

## Original Research Article

# Predictors of insulin resistance among women with acne vulgaris and polycystic ovarian syndrome presenting to a tertiary care hospital in North India

Mini Chandra<sup>1</sup>, Koshinder Vats<sup>1</sup>, Palak Garg<sup>2</sup>, Abhishek Tibrewal<sup>3\*</sup>

<sup>1</sup>Department of Dermatology, Venerology and Leprology, Muzaffarnagar Medical College, Uttar Pradesh, India

<sup>2</sup>Department of Dermatology, Venerology and Leprology, National Institute of Medical Sciences and Research, Jaipur, Rajasthan, India

<sup>3</sup>Department of Epidemiology and Biostatistics, Independent Consultant, Gurugram, Haryana, India

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### \*Correspondence:

Dr. Abhishek Tibrewal,

E-mail: dr.abhishek08@ hotmail.com

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## ABSTRACT

**Background:** Acne vulgaris is now being increasingly associated with hyperandrogenism or metabolic syndrome. The aim of the study was to know the burden and determinants of insulin resistance among females suffering from acne and polycystic ovarian syndrome (PCOS).

**Methods:** This prospective observational study included non-pregnant females with acne and PCOS aged 14 to 36 years. PCOS was diagnosed using Rotterdam criteria. Insulin resistance (IR) was confirmed using HOMA-IR values. Important history was ascertained, and hormonal essays were done. SPSS version 22 was used for the analyses.

**Results:** The average age of the 81 subjects was 22 (IQR: 19-23) years and median duration of acne was 8 (7-9) months. Their median (IQR) insulin level was 10.5 (8.4 - 18.5), fasting blood glucose was 82 (73.2 - 90) and HOMA-IR value was 2 (1.7 - 3.9). A total of 27 (33.3%) were diagnosed with IR. Subjects having IR had significantly lower FSH (median=3.1, IQR: 2.3-6.3), LH (3.0, 1.2-3.3) and insulin level (median=26.0, 18.5-28.5) versus those without IR ( $p=0.04$ ,  $p=0.04$  and  $p<0.001$  respectively). Subjects with IR were more likely to be having irregular menses, weight gain, and acanthosis nigricans versus those without IR.

**Conclusions:** One-third of the patients with acne and PCOS also had IR according to the HOMA-IR values. All women with acne and PCOS should be considered for underlying IR and examined for other sign of impaired glucose tolerance.

**Keywords:** Acne vulgaris, PCOS, Insulin resistance, HOMA-IR, India

## INTRODUCTION

Acne vulgaris is one of the most common dermatological condition affecting youth. The reported prevalence of acne varies from 35 to over 90% of adolescents at some stage.<sup>1,2</sup> However, the prevalence of acne varies in different age groups of different countries. The pathogenesis of acne is majorly hormonal and hormones implicated in acne pathogenesis include androgens, estrogens, progesterone,

insulin and insulin-like growth factor-1, CRH, adrenocorticotrophic hormone (ACTH), melanocortins, glucocorticoids, and growth hormone (GH).<sup>3</sup> Insulin stimulates the growth and maturation of sebaceous glands. This action is mediated through upregulation of growth hormone receptors on the sebocytes by insulin.<sup>4</sup> Moreover, insulin inhibits sex-hormone binding globulin (SHBG) production from the liver and further plays a positive feedback effect on adrenal and ovarian androgenesis.<sup>5</sup>

Therefore the association between PCOS and IR with patients of acne vulgaris is commonly found in females from age group 14 to 36 years of age.

