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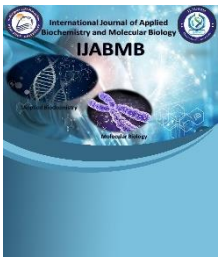


Acne Vulgaris, Body Mass Index, Insulin Resistance and Retinoic Acid Receptor Gamma: Any Relationship?

Ebtehal G. Abdelhady M.D.[1*], Reham K. Hassan M.B.B.CH[2], Yasser M. Gohary M.D.[3] and Ahmed R. Sayed M.D.[1]

[1]Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Beni-Suef University, Beni Suef, Egypt.

[2] Beni-Suef Specialized Hospital, Beni-Suef, Egypt.

[3] Dermatology Department, Faculty of Medicine, Beni-Suef University, Beni Suef, Egypt.

Corresponding author:

Ebtehal G. Abdelhady

Lecturer of Medical Biochemistry, Faculty of Medicine, Beni-Suef University

Email: dr.ebtehalgamal@gmail.com

Tel: 00201147317831

Running Title: Acne Vulgaris relation to BMI, IR, and RAR-γ

Abstract:

Background: Acne vulgaris (AV) is a common chronic inflammatory disease of the pilosebaceous units associated with long-term sequelae and complications. Little is known about the association of acne with body mass index (BMI). Among retinoic acid receptors (RARs) α, β, and γ, the messenger RNA level of RAR-γ is the most readily detectable by Northern blotting in human and mouse skin. This observation suggests that RAR-γ may play a critical role in the modulation of the therapeutic benefits of isotretinoin in skin.

Objective: The aim of the present study is to investigate the relation between BMI and severity of acne, and to find out if there is a link between BMI and RAR-γ in skin tissues of acne patients, and the subsequent supposed effect on therapy response by isotretinoin.

Patient and Methods: In this study, 60 acne vulgaris patients were conducted. They were classified according to their BMI into 3 subgroups; group I: 12 normal weight, group II: 21 overweight, and group III: 27 obese individuals. Global Acne Grading System (GAGS) was calculated for acne severity. Insulin resistance was checked (by measuring serum glucose level, insulin level and Homa-IR score) and RAR-γ levels were evaluated in skin biopsies by ELISA.

Results: Serum glucose level, insulin level and Homa-IR score were significantly higher in obese patients as compared to both normal weight and overweight ones, while no significant difference was observed between patients of normal weight and overweight. The RAR-γ level was significantly lower in obese individuals than those with normal weight, and it was also significantly lower in overweight than normal weight. There was non-statistically significant difference in RAR-γ levels between overweight and obese individuals.

A statistically significant linear negative correlation was noticed between RAR-γ levels and the serum glucose level (r= -0.519, p=0.001), insulin (r= -0.485, p=0.001), Homa-IR (r= -0.485, p=0.001), and BMI (r= -0.470, p=0.001) in all studied subjects collectively.

Conclusion: Tissue levels of RAR-γ were down regulated in acne patients in relation to their BMI. There was no association between BMI and severity of acne in the current study. Larger studies are needed to confirm these findings. Better characterization of role of RAR-γ could constitute a therapeutic avenue to the treatment of Acne Vulgaris.

Keywords: Acne Vulgaris, RAR-γ, BMI, Insulin Resistance

Introduction:

Acne vulgaris (AV) is a common inflammatory skin condition of the pilosebaceous unit that affects most individuals between 12 and 25 years of age (1). It manifests in two forms: classic acne, which usually appears at the age of 14, and late-onset acne, which occurs around the age of 30. Although females are more prone to acne, males are more likely to develop severe forms (2).

The major pathogenic factors that contribute to the onset and progression of acne lesions are the alteration of the keratinization process, increased sebum production, colonization with Cutibacterium acnes (C. acnes, formerly: Propionibacterium acnes), and inflammation. However, it is worth noting that genetic factors also play a significant role (3-5). Altered keratinization can lead to the formation of comedones, while changes in sebum composition such as a reduction in the amount of linoleic acid can cause hyperkeratinization (6,7). Hormones, especially androgens, are powerful inductors of sebaceous gland secretion and modulate keratinocyte proliferation (1,2). Excessive sebum production creates a favorable environment for bacterial growth, which, in turn, leads to inflammation(7) .

The prevalence of obesity has risen globally. Several metabolic diseases, including diabetes, metabolic syndrome, and polycystic ovarian syndrome (PCOS), are associated with obesity. Acne vulgaris may worsen because of the hyperandrogenism that obesity fosters within the body. The body mass index has been mentioned in a few studies as a possible risk factor for the emergence of AV(8) .

Metabolic syndrome (MetS) is a highly complex illness defined by a combination of pathological conditions, such as insulin resistance (IR), high blood pressure, abdominal obesity, and dyslipidemia, which may contribute to the development of type 2 diabetes as well as cardiovascular disorders (9,10). Moreover, MetS has been linked to many medical conditions, including skin disorders (11). Emerging research reveals a link between MetS and the occurrence and magnitude of acne vulgaris, a prevalent skin disorder affecting approximately 80% of adolescents(12) .

