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CENTRAL OBESITY IS AN INDEPENDENT RISK FACTOR FOR INSULIN RESISTANCE IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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ABSTRACT The objective of study was to compare insulin resistance and its manifestations among obese and non-obese PCOS women and to identify the subset of PCOS women who are most insulin resistant. Obesity was determined based on body mass index and central obesity based on waist to hip ratio. Insulin resistance was determined using fasting glucose to insulin ratio less than 4.5. Eighty PCOS women were included of whom 52.5% were obese. Insulin resistance was seen in 79.5% of women with central obesity and only 27.8% of those without central obesity. Central obesity was independent risk factor for insulin resistance.

KEYWORDS : Insulin Resistance, Obesity, Polycystic Ovary Syndrome, Waist-to-hip Ratio

INTRODUCTION:

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among women of reproductive age with high prevalence in Indian women [1-2]. PCOS is more commonly associated with obesity, specifically android (central) obesity [3]. Few studies have shown increased insulin resistance (IR) in obese PCOS women [4-5]. They also demonstrated association of obesity with reproductive dysfunction including menstrual irregularities, infertility and complications during pregnancy. Although obesity is often associated with metabolic disorders, lean women with PCOS have also been found to have hyperinsulinemia, IR and dyslipidemia [6]. The objective of this study was to compare clinical and biochemical IR, prevalence of infertility, menstrual irregularities and clinical and biochemical hyperandrogenism among obese and non-obese PCOS women. Another objective was to identify the subset of PCOS women who are most insulin resistant which may therefore be useful for selecting women who will respond to insulin sensitizer therapy.

METHODS:

This was an observational study conducted at a tertiary care gynaecology centre in India. Clearance was obtained from scientific committee and the Institutional ethics committee. The study protocol was explained to the patient in detail and informed, written consent was obtained from them. The study subjects included patients who were diagnosed to have PCOS according to Rotterdams criteria: i.e presence of atleast 2 among (i) oligomenorrhoea or anovulation (fewer than 6 menses in preceding year), (ii) clinical and/or biochemical evidence of hyperandrogenism (total testosterone ≥ 0.6ng/ml) & (iii) polycystic ovaries defined as presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter and/or increased ovarian volume (>10ml) [6]. Patients with hypothyroidism, Cushing's syndrome, hyperprolactinemia, adrenal tumors and those with current or previous use of oral contraceptive pills, glucocorticoids, antiandrogens, ovulation induction agents, oral hypoglycemic drugs, insulin sensitizers, sodium valproate, aspirin, statins and other hormonal drugs were excluded. History was obtained from the patient in the pre-designed case proforma. Complete physical examination was done with special emphasis to look for presence of obesity (by BMI and waist: hip ratio) and to look for clinical signs of hyperandrogenism. Body Mass Index (BMI) was calculated by using the Quetlet formula: BMI = weight (in kgs) / height^2 (in metres). Central obesity was determined using WHO definition and was taken as waist circumference more than 88 cm or waist to hip ratio more than 0.85 [7]. Waist circumference (in centimeters) was measured with a non-elastic tape midway between lowest part of the ribcage and highest point on iliac crest. Hip circumference was measured at the maximum girth of hip. The waist /hip ratio was calculated as waist circumference divided by hip circumference. All women underwent USG pelvis and serum estimation of fasting glucose, fasting insulin, LH, FSH, TSH, free testosterone and 17-hydroxy progesterone. Fasting glucose levels were obtained by glucose oxidase method. Fasting insulin was determined by double antibody radioimmunoassay method. Fasting blood samples were collected in the morning after overnight fasting. For LH and FSH measurements, samples were collected during early follicular phase (day 2 to 5) of menstrual cycle. Free testosterone levels and 17-OHP estimation was done using radioimmunoassay kit. Presence of insulin resistance was determined by using fasting glucose to fasting insulin ratio. A fasting glucose (FG) to fasting insulin (FI) ratio less than 4.5 was taken as insulin resistance. Fasting glucose-to-insulin ratio is a reliable method for calculating insulin resistance in PCOS women [8].

STATISTICAL ANALYSIS:

Continuous data were expressed as mean ± standard deviation (SD) and categorical data as percentages. Continuous variables were compared between obese and non-obese women by independent sample t-test whereas categorical variables were compared using chi-square test. Logistic regression analysis was done to identify independent association with IR. p value less than 0.05 was taken as significant. To perform all these functions, SPSS version 16 statistical packages were utilized.

