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Determination of Source of Hyperandrogenism and Comparisons of Hormonal and Metabolic Profile in Different Phenotype of PCOS: A Hospital Based Study

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Abstract

Objective: Metabolic parameters in polycystic ovary syndrome (PCOS) correlate to their phenotypic presentations and sources of hyperandrogenism. Till date no studies have evaluated the source of hyperandrogenism among phenotypic variants of PCOS. Therefore we determined the sources of hyperandrogenism and compared the metabolic parameters in different phenotypes of PCOS.

Material method: Study included 120 PCOS patients and 15 age matched controls. PCOS were diagnosed by revised Rotterdam criteria (2003). Different phenotypic presentations like polycystic ovary (P), ovulatory dysfunction (O) and hyperandrogenism (H) were evaluated and compared for anthropometrical, hormonal and metabolic parameters. They were correlated with the source of androgen excess following post Leuprolide acetate (20 µg/kg) 17-OHP and post synacthen (250 µg) DHEAS measurement.

Result: This study had 2 phenotypic presentations i.e. PHO (80%) and OH (20%) out of 4 phenotypic presentations described by Rotterdam among all PCOS (may be due to referral bias). Among obese PCOS 87.5% had PHO and 12.5% had OH phenotypes, while it was 75% and 25% in normal weight PCOS. PHO phenotypes had adrenal and ovarian source of hyperandrogenism. Fasting insulin and HOMA-IR were higher in non-obese PHO than obese PHO but statistically insignificant. Serum DHEAS (delta steroid) had a negative but serum testosterone (keto steroid) had positive correlation with IR in PCOS.

Conclusion: Both adrenal and ovarian hyperandrogenism was found in PHO as compared to OH phenotype that had only ovarian hyperandrogenism. Normal weight PCOS had less chance of getting ultrasound abnormalities compared to obese PCOS. PHO phenotypes, who had a greater degree of serum DHEAS had a better metabolic profile despite a greater BMI. So our result suggests that distinction between source of hyperandrogenism and evaluation of different phenotype is beneficial in predicting metabolic risk and future management.

Keywords: PCOS; Ovarian hyperandrogenism; adrenal hyperandrogenism; HOMA-IR

Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women of reproductive age, which has multiple etiologies with heterogeneous presentations. Worldwide prevalence is approximately 4-11.9% [1]. According to Nidhi et al. prevalence of PCOS in Indian adolescents is 9.13% [2]. PCOS includes polycystic ovary (P), ovulatory dysfunction (O) and hyperandrogenism (H). Ehrmann et al. described hyperandrogenism in PCOS as ovarian dysfunction (25%), adrenal dysfunction (25%) or both (33%) [3]. Various studies suggested that ovarian and adrenal androgens have opposing effects on body weight and insulin metabolism in women with PCOS [4,5]. High testosterone (keto steroid) levels are linked with obesity, in particular with an abdominal fat distribution, as well as with insulin resistance and a higher prevalence of glucose intolerance, while the role of adrenal androgens (serum DHEAS (delta steroid)) is less clear relating to metabolic disturbances [6,7]. One study suggested a positive association of high DHEAS levels with hypertension [8]. Conversely, Brennan et al. and Chen et al. found an independent association of high DHEAS levels with decreased insulin resistance associated with a beneficial metabolic phenotype, like abdominal obesity and dyslipidemia [2,6].

Subject and Method

One hundred twenty patients with PCOS diagnosed by the revised Rotterdam criteria (2003) [9] were taken for the study. Fifteen age matched control were included in the study to find out the normal mean and standard deviation of different hormonal parameter in the community. Those patients who had any known medical illnesses like diabetes mellitus, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), Cushing's syndrome, hyperprolactinemia, congenital adrenal hyperplasia, active thyroid disorder or were on medications like corticosteroids, oral contraceptives, metformin etc which could alter the endocrine and metabolic parameters were excluded from the study. Institutional Ethical Committee clearance and informed consent was obtained from all subjects involved in the study. The study was

conducted in the department of Endocrinology of a tertiary care teaching hospital catering the health needs of people of eastern part of India from September 2012 to October 2014.