It is hypothesized that IR, which is a key component of MetS, causes the occurrence of acne vulgaris. Insulin stimulates the synthesis of androgens, which trigger the sebaceous glands in the skin to generate more sebum, which is a vital part in the development of acne vulgaris. IR leads to elevated insulin concentrations, which can result in enhanced androgen and sebum secretion. Moreover, patients with acne vulgaris and IR showed increased sebum production levels and more severe acne(13) .

Retinoids, derived from vitamin A, are the mainstays of acne treatment given they address the key pathogenic pathways of acne (14). Retinoids are synthetic or natural derivatives of vitamin A, including retinol, retinal, 13-cis retinoic acid (isotretinoin), and adapalene (15). Retinoids exert their effects through the binding of their nuclear receptors leading to downstream biological effects. For acne, retinoids can be administered both topically in a variety of formulations and combinations as well as systemically. With judicious use, this class of medication is well tolerated and very efficacious in managing acne. Furthermore, there is evidence showing its role in improving and preventing one of the most challenging post-acne changes, atrophic acne scarring(14) .

Three subtypes of retinoic acid receptors (RAR) exist; RAR-α, RAR-β, and RAR-γ. The three RAR subtypes vary in their localization. RAR-α and RAR-β have a widespread expression within the body, whereas RAR-γ is more tissue-specific. RAR-γ comprises 90% of the receptors found in the skin, with RAR-α accounting for most of the remaining 10%. RAR-γ is mainly expressed in structural cells such as keratinocytes and fibroblasts, and RAR-α predominantly in immune cells such as Langerhans cells and T cells(16) .

Although the precise function of each subtype in acne pathogenesis is yet to be defined, evidence supports RAR-γ playing a key role. RARs are involved in tissue homeostasis, through control of skin cell differentiation and proliferation. Their canonical mechanism involves transcriptional regulation via binding to target gene promoters, such as those involved in keratin production, although RARs also have non-genome-related actions(16) .

Isotretinoin is extremely effective in treating acne given it addresses the primary etiologic factors associated with acne. It decreases sebum production, targets comedogenesis, and minimizes colonization with Cutibacterium acnes. Its use over time has expanded from treating only patients with severe nodulocystic disease to patients with less severe disease who fail conventional therapies, exhibit extensive scarring, suffer from significant psychosocial distress, and those with acne fulminans (14).

Herein we suggested a link between the BMI, insulin resistance and the severity of acne, and between BMI and RAR-γ levels in the skin tissues of acne patients. Hence, a subsequent supposed effect of RAR-γ levels on patients' response to isotretinoin.

Patients and methods

This cross-sectional study included a total of 60 patients with acne vulgaris randomly chosen. Patients who started any treatment rather than isotretinoin or had never received treatment were included. Patients were classified according to their body mass index into three subgroups: group (I) 12 normal weight, group (II) 21

overweight and group (III) 27 obese patients. Ethical approval from Beni-Suef University research ethical committee (REC), Faculty of Medicine, Beni-Suef University (Approval Number: FMBSUREC/03052020/Yahia) and informed consent were obtained from the participants in this study. To be enrolled in the study, patients had to be between the ages of 12 and 30 years and diagnosed as acne vulgaris. Patients under the age of 12 and above 30 years, and patients with acne vulgaris who started isotretinoin treatment were all excluded.

Detailed history taking were obtained from all participants including age (years), sex, and duration of acne vulgaris (years). Physical examination was done. Highet (in meters) and weight (in kilograms) were measured without shoes and shirts, then the BMI (kg/m^2) was calculated (weight in kilograms divided by the square of their height in meters). Patient is considered normal weight ($18.5 \leq BMI < 25\ kg/m^2$), overweight if ($25 \leq BMI < 30\ kg/m^2$), and obese if ($BMI \geq 30\ kg/m^2$) (17).

Patients were diagnosed on clinical examination, presenting with comedones (white head or black head), papules and pustules, and nodules (raised bumps with obvious inflammation) in a sebaceous distribution (18).

In our work, severity of acne lesions was evaluated as not present (0), mild (1), moderate (2), and severe (3). Evaluation of acne vulgaris severity was done using the Global Acne Grading System (GAGS). Briefly, GAGS consider six locations of the face and chest/upper back with a factor for each location based on surface area (forehead = 2, Right cheek = 2, Left Cheek =2, Nose = 1, Chin = 1, Chest and Upper back = 3), distribution and density of pilosebaceous units. Each region would be given a score depending on the type of lesions (No lesion =0, One comedone = 1, Papule=2, One pustule = 3, One nodule = 4) and the sum of scores multiplied by the factors (Local score = Factor × Grade from 0 to 4), the sum of local scores gives the global score (0–52). The severity is graded as mild if the score was 1–18, moderate with scores from 19–30, severe with scores from 31–38, and as very severe if the score is more than 38(19**)**.

Involved skin lesions were biopsied under local anesthesia using a 4-mm punch. The biopsies were kept in phosphate buffer saline and stored at −70°C until processing.

