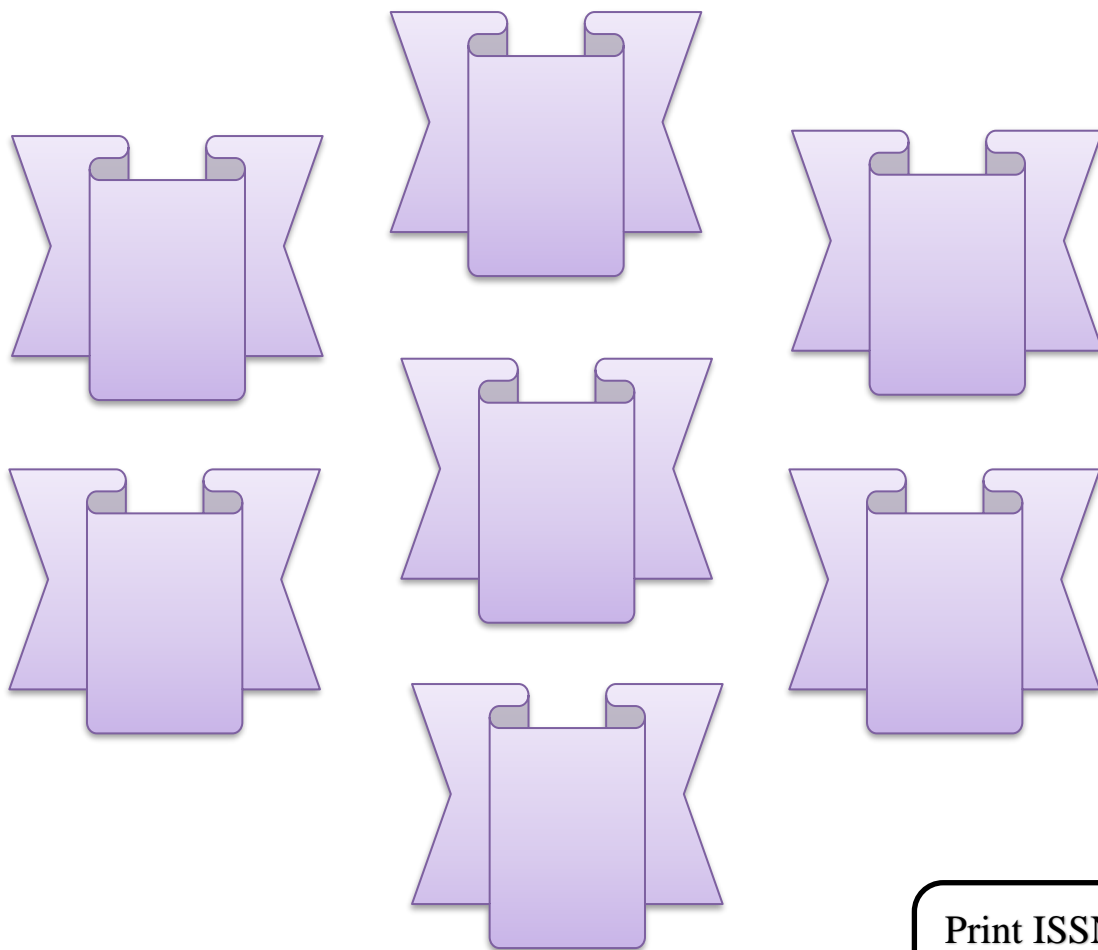


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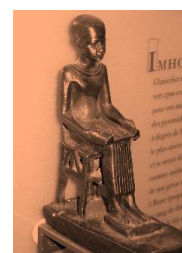


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Original Article

Comparative Study between Topical Metformin 30% Cream and Topical Adapalene 0.1 % Cream in The Treatment of Acanthosis Nigricans [Clinicodermoscopic Study]

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ABSTRACT

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Background: Acanthosis nigricans [AN] is a common cutaneous disorder with multiple etiologies. For cosmetic purposes, dermatologists usually recommend topical keratolytics, laser treatments, or chemical peels. The treatment of AN with a topical retinoid called adapalene has a high rate of success. Metformin, an insulin sensitizer, was proposed as a therapy option for AN by focusing on the insulin resistance connected to AN.

