular cycles and in women with prolonged irregular menstrual cycles test was conducted later in the cycle depending upon the duration of cycle. Ultrasonography (transvaginal or transabdominal) was done on day 2 or 3 of last menstruating period and on any particular day for oligomenorrheic women for recording the presence or absence polycystic ovarian morphology.

After evaluation, women were diagnosed to have PCOS according to Rotterdam criteria which include presence of two of three of following characteristics (after exclusion of other hyperandrogenic disorders like Cushing’s syndrome, congenital adrenal hyperplasia, and adrenal adenoma): [16]

1. Menstrual cycle abnormalities (amenorrhea or oligomenorrhea)
2. Clinical and/or biochemical HA
3. Ultrasound appearance of polycystic ovaries

After diagnosis of PCOS was made, patients were segregated in four different phenotypes according to Rotterdam criteria: [17]

- **Type A (O+ P+HA):** Oligo/anovulation (O), polycystic ovaries on ultrasound (P) and hyperandrogenism (HA).
- **Type B (O+HA):** Oligo/anovulation (O) and hyperandrogenism (HA).
- **Type C (P+HA):** Polycystic ovaries (P) and hyperandrogenism (HA).
- **Type D (O+P):** Oligo/anovulation (O) and polycystic ovaries (P).

All subjects were assessed for lipid profile by measurement of fasting total cholesterol, HDL cholesterol, non-HDL cholesterol, calculated Low density lipoprotein (LDL) cholesterol, and serum TGs. Eventually, VAI was calculated.

\[
\text{Females : } \text{VAI} = \frac{WC}{36.58 + (1.89 \times \text{BMI})} \times \frac{\text{TG}}{0.81} \times \frac{1.52}{\text{HDL}}
\]

where WC is expressed in cm, BMI in Kg/m², TG in mmol/L, and HDL in mmol/L.

Women with PCOS and controls were assessed for glucose metabolism by measuring fasting serum insulin, fasting blood glucose, 2 hour 75 gm glucose tolerance test and finally HOMA- IR was calculated.
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\[ \text{(HOMA IR)} = \frac{\text{Fasting Serum Insulin (IU/ml)} \times \text{Fasting Blood Glucose (mg/ml)}}{405} \]

Thereafter, women with PCOS were assessed for cardiometabolic risk and classified as: “at risk” (any one of the following: - cigarette smoking, obesity, hypertension, dyslipidemia, impaired glucose tolerance, family history of premature cardiovascular disease) and “at high risk” (any one of the following: - metabolic syndrome, type 2 diabetes mellitus, overt renal or vascular disease). Finally, VAI was correlated with cardiometabolic risk in different phenotypes of women with PCOS.

**RESULTS**

Mean age of the women enrolled in the study was 24.20 ± 3.98 years in cases and 25.46 ± 4.32 years in controls. Infertility was the most common presenting complaint (55%). Most common menstrual irregularity in women with PCOS was oligomenorrhea (94%) while 2% had hypomenorrhea, 1% polynoemorrhea, and 3% had regular cycles. 37% had hirsutism, i.e. FG score > 8 and 30% had acne. A total of 19% of women with PCOS had family history of diabetes mellitus.

Prevalence of phenotypes A (O+P+HA), B (O+HA), C (P+HA) and D (O+P) was 34%, 6%, 3%, and 57%, respectively in our study. Maximum number of patients was women with oligo/anovulation with polycystic ovaries without hyperandrogenism. (i.e. type D).

Mean value of VAI was significantly higher (P < 0.001) in cases as compared to controls (2.07 vs. 1.27). Distribution of mean VAI in phenotype A (O+P+HA), B (O+HA), C (P+HA), and D (O+P) was 2.46, 2.48, 1.47, and 1.70, respectively and higher VAI values were majorly present in classic phenotype with all three components, i.e. A (O+P+HA) than in phenotype D (O +P) i.e. one without hyperandrogenism and controls [Table 1].

On assessing cardiometabolic risk in women with PCOS according to AES consensus statement 2010, 56% of cases were at risk and 12% at high risk, respectively. Metabolic syndrome was prevalent in 11% of cases and 1% had type 2 diabetes mellitus [Table 2].