Historically, several rare syndromes of extreme insulin resistance, acanthosis nigricans, and hyperandrogenism were described during the 1970s.<sup>6</sup> Till then, PCOS was not much understood except being a vague reproductive disorder.<sup>7,8</sup> In 1980s, it was reported that PCOS is also associated with increased insulin response upon oral glucose tolerance test, which indicates insulin resistance.<sup>9</sup><sup>11</sup> In a landmark study done by Donald et al, it was reported that derangements in glucose homeostasis was a feature of PCOS, specially of the anovulatory phenotype.<sup>12</sup> In Pima Indians study and in the Nurses Health Study II too, the risk for T2D was significantly increased in women with menstrual irregularity.<sup>13,14</sup> It is notable that the clinical signs of hyperandrogenism, which is a hallmark of PCOS, like acne, hirsutism, seborrhoea, alopecia, and in extreme cases virilization, have also been associated with IR and hyperinsulinemia.<sup>15</sup>

IR is defined as reduced insulin sensitivity (IS) and refers to an increased patient.<sup>16</sup> But insulin resistance may be present in PCOS independently of amount of insulin needed to perform its metabolic actions.<sup>17</sup> Though, it may seem probable that insulin resistance linked to PCOS can be attributed to obesity, which occurs in a large number of PCOS obesity too.<sup>18</sup>

Though the pathophysiology has been extensively studied, there is paucity of studies done on prevalence and associated factors of insulin resistance among acne patients with PCOS in India. The aim of the study was to know the burden and determinants of IR among females suffering from acne and PCOS.

## METHODS

The present study was a prospective observational study conducted among 100 patients of acne vulgaris, who presented to the out-patient department of the dermatology and venerology department of our hospital. The study duration was 14 months, starting from December 2018 till January 2020.

### *Inclusion and exclusion criteria*

The study subjects were 14 to 36 years old, non-pregnant females, who agreed to be a part of the study. Patients who were smokers, pregnant or lactating, taking hormonal therapy like hormonal contraceptive and antiandrogen therapy, and suffering from any chronic disease, like hypertension, diabetes mellitus, vascular disorder, and systemic inflammatory disorder, were excluded from the study.

Out of 100 acne patients, 81 subjects were diagnosed with PCOD and have been included in the study. The rest of the 19 subjects have been excluded from analysis.

## *Operational terms and definitions*

### *Acne*

Acne is a chronic inflammatory disease of pilosebaceous follicles characterized by comedones, papules, pustules, nodules and often scars.<sup>19</sup> Acne vulgaris was graded based on the severity of acne vulgaris using grading based on clinical examination, lesion counting, and those that require instruments such as photography, fluorescent photography, polarized light photography, video microscopy and measurement of sebum production. The two commonly used measures are grading and lesion counting.

Acne vulgaris was graded by Indian authors, using a simple grading system, which classifies acne vulgaris into four grades as follows: (a) Grade 1: comedones, occasional papules; (b) Grade 2: papules, comedones, few pustules; (c) Grade 3: predominant pustules, nodules, abscesses; and (d) Grade 4: mainly cysts, abscesses, widespread scarring.<sup>20</sup>

### *Menstrual history and irregularity*

We enquired about the cycle lengths, irregularities, duration of bleeding, number of sanitary pads used in each cycle, and presence of cramps. Menstrual irregularities were defined as Fewer than 9 periods a year or periods longer than 40 days apart.<sup>21</sup>

### *Hormonal assays*

The serum concentration of hormones like testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were estimated with the help of radioimmunoassay.

### *Homeostatic model assessment (HOMA-IR)*

Value was calculated for assessing the IR.

### *Formula*

$$\frac{\text{Fasting insulin levels (}\mu\text{g/ml)} \times \text{fasting glucose (mmol/l)}}{22.5}$$

Value over 2 indicates insulin resistance.<sup>22,23</sup>

### *PCOS*

PCOS was diagnosed using the ESHRE/ASRM (Rotterdam), 2003 diagnostic criteria.<sup>12,24</sup>

According to these criteria, PCOS is confirmed if two of the following conditions are present, in addition to exclusion of related disorders: (a) oligo- or anovulation; (b) clinical and/or biochemical signs of hyperandrogenism; (c) polycystic ovaries. Polycystic ovaries were diagnosed using pelvic ultrasonogram (USG), using either a 3.5 MHz transabdominal (full bladder technique) or a 5 MHz

transvaginal probe. Polycystic ovary diagnosis was based upon the presence of multiple small subcapsular cysts (diameter 2-8 mm) with dense echogenic stroma. Polycystic ovary was not diagnosed in cases with multiple small cysts scattered throughout the ovary without dense echogenic cores.

