Type of the Paper (Research article)

Effect of isotretinoin treatment on Biotinidase level and depression degree in Acne Vulgaris Patients (Randomized Control Trail)

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Received: 28 August, 2024 Reviewed: 28 September, 2024
Accepted: 12 October, 2024 Published online: 2 November, 2024

Abstract:

Introduction: Acne vulgaris is considered a persistent inflammatory condition affecting the sebaceous follicles. The strongest inhibitor of sebum production is isotretinoin. Isotretinoin treatment may cause acquired biotin deficiency by decreasing biotinidase activity. The burden of severe acne may be reflected in depression and suicidal thoughts rather than being a side effect of isotretinoin drugs.

Aim of the study: To assess the effects of isotretinoin on the biotinidase serum level in acne patients and to correlate these changes with depression and acne scores.

Subjects and Methods: The current randomized control trial study divided the patients according to their diseased arms as interventional arm and control arm. Each arm included 22 acne patients aged between 18 and 30 years. Interventional arm received isotretinoin treatment for two months. Level of biotinidase, depression and acne scores assessed before and after the intervention.

Results: At baseline assessment, the interventional group showed no statistically significant difference in biotinidase level, but showed a significantly higher level of depression score (16.27 ±9.93), versus (10±4.32) in the control group (p =0.01). The interventional group showed a high statistically significant decrease in biotinidase level from (1389.09 ±499.68) to (716.86 ±212.18) (p <0.001) and an increase in depression score from (16.27±9.93) to (24.59±12.11) (p =0.007) after two months. Acne score showed a significant positive correlation with depression score after isotretinoin intake.

Conclusion: When isotretinoin is used to treat acne, the biotinidase level decreases and the depression score increases.

Keywords: Acne; Biotinidase; Depression; Isotretinoin.

1. Introduction

Resulting of androgen-induced increased sebum production, altered keratinization, inflammation, and bacterial colonization of hair follicles on the face, neck, chest, and back, acne is a pilosebaceous unit chronic inflammatory disease [1]. It is mainly an adolescent disease, though it can afflict people of any age [2]. The severity of the condition, the patient's preferences, and tolerability all play a role in the treatment decision. One medication of choice for moderate to severe acne is isotretinoin [3]. Isotretinoin has anti-inflammatory properties, lowers surface and ductal C. acnes, affects comedogenics, and significantly reduces sebum production [4]. Inadequate dietary intake of biotin, drug-vitamin interactions, and elevated biotin catabolism in smokers and pregnant women are the possible causes of biotin insufficiency [5]. Reduced activity of biotinidase, an enzyme essential to intestinal biotin absorption, can also cause a biotin deficit.5 Acquired biotin deficiency can be brought on by medications like isotretinoin, pregnancy, extended antibiotic usage that disrupt normal flora, intoxication, and malabsorption [6]. A mutation in the biotinidase enzyme or a reduction in enzyme activity brought on by medications like isotretinoin are the causes of the biotin deficit [7]. It is believed that metabolites of isotretinoin impact the liver and lower biotinidase function [7]. Low biotinidase activity may be caused by isotretinoin isomers and metabolites acting in the liver.8 Partial biotinidase deficiency may be linked to certain dermatological adverse effects associated with isotretinoin medication, such as baldness and skin fragility [8]. Numerous studies have looked at the possibility of using micronutrient supplements as an adjuvant to antidepressant therapy since micronutrient deficiencies may contribute to the development of depression [9]. Furthermore, depression and B vitamin deficiencies have been connected [10]. The serious form of acne has been linked to suicidality and despair [11]. This work aimed to evaluate changes in serum level of biotinidase in acne patients on isotretinoin treatment and associated it with depression and acne scores. The current study was the first study that evaluated the role of isotretinoin in inducing depression and its relation to biotinidase levels in acne patients.

2. Subjects & Methods

2.1. Subjects

The current randomized control trial study was carried out in Fayoum University -Faculty of Medicine- Dermatology, STDs and Andrology department, during the period from August to December 2023 and enrolled 44 patients. Patients were divided into two groups; the interventional arm (received isotretinoin treatment (10 mg/day) for two months, and the control arm. Cases allocated in study arms by permuted block randomization with sealed opaque envelopes. Both arms were matched in age and sex distribution with no chronic comorbidities (hebetic, kidney disease, diabetes mellitus, hypertension or hyperlipidemia). Pregnant women and females with irregular menstrual periods or hirsutism were excluded from the study. Each arm included 22 acne patients aged between 18 and 30 years with moderate to severe degrees of acne.

