https://doi.org/10.31925/farmacia.2024.6.12 **ORIGINAL ARTICLE**

THE RELATIONSHIP BETWEEN INSULIN RESISTANCE, BODY COMPOSITION, AND SEVERE ACNE: A CROSS-SECTIONAL ANALYSIS

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Abstract

Recent evidence suggests a potential link between acne severity and insulin resistance (IR). This cross-sectional study of 152 acne patients explored this association, considering factors such as fat-free mass (FFM), fat mass (FM), visceral fat (VF) and glutathione peroxidase (GPx) activity. Patients were categorized into two groups: a control group (CG, N = 80) with acne but no IR and an IR group (IRS-G, N = 72) with both acne and IR. The study assessed the likelihood of severe acne in the presence of IR and evaluated its relationship with body composition indices. Severe acne was significantly more common in the IRS-G ($p < 0.05$), which also displayed higher BMI, FM and VF ($p < 0.05$) and lower GPx activity ($p < 0.001$) compared to the CG. Elevated HOMA-IR values correlated positively with BMI, FM, VF and acne severity ($p < 0.001$) and negatively with GPx activity ($p < 0.001$). These findings highlight that IR, alongside higher BMI, FM, VF, and reduced GPx activity, strongly predicts severe acne. IR and associated metabolic parameters significantly influence acne severity. Larger, multicentre prospective studies are warranted to confirm these findings and elucidate the mechanisms underlying this relationship.

Rezumat

Dovezi recente sugerează o posibilă legătură între severitatea acneei și rezistența la insulină (RI). Acest studiu transversal, realizat pe 152 de pacienți cu acnee, a investigat această asociere, analizând factori precum masa fără grăsime (FFM), masa grasă (FM), grăsimea viscerală (VF) și activitatea glutation-peroxidazei (GPx). Pacienții au fost împărțiți în două grupuri: un grup de control (CG, N = 80) cu acnee, dar fără RI, și un grup cu RI (IRS-G, N = 72), având atât acnee, cât și RI. Studiul a evaluat probabilitatea de apariție a unei forme severe de acnee în prezența RI și a analizat relația acesteia cu indicii de compoziție corporală. Acneea severă a fost semnificativ mai frecventă în grupul IRS-G ($p < 0,05$), care a prezentat valori mai ridicate ale IMC, FM și VF ($p < 0,05$) și activitate GPx mai scăzută ($p < 0,001$) comparativ cu grupul de control. Valorile crescute ale HOMA-IR s-au corelat pozitiv cu IMC, FM, VF și severitatea acneei ($p < 0,001$) și negativ cu activitatea GPx ($p < 0,001$). Aceste rezultate indică faptul că RI, asociată cu IMC, FM, VF mai ridicate și activitate GPx scăzută, este un predictor puternic al acneei severe. RI și parametrii metabolici asociați influențează semnificativ severitatea acneei. Sunt necesare studii prospective mai mari, multicentrice, pentru confirmarea acestor concluzii și clarificarea mecanismelor implicate.

Keywords: acne vulgaris, fat mass, insulin resistance, oxidative stress

Introduction

The acne vulgaris represents a highly prevalent dermatological disorder in Westernized populations, targeting the human sebaceous follicle and afflicting approximately 85% of adolescents [18, 27]. The implications of insulin resistance (IR) in the development and progression of acne are currently not explicitly understood, despite the latest studies that suggest a potential linkage between the two [34]. Elevated expression of the mechanistic target of rapamycin complex 1 (mTORC1) has been observed in individuals with acne, and this is closely linked to IR, type 2 diabetes, obesity and certain malignancies like prostate carcinomas and melanomas. The activation of ribosomal protein S6 kinase beta-1, associated with an elevated activity of mTORC1, triggers the phosphorylation of insulin receptor substrate-1, causing IR. Furthermore, a notable association has been discovered between

a decline in the expression of insulin, mTORC1 and insulin-like growth factor 1 with a lower occurrence rate of acne [26, 27].