A thorough physical examination was done by a single examiner that included measurement of weight, height and body mass index (BMI). BMI was calculated using the formula: weight (kg)/ height^2 (meter). Waist circumference (WC) was measured with the patient standing and taking a point midway between the lower costal margin and the iliac crest at the mid axillary line. Normal weight: 18.0-22.9 kg/m^2 , Overweight: 23.0-24.9 kg/m^2 , Obesity: >25 kg/m^2 and central obesity: WC>80 cm were defined according to Mishra et al. [9].

All patients were asked to give a detailed menstrual history including age of menarche, regularity, duration, and number of cycles per year. Oligomenorrhoea (O) is defined as an intermenstrual interval of >35 days or a total of <9 menses per year and amenorrhea as absence of menstruation during last 6 months or more. Hyperandrogenism (H) was assessed by both clinical and biochemical parameters. Biochemical hyperandrogenemia was defined by a serum level of total testosterone (TT (keto steroid)) or dehydroepiandrosterone sulphate (DHEAS (delta steroid)) greater than mean ± 2 standard deviation (SD) above the control. Hirsutism was used as a parameter for clinical hyperandrogenism which is assessed by using modified Ferriman-Gallwey (FG) score counting nine specified body areas by a single observer with a good reproducibility. A score of ≥ 8 out of a total of 36 was taken as significant. A transabdominal ultrasonography was done in all cases to demonstrate the feature suggestive of PCOS (i.e. presence of more than 12 peripheral ovarian follicles, each between 2-9 mm and ovarian volume >10 cm^3 suggestive of PCOS) [10].

Blood samples were obtained from patients in a fasting state for biochemical evaluation. Lipid profile, fasting plasma glucose (FPG), 2 hour 75 gm OGTT (Impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and T2DM were diagnosed according to ADA 2011 criteria [11]. IFG was defined as having FPG levels ranging from 100-125 mg/dl and IGT when a 2 hour post glucose value in OGTT was between 140 to 199 mg/dl. A patient having FPG of ≥ 126 mg/dl or a 2 hour post glucose value of ≥ 200 mg/dl was considered to have diabetes mellitus. Samples for hormonal analysis including basal 17-hydroxy progesterone (17-OHP), free tri iodo thyronine (fT3), free tetra iodo thyronine (fT4), thyroid stimulating hormone (TSH), prolactin, leutinizing hormone (LH), follicle stimulating hormone (FSH), TT, serum DHEAS and serum fasting insulin was collected between days 3rd to 7th (early follicular phase) of spontaneous menstrual cycle or anytime in amenorhoeic patients (>2 months) [12].

Overnight dexamethasone suppression test (ODS) was done to rule out Cushing's syndrome. Post Leuprolide acetate (20 μg/kg) serum 17-OHP (here after referred as stimulated 17 OHP) and Post synacthen (250 μg) serum DHEAS (here after referred as stimulated DHEAS) was measured to look for the source of hyperandrogenism. The response to Leuprolide acetate was considered positive if the peak serum stimulated 17-OHP concentration was greater than 2 SD above the mean values in 15 controls and diagnosed as ovarian hyperandrogenism. The response to Synacthen was considered positive if the peak serum stimulated DHEAS concentration was greater than 2 SD above the mean values in 15 controls and diagnosed as adrenal hyperandrogenism [12].

