

Role of Insulin Resistance in Patients of Acne Vulgaris and Hirsutism in the Western Part of India- A Cross-Sectional Study

Abstract

Background: Despite being common and easy to treat conditions, acne and hirsutism may have a striking consequence on one's perception of self. Though understanding the pathogenesis of acne and hirsutism has undergone a major paradigm shift, one of them being insulin resistance (IR), extensive research is still underway. The purpose of the study is to establish causal relationship linking IR with acne vulgaris and hirsutism, as well as to assess severity of the two with increasing IR. **Materials and Methods:** A cross-sectional observational study was conducted in the dermatology department. Patient's detailed clinical history and necessary parameters like height, weight, body mass index (BMI), etc., were recorded in predefined proforma, noting signs and symptoms of underlying IR, along with acne severity calculated by global acne grading system (GAGS) and hirsutism severity by modified Ferriman Gallwey score (mFG), then analyzing using Pearson's correlation test to establish correlation between IR and acne with/without hirsutism and hirsutism alone. **Results:** A total of 349 patients included in our study were divided into three groups, (i) Acne-only (N = 308) group showed statistically significant correlation of IR with acne severity ($P < 0.0001$) and recurrence ($P < 0.0001$). (ii) In hirsutism-only (N = 24) group, homeostatic model assessment for insulin resistance (HOMA-IR) was strongly associated with modified Ferriman-Gallwey score and recurrence suggesting raised insulin resistance with increased severity of hirsutism ($P < 0.0001$) and recurrence ($P < 0.007$). (iii) In acne + hirsutism (N = 17) group, raised BMI was found to be positively associated with IR but not with severity of both conditions. **Conclusion:** IR has emerged as an important contributory, if not, causative event in pathogenesis of severe, resistant acne, and hirsutism. These conditions have great deal of impact on the psychological health of those affected necessitating different approach to manage such cases.

Keywords: Acne, BMI, global acne grading system, hirsutism, HOMA-IR, IR, mFG

Introduction

Acne vulgaris and hirsutism are globally prevalent entities frequently encountered in dermatology practice. They have varied etiopathologic mechanisms. Acne vulgaris is a complex chronic inflammatory disease of the pilosebaceous unit, caused due to interplay of multiple environmental, host factors and genetic factors. It is attributable to increased sebum production, sebaceous gland hypertrophy and hyperplasia, follicular hyperkeratinization, and *Cutibacterium acnes* proliferation.^[1]

Hirsutism, one of the most distressing conditions for females especially in younger age groups, refers to excess terminal hair in a woman that occurs in a male pattern involving areas such as the upper lip, chin, chest, abdomen, pelvis, upper back, lower back, upper arms, and thighs.^[2]

Out of many emerging theories for pathogenesis of acne and hirsutism, insulin

resistance (IR) has gained scientific ground in recent years. IR with relative decline in uptake of circulating glucose by insulin-responsive tissues given the same concentration of plasma insulin results in hyperglycemia acting as a major pathogenic mechanism for adverse macro- and micro-vascular consequences. This incidence has only inflated, encumbered with the surge in modern technology and sedentary life-style.

IR not only contributes to acne or hirsutism, but also a variety of skin disorders like acanthosis nigricans, psoriasis, androgenetic alopecia, vitiligo vulgaris, etc. It is also associated with many major metabolic disorders like diabetes mellitus (DM), dyslipidemia, polycystic ovarian syndrome (PCOS) and cardio-vascular diseases like ischemic heart disease. Along with the above consequences, there has remained constant psychological impact which is noted due to acne vulgaris and hirsutism.

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The study is intended to analogize IR with acne vulgaris and hirsutism which may serve as early clinical indicators to identify the serious complications that may follow due to the same.

Materials and Methods

A cross-sectional type observational study was conducted in the department of dermatology, from September 2018 to November 2020 after institutional review board approval.

Patients presenting to dermatology outpatient department with complaints of acne and hirsutism satisfying the inclusion and exclusion criteria were enrolled in the study after informed written consent. Subjects of age greater than 12 years, diagnosed with acne vulgaris and hirsutism, willing to participate and consent, were included, while those reported with thyroid dysfunction, hypertension, atherosclerotic vascular disease, malignancy, pregnancy, lactating mothers or any other systemic inflammatory diseases or those subjects taking medications known to affect insulin metabolism, previous treatment with oral retinoids, hormone treatment for any reason, and use of alternative system of medicine in the previous three months were excluded from the study.