However, multiple etiopathological variables have been identified in the onset of IR. Initially, adipose tissue located in the visceral fat deposit has been widely regarded as a primary factor in the onset of the IR. Increasing data has been corroborating the significance of the activity of adipose tissue in the emergence of metabolic dysregulations, regardless of the size or arrangement of adipose tissue. Reduced ability for fat cell differentiation and the formation of new blood vessels, together with the enlargement of fat cells, can initiate a harmful cycle of inflammation that results in dysfunction of the fat tissue beneath the skin and the accumulation of fat in abnormal sites [32]. Thus, the composition and positioning of body fat can play a significant role in causing metabolic abnormalities in certain tissues and may consequently lead to tissue-specific IR [29]. Moreover, ectopic fat deposition in the liver and IR are commonly observed in obese patients. Insulin transmission impairment is one of the causes of IR, and ectopic fat accumulation has been proven to contribute to the disruption of insulin signalling [3].

Recent data showed a significant correlation between obesity indices such as body weight, body mass index (BMI), waist circumference, fat mass (FM), visceral fat (VF) and IR [22], a hypothesis that opens research directions and implications in groups of patients with acne. Nonetheless, heightened oxidative stress is a harmful component that contributes to IR, reduced glucose tolerance, malfunction of β-cells, and eventually, the development of type 2 diabetes and other conditions related to oxidative stress [35].

The phenomenon of oxidative stress represents an unbalance within the generation of reactive nitrogen and oxygen species and the ability of the body's anti-oxidant defence mechanism to counteract them [1]. A stable equilibrium of reactive oxygen and nitrogen species is upheld by the body's intrinsic antioxidant defence mechanisms, which include both enzymatic and non-enzymatic components. Glutathione peroxidases (GPx), catalase and superoxide dismutase are three essential enzymes that inhibit the generation of reactive radical species. Recent findings indicate that elevated amounts of reactive oxygen and nitrogen species play a role in the advancement of oxidative stress in obesity. This occurs by triggering inflammatory pathways, which ultimately result in the emergence of pathological conditions, such as IR. Furthermore, the reduced presence of components in the system that provides antioxidant protection in individuals with obesity heightens their vulnerability to oxidative harm to tissues and exacerbates the development of associated health conditions [31].

In recent years, it has become clear that individuals with acne not only experience elevated levels of oxidative stress within their skin, but also face systemic implications [7]. Furthermore, the presence of oxidative stress in acne may not only be a result of the condition, but rather, oxidative stress may be an initial occurrence that contributes to the development of acne [5].

Given the complex implications of oxidative stress across numerous pathophysiological pathways, it is plausible that the resultant systemic oxidative damage links IR, obesity and acne through a shared pathogenic mechanism. From this perspective, IR, obesity and GPx activity appear to be pivotal in the pathogenesis of acne [6, 15]. Despite this, existing research has provided limited insights into the association between IR and acne severity, with very few studies offering a comprehensive analysis of body composition and GPx activity in relation to this condition.

The present study seeks to address this gap by evaluating the potential etiological link between severe acne and IR. Additionally, it aims to explore the inter-relationships between IR and acne in conjunction with parameters such as fat-free mass (FFM), FM, VF and GPx activity. By investigating these connections, this research will contribute novel insights into the interplay between metabolic dysfunction and acne, potentially enhancing the understanding of acne's underlying mechanisms and its associations with systemic metabolic disorders.

Materials and Methods

Design and methods

The present cross-sectional analysis included 152 patients diagnosed with acne from November 2022 to June 2024 at a private hospital and various dermatology offices in Oradea, Romania, aiming to investigate the potential etiological association between the severity of acne and IR, as well as the relationships between IR, acne and measures of body composition including FFM, FM, VF and GTPx activity.

All patients included in the study had different stages of acne evaluated through the global acne severity scale (GEA) [14]. The dermatologists assessed the severity of the acne, based on the criteria established in our previous investigations [6, 8]. Patients with a score of 1 or 2 were classified as having “mild acne” (grade 1), characterized by a few open or closed black-heads, a small number of papules and less than half of the face affected. “moderate acne” (grade 2) was assigned to those with a score of 3, involving more than 50% of the face and numerous pustules, papules and blackheads, potentially with inflammatory lesions or a solitary nodule. Those with a score of 4 or 5 were categorized as having “severe acne” (grade 3), affecting the entire face with numerous papules, pustules, occasional nodules and blackheads [8].

The homeostasis model assessment of insulin resistance (HOMA-IR) was used to assess IR from basal glucose and insulin levels, using the following formula:

HOMA-IR = [insulin (μU/mL) × glucose level (mg/dL)]/405.

The diagnosis of IR was established when the HOMA-IR values was greater than 2 mmol/L [23].

