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Research Article

Association of serum zinc and vitamin E levels with *Acne vulgaris* in Bangladeshi acne patients

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ABSTRACT

The serum level of zinc and vitamin E were measured to understand the association of various nutrients on acne pathogenesis. Both zinc and vitamin E are antioxidants used as a supplement in acne treatment. However, their effect and status in acne patients are not fully understood. This study included 48 acne patients and 48 sex- and age-matched healthy controls. The zinc and vitamin E concentration was measured in the serum by flame atomic absorption spectroscopy (AAS) and HPLC methods. Compared to the healthy control, a significant deficiency of serum vitamin E level in acne patients (p<0.001) was found, although the patients were not deficient in serum zinc level (p=0.22). In addition, female acne patients had a slightly lower zinc level than male patients (p=0.06). The low serum vitamin E level suggests that supplementation of vitamin E might be helpful in acne treatment. However, further studies are required to understand the dose and mechanism of vitamin E supplements in acne treatment.

Introduction

According to the Global Burden of Disease (GBD) study, acne vulgaris affects ~85% of young adults aged 12–25 years (Hay et al., 2014). However, the severity and consequences of acne are underrated in low economic countries like Bangladesh. While acne may not seem like a serious health condition, it can cause significant psychological issues, including stress, anxiety, and social phobia. Acne, also called acne vulgaris, is a multifactorial dermatosis, which occurs most often during puberty. It is a chronic inflammatory disease of the pilosebaceous unit and is characterized by the formation of non-inflammatory open and closed comedones and inflammatory papules, pustules, nodules, and cysts. The sequence of events involved in acne pathogenesis is yet to be revealed. Colonization of the pilosebaceous follicle by *Cutibacterium acnes* (also known as *Propionibacterium acnes*) is a major factor for the inflammatory reaction in acne vulgaris (Dessinioti and Katsambas, 2010). Among others, immunological conditions, genetic predispositions, hormonal irregularities, particularly androgens, mental health, and environment play an important role.

Diet may play a significant role in the pathogenesis of acne (Kucharska et al., 2016). Glycemic load, fatty foods, chocolate, and dairy products are also associated with the development of acne (reviewed in Kucharska et al., 2016). Acne is less common in African-Americans and Asians than in the Caucasian population (Wolf et al., 2004).

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These indicate the association of distinctive dietary habits of these populations with acne. Reactive oxygen species produced by neutrophils participate in the inflammatory progression of acne; thus, antioxidants are suspected of playing an important role in acne treatment. Studies have shown various patterns of association of nutritional factors, including vitamins and minerals, such as vitamin A and E, zinc, selenium, and copper, in the pathogenesis of acne in a different population (Kucharska et al., 2016; Ozuguz et al., 2014; Ikaraoha et al., 2017). To understand the association of various nutrients on acne pathogenesis, from the literature, we narrowed down zinc and vitamin E to be two of the most potential candidates and studied their serum levels in acne patients.

The detailed role of vitamin E in skin biology is yet to be investigated. Vitamin E is a group of compounds, including tocopherols and tocotrienols. In plasma, the stable form of vitamin E is D-α-tocopherol. Alpha-tocopherol protects biological membranes by its antioxidant activity from the free radicals produced in cells in a stressed condition. It accentuates the immune system, protects skin against UV radiation, and preserves the membranes from peroxidation. The role of zinc in acne pathogenesis is the most studied of all nutrients, although studies have shown variation in results regarding the association of zinc with acne pathogenesis (Ozuguz et al., 2014; Ikaraoha et al., 2017; Nasiri et al., 2009; Mogaddam et al., 2014; Kaymak et al., 2007; Michaëlsson and Ljunghall, 1990).