Assays

LH, FSH, TT and S.DHEAS concentrations were determined by chemi-luminescent immunometric assays (e-411 Cobas, Roche Diagnostics). The intra and inter assay coefficient of variation were between 3.6% to 6.7%. The plasma glucose level was determined by glucose oxidase peroxidase method. Fasting serum insulin level measured by chemiluminescent immunometric assays (e-411 Cobas, Roche Diagnostics) with Intra and inter assay coefficient of variability was 6.0% and 8.0%. Insulin resistance (IR) was quantified by calculating homeostatic model assessment of IR (HOMA-IR) (fasting Insulin mIU/L × fasting Glucose (mg/dl)/405). Women with PCOS were divided into four groups, based on phenotype, according to their clinical characteristics: PHO (polycystic ovary, hyperandrogenism and ovulatory dysfunction), OH (ovulatory dysfunction and hyperandrogenism), PH (polycystic ovary and hyperandrogenism) and PO (polycystic ovary and ovulatory dysfunction).

Statistical Analysis

Differences in basal characteristics and laboratory data among the groups were analyzed by unpaired t test for normally distributed parameters, and Mann-Whitney test for dual-wise comparisons for parameters with skewed distribution. Pearson correlations were used to examine the relationship between DHEAS levels, serum testosterone and HOMA-IR values. SPSS 17.0 software was used for analyses. Values were described as mean ± SD and p value <0.05 was considered as statistically significant.

Results

The PCOS patients in our study were relatively younger compared to control and had oligomenorrhic cycle. Hirsutism was significant in PCOS patients as compared to control, had impaired glucose tolerance and higher value of insulin resistance (HOMA-IR-4 ± 1.82). Both the groups were euthyroid. Stimulated S.DHEAS and stimulated S.17-OHP value in controls were used as cutoff for identification of source of hyperandrogenism (Table 1). Serum DHEAS had a negative (Pearson correlation -0.314, P-0.007) but serum testosterone had significant positive correlation (Pearson correlation 0.312, P-0.014) with insulin resistance in PCOS patients (Figures 1 and 2).

Forty percent of PCOS patients were obese whereas rest were non obese. The present study had 2 phenotypic presentations of PCOS i.e. PHO and OH. 80% had PHO and 20% had OH phenotype at the time of presentation. Mean BMI in PHO was higher than OH but was statistically insignificant. Mean FG scores in PHO was greater than OH phenotypes which were statistically significant (Table 2). OH phenotype had more oligomenorrhic cycle and a worse metabolic profile as compared to classical PHO phenotype. Dyslipidemia was more evident in OH phenotype however it was statistically not significant. Mean serum TT was significantly higher in PHO phenotype compared to OH phenotype. Among OH phenotypes only stimulated 17OHP was crossing the cutoff confirmed an ovarian source of hyperandrogenism, but on the other hand, PHO phenotypes had both adrenal and ovarian source of hyperandrogenism (crossed the cutoff of stimulated 17 OHP and stimulated DHEAS) (Table 2).