Blood glucose was assessed using a Colorimetric Assay kit (Catalogue No.: ab282922, Abcam, USA), and the quantitative sandwich ELISA technique using the Human Insulin Kit was used to quantify the serum insulin concentration (Catalogue No.: E0010Hu, BT LAB, China). The following formula was used to test insulin resistance using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR): HOMA-IR is calculated as follows: Fasting blood sugar (mmol/L) x Fasting insulin (μIU/mL)/22.5. Tissue levels of RAR-γ were quantified by ELISA (Sun Red China, catalogue number 201-12-1526).

Statistical analysis

Data were presented as means ± standard deviation (SD), minimum, maximum, numbers and percentages. The significance of difference was tested using Student's t-test to compare the mean of two groups of parametric data and the ANOVA test to compare the mean of > two groups of parametric data. For continuous non-parametric data, the Mann-Whitney U test was used. Chi-square test was used for categorical parameters. Spearman's relationship coefficient was considered. A statistical significance is considered when a P value was ≤ 0.05, and a P value < 0.001 was considered highly significant. All data were tabulated, coded, and analyzed using the SPSS version 25 (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) for Microsoft Windows 10.

Results

Clinical, anthropometric, and biochemical parameters of the study population

This cross-sectional study included 60 AV patients, their age ranged from 12 to 30 years old, with a mean age of 21.47±4.39 years. The study included 23 (38.3%) males and 37 (61.7%) females.

Participants' weight ranged from 58 to 108 kg, with an average weight of 80.72 ± 13.73 kg, their height ranged from 1.64 to 1.85m with an average height of 1.64 ± 0.09 m. The calculated BMI ranged from 21.20 to 46.31 kg/m^2 with an average BMI of 30.13 ±5.81 kg/m^2. The duration of disease was 2.29 ± 1.12 years, with minimum 1.0 year and maximum 6.0 years. As regard GAGS score, mild was the score of 35 (58.3%) patients, while 22 (36.7%) of them scored moderate, and only 3 (5%) patients ranged from severe to very severe.

The average glucose level in our patients was 6.47 ±1.64 mmol/L, ranged from 4.20 to 10.90 mmol/L. the mean insulin level was 10.07 ± 3.09 μIU/mL, ranged between 5.1 and 18.7 μIU/mL. Ultimately, mean HOMA-IR was 3.01 ± 1.56, ranged from 1.05 to 8.48. The clinical and anthropometric, and biochemical parameters of the patients are summarized in Table (1).

Comparison between the studied groups as regards their clinical, anthropometric, and biochemical characteristics.

They were classified according to their body mass index into three subgroups: group I included 12 (20%) normal weight, group II had 21 (35%) overweight and group III with 27 (45%) obese AV patients. There were non-statistically significant differences among the studied groups as regards the disease duration and GAGS score.

Serum glucose level was significantly highest among obese individuals as compared to both normal weight (7.06 ±1.83 vs 6.13 ±1.02, p0.05) and overweight (7.06 ±1.83 vs. 5.91 ±1.48, p0.016). There was non-statistically significant difference between normal weight and overweight regarding serum glucose level (6.13 ±1.02 vs 5.91 ±1.48, p0.708).

Serum insulin level was significantly highest among obese individuals as compared to both normal weight (11.79 ±3.33 vs. 8.76 ±1.71, p=0.001) and overweight (11.79 ±3.33 vs. 8.61 ±2.20, p=0.002). There was non-statistically significant difference between normal weight and overweight regarding serum insulin level (8.76 ±1.71 vs. 8.61 ±2.20, p=0.880).

Table (1) Clinical, anthropometric, and biochemical characteristics of the whole study population

Parameter		Mean ± SD (Min-Max)	n (%)
Clinical parameters			
Age (years)		21.47 ± 4.39 (13.0 - 30.0)	-
Sex (M/F)		-	23 (38.3) / 37 (61.7)
Disease duration (years)		2.29 ± 1.12 (1.0 – 6.0)	-
GAGS score	Mild	-	35 (58.3)
	Moderate	-	22 (36.7)
	Severe – very severe	-	3 (5.0)
Anthropometric parameters			
Weight (kg)		80.72 ± 13.73 (58.0 - 108.0)	-
Height (m)		1.64 ± 0.09 (1.49 - 1.85)	-
BMI (kg/m^2)		30.13 ± 5.81 (21.2 - 46.31)	-
Normal weight		-	12 (20)
Overweight		-	21 (35)
Obese		-	27 (45)
Biochemical characteristics			
Glucose (mmol/L)		6.47 ±1.64 (4.20 - 10.90)	-
Insulin (µIU/mL)		10.07 ± 3.09 (5.1 - 18.7)	-
HOMA-IR		3.01 ± 1.56 (1.05 - 8.48)	-

The HOMA-IR score (for estimating insulin resistance) was significantly highest among obese individuals as compared to both normal weight (3.82 ±1.79 vs. 2.37 ±0.54, p=0.004) and overweight (3.82 ±1.79 vs. 2.32 ±1.09, p=0.001). There was non-statistically significant difference between normal weight and overweight regarding Homa-IR score (2.37 ±0.54vs. 2.32 ±1.09, p=0.918). Biochemical results were demonstrated in Figure (1, 2, and 3).