2.2. Methods

Clinical history was taken from patients about demographic characteristics as (age, and sex) in addition to disease characteristics in the form of family history of acne, history of chronic disease, preset skin disease, previous treatment to acne, age of acne onset, pattern of acne onset, acne course and duration. A general examination was performed to exclude any systemic disease. Dermatological examination to diagnose acne severity degree before and after intervention using the Global Acne Grading System (GAGS). GAGS examine six areas of the face with a factor based on pilosebaceous units surface area distribution, and density (each of forehead, right cheek, and left cheek = 2, nose, chin = 1, upper back, and chest = 3). Considering the different types of lesions in each area (none = 0, one comedone, papule, pustule, and nodule; graded from 1 to 4), a score would be assigned (local score = Grade from 0 to 4 × factor). The global score ranged between (0 and 52) is the sum of the local scores. Severity is categorized as very severe scored above 38, severe with scores from 31 to 38, moderate degree scored from 19 to 30, and mild scored between 1 and 18. 12 The Beck Depression Inventory (BDI) was used in the evaluation of depression degree among patients before and after intervention. There are 21 groups of assertions in the inventory, each with a four-point scoring system. Each statement was scored between 0 and 3. The value of the score ranged between 0 and 63,

with higher scores denoting severe depression. A score in the range of 0–13 denotes no or minimal depression, mild depression (14–19), moderate depression (20–28), and severe depression (29–63). 13 Human Biotinidase (BTD) ELISA kit is used by ELK Biotechnology CO., LTD (china) to measure BTD levels in human serum, plasma, culture media, or any other biological fluid by the manufacturer's instructions. It was assessed before and after the intervention.

2.3. Statistical Methods

Data analysis was done using version 22 of the Statistical Package of Social Science (SPSS) software (SPSS Inc., Chicago, IL, USA). Basic descriptive analysis evaluates the dispersion of the quantitative data using standard deviations and IQR, the central tendency of the qualitative data using percentages and numbers, and the dispersion of the quantitative data using arithmetic means and medians. The independent T-test or Mann-Whitney test is used to compare independent quantitative data. The paired t-test and Wilcoxon tests are used to compare two dependent quantitative data sets. Test of chi-square applied to qualitative data. The MC-Nemar test is utilized for qualitative data that is paired dependent. P-values were considered statistically significant if they were less than 0.05.

3. Results

Forty-four patients were enrolled in the current study. The mean age of the study group was (21.07 ±3.6) years. 21 (47.7%) were males, versus 23 (52.3%) were females. Cases were divided into two arms interventional (patients with moderate to severe degrees of acne vulgaris) and control arms with no statistically significant difference as regards age and sex (p =0.48, and 0.76) respectively. Among interventional arms, marital status was as follows, 18 (81.8%) for single, and 4 (18.2%) for married. Only 2 (9.1%) had a positive family history, and 20 (90.9%) had no positive family history of acne. Regarding food habits, in nearly half of cases, 10 (45.5%) ate junk food, while 4 (18.2%) ate chocolate and 3 (13.6%) ate spicy food and the same for carbohydrate food and 2 (9.1%) ate dairy products. Regarding the course of the disease, 18 (81.8%) had gradual onset. Of all patients,

22 (100%) had a progressive course, and 20 (90.90%) recorded no previous history of isotretinoin intake. The mean age of onset of acne among interventional cases was (20.4 ±3.34) years with a mean acne duration of 1.02 ±0.52 years.

There was a high statistically significant difference between the interventional group and control regarding baseline depression score with higher score value and higher percentage of moderate and severe depression degree in the interventional group (22.7%, and 13.6% respectively, p =0.01). There was no statistically significant difference between interventional and control regarding baseline biotinidase level (**Table 1**).

Table 1. Baseline Depression score and biotinidase level between the studied groups.

Baseline assessment		**Interventional Group (n=22)**	**Control group (n=22)**	***P*-Value**
Biotinidase level		1389.09 ±499.68	1393.18 ±461.24	0.981
Depression score		16.27 ±9.93	10 ±4.32	0.010*
Depression degrees	Minimal	9 (40%)	19 (72.7%)	0.018*
	Mild	5 (22.7%)	6 (27.3%)	
	Moderate	5 (22.7%)	0 (0%)	
	Sever	3 (13.6%)	0 (0%)	

* significant at p <0.05.