Patient's detailed clinical history and necessary parameters like height, weight, and body mass index (BMI) were obtained and recorded in predefined proforma including specific questions suggestive of signs and symptoms of underlying IR. These questions included those pertaining to unexplained rapid weight gain/loss, feeling of fatigue and weakness, increased/decreased appetite, presence of seborrhea, excessive hair loss, deepening of voice, menstrual irregularities and recurrent gum/skin/vaginal/bladder infections. Patients' fasting blood sugar (FBS), fasting insulin levels were done to obtain the homeostatic model assessment for insulin resistance (HOMA-IR). HOMA-IR of greater than 2.5 was considered significant and suggestive of IR. Acne severity was calculated by global acne grading system (GAGS) and hirsutism severity was calculated by modified Ferriman Gallwey score (mFG).

The obtained data was recorded and analyzed using Pearson's correlation test with SPSS version 1.0.0.1406 to establish the correlation between IR and acne as well as hirsutism. Confidentiality of all the data was maintained throughout the study.

Results

The study had 349 patients which were divided into three groups. Group-1 had 308 (88%) patients who presented with only acne. Group-2 had 24 (7%) patients with only hirsutism, and 17 (5%) patients presenting with both acne and hirsutism were classified into group-3.

Mean age in the present study was 24.83 years. Acne – only group had maximum patients lying below the age of

20 (N = 158), while the age-group between 21 years and 30 years formed the prime section for groups 2 (N = 13) and 3 (N = 8).

No much gender disparity was noted as female (N = 176): male (N = 173) ratio was – 1.01:1; although, group-1 accounted 173 (56.17%) males and 135 (43.83%) females, with male: female ratio being 1.28:1, showing slight male preponderance. Group-2 and 3 encompassed 24 and 17 females, respectively.

A positive family history of DM-II was seen in 52 patients (14.89%). In group-1, 44 subjects (14.28%) had a positive family association of DM-II, while the same was seen in four subjects (16.67%) of group-2, and 4 subjects (23.52%) of group-3.

In our study, out of 308 patients of group-1, there were 173 males and 135 females. About 128 males were found to have positive signs and symptoms of IR while the same was noted in 40 females.

Group-1 had 156 naïve acne patients in which 54 patients had IR, while from 152 patients having recurrent acne, 114 had IR which suggests a possibility of strong correlation.

Maximum population (N = 152) lied within normal BMI ranging from 18.5 to 24.9, having mean BMI of 24.28, with 63 patients (41.44%) showing significant association with IR. There was a strong association for IR (100%) seen in all 21 patients of group-1 lying in BMI >30 range. 80 subjects out of 92 (86.95%) within the overweight category (BMI = 25–30) had IR. Only 3 out of total 42 patients (7.14%) had IR in the underweight category (BMI <18.5).

The mean FBS, mean fasting insulin and mean HOMA-IR were significantly high. BMI was very strongly associated with raised HOMA-IR (>2.5 s/o IR), GAGS, age, and recurrence in this group ($P < 0.01$). There was a remarkable association of BMI with age ($P < 0.05$) but not with gender ($P > 0.05$), as shown using Pearson's correlation in Table 1.

Majority of patients with IR were found to be significant in moderate (46%), severe (88%), and very severe (59%) acne groups graded using GAGS as shown in Figure 1.

In group-2, 24 females diagnosed with hirsutism were included in the study with presence of IR in 14 of them. About 10 out of 14 patients with IR were naïve, while others had recurrent hirsutism.

Mean BMI of hirsutism patients was 24.28. Presence of IR with BMI >30 was seen in 2 subjects. 7 out of 9 patients in the overweight BMI range of 25–30 had IR, while 5 out of 9 patients in the normal BMI range had IR.

Age was the only factor associated with raised BMI ($P < 0.05$) when Pearson product-moment correlation