Table (2) Comparison between the studied groups as regard their clinical, anthropometric, and biochemical characteristics

Parameter		Group I Normal weight (n = 12)	Group II Overweight (n = 21)	Group III Obese (n = 27)	Total (n = 60)	p-value
Clinical parameters						
Age (years)		20.58 ± 5.30 (13 - 30)	21.38 ± 4.50 (14 - 28)	21.93 ± 3.97 (15 - 29)	21.47 ± 4.39 (13.0 - 30.0)	
Sex (M/F), n (%)		7 (58) / 5 (42)	9 (43) / 12 (57)	7 (26) / 20 (74)	23 (38) / 37 (62)	
Disease duration (years)		2.06 ± 0.9 (1.0 - 4.0)	2.45 ± 1.28 (1.0 - 6.0)	2.25 ±1.06 (1.00 - 5.0)	2.29 ±1.12 (1.00 - 6.0)	0.634[a] 0.350[b] 0.626[c] 0.560[d]
GAGS score	Mild	6 (50.0%)	12 (57.1%)	17 (63.0%)	35 (58.3%)	0.640
	Moderate	6 (50.0%)	7 (33.3%)	9 (33.3%)	22 (36.7%)	
	Severe – very severe	0 (0.0%)	2 (9.5%)	1 (3.7%)	3 (5.0%)	
Biochemical characteristics						
Glucose (mmol/L)		6.13 ± 1.02 (4.30 - 7.40)	5.91 ± 1.48 (4.20 - 10.90)	7.06 ± 1.83 (4.30 - 10.30)	6.47 ±1.64 (4.20 - 10.90)	**0.038*[a]** 0.708[b] **0.050*[c]** **0.016*[d]**
Insulin (µIU/mL)		8.76 ± 1.71 (6.10 - 12.10)	8.61 ± 2.2 (5.10 - 12.80)	11.79 ± 3.33 (8.3 - 18.7)	10.07 ± 3.09 (5.1 - 18.7)	**<0.001*[a]** 0.880[b] **<0.001*[c]** **0.002*[d]**
HOMA-IR		2.37 ± 0.54 (1.39 - 3.15)	2.32 ±1.09 (1.05 - 6.20)	3.82 ±1.79 (1.68 - 8.48)	3.01 ± 1.56 (1.05 - 8.48)	**0.001*[a]** 0.918[b] **0.004*[c]** **<0.001*[d]**

BMI Body Mass Index, GAGS Global Acne Grading System, HOMA-IR Homeostatic Model Assessment for Insulin Resistance. All data presented as mean SD (minimum – maximum) except sex presented as number (percentage). p <0.05 was considered statistically significant. a Overall comparison between all groups collectively. b Comparison between normal weight vs. Overweight. c Comparison between normal weight vs. Obese. d Comparison between overweight vs. Obese

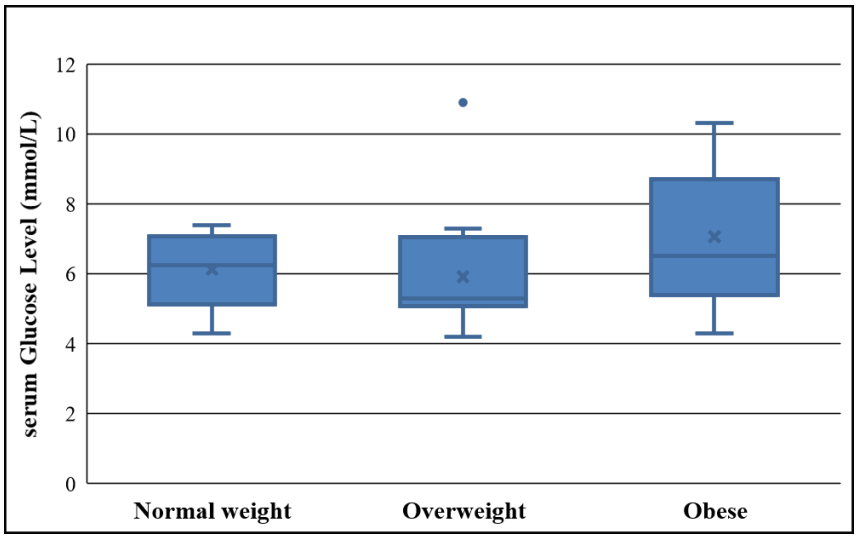


Figure (1): Comparison of Serum Glucose Level among Studied Population According to Their BMI