Subjects with hormonal disorders or other metabolic conditions, including hypertension, dyslipidaemia, diabetes, as well as those taking systemic antibiotics, isotretinoin, antiandrogens, or oral contraceptives, were excluded due to the potential for introducing biases.

Patients were divided into two groups: the control group (CG, N = 80) with acne but no IR and the IR group (IRS-G, N = 72) with both acne and IR. The odds of developing more severe acne in the presence of IR and depending on the evaluated body composition parameters were evaluated.

Furthermore, GPx activity was measured using a photometric method, which requires the analysis of whole blood preserved with EDTA anticoagulant, maintained at a temperature of 2°C - 8°C, with a minimum volume of 2 mL. The normal range for GPx activity is 4171 - 10881 U/L[4] [6]. Weight status was determined by BMI values. Body indices were measured using a Tanita eight-electrode multifrequency bioelectrical impedance (BIA) device, model MC780MA (Tanita Corporation, Tokyo, Japan). A trained team performed the BIA measurements according to standard procedures [36]. The ambient temperature was 25°C. BMI, FFM, FM and VF were assessed after an over-night fast and categorized according to the manufacturer's instructions [33, 36].

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Research Commission of the Medicine and Pharmacy Faculty, University of Oradea, Oradea, Romania. Informed consent was obtained from all the subjects involved in the study.

Statistical analysis

A comprehensive statistical evaluation was performed, including descriptive statistics, central tendency, dispersion measures and frequency tables. The Shapiro-Wilk test indicated data set is not distributed according to a normal distribution, necessitating non-parametric tests. The Mann-Whitney test was used for comparing two distinct groups, while the Kruskal-Wallis test was used for comparing multiple different groups. For assessing the relationship between the data, the Spearman coefficient was computed. The level of significance was established at $\alpha = 0.05$. The data was collected utilizing the Microsoft Excel database, while the statistical analysis was conducted using the JASP v19.0 software [19].

Results and Discussion

In this cross-sectional study of 152 patients (mean age 22.1 years), IR was present in 47.37% of patients. The HOMA-IR ranged from 0.7 to 7.4 mmol/L, with an average value of 2.52 mmol/L. The groups were demographically similar, with no significant differences in gender distribution (76.25% female in CG *vs.* 76.39% in IRS-G, p = 0.948) or urban residency (83.75% in CG *vs.* 70.83% in IRS-G, p = 0.066). However, severe acne was significantly more prevalent in the IRS-G (64.6% vs. 28.8% in CG, p < 0.001) (Table I).

Table I

Demographic and clinical characteristics of the patients

Characteristics	CG (N = 80)		IRS-G (N = 72)		p
	N	%	N	%	
Age (Mean ± SD)	21.95 ± 4.06		22.37 ± 4.55		0.626
Women	61	76.25	55	76.39	0.984
Men	19	23.75	17	23.61	
Urban	67	83.75	51	70.83	0.056
Rural	13	16.25	21	29.17	
Mild acne	26	32.5	6	8.3	< 0.001
Moderate acne	31	38.7	18	25.3	
Severe acne	23	28.8	48	64.7	

In the IRS-G, severe acne was significantly more frequent than moderate and mild acne (64.7% *vs.* 25.3%, p = 0.001, and 64.7% *vs.* 8.3%, p < 0.001, respectively), whereas in the CG, moderate and mild acne predominated (38.7% *vs.* 32.5%, p = 0.59) with a slightly lower percentage of severe acne (28.8%, p = 0.77 and 0.34). Figure 1 shows the frequency of acne stages in both groups.

The descriptive analysis indicated that GPx had an average value of 5747.95 U/L[4], with a range from 3691.0 to 10769, and higher values in the CG. BMI values ranged from 22.10 kg/m² to 39.0 kg/m², with an average of 27.00 kg/m². Body parameter values ranged from 45.1 kg to 74.2 kg, with an average of 53.8 kg for FFM, from 13.8% to 45% with an average of 34.4% for FM and from 0 to 19 with an average of 6.7 for VF. In the IRS-G, the average values of BMI, FM and VF were higher than in the CG, while FFM values were slightly lower than in the CG.