The importance of zinc is easily understandable because it is used as a cofactor by 300 metalloenzymes and more than 2000 transcription factors. In cell culture, zinc salts inhibit *acnes*, the causal agent of acne (Bae and Park, 2016). The antioxidant activity of zinc in cell culture, animal models, and human is also well established. While acne is an inflammatory dermatosis, zinc acts as an anti-inflammatory factor by decreasing NF-kB signaling and several inflammatory factors, such as tumor necrosis factor-α (TNF-α), IL6, Toll-like receptor-2. However, the exact role of these micronutrients in acne pathogenesis or whether they are the cause or the effect of acne is unknown yet. Inconsistent results have been found across the studies regarding the degree of association between different populations worldwide. We hypothesized that a reduction in zinc and vitamin E levels is associated with acne pathogenesis in Bangladeshi patients.

Method

Study population and design

This study was conducted among patients attending the Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU) hospital diagnosed with acne vulgaris dermatologists. Acne patients included in this study were 11 years old, had no cosmetic induced acne, were not pregnant or lactating, and had no malabsorption syndrome, chronic kidney, or liver disease. Patients were not under any active immunosuppressive treatment and hand no history of active malignancy, oral contraceptive pills, iron intake, and corticosteroids. The control group was not

under any treatment or medication and had no past or family history of acne or any chronic diseases. None of the groups were taking any vitamin pills. Each participant has explained the nature of the study, and written consent was taken for each subject belonging to the patient and control group. Parents' consent was taken for individuals who were below 18 years old. Participants completed a structured questionnaire covering on age, gender, medical, and family history of acne and other chronic diseases. Questionnaires were filled up by the parents of patients who were under 18 years. This study was reviewed and approved by both the Institutional Review Board of BSMMU (No. BSMMU/2016/7941) and the Ethical Review Committee (ERC) of the Department of Biochemistry and Molecular Biology, University of Dhaka (No. BMBDU-ERC/EC/17/02), since samples were collected from patients attending BSMMU and experiments and analysis were conducted in the Department of Biochemistry and Molecular Biology, University of Dhaka. The study was conducted between August 2016 to February 2017.

Collection of blood

Three (3.0) ml of venous blood was collected from patients and controls through an aseptic venipuncture from the antecubital vein in a plain test tube and allowed to clot. Serum was separated from blood immediately at room temperature and stored at -20^0C until analysis. Blood samples of 48 patients suffering from acne vulgaris were collected along with age and a sex-matched equal number of healthy individuals.

Measurement of serum vitamin E and zinc level

Serum level of vitamin E was measured by High-Performance Liquid Chromatography (HPLC) according to a slightly modified method of Yang et al. (2019), and serum level of zinc was measured by flame atomic absorption spectroscopy (AAS) method using a Perkin Elmer, Analyst 800 Atomic Absorption Spectrophotometer. In brief, α-tocopherol was extracted by mixing 0.5 mL serum with 2 mL of hexane in a vortex mixer three times (60 sec each time), and phases were separated by centrifugation. The upper organic phase was transferred and dried under nitrogen. The residue was dissolved in 100 μL of methanol, and vitamin E was determined with a common C18 column thermo stated at 25^oC, using a simple isocratic elution of methanol /acetonitrile (85:15, v/v) at a flow rate of 1.0 mL/min. The injection volume was 20 μL and the run time of each sample was 10 min. On the other hand, zinc was determined by a specific hollow cathode lamp using standard Zn solutions after the mineralization of blood samples in a microwave system. Samples were aspirated through a nebulizer, and the absorbance was measured with a blank as reference. Deionized distilled water was used as a blank. Blank and standard solutions were used for the calibration of the atomic absorption spectrophotometer.

Statistical analysis

Data were recorded and analyzed by using GraphPad Prism. An unpaired parametric t-test with a 95% confidence interval was used to find any significant difference in serum zinc and vitamin E level between the patients and healthy volunteers. P-value was considered statistically significant at $p<0.05$. Values are expressed as mean ± standard deviation.

