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ORIGINAL ARTICLE

The Combination of Oral Metformin and Topical Adapalene Gel in The Treatment of Female Patients with Acne Vulgaris

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ABSTRACT

Background: Acne vulgaris (AV) is a common chronic skin condition affecting millions of people around the globe. Its main target is the pilosebaceous unit, and this condition has different etiological factors with a complex interaction. Several treatments, either topical or systemic, are used in acne treatment. Metformin is an oral hypoglycemic drug, but it was found to be beneficial in chronic inflammatory skin conditions. This research aimed to evaluate the efficacy of oral metformin as an adjuvant to topical adapalene gel in the treatment of female patients with AV.

Methods: Thirty females suffering from mild to moderate AV were included in this clinical trial, managed using oral metformin (500 mg twice daily), along with nightly topical applications of adapalene gel for 12 weeks. The clinical outcomes were assessed using the Total Lesion Count (TLC), the Global Acne Grading System (GAGS), and the Dermatology Life Quality Index (DLQI) for evaluation of both the severity of acne in addition to its impact on the patients' quality of life.

Results: The current study findings revealed a significant reduction in GAGS (P = 0.001) and TLC (P = 0.001) after the treatment between the 2 groups. Regarding the therapeutic response based on the reduction in total lesion count (TLC), 11 patients (36.7%) demonstrated marked improvement, 16 patients (53.3%) exhibited moderate improvement, and 3 patients (10%) showed mild improvement. A significant reduction of DLQI was also seen after treatment (P = 0.001). Minimal adverse effects were observed, mainly gastrointestinal troubles.

Conclusions: Oral metformin could be a safe and effective adjuvant to topical adapalene in the treatment of AV with minimal side effects.

Keywords: Acne vulgaris; Adapalene; Metformin; Treatment.

INTRODUCTION

Acne vulgaris is a common skin condition usually seen with puberty and may aggravate during adolescence, but it can occur at any age. It affects not just the skin but may also lead to severe psychological distress. Hence, the treatment at an appropriate time becomes paramount for improving skin appearance and enhancing the patient's quality of life as well as self-esteem [1].

Acne vulgaris is a complex condition with multifactorial causes. The four main pathogenic factors involved in its progress are higher sebum production, colonization and overgrowth of Propionibacterium acnes (P. acnes), abnormal keratinization of the pilosebaceous duct, as well as an inflammatory reaction that activates the immune system, involving both innate and adaptive immunity. Other factors include genetic predisposition, hormonal imbalance, oxidative stress, dietary components, and disturbance of gut microbiome [2].

General principles of acne treatment are based on reducing sebum secretion,

normalizing ductal hyper cornification, lowering P. acnes colonization, and exerting anti-inflammatory effects [3]. Several topical and oral treatments are available for AV. The topical treatments used in first-line therapies for AV include retinoids, benzoyl peroxide, and azelaic acid, as well as various combinations of these therapies. In more recalcitrant or severe cases of AV, systemic medications, such as antibiotics, isotretinoin, and hormonal therapies, are routinely used. However, the side effects attributable to these treatments necessitated the exploration of newer and safer but also efficacious therapeutic alternatives [4].

Adapalene is a topical retinoid that serves as a first-line treatment for AV by decreasing keratinocyte proliferation and normalizing its differentiation. However, it is often used in combination with other treatments rather than monotherapy [5].

Metformin is an oral hypoglycemic drug, but it has been found to be effective in the treatment of several skin diseases, including AV in patients with polycystic ovary syndrome (PCOS) [6,7]. This may be attributed to its anti-inflammatory, anti-androgenic, and antioxidant effects [8-11].

So, this research aimed to evaluate the efficacy of oral metformin as an adjuvant to the topical adapalene gel use in the management of female patients with AV

METHODS

The clinical trial enrolled thirty female subjects suffering from acne vulgaris aged 12 to 25 years. It was conducted at the Dermatology, Venereology, and Andrology Department of Zagazig University Hospitals from June 2024 to December 2024. The study received ethical approval from the Zagazig University Institutional Review Board (ZU-IRB) under code IRB (#66/17 Jan-2024) and was conducted following the principles outlined in the Declaration of Helsinki, which is also an integral part of the World Medical Association's Code of Ethics for Research Involving Humans. All participants provided informed written consent prior to their inclusion in the study.

Sample size: Using a statistical power of 80% and a 95% confidence interval, the OpenEpi software calculated an estimated sample size of 30 patients based on a mean statin level of 0.93 ± 0.2 and a mean metformin level of 0.75 ± 0.12.