Phenotypically speaking, 88% of women with PCOS with phenotype A (O+P+HA), 67% of B (O+HA), 67% of C (P+HA), and 55% of D (O+P) were at increased risk for cardiometabolic disease implying that maximum prevalence of increased risk for cardiometabolic disorder is in women with all three components (O+P+HA). Moreover, maximum values of mean VAI were observed in those cases that were at high risk for developing cardiometabolic disorder in future, thus inferring that increased VAI values was associated with increased cardiometabolic risk [Table 3].

On statistical analysis, VAI had a positive correlation with WHR and HOMA-IR in both cases and controls. VAI is also positively correlated with cardiometabolic risk in women with PCOS [Table 4].

As well, on plotting Receiver Operating Characteristics (ROC) curve for association of different metabolic factors with cardiometabolic risk, area under curve (AUC) was maximum for VAI (AUC 0.793) followed by HOMA-IR (AUC 0.761) and WHR (AUC 0.742). Cut off values of VAI in our study were 1.55 [Table 5, Graph 1].

**DISCUSSION**

Women with PCOS frequently exhibit central obesity, glucose intolerance, atherogenic dyslipidemia, and hypertension, which are characteristic risk factors of a metabolic syndrome, type 2 diabetes, and cardiovascular disease.[19-24] In view of increased risk, androgen excess society recommends regular screening for prevention of cardiometabolic disease in these women.[2] The metabolic syndrome represents a constellation of closely related

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**Table 1: Variations of visceral adiposity index in phenotypes of PCOS and controls**

| VAI   | A (O+P+HA) | B (O+HA) | C (P+HA) | D (O+P) | Controls (n=50) |
|-------|------------|----------|----------|---------|----------------|
| <1.5  | 5 (15%)    | 1 (3%)   | 2 (6%)   | 26 (76%)| 39 (78%)       |
| 1.5-3 | 19 (36%)   | 3 (5%)   | 1 (2%)   | 30 (57%)| 11 (22%)       |
| >3.45 | 7 (70%)    | 2 (20%)  | -        | 1 (10%) | 0 (0%)         |
| >4.5  | 3 (100%)   | 2.48     | 1.47     | 1.70    | 1.27           |
| Mean  | 2.46       | 2.48     | 1.47     | 1.70    | 1.27           |

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**Graph 1:** Receiver Operating Characteristics (ROC) curves of cardiometabolic risk factors
cardiovascular risk factors, and several studies have observed an increased prevalence of metabolic syndrome in women with PCOS. In the present study, 68% of women with PCOS were assessed to have increased cardiometabolic risk. Metabolic syndrome was prevalent in 11% of cases and 1% had type 2 diabetes mellitus, while none seen in controls. Similar increase in prevalence of metabolic syndrome in PCOS cases was also observed in studies by Amato (27.7%), Mehrabian et al. (24.9%), and Kar (35%).

Visceral obesity is associated with increased adipocytokines production, proinflammatory activity, deterioration of insulin sensitivity, increased risk of developing diabetes, “high-triglyceride/low-HDL cholesterol dyslipidemia, hypertension, atherosclerosis, and higher mortality rate. Increased cardiometabolic risk in women with PCOS is mainly attributed to increased visceral fat in these women. WC is a major clinical parameter used for the indirect evaluation of increased visceral fat. Nevertheless, WC alone does not help in distinguishing between subcutaneous and visceral fat mass. This is a considerable drawback, given that visceral adipose tissue and not subcutaneous adipose tissue plays a decisive role in the genesis of cardiovascular squeals. Thus, sex-specific index (VAI) was developed to estimate the visceral adiposity dysfunction associated with cardiometabolic risk in various phenotypes of PCOS.
disorders including PCOS.\(^7\) In the last 3 years, there has been extensive research regarding the role of VAI in assessing visceral adipose dysfunction in metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, and in PCOS\(^{13-15}\) but no study had been done in India regarding VAI in PCOS so far.