Results

Of the 48 patients included in the study, 29 (60.4%) were women, and 19 (39.6%) were men. Patients had a mean age of 22.04±6.34 years, ranging from 11 to 35 years (Table 1). Of the 48 healthy volunteers included in the study, 30 (62.5%) were women, and 18 (37.5%) were men. The mean age of the volunteers was 22.06±6.55 years, ranging from 11 years to 35 years. Serum vitamin E level was significantly lower ($p<0.001$, two-sample t-test) in acne patients (0.797±0.58 µg/mL) compared to the healthy volunteers (3.7±0.7 µg/mL) (Table 1 and Fig. 1).

Mean serum zinc level was slightly lower in acne patients (0.94±0.27 µg/mL) compared to the healthy volunteers (1.01±0.33 µg/mL). However, there was no significant difference between these two study groups ($p=0.22$, two-sample t-test) (Table 1, and Fig. 1). Further, in acne patients, the zinc level of female (0.87±0.25 µg/mL) was slightly lower compared to male (1.03±0.26 µg/mL) (data not shown), though not statistically significant ($p=0.06$, two-sample t -test).

Table 1. The demographic data and laboratory measures of acne patients and healthy controls.

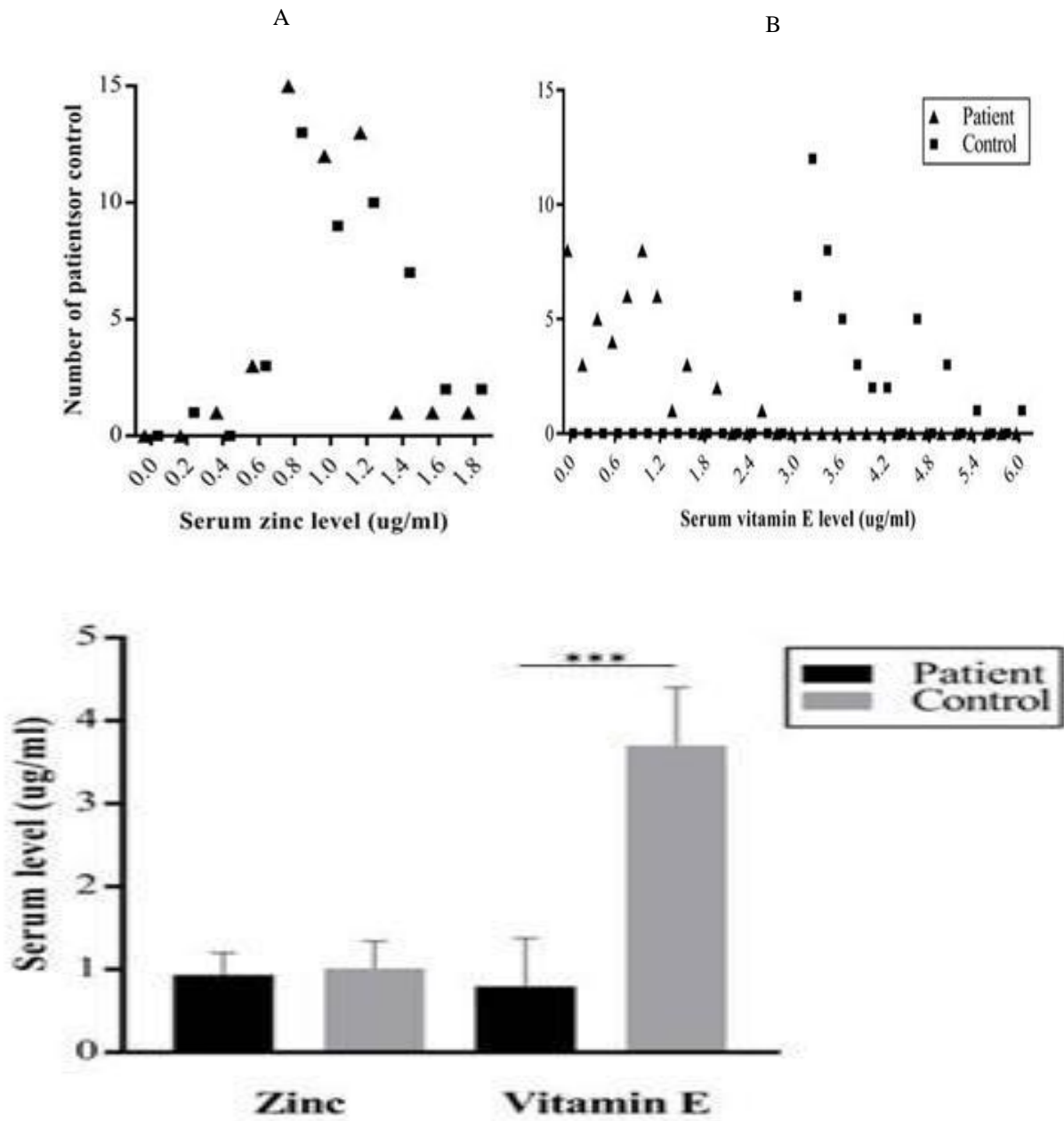|	Study subjects					
Variable	**Acne patients**			**Healthy controls**		
Gender						
Female	29 (60.4%)			30 (39.6%)		
Male	19 (62.5%)			18 (37.5%)		
Age (year) (mean±SD)	22.04±6.34			22.06±6.55		
Serum level (µg/mL)	**Minimum**	**Maximum**	**(Mean±SD)**	**Minimum**	**Maximum**	**(Mean±SD)**
Vitamin E	0.01	2.53	0.80±0.58*	2.91	5.99	3.70±0.70
Zinc	0.04	1.80	0.94±0.27	0.11	1.80	1.01±0.33

