Role of hormones and blood lipids in the pathogenesis of acne vulgaris in non-obese, non-hirsute females

Ola Ahmed Bakry, Rania Mohamed Azmy El Shazly[1], Shawky Mahmoud El Farargy, Dalia Kotb

Departments of Dermatology, Andrology and STDs, and [1]Medical Biochemistry, Faculty of Medicine, Menoufiya University, Menoufiya, Egypt

ABSTRACT

Context: Acne vulgaris (AV) is a common disease affecting all ages and ethnic groups. Androgens, skin and serum lipids, inflammatory signaling and regulatory neuropeptides seem to be involved in this multi-factorial process. **Aim:** The aim of this work was to determine hormonal levels and lipid profile in non-obese, non-hirsute females with AV. **Subjects and Methods:** A total of 60 non-obese, non-hirsute female cases with different grades of AV and 60 age- and gender-matched healthy volunteers were included. Measurement of serum total and free testosterone, sex hormone binding globulin (SHBG), estradiol and progesterone and blood lipids was done during the luteal phase of the menstrual cycle. **Results:** Total testosterone, free testosterone (FT) and progesterone levels were significantly higher ($P < 0.001$ for all) while estradiol levels ($P < 0.001$) and SHBG ($P < 0.01$) were significantly lower in cases than controls. Total cholesterol and low density lipoprotein cholesterol (LDL-C) levels were significantly higher ($P < 0.001$ for both) while high density lipoprotein cholesterol (HDL-C) and apolipoprotein A-1 (ApoA-1) levels were significantly lower ($P < 0.001$ for both) in cases than controls. Higher values of FT ($P = 0.03$) and SHBG ($P = 0.02$) and lower values of estradiol ($P = 0.04$) levels were significantly in favor of severe acne. Higher values of cholesterol ($P < 0.001$) and LDL-C ($P = 0.03$) and lower values of HDL-C ($P = 0.01$) and ApoA-1 ($P = 0.02$) levels were significantly associated with severe acne. **Conclusion:** Changes in hormone levels and lipid profile in non-obese and non-hirsute females with AV should be considered in disease pathogenesis and in treatment prescription of these patients.

Key words: Acne vulgaris, female, hormones, lipid profile

Access this article online

Website: www.idoj.in

DOI: 10.4103/2229-5178.144506

Quick Response Code:

Address for correspondence:
Dr. Ola Ahmed Bakry, Department of Dermatology, Andrology and STDs, Menoufiya University Hospital, Shibeen El Koom, 32817 Menoufiya Governorate, Egypt.
E-mail: olabakry8@gmail.com

INTRODUCTION

Acne vulgaris (AV) is a chronic inflammatory disease of the pilosebaceous unit.[1] The pathogenesis of acne, is currently attributed to multiple factors such as increased sebum production, alteration of the quality of sebum lipids, androgen activity, interaction with neuropeptides, exhibition of pro- and anti-inflammatory properties, follicular hyperkeratinization and proliferation of *Propionibacterium acnes*.[2]

Both clinical observations and experimental evidences confirmed the importance of hormones in the pathophysiology of acne. Hormones are well-known for their effects on sebum excretion. It has also been suggested that hormones play a role in follicular hyperkeratinization seen in acne follicles.[3]

Several clinical studies pointed to a major role of androgens in the pathogenesis of acne.[4] Androgens play an essential role in increasing the size of the sebaceous glands and stimulating sebum production[4] as well as in stimulating keratinocyte proliferation in the ductus seboglandularis and the acro-infundibulum.[5] Acne begins to develop at the time of adrenarche when the adrenal gland starts to produce large quantities of dehydroepiandrosterone sulfate, a precursor for testosterone.[6] Conditions of hyperandrogenism are associated with increased sebum production and the development of severe acne.[7] The relevance of hyperandrogenism in male patients is often not considered, whereas in women or prepubertal children suffering from acne, disorders of androgen metabolism are readily suspected.[8]

Acne-prone skin exhibits higher androgen receptor density[9] and higher 5α-reductase

activity[10] than uninvolved skin. In addition, anti-androgens reduce the synthesis of sebaceous lipids and improve acne,[11] whereas androgen-insensitive subjects who lack functional androgen receptors do not produce sebum and do not develop acne.[12]