Aim of the work: This study was done to compare the efficacy and safety of topical 30% metformin cream with topical 0.1 adapalene cream.

Patients and Methods: There were 40 instances of AN in the most recent study. Two sets of cases, each with 20 patients, were randomly assigned: Group A [the metformin group] and Group B [the adapalene group]. The patients had a thorough dermatological examination along with a general clinical evaluation. The initial assessment included the calculation of HOMA-IR, assessment of disease severity, digital photographs, and dermoscopic assessment. After completion of treatment, clinical response and the degree of improvement were determined in the cases within the two groups. Follow-up was done for 2 months after treatment.

Results: All clinical and dermoscopic results evaluated following treatment show statistically significant variance across the tested groups in terms of the degree of improvement. In the adapalene group, the extent of improvement was greater. The mean ANASI score for the metformin group decreased from 32.4 to 27.8 pre- and post-operatively, while for the adapalene group, it decreased from 26.8 to 18.4. The Adapalene group had a larger percent change, although there is no statistically significant distinction between them.

Conclusion: Adapalene 0.1% cream was more successful than Metformin 30% cream in treating acanthosis nigricans with minimal and tolerable side effects. There was no difference between the two therapy regimens in terms of the chance of recurrence.

Keywords: Acanthosis Nigricans; Metformin; Adapalene; Dermoscopy.



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INTRODUCTION

Acanthosis nigricans [AN] is characterized by symmetrical, hyperpigmented, velvety lesions, which can occur especially in the armpits, groin, neck, antecubital, popliteal fossae, and umbilical region. Less often, it affects the eyelids, palms, soles of the feet, nipples, and phalanges [1].

The current high incidence of AN is caused by the growing rates of diabetes and obesity. Depending on factors including age, race, type of obesity, degree of obesity, and concurrent endocrinopathy, the incidence varies from 7 to 74% [2].

Dermatological issues are like the tip of an iceberg, indicating the existence of systemic issues such as metabolic disease [mainly], endocrine syndrome, cancer, pharmaceutical side effects, and hereditary components. This causes doctors to investigate which of these illnesses lurks under the surface [3].

The quality of life is affected by how the cutaneous lesion appears after being treated cosmetically, notwithstanding the therapy's attempts to address the underlying causes [4].

Clinical researchers may use case studies and smaller-powered clinical trials that are accessible in the literature to generate treatment plans for individuals with AN. Treatment methods used for cosmetic reasons constitute a diverse palette of techniques and a range of outcomes [5].

Adapalene, a topical retinoid of the third generation, is often utilized to treat mild to severe acne vulgaris [6]. For AN, topical retinoid is considered first-line treatment. It is epidermopoietic and causes a reduction in the stratum corneum replacement time. It corrects hyperkeratosis and causes a near-complete reversion to the normal state [7]. Adapalene absorbs relatively little through the skin. The most commonly reported adverse effects include erythema, dryness, peeling, and burning [8].

This required the use of another drug with high efficacy and fewer side effects. Metformin is an insulin-sensitizing agent that lowers blood sugar levels, hyperinsulinemia, body weight, and fat mass [9].

In addition to that, it also has melanopenic action when applied topically by decreasing

cAMP accumulation and cAMP-responsive element-binding protein phosphorylation. This inhibitory effect is correlated with decreased expression of master genes of melanogenesis, microphthalmia-associated transcription factor, tyrosinase, dopachrome tautomerase, and tyrosinase-related protein-1 [10], and show good results in treating melasma [11].

PATIENTS AND METHODS

This is a triple-armed, single-blinded, randomized clinical trial that was conducted at the outpatient clinic of the Andrology Department, Al-Azhar University [Damietta].

The study included 40 patients with AN who were randomly distributed according to the treatment regimen into two groups: Group A [20 cases]: cases received topical metformin 30% cream once daily for 2 months, and Group B [20 cases]: cases received topical adapalene 0.1 cream once daily for 2 months. Both genders with an age above 18 years were included in the study. Exclusion criteria: patients receiving another treatment modality for AN; pregnant and lactating females; patients with malignancy-associated AN; patients with genetic or autoimmune AN; and patients with syndromic AN.

