Role of growth hormone and insulin-like growth factor-I in hyperandrogenism and the severity of acne vulgaris in young males

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ABSTRACT

الأهداف: دراسة الترابط بين مستوى كل من هرمون النمو، والعامل المناظر للأنسولين– 1، وهرمونات الجنس الذكرية مع شدة حب الشباب لدى المرضى الذكور العراقيين، وتأثير ذلك على ارتفاع مستوى الدهون لديهم.

الطريقة: أُجريت هذه الدراسة المقارنة بين المرضى والأصحاء في قسم الكيمياء الحيوية، كلية الطب، جامعة بغداد، وقسم الأمراض الجلدية، مستشفى بغداد، بغداد، العراق وذلك خلال الفترة من يناير إلى نوفمبر 2010م. لقد قمنا باختيار عينة من الذكور المتطوعين، وقمنا بتحليل مستوى الهرمونات لديهم، بالإضافة إلى المقاييس الحيوية الكيميائية.

النتائج: لوحظ ارتفاع في مستوى هرمون النمو والعامل المناظر للأنسولين– 1 في أمصال مرضى حب الشباب الشديد الدرجة مقارنة مع أمصال الأشخاص الأصحاء والمرضى المصابين بحب الشباب الأقل والمتوسط الشدة وبمستوى إحصائي واضح من الناحية الإحصائية (p=0.0001). كما لوحظ أيضاً ارتفاع في مستوى هرمونات الجنس الذكرية (الأندروستيني دايون، والأبي أندروستيرون سلفيت، والتيستوستيرون الكلي) في أمصال مرضى حب الشباب الشديد الدرجة مقارنة مع المرضى المصابين بحب الشباب الأقل والمتوسط الشدة والأشخاص الأصحاء وبمستوى إحصائي واضح من الناحية الإحصائية (p=0.0001). ووجدنا أيضاً ارتفاع إحصائي واضح من الناحية الإحصائية في تركيز الدهون لدى مرضى حب الشباب الشديد الدرجة مقارنة مع مجموعة الأصحاء ومرضى حب الشباب الأقل والمتوسط الشدة (p=0.005). وأظهرت النتائج علاقة واضحة من الناحية الإحصائية بين المقاييس التي تمت دراستها.

خاتمة: تبين هذه النتائج الدور المهم لهرمون النمو، والعامل المناظر للأنسولين– 1، والهرمونات الجنسية الذكرية في شدة انتشار وظهور حب الشباب، بالإضافة إلى أهمية تثبيط هذه الهرمونات لتقليل الإصابة بهذا المرض. كما أن مثل هؤلاء المرضى قد يصابون بارتفاع مستوى الدهون في الدم بعد إصابتهم بفرط الأندروجينية.

Objectives: To evaluate the association of growth hormone (GH), and insulin-like growth factor-1(IGF-1) in the production of male sex hormones and the severity of acne in Iraqi male patients, and to assess their role in development of secondary hyperlipidemia in such patients.

Methods: We conducted this case-control study and single-center measurement of hormones and selected biochemical parameters in a cohort of volunteer males in the Department of Biochemistry College of Medicine, Baghdad University, and in the Dermatology Department, Baghdad Teaching Hospital, Iraq, from January 2010 to November 2010.

Results: The mean serum levels of GH and IGF-1 of severe acne patients were significantly increased when compared with mild-, moderate acne patients, and healthy controls (p=0.0001). Also, the mean serum total testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS) levels were significantly increased in severe acne compared with those of mild- (p=0.0001), moderate acne patients (p=0.005), and healthy males (p=0.0001). The mean values of lipid parameters significantly differed in severe acne patients in comparison with other acne groups and controls (p=0.004). The results also revealed a significant correlation between the studied parameters.

Conclusion: The study showed a significant elevation of serum GH and IGF-1, which enhanced androgen hormone production and the development of severe acne. These patients may develop hyperlipidemia secondary to their hyperandrogenism.

Saudi Med J 2012; Vol. 33 (11): 1196-1200

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Received 16th July 2012. Accepted 29th September 2012.

