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Evaluation of Serum Levels of Uric acid and Bilirubin in Iraqi Patients with Rosacea

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ABSTRACT

Background: *Rosacea is a chronic inflammatory skin disease that affects the face with no clear etiology. It is distinguished by prominent involvement of the central face with erythema that may be permanent or temporary, inflammatory pustules, papules and telangiectasia or connective tissue hyperplasia. The role of uric acid and bilirubin in the pathogenesis of rosacea is explained by two theories. The first one states that uric acid and bilirubin alleviate rosacea by their antioxidant effects, while the second one postulates that uric acid exacerbate rosacea by its proinflammatory effects.* ***Aim of study:*** *The aim of this study is to evaluate serum levels of bilirubin and uric acid in patients with rosacea and compare them with control group.* ***Methodology:*** *This is a case-control study that included 80 subjects (40 patients and 40 controls) and was done at Al Sader Medical City/department of dermatology in Al Najaf City, from the 1st of January 2022 to the end of December 2022. Patients were recorded (age, sex, family history of rosacea), as well as clinical information (duration of illness, involvement sites, and rosacea subtypes). Collect samples of blood from all participants and the levels of total serum bilirubin and uric acid were recorded.* ***Results:*** *The present study reported female predominance. Erythemato-telangiectatic rosacea was the most common type. Serum uric acid and bilirubin levels were significantly lower in the rosacea group than the control group.* ***Conclusions:*** *The study supports the hypothesis of antioxidant activity of uric acid and bilirubin and in contrast with the hypothesis of proinflammatory activity of uric acid.*

Keywords: Rosacea, Serum Bilirubin, Serum Uric Acid.

Article Information

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INTRODUCTION

Rosacea is a chronic facial skin disease defined by central facial involvement with erythema, inflammatory pustules or papules, telangiectasia, or connective tissue hyperplasia[(1).] Persistent erythema lasting at least 3 months with a propensity to sparing the periorbital skin is a characteristic of erythemato-telangiectatic rosacea [(2)]. Transient erythema, often known as flushing, generally lasts less than 5 minutes and may extend to the neck, frequently accompanied by a sensation of hotness. Less frequent manifestations include

erythematouse scaling plaques, phymatous changes (skin hypertrophy with sebaceous gland hyperplasia), edema, and ocular symptoms [2]. Rosacea is divided into 4 subgroups: Erythemato-telangiectatic, papulopustular, phymatous and ocular, based on the signs and symptoms that frequently coexist [3]. The underlying pathophysiology of rosacea is unknown, but The new pathophysiologic theories of rosacea implicate an regulate innate immune system prone to excessively induce inflammation and vasodilation with neurogenic upregulation [4].

Uric acid and bilirubin as antioxidants: Reactive oxygen species (ROS) are oxygen-based molecules with high chemical reactivity. ROS include free radicals (superoxide and hydroxyl radicals) and non radical species (hydrogen peroxide), which can be produced even at resting conditions in a number of ways [5] . Increased ROS production and/or decreased antioxidant levels forming a state of oxidative stress and make susceptibility of biological molecules and membranes to react with free radicals [6]. Uric acid is produced by a xanthine oxidoreductase (XOR)-catalyzed reaction, and shown to have both antioxidant and pro-oxidant properties in vitro by scavenging and production of reactive oxygen species (ROS) [7].Uric acid (UA) is the end product of the common pathway of purine metabolism, is a natural antioxidant with metal-chelating properties and reacts with nitrogen radicals and superoxide[8] .

Bilirubin is the end product of heme metabolism converted from biliverdin by biliverdin reductase (BVR) which is a cytotoxic waste product. However, most recent studies on the physiological functions of bilirubin focus on its antioxidant effects. Bilirubin has powerful antioxidant activity and has been shown to be capable of protecting from 10,000 fold molar excess of hydrogen peroxide [9]. In summary, UA and bilirubin in the serum can both have antioxidant effects and reduce global oxidative stress.

PATIENTS AND METHODS

This study was done in the out-patient Department of Dermatology and Venereology, in Al-Sader Medical City in Al Najaf City during the period from the 1st of January 2022 to the end of December 2022. The study was approved by a local ethics committee. All participants were know about the study and take a written consent. A total of 80 subjects (40 patients and 40 controls) were involved. The patient's sociodemographic characteristics were recorded (age, sex, family history of rosacea), as well as clinical information (duration of illness, involvement sites, rosacea subtype, and severity). The participants involved were patients with rosacea who were diagnosed clinically in the dermatology clinic in Al-Sader Medical City and controls (healthy subjects without rosacea).