Table 1: Pearson's correlations in acne only group

	BMI	HOMA- IR	GAGS	Age	Gender	Naïve/Recurrent
BMI						
Pearson Correlation	1	0.814**	0.627**	0.186**	0.078	0.386**
Sig. (2-tailed)		0.000	0.000	0.001	0.173	0.000
<i>n</i>	308	308	308	308	308	308
HOMA- IR						
Pearson Correlation	0.814**	1	0.751**	0.103	0.057	0.279**
Sig. (2-tailed)	0.000		0.000	0.070	0.321	0.000
<i>n</i>	308	308	308	308	308	308
GAGS						
Pearson Correlation	0.627**	0.751**	1	0.095	0.003	0.365**
Sig. (2-tailed)	0.000	0.000		0.096	0.952	0.000
<i>n</i>	308	308	308	308	308	308
Age						
Pearson Correlation	0.186**	0.103	0.095	1	-0.039	0.002
Sig. (2-tailed)	0.001	0.070	0.096		0.492	0.976
<i>n</i>	308	308	308	308	308	308
Gender						
Pearson Correlation	-0.078	0.057	0.003	-0.039	1	-0.018
Sig. (2-tailed)	0.173	0.321	0.952	0.492		0.753
<i>n</i>	308	308	308	308	308	308
Naïve/Recurrent						
Pearson Correlation	0.386**	0.279**	0.365**	0.002	-0.018	1
Sig. (2-tailed)	0.000	0.000	0.000	0.976	0.753	
<i>n</i>	308	308	308	308	308	308

BMI: body mass index; HOMA-IR: homeostasis model assessment-insulin resistance; GAGS: global acne grading system, **Correlation is significant at the 0.01 level (2-tailed)

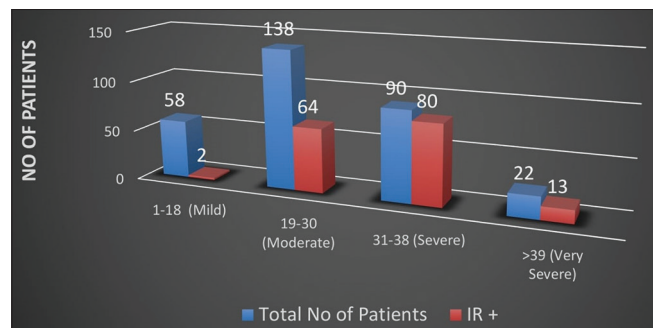


Figure 1: Graph showing severity of acne and insulin resistance association

was conducted. 6 (25%) subjects with an increased BMI belonged to the age group of 21–30, while 5 (20.8%) belonged to the age group of 31–40. Increased BMI was associated with raised HOMA-IR (>2.5 s/o IR), age and recurrence in this group ($P < 0.01$), but not with modified Ferriman Gallwey score. HOMA-IR was strongly associated with modified Ferriman Gallwey score and recurrence. [Table 2]

In group-3, 17 females presented with both acne and hirsutism. Among these 17 patients, 13 patients were newly diagnosed cases of acne with hirsutism, while 4 had recurrent disease. Out of the 4 patients with recurrent disease, 3 had IR; and out of 13 naïve patients, 7 had IR. BMI was significantly high in those who had IR (mean BMI 26.8) as shown in Figure 2.



Figure 2: Graph showing BMI and IR association in group-2 (acne + hirsutism)

For 17 patients of group-3, Pearson correlation conducted showed BMI was not associated with raised GAGS and raised mFG. In addition, raised IR did not correspond with increased severity of either acne or hirsutism ($P > 0.05$) as shown in Table 3.

Discussion

The study had 349 patients which were divided into three groups. Group-1 had 308 patients who presented with only acne. Group-2 had 24 patients with only hirsutism, while 17 patients presenting with both acne and hirsutism were classified into group-3.

Mean age in the present study was 24.83 years, while the mean age in studies done by Nagpal *et al.*,^[3] Ünlühizarci *et al.*,^[4] and Wankhade *et al.*^[5] were 22.7, 31.3, and 24.8 years respectively. Majority of the patients (N = 163) were below

Table 2: Correlations in Hirsutism only group

	Age	BMI	HOMA-IR	mFG score	Naïve/Recurrent
Age					
Pearson Correlation	1	0.491*	0.338	0.191	0.320
Sig. (2-tailed)		0.015	0.107	0.370	0.127
<i>n</i>	24	24	24	24	24
BMI					
Pearson Correlation	0.491*	1	0.493*	0.313	0.634**
Sig. (2-tailed)	0.015		0.014	0.136	0.001
<i>n</i>	24	24	24	24	24
HOMA-IR					
Pearson Correlation	0.338	0.493*	1	0.717**	0.537**
Sig. (2-tailed)	0.107	0.014		0.000	0.007
<i>n</i>	24	24	24	24	24
mFG score					
Pearson Correlation	0.191	0.313	0.717**	1	0.475*
Sig. (2-tailed)	0.370	0.136	0.000		0.019
<i>n</i>	24	24	24	24	24
Naïve/Recurrent					
Pearson Correlation	0.320	0.634**	0.537**	0.475*	1
Sig. (2-tailed)	0.127	0.001	0.007	0.019	
<i>N</i>	24	24	24	24	24