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Acne vulgaris, the most common cutaneous disorder, is manifested by comedones, papules, pustules, and cysts. The etiology of the acne appears to be multifactorial, involving follicular hyperkeratinization, hormonal function, proliferation of propionibacterium acnes, increased sebum production, and inflammation. Acne vulgaris occurs at the same time as sebaceous gland development, and is associated with sebaceous gland hyperactivity.[1] Serum levels of insulin-like growth factor-1 (IGF-1) and growth hormone (GH) are highest during puberty, the time at which sebum production begins and at which the onset of acne is most common. Accordingly, elevated levels of GH and IGF-1 may play a role in the progression and development of acne.[2] Dehydroepiandrosterone sulfate (DHEAS), the major adrenal androgen precursor, appears to play an important role in increasing the sebaceous gland size, stimulating sebum production, and stimulating keratinocyte proliferation in the pilosebaceous unit.[3,4] Several studies have shown that elevated serum levels of androgens, DHEAS, and testosterone correlate with sebum overproduction and acne.[1] An association between acne and diet has also been investigated with variable results, with some studies suggesting a correlation between carbohydrate- and fat-rich diets and the development of acne,[5] and others indicating no such relationship.[6] On literature review, we found several studies[2] conducted on female patients with acne to investigate the pathogenesis of this disease, however, few involved male acne patients. Therefore, the aim of the present study is to evaluate the serum levels of GH, IGF-1, total testosterone, androstenedione, and DHEAS in male Iraqi patients with acne vulgaris and to assess their correlation with the severity of acne. This study was also designed to investigate the serum concentrations of lipid profile parameters and fasting serum glucose in these patients.

Methods. We carried out this case controlled study in the Department of Biochemistry, College of Medicine, University of Baghdad, and in the Department of Dermatology and Venereology, Baghdad Teaching Hospital, Iraq from January 2010 to November 2010. This study consisted of 40 male Iraqi patients with acne vulgaris aged (18-30 years) who were subdivided into 3 groups according to their severity of acne:[7] 13 patients with mild acne, 13 patients with moderate acne, and 14 patients with severe acne. Scoring of the severity of acne vulgaris was as follows: mild acne in which the count of papules is less than 10, and the count of pustules is less than 20; moderate acne in which the count of papules ranges from 10-30, and the count of pustules ranges from 20-40; and severe acne in which the count of papules is more than 30, and the count of pustules is more than 40. All patients consumed a similar dietary intake. Exclusion criteria included diabetes mellitus, genetic hyperlipidemia, and any other metabolic disease. Patients on hormonal therapy were also excluded. Formal consent was taken from each patient, after full explanation regarding the nature of disease, duration, treatment, prognosis, and the disease complication. Forty healthy males without acne aged 18-30 years were included in this study as a control group. We received ethical approval from the Scientific Committee of the Biochemistry Department, College of Medicine, University of Baghdad, Iraq.

Five milliliters of peripheral venous blood were aspirated from each patient and control into a plain test tube and allowed to clot for 20-30 minutes, followed by centrifugation at 2500 rpm for 10-15 minutes. The separated serum was stored at -20°C until the day of assay. Investigation included serum measurements of GH, IGF-1, total testosterone (T), androstenedione, and DHEAS using an enzyme linked immunosorbent assay (ELISA) technique based on the methods described by Demers.[8] Fasting serum glucose and lipid profile parameters including total cholesterol (Tch), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), and low density lipoprotein-cholesterol (LDL-C) were also measured in patients and control groups using spectrophotometric procedures based on the methods reported by Sacks,[9] and Rifai and Warnick.[10] All material kits for the measured parameters were provided from HUMAN GmbH, Wiesbaden, Germany. The ELISA study was performed using Biotek Instrument, Highland Park, NJ, USA. Spectrophotometric methods were achieved by using Human-Spectrophotometer-Germany Mtd Gmbh, Uffing, Germany.

We used the Statistical Package for Social Sciences (SPSS Inc., Chicago IL, USA) version 15, and Minitab analysis programs (Minitab Inc, version 15, PA, USA) for all statistical studies. We used ANOVA and Student's t-tests to test for statistical significance. Linear regression was utilized to test for correlation between different studied parameters, and the significance of the r-value was assessed by related t-test. *P*-values of less than 0.05 were considered significant.