The role of estrogens in the development of acne remains unclear. Estradiol, the major active estrogen, is produced from testosterone by aromatase. It is hypothesized that, estrogens may impact sebum secretion by several mechanisms.[13]

The effect of progesterone on sebaceous glands has been a matter of dispute. The fluctuation of sebum production in women during the menstrual cycle has been blamed on progesterone. Progesterone is a competitive inhibitor of 5α-reductase and might be expected to reduce sebaceous gland activity. However, in humans, its sebosuppressive effect is minimal.[14]

Human sebum is comprised mainly of triglycerides (TGs) (40-60%), wax esters (19-26%) and squalene (11-15%), with some cholesterol and cholesterol esters.[15] Increased sebum production and alteration of the quality of sebum lipids play a major role in acne pathogenesis.[16]

Whether androgens are elevated in adult females with acne or not is a matter of debate and controversy. Some studies reported hyperandrogemenia in these cases[17-20] while others showed no evidence of the same and the disease is mediated by end-organ hyper-response to normal circulating androgens.[21-22] Serum levels of estradiol and progesterone were not extensively studied in AV cases. In addition, the relationship between blood lipids such as cholesterol, TGs, plasma lipoprotein, apolipoprotein and acne is not widely reported. Therefore, the aim of this study was to evaluate hormone levels and lipid profile in non-obese, non-hirsute female patients with AV.

SUBJECTS AND METHODS

Ethics

A written consent form approved by The Committee of Human Rights in Research of Menoufiya University was obtained from every participant. This was also in accordance with the Helsinki declaration of 1975 (revised in 2000).

Studied population

This study is a case-control one that was conducted on two groups.

Group A

A total of 60 female patients with AV who were collected from Dermatology outpatient clinic, Menoufiya University Hospital, during the period from June 2011 to February 2012. Patients included 20 cases with mild acne (Group A 1), 20 cases with moderate acne (Group A 2) and 20 cases with severe acne (Group A 3). Grading of AV was done according to global acne grading system [Table 1].[23]

Group B

Sixty age- and gender-matched healthy volunteers as a control group.

Exclusion criteria

Patients with one or more of the following was excluded:

- Obesity, hirsutism and/or irregular cycles
- Pregnancy and lactation
- Oral contraceptive pills intake or any form of hormonal therapy
- Smoking
- History of cardiovascular disease
- Known history of lipid metabolic disorder or intake of drugs that affect lipid metabolism.

Laboratory investigations

Lipid profile including serum total cholesterol, TGs, high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) were measured in blood samples drawn after a 12-h fast and plasma was separated immediately by refrigerated centrifugation at 2500-3000 rpm for a period of 10 min. Samples were processed immediately or in the 1st week following preservation at −20°C. Serum apolipoprotein A-1 (ApoA-1) was determined using BINDA RID™ Kit-United Kingdom. Hormonal profile including serum estradiol (E2), total testosterone (TT) and progesterone were estimated by Immulite 2000. Sex hormone binding globulin (SHBG) was measured using Immuno-Biological Laboratories, America enzyme-linked immunosorbent assay (ELISA) kit and free testosterone (FT) was measured by ELISA Gen Way Biotech, San Diego. All samples were taken during the luteal phase of the menstrual cycle.

Reference ranges of the measured parameters were collected [Table 2].

Table 1: The global acne grading system[23]

Location	Factor
Forehead	2
Left cheek	2
Chin	1
Right cheek	2
Nose	1
Chest and upper back	3

Calculation: Each type of lesion is given a value depending on severity: no lesions=0, comedones=1, papules=2, pustules=3 and nodules=4. The score for each area (local score) is calculated using the formula: Local score=Factor×grade (0-4). The global score is the sum of local scores and acne severity was graded using the global score. A score of 1-18 is considered mild, 19-30, moderate; 31-38, severe; and>39, very severe