Parameters	PCOS (n-120)	Reference group (n-15)	P value
	Mean ± SD	Mean ± SD	
Age (Yr)	20.4 ± 3.6	20.73 ± 4.44	0.775
BMI(kg/m^2)	24.1 ± 6.2	24.61 ± 3.36	0.799
No. of menstrual cycle/year	3.8 ± 2.4	10.00 ± 0.00	0
FG Score	13.9 ± 4.5	3.73 ± 1.66	0
FPG (mg/dl)	84.7 ± 10.06	87.53 ± 8.61	0.32
2 hr 75 gm PPG (mg/dl)	149.5 ± 44.8	112.07 ± 15.20	0.063
Fasting Insulin (mIU/ml)	11.7 ± 8	5.36 ± 1.30	0.033
HOMA- IR (mIUxmg/dl)	4 ± 1.82	1.17 ± 0.33	0.034
S. Cholesterol (mg/dl)	165.4 ± 21.6	162.27 ± 17.53	0.6
S. Triglyceride (mg/dl)	117.3 ± 26.03	117.53 ± 20.90	0.975
S.HDL (mg/dl)	41.3 ± 5.6	41.40 ± 4.53	0.98
S.LDL (mg/dl)	98.8 ± 14.5	94.67 ± 17.56	0.347
S.VLDL (mg/dl)	24.1 ± 5.7	23.56 ± 4.83	0.749
FT3 (pg/ml)	3.1 ± 0.4	2.06 ± 0.35	0.086
FT4 (ng/dl)	1.21 ± 0.18	1.09 ± 0.13	0.079
TSH (mIU/ml)	2.1 ± 1.09	1.92 ± 0.76	0.426
LH (mIU/ml)	7.4 ± 3.8	4.55 ± 1.77	0.005
FSH (mIU/ml)	4.8 ± 1.7	4.09 ± 1.31	0.133
S. Testosteron (ng/dl)	89.6 ± 82.8	21.26 ± 3.96	0.004
17 OHP (ng/ml)	1.11 ± 0.54	1.30 ± 0.53	0.241
DHEAS (µg/dl)	228.4 ± 133.4	133.33 ± 20.40	0.004
S. Prolactin (ng/ml)	18.6 ± 12.2	13.72 ± 3.98	0.13
Post GNRH17 OHP (ng/ml)	3.8 ± 2.7	1.84 ± 0.33	0.006
Post Synacthen DHEAS (µg/dl)	304.4 ± 225.2	149.33 ± 24.29	0

Table 1: Comparison between PCOS patients and control.

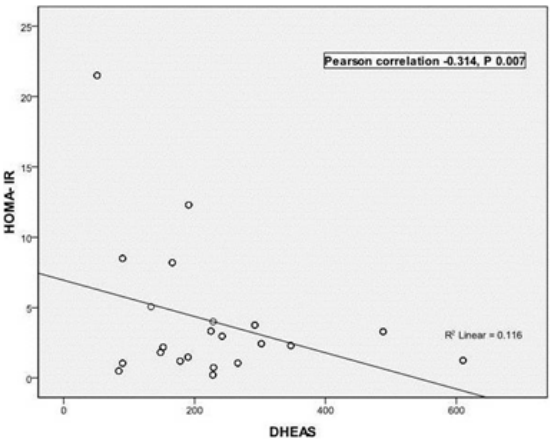

Figure 1: Pearson correlation between Serum DHEAS and HOMA-IR.

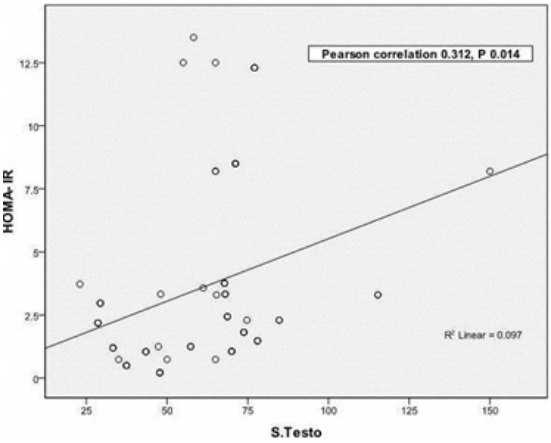

Figure 2: Pearson correlation between Serum Testosterone and HOMA-IR.

Among obese PCOS patients, 87.5% had PHO and 12.5% had OH phenotype while in normal weight PCOS patients 75% had PHO and 25% had OH phenotype (Figure 3). Obese PHO were younger then obese OH phenotypic groups, but in non-obese groups both phenotypes had same mean age of presentation. Though both obese and normal weight PHO had impaired glucose tolerance obese were good glycemic status compared to non-obese (P value-0.005). Both obese and normal weight PHO had adrenal and ovarian source of hyperandrogenism in the form of higher stimulated S.DHEAS and stimulated S.17 OHP from control cut off.