Inclusion criteria: thirty female patients with acne vulgaris whose ages ranged from 12 to 25 years old.

Exclusion criteria: Patients with acne conglobata or acne fulminans, those receiving any treatment for acne vulgaris during the previous month, pregnant or lactating patients, those with a history of allergy to the studied drugs, and those with any systemic or other dermatological disorders, PCOS, or any manifestations of hyperandrogenism were all excluded.

A detailed personal history was taken, and the complete general physical examination was performed on all patients. Weight in addition to the height was evaluated among all participants. Body mass index (BMI) measurement was determined using standard calculations of the patient's weight in kilograms divided by height in meters squared (kg/m^2).

A dermatological examination was done to determine the skin phototype and acne lesion characteristics, including type, distribution, severity, and number of lesions, and to exclude any manifestations of hyperandrogenism.

Laboratory investigations, including serum testosterone level (total and free), lipid profile, fasting blood glucose level, and pelviabdominal ultrasound, were done to exclude those with any abnormalities, including PCOS.

All patients received oral metformin hydrochloride 500 mg tablets twice daily and were instructed to apply topical

adapalene 0.1% gel once at night for 12 weeks.

Photographs of lesions were taken at baseline, every 4 weeks, and 2 weeks after the end of therapy. The Global Acne Grading System (GAGS) was used to assess acne severity before and after treatment [12]. The total lesion count (TLC) was calculated before and after treatment from the following formula: TLC = no. of comedones + no. of papules + no. of pustules [13]. The clinical response evaluated the treatment according to the percentage reduction in total lesion count (TLC) as marked improvement if 75-100% reduction; moderate improvement if 50-75% reduction; mild improvement if 25-50% reduction; and no improvement if less than 25% reduction. This kind of classification affords a uniform means of objective assessment of treatment efficacy on acne lesions [14]. Dermatology Life Quality Index (DLQI) was assessed before and after treatment [15]. Patient satisfaction was assessed after treatment as unsatisfied or slightly satisfied. Satisfied, or very satisfied. No adverse effects were recorded.

Statistical Analysis:

We used IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp., 2015) to gather, arrange, and code all of the data for the statistical study. The qualitative variables were denoted by N (count) and % (percentage), whereas the quantitative variables were shown by mean ± standard deviation, median, and range. The marginal homogeneity test was applied to ordinal variables with paired data, and the Wilcoxon signed-rank test to quantitative variables with paired data that did not follow a normal distribution. To determine statistical significance, a p-value lower than 0.05 was utilized.

RESULTS

Thirty female patients with an acne vulgaris diagnosis participated in the research. The ages of the participants varied from twelve to twenty-five years old, with an average age of eighteen and a half years. Thirteen individuals (43.3%) had a positive family history of acne. One hundred percent of patients had their faces affected, whereas sixteen percent of patients had their backs affected. (Table 1) summarizes the demographic and clinical data collected from the research population at the baseline.

After treatment, we found a significant reduction in the GAGS score (P=0.001) as compared to before treatment. Before treatment, 18 patients (60%) had mild acne and 12 (40%) had moderate acne. After treatment, 28 patients (93.3%) had mild acne and 2 (6.7%) had moderate acne, with a significant improvement of GAGS grades (P=0.002) (Table 2).

The count of comedones, papules, and pustules significantly reduced after treatment (P = 0.2, 0.001, 0.001, respectively). Moreover, the TLC significantly reduced after treatment (P = 0.001) (Table 3). Regarding the therapeutic response according to TLC reduction, 11 patients (36.7%) showed marked improvement (Figure 1), there was a moderate improvement in 16 individuals (53.3%), and a mild improvement in 3 patients (10%).

The DLQI significantly reduced after treatment (P = 0.001), with a significant improvement in DLQI grades (P < 0.001) (Table 4). At the end of treatment, 13 patients (43.3%) were very satisfied, 15 patients (50%) were satisfied, and 2 patients (6.7%) were slightly satisfied.

Adverse effects were observed, including gastrointestinal (GIT) upset in 11 patients (36.7%), weight loss in 2 patients (6.7%), and dizziness in 1 patient (3.3%). Also, erythema and dryness were detected in 11 patients (36.7%) and 5 (16.7%), respectively, with 14 patients (46.7%) developing post-inflammatory

hyperpigmentation.