Table 2: Reference ranges of measured hormones and lipids

Hormone (luteal phase)	Lower limit	Upper limit
TT (ng/dL)	6	80-85
FT (pmol/L)	20.8	107.5
SHBG (ng/ml)	5	32.8
E2 (pg/mL)	50	241
Prog (ng/dL)	100	500
Lipid (mg/dL)	**Normal**	**Abnormal**
Chol	<200	>239
TGs	<150	>200
HDL-C	>59	<40
LDL-C	<100	160-189
ApoA-1	5.0	<1.5

TT: Total testosterone, FT: Free testosterone, SHBG: Sex hormone binding globulin, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, E2: Estradiol, Prog: Progesterone, Chol: Cholesterol, TGs: Triglycerides, ApoA-1: Apolipoprotein A-1

Statistical analysis

Results were collected, tabulated and statistically analyzed by statistical package SPSS version 11 (Chicago, USA). Data were statistically described in terms of range, mean ± standard deviation (±SD), frequencies (number of cases) and relative frequencies (percentages) when appropriate. Student's *t*-test was used for comparison between two groups having quantitative variables. ANOVA (*F*-test) was used for comparison between three or more groups having quantitative variables. P <0.05 was considered to be statistically significant.

RESULTS

Studied population

Clinical data of studied cases is summarized in Table 3. Ages of the control group ranged from 13 to 28 years with a mean ± SD age of 20.35 ± 4.04 years. Their body weight ranged from 42 to 75 kg with a mean ± SD value of 52.23 ± 15.98 kg. Their body mass index ranged from 19.9 to 24.1 kg/m^2 with a mean ± SD value of 26.4 ± 6.2 kg/m^2.

LABORATORY RESULTS

TT was elevated in 42 acne patients (70%) and 2 control subjects with statistically significant difference in its mean value between patients and controls (P < 0.001) [Table 4]. These cases showed also decreased SHBG and elevated FT.

Levels of SHBG and FT were normal in all studied control subjects. There was a statistically significant difference in mean level of FT and SHBG between cases and controls (P < 0.001, P < 0.01 respectively) [Table 4].

Table 3: Clinical data of studied cases

Variable	No=60
Age (years)	
Range	15-27
Mean±SD	19.01±3.32
Body weight (kg)	
Range	45-78
Mean±SD	56.4±17.8
BMI (kg/m^2)	
Range	20.5-23.4
Mean±SD	25.3±5.9
Disease duration (months)	
Range	6-18
Mean±SD	2.16±2.52
	No (%)
Site	
Mid face (forehead and chin)	15 (25)
Cheeks	12 (20)
Mid face and cheeks	23 (38.3)
Face and back	10 (16.7)
Predominant lesions	
Comedones	13 (21.6)
Papules and pustules	27 (45)
Nodules	20 (33.4)

SD: Standard deviation, BMI: Body mass index

Table 4: Comparison of hormone levels and lipid profile in cases and healthy controls (values are expressed in mean±SD)

Variable	*X*±SD (*N*=60)		*T* test	*P* value
	Group A	Group B		
TT (ng/dL)	69.80±7.45	43.34±3.58	15.248	<0.001*
FT (pmol/L)	22.89±5.25	13.47±2.58	11.634	<0.001*
SHBG (ng/dL)	74.93±3.15	93.66±18.33	9.56	<0.01*
E2 (pg/mL)	147.83±9.14	173.08±5.55	11.623	<0.001*
Prog (ng/dL)	12.57±1.52	8.14±0.77	12.425	<0.001*
Chol (mg/dL)	183.73±8.21	167.25±4.70	8.502	<0.001*
TGs (mg/dL)	87.51±4.15	86.90±2.29	0.603	0.07
HDL-C (mg/dL)	36.06±3.18	40.80±1.96	6.241	<0.001*
LDL-C (mg/dL)	129.91±11.05	109.35±5.35	7.988	<0.001*
ApoA-1 (mg/dL)	132.22±5.71	161.03±5.51	19.335	<0.001*

TT: Total testosterone, FT: Free testosterone, SHBG: Sex Hormone Binding Globulin, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, E2: Estradiol, Prog: Progesterone, Chol: Cholesterol, TGs: Triglycerides, SD: Standard deviation, ApoA-1: Apolipoprotein A-1. *Significant

Serum E2 was low in 45 patients (75%) and three control subjects. Its mean value was significantly lower in cases than controls (P < 0.001). Serum progesterone was elevated in 40 patients (66.6%) and normal in all control subjects with statistically significant difference between both groups (P < 0.001) [Table 4].