The interventional group showed a statistically significant decrease in Biotinidase level and an increase in depression score after two months of treatment (p <0.001, and =0.004 respectively). In addition, there was a significant improvement in acne degree after treatment and an increase in severe depression degree from 13.6% to 50% after isotretinoin treatment (**Table 2**).

Table 2: Comparison of Acne score, Depression score and biotinidase level follow-up after isotretinoin treatment among the interventional group.

Baseline assessment		Before treatment	After treatment	*P*-Value
Acne severity score		27.95 ±5.6	27.68 ±8.9	0.884
Biotinidase level		1389.09 ±499.68	716.86 ±212.18	<0.001*
Depression score		16.27 ±9.93	24.59 ±12.11	0.004*
Depression degrees	Minimal	9 (40%)	19 (72.7%)	0.018*
	Mild	5 (22.7%)	6 (27.3%)	
	Moderate	5 (22.7%)	0 (0%)	
	Sever	3 (13.6%)	0 (0%)	
Acne severity degree	Mild	------	4 (18.2%)	0.012*
	Moderate	14 (63.6%)	8 (36.4%)	
	Sever	8 (36.4%)	8 (36.4%)	
	Very severe	------	2 (9.1%)	

* significant at p <0.05.

At the end of the intervention, the interventional group showed a statistically significant lower level of Biotinidase and a higher level of depression score, with an increase in severe degree of depression 50% versus 72.7% in control had minimal degree of depression (**Table 3**).

Table 3. Comparison of Depression score and biotinidase level between the studied groups at the intervention of treatment.

Baseline assessment		Interventional Group (n=22)	Control group (n=22)	*P*-Value
Biotinidase level		716.86 ±212.18	1393.18 ±461.24	<0.001*
Depression score		24.59 ±12.11	10 ±4.32	<0.001*
Depression degrees	Minimal	5 (22.7%)	19 (72.7%)	0.018*
	Mild	4 (18.2%)	6 (27.3%)	
	Moderate	2 (9.1%)	0 (0%)	
	Sever	11 (50%)	0 (0%)	

* significant at p <0.05.

There was a high positive correlation between baseline biotinidase level and its level two months of isotretinoin treatment. There was a statistically significant correlation between baseline acne score and baseline depression score (at both bassline and two months after treatment with isotretinoin) (**Table 4**).

Table 4: Correlation between biotinidase level and acne score with other variables among the interventional group.

Variables		Biotinidase level (Baseline)	Biotinidase level (2 m post-treatment)	Acne score (Baseline)	Acne score (2 m post-treatment)
Age of onset of acne	r	-0.214	-0.158	0.073	0.162
	p	0.339	0.483	0.746	0.470
Duration	r	-0.155	-0.270	-0.376	0.019
	p	0.491	0.225	0.093	0.932
Depression score (Baseline)	r	0.118	0.121	0.571	0.485
	p	0.602	0.593	0.006*	0.022
Depression score (2m post-treatment)	r	-0.109	-0.025	0181	0.919
	p	0.628	0.912	0.421	0.000*
Biotinidase level (Baseline)	r	-------	-------	0.088	-0.107
	p	-------	-------	0.696	0.635
Biotinidase level (2m post-treatment)	r	0.912**	-------	0.142	-0.076
	p	0.000	-------	0.530	0.738

* significant at $p < 0.05$.

The multivariate linear regression model analysis illustrated that acne scores after treatment show a statistically significant prediction effect ($p < 0.001$) to depression scores after treatment among the interventional group with no significant prediction power to other variables ($p > 0.05$) (**Table 5**).

Table 5: Multivariate linear regression analysis to determine the power of different variables in the prediction of depression score after treatment.

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% CI for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-3.735	8.652	----	-0.432	0.673	-22.427	14.957
Age	-.799	5.183	-0.245	-0.154	0.880	-11.997	10.398
Sex	-4.373	2.740	-0.184	-1.596	0.134	-10.292	1.546
Acne onset age	1.443	5.182	0.398	0.278	0.785	-9.753	12.639
Duration	-6.083	6.541	-0.260	-0.930	0.369	-20.215	8.049
Biotidinase pre-treatment	0.000	0.005	-0.005	-0.023	0.982	-0.012	0.012
Biotidinase Post-treatment	0.005	0.013	0.086	0.384	0.707	-0.023	0.033
Acne score. Per-treatment	-0.345	0.287	-0.161	-1.203	0.251	-0.966	0.275
Acne score. Post-treatment	1.276	.134	0.936	9.491	0.000*	0.986	1.566

* significant at p <0.05.