The research was carried out in compliance with the 2013 revision of the Helsinki Standards [12]. After receiving clearance from the local ethics committee, the faculty of medicine at Al-Azhar University [Damietta], and receiving written or verbal informed consent from each included patient, the research was carried out.

The following treatments were given to all patients: a thorough review of medical history, general evaluation, dermatological examination, and inspection for skin tags that most often form in the axillae, groin, submammary, back of the neck, palms, antecubital and popliteal fossae, and groin folds [2].

The following formulae were used to calculate insulin resistance: homeostatic model of assessment for insulin resistance [HOMA-IR] = fasting insulin [μ U/ml] \times fasting glucose [mg/dl]/405 [13].

Assessment of disease severity

The area was determined by multiplying the length by the entire area of the side of the neck

[measured from a point at the inter-clavicular space to a position at the intersection of the chin and upper neck when the neck is fully extended] by the width [calculated from a point just below the nape hairline to a point at the intersection of the chin and top neck]. The impacted area was then determined by summing the longest length and the longest breadth. Then a percentage was determined. Depending on the level of deviation, a value was set for the coloration and thickness. The score was then calculated by multiplying the area value by the pigmentation value, thickness value, and their total. The authors developed the Acanthosis Nigricans Area and Severity Index [ANASI] score as a unique scoring method for evaluating AN both before and after treatment. One properly qualified and blinded investigator conducted the evaluation since the scoring method was new.

Digital photographs

Photography was done at baseline and after treatment using the digital camera [8-megapixel camera, iSight] of the iPhone 6, made in China by Alliance for American Manufacturing. All patients were photographed in similar postures and lighting.

Dermoscopic assessment

Utilizing a Dermalite 4 dermoscopy [an attachment piece was used to connect the dermoscope to the digital camera].

Clinical assessment and follow-up

Follow-up was done for 2 months after treatment. All patients were evaluated clinically and photographically, taking patient satisfaction into consideration. Photographed images were taken of every participant before and after treatment.

As secondary results, the investigator's and parents' global assessment scales were employed to assess the overall success rate. On a scale from 0 to 6, the IGE and PGE scales were examined [0 = clear, 1 indicates almost clear or a >90% improvement, 2 indicates a 75% improvement, 3 indicates a 50% improvement, 4 indicates a 25% improvement, 5 indicates no change, and 6 indicates a worsening].

Statistical analysis of data: SPSS version 27 was utilized to code, process, and analyze the obtained data [IBM, SPSS Inc., Chicago, IL,

USA]. The qualitative data was shown as percentages and numbers. The comparison between groups was done using the Chi-Square test. The Kolmogorov-Smirnov test evaluated the normalcy of quantitative data. Independent sample t-tests and Mann-Whitney U tests were utilized to compare two independent groups with parametric quantitative variables, respectively, if the data were non-parametric. A one-way ANOVA test was used to compare three or more independent groups with parametric quantitative variables, and if the data were non-parametric, a Kruskal-Wallis test was used. Two sets of quantitative parametric data were correlated using Pearson's correlation coefficient. P values less than 0.05 are regarded as significant for all tests.

RESULTS

In terms of mean age and sex, there was no statistically substantial variation between the groups. Additionally, there was a non-statistically substantial variation in mean HOMA-IR across the study groups. Regarding body mass index, hypertension, diabetes, or smoking history, there was no statistically substantial variation between the tested groups [table 1].

All dermoscopic results evaluated following treatment show statistically significant variance across the tested groups in terms of the degree of improvement, with better improvement detected for group B than group A [table 2].

There was statistically substantial variation between study groups regarding clinical improvement. There was a statistically significant higher percent of complications in group B than group A [75% versus 20%]. Erythema, dryness, peeling, and burning are the most frequently encountered side effects, but they were tolerable, mild, and didn't require stopping treatment. However, there was no statistically substantial variation between study groups regarding the recurrence rate [table 3].