Results. **Table 1** shows the mean (±standard deviation [±SD]) values of age and body mass index (BMI) of acne patient groups and control males. There was no significant difference in age between the acne patient groups and controls. There was no significant difference in BMI between the moderate acne group and control

males (p=0.321), while the mean BMI values in the mild acne (p=0.001) and severe acne (p<0.015) groups were significantly different to that of controls group. **Table 2** shows the mean (±SD) values of the measured serum hormones for healthy controls and patients with acne vulgaris. The mean value of serum GH of severe acne type was significantly higher than that of moderate acne, mild acne, and healthy controls (p=0.0001 for all). Similarily, the mean value of serum IGF-1 level of severe acne type was significantly increased compared to that of moderate type, mild type, and healthy controls (p=0.0001 for all).

With regard to male sex hormones (**Table 2**), the severe acne group had significantly increased serum levels of androstenedione, DHEAS, and total testosterone compared with those of control males (p=0.0001). The severe acne group also showed a significant elevation of serum levels of these 3 sex hormones compared to those of mild acne (p=0.0001) and moderate acne (p<0.005). **Table 3** illustrates the mean (±SD) values of fasting

Table 1 - Mean (±SD) values of age and body mass index (BMI) of mild-, moderate-, and severe acne groups and control group.

Parameter	Controls (n=40)	Mild acne (n=13)	Moderate acne (n=13)	Severe acne (n=14)
Age (years)	21.65±3.78	21.71±4.21 NS	22.85±3.36 NS	21.85±3.65 NS
BMI (Kg/m^2)	23.02±1.43	21.41±1.0*	22.80±0.62 NS	23.95±0.77*

BMI - body mass index, *T-test - revealed a significant difference between severe acne patients and controls (p<0.015), mild acne patients and controls (p<0.001), NS - No significant difference between moderate acne patient and controls (p=0.321), confidence intervals for differences in means was 0.95%

Table 2 - Mean (±SD) values of GH, IGF-1, androstenedione, DHEAS, and total testosterone in mild-, moderate-, and severe acne groups and controls.

Parameter	Controls (n=40)	Mild acne (n=13)	Moderate acne (n=13)	Severe acne (n=14)
GH (μIU/ml)	57.57±4.36	56.52±1.84	62.11±1.34	72.62±6.08*
IGF-1(ng/ml)	243.23±59.84	335.98±18.15	365.84±16.97	440.76±46.71*
Androstenedione (ng/ml)	2.97±0.99	2.37±0.47	3.04±0.66	3.97±0.53†,‡
DHEAS (μg/ml)	2.90±0.27	2.38±0.46	2.73±0.63	4.05±0.96†,‡
Total testosterone (ng/ml)	5.61±0.94	5.03±0.59	5.65±0.28	6.90±0.85†,‡

GH - growth hormone, IGF-1 - insulin like growth factor-1, DHEAS - dehydroepiandrosterone sulfate, *t-test; for GH and IGF-1 revealed a significant difference between severe acne and controls as well as between severe acne with mild-, and moderate-acne, p<0.0001, †t-test between severe acne and controls as well as severe acne and mild acne, p<0.0001, ‡ t-test between severe acne and moderate acne p<0.005, confidence intervals for differences in means was 0.95%.

Table 3 - Mean (±SD) values of serum fasting glucose, total cholesterol, TG, HDL-C, and LDL-C in mild, moderate, and severe acne groups and controls.

