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Evaluation of serum hepcidin level in acne vulgaris patients

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Abstract---Background: Acne vulgaris is a pilosebaceous unit inflammatory condition. Although acne is not life-threatening, it can cause psychological issues such as low self-esteem and anxiety in people who suffer from it. Acne scarring is a common and unpleasant consequence of acne vulgaris. Predicting scarring liability can modify treatment protocol and aid in the prevention of such disfigurement. Methods: This study included 82 participants divided into 3 groups: 26 patients with acne vulgaris without scars, 36 patients with acne vulgaris with scars and 20 control. Serum hepcidin level was assessed by a commercially available double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) kit. Results: Serum hepcidin is significantly higher in patients suffering from acne without acne scars than patients suffering from acne with acne scars ($p < 0.05$). serum hepcidin is significantly higher in the control group than patients with active acne with scars ($p < 0.05$). There was a statistically significant difference between serum hepcidin level in control versus severe acne scars ($p < 0.05$). Serum hepcidin level acts as a predictor of occurrence of acne scars and occurrence of severe acne scars. Serum hepcidin level can be used as an indication for beginning aggressive and specific acne treatment as systemic retinoid.

Keywords---acne scars, acne vulgaris, hepcidin, inflammatory condition, patients.

Introduction

Acne vulgaris is a very common cutaneous inflammatory disorder. It is a chronic inflammatory disorder of the pilosebaceous unit typically affecting areas with a high density of hormonally-responsive sebaceous glands such as the face, neck, chest, upper back, and upper arms (Stewart and Bazergy, 2018). Acne vulgaris is a polymorphic disease in which many types of lesions coexist: primary lesions representing active acne, such as comedones, and inflammatory lesions, such as papules, pustules and nodules (Semyonov, 2010, Tan et al, 2017). Acne is always accompanied with erythema, desquamation, discomfort, itching, burning, and dyschromia (Mohiuddin, 2019). Acne has been associated with discomfort and a significant psychological effect in the form of stress, social phobia disorder (SAD), fear, anxiety, and even suicide, despite the fact that it is a non-life threatening condition (Baldwin, 2020, Yang et al, 2020, Stamu-O'Brien et al, 2021).

Four processes play the main role in the formation of acne lesions includes androgen-mediated stimulation of sebaceous gland activity, abnormal keratinization leads to plugging of the follicles (comedonal formation), proliferation of the bacterium *Propionibacterium acnes* (*P.acnes*) within the follicles and inflammation (Baldwin, 2020, Yang et al, 2020). Other factors involved in the pathogenesis of acne as diet, medications, occupational factors, pollution, climatic conditions, psychological and lifestyle factors (Cong et al, 2019). These exposome factors disrupt the natural skin barrier and microorganisms, resulting in hyperseborrhea, abnormal keratinization of the pilosebaceous duct, loss of skin microbial diversity and inflammation (Rocha and Bagatin, 2018).

Acne scars are permanent complications of acne vulgaris which can cause significant psychological distress, poor self-esteem, and social isolation (Nitayavardhana et al, 2020). Scarring is a result of abnormal wound healing or resolution after the injury that happens in the sebaceous follicle through inflammation of acne (Goodarzi et al, 2020). Acne scars are categorized into three types: atrophic, hypertrophic, and keloidal. Based on their appearance, atrophic scars are categorized as an ice pick, rolling, or boxcar scars (Roh and Chung, 2020).

TGF- β signaling plays a role in a variety of biological processes and functions as cell growth, differentiation, and apoptosis (Ismaeel et al, 2019). Significant quantities of latent TGF- β are stored in the matrix in most tissues; consequently, conversion of latent TGF- β to active TGF- β is the primary regulator of TGF- β signaling (Biernacka et al, 2011).

Moon et al., identified distinctive features arising in early acne lesions progressing into atrophic scars which are excessive destruction of elastic fibers and collagen fibers, aggressive inflammation mediated by innate immunity and Th17 and Th1 cells, an impediment to keratinocyte proliferation and aberrant TGF- β 1 signaling serving as a hub modulating all of these events (Moon et al, 2019). The major pathway of TGF- β 1 induced myofibroblast differentiation is mediated via Smad mother against decapentaplegic (Smad) activation by the TGF- β 1 receptor complex, leading to Smad2 and Smad3 complex association with Smad4 and translocation into the nucleus. Smad3 binding to Smad binding elements in the

promoter region regulates alpha smooth muscle actin (α -SMA) transcription in conjunction with a variety of transcription factors, to further enhance the deposition of ECM proteins. The imbalance of the synthesis and degradation of ECM results in scarring (Zhao et al, 2017).