In contrast OH phenotypes had only ovarian source of hyperandrogenism in the form of higher stimulated S. 17 OHP from control cut off (Table 3). Fasting insulin and HOMA-IR in non-obese PHO were higher than obese but it was statistically insignificant. Though the mean serum testosterone in obese PHO phenotypes was lower than non-obese but they had significantly higher serum DHEAS compared to non-obese phenotypes (Table 3).

Parameters	PHO (n-96)	OH (n-24)	P Value
	Mean ± SD	Mean ± SD	
Age (Yr)	20.33 ± 3.62	20.75 ± 4.00	0.908
BMI(kg/m^2)	24.40 ± 5.44	23.32 ± 8.91	0.822
FG score	15.50 ± 8.78	13.50 ± 2.60	0
No. of menstrual cycle/year	4.44 ± 2.31	1.50 ± 1.56	0
FPG (mg/dl)	84.88 ± 9.30	84.00 ± 13.14	0.589
2 hr 75 gm PPG (mg/dl)	143.69 ± 38.96	157.00 ± 65.54	0.075
FBS Insulin (mIU/ml)	14.61 ± 13.10	25.62 ± 37.02	0.018
HOMA- IR (mIUxmg/dl)	3.48 ± 3.23	6.10 ± 9.31	0.022
S. Cholesterol (mg/dl)	161.44 ± 22.45	166.50 ± 18.42	0.67
S. Triglyceride (mg/dl)	100.56 ± 26.10	121.50 ± 18.35	0.031
S.HDL (mg/dl)	40.69 ± 5.80	41.00 ± 4.72	0.63
S.LDL (mg/dl)	98.25 ± 14.76	101.00 ± 13.77	0.551
S.VLDL (mg/dl)	20.12 ± 5.73	25.00 ± 3.69	0.014
LH (mIU/ml)	7.32 ± 3.73	7.70 ± 3.51	0.018
FSH (mIU/ml)	5.65 ± 1.69	4.63 ± 1.74	0.057
S. Testosterone (ng/dl)	142.74 ± 109.25	109.98 ± 92.21	0.015
S. 17 OHP (ng/ml)	1.27 ± 0.87	1.07 ± 0.44	0.276
S. DHEAS (µg/dl)	253.38 ± 134.22	128.82 ± 70.84	0
S. Prolactin (ng/ml)	17.47 ± 8.36	23.31 ± 21.73	0.085
Post GnRH 17 OHP (ng/ml)	4.07 ± 3.63	3.76 ± 2.47	0.022
Post Synacthen DHEAS (µg/dl)	283.1 ± 69.98	147.1 ± 146.59	0

Table 2: Comparison of clinical, metabolic and hormonal variable in different phenotypes of PCOS patients.

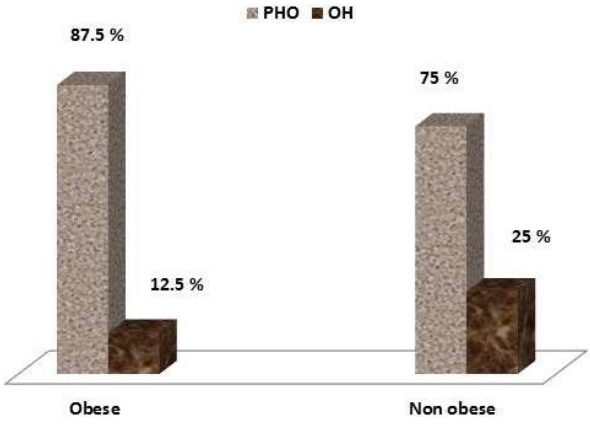

Figure 3: percentage of phenotypic presentation between obese and non-obese PCOS.