### Ethical consideration

The study was prior approved by the ethical committee of the hospital. All the study subjects were explained in detail about the study in the language of their understanding and their informed consent was taken in writing. Confidentiality of the patients was maintained throughout the study.

### Statistical analysis

All the variables were recorded in Microsoft excel. Statistical software (SPSS version 22) was used for the statistical analyses. All the variables were tested for normality using Kolmogorov-Smirnov test.

The categorical variables were summarized as frequencies and percentages, while continuous variables as medians and interquartile range (IQR; 25th to 75th percentiles), since most of the variables were observed to be non-normally distributed.

The association of variables with the outcome (IR) was assessed using the Chi-square statistic or Fischer exact test for categorical variables and Mann-Whitney U test for the continuous variables. The association of different categorical variables with the outcome was assessed using an odds ratio with a 95% confidence interval (CI). The correlation of different continuous variables was assessed using Spearman's correlation test.

All tests were 2-sided and  $p < 0.05$  was considered statistically significant.

## RESULTS

Out of 100 women who presented with acne vulgaris, 81 (81%) were confirmed as having PCOS basis the ultrasonography findings. We have excluded the non-PCOS subjects from further analysis. The average age of study subjects was 22 years (IQR: 19-23 years) and the median duration of acne was 8 months (IQR: 7-9 months). The laboratory findings of study subjects have been presented in Table 1.

Out of the 81 PCOS patients included in the study, 27 (33.3%) women were diagnosed with insulin resistance. Table 2 depicts association of different continuous variables with insulin resistance among acne vulgaris patients with PCOS. It was seen that subjects having

insulin resistance had lower FSH (median=3.1, IQR: 2.3-6.3), LH (median=3.0, IQR: 1.2-3.3), and insulin level (median=26.0, IQR=18.5-28.5), as compared to subjects without insulin resistance, and the difference was statistically significant ( $p=0.04$ ,  $p=0.04$  and  $p < 0.001$  respectively). The HOMA-IR value of subjects with IR was higher (median=4.9, IQR: 3.6-5.4) as compared to subjects without IR (median=1.8, IQR: 1.6-2.0), and the difference was statistically significant ( $p$  value  $< 0.001$ ).

IR was more commonly seen among subjects having severe acne (11, 40.7%), as compared to subjects without insulin resistance (11, 20.4%). Subjects with IR were 2.2 times more likely to be having irregular menses (OR, 2.2; 95% CI: 0.7-7.5,  $p$  value=0.19), 1.5 times more likely to have suffered weight gain (OR, 1.5; 95% CI: 0.6-3.7,  $p$  value=0.43), and 2.1 times more likely to be having acanthosis nigricans (OR, 2.1; 95% CI: 0.7-5.7,  $p$  value=0.16), as compared to subjects without insulin resistance. Other associations between insulin resistance and categorical variables have been depicted in Table 3.

The correlation of different variables among acne vulgaris patients with PCOS and insulin resistance has been given in Table 4. FSH levels showed significant correlation with LH levels ( $r=0.64$ ,  $p < 0.001$ ) and DHEA ( $r=0.39$ ,  $p=0.04$ ). LH levels were significantly correlated with FSH ( $r=0.64$ ,  $p < 0.001$ ), LH/FSH ratio ( $r=0.46$ ,  $p=0.01$ ), and DHEA ( $r=0.38$ ,  $p=0.04$ ). It was seen that the LH/FSH ratio was significantly correlated with LH levels ( $r=0.47$ ,  $p=0.01$ ). DHEA levels were correlated significantly with FSH ( $r=0.39$ ,  $p=0.04$ ), and LH levels ( $r=0.39$ ,  $p=0.04$ ). Insulin level had significant correlation with HOMA-IR ( $r=0.74$ ,  $p < 0.001$ ). Fasting blood sugar level was significantly correlated with LH ( $r=0.42$ ,  $p=0.03$ ) and insulin level ( $r=-0.57$ ,  $p=0.002$ ). HOMA-IR value had significant correlation with insulin level ( $r=0.74$ ,  $p < 0.001$ ).