Hepcidin has an antifibrotic activity via inhibiting transforming growth factor β 1 (TGF- β 1) mediated Smad3 phosphorylation. Hepcidin levels are inversely correlated with exacerbation of fibrosis in patients, and also that was confirmed in an animal models (Han et al, 2016).

Patients and methods

After approval of the study by the Research and Ethical Committee at Sohag faculty of medicine, this study included eighty two participants divided into 3 groups: patients with acne vulgaris without scars, patients with acne vulgaris with scars and control. Subjects suffering from iron deficiency anemia, taking iron supplement, on medical treatment for acne vulgaris in the last three months, hepatic patients and hypoxic patients were excluded from the study.

The participants were subjected to complete history taking and general clinical and cutaneous examination. Acne vulgaris was classified according to global acne grading system (Zohra et al, 2017), acne scars were classified according to Goodman and Baron qualitative grading system (Goodman and Baron , 2006). Three ml blood was collected by aseptic venipuncture into redtop plain glass tubes. Blood samples were allowed to coagulate during 30-60 minutes. Serum was obtained by centrifugation at 1262 g for 10 minutes, aliquoted, and immediately frozen at -20°C until analyzed to determine serum hepcidin level. Serum hepcidin concentration was assessed by a commercially available double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) kit.

Statistical analysis

The collected data was coded and verified prior to computerized data entry. The collected data was statistically analyzed using Statistical Package for the Social Science (SPSS) version 16 program and expressed in tables and charts. Receiver operating curve (ROC) was used to evaluate the diagnostic performance of serum hepcidin level.

Results

This study included 82 participants divided into 3 groups ; 26patients with acne vulgaris without scars ,36 patients with acne vulgaris with scars, 20 normal persons do not suffer from acne vulgaris (control). In comparison of serum hepcidin level between control and the two groups (patients with active acne without acne scars and active acne with acne scars): there was no statistically significant difference between serum hepcidin level in the control and patients with active acne without acne scars ($p>0.05$) but there was statistically significant difference between serum hepcidin level between the control and patients with active acne with acne scars ($p<0.05$) (figure 1, table1). Among the studied parameters; hepcidin level showed no statistically significant difference with acne

duration ($p > 0.05$). In comparison of serum hepcidin level between patients with active acne without acne scars and active acne with acne scars there was statistically significant difference ($p < 0.05$). Hepcidin level showed no statistically significant difference with acne severity ($p > 0.05$). There was no statistically significant difference between serum hepcidin level and mild or moderate acne scar ($p > 0.05$) but there was statistically significant difference between serum hepcidin level and severe acne scar ($p < 0.05$) (figure 2, table2)

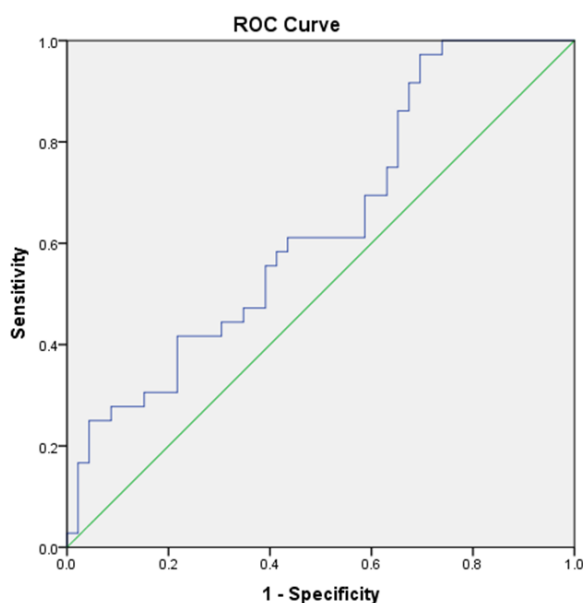


Figure 1. Receiver operator characteristic (ROC) Curve of serum hepcidin as predictor of occurrence of scar when smaller result is positive

Table 1
ROC curve parameters of serum hepcidin as predictor of occurrence of scar when smaller result is positive

Variable	Cut off point	AUC (Area under the curve)	p-value	Sensitivity (%)	Specificity (%)	PPV (%) (Positive predictive value)	NPV (%) (Negative predictive value)	Accuracy rate
Serum hepcidin	300ng/dl	0.635	<0.036	55%	61%	52.6%	57.1%	63.5%

From ROC curve, it was demonstrated that serum hepcidin had the area under the curve (AUC) 0.635 with 55% sensitivity and 61% specificity at cutoff point 300ng/dl.