*$p<0.001$

Fig. 1. Serum zinc and vitamin E level in Bangladeshi acne patients.
(A-B) Frequency distribution of serum vitamin E (A) and zinc (B) in acne patients (triangular symbol) and healthy volunteers (square symbol). (C) Comparison of serum vitamin E and zinc levels between acne patients (black bars) and healthy volunteers (grey color).

Discussion

Despite the high prevalence of acne and the known relevance of nutrition with acne, studies on their association are relatively scarce. A limited number of nutritional studies has found with a number of nutrients including vitamin E, zinc, vitamin A (Ozuguz et al., 2014; El-Akawi et al., 2006), selenium (Michaëlsson, 1990), and copper (Ikaraoha et al., 2017) deficient in acne patients. This deficiency could either partly play a role in triggering acne or be the effect of acne pathogenesis. Zinc is the most studied among them though some of these studies contradict each other. Studies of the other nutrients are the only handful and demand further confirmation. Ours is the first study on Bangladeshi acne patients to measure their serum vitamin E and zinc level and compare to healthy Bangladeshis.

Although in this study, no significant deficiency of zinc level was found in acne patients, patients were severely deficient in serum vitamin E level. Serum vitamin E reference value for adults is 5.5-17 µg/ml. In this study, the maximum value for serum vitamin E level among the 48 healthy Bangladeshi was 5.99 µg/ml, close to the lower range of the reference value. Besides the severe deficiency in vitamin E (0.80±0.58 µg/ml) in acne patients, the mean serum value of vitamin E in healthy Bangladeshi (3.70±0.70 µg/ml) is below the range of reference value as well (Table 1). Recommended daily consumption of vitamin E for men and women is respectively l0 mg and 8 mg. Vegetable oils, nuts, seeds, grains, and green leafy vegetables are sources known to be rich in vitamin E. Sources of zinc include meat, fish, eggs, milk, beans, nuts, etc. The daily zinc requirement for an adult is 10-15 mg. The reference value of serum zinc is 0.6-1.10 ug/ml. In our study, the mean serum level of zinc in both acne patients (0.94±0.27 µg/ml) and healthy controls (1.01±0.33 µg/ml) remained in the reference value (Table 1).