Based on the data obtained from the descriptive statistics, the Mann-Whitney test was used to ascertain if there existed any significant differences between the groups. The average values of BMI, FM and VF were significantly higher in the IRS-G compared to the CG (26.55 ± 4.49 *vs.* 29.26 ± 5.51, p = 0.004; 31.634 ± 8.383 *vs.* 37.42 ± 7.60, p < 0.001; and 5.688 ± 4.304

vs. 6.241 ± 4.490, p < 0.001), while the enzymatic activity of GTPx was significantly lower (5493.09 ± 1001.65 *vs.* 6252.01 ± 1481.23, p < 0.001) (Figure 2 a-e).

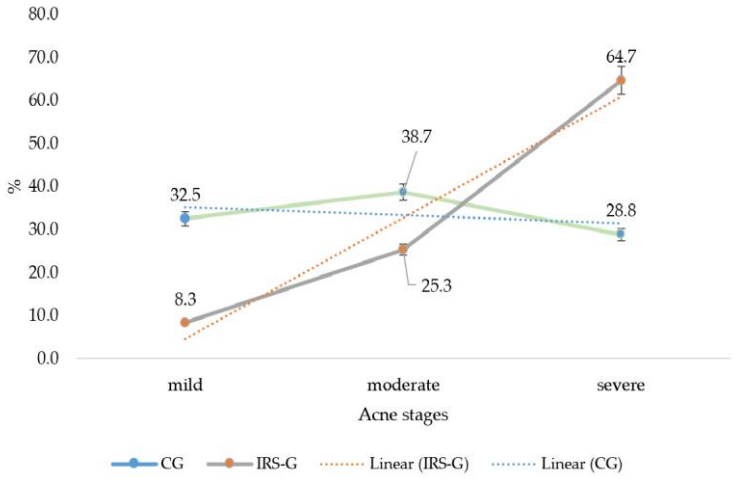

Figure 1.
Acne stages frequency in each group

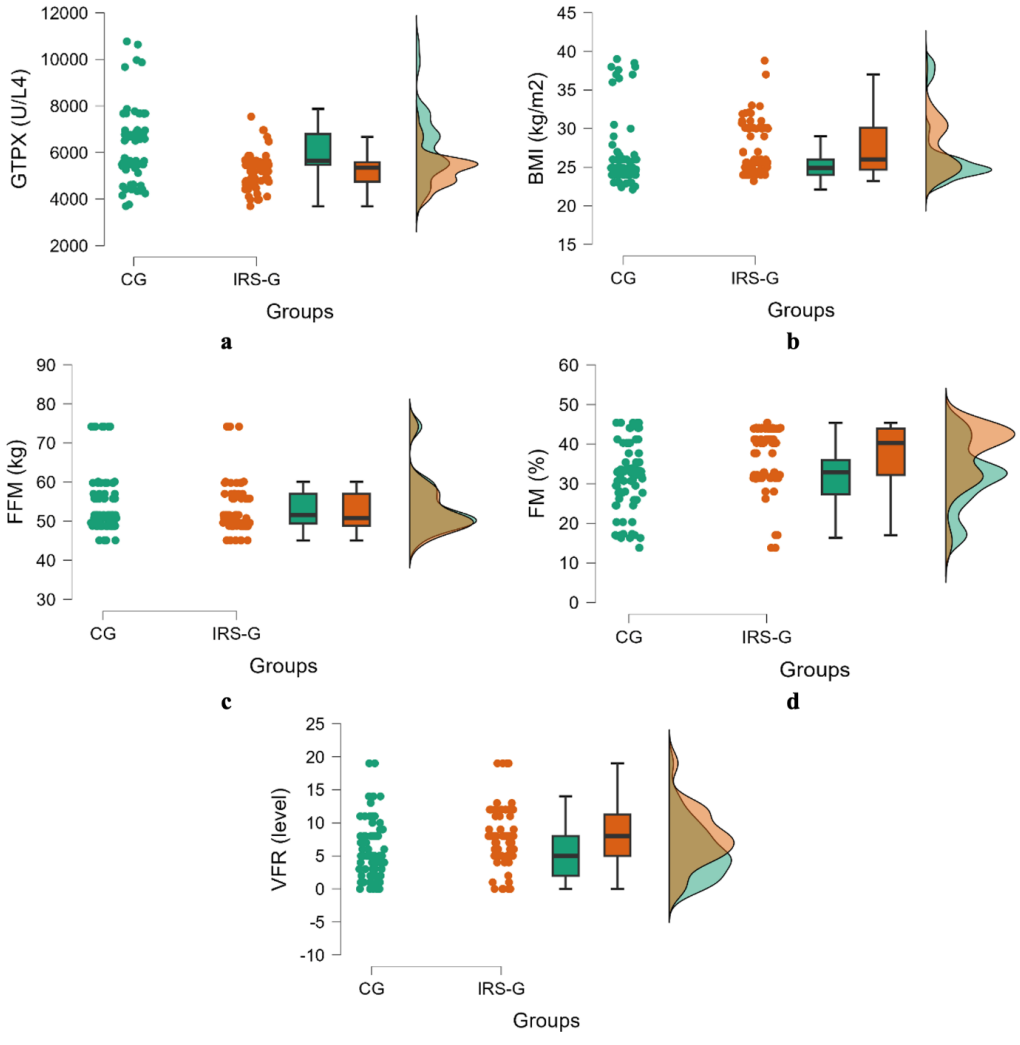

Figure 2.
Distribution of tested parameters by groups: (a) GTPX, (b) BMI, (c) FFM, (d) FM, (e) VF

Table II

BMI, body composition and GPx in comparison with reference values

Parameters	CG		IRS-G		p
	N	%	N	%	
Glutathione peroxidase (U/L[4])					
< 4171 U/L[4]	3	3.8	6	8.3	0.317
4171 – 10881 U/L4	77	96.2	66	91.7	0.744
> 10881 U/L[4]	0	0.0	0	0.0	-
Body mass index (kg/m^2)					
Normal weight	43	53.7	21	29.2	0.163
Overweight	25	31.3	23	31.9	0.078
Obese	12	15.0	28	38.9	0.001
Fat mass (%)					
Under	11	18.7	4	5.6	0.071
Normal	34	42.5	19	26.4	0.189
High	19	23.8	33	45.8	0.039
Very High	16	20.0	16	22.2	0.862
Visceral fat (level)					
Normal	66	82.5	51	70.8	0.792
High	12	15.0	17	23.6	0.695
Very high	2	2.5	4	19.1	0.999

A comprehensive examination of the parameters relative to reference values was carried out to emphasize the distinctions between the two groups (Table II). The prevalence of obesity in the IRS-G group was significantly higher compared to the control group ($p = 0.001$). Upon analysing the body composition characteristics, it has been shown that a considerable number of patients from this group had significantly elevated levels of FM, which exceeded the established reference limits, comparative with CG ($p = 0.039$). Furthermore, the IRS-G group exhibited a higher percentage of patients with GPx values below 4171 U/L[4] compared to the CG group, but the difference was not statistically significant.