Parameter	Obese PHO (n=42)	Non obese PHO (n=54)	Mann Whitney U test	Obese OH (n=6)	Non obese OH (n=18)	Mann Whitney U test
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Age	18.6 ± 3.2	21.6 ± 3.2	0.004	20 ± 4	21.4 ± 3.5	0.15
BMI (kg/m^2)	29.4 ± 2.6	20.4 ± 3.3	0	29 ± 8.5	22.3 ± 8.4	0.77
FPG (mg/dl)	82.5 ± 10.7	87.8 ± 5.4	0.011	87.5 ± 13.5	81.3 ± 11.3	0.15
2 hr 75 gm OGTT (mg/dl)	142.8 ± 39.02	154.8 ± 31.1	0.005	167.5 ± 78.5	147.7 ± 45.7	0.39
S. Cholesterol (mg/dl)	160.8 ± 25.5	173.5 ± 14.3	0.019	163.5 ± 18.5	162.8 ± 17.4	0.15
LDL (mg/dl)	94.3 ± 14.7	103.2 ± 12.7	0.015	99 ± 14	103.2 ± 12.4	0.77
HDL (mg/dl)	45 ± 3.5	39.1 ± 5.8	0	40.5 ± 4.5	40.3 ± 4.5	0.15
Non HDL Cholesterol (mg/dl)	123.4 ± 14.2	125.2 ± 12.5	0.014	120.4 ± 16.8	125.2 ± 12.7	0.34
Insulin (mIU/ml)	11.7 ± 3.7	16.8 ± 16.6	0.303	11.8 ± 0.2	5.2 ± 4.7	0.15
HOMA-IR	2.5 ± 0.8	4.22 ± 4.05	0.779	2.3 ± 0.1	1 ± 0.9	0.04
Mod. FG score	13.1 ± 2.7	13.7 ± 2.3	0.04	12.5 ± 0.5	10.7 ± 1.1	0.02
Testosterone (ng/dl)	79.1 ± 47.01	100.7 ± 84.6	0.086	46.7 ± 18.2	41.9 ± 10.8	0.44
DHEAS (µg/dl)	235.1 ± 83.6	189.7 ± 45.2	0.024	101.5 ± 50.4	143.5 ± 63.2	0.15
Post GnRH 17 OHP (ng/ml)	3.7 ± 1.8	3.8 ± 2.8	0.92	6.6 ± 3.3	2.8 ± 2.6	0.04
Post synacthen DHEAS (µg/dl)	246.1 ± 77.01	229 ± 50.4	0.22	137.4 ± 58.6	156.8 ± 67.7	0.15

Table 3: Comparison of metabolic and hormonal profile between obese and non-obese phenotypically different PCOS.

Discussion

PCOS patients in this study had insulin resistance, hyperinsulinemia with impaired glucose tolerance, dyslipidemia and hirsutism. Wild et al. in their study in PCOS found dyslipidemia (high triglyceride, low HDL and high non HDL cholesterol) which had been attributed to multiple factors including androgen excess, insulin resistance, excess estrogen exposure and environmental factors [13]. In the present study dyslipidemia in PCOS might be contributed by the same factor as described by Wild et al.

It has been suggested that ovarian and adrenal androgens have opposing effects on body weight and insulin metabolism in women with PCOS. Studies showed that high total testosterone (TT) and free testosterone (FT) levels are associated with an adverse metabolic phenotype in women with PCOS but role of adrenal androgens (DHEAS) in metabolic disturbances is less clear [7]. Schunkert et al. suggested a positive association of high DHEAS levels with metabolic disturbances such as hypertension whereas Brennan et al. found an independent association of high DHEAS levels with decreased insulin resistance in a cohort of 352 women with PCOS [5,8]. Chen et al. demonstrated in 318 women with PCOS that despite a positive correlation of DHEAS levels with testosterone, high DHEAS levels were positively associated with a beneficial metabolic phenotype, including parameters such as abdominal obesity, insulin resistance, and dyslipidemia [14]. In our study Serum DHEAS had a negative but serum testosterone had significant positive correlation with insulin resistance in PCOS.