In our study, majority of cases (53%) had VAI in the range of 1.5–3.0, while maximum number of controls (78%) had VAI < 1.5. Mean value of VAI is 2.07 ± 0.91 in cases and 1.27 ± 0.63 in controls (\(P\) value < 0.001). Even though the cases and controls were BMI matched, higher values of VAI in cases can be explained due to increased WC to some point and majorly due to deranged lipid functions in PCOS. Study of Amato\(^{11}\) also had increased VAI in cases as compared to controls.

Like our study, studies by Amato\(^{11}\) and Tehrani et al.\(^{14}\) observed that complete phenotype, i.e. phenotype A with all three components had increased prevalence of obesity, hyperandrogenism, insulin resistance, deranged lipid functions, inflammatory markers like C- Reactive protein (CRP), metabolic syndrome, and also associated with higher VAI values as compared to phenotype D (O+P), i.e. without hyperandrogenism [Table 6].

Higher VAI values were observed in those cases that were at high risk for developing cardiometabolic disorder in future, thus inferring that increased VAI values was associated with increased cardiometabolic risk in women with PCOS. In our study, VAI had the maximum association with cardiometabolic risk in women with PCOS. In the last 3 years, there has been extensive research regarding the role of VAI in assessing visceral adipose dysfunction in metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, and in PCOS but no study had been done in India regarding VAI in PCOS so far.

The study concluded that the VAI was a simple and effective tool for assessing cardiometabolic risk in these women. Although VAI is not a diagnostic tool for cardiovascular and cerebrovascular events as it includes physical (BMI and WC) and metabolic (TG and HDL) parameters; however, it indirectly reflects other nonclassical risk factors, i.e. altered production of adipocytokines, increased lipolytic activity, and plasma-free fatty acids occurring in women with PCOS.\(^7\) Moreover, VAI also showed a strong association with the rate of peripheral glucose utilization during euglycemic–hyperinsulinemic clamp, visceral adipose tissue measured with MRI,\(^7\) and also with visceral fat area measured by CT scan.\(^{13}\) Thus, for these reasons, larger studies are required in the future to identify the precise cut-off reference value of VAI for assessing cardiometabolic risk in patients with PCOS as this can help conjuring personalized therapeutic programs for the patients at risk.

**CONCLUSION**

The study concluded that the VAI was a simple and effective tool for assessing the cardiometabolic risk in women with PCOS, but further studies are required in order to extrapolate the index in the clinical management of PCOS patients.

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**Conflicts of interest**

There are no conflicts of interest.

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### Table 6: Distribution of VAI in different studies

| Studies          | A (O+P+HA) | B (O+HA) | C (P+HA) | D (O+P) | Controls | \(P\)     |
|------------------|------------|----------|----------|---------|----------|----------|
| Amato\(^{11}\) in 2011 | n=84       | 30       | 60       | 100     | 52       | 0.001    |
| Mean             | 2.45±1.63  | 2.49±1.46| 1.68±1.00| 2.25±1.40| 1.62±0.84|          |
| Tehrani\(^{14}\) et al. in 2014 | n=57       | 30       | 60       | 100     | 52       | 0.001    |
| Mean             | 2.6 (1.8-3.4)| 2.6 (1.6-3.6)| 2.5 (1.9-3.1)| 2.3     |          |          |
| Our study        | n=43       | 6        | 3        | 57      | 50       | <0.001   |
| Mean             | 2.46       | 2.48     | 1.47     | 1.70    | 1.27     |          |

### Table 7: Characteristics of ROC curve in different studies

| Studies          | No. of patients | Cut off value | AUC   | Sensitivity (%) | Specificity (%) |
|------------------|-----------------|---------------|-------|-----------------|-----------------|
| Amato\(^{11}\) in 2011 | 241             | 1.82          | 0.760 | 71.43           | 75              |
| Oh et al.\(^{12}\) in 2013 | 180             | 1.79          | 0.880 | 82.6            | 84.7            |
| Tehrani et al.\(^{14}\) in 2014 | 175             | 1.8           | 0.660 | 60              | 62              |
| Our study        | 100             | 1.55          | 0.793 | 62              | 86              |
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