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The Association between Serum Zinc Levels and Zinc Supplementation in Topical Retinoids Treated Acne Vulgaris Patients: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract **Original Research Article**

Background: The association between serum zinc levels and zinc supplementation, with topical retinoids treatment in acne vulgaris patients presents a multifaceted interplay involving both physiological and therapeutic aspects. ***Objective*****:** To evaluate the association between serum zinc levels and zinc supplementation with topical retinoid-treated in acne vulgaris patients. ***Method*****:** A clinical trial was carried out at the Department of Pharmacology and Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, spanning from March 2020 to January 2022, with participant enrollment commencing in April 2021. This study encompassed 122 recently diagnosed mild to moderate acne vulgaris (AV) patients who received 20 mg of zinc sulfate or 20mg of placebo tablet twice daily orally with topical retinoid treatment. Notably, nine participants withdrew from the study for various reasons, resulting in a cohort of 113 individuals for per-protocol (PP) analysis. The investigation featured both baseline and after 8-week follow-up assessments, scrutinizing GAGS acne severity scores and serum zinc levels. ***Results*****:** After 8 weeks of intervention, serum zinc levels in the intervention arm significantly increased from the baseline (100.39 ± 22.26 vs. 59.03 ± 15.76, P = 0.00), and they were also significantly higher than in the control arm. Likewise, the GAGS score in the intervention arm significantly decreased after 8 weeks compared to the baseline (12.03 ± 5.39 vs. 16.74 ± 6.09, P = 0.00) and was significantly lower than in the control arm. Also shows a correlation between serum zinc level and GAGS score which was observed after 8 weeks of intervention. ***Conclusion*****:** Our study suggests that combining zinc supplementation with topical retinoids for acne treatment depends on factors like patient traits, baseline zinc levels, formulations, and duration. While findings vary, there's an overall trend toward better outcomes with this combination. Zinc's anti-inflammatory, sebum control, and immunomodulation, along with retinoids' comedolytic and anti-inflammatory effects, create potential for more effective acne management.

Keywords: Zinc Supplementation, Topical Retinoids, Acne Vulgaris Patients, GAGS score, Serum zinc level.

INTRODUCTION

Acne vulgaris is a prevalent dermatological disorder characterized by the formation of comedones, papules, pustules, and, in severe cases, nodules and cysts. Its multifactorial nature involves intricate interplays of factors such as increased sebum production, follicular hyperkeratinization, inflammation, and colonization by Propionibacterium acnes. As such, its management often necessitates a multifaceted approach targeting different facets of its pathogenesis [1-3].

Zinc, an essential trace element, has gained attention for its potential role in the management of acne. Zinc exhibits anti-inflammatory, antioxidant, and immunomodulatory properties that can potentially attenuate the inflammatory response associated with acne lesions. Additionally, zinc has demonstrated the ability to regulate sebum production and inhibit the growth of Propionibacterium acnes, making it an intriguing candidate for adjunctive therapy in acne management.

Topical retinoids, well-established in acne treatment, offer comedolytic and anti-inflammatory effects that target follicular hyperkeratinization and inflammation, respectively. However, retinoid therapy can be accompanied by skin irritation and dryness, leading to challenges in treatment adherence. This has prompted the exploration of combination therapies to enhance efficacy while mitigating adverse effects [4-9].

The relationship between serum zinc levels and acne severity has been a subject of investigation. Low serum zinc levels have been associated with more severe cases of acne, hinting at the potential involvement of zinc deficiency in the pathogenesis of the condition. Furthermore, considering zinc's role in various physiological processes related to skin health, its supplementation might offer benefits beyond its direct effects on acne lesions [8-10].

This paper aims to delve into the complex interplay between serum zinc levels, zinc supplementation, and topical retinoid-treated acne vulgaris patients. By examining the existing body of research, we seek to elucidate the potential association between serum zinc levels and acne severity, as well as the implications of zinc supplementation in conjunction with topical retinoid therapy. Understanding these connections could provide valuable insights into the multifaceted dynamics at play in acne pathogenesis and guide more effective treatment strategies.

In the following sections, we will review relevant studies exploring the correlation between serum zinc levels and acne severity, investigate the effects of zinc supplementation on acne outcomes in patients receiving topical retinoid therapy, and discuss the broader implications of these findings in the context of personalized acne management. Through this exploration, we aim to contribute to a comprehensive understanding of the intricate relationship between zinc, retinoids, and the management of acne vulgaris.