Plasma cholesterol was high in 20 patients (33.3%) and high normal in 30 patients (50%), HDL-C was low in 43 patients (71.6%) and LDL-C was high in 15 patients (25%) and high normal in 20 patients (33.3%). ApoA-1 was low in 48 patients (80%). TGs were high in 15 (25%) patients. Total cholesterol, HDL-C, LDL-C, ApoA-1 and TGs were normal in all studied control subjects.

Statistically significant difference in the mean values of plasma cholesterol, HDL-C, LDL-C and ApoA-1 was found between cases and controls ($P < 0.001$ for all). TGs levels were elevated in patients when compared with controls, but this elevation was not statistically significant ($P = 0.07$) [Table 4].

Relationship between measured parameters and acne severity in studied cases

Regarding disease severity, there was no statistically significant difference in the mean value of TT among different patients' subgroups ($P > 0.05$). There was a statistically significant difference in FT ($P = 0.03$) and SHBG levels ($P = 0.02$) between the three patient subgroups, with higher levels favouring severe disease [Table 5].

Serum E2 levels decreased with increased severity and the difference was statistically significant among the different acne subgroups ($P = 0.04$). Differences in progesterone levels among acne subgroups were not statistically significant ($P > 0.05$) [Table 5].

Mean values of cholesterol ($P < 0.001$) and LDL-C ($P = 0.03$) were significantly higher in severe disease while mean values of HDL-C ($P = 0.01$) and ApoA-1 ($P = 0.02$) were significantly lower in severe acne. Levels of TGs were not significantly different among the acne subgroups ($P > 0.05$) [Table 5].

Table 5: Hormone levels and lipid profile in non-hirsute, non-obese females with different grades of acne vulgaris (values are expressed in mean±SD)

Variable	X±SD (*N*=20)			ANOVA test	*P* value
	A1	A2	A3		
TT (ng/dL)	63.35±5.25	71.25±6.36	74.80±5.67	1.639	0.49
FT (pmol/L)	19.77±1.6	21.65±2.25	26.35±8.3	3.357	0.03*
SHBG (ng/dL)	69.11±4.38	73.23±1.49	78.2±3.23	2.37	0.02*
E2 (pg/mL)	155.19±8.72	147.36±6.43	140.94±5.90	6.325	0.04*
Prog (ng/dL)	12.56±1.35	12.26±1.28	12.89±1.87	0.838	0.93
Chol (mg/dL)	178.7±6.34	179.3±4.81	193.1±2.69	10.253	<0.001*
TGs (mg/dL)	88.30±3.94	87.25±4.37	87.0±4.21	0.856	0.72
HDL-C (mg/dL)	38.10±1.74	37.95±1.57	32.15±1.34	2.325	0.01*
LDL-C (mg/dL)	122.25±6.72	123.95±5.42	143.55±3.13	6.325	0.03*
ApoA-1 (mg/dL)	135.21±3.58	134.85±3.43	126.60±5.15	3.587	0.02*

TT: Total testosterone, FT: Free testosterone, SHBG: Sex hormone binding globulin, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, E2: Estradiol, Prog: Progesterone, Chol: Cholesterol, TGs: Triglycerides, SD: Standard deviation, ApoA-1: Apolipoprotein A-1, ANOVA: Analysis of variance. *Significant

There was a significant positive correlation between TT and total cholesterol ($r = 0.3$, $P = 0.003$) and between TT and LDL-C ($r = 0.4$, $P = 0.001$). There was a significant negative correlation between TT and HDL-C ($r = -0.4$, $P = 0.001$) [Figure 1].

There was a significant positive correlation between E2 and HDL-C ($r = 0.6$, $P = 0.001$) and between E2 and ApoA-1 ($r = 0.3$, $P = 0.001$). There was a significant negative correlation between E2 and total cholesterol ($r = -0.5$, $P = 0.001$) and between E2 and LDL-C ($r = -0.5$, $P = 0.001$) [Figure 2].