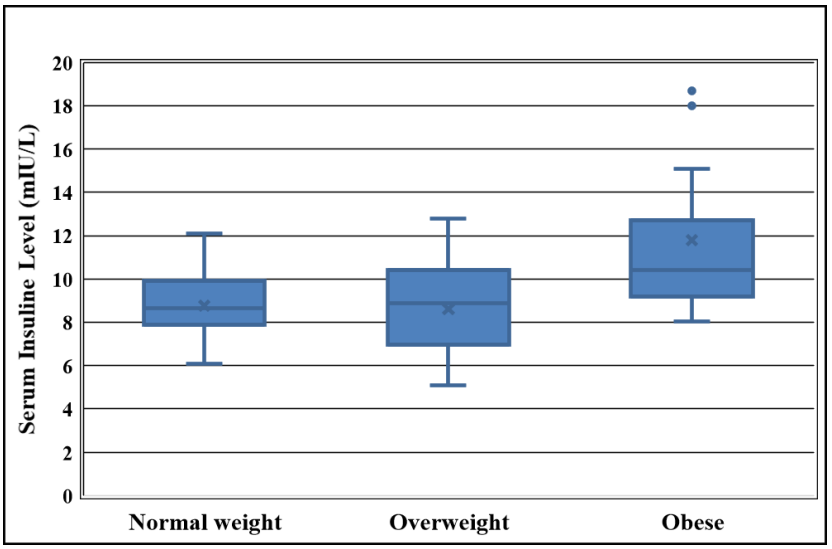


Figure (2): Comparison of Serum Insulin Level among Studied Population According to Their BMI

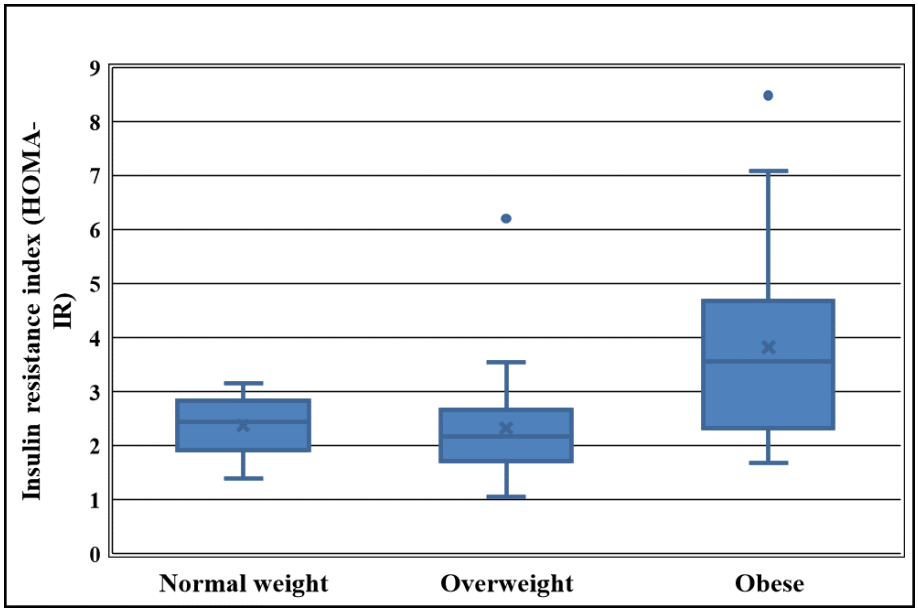


Figure (3): Comparison of Insulin resistance index (HOMA-IR) Score among Studied Population According to Their BMI

ELISA measurement of the retinoic acid receptor (RAR-γ)

According to the results of the ELISA test, RAR-γ level was 0.58 ± 0.35, with minimum 0.11, and maximum 1.20. RAR-γ level was the lowest among obese individuals. Its level was significantly lower in obese as compared with normal weight individuals (0.46 ± 0.39 vs. 0.87 ± 0.25, p 0.001), and significantly lower in overweight compared to normal weight individuals (0.55 ± 0.25 vs 0.87 ± 0.25, p 0.006). There was non-statistically significant difference in RAR-γ level between overweight and obese individuals (0.55 ± 0.25 vs 0.46 ± 0.39, p 0.382) as shown in Table (3) and Figure (4).

Table (3): Comparison of RAR-γ expression among the studied groups.

	Group I Normal weight (n = 12)	**Group II Overweight (n = 21)**	**Group III Obese (n = 27)**	**Total (n = 60)**	**p-value**
RAR-γ	0.87 ±0.25 (0.31 - 1.05)	0.55 ±0.25 (0.21 - 1.04)	0.46 ±0.39 (0.11 - 1.20)	0.58 ± 0.35 (0.11 - 1.20)	**0.002*[a]** **0.006*[b]** **0.001*[c]** **0.382*[d]**

P-value <0.05 was considered statistically significant, [a]*The overall p-value for all groups collectively,* [b] *Normal weight vs. Overweight,* [c] *Normal weight vs. Obese,* [d] *Overweight vs. Obese.*