RESULTS:

A total of 80 women fulfilled the definition of PCOS using Rotterdam criteria. 38 (47.5%) of them had normal BMI (BMI ≤ 24.99) and 42 (52.5%) were either overweight or obese (BMI ≥ 25). The mean age at presentation was 24.2 ± 5.5 years. Central obesity was seen in 44 (55%). Menstrual irregularity was seen in 56 (70%), infertility in 2 out of 38 eligible patients (65.8%), acne in 51 (63.7%), hirsutism in 41 (51.2%) and alopecia in 6 (7.5%). Acanthosis nigricans was found in 36 (45%). Insulin resistance was present in 45 (56.25%).

COMPARISON OF OBESE AND NON-OBESE PCOS:

Table 1 shows the comparison between obese and non-obese PCOS. There was no difference in age of presentation, age at menarche, LH, FSH and TSH levels. The clinical prevalence of menstrual irregularities, acne, hirsutism, infertility and alopecia were also similar between the two groups. The prevalence of insulin resistance was significantly higher in

obese (69.05%) PCOS as compared to non-obese (42.1%); p = 0.024. Thirty-eight of 42 obese women met the criteria for central obesity, whereas 6/38 non-obese women met the definition of central obesity. Acanthosis nigricans was found significantly higher in obese PCOS women (61.9%) as compared to non obese PCOS women (26%) (p = 0.002). There was a significantly higher free testosterone levels in obese women (Obese PCOS: 4.24 ± 5.35ng/ml; Non-obese PCOS: 1.95 ±3.19ng/ml, p = 0.02). The mean 17-OHP level was 0.840±0.75ng/ml in non-obese women as compared to obese women in whom the 17-OHP level was 1.54 ± 1.16ng/ml (p = 0.002).

INSULIN RESISTANCE AND OBESITY IN PCOS:

Of the 80 PCOS women included in the study, 45 met the definition of IR based on fasting glucose to insulin ratio. **Table 2** shows the comparison between PCOS women with or without IR. As evident from table 2, women with IR had higher BMI (p < 0.0005), higher waist-to-hip ratio (p < 0.0005), higher fasting insulin levels (p < 0.0005), higher testosterone levels (p < 0.0005), higher 17-OHP level (p < 0.0005), increased prevalence of acanthosis and alopecia. On logistic regression analysis, waist-to-hip ratio was the only variable significantly associated with presence of IR. IR was not present in any of the 4 obese women who did not have central obesity. Similarly, all 6 non-obese PCOS with presence of central obesity had IR **[Figure 1]**. This suggests that central obesity, but not BMI has a key role in development of IR in PCOS women. Inversely, 42.1% of non-obese PCOS and 27.8% of PCOS without central obesity had IR. Hence, although less common than in obese, still lean PCOS with IR is an emerging entity.

DISCUSSION:

In the present study on 80 PCOS women, 52.5% were obese and 55% were having central obesity. Higher waist-to-hip ratio was the only factor independently associated with presence of IR suggesting that women with central obesity are at the maximum risk of development of IR. PCOS patients with IR also had higher testosterone and 17-OHP level.

Data on association of obesity and insulin resistance in various studies across the globe are contrasting. While studies by Dunaif & Finegood, Meher-Un Nisa, Vrbikova et al., Eagleson etal. and Carmina & Lobo [4, 9-11] propose that prevalence of insulin resistance is significantly higher among obese PCOS women, other studies by Grulet et al., Takeuchi et al. [12] and Kalra et al. [13] report that insulin resistance is a feature of PCOS independent of obesity. Central obesity was the only independent association with IR in our study on PCOS women. Central obesity has been shown to be significant predictor of metabolic syndrome and non-alcoholic fatty liver disease [14].

Another important thing to take note of is that although insulin resistance was lower in lean PCOS women as compare to the obese women, it was still a very high percentage of lean PCOS women (42.1%). Thus implying that although obesity is a major risk factor for development of insulin resistance, a large chunk of these insulin resistant PCOS women are lean PCOS women who will require treatment with insulin sensitizers. It also implies that irrespective of clinical signs or symptoms and BMI status, all PCOS women in India should be assessed for presence or absence of insulin resistance to determine the candidates for insulin sensitizer therapy.