Exclusion criteria for the rosacea group were the presence of medical disease that may alter uric acid and bilirubin (hyperuricemia, heart disease, kidney or liver failure, biliary disease, malignancy), the drugs that increase uric acid (e.g., anti diuretics), immunosuppressive drugs, a history of surgery or trauma in the past month and any treatment for rosacea in the past month. The control group was selected from health individuals who had visited a hospital for routine medical checkup.

As for laboratory analytical instruments, Beckman Coulter Av 480 was used. The normal value for serum uric acid was 2.6-6 mg/dl. While those for total serum bilirubin were 0.2-1.2 mg/dl.

STATISTICAL ANALYSIS

All data were done by using SPSS, Version 16 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA), and a *p-value* less than 0.05 was considered statistically significant. Continuous variables are expressed as the mean ± standard deviation.

RESULTS

The age distribution of the patients ranged from (25-72 years) with a mean of (44.3 years ± 12.5 SD). The age distribution of the controls ranged from (22-75 years) with a mean of (44.0 years ± 13.0 SD). No significant difference in age was detected between the two groups. Concerning sex distribution, there were 8 males and 32 females in the patient group, and 7 males and 33 females in the control group, with no significant difference detected between the two groups; as illustrated in table (1). The mean duration of illness of the studied sample was (2.9 years ± 2.8 SD). Regarding family history of Rosacea more than half (55.0%) had a negative family history. As for the type of rosacea, the majority had erythemato-telangiectatic rosacea (72.5%); as illustrated in Table (2). Regarding severity, 12 (30.0%) had mild rosacea, 19 (47.5%) had moderate rosacea, and 9 (22.5%) had severe rosacea .

Regarding serum uric acid and bilirubin levels in both cases and controls, patients with rosacea had significantly lower levels than individuals without the disease as illustrates in Table (3). Regarding severity and serum level of uric acid and bilirubin no significant difference; as illustrated in Table (4). No significant difference in serum uric acid and bilirubin was detected between participants <40 years and those >40 years; as illustrated in table.(5)

A significant difference in serum uric acid and bilirubin was detected between male participants and female participants, as male participants showed higher serum uric acid and bilirubin levels than females; as illustrated in table. (6)

(1): Sociodemographic characteristics of the studied sample.

Items	Cases	Controls	P value
Age			
<40 years	12	13	0.85
	15.0%	16.3%	
≥40 years	28	27	
	35.0%	33.8%	
Mean ± SD	44.5 ± 12.0	44.0±13.0	
Sex			
Male	8	7	0.77
	10.0%	8.8%	
Female	32	33	
	40.0%	41.3%	

Table (2): Clinical characteristics of rosacea patients.

Family history	No. of patients	Percentage
Positive	18	45.0%
Negative	22	55.0%
Total	40	100.0%
Rosacea subtype		
Erythemato-telangiectatic	29	72.5%
Papulopustular rosacea	9	22.5%
Phymatous rosacea	2	5.0%
Total	40	100.0%

Table (3): Serum uric acid and bilirubin levels in cases and controls.

Items	Cases	Controls	P value
Serum uric acid	4.16mg/dl ±0.79	5.0mg/dl ± 0.7	**<0.001**
Serum bilirubin	0.51mg/dl ± 0.28	0.62mg/dl± 0.15	**0.041**

Table (4): Serum uric acid and bilirubin levels in different severity groups.

Items	Mild	Moderate	Severe	P value
Serum uric acid	4.09mg/dl ± 0.94	4.18mg/dl ± 0.76	3.54mg/dl ± 0.78	0.161
Serum bilirubin	0.48mg/dl± 0.14	0.52mg/dl ± 0.30	0.40mg/dl ± 0.15	0.458

Table (5): Relationship between age group and serum uric acid and bilirubin.

Items	<**40** years	≥**40** years	**P value**
Serum uric acid			
Mean ± SD	4.4 ± 0.77	4.6 ± 0.8	0.170
Serum bilirubin			
Mean ± SD	0.50 ± 0.15	0.59 ± 0.26	0.141

Table (6): Relationship between sex and serum uric acid and bilirubin.