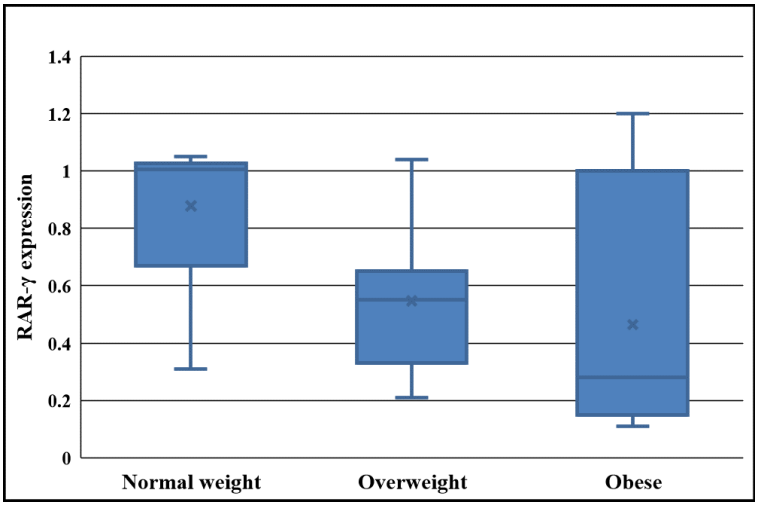


Figure (4): Comparison of RAR-γ expression among Studied Population According to their BMI.

Comparison of RAR-γ expression among the studied Population according to categorical parameters:

There were non-statistically significant association between RAR-γ expression level and gender or GAGS in the studied population, (p >0.05), Table (4).

Table (4): Comparison of RAR-γ expression among Studied Population According to categorical parameters:

RAR-γ expression	n	Mean ± SD (Min-Max)	p-value
Sex			
Male	23	0.60 ± 0.36 (0.15 - 1.05)	0.650
Female	37	0.56 ± 0.35 (0.11 - 1.20)	
GAGS			
Mild	35	0.57 ± 0.35 (0.12 - 1.20)	0.670[a] 0.755[b] 0.442[c] 0.374[d]
Moderate	22	0.60 ± 0.39 (0.11 - 1.05)	
Severe – very severe	3	0.41 ± 0.13 (0.32 - 0.55)	

Statistical analysis was done by one way ANOVA test followed by post-hoc test. p-value ≤0.05 was considered statistically significant, [a] *Overall p-value for all groups collective,* [b] *Mild vs. Moderate,* [c]*Mild vs. Severe – very severe,* [d] *Moderate vs. Severe – very severe.*

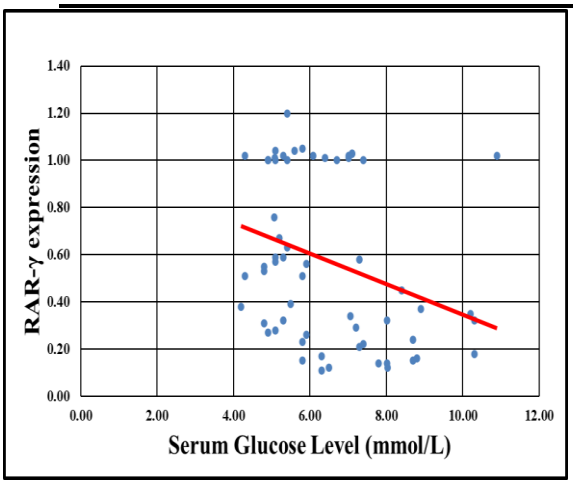
According to correlation coefficient analysis, we obtained a statistically significant linear negative correlation between RAR-γ expression and the serum glucose level (r -0.519, p0.001), Insulin (r -0.485, p0.001), Homa-IR (r -0.485, p0.001), and BMI (r -0.470, p0.001) in all studied subjects collectively (Figure 5).

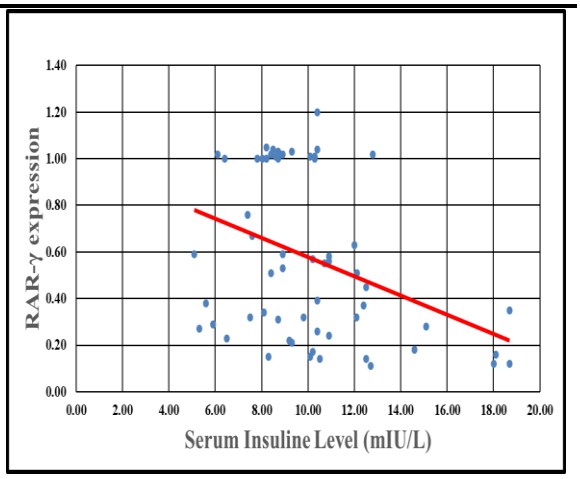
However, when we correlate the RAR-γ levels with those studied parameters (glucose level, insulin, and Homa-IR) in each group separately, only obese group showed a statistically significant linear correlation while the normal and overweight groups showed non-statistically significant linear correlation (p >0.05). Hence, the significant negative correlation was due to the obese group only.