CONCLUSION:

Central obesity is an independent risk factor for development of IR in women with PCOS. All women with PCOS irrespective of presence or absence of obesity should be evaluated for presence of IR by biochemical test to identify need for insulin sensitizers.

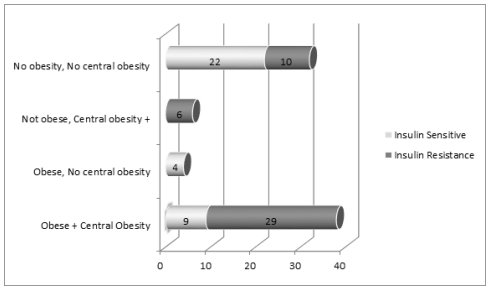
Table 1: Comparison between obese and non-obese women with Polycystic Ovary Syndrome

	Obese n = 42	Non-obese n = 38	p value
Age at presentation (yrs)	24.5 ± 5.5	23.9 ± 5.6	0.627
Age at menarche (yrs)	11.7 ± 1.2	11.3 ± 1.1	0.094
Acne (%)	27 (64.3%)	24 (63.2%)	1
Menstrual irregularities (%)	32 (76.2%)	24 (63.2%)	0.230
Alopecia (%)	4 (9.5%)	2 (5.2%)	0.678
Infertility (%)	13/20 (65%)	12/18 (66.7%)	1
Hirsutism (%)	23 (54.8%)	18 (47.4%)	0.655
Acanthosis Nigricans (%)	26 (61.9%)	10 (26.3%)	0.002
BMI (kg/m2)	31.1 ± 4.1	21.7 ± 1.7	< 0.0005
Waist-to-hip ratio	0.95 ± 0.23	0.63 ± 0.17	< 0.0005
Central Obesity (%)	38 (90.5%)	6 (15.8%)	< 0.0005
Fasting Insulin (μIU/ml)	28.28 ± 25.9	17.42 ± 13.8	0.023
Fasting glucose to insulin ratio	4.89 ± 3.67	7.95 ± 6.44	0.013
Insulin Resistance (%)	29 (69%)	16 (42.1%)	0.024
Lutenizing Hormone (mIU/ml)	18.37 ± 14.9	21.38 ± 13.39	0.347
Follicle Stimulating Hormone (mIU/ml)	10.82 ± 7.68	12.23 ± 10.4	0.492
Testosterone (ng/dl)	4.24 ± 5.35	1.95 ± 3.19	0.022

Table 2: Comparison between those with and without Insulin Resistance among women with Polycystic Ovary Syndrome

	Insulin Resistance n = 45	Insulin Sensitive n = 35	p value
Age at presentation (yrs)	24 ± 4.87	24.4 ± 6.37	0.734
Age at menarche (yrs)	11.62 ± 1.2	11.34 ± 1.2	0.305
Acne (%)	32 (71.1%)	9 (25.7%)	< 0.0005
Menstrual irregularities (%)	34 (75.5%)	22 (62.8%)	0.232
Alopecia (%)	6 (13.3%)	0	0.033
Infertility (%)	13/19 (68.4%)	12/19 (63.1%)	1
Acanthosis Nigricans (%)	27 (60%)	9 (25.7%)	0.003
BMI (kg/m2)	28.5 ± 5.9	24.2 ± 4.4	< 0.0005
Obese (%)	29 (64.4%)	13 (37.1%)	0.024
Waist-to-hip ratio	0.9 ± 0.25	0.65 ± 0.2	< 0.0005
Central Obesity (%)	35 (77.8%)	9 (25.7%)	< 0.0005
Fasting glucose (mg/dl)	88.6 ± 26.5	82.8 ± 24.9	0.324
Fasting Insulin (μIU/ml)	33.6 ± 23.6	9.7 ± 4.45	< 0.0005
Fasting glucose to insulin ratio	3.16 ± 1.05	10.44 ± 5.9	< 0.0005
Lutenizing Hormone (mIU/ml)	21 ± 15.5	18.2 ± 12.3	0.388
Follicle Stimulating Hormone (mIU/ml)	11.6 ± 9.3	11.3 ± 8.85	0.881
Testosterone (ng/dl)	4.7 ± 5.4	1.18 ± 1.99	< 0.0005

Figure 1: Insulin resistance in women with obesity calculated by BMI versus those having central obesity



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