DISCUSSION

AV is a chronic inflammatory, exclusively human disease, mostly affecting the pilosebaceous units located on the face, chest, shoulders and back. Its pathogenesis is multifactorial. Abnormal follicular differentiation, increased cornification, enhanced sebaceous gland activity, hyperseborrhea, bacterial hypercolonization, as well as inflammation and immunological host reaction are the major contributors.[2] Other factors such as diet, exposure to sun, poor hygiene, stress and genetics are believed to cause or worsen acne symptoms.[1,3]

Androgen receptors have been localized to the basal layer of the sebaceous gland and the outer root sheath keratinocytes of the hair follicle. The major androgens that interact with the androgen receptors are testosterone and dihydrotestosterone.[24]

The sebaceous gland has been shown to express all the necessary enzymes for the biosynthesis of testosterone de novo from cholesterol, from 5α-reduced substances ingested in dairy products,[25] or in a shortcut from circulating dehydroepiandrosterone.[26]

Several early experiments have shown that androgens stimulate sebum secretion. Prepubertal boys given injections of testosterone were shown to have increased sebum production and increase in the size of their sebaceous glands. In addition, systemic administration of testosterone were shown to exert similar effects.[3] It is not known if androgens act directly on the epithelial cells within the pilosebaceous unit, indirectly by regulating the production of growth factors by dermal fibroblasts, or by both mechanisms.[3]

Although dihydrotestosterone is approximately 5-10 times more potent than testosterone in its interaction with the androgen receptors, the role for testosterone in mediating sebum production can not be excluded.[27]

In the current study, TT level was elevated in 70% of patients with statistically significant difference in hormone levels between patients and controls. Elevated TT level has

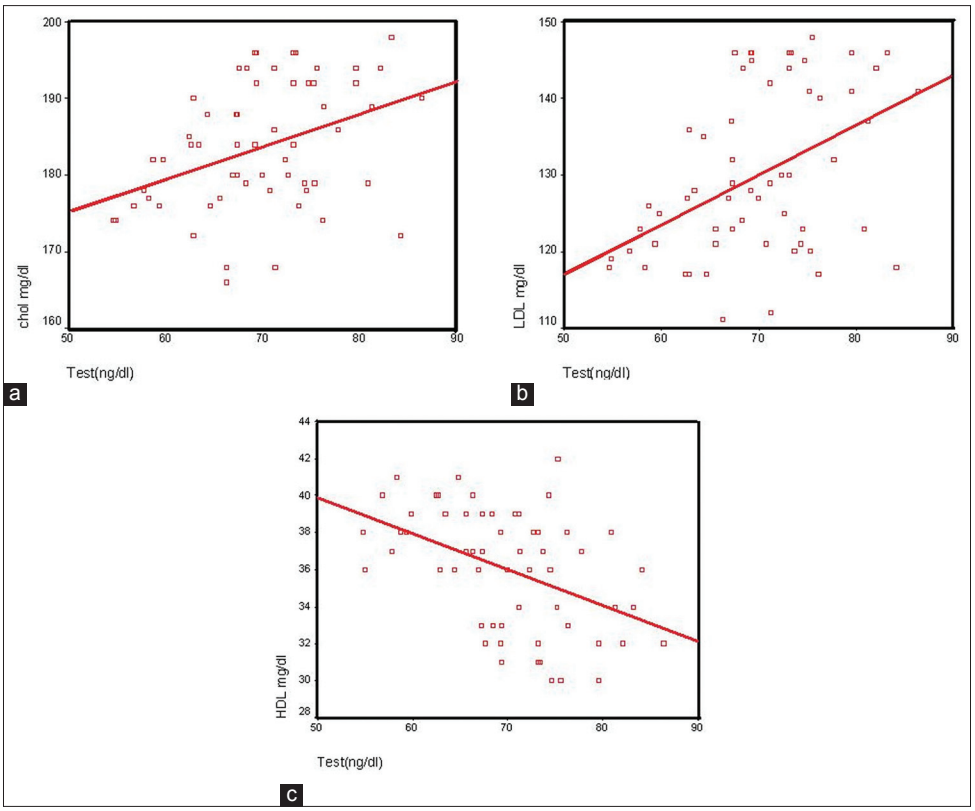

Figure 1: (a) A significant positive correlation between total testosterone (TT) and total cholesterol (r = 0.3, P = 0.003) and (b) between TT and low density lipoprotein cholesterol (r = 0.4, P = 0.001). (c) A significant negative correlation between TT and high density lipoprotein cholesterol (r = −0.4, P = 0.001)