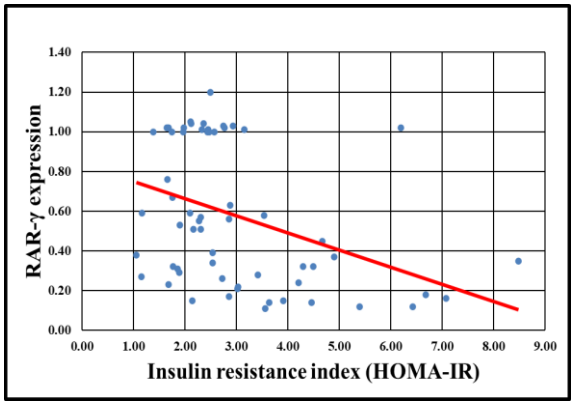
Table (5): Correlation of RAR-γ levels with numerical parameters among the studied population

		Total (n = 60)	**Group I Normal weight (n = 12)**	**Group II Overweight (n = 21)**	**Group III Obese (n = 27)**
Age	**r**	-0.031,	0.232	-0.037	-0.084
	p-value	0.812	0.468	0.874	0.678
Disease Duration	**r**	-0.064	-0.243	-0.173	0.027
	p-value	0.627	0.447	0.454	0.893
Glucose	**r**	**-0.519**	0.008	-0.322	**-0.624**
	p-value	**<0.001***	0.979	0.155	**0.001***
Insulin	**r**	**-0.357**	-0.277	0.365	**-0.508**
	p-value	**0.005***	0.383	0.104	**0.007***
Homa-IR	**r**	**-0.485**	-0.153	-0.038	**-0.594**
	p-value	**<0.001***	0.635	0.870	**0.001***
Weight	**r**	**-0.434**	-0.363	0.107	**-0.656**
	p-value	**<0.001***	0.246	0.646	**<0.001***
Height	**r**	0.124	-0.246	0.262	0.010
	p-value	0.345	0.441	0.251	0.959
BMI	**r**	**-0.470**	-0.389	-0.182	**-0.620**
	p-value	**<0.001***	0.211	0.430	**0.001***

*r= Spearman's rank correlation coefficient, *p-value ≤0.05 is considered significant.*







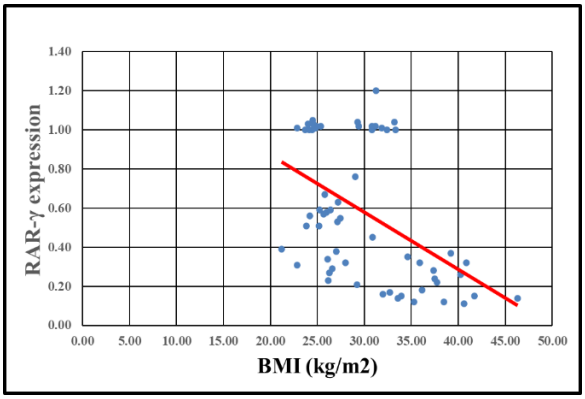


Figure (5) A Correlation between RAR-γ expression level and serum glucose, serum Insulin, Homa-IR score, and BMI in all studied population

Discussion

Acne vulgaris is a chronic, inflammatory, skin condition that involves the pilosebaceous follicles and is influenced by a variety of factors including genetics, androgen-stimulation of sebaceous glands with abnormal keratinization, colonization with Cutibacterium acnes (previously called Propionibacterium acnes), and pathological immune response to inflammation (20). It is one of the most common skin disorders affecting mostly the adolescent age group that frequently continues into adulthood (21).

Obesity is an emerging problem. It is one of the biggest problems in western countries but nowadays, the problem is increasing even in low and middle-income countries (22). According to the report of WHO, in 2019, 39% of adults were overweight and 13% were obese (23). Obesity is associated with peripheral hyperandrogenism; hence obesity may be associated with development of severe acne (24). Body Mass Index (BMI) is used to accurately measure obesity (25). There are controversial findings regarding the association between acne and BMI (26).

The retinoid family includes retinol and its natural derivatives such as retinaldehyde, retinoic acid, and retinyl esters, as well as many synthetic derivatives **(27).** Retinoids interact with cellular and nucleic acid receptors including the cellular retinoic acid-binding protein (CRABP) types I and II, the cellular retinol binding protein, and the nuclear retinoic acid receptor family called RARs. Their action consists in the regulation of cellular differentiation improving photoaging through the increase of epidermal proliferation leading to skin thickening and deposition of glycosaminoglycans (28). Retinoids exert their activity by binding non-selectively to intranuclear retinoic acid receptors, the three main subtypes of RAR— α, β, and γ— are nuclear hormone receptors whose activation causes regulation of cell growth, differentiation, and apoptosis. RAR-γ is the predominant subtype found in the skin (29).

It is hypothesized that a drug selective for RAR-γ could preferentially act on the skin and effectively treat acne while mitigating adverse effects of skin irritation; however, the clinical significance of this selectivity is not currently known **(**30**).**

Based on this published data, this study suggests a correlation between a patient's BMI and the level of RAR- γ expression in skin tissues, it was a cross-sectional study designed with an aim to correlate between the overweight/obesity and severity of acne, and to find if there is a link between BMI and the amount of expression of RAR-γ in skin tissues of acne patients, and the subsequent supposed effect on therapy response by isotretinoin.

The current study was conducted into 60 patients of acne Vulgaris chosen randomly and classified according to their body mass index into three subgroups (group (I) normal weight individuals, group (II) overweight individuals and group (III) obese individuals).