Objective

To evaluate the association between serum zinc levels and zinc supplementation with topical retinoid-treated in acne vulgaris patients.

METHODOLOGY

Study Type and Location

The research adopted a randomized, double-blind, placebo-controlled design, ensuring random participant allocation, unbiased outcomes through double-blind procedures, and a placebo control group. It was conducted at the Department of Pharmacology and Department of Dermatology and Venereology at Bangabandhu Sheikh Mujib Medical University.

Study Duration

The study spanned from March 2020 to January 2022, commencing enrollment in April 2021 following Institutional Review Board approval (IRB).

Study Population

Newly diagnosed mild and moderate acne vulgaris (AV) patients undergoing topical retinoid treatment constituted the study population.

Sample Size

Using a predefined formula, each study arm initially comprised 56 participants, with an allowance for a 10% dropout rate, ultimately resulting in 61 participants per arm. Patient selection employed a consecutive sampling approach, ultimately including 122 patients meeting specified criteria.

Randomization

After completing screening and baseline measurements, participants were randomly assigned to one of two arms: (i) 20 mg zinc sulphate tablet or (ii) 20 mg placebo tablet for 8 weeks. Treatment assignment was done by online graph pad software using a computer from the website (http://www.graphpad.com/quickcales/ranMenu) which automatically generated two distinct sets of random numbers after giving necessary inputs, by one senior faculty member from department of Microbiology BSMMU. All subjects and investigators were blind to the treatment condition and remained blinded until unblinding the codes during data analysis.

Intervention schedule

Patients were instructed to take 20 mg zinc sulphate or 20 mg placebo tablet: 1 tablet twice daily after meals for 8 weeks along with topical retinoids given by the Dermatologist. Patients were scheduled for assessments at the end of 8 weeks of the treatment. Zinc or placebo tablets were provided free of charge. 3 ml blood was collected from all AV patients (both intervention and control arm) at baseline and after 8 weeks.

Assessment Tools

Data collection instruments included a sociodemographic questionnaire and the Global Acne Grading System (GAGS) to assess acne severity [10].

Outcome Measures

Primary outcomes involved assessing AV severity using GAGS score, while secondary outcomes encompassed serum zinc level measurement.

Inclusion and Exclusion Criteria

Inclusion criteria encompassed newly diagnosed mild and moderate AV patients aged 11-35, irrespective of gender. Exclusion criteria accounted for factors such as cosmetic-induced acne, oral contraceptive use, pregnancy, and lactation.

Study Procedure

The study encompassed various phases, including medicine procurement, packaging, storage, randomization, blinding, and allocation concealment. Patients were enrolled, treated, and evaluated within a designated timeframe.

Data Collection

Adherence to CONSORT principles ensured detailed data collection, including comprehensive explanations, informed consent, and rigorous demographic recording. Assessments were conducted, with blood samples collected both at baseline and after 8 weeks and with GAGS score at baseline and after 8 weeks.

Laboratory Parameter

The study involved estimating serum zinc levels as a critical laboratory parameter, both before and after the intervention.

Documentation

A rigorous documentation process encompassed all patient data, including questionnaires, prescriptions, and serum zinc level reports.

Data Analysis

Following the unblinding process, data were categorized into two arms, and a series of statistical tests, including chi-square, t-tests, and Pearson correlation coefficient test, were applied, with statistical significance set at $p \leq 0.05$.

RESULTS

According to the Consolidated Standards of Reporting Trials (CONSORT) principle, total one hundred and twenty-two (122) patients were enrolled based on the study's eligibility criteria. Of which, sixty-one (61) patients received a placebo, and sixty-one (61) patients received an intervention. A total of six (6) patients from the control arm and three (3) patients from the intervention arm dropped out from the study. So fifty-five (55) patients from the control arm and fifty-eight (58) patients from the intervention arm completed the study.