Items	Male	Female	P value
Serum uric acid			
Mean ± SD	5.0 ± 1.01	4.4 ± 0.7	0.041
Serum bilirubin			
Mean ± SD	0.78 ± 0.36	0.51 ± 0.16	0.013

DISCUSSION

Rosacea is a chronic inflammatory skin disease and underlying etiology not known. In the pathogenesis of rosacea, oxidative stress may play important role in induce inflammation [10]. In a recent study there is a role of oxidative stress in pathophysiology of rosacea and there is no study addressing the potential roles of bilirubin and uric acid in Iraqi patients with rosacea. For this reason, the purpose of this study was to assign the level of serum bilirubin and uric acid in patients with rosacea. It is noteworthy to mention that up to our knowledge, this relationship has been assessed only by Turkmen et al. 2020 [11].

Thus, this is the first Iraqi study to evaluate this relationship and role in pathogenesis in patients with rosacea. In the current study, rosacea showed female predominance. This is in accordance with the literature; such as the systematic review by (Gether et al. 2018), and (Chosidow et al., 2011)[12,13], who found a significant female predominance.

Concerning rosacea subtype, Erythemato-telangiectatic rosacea was the most common type followed by the papulopustular subtype. This come with systematic review by (Barakji et al. 2022) revealed that Erythemato-telangiectatic rosacea was the most prevalent followed by papulopustular rosacea, phymatous rosacea, and ocular rosacea [14]. The absence of cases of ocular rosacea in the present study can be attributed to its small sample size.

In this study has been found that serum uric acid and total bilirubin levels were significantly lower in cases than control group, which is in concordance with the study by (Turkmen et al. 2020). Furthermore, (Turkmen et al.) also examined the differences in serum direct and indirect bilirubin and found significantly lower levels in the rosacea group [11]. This can be explained by the antioxidant activity of uric acid and bilirubin. So the antioxidants are play a major role in defense against oxidative stress and uric acid is the antioxidant, accounting for up to 60% of serum free radical scavenging capability, it has been hypothesized that this is the reason humans have a serum uric acid that is higher than other mammals [15]. Previous research showed that reactive oxygen species activity higher in samples taken from skin biopsy in patients with rosacea [16,17]. The research by (Erdogan et al. 2018), assessed total antioxidant status (TAS), advanced oxidation protein products (AOPP), serum total oxidant status (TOS), and oxidative stress index (OSI), in patients with rosacea and compared them with those of healthy controls. Although no variations were detected between two groups in terms of OSI levels, the levels of AOPP, TAS, and TOS levels were significantly higher patients with rosacea[17].

As mentioned earlier, there is a lack of previous research assessing antioxidant properties of uric acid and bilirubin in rosacea patients. As for other dermatological diseases, (Lie et al., 2018) and (Turkmen et al. 2018) assessed uric acid and bilirubin in patients with pemphigus vulgaris and vitiligo, respectively and detected significantly lower levels in the cases group, which is in line with the present study [18,19].

It should be noted however, that this study was based on the hypothesis of antioxidant activities of uric acid and bilirubin. In contrast to the later hypothesis, there is abundant evidence that UA is a significant proinflammatory component that may aggravate rosacea [20]. The involvement of oxidative stress in the etiology of rosacea has recently been the subject of several investigations. It is believed that neutrophils' production of reactive oxygen species during the initial inflammatory reaction has a significant role in rosacea. Due to endothelial cell damage brought on by oxidative stress and ROS, innate immunity is suppressed, lipid balance is negatively impacted, keratinocytes and fibroblasts produce cytokines and inflammatory mediators, and cathelicidin production is increased [21].

This hypothesis was supported by (Karaosmanoglu et al. 2020) that found significantly higher uric acid levels in the rosacea group, which lead the authors to conclude that the proinflammatory effects of uric acid is higher than its antioxidant effect [22].

Study limitations

The small sample size of the current study, the non-random sampling, and the single center setting hinders from generalizing our findings to the entire population.

CONCLUSION

In conclusion, serum uric acid and bilirubin levels were significantly lower in the rosacea patients, Our research come with the hypothesis that oxidative stress and antioxidant factors are important in the pathogenesis of rosacea. In rosacea patients that have low antioxidant status may be benefit to use precursors for bilirubin and uric acid as replacement therapy.

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