There was a statistically significant difference between the studied groups as regards the ANASI score post-treatment. The percentage of change was higher among group B than group A [31.3% versus 14.2%] without a statistically significant difference between them [table 4].

In group [A], there was a statistically significant relation between ANASI score

percent of change and skin type with higher mean among skin type II than type III and IV. Higher percent of change in ANASI score is detected among cases with moderate improvement than mild improvement with statistically significant

association. Among group [B], a statistically significant relation between ANASI score percent of change and underarm with higher mean of ANASI score percent of change among cases with positive underarm affection [table 5].

Table [1]: Baseline clinical and demographic details of the studied individuals

		Group A [n=20]	Group B [n=20]	P value
Age/years	Mean ± SD	27.70±5.93	27.40±5.37	0.868
Sex, n [%]	Male	2 [10%]	4 [20%]	0.661
	Female	18 [90%]	16 [80%]	
BMI[Kg/m ²]	Mean ± SD	32.22±5.02	29.38±4.77	0.08
Smoking, n [%]	Non- smoker	18 [90%]	16 [80%]	0.661
	Smoker	2 [10%]	4 [20%]	
HOMA-IR	Mean ± SD	3.25±1.70	4.13±1.27	0.072
Skin type, n [%]	II	4 [20%]	2 [10%]	0.133
	III	4 [20%]	10 [50%]	
	IV	12 [60%]	8 [40%]	
Neck, n [%]		16 [80%]	16 [80%]	1.0
Underarm, n [%]		16 [80%]	12 [60%]	0.168
Family history of AN, n [%]		8 [40%]	8 [40%]	1.0
Family history of diabetes, n [%]		12 [60%]	0 [0%]	<0.001*
Family history of obesity, n [%]		12 [60%]	4 [20%]	0.01*
Family history of hypertension, n [%]		16 [80%]	4 [20%]	<0.001*

Table [2]: Comparison of dermoscopic findings improvement after treatment between studied groups

Dermoscopic sign	Degree of improvement	Group A [n=20]	Group B [n=20]	P value
Crist cuits, n [%]	Mild	12 [60%]	0 [0%]	<0.001
	Moderate	8 [40%]	4 [20%]	
	Good	0 [0%]	16 [80%]	
Sulcus cuits, n [%]	Mild	12 [60%]	0 [0%]	<0.001
	Moderate	8 [40%]	4 [20%]	
	Good	0 [0%]	16 [80%]	
Papillary projection, n [%]	Mild	12 [60%]	0 [0%]	<0.001
	Moderate	8 [40%]	4 [20%]	
	Good	0 [0%]	16 [80%]	
Hyperpigmented dots, n [%]	Mild	12 [60%]	0 [0%]	<0.001
	Moderate	8 [40%]	4 [20%]	
	Good	0 [0%]	16 [80%]	
Crypts, n [%]	Mild	12 [60%]	0 [0%]	<0.001
	Moderate	8 [40%]	4 [20%]	
	Good	0 [0%]	16 [80%]	

Table [3]: Clinical improvement, complications and recurrence of the study groups

Variables		Group A [n=20]	Group B [n=20]	P value
Clinical improvement, n [%]	Mild	12 [60%]	0 [0%]	<0.001
	Moderate	8 [40%]	4 [20%]	
	Good	0 [0%]	16 [80%]	
Complications, n [%]		4 [20%]	15 [75%]	<0.001
Recurrence, n [%]		12 [60%]	15 [75%]	0.08

Table [4]: Comparison of ANASI score change between groups

		Group A [n=20]	Group B [n=20]	P value
ANASI score, mean ± SD	Pre	32.40±11.19	26.80±8.17	0.08
	post	27.80±10.43	18.40±4.19	0.001
Percent of change		14.2%	31.3%	0.191

Table [5]: Relation between ANASI score improvement percent and different variables among studied groups