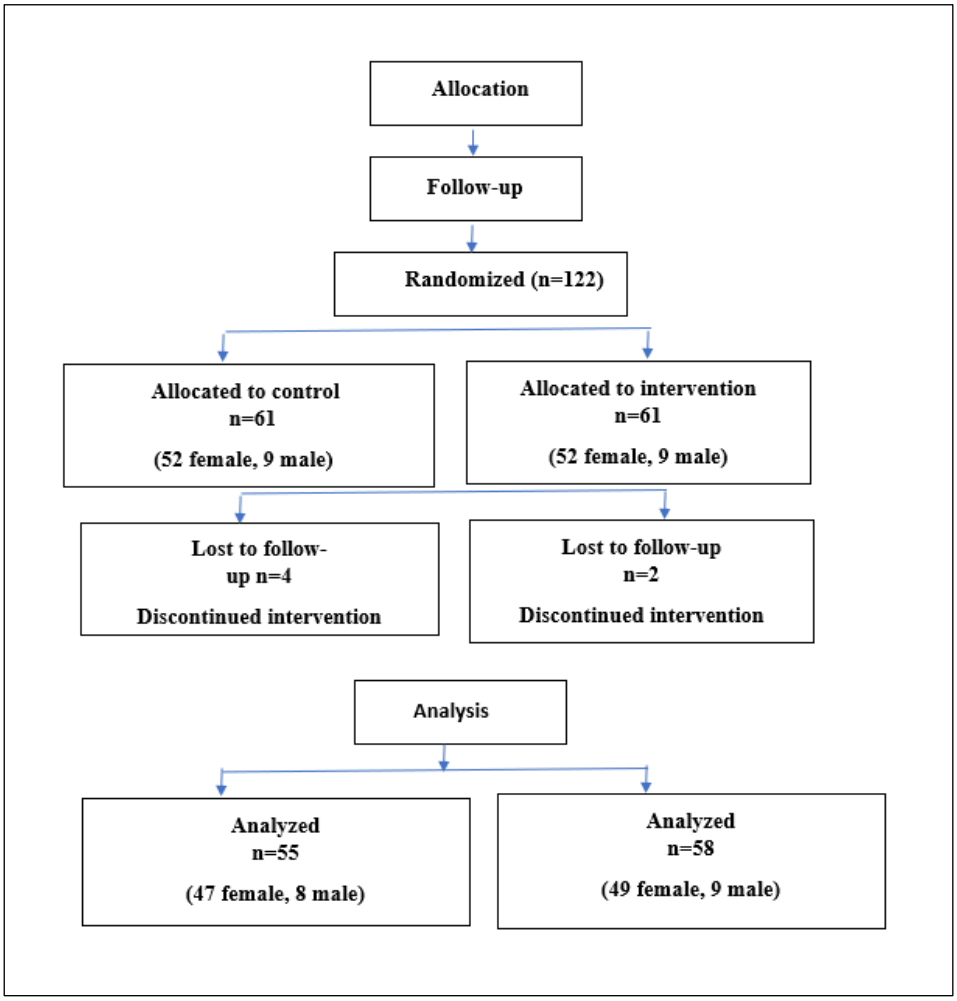

Figure I: Flowchart of Consolidated Standards of Reporting Trials (CONSORT)

Table I shows the age and BMI of patients. There was no significant difference between arms in age and BMI. The patient's age was (20.57± 4.45; range 13-35 years) in the control arm. At the same time, the age of the patients in the intervention arm was (20.52 ± 4.69; range 13-30 years). The difference was not statistically significant (P = 0.95). The patient's BMI was (22.67 ± 3.76; range 16.2-33.9) in the control arm. At the same time, the BMI of the patients in the intervention arm was (22.43 ± 2.99; range 16.3-32.8). The difference was not statistically significant (P=0.69).

Table-I: Demographic Characteristics (Age and BMI) of the Patients at the Time of Enrolment (Baseline)

Variables		control (n=61)	Intervention (n=61)	P-value
Age (years)	Mean ± SD	20.57 ± 4.45	20.52 ± 4.69	0.95
	Range	13-35	13-30	
BMI (kg/m2)	Mean ± SD	22.67 ± 3.76	22.43 ± 2.99	0.69
	Range	16.2-33.9	16.3-32.8	

Unpaired t-test was done

Table II shows the gender of patients. 14.75% (9/61) patients were male in the control arm, and 85.24% (52/61) were female. While in the intervention arm, 14.75% (9/61) patients were male, and 85.24% (52/61) were female. The difference was not significant (P = 1).

Table II: Demographic Characteristics (Gender) of the Patients at the Time of Enrolment (Baseline)

Variables	control (n=61)	Intervention (n=61)	P-value
Male	9 (14.75%)	9 (14.75%)	
Female	52 (85.24%)	52 (85.24%)	1

Chi-square (x2) test was done Significant P-value < 0.05

Table III shows, at baseline, the serum zinc was 62.72 ± 16.00 (range 16-98) in the control arm compared to 59.03 ± 15.76 (range 18-93) in the intervention arm. The difference was not statistically significant (P=0.21).