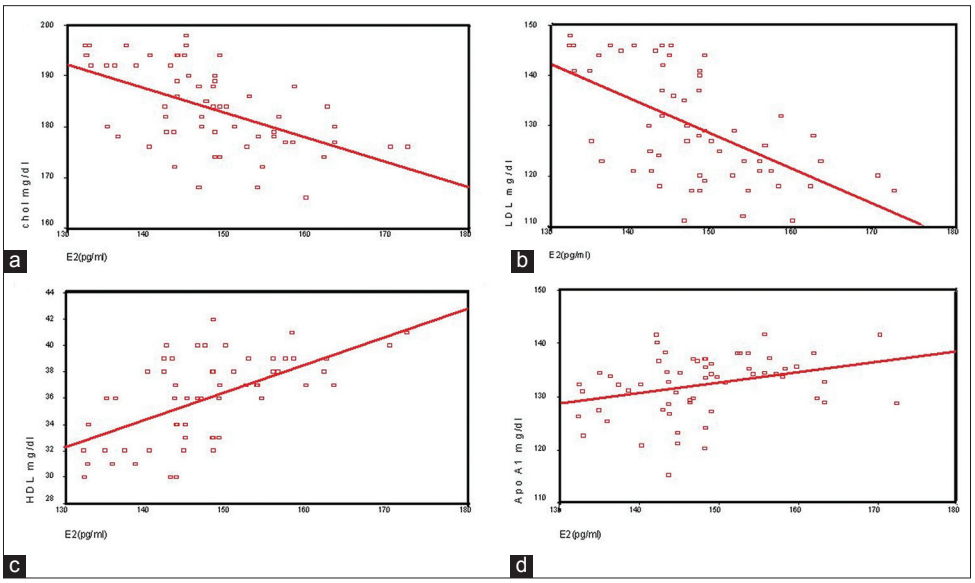

Figure 2: (a) A significant positive correlation between estradiol (E2) and high density lipoprotein cholesterol (r = 0.6, P = 0.001) and (b) between E2 and apolipoprotein A-1 (r = 0.3, P = 0.001). (c) A significant negative correlation between E2 and total cholesterol (r = −0.5, P = 0.001) and (d) between E2 and low density lipoprotein cholesterol (r = −0.5, P = 0.001)

been reported in 30% to 90% of females with acne although some of these studies have mixed hirsute and non-hirsute patients.[17-20]

Contrary to our results, some authors detected TT to be within normal limits in the majority of non-hirsute females with acne. Other investigators did find "high normal" TT levels.[21] For this reason, it has been hypothesized that androgens may play only a permissive role in priming or initiating acne development. There may be increased local production of androgens within the sebaceous glands of patients with acne. Alternatively, the sebaceous glands from patients with acne may be more

sensitive to the effects of androgens. Therefore, it is unclear as to whether acne is mediated by serum androgens, locally produced androgens or a combination of both.[22]

In the present study, there was no significant association between TT and the severity of acne. Similar results were reported in previous similar studies.[17,19]

In the current work, FT was increased and SHBG was decreased in 70% of cases with significant differences between cases and controls. Similar results were reported by Slayden *et al*.[28] in 63% of studied acne patients. The differences among acne subgroups regarding levels of FT and SHBG were statistically significant. Similar results were reported previously.[18,19]

The role of estrogens in the development of AV is not very clear. Estrogens may directly oppose the effects of androgens within the sebaceous gland, inhibit the production of androgens by gonadal tissue through a negative feedback loop on pituitary gonadotropin release, or regulate genes that negatively influence sebaceous gland growth or lipid production.[3]

In our study, E2 was decreased in 75% of patients with statistically significant difference in hormone levels between patients and controls. Similar result was detected by Arora *et al*.[29] Going with that finding, Russell[30] suggested that exogenous estrogens have a beneficial effect on acne. This is also supported by the fact that, acne is most common at puberty due to the low level of estrogens during the first few menstrual cycles.[12] The significant association between low E2 and acne severity, demonstrated in the current work, was not reported in previous similar studies.