To analyse in more detail the association between HOMA-IR and the studied parameters, the IRS-G group was divided into three subcategories: I (HOMA-IR 2 - 2.5 mmol/L, N = 8), II (HOMA-IR 2.6 - 5 mmol/L, N = 44) and III (HOMA-IR > 5 mmol/L, N = 20). The Kruskal-Wallis test was applied within these categories to determine the statistical significance of the observed differences. The results showed the statistically significant differences ($p < 0.05$) in the FM, VF categories and acne stage. Whether the variable was examined as continuous or categorical, FM showed these differences. Severe acne had the highest prevalence rate, regardless of subcategory, with a higher percentage in subcategories II and III (70.7% and 60%, respectively), while mild acne was only present in subcategories I and II, at proportions of 37.5% and 6.8%, respectively (Table III).

Table III

Distribution of body composition, GPx activity and acne severity across HOMA-IR categories

Parameters		HOMA_categ			p
		I	II	III	
Body mass index (mean ± SD)		27.89 ± 5.87	30.00 ± 5.70	28.10 ± 4.85	0.091
Weight status (N/%)	**Normal**	3/37.5	14/31.8	4/20	0.721
	Overweight	3/37.5	14/31.8	6/30	
	Obesity	2/25	16/36.4	10/50	
Fat free mass (mean ± SD)		50.93 ± 3.03	54.18 ± 7.48	52.18 ± 6.31	0306
Fat mass (mean ± SD)		27.78 ± 9.55	37.50 ± 6.99	41.73 ± 4.65	< 0.001
Fat mass categories (N/%)	**Under**	2/25	2/4.5	0/0.0	< 0.001
	Normal	5/62.5	13/29.5	1/5.0	
	High	1/12.5	17/38.6	15/75.0	
	Very High	0/0.0	12/27.4	4/20.0	
Visceral fat (mean ± SD)		5.87 ± 4.51	7.89 ± 4.61	9.23 ± 3.99	0.233
Visceral fat categories (N/%)	**Normal**	7/87.5	36/81.8	8/40	0.016
	High	1/12.5	7/15.9	9/45	
	Very high	0/0.0	1/2.3	3/15	
Glutathione peroxidase (mean ± SD)		5516.755 ± 1014.26	5499.000 ± 1148.43	5331.875 ± 367.72	0.883
Glutathione peroxidase categories (N/%)	**Under**	0/0.0	4/9.1	2/10	0.659
	Normal	8/100.0	40/90.9	18/90	
	Over	0/0.0	0/0.0	0/0,0	
Acne stage	**Mild**	3/37.5	3/6.8	0/0.0	< 0.001
	Moderate	1/12.5	9/20.5	8/40.0	
	Severe	4/50	32/70.7	12/60.0	