Possible mechanism for the beneficial effect of DHEAS on metabolic parameters in PCOS could be:

1. DHEA decreases gluconeogenesis by suppressing the activity and expression of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (two key enzymes in gluconeogenesis). Furthermore, DHEA increases glucose uptake in hepatocytes and increases insulin binding to its receptor.
2. High circulating levels of glucose or insulin might impact DHEAS synthesis in the adrenal gland, which might be mediated via insulin action on the latter.
3. DHEAS supplementation in women aged 40 to 70 years leads to an increase in insulin like growth factor (IGF-1) levels as well as an improvement of physical and psychological well-being but without a significant change in insulin sensitivity [15-17]. Further Kameda et al. found that decreased level of DHEAS is associated with the development of type 2 DM [18].

In our study all patients of PCOS had oligomenorrhea and hyperandrogenism. According to the individual combinations of these features, 96 (80%) of these women had the classic phenotype (PHO), whereas 24 (20%) had oligomenorrhea, hyperandrogenism but normal morphology of ovary (OH). Baldani et al. and Cinar et al. described four phenotypic presentations in PCOS as PHO, OH, PH and PO [19,20]. Baldani found 56.7%, 2.3%, 14.3% and 26.7% of PHO, OH, PH and PO phenotype in their study respectively. Our study had 2 phenotypic presentations which could be due to referral bias. In agreement to Cinar et al., we also found significantly higher serum testosterone and DHEAS in PHO compared to OH phenotypes. Both

stimulated S.DHEAS and stimulated S.17 OHP gives a clue that PCOS with poly cystic ovary had both adrenal and ovarian sources of hyperandrogenism as compared to OH phenotypes which had predominant ovarian source. Similar to Cinar et al. this study also had significantly higher fasting serum insulin and HOMA-IR in PHO as compared to OH phenotypes.

With a cutoff BMI of 25 kg/m^2, 48 females (40%) were obese and 72 females (60%) were normal weight PCOS. Gambineri et al. reported that 50% of PCOS patients were obese while Legro and colleagues reported in their 254 cases of PCOS that 78% of PCOS women were overweight (BMI ≥ 25 kg/m^2), and 73% were obese (BMI ≥ 27 kg/m^2) [21,22]. Ganie et al. in their study of 168 PCOS patients in India found the mean BMI in their study to be 26.89 kg/m^2 with 66% had BMI ≥ 25 kg/m^2, which was much higher than our study [23]. Other studies in India have also reported a higher mean BMI in PCOS patients ranging from 25 to 28 kg/m^2 [24,25]. The lower BMI in our patients could be due to the geographical, ethnic or dietary factors. Moran et al. showed that magnitude of overweight and obesity is directly related to insulin resistance in PCOS patients [26]. One key finding in this study was that the obese PHO phenotypes were metabolically healthier as compared to non-obese PHO phenotypes despite a greater BMI in the former groups. High DHEAS in the obese PHO phenotypes could have contributed to the possible difference. Kiddy et al. reported a greater prevalence hirsutism and menstrual disorders in obese than non-obese PCOS patients in contrary to our study where these features were more in non-obese PHO phenotype because of high serum testosterone compared to other phenotypic variants [27].

Conclusion

Both adrenal and ovarian hyperandrogenism was found in PHO phenotype as compared to OH who had only ovarian hyperandrogenism. PCOS with evidence of adrenal source of hyperandrogenism (high delta steroid) were metabolically better than those subsets who had only ovarian source of hyperandrogenism in spite of higher BMI. Normal weight PCOS had more chance of getting normal sonography compared to obese PCOS. Basing on our results, we suggest that documentation of source of hyperandrogenism and their phenotypic differentiation is as vital as documentation of level of hyperandrogenism in a PCOS patient. It will be of great help in stratifying and prognosticating PCOS patients with adverse metabolic profiles.

Limitation of the Study

This study included less number of cases with only 2 phenotypic presentations; might be due to referral bias. But the observations were statistically significant and it needs further study to validate our result in future.

Declaration of Interest and Funding

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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