Studies on the association of vitamin E with acne are scarce (Ozuguz et al., 2014; El-Akawi et al., 2006). However, our study results are in the same tone as these previous studies. In addition, these studies have found a lower level of vitamin E in severe acne patients compared with mild patients indicating the degree of deficiency correlates with acne severity (Ozuguz et al., 2014; El-Akawiet al., 2006). However, whether the low vitamin E level is due to the low dietary intake or any secondary reason is yet to be studied. It is assumed that vitamin E levels may be depleted in acne patients, as antioxidants are consumed to scavenge the oxygen free radicals during the inflammatory phase of acne development. Selenium helps in the antioxidant activity of vitamin E. Accordingly, studies have found low serum selenium levels in acne patients (Michaëlsson, 1990). This study suggests that supplementation of vitamin E with other anti-acne drugs will possibly benefit acne patients.

The concept of using vitamin E in acne treatment is not new. Vitamin E has been found effective as a supplement to isotretinoin (13-cis-retinoic acid) drugs to treat acne. Isotretinoin can be considered the most effective broad-spectrum drug to treat acne (reviewed in Layton, 2009). Among the multiple mechanisms isotretinoin fights acne, one is that it reduces sebum production and thus reduces the formation of comedones. Studies comparing the treatment outcome of two groups of patients, one treated with isotretinoin, other with both isotretinoin and

vitamin E, showed a better outcome in the latter group (Fabbrocini et al., 2014). Intriguingly, serum vitamin E level is reduced after the isotretinoin treatment (Aktürk et al., 2013). The most common adverse effect of isotretinoin use is cheilitis (Layton, 2009), significantly decreasing by concurrent use of vitamin E as it prevents the sebum oxidation and has hydration properties (Fabbrocini et al., 2014). This study shows that vitamin E is inherently deficient in acne patients; thus, we can emphasize vitamin E in acne treatment. However, studies in disagreement did not find any added benefit of vitamin E supplementation to isotretinoin (Kus et al., 2005; Strauss et al., 2000. Thus, the role of vitamin E in acne pathogenesis and treatment requires further studies for confirmation.

Unlike vitamin E studies, there are a good number of studies on zinc level in acne patients though the findings varied (Ozuguz et al., 2014; Ikaraoha et al., 2017; Nasiri et al., 2009; Mogaddam et al., 2014; Kaymak et al., 2007; Michaëlsson and Ljunghall, 1990; Michaëlsson, 1990). While both of the studies on the Turkish population found significant zinc deficiency in acne patients (Ozuguz et al., 2014; Kaymak et al., 2007), other studies on patients from Iran (Nasiri et al., 2009; Mogaddam et al., 2014) and Nigeria (Ikaraoha et al., 2017) found no significant difference when compared to the healthy volunteers in coherence to this study. The study of El-Dibany and Elhassi (2019) also reported no correlation between serum zinc level and severity of acne. In a study, Michaelsson and Ljunghall (1990) found that despite having normal zinc levels in the blood, Swedish patients suffering from acne and other dermatitis had significantly lower epidermal

zinc levels. A mild correlation between the degree of zinc deficiency and acne severity was found in some studies (Ozuguz et al., 2014; Mogaddam et al., 2014), while others found no correlation (Ikaraoha et al., 2017; Kaymak et al., 2007). Thus, further studies are required to conclude the association of zinc deficiency in Bangladeshi acne patients.