Variables		Group A [n=20]		Group B [n=20]	
		ANASI score % of change	P value	ANASI score % of change	P value
Smoking	Negative	15.97±5.20	0.719	30.83±5.20	0.215
	Positive	14.58±2.95		25.0±0.0	
Skin type	II	25.0±0.0	< 0.001	36.67±4.71	0.471
	III	12.5±0.0		28.67±10.68	
	IV	13.89±2.05		29.17±4.45	
Neck	Negative	16.67±0.0	0.719	33.33±0.0	0.335
	Positive	15.63±5.59		28.75±9.06	
Underarm	Negative	12.5±0.0	0.139	25.0±8.91	0.035
	Positive	16.67±5.27		32.78±6.41	
Clinical improvement	Mild	13.89±2.0	0.028	33.3±0.0	0.335
	Moderate	18.75±6.68		28.75±9.05	
Recurrence	Negative	14.58±2.23	0.374	32.22±13.47	0.575
	Positive	16.67±6.15		29.22±7.55	

DISCUSSION

This is the first study to compare the effectiveness and safety of topical 30% metformin cream versus topical adapalene 0.1 cream in the management of AN. The current study included 40 cases with AN who were randomly distributed according to the treatment regimen into two groups [each of 20 patients]; Group A [cases received topical metformin 30% cream once daily for 2 months] and Group A [cases received topical adapalene 0.1 cream once daily for 2 months].

In addition to making it easier to evaluate the effectiveness of the therapies using numbers, randomization regarding the side was not undertaken since the operations were carried out by more than one investigator.

In the current study, there was no statistically substantial variation between groups regarding their mean age and sex. The mean age of group A was 27.70±5.93 years versus 27.4±5.37 years for group B. Among group A, 90% are females, versus 80% of group B [matched groups]. This agreed with **Zaki et al.** [14], who conducted comparative split-neck research on 20 patients with acanthosis. The results showed that one male and 19 females represented 95% of the cases. This was also in accordance with **Abu Oun et al.** [15], who included twenty Egyptian participants with AN, with an average age of 27.15 ± 8.93 and a range of ages from 18 to 44; 16 of them were female.

The high female prevalence may be explained by the higher prevalence of hyperpigmentary

lesions in females, where female hormonal activity is thought to be one of the main contributing factors [16]. Another reason might be that women often care more about how they come across and voice their complaints early than men do.

Skin in body folds and creases is most often impacted by AN [17]. In the current study, neck affection was seen in 80% of the cases in both groups as the most common affected site. The next most common affected site was the underarm, which was seen in 80% of groups A and 60% of groups B. According to **Afify et al.** [18]'s research, the submammary area [4%] was the least common, with the neck [80.0%] and axilla [68.0%] being the most frequent locations of AN.

In a similar vein, **Puri** [19] observed a neck affliction in 93.3 percent of the patients covered, followed by the axilla [66.6 percent] and flexural regions [40%]. Additionally, 100% of the subjects in **Kamel et al.** [20]'s study on the relationship between AN and metabolic syndrome showed neck affection. 76.7% of cases impacted the axilla.

Dermoscopy is a non-invasive, commonly used, simple to use, and helpful method for assessing skin problems, including a change in color and skin structure; it gives a clear view of the morphological traits of the lesions. Dermoscopy may also be used to assess how well AN respond to therapy [21].

Dermoscopy of AN showed linear crista cutis and sulcus cutis with hyperpigmented dots [corresponding to papillomatosis] in the crista

cutis ^[22]. Maturation hyperpigmentation syndrome dermoscopy exhibits brown rings and clods with perifollicular accentuation but lacks crista and sulci ^[23].

This was shown in the current study, where all cases among groups A and B have the following presentations: cristae, sulci, papillary projection, hyperpigmented dots, and crypts.

In the current research, there was a statistically substantial improvement in both groups after treatment as compared to the before-treatment value. This was reflected by the decrease in the ANASI score in both groups. There is statistically substantial variation between the studied groups as regards the ANASI score post-treatment, with a higher percentage of change in the adapalene group.