Parameter	Controls (n=40)	Mild acne (n=13)	Moderate acne (n=13)	Severe acne (n=14)
Fasting serum glucose (mg/dl)	5.60±0.68 mmol/l	5.25±0.44 mmol/l	6.03±0.40 mmol/l	6.77±0.37 mmol/l*†
Total cholesterol (mg/dl)	4.42±0.85 mmol/l	3.93±0.38 mmol/l NS	4.45±0.52 mmol/l NS	7.12±2.14 mmol/l*‡
TG (mg/dl)	1.05±0.35 mmol/l	0.85±0.13 mmol/l NS	1.02±0.12 mmol/l NS	1.58±0.47 mmol/l*§
HDL-C (mg/dl)	1.52±0.42 mmol/l	1.68±0.43 mmol/l NS	1.20±0.11 mmol/l	1.09±0.12 mmol/l*
LDL-C (mg/dl)	2.42±0.99 mmol/l	1.86±0.68 mmol/l	2.78±0.56 mmol/l	5.30±2.02 mmol/l *,‡

TG - triglyceride, HDL-C - high density lipoprotein-cholesterol, LDL-C - low desity lipoprotein-cholesterol, *t-test for fasting serum glucose, total cholesterol (Tch), TG, LDL-C, HDL-C significant differences between severe acne type and controls as well as between severe acne and mild acne, p<0.0001, †t-test for serum glucose between severe acne and moderate acne, p<0.001, ‡t-test for Tch and LDL-C between severe and moderate acne groups, p<0.003, §t-test for TG between severe acne and moderate acne type, p<0.004. Confidence intervals for differences in means was 0.95%.

serum glucose, Tch, TG, HDL-C, and LDL-C in acne patient groups and control males. Mean fasting serum glucose was significantly increased in severe acne patients compared with mild acne (p=0.0001), moderate acne (p=0.001), and control males (p=0.0001). The mean values of serum Tch and LDL-C were significantly increased in the severe type compared with those of mild type (p=0.0001), moderate type (p=0.003) and the controls group (p=0.0001). Also, patients with severe acne had a significantly increased mean serum TG concentration compared with that of patients with mild acne (p=0.0001), moderate acne (p=0.004), and healthy controls (p=0.0001). Patients with mild and moderate acne had mean values of serum Tch, LDL-C, and TG concentrations that are statistically comparable to that of controls (p=0.05). Furthermore, severe acne patients had significantly lower mean values of serum HDL-C when compared with that of mild acne patients (p=0.0001) and the control group (p=0.002).

The results of the present study also revealed that in patients with severe acne, there was a significant positive correlation between BMI values and the levels of GH (r=0.703, p=0.0001) and IGF-1 (r=0.452, p=0.0001). Also, in severe acne group, serum levels of GH were significantly positively correlated with the serum concentrations of IGF-1 (r=0.851, p=0.0001), androstenedione (r=0.762, p=0.0001), DHEAS (r=0.734, p=0.0001) and total testosterone (r=0.856, p=0.0001). Similarly, IGF-1 levels of severe acne patients were significantly positively correlated with the levels of androstenedione (r=0.629, p=0.0001), DHEAS (r=0.583, p=0.0001) and total testosterone (r=0.681, p=0.0001). Serum TG levels were significantly positively correlated with total testosterone levels (r=0.908, p=0.0001) and DHEAS serum levels (r=0.700, p=0.016) in the severe acne group.

Discussion. The present study demonstrates significant increased serum levels of GH and IGF-1 in male Iraqi patients with severe acne when compared with healthy controls and less severely affected patients with mild and moderate acne. The IGF-1 is the key hormone mediator in regulation of androgen synthesis from both the adrenal and gonadal glands, amplifying cutaneous androgen activity and enhancing proliferation of sebaceous follicles.[11] Smith et al[12] observed that IGF-1 increases lipid production in sebocytes in vitro via the activation of IGF-1 receptors through multiple pathways. Vora et al[1] noted that an increase in serum IGF-1 levels may lead to increased facial sebum secretion, with a position correlation between serum IGF-1 levels and acne lesion counts in women.