On assessment after 8 weeks, the serum zinc was 57.94 ± 15.47 (range 24-90) in the control arm compared to 100.39 ± 22.26 (range 74-170) in the intervention arm. Serum zinc levels of the intervention arm were significantly (P = 0.00) higher than that of the control arm.

After 8 weeks, the serum zinc levels were significantly increased (P=0.00) from the intervention arm's baseline and significantly decreased (P= 0.00) from the baseline in the control arm.

Table-III: Comparison of Serum Zinc Levels between Control and Intervention Arms (at Baseline and After 8 Weeks of Treatment)

Serum Zinc level (µg/dL)				
		Control (n=55)	Intervention (n=58)	P-value[a]
Baseline	Mean ± SD	62.72 ± 16.00	59.03 ± 15.76	0.219
	Range	16-98	18-93	
After 8 weeks	Mean ± SD	57.94 ± 15.47	100.39 ± 22.26	0.000
	Range	24-90	74-170	
P-value[b]		0.003	0.000	

aUnpaired t-test was done bPaired t-test was done Significant P-value < 0.05

Figure II shows serum zinc levels (mean ± SD) in the control and intervention arms at baseline and after 8 weeks of treatment. Here blue bar indicates baseline, and red suggest after 8 weeks of treatment.

Table IV shows, at baseline, the GAGS score was 16.07 ± 6.54 (range 6-29) in the control arm compared to 16.74 ± 6.09 (range 8-29) in the intervention arm. The difference between the GAGS score of the control and intervention arm was not statistically significant (P = 0.57).

On assessment after 8 weeks, the GAGS score was 15.27 ± 6.32 (range 6-29) in the control arm compared to 12.03 ± 5.39 (range 4-20) in the intervention arm. The GAGS score of the intervention arm was significantly (P = 0.00) lower than that of the control arm.

After 8 weeks, the GAGS score significantly decreased (P = 0.00) from the baseline control and intervention arm.

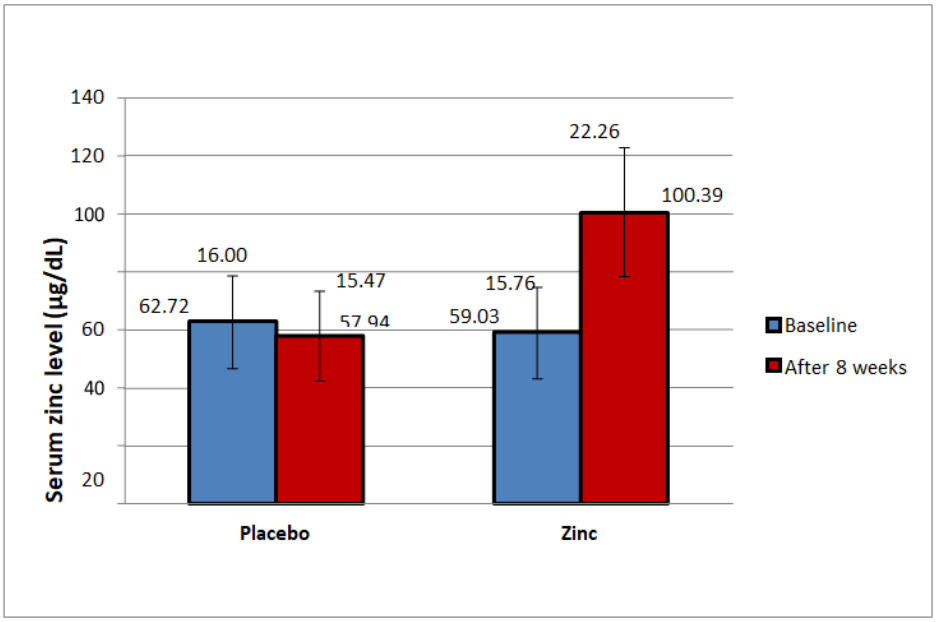

Figure II: Comparison of Serum Zinc Levels between Control and Intervention Arms (at Baseline and After 8 Weeks of Treatment)