**Table 1: Demographic and laboratory findings of study subjects (N=81).**

Variables	Median (inter-quartile range)
Age (years)	22 (19-23)
Duration of acne (months)	8 (7-9)
FSH (IU/l)	5.8 (3-6.8)
LH (IU/l)	3.1 (1.7-5.2)
LH/FSH ratio	0.7 (0.5-1)
DHEA ( $\mu\text{g/dl}$ )	285.5 (117.2-459.7)
Testosterone (ng/dl)	53.3 (37.7-70)
Insulin (mIU/l)	10.5 (8.4-18.5)
Fasting blood sugar (mg/dl)	82 (73.2-90)
HOMA-IR	2 (1.7-3.9)

FSH: follicle stimulating hormone; LH: luteinizing hormone; DHEA: dehydroepiandrosterone; HOMA-IR: homeostatic model assessment of IR; IQR: interquartile range; PCOD: polycystic ovarian syndrome/disease.

**Table 2: Association of different continuous variables with IR among acne vulgaris patients with PCOS (N=81).**

Variables	IR		P value
	Yes (N=27)	No (N=54)	
	Median (IQR)	Median (IQR)	
Age (years)	22 (18-23)	21 (19-23)	0.9240
Duration of acne (months)	8 (7-10)	8 (7-9)	0.3290
FSH (IU/l)	3.1 (2.3-6.3)	6 (3.2-7.2)	0.0390
LH (IU/l)	3.0 (1.2-3.3)	3.1 (2.9-5.5)	0.0360
LH/FSH ratio	0.7 (0.5-1)	0.7 (0.5-1)	0.3890
DHEA (µg/dl)	213.3 (103.1-333)	335.5 (118.6-526.7)	0.0580
Testosterone (ng/dl)	55 (34.6-67.2)	52.4 (38.8-70.7)	0.6850
Insulin (mIU/l)	26.0 (18.5-28.5)	8.9 (7.8-11.0)	<0.001
Fasting blood sugar (mg/dl)	82 (72-92)	82.8 (73.3-89.0)	0.5150
HOMA-IR	4.9 (3.6-5.4)	1.8 (1.6-2.0)	<0.001

FSH: follicle stimulating hormone; LH: luteinizing hormone; DHEA: dehydroepiandrosterone; HOMA-IR: homeostatic model assessment of IR; IQR: interquartile range; PCOD: polycystic ovarian syndrome/disease.

**Table 3: Association of different categorical variables with insulin resistance among acne vulgaris patients with PCOD (N=81).**

Variables	IR		P value	Odds ratio (95% CI)	
	Yes (N=27) (%)	No (N=54) (%)			
Acne site	Cheeks	10 (37)	10 (18.5)	0.451	NA
	Chin	5 (18.5)	8 (14.8)		
	Full face	1 (3.7)	7 (13)		
	Cheeks, chin	8 (29.6)	23 (42.6)		
	Cheeks, forehead	2 (7.4)	4 (7.4)		
	Chin, forehead	0 (0)	1 (1.9)		
	Cheek, forehead, chin	1 (3.7)	1 (1.9)		
Acne severity	Mild	7 (25.9)	17 (31.5)	0.146	NA
	Moderate	9 (33.3)	26 (48.1)		
	Severe	11 (40.7)	11 (20.4)		
Menstrual history	Irregular	23 (85.2)	39 (72.2)	0.194	2.2 (0.7-7.5) Reference
	Regular	4 (14.8)	15 (27.8)		
Weight gain	Yes	16 (59.3)	27 (50)	0.431	1.5 (0.6-3.7) Reference
	No	11 (40.7)	27 (50)		
Hirsutism	Yes	16 (59.3)	34 (63)	0.746	0.9 (0.3-2.2) Reference
	No	11 (40.7)	20 (37)		
Hairfall	Yes	17 (63)	34 (63)	1.00	1 (0.4-2.6) Reference
	No	10 (37)	20 (37)		
Seborrhoea	Yes	20 (74.1)	41 (75.9)	0.855	0.9 (0.3-2.6) Reference
	No	7 (25.9)	13 (24.1)		
Acanthosis nigricans	Yes	10 (37)	12 (22.2)	0.158	2.1 (0.7-5.7) Reference
	No	17 (63)	42 (77.8)		