The present research's findings about adapalene were in accordance with those of **Treesirichod et al.** ^[7], who carried out a split comparison analysis of the hyperpigmentation on the neck in 16 individuals with childhood AN. For four weeks, patients received treatment with topical 0.1% adapalene gel. The authors demonstrated that at weeks 2 and 4, respectively, the mean skin color ratio of the treated side was considerably lower than the baseline scores [30.1%, 18.3%, and 12.9%, $P < 0.001$], with noticeable skin improvement at 60.7% \pm 28.5%. The ratio of the proportion of skin color changes was comparable with assessments of efficacy made using the IGE and PGE scales.

In one randomized controlled experiment, 16 Thai infants with AN were given 0.1% adapalene to the afflicted side of the neck, and the amount of skin darkening was reported to be minimized as a consequence. Skin irritation was minimal to nonexistent, and the therapeutic effect was linked to a shift in epidermal keratinization ^[24]. Adapalene 0.1% and tretinoin 0.025% were shown to have comparable effectiveness in 2019's split-neck comparative randomized controlled study for juvenile AN lesion ^[25].

A case report of a 14-year-old child with AN and hyperinsulinemia revealed that metformin had no effect on the condition ^[26]. The neck and axilla lesions of 40 individuals with AN and IR who took 500 mg of metformin three times a day for three months significantly improved. Twenty placebo-controlled participants did not have the same improvement ^[5]. After eight years on

metformin, a normal-weight teenage male with AN and IR demonstrated full clearance ^[27], while **Hermanns-Lê et al.** ^[28] found that three obese teenagers receiving metformin showed improvement in IR and AN.

In one Indian clinical study, metformin 500 mg was administered three times per day for three months to 40 patients with AN and insulin resistance [as determined by the Homeostatic Model Assessment for Insulin Resistance]. Patients on metformin showed statistically and clinically substantial improvement in AN of the neck and axilla but not in AN of the knuckles, fingers, or elbows when compared to 20 placebo-treated control patients ^[29].

Another case report details the eradication of widespread AN with persistent IR in a youngster with extensive IR following two years of metformin treatment ^[30].

In **Lehraiki et al.** ^[10], both in vitro and in vivo studies on metformin's impact on melanogenesis were conducted. For eight weeks, they topically applied metformin 30% to the tails of mice, and they saw that this caused the mice's tails to become less pigmented. Additionally, they verified that metformin had an anti-melanogenic impact on human skin biopsies and reconstituted epidermis. They came to the conclusion that topical metformin had a depigmenting effect and offered a therapeutic plan for utilizing metformin to treat hyperpigmentation conditions topically.

In the current study, there is a statistically significant higher percent of complications among group B than group A [75% versus 20%]. In the study conducted by **Treesirichod et al.** ^[7], at week 2, there were eight patients [50%] who had cutaneous irritation overall. By week 4, there were only four patients [25%] left. Erythema and a burning feeling were both present in one subject.

These findings indicate that topical metformin is both safer and more tolerable than adapalene, but it does not have the same effectiveness as adapalene, and the therapy must be continued for a longer period of time to achieve clinical remission.

In the current research, there was a statistically substantial relationship between ANASI score percent of change and underarm affection, with a higher mean among ANASI score percent of change among cases with

positive underarm affection. A lower mean percent of change in ANASI score is detected among positive AN, hypertension, and obesity, with a statistically significant association.

This disagreed with **Treesirichod et al.** [7], who showed that the percentage change in the skin color ratio and age, body weight, weight fluctuations during the course of the research, and/or BMI have not shown any statistically substantial link. For people who are obese, therapy and a weight-control strategy may be helpful. However, the underlying problems should be the focus of therapy.

The variation could be explained by the different ages of the included cases in the two study groups.

Limitations: The current study had some limitations. The recruitment of the cases from a single center and the short duration of follow up are the two main limitations. The sample size [although it is considerable for this disease], but it could also affect the power of the obtained results.

Conclusion: Comparing topical metformin 30% cream to topical adapalene 0.1% cream, the effectiveness of the latter for treatment of acanthosis nigricans was found to be higher, but it was associated with a higher incidence of local complications. Regarding the risk of recurrence, no differences between the two treatment regimens were found.

Conflict of Interest and Financial Disclosure: None.

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