Table IV: Comparison of GAGS Score Between Control and Intervention Arms (at Baseline and After 8 Weeks of Treatment)

GAGS Score				
		Control (n=55)	Intervention (n=58)	P-value[a]
Baseline	Mean ± SD	16.07 ± 6.54	16.74 ± 6.09	0.575
	Range	6-29	8-29	
After 8 weeks	Mean ± SD	15.27 ± 6.32	12.03 ± 5.39	0.004
	Range	6-29	4-20	
P-value[b]		0.000	0.000	

aUnpaired t-test was done bPaired t-test was done Significant P-value < 0.05

Figure-III shows the GAGS score (mean ± SD) in the control and intervention arms at baseline and after 8 weeks of treatment. Here blue bar indicates baseline, and red suggest after 8 weeks of treatment.

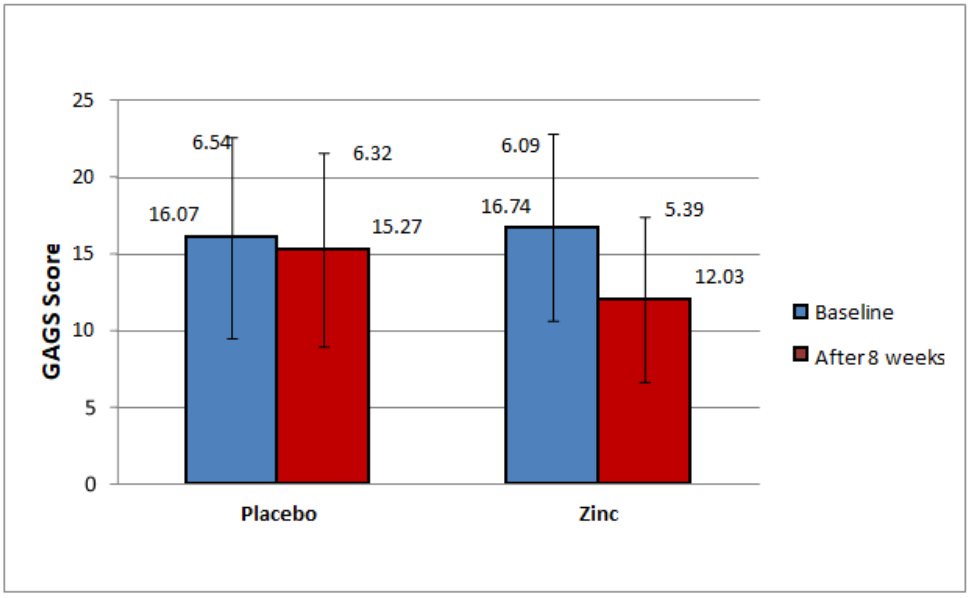

Figure III: Comparison of GAGS Score between Control and Intervention Arms (at Baseline and After 8 Weeks of Treatment)

Figure-IV shows a correlation between serum zinc levels and GAGS score, which was observed after 8 weeks of administration of zinc sulphate in addition to topical retinoids. The value of Pearson correlation coefficient was - 0.12, which was a negative correlation. Therefore, there was a negative linear correlation between serum zinc levels and GAGS score.