Table (1): Baseline demographic and disease characteristics of the studied patients

Variables	Acne patients (n=45)
Age (in years)	
Mean ± SD	18.67±2.6
Median (range)	18(15-24)
Body Mass Index (kg/m^2)	
Mean ± SD	23.6±2.02
Median (range)	23 (22-28)
Disease duration (years)	
Mean ±SD	1.13±0.65
Median(range)	1(0.5-2)
	N (%)
Body Mass Index grade	
Normal weight	36 (80%)
Overweight	9 (20%)
Skin phototype	
II	6 (13.3%)
III	27 (60%)
IV	12 (26.7%)
Family history of acne vulgaris	
Negative	24 (53.3%)
Positive	21 (46.7%)
Site of lesion	
Face	45 (100%)
Back	5(11.1%)
Predominant lesion type	
Inflammatory	27 (60%)
Non-inflammatory	18 (40%)
Exacerbating factors	
Menstruation	42 (93.3%)
Stress	3 (6.7%)
Trauma	6 (13.3%)
Previous treatment	
Topical treatment	5 (11.1%)
Systemic treatment	8 (17.8%)

Table (2): Global Acne Grading System (GAGS) score before and after treatment.

Variables	Acne patients (n=45)		P-value
	Before treatment	After treatment	
GAGS score			
Mean ± SD	16.53±2.86	9.87±3.4	0.001 [a] *
Median (range)	16 (12-22)	10 (4-16)	
	N (%)	**N (%)**	
GAGS grades			
Mild	33 (73.3%)	43 (95.6%)	0.002 [b] *
Moderate	12 (26.7%)	2 (4.4%)	

[a] using Wilcoxon signed ranked test
b using Marginal homogeneity test
* P value < 0.05 was considered statistically significant

Table (3): Count of acne lesions before and after treatment.

Variables	Before treatment	After treatment	*P*-value [a]
Number of comedones			
Mean ± SD	20.87±15.74	8.87±6.895	0.002*
Median (range)	15 (3-64)	10 (1-23)	
Number of papules			
Mean ± SD	15.27±8.75	2.53±2.199	0.001*
Median (range)	11 (6-32)	2 (0-6)	
Number of pustules			
Mean ± SD	3.27±3.595	0.47±0.74	0.001*
Median (range)	3 (0-15)	0 (0-2)	
Total lesion count			
Mean ± SD	39.33±19.93	12.13±7.18	0.001*
Median (range)	34 (13-96)	12 (3-26)	

[a] using Wilcoxon signed ranked test
* *P* value < 0.05 was considered statistically significant

Table (4): Dermatology life quality index (DLQI) before and after treatment.

Variables	Acne patients (n=45)				*P*-value
	Before treatment		After treatment		
DLQI					
Mean ± SD	9.33±3.296		4±2.39		0.001 [a] *
Median (range)	9 (3-16)		4 (1-8)		
	N	**%**	**N**	%	
DLQI grades					
• **Very large effect**	15	33.3	0	0	
• **Moderate effect**	24	53.3	9	20	0.0001 [b] *
• **Small effect**	6	13.3	27	60	
• **No effect**	0	0	9	20	

[a] using Wilcoxon signed ranked test
[b] Marginal homogeneity test
* *P* value < 0.05 was considered statistically significant