In men, increased levels of androgen hormones may influence acne development for example, DHEAS and androstenedione levels have been correlated with clinical acne lesion counts (total, comedo, and inflammatory). The IGF-1 may stimulate DHEAS production by the adrenal gland, or even within the skin itself. The IGF-1 is a potent stimulator of DHEAS and other androgen hormones by enhancing the gene expression of steroidogenic enzymes that are responsible for converting cholesterol into steroid precursors for the synthesis of androgens. Steroidogenic enzymes are expressed in human sebaceous glands, where they play a role in local androgen production. For example, IGF-1 can induce 5α-reductase in human skin fibroblasts, leading to an increased conversion of testosterone to dihydrotestosterone DHT.[2] Stimulation of steroidogenic enzymes by IGF-1 may be mediated through sterol response element-binding proteins-1 (SREBPs-1), nucleotide sequences found in the promoter regions of several lipogenic genes in the cholesterol and fatty acid biosynthesis pathways. The IGF-1 has been found to increase lipogenesis in an experimental sebocyte model, accompanied by an increase in expression of SREBPs-1 mRNA and protein.[12] This is in keeping with the current study, where significant elevation of the male sex hormones (androstenedione, DHEAS, and total testosterone) in the severe acne group was associated with a positive correlation with levels of IGF-1 and GH.

Stimulation of lipogenesis by IGF-1 may occur via the phosphoinositide 3-kinase (PI3K) pathway.[13] High carbohydrate diets can stimulate insulin- and IGF-1-mediated PI3K/Akt activation, increasing sebaceous lipogenesis, sebocyte, and keratinocyte proliferation, which can aggravate acne.[11] Prolonged consumption of a high carbohydrate diet may cause long-term hyperinsulinemia and insulin resistance, which can simultaneously elevate free IGF-1 while reducing insulin-like growth factor binding protein 3 (IGFBP-3). Free IGF-1 directly stimulates basal keratinocyte proliferation, whereas IGFBP-3 has an inhibitory action, irrespective of its IGF-1 receptor activity.[14,15] A large interventional study[16] confirmed that diets with a low content of carbohydrate foods reduced serum free testosterone and fasting glucose, while improving insulin metabolism and increasing SHBG levels.

The correlation of dietary factors to acne development has been variable. Smith et al[5] suggested that prolonged ingestion of a glycemic rich diet may augment the biological activity of sex hormones and IGF-1 by increasing their free fractions, which may aggravate potential factors involved in acne development.[5] It has also been observed that a low glycemic-load diet may improve insulin sensitivity and acne symptoms.[17]

However, these results were not corroborated by Kaymak et al,[18] who found that glycemic index, insulin, leptin, and IGF-1 levels in acne sufferers were not significantly different from a control group. Recently, Abulnaja et al[19] found a significant elevation in serum levels of testosterone, TG, and LDL-C, with a corresponding significant decrease in serum HDL-C, in obese female Saudi acne sufferers compared with a control group.[19] These observations were corroborated in the present study, in which the severe acne group demonstrated a significant increase in serum levels of Tch, TG, LDL-C, and a significant decrease in serum HDL-C, compared with the mild and moderate acne patients as well as the control group. Furthermore, the current study demonstrates a significant positive correlation between total testosterone and serum glucose and TG levels, in keeping with the hypothesis raised by Abulnaja[19] that any degree of hyperandrogenism increased the risk of developing hyperlipidemia or other metabolic derangements. In the present study, limitations include the difficulties in inclusion of both male and female acne patients.

In conclusion, male Iraqi acne patients, particularly those suffering from the severe type, have a significant elevation of serum levels of GH and IGF-1, which can stimulate androgen hormone synthesis and secretion, leading to the proliferation of sebocytes and keratinocytes resulting in aggravation of acne. Increased androgen stimulation, particularly testosterone and DHEAS, may contribute to hyperlipidemia and other metabolic disturbances. A further contributory factor may be high glycemic load diets and hype rglycemia, which may be involved in the elevation of free IGF-1 and androgen hormones, and hence may aggravate acne. Further studies into the use of a pharmaceutical IGF-1 inhibitor are needed, as a potential new approach for the treatment of acne.

Acknowledgment. *The author wishes to thank Maysaa J. Majeed, PhD student, Biochemistry Department, College of Medicine, Zainab N. Anbar, MSc, College of Pharmacy, Khasan M. Al-Farat, Al-Awasat Hospital, Najef, Rachel Abots, Clincal Oncology City, Hospital Campus Nottingham, Mohammed Mohammed, PhD, College of Medicine, Baghdad, Iraq, and Rachel Abots, Clinical Oncology City, Nottingham, United Kingdom.*

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