To assess the level of correlation between the HOMA-IR and the variables under investigation the Spearman coefficients have been determined. A strong positive correlation was observed with BMI, FM, VF and acne stage ($\rho = 0.272$, $p < 0.001$; $\rho = 0.447$, $p < 0.001$; $\rho = 0.416$, $p < 0.001$).

Additionally, when GPx was evaluated, a significant negative correlation was detected ($\rho = -0.403$, $p < 0.001$). The correlation between acne severity and body parameters was also analysed, revealing the same trend of association as observed with HOMA-IR. The severity of acne increased significantly ($p < 0.05$)

with higher BMI, FM and VF, and decreased GPx activity (Table IV).

Logistic regression analysis was used to determine the impact of various parameters on the probability of individuals having severe acne. At χ^2 (145) = 76.822, $p < 0.001$, the logistic regression model demonstrated statistical significance. The main predictors for severe acne were BMI, VF level, GPx activity and IRS. The probability of the occurrence of severe acne increased with increasing BMI, VF level, the presence of IR and decreasing GTPX (Table V).

Table IV

The degree of association of the HOMA-IR and acne stage with the studied variables

Studied variables	Spearman coefficient (ρ ∗)	p	Spearman coefficient (ρ ∗)	p
	HOMA-IR		Acne stage	
BMI (kg/m^2)	0.272*	< 0.001	0.560*	< .001
FFM (kg)	-0.069	0.339	-0.043	0.598
FM (%)	0.447*	< 0.001	0.288*	< .001
VFR (level	0.310*	< 0.001	0.395*	< .001
GPx (U/L^4)	-0.403*	< 0.001	-0.456*	< .001
Acne stage	0.416*	< 0.001	-	-

* significant values

Table V

Logistic regression analysis of variables influencing acne severity

Variable	Regression coefficient	OR	Wald Statistic	p
(Intercept)	-0.309	0.734	0.028	0.867
HOMA-IR (mmol/L)	-0.143	0.867	0.337	0.562
GPx (U/L^4)	-0.001	0.999	17.746	< 0.001
FM (%)	-0.036	0.965	1.464	0.226
BMI (kg/m^2)	0.239	1.270	13.305	< 0.001
VFR (level)	0.119	1.126	5.384	0.020
IRS (Yes)	1.536	4.647	3.142	0.076

Recent interest in the link between IR and acne vulgaris has largely focused on underlying mechanisms, often overlooking the role of antioxidant enzymes and body fat characteristics. Given that obesity contributes to IR [37] and is associated with higher oxidative stress [12], this study explored the possible correlations between IR and acne, a skin condition also marked by the inflammatory processes [2] and oxidative stress [20], following the relationship of IR and acne with FFM, FM, VF and GPx activity.

Multiple studies indicate that obesity is not adequately defined by BMI [21, 28] alone, as individuals with similar BMI may have different FM, FFM and fat distribution [13]. More comprehensive tests, including body composition analysis, could better identify IR in adolescents, particularly those who appear lean, but are IR [38].