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). BMI: body mass index; HOMA-IR: homeostasis model assessment-insulin resistance; mFG: modified Ferriman Gallwey score

Table 3: Correlations in acne + hirsutism group

	Age	BMI	HOMA- IR	GAGS	mFG score	Naïve/Recurrent
Age						
Pearson Correlation	1	0.155	0.584*	0.485*	-0.195	0.267
Sig. (2-tailed)		0.553	0.014	0.049	0.453	0.300
<i>n</i>	17	17	17	17	17	17
BMI						
Pearson Correlation	0.155	1	0.517*	0.257	0.235	0.315
Sig. (2-tailed)	0.553		0.034	0.318	0.365	0.219
<i>n</i>	17	17	17	17	17	17
HOMA-IR						
Pearson Correlation	0.584*	0.517*	1	0.461	-0.246	0.174
Sig. (2-tailed)	0.014	0.034		0.063	0.341	0.503
<i>n</i>	17	17	17	17	17	17
GAGS						
Pearson Correlation	0.485*	0.257	0.461	1	-0.139	-0.062
Sig. (2-tailed)	0.049	0.318	0.063		0.595	0.813
<i>n</i>	17	17	17	17	17	17
mFG score						
Pearson Correlation	-0.195	0.235	-0.246	-0.139	1	0.072
Sig. (2-tailed)	0.453	0.365	0.341	0.595		0.784
<i>n</i>	17	17	17	17	17	17
Naïve/Recurrent						
Pearson Correlation	0.267	0.315	0.174	-0.062	0.072	1
Sig. (2-tailed)	0.300	0.219	0.503	0.813	0.784	
<i>n</i>	17	17	17	17	17	24

*Correlation is significant at the 0.05 level (2-tailed). BMI: body mass index; HOMA-IR: homeostasis model assessment-insulin resistance; GAGS: global acne grading system; mFG: modified Ferriman Gallwey score

20 years of age, which typically correlates with onset of puberty, when sebum production increases.^[6]

After reaching the young adulthood, acne prevalence rates follow a decreasing trend with increasing age^[6] which

corroborates with our findings of least number of patients in the study lying above 41 years age group.

There were 173 males and 135 females out of 308 patients of group-1, while Nagpal *et al.*^[3] included 100 male cases with age matched 100 male control, while Munichandrappa *et al.*^[7] included 45 age and sex matched cases and controls, in which 19 males and 26 females were included in each group. In the study by Collier *et al.*,^[8] acne is more frequent in women than men, probably due to earlier onset of puberty in the prior. However, no major gender disparity was noted in our study as female (176): male (173) ratio was – 1.01:1 which contrasted with studies by Abdelmawla *et al.*,^[9] Munichandrappa *et al.*,^[7] and Lynn *et al.*^[10].

As of now, studies considering family history of DM-II as a risk factor for developing acne and hirsutism along with IR are scarce in the literature in Asian population.^[11] Our study has shown that 52 patients (14.89%) were having family history of DM-II.

Skin manifestations of IR (e.g. acrochordons, acanthosis nigricans, androgenetic alopecia, acne, and hirsutism) offer a reliable and real time way to detect IR.^[12]

The symptoms and signs pertaining to appetite, weight gain, fatigue may serve as good screening tools for at risk patients, although not specific for IR. This was supported in our study by the most common complaint encountered was of unexplained rapid weight gain in all the three groups, followed by fatigue and weakness in groups-1 and 2.

In group-1, 34% of naïve acne subjects and 75% subjects with recurrent acne had IR which suggests a possibility of strong correlation and should be studied further. No previous studies have evaluated association between IR and recurrence of acne. IR was seen in moderate, severe, and very severe acne groups which was comparable to the Nagpal *et al.*^[3] study for the latter two groups. However, Balato *et al.*^[13] and Munichandrappa *et al.*^[7] did not draw any parallels between acne severity and HOMA-IR levels. Obese (BMI >30) and overweight individuals (BMI >24) tend to have higher glycemic loads and androgen levels which may increase sebum secretion and induce hyperinsulinemia (high IR), promoting the formation of acne lesions. Ray *et al.*^[14] has discussed the positive correlation between blood glucose and acne severity. Hyperglycemia, in turn, stimulates insulin secretion, increases androgen synthesis causing acne, and decreases availability of binding protein for insulin-like growth factor-1 (IGF-1) which facilitates effects of IGF-1 on basal keratinocyte proliferation. In a case control study done by Nagpal *et al.*,^[3] mean BMI was 22.9 in cases and 23.4 in controls while in our study mean BMI in group-1 was 24.28. In present study, BMI and HOMA-IR in group-1 were strongly associated with GAGS and recurrence which suggests that raised BMI and IR are strongly associated with increased