4. Discussion

Increased sebum production, keratinization, and bacterial colonization of hair follicles are the hallmarks of acne, a chronic inflammatory illness [1]. The only medication that affects every key etiological component linked to acne is isotretinoin [14]. It influences cell-cycle development, cellular differentiation, cell survival, and apoptosis to accomplish this amazing efficacy [14]. In addition to being beneficial for mild to moderate acne, it is also used to treat moderate to severe forms of acne vulgaris. It can be used as a second-line treatment for acne when a satisfactory response to systemic antibiotics, such as doxycycline, and topical therapy cannot be achieved within three months of therapy [15]. Up to 15% of patients on isotretinoin get abnormal liver tests; nevertheless, significant increases exceeding three times the upper limit of normal or necessitating drug discontinuation are uncommon (<1%) [16]. Some of the mucocutaneous side effects that patients with isotretinoin experience may be caused by decreased enzyme activity because of the drug's toxic effects on the liver and consequent disruption of biotin metabolism [17]. In our thesis, there was no significant difference in age and sex between acne patients and control that indicated proper matching in our sample. In our study, only (9.1%) had a positive family history of acne. Anaba and Oaku, (2021) demonstrated although a family history of acne has been linked to an increased chance of developing acne illness, it has not been linked to the severity of acne [18]. Studies revealed genetic loci encompassing genes that may be involved in biological pathways and processes underpinning family history-linked acne [19]. Regarding food habits, nearly half of the cases ate junk food and chocolate. The consumption of carbohydrates, high glycemic index foods, and elevated glycemic loads has a small but noteworthy prooncogenic effect. Numerous research investigations have demonstrated that diet plays a major role in the pathophysiology of acne [20]. Acne flare-ups are also exacerbated by milk and chocolate. On the other hand, meals high in omega-3 fatty acids have a therapeutic impact by suppressing the generation of inflammatory cytokines [21]. In agreement with our study, Perez et al., (2021) found that most acne patients have gradual onset and progressive course [22]. in agreement with current study findings Molla and Alrizqi, (2021) found a positive relation in patients' acne and

depression scores [24]. Numerous studies have demonstrated that dermatological conditions including psoriasis, eczema, and acne have an impact on patients' psychological well-being, relationships, and everyday activities. They also raise the risk of anxiety and depression [25]. One of the most prevalent dermatological conditions, acne can significantly lower a person's quality of life when it comes to their health. It impacts a person's self-consciousness, anger, and frustration, as well as their ability to engage in social and recreational activities and build meaningful relationships with others [26]. Depression is more common in people with acne, with prevalence rates of up to 30% recorded in those with moderate to severe acne [27]. In our study, biotindase level showed a significant decrease after treatment with isotretinoin, the results were in the same line with the results of Manzoni and Cunha (2018) [28] and Aksac et al. (2021) [29]. Biotin known as B7 and H vitamins, is involved in protein, carbohydrate and fat metabolism and deficiency leads to central nervous system symptoms such as depression, hallucination, and lethargy [30]. In our study, an increase in acne score was associated positively with an increase in depression score. In agreement with our study, Berry et al., (2021) study, found that the severity of acne scores correlated significantly with depression scores [11]. There is a direct association between the severity of acne and the degree of depression, as well as anxiety. For patients to prevent acne's detrimental consequences on their mental and social health, their primary care physician should regularly evaluate them psychiatrically [31].

5. Conclusion

From the present study, we concluded that cases with moderate to severe degrees of acne and received isotretinoin treatment show a decrease in biotindase level, and an increase in depression score. An increase in acne score is associated with an increase in depression score among cases. Psychologic assessment and follow-up of acne patients during isotretinoin therapy is a must. Biotin supplements should be advised during the isotretinoin treatment course.

Ethical approval and consent to participate: This investigation was carried out with ethical approval from the research ethical committee of the faculty of medicine at Fayoum University. Approval ID was (M 558) session (90) dated 9 January 2022. The Pan African Clinical Trial Registry (PACTR) has approved the current investigation as a clinical trial as well. Patient consent was taken after explaining the procedure. Patients had the right to withdraw from the trial at any time.

Funding: The authors do not have any financial sources to disclose for this manuscript.

Conflicts of Interest: All authors declare they have no conflicts of interest.

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