In this cross-sectional study of 152 acne patients, 47.37% had IR (HOMA-IR > 2.0 mmol/L). Severe acne was more prevalent in the IR group (IRS-G) compared to the control group (CG). Subgroup analysis within IRS-G confirmed that the severe acne was significantly more common across all subgroups. These findings are in line with the results from previous investigations that found correlations between IR and the presence of acne vulgaris, suggesting that individuals with reduced sensitivity to insulin may have a higher susceptibility to developing acne lesions [16, 30]. Over half of the participants were overweight or obese, with the IRS-G group showing significantly higher obesity rates ($p = 0.001$). FM and VF levels were significantly higher in IRS-G ($p < 0.005$), while FFM did not differ significantly ($p = 0.339$). These results support the hypothesis that body fat distribution affects IR, and that FM and VF are strong IR predictors and are in line with other studies' findings [13, 15]. Previous research highlighted the role of body composition in predicting IR, demonstrating that body weight, waist circumference, BMI, FM and VF are all strongly associated with IR. Notably, body weight, FM and VF were found to be marginally more effective predictors of IR compared to waist circumference and BMI within a healthy young adult male cohort [22]. This underscores the importance of considering body composition, particularly FM and VF, when assessing metabolic risk. Moreover, FM and FFM are linked to various cardiometabolic disorders [10], further highlighting their relevance in understanding the complexities of IR and supporting their inclusion in the present study's analysis.

Correlation analysis between HOMA-IR and acne severity, in conjunction with selected body composition parameters, revealed a consistent association trend. Both HOMA-IR values and acne severity significantly increase ($p < 0.05$) with rising BMI, FM, VF, while decreasing with an increase in FFM. However, data on the causality between VF and IR are still inconsistent in the scientific literature and further in-depth studies are needed. Several researchers have documented that visceral adipose tissue significantly contributes

to metabolic risk [4,32], while others have proposed that subcutaneous adipose tissue could potentially be protective for IR [25].

Oxidative stress, caused by the generation of free radicals, has been shown to negatively impact acne development by generating proinflammatory cytokines through various biochemical pathways [20]. Additionally, it can impact IR by influencing the process of insulin receptor signal transduction [17]. In this medical context, the role of endogenous antioxidant systems becomes essential in the management of these conditions. The evaluation of GPx indicated a significantly lower mean value in the IRS-G compared to the CG ($p < 0.001$). When the correlation between HOMA-IR and acne severity with GPx was tested, a significant negative association was found in both cases. The values exhibit a negative correlation with the rise in GPx activity. These observations are also correlated with the results of other studies showing that increased GPx antioxidant activity plays a potential role in improving IR [11, 39] and the development of acne [6]. However, the design of the study is essential for drawing conclusions in this context, as a positive statistically significant association between GPx activity and IR was observed in pregnant patients [9]. Moreover, studies indicate that elevated GPx1 activity might disrupt insulin functionality by excessively neutralizing intracellular reactive oxygen species, which are necessary for enhancing insulin sensitivity [24], making further investigations necessary to clarify the impact of overexpression and under expression of GPx.

In the last part of the present study, a logistic regression analysis was applied to determine the impact of GPx, BMI, selected body parameters and the presence of IR on the probability that individuals have severe acne. The results indicates that multiple factors are involved in the severity of acne, with obesity-related factors (BMI, VF level), metabolic disturbances (IRS) and antioxidant defense (GPx activity) all playing significant roles. The positive association of BMI, VF and IRS with severe acne and the negative association of GPx activity suggest that addressing obesity, improving insulin sensitivity and enhancing antioxidant capacity through lifestyle changes or medical interventions might help in managing severe acne.

The study is distinctive, as one of the few that have examined the link between body composition, IR and the severity of acne in patients with acne. Nevertheless, this research does have certain limitations coming from the nature of the study (*i.e.*, cross-sectional design) and the relatively small number of patients included in the analysis. On the other hand, additional thorough investigation, which includes a bigger sample size and more homogeneous groups in terms of age and gender, as well as following individuals over an extended period, is necessary to generate more accurate results and gain a more comprehensive knowledge of the studied connections.

Conclusions

This study highlights the significant relationship between body composition, IR and acne severity. Patients with both acne and IRS tend to have more severe acne, higher BMI, FM, VF, and lower GPx activity compared to those without IRS. Obesity, particularly with increased FM and VF, exacerbates IR and oxidative stress, worsening acne severity. Reduced GPx activity is linked to higher IR and more severe acne, indicating the importance of antioxidant defences. BMI, VF, GPx activity and IR presence are potential predictors of severe acne, suggesting that targeting these factors could enhance acne treatment. However, the larger multicentre prospective studies are needed to validate these findings and clarify the underlying mechanisms.

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Conflict of interest

The authors declare no conflict of interest.

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