severity of acne and recurrence, similar to Nagpal *et al.*,^[3] while differing from Gayen *et al.*^[15] showing no statistical significance between BMI and acne-severity.

In group-2, 10 out of 14 patients with IR were naïve, which further needs to be studied in detail with a larger sample size as correlation between IR and recurrence of hirsutism has not been studied in the past in Asian population. Mean BMI of hirsutism patients was 24.28 in our study, while it was 31.8 in Ünlühizarci *et al.*^[4] and 32.1 in Wankhade *et al.* studies.^[5] This variation can be due to racial factors as these studies are from western countries. HOMA-IR was strongly associated with modified Ferriman Gallwey score and recurrence which suggests that raised IR are strongly associated with increased severity of hirsutism and recurrence, and these findings are consistent with reference studies. Hirsutism only patients also showed a positive correlation between hirsutism and IR. Hirsutism has a polyfactorial etiology which includes either increased production of androgens due to PCOS, congenital or delayed adrenal hyperplasia, hyperinsulinemia, obesity, Cushing's disease, hyperprolactinemia, ovarian tumors, adrenal gland tumors, certain medications (e.g. danazol, phenytoin, etc.), or maybe idiopathic. The condition has high levels of IGF and androgens. Hyperinsulinemia increases serum IGF-1 levels and reduces serum insulin-like- growth factor binding protein-3 (IGFBP3), influencing proliferation and apoptosis of keratinocytes. While insulin and IGF induces androgen production, they simultaneously inhibit sex hormone binding globulin synthesis, thereby increasing androgen bioavailability. These androgens cause terminalization of vellus hair over body giving a masculine look in females.^[16]

A worthwhile observation was made that most of the subjects having acne over zygomatic arch, chin and mandibular region, of grades 3 and 4, lying in very severe and severe groups, had IR.

Also, most patients of hirsutism with IR had involvement of upper lip, chin, and upper neck areas.

In group-3, comprising of acne and hirsutism, 75% subjects with recurrent disease and 53% patients with naïve acne with hirsutism had IR, which may suggest that if acne and hirsutism both are seen simultaneously, IR can be an underlying etiology. BMI (mean – 26.8) was significantly high in those who had IR, supported by Ünlühizarci *et al.*^[4] and Wankhade *et al.*^[5] where mean BMI was 31.8 and 32.1, respectively. Raised BMI was found to be positively associated with IR but not with severity of acne and hirsutism. In addition, it showed lack of correlation between severities of diseases with IR, which needs to be further evaluated with a larger sample size, as the sample size of this group in our study was less (17).

Thus, we recommend a strong degree of clinical suspicion of IR in recurrent and severe grades of acne along with

hirsutism. Investigations favoring early diagnosis should be undertaken so that prompt treatment can be started at the earliest.

Limitations

The sample size for the third group (acne with hirsutism) was small. Furthermore, the study had no control groups which could further help to evaluate associations between IR and severities of acne, and hirsutism, drawing conclusions in a better way.

Conclusion

Despite being common and easy to treat conditions, acne and hirsutism may have an enormous repercussion on fragile sense of self-esteem and mental health in the tender adolescent age-group leading to body-image disorders. Hence, it becomes very important to identify a potential cause of these common conditions to facilitate adequate and timely treatment.

Though understanding of the pathogenesis of acne and hirsutism has undergone a major paradigm shift, still research is underway. IR has emerged as an important contributory, if not, causative event in pathogenesis of severe and resistant acne and hirsutism, necessitating a different approach to manage such cases. Fasting insulin levels and HOMA-IR will definitely help to identify the individuals at risk and to predict the degree of relapse as well as resistance to treatment.

Most of the studies are case control studies with few cross-sectional studies conducted over the above correlation in India. More similar studies with larger sample size and more specific indicators of IR are required to widen the spectra.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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