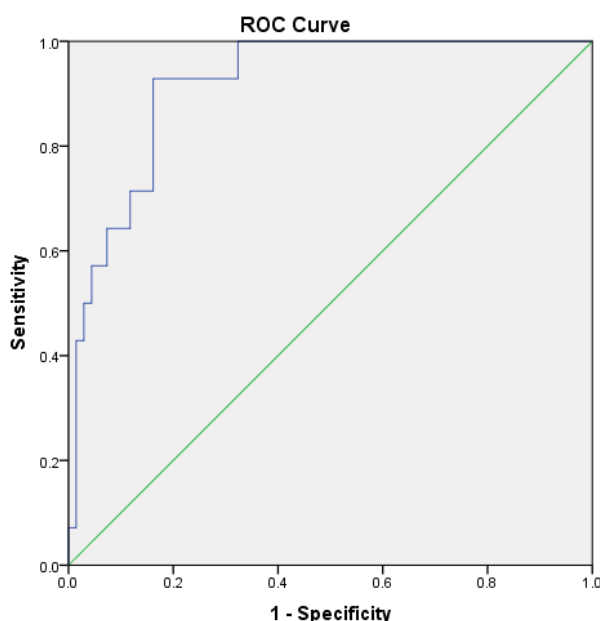


Figure 2. Receiver Operator Characteristic (ROC) Curve of serum hepicidin as predictor of occurrence of severe scar when smaller result is positive

Table 2
ROC curve parameters of serum hepicidin as predictor of occurrence of severe scar when smaller result is positive

Variable	Cut off point	AUC (Area under the curve)	p-value	Sensitivity (%)	Specificity (%)	PPV (%) (Positive predictive value)	NPV (%) (Negative predictive value)	Accuracy rate
Serum hepicidin	300 ng/dl	0.918	<0.0001	100%	65%	37%	100%	91.8%

From ROC curve, it was demonstrated that Serum hepicidin had the area under the curve (AUC) 0.918 with 100% sensitivity and 65% specificity at cutoff point 300ng/dl.

Discussion

Acne vulgaris is one of the most common skin diseases. More than 85% of young individuals are affected by acne vulgaris worldwide and can suffer from the disease into adulthood (Sun et al, 2020). Possible outcomes of the inflammatory acne lesions are postinflammatory hyperpigmentation and postacne scars. Although these scars can be treated in a number of ways, patients with acne are concerned about acne scars, even those with a diameter of less than 2 mm because they may have negative effects on different aspects of life including anxiety, daily activities, social activities, study, work, and interpersonal relationships (Hazarika and Archana, 2016).

Acne scars can be classified into atrophic and hypertrophic, or keloidal scars. The two key modifiable factors that are linked to acne scars formation are a time delay between onset of acne and effective treatment and the extent/duration of inflammation (Thiboutot et al, 2009). Hepcidin has an antifibrotic activity via inhibiting transforming growth factor β 1 (TGF β 1) mediated Smad3 phosphorylation. Hepcidin levels are inversely correlated with exacerbation of fibrosis in patients, and also that was confirmed in animal model (Han et al, 2016). In this study, we found that the serum hepcidin is significantly higher in patients suffering from acne without acne scar than patients suffering from acne with acne scar and this is consistent with that in El-Taweel et al, (2018).

More over in our study we found statistically significant higher serum hepcidin level in control group than patient with active acne with scar ($p < 0.05$), while there was no statistically significant difference between serum hepcidin level in the control vs patients with active acne without acne scars ($p > 0.05$). Also we found that serum hepcidin level in patients with active acne without acne scars is significant higher than serum hepcidin level in patients with active acne with acne scars ($p < 0.05$) and this finding support hepcidin antifibrotic activity in consistent with finding by ElTaweel et al, (2018) and Han et al,(2016) . As regard serum hepcidin level and acne scar severity we found no statistically significant difference between serum hepcidin level in control vs mild or moderate acne scar ($p > 0.05$) but there was statistically significant difference between serum hepcidin level in control vs severe acne scar ($p < 0.05$). In this study, serum hepcidin acts as predictor of occurrence of acne scar in general. From ROC curve, we demonstrated that serum hepcidin had the area under the curve (AUC) 0.635 with 55% sensitivity and 61% specificity at cutoff 300ng/dl . Our results is confirmed by El-Taweel et al, (2018) who has area under the curve (AUC) 0.9149 with 80% sensitivity and 100 % specificity at cutoff 154.6 ng/dL.

Conclusion

Serum hepcidin level acts as a predictor of occurrence of acne scars and occurrence of severe acne scars. Also, serum hepcidin level can be used as an indication for beginning aggressive and specific acne treatment as systemic retinoid.

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