Acne has been found more commonly in females (31). Our study has also confirmed the similar finding, there was slightly female preponderance with female/male ratio of 1.6:1, similar results was reported in a study designed to find out the association between different categories of BMI and severity of acne where females were predominant with female/male ratio of 1.4:1 (22). Participants' age was ranged from (13) to (30) years old with an average age of (21.47 ±4.39) years old, this finding went in line with the previously known facts that acne is affecting mostly the adolescent age group that frequently continues into adulthood (32).

There are still controversial reports regarding the association between BMI and acne (26). There have been several studies which have confirmed the association between acne and BMI. Jancin, 2012 (33) conducted a study in female teens and reported that moderate to severe acne was more prevalent among overweight and obese individuals**.**

Alan & Cenesizoglu, 2014 (34) also observed a positive correlation between BMI and severity of acne, the groups with higher BMI had severe grades of acne. Burris et al., 2018 (35) observed a significant association between acne lesion counts and BMI in men aged 18 to 25 years.

Those findings were also confirmed by Lu et al., 2017 (36) severe acne was observed in overweight and obese individuals of age 18-25 years. A study conducted on Italian adolescents and young adults reported that the acne risk was reduced with lower BMI, especially in males (37). Tsai et al., 2016 (38) conducted in school children in Taiwan, acne was less prevalent in those having lower BMI (< 18.5). A study by Halvorsen et al., 2012 (39) also showed that overweight and obesity were associated with acne in girls of age 18 and 19 years.

On the other hand, there are studies that have rejected the link between BMI and acne severity. Borgia et al., 2004 (40) conducted exclusively in adult women found no difference in BMI when compared to severity of acne**.** Yang et al., 2010 (41) from Taiwan has even highlighted a negative phenomenon, obese women presented with less acne than the non-obese cases. Also, Anaba & Oaku, 2021 (42) conducted to document the role of diet and BMI as risk factors and cause of severity of adult female acne concluded that diet and BMI are not risk factors for AFA, and severity of AFA is independent of diet, and BMI.

In our study, there were underweight and overweight individuals in all the grades of acne. Acne Assessment comparison between the three studied groups according to their BMI, acne disease duration (years) was highest among overweight individuals; however, this difference was of non-statistically significant meaning. Also, GAGS score showed non-statistically significant difference between the three studied BMI groups. In line with our findings the reported non-significant association between BMI and severity of acne (22).

Many metabolic disorders such as dyslipidemia, obesity, metabolic syndrome and PCOS show comorbidity with acne (43). Shalom et al., 2015 (44) in a large cross-sectional study including 3207 patients with acne vulgaris and 6412 age- and sex-matched control patients, acne vulgaris was found to be significantly associated with metabolic syndrome. In the current study, serum glucose, insulin levels and Homa-IR score (for estimating insulin resistance) were significantly highest among obese individuals as compared to both normal weight and overweight. There was non-statistically significant difference between normal weight and overweight regarding serum glucose insulin levels and Homa-IR score. In accordance with our findings, Ray et al., 2012 (45) have discussed the positive correlation between blood glucose and severity of acne**.** This was attributed to increased blood glucose which in turn stimulates increased insulin secretion. Increased insulin decreases the availability of binding protein for IGF-1 which facilitates the effects of IGF-1 on basal keratinocyte proliferation. Also, insulin stimulates synthesis of androgens which can cause acne (46).

RAR-γ is the most dominant subtype of retinoic acid receptor in the skin, along with small amounts of RAR-α (30), there is little information about the skin expression of RAR-γ in acne patients according to their BMI.

To the best of our knowledge, for the first time, the current study examined the expression of RAR-γ in skin tissues of acne patients according to their BMI. The RAR-γ expression was lowest among obese individuals. The expression level was significantly lower in obese as compared with normal weight individuals, and significantly lower in overweight compared to normal weight individuals, while there was non-statistically significant difference in RAR-γ expression level between overweight and obese individuals.

The reason for significant downregulation of RAR-γ gene in overweight and obese individuals may be only related to relatively small sample size in the present study; to better interpret the results, further in vivo research is recommended in this area with larger sample sizes and measurement of serum and tissue expression of retinoic acid and RAR-γ.

In the current study, there was non-statistically significant association between RAR-γ expression level and gender in the studied population. We reported non-statistically significant association between RAR-γ expression level and Global Acne Grading System (GAGS) in the studied population. We obtained a statistically significant linear negative correlation between RAR-γ expression and the Serum glucose level, Insulin, Homa-IR, and BMI in all studied subjects collectively, however, this significantly negative correlation was due to the obese group.

Our study has several limitations. First, we were unable to account for potential confounders of the BMI-acne association, including previous acne treatments, treatment with acnegenic drugs, oral contraceptive use, and diet. Another limitation is in the number of patients studied. The number of patients studied was limited by a combination of acne, being typically a teenage problem, and the study being conducted at a tertiary hospital with attendance by those with more severe acne.

Conclusions:

Acne vulgaris is a common, chronic inflammatory skin disorder with a negative impact on quality of life and selfesteem. Now, no clear conclusion can be drawn for the association between expression of RAR-γ in skin tissues of acne patients, and their BMI. From the results of the current study there was non-statistically significant association between the three BMI studied groups and acne severity as assessed by GAGS score.

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