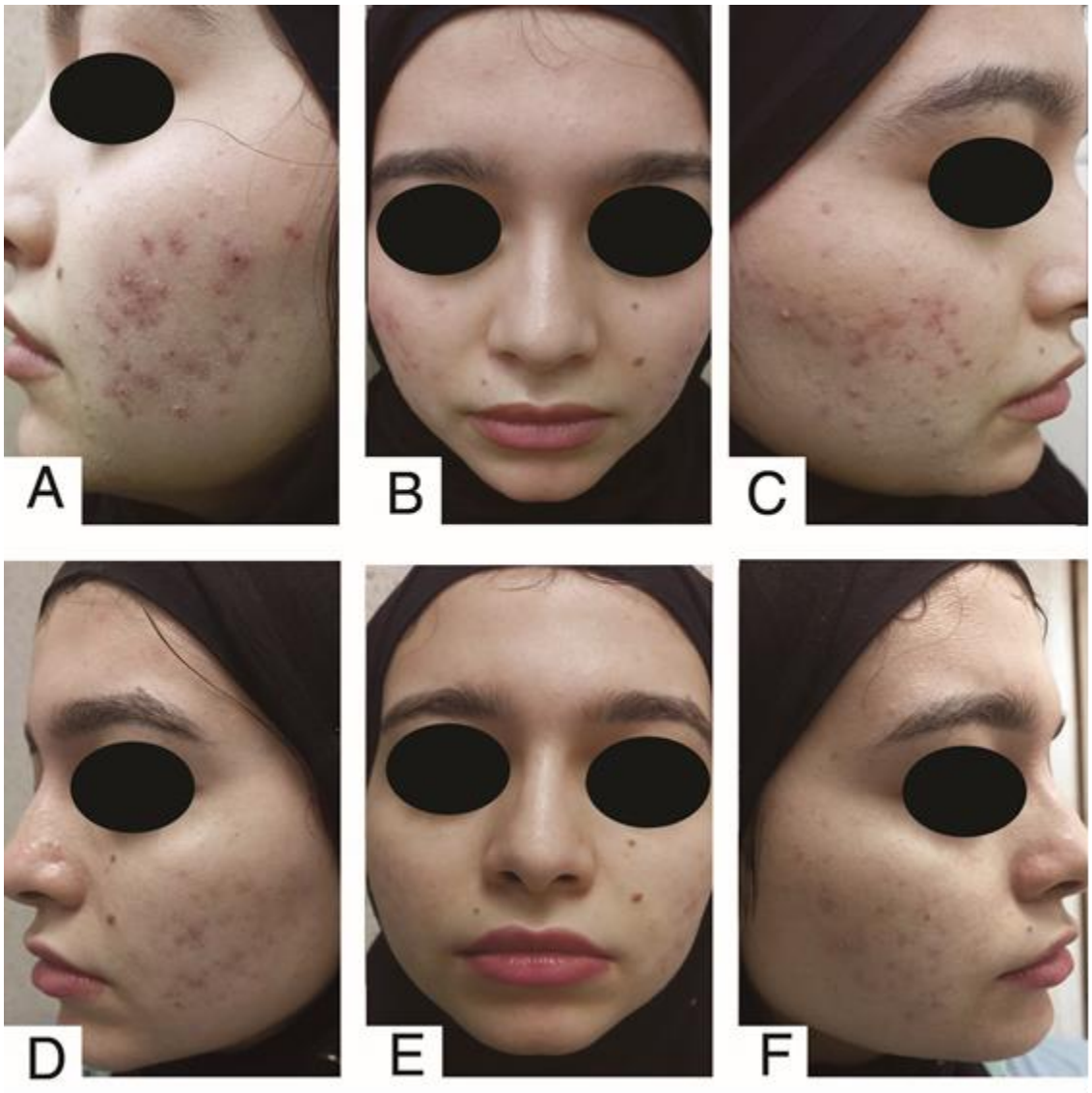

Figure (1): A case of moderate acne vulgaris before treatment (**A-B-C**) showing marked Improvement **(D-E-F)** after treatment with oral metformin and topical adapalene gel for 12 weeks.

DISCUSSION

This research examined the effectiveness of two acne treatments: oral metformin (500 mg twice a day) and topical adapalene gel (one overnight). By the conclusion of the 12-week period, GAGS scores had dropped significantly, but GAGS grades had improved significantly. Additionally, there was a marked decrease in the number of comedones, papules, and pustules, suggesting a notable decrease in TLC.

Based on the TLC reduction, clinical improvement was assessed as marked in 36.7% of patients, moderate in 53.3%, and mild in 10%. There was a tremendous and statistically relevant enhancement in DLQI

following treatment. As for patient satisfaction, 43.3% of the participants reported being very satisfied with treatment outcomes, 50% being satisfied, and 6.7% being slightly satisfied.

According to our results, the existing studies have shown that oral metformin is effective in the treatment of acne vulgaris either as a mono-drug therapy or in combination with other drugs.

Sadati et al. [16] evaluated the efficacy of metformin (500 mg twice daily) versus doxycycline (100 mg once daily) in the treatment of 40 patients with moderate acne also receiving 5% topical benzoyl peroxide gel at night. At 2 months, both groups showed significant reductions in GAGS score, TLC, number of inflammatory and non-inflammatory lesions, and Cardiff Acne Disability Index (CADI) with no statistically significant difference between both groups.

Robinson et al. [17] likewise examined the adjunctive effect of metformin on the therapy in 84 patients with moderate to severe facial acne. The patients were randomized into two groups; they had all been given 2.5% topical benzoyl peroxide in combination with tetracycline orally (250 mg twice a day). One group received additional metformin (850 mg once daily). At the 12th week of treatment, the metformin group showed a significantly higher success rate compared to the control (66.7% vs. 43.2%; $p = 0.04$).