PCOD: polycystic ovarian syndrome/disease; NA: not applicable; CI: confidence interval.

**Table 4: Correlation of different variables among acne vulgaris patients with PCOS and insulin resistance (N=27).**

Variables		FSH	LH	LH/FSH ratio	DHEA	Testosterone	Insulin	HOMA-IR
Age	ρ	-0.284	-0.329	-0.124	-0.333	-0.046	-0.081	-0.149
	P value	0.151	0.094	0.539	0.09	0.821	0.687	0.459
Duration	ρ	-0.069	-0.153	-0.235	-0.025	0.093	0.156	0.142
	P value	0.731	0.446	0.238	0.903	0.644	0.437	0.48
FSH	ρ	1	0.674	-0.227	0.389	0.242	-0.25	-0.129
	P value	-	<0.001*	0.255	0.045*	0.223	0.209	0.523

Continued.

Variables		FSH	LH	LH/FSH ratio	DHEA	Testosterone	Insulin	HOMA-IR
<b>LH</b>	$\rho$	0.674	1	0.465	0.388	-0.038	-0.229	-0.028
	P value	<0.001*	-	0.015*	0.046*	0.852	0.25	0.889
<b>LH/FSH ratio</b>	$\rho$	-0.227	0.465	1	0.087	-0.241	0.08	0.185
	P value	0.255	0.015*	-	0.667	0.227	0.691	0.356
<b>DHEA</b>	$\rho$	0.389	0.388	0.087	1	0.189	-0.254	-0.127
	P value	0.045*	0.046*	0.667	-	0.344	0.201	0.528
<b>Testosterone</b>	$\rho$	0.242	-0.038	-0.241	0.189	1	-0.085	-0.212
	P value	0.223	0.852	0.227	0.344	-	0.672	0.288
<b>Insulin</b>	$\rho$	-0.25	-0.229	0.08	-0.254	-0.085	1	0.774
	P value	0.209	0.25	0.691	0.201	0.672	-	<0.001*
<b>Fasting blood sugar</b>	$\rho$	0.358	0.419	0.117	0.352	-0.145	-0.567	-0.105
	P value	0.066	0.03*	0.562	0.071	0.471	0.002*	0.602
<b>HOMA-IR</b>	$\rho$	-0.129	-0.028	0.185	-0.127	-0.212	0.774	1
	P value	0.523	0.889	0.356	0.528	0.288	<0.001*	-

$\rho$ : Spearman's correlation, \*significant values ( $p < 0.05$ ); FSH: follicle stimulating hormone; LH: luteinizing hormone; DHEA: dehydroepiandrosterone; HOMA-IR: homeostatic model assessment of IR.

## DISCUSSION

PCOS is the most common endocrine and metabolic disturbance in women of reproductive age.<sup>25</sup> In the current study too, a PCOS prevalence of 81% was detected among the females who had acne. Though the prevalence of PCOS varies greatly among studies, but such a high prevalence in the current study might be due to the use of 2003 Rotterdam criteria as it includes additional phenotypes.<sup>24</sup> PCOS is also associated with peripheral IR and hyperinsulinemia, and obesity amplifies the degree of both abnormalities.<sup>26-28</sup> IR is requirement of a higher level of insulin by the body for performing normal metabolic activities. IR is reported in 40-75% of women suffering from PCOS.<sup>29-34</sup> In the present study, 33.33% of women having PCOS and acne, also had insulin resistance. Cut-off point for insulin resistance was found to be different in different ethnic groups and these differences could be due to race and ethnicity.