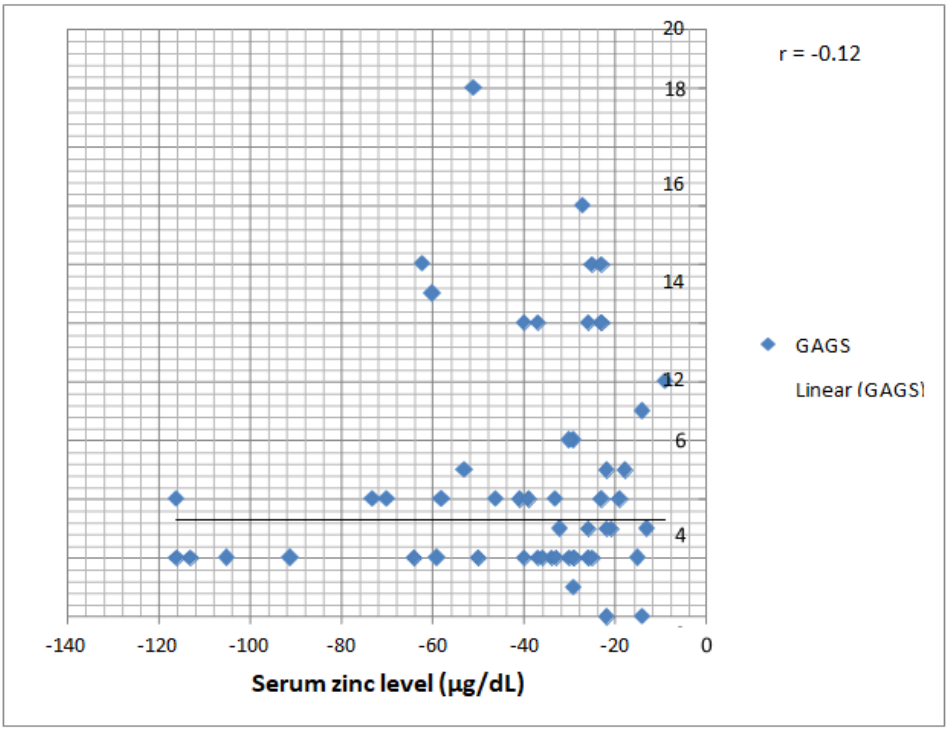

Figure IV: Correlation Between Serum Zinc Levels and GAGS Score After 8 Weeks of Treatment

DISCUSSION

Acne vulgaris is the most common cutaneous disorder affecting adolescents and young adults. Previous studies have shown a correlation between zinc levels with severity and type of acne lesions. Oral and topical combinations of zinc may be of therapeutic value.

Daily supplementation of 20 mg of zinc sulphate for 8 weeks, the acne severity score (GAGS score) significantly decreased from the baseline in the intervention arm. One study revealed the maximum acne severity score reduction was observed after 3 to 6 weeks of supplementation with zinc sulphate [11]. Another trial found a significant decrease in papules, infiltrates, and cysts after 12 weeks of zinc supplementation [12]. However, another study reported no difference between the zinc supplementation and control groups.Perhaps improvement was not significant because of a limited number of patients [13].

The present study revealed a significant increase in serum zinc level in response to 8 weeks of oral zinc sulphate supplementation. Similarly, serum zinc level was increased with zinc supplementation after 12 weeks [11].

One study reported a decrease in the serum zinc level in acne patients, similar in this study at baseline [3]. Most patients found decreased serum zinc levels in this study, similar in several studies [14, 15]. Serum zinc level was average for some of the patients in this study. Whereas other study reported that serum zinc levels were normal in acne patients but lower than in the healthy group [16].

The present study demonstrated a diminution of acne severity score with an increased serum zinc level. The changes in the GAGS score were negatively correlated with the changes in the serum zinc level, which suggests an improvement in acne symptoms and adds further evidence towards the effect of zinc in acne vulgaris. One study revealed a significant correlation between serum zinc level and severity of acne vulgaris. [14] Two other studies also found a negative correlation between acne severity and zinc level. But these study findings are observed at baseline because they could not measure serum zinc levels after the intervention [17, 18].

Zinc acts as an anti-inflammatory agent. It reduces acne severity by maintaining the structural movement of skin epithelium [3]. Zinc determines macrophages' phagocytic activity and migration rate, interfering with the inflammatory process [11]. Increased levels of zinc influence several functions of cells. Action on cell membranes has observed that mast cells are inhibited from releasing histamine and alter

inflammatory processes [11]. The present study shows that serum zinc levels raised after zinc supplementation and GAGS score (i.e., reflecting acne severity) reduced. The present study shows that serum zinc levels raised after zinc supplementation and GAGS score (i.e., reflecting acne severity) reduced.

Retinoids are vitamin A derivatives that accelerate the differentiation and proliferation of cells and alter the abnormal desquamation— finally, suppression of microcomedones formation and expulsion of mature comedones. Zinc is also essential for continuing normal blood levels of vitamin A. Therefore, topical retinoids (either tretinoin or adapalene) and zinc supplements are necessary for normal epithelial differentiation.

This study may postulate that zinc supplementation and topical retinoids might help reduce the severity of acne vulgaris. This zinc supplementation may also increase treatment success rate by decreasing severity and complication.

CONCLUSION

Zinc sulfate had significantly reduced acne symptoms in the intervention arm compared to the control arm and a correlation between serum zinc levels with acne severity and type of acne lesions (GAGS score). So, zinc sulfate is a chief option for maintenance therapy and sustained any better zinc level may improve or prevent the recurrence of acne vulgaris.

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