In addition, the metformin group showed a greater mean percentage reduction in TLC (71.4% vs. 65.3%), inflammatory lesions (83.1% vs. 75.6%), and non-inflammatory lesions (44.9% vs. 37.4%) with non-statistically significant variations ($p > 0.05$), suggesting there was a trend in favor of metformin, that is, apparently improved clinical effects, but lacking statistical significance.

Meanwhile, Kamboj et al. [18] evaluated the efficacy of oral metformin monotherapy (1000 mg once daily) in 30 patients with AV without PCOS. At 3 months, the GAGS score significantly reduced with a significant reduction of serum free testosterone levels, probably due to a significant increase of sex hormone binding globulin (SHBG) ($p < 0.05$). Moreover, there was a significant reduction in the expression of lipogenic genes and FOXO1.

Furthermore, Nazari et al. [6] and Fabbrocini et al. [7] reported significant improvement of acne severity following treatment with oral metformin in females with PCOS and men with altered metabolic profiles, respectively.

In the current study, side effects developed, including GIT upset in 36.7%, weight loss in 6.7%, and dizziness in 3.3%. However, these side effects were generally mild and transient and mostly due to metformin administration. Additionally, erythema and dryness were noted in 36.7% and 16.7% of patients, respectively, mostly due to topical adapalene application. About 46.7% of patients developed post-inflammatory hyperpigmentation, which is a common complication of AV.

Similarly, Sadati et al. [16] reported mild-to-moderate GIT discomfort in 3 patients (15%) in the metformin group, especially when administered on an empty stomach. Also, Robinson et al. [17] reported mild GIT symptoms not exceeding two weeks, including nausea, vomiting, abdominal discomfort, and bloating, in 31.7% of their patients.

The results presented here highlight the safety and efficacy of combining oral metformin with topical adapalene gel for treating acne vulgaris. The specific mechanism by which metformin initiates its anti-acne effects is still a matter of debate, yet a few pathways have been presented for

consideration. It has recently been suggested that metformin inhibits inflammation by inhibiting the TLR4-associated nuclear factor-kB (NF-kB) signaling pathway and suppressing the NOD)-like receptor domains-containing protein 3 (NLRP3) inflammasome. This leads to reduced pro-inflammatory cytokines including tumor necrosis factor (TNF-ά), IL-17A as well as interleukin (IL)-1β, thus decreased inflammatory response [8,19].

Also, by lowering serum insulin in addition to the insulin-like growth factor-1 (IGF-1) levels, metformin enhances insulin sensitivity, which is a factor in the pathogenesis of acne in some patients [20]. Second, the reduction of IGF-1 levels may downregulate the mammalian target of rapamycin complex-1 (mTORC1), which is considered a key pathway that enhances the lipogenesis of sebaceous glands, excessive proliferation of keratinocytes, and inflammation in acne skin [9,17].

One mechanism by which metformin may reduce androgenic effects is by increasing the synthesis of sex hormone-binding globulin (SHBG) and decreasing levels of insulin-like growth factor-1 (IGF-1). This elevation in SHBG enhances the binding of free androgens in the bloodstream, thereby reducing their bioavailability. Additionally, the reduction in IGF-1 levels enhances the activity of forkhead box protein O1 (FoxO1), which plays a critical role in inhibiting androgen receptor signaling pathways [10].

In addition to its anti-inflammatory effects, metformin has been demonstrated to reduce reactive oxygen species (ROS) generation via inhibiting mitochondrial complex I [11]. Interestingly, recent studies have reported a significantly reduced diversity in the gut microbiome of patients with acne. However, after three months of metformin therapy, the gut microbiota diversity improved, reaching levels comparable to those observed in healthy individuals [21]. This suggests a potential role of metformin in modulating the gut-skin axis, which may contribute to its therapeutic effects in acne management.

Limitations of the current study include the small sample size, so a larger sample size would provide greater statistical power. Moreover, the duration of follow-up may have been insufficient to capture long-term outcomes.

Conclusions: The current study demonstrated that oral metformin was a safe and effective adjuvant to topical adapalene gel in the treatment of acne vulgaris. Therefore, it can be a promising alternative to oral anti-acne medications with minimal side effects. Future studies are still needed to investigate the underlying mechanism of action of metformin in acne treatment and to evaluate its efficacy either as mono-therapy or in combination with other acne treatments. Moreover, comparing the efficacy of metformin versus other acne treatments is required.

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