Treatment of acne depends on the severity and type of acne. Antibiotics, antimicrobial agents, isotretinoin, lactoferrin (an iron-binding protein), hormone, and zinc are currently practiced in acne treatment (reviewed in Trivedi et al., 2018). The use of zinc to treat inflammatory dermatoeses has been thoroughly reviewed by gupta et al., (2014). Lotion, paste, and injection of zinc salts are used to treat a number of dermal conditions. Topical 5% zinc sulfate was found to be more effective than 2% tea lotion in treating mild to moderate acne vulgaris (Sharquie et al., 2008). Reportedly, severe grades of acne respond better to oral zinc sulfate drugs (Bae et al., 2010). Oral administration of both the sulfate and gluconate zinc salts effectively treated moderate to severe acne vulgaris (Bae et al., 2010). On the other hand, Cochran et al. (1985) evaluated the efficacy of topical zinc therapy in mild to moderate acne vulgaris and reported no difference between placebo- and zinc-treated participants regarding either the number or the type of acne lesions over 12 weeks. They suggested that topical zinc therapy alone is not of significant benefit in the treatment of acne vulgaris.

Supplement of zinc acetate with erythromycin antibiotic ensured better topical absorption of erythromycin in acne patients (Langner et al., 2007). The combination of zinc with antioxidants has also been found effective

(James et al., 2009). However, how exactly zinc exerts its inhibitory effect on acne is not known. The therapeutic effect of zinc is probably not to deficient in the acne-compensate the zinc patients; rather, possible mechanisms of action may include anti-inflammatory property of zinc (Prasad, 2014), increment of topical absorption of antibiotic when used with antibiotic (Langner et al., 2007), inhibition of *C. acnes* lipases and free fatty acid levels (reviewed in Bae et al., 2010), and suppression of sebum production by its anti-androgenic activity (Piérard-Franchimont et al., 1995). The dosage of zinc needs to be tuned with its accompanied medication to minimize the gastrointestinal side effects of zinc in some patients (Meynadier, 2000). Safe use of zinc requires a better understanding of the mechanism of action and how it is associated with acne progression.

Our study is primarily limited to the fact that acnes were not graded as per severity and duration. Thus, we considered acne patients of any acne stage and duration, and we cannot rule out that a refined categorization of acne patients with a sufficient sample size per category could produce a different statistical outcome. However, considering the socioeconomic status of Bangladesh and that BSMMU is a public hospital where service charges are heavily subsidized, minimum inference can be drawn that patients with mild dermatological conditions were not enrolled in this study. We stick to the possibility that primarily moderate to severe acne vulgaris patients were enrolled in this study. This statement does not nullify the essentiality of acne grading, and we could not draw any association of acne severity with serum zinc or vitamin E level due to this limitation. The second limitation originates from the fact that non-prescribed medications can

easily be purchased in Bangladesh. Unless the disease state is too severe and badly requires a doctor's attention, a significant number of people buy generics to treat them. Thus, apart from the drugs mentioned in the exclusion criteria, we cannot rule out that they were not under any other regimen, which may include vitamins and antimicrobials. Finally, the age range of patients enrolled in this study is relatively broad (11-35 years, mean age 22.04±6.34 years) and included both men and women from various socioeconomic statuses. Since the causes and expression of acne could vary according to age, sex, diet, and environment, we cannot ignore that a more refined categorization of patients could shed more light on the study.

Although we did not see any difference in zinc level between patients and healthy people, a larger sample size with a better categorization of patients according to age, sex, severity, and acne duration could zoom in on the actual status of zinc level in each category. This may explain why the previous studies on zinc levels in acne patients did not support each other. Suppose we assume that serum zinc level is reduced in only particular groups of acne patients. In that case, chances are higher that this reduction will be masked by other categories where zinc level does not change.

In conclusion, Bangladeshi acne patients had a severe deficiency in vitamin E but showed no measurable change in zinc level. Understanding the association of nutrients in acne is crucial to device optimum acne treatment. Studies show that using vitamin E and zinc as treatment supplements may minimize the duration and dosage of antibiotics to treat acne. This is excitingly promising as the emergence of resistant strains is an alarming issue-antibiotic worldwide.

Declaration of interest statement

The authors declare that they have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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