Another study from Pakistan also reported similar prevalence (34.78%) of IR in PCOS patients.<sup>35</sup> The findings of the Pakistan study are congruent to our study due to the similar ethnic backgrounds of the study subjects and same age groups included in both the studies. However, a study from Thailand reports much lower prevalence of IR (20.0%), owing to younger and thinner population.<sup>36</sup> A Chinese study reported that the prevalence of IR was lower when using HOMA-IR than when using the euglycemic-hyperinsulinemic clamp method (27.9% vs 56.7%).<sup>25</sup> A recent study in Caucasians also showed that the surrogate markers of IR like HOMA-IR, resulted in a lower prevalence of IR compared with the M value that is derived from the euglycemic-hyperinsulinemic clamp method.<sup>37</sup> Hence, the lower prevalence of IR detected in our study is because of use of the HOMA-IR method.

In the present study, IR was more commonly seen among subjects having severe acne, irregular menses, weight gain and acanthosis nigricans. Acne is a common component of seborrhea-acne-hirsutism-androgenetic alopecia (SAHA)

syndrome, PCOS, and hyperandrogenism, insulin resistance, and acanthosis nigricans (HAIR-AN) syndrome, all of which are linked to insulin resistance.<sup>38</sup>

It was seen in the current study that subjects having insulin resistance had lower FSH, LH, and DHEA and higher insulin level and HOMA-IR. Higher fasting insulin levels and HOMA-IR have been reported in acne patients as compared to non-acne controls.<sup>39</sup> Another study from north India has reported higher levels of insulin level and HOMA-IR among PCOS patients.<sup>40</sup> A significant increase in HOMA-IR level, in absence of raised fasting blood glucose suggests that women with PCOS have normal glucose tolerance as compared to people suffering from type 2 diabetes.<sup>41</sup> However, hyperinsulinemia resulting from insulin resistance make women with PCOS highly susceptible to developing type 2 diabetes and metabolic syndrome.<sup>42,43</sup> These associated metabolic derangements greatly increase a woman's lifetime risk to develop cardiovascular co-morbidities. The present study did not report an increased LH/FSH ratio associated with insulin resistance and the finding is congruent with another study done by Dasgupta et al.<sup>44</sup> Though it may be expected that increased insulin level will affect ovarian steroidogenesis and LH secretion, in many studies this direct effect has not been elucidated.<sup>45</sup> Although its etiology has not yet been fully elucidated, knowledge and understanding of the abnormality in the hypothalamus-pituitary axis, steroidogenesis and insulin resistance are of utmost importance for early, effective and safe treatment.<sup>46</sup> Acne is no more indicative of just a dermatological condition but is manifestation of a complicated systemic disease prodrome. The association of acne with PCOS and insulin resistance mandates a thorough hormonal investigation and prompt treatment of such patients.

## Limitations

Limitation was small sample size and need for use of more robust methods for evaluating insulin resistance like the euglycemic-hyperinsulinemic clamp method, which was

considered to be the gold standard for diagnosing insulin resistance. Some important dependent variables were also missing in this study that could have given some insights about the associating factors of IR like BMI and waist-hip ratio.

## CONCLUSION

One-third of the patients with acne and PCOS also had insulin resistance according to the HOMA-IR values. IR was more commonly seen among subjects having severe acne, irregular menses, weight gain and acanthosis nigricans. The women with IR also had lower FSH, LH, and DHEA and higher insulin level and HOMA-IR values. All women with acne and PCOS should be considered for underlying insulin resistance and examined for other sign of impaired glucose tolerance.

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