The demonstrated results of significantly increased androgens and decreased estradiol in studied cases may provide evidence about the value of hormonal therapy in the management of these cases. Hormonal treatment may be beneficial even in the absence of signs of androgen excess.

The role of progesterone in AV is not well-documented. Progesterone administration can produce acne and when given to elderly women, it increases sebum production, but no such effect could be demonstrated in young women.[14]

In the present study, progesterone was elevated in 66.6% of patients with statistically significant difference in hormone levels between patients and controls. This was similar to what was previously reported by Marynick *et al.* in male patients with acne.[31] The possible mechanism by which progesterone aggravates acne lesions, is by increasing sebum secretion and stimulating the proliferation of keratinocytes.[32]

In the present work, no significant association was found between serum progesterone levels and the severity of acne. This finding is at variance with a previous study in which serum progesterone levels were found to be higher in females with severe AV, ascribed to an increase in serum cholesterol, the immediate precursor of progesterone.[29] This is an area that merits further research on larger number of cases with different grades of acne.

The effect of exercise on the female endocrine function was previously studied with varying results. TT concentrations remained unchanged[33] or elevated[34] after acute resistance exercise. FT has been shown to be elevated by 25% in young women after acute resistance exercise.[35] The effect of chronic exercise on resting testosterone concentrations showed elevations[36] no differences[37] or reductions.[38] Experimental studies reported that, resistance training elicits a significant increase in androgen binding capacity at the receptor level.[39]

Acute elevations of SHBG have been reported in some studies[40] whereas reductions[41] and no changes in its concentrations have been reported in others.[37]

Exercise was reported also to lower estrogen and progesterone levels in women.[42] Therefore, whether non-obese, non-hirsute females with acne will benefit from exercise or not remains questionable. Clinical trials testing the effect of exercise on acne patients are recommended for firmer conclusion.

Regarding lipid profile, the current study showed that both cholesterol and LDL-C were significantly higher in patients than controls. Similar results were reported by Abulnaja[43] in obese acne females. Arora *et al*.,[29] in their study, have reported similar findings, but the studied populations included obese and non-obese cases. Contrarily, Akawi *et al.*,[44] reported that total cholesterol levels were not significantly elevated in non-obese acne patients compared with healthy controls. Vergani *et al*.[45] did not find a significant difference in LDL-C levels between acne patients and controls.

Total cholesterol levels may affect the development of AV because both adrenal and gonadal androgens are synthesized from cholesterol derived from the plasma.[29]

In the present work, HDL-C and ApoA-1 were significantly lower in patients than controls. Similar results were obtained in previous studies.[29-31]

Cholesterol ester transfer protein could play a role in increased LDL-C and decreased HDL-C levels. It transfers the esterified cholesterol from HDL to VLDL and LDL and replaces it with TGs. LDL, so altered, is a potential substrate for hepatic lipase. The enzyme plays a major role in lipoprotein metabolism as a lipolytic enzyme and hydrolyzes TGs and phospholipids in chylomicron remnants, IDL and HDL. It has been reported in literature that, hepatic lipase activity is increased by androgens

and decreased by estrogens. In the present study, patients of AV had increased androgen levels and decreased estrogen levels, which increases hepatic lipase activity. If the activity of the enzyme is high enough, lipolysis will generate smaller, denser particles. This subfraction binds less well to the LDL receptor in comparison with its larger counterparts, which has the consequence of prolonging its lifetime in the circulation. This might be the reason for increased LDL-C levels in patients' group.[46]

In the present study, levels of cholesterol and LDL-C increased with increased acne severity. This finding has not been discussed before. Levels of HDL-C and ApoA-1 decreased, with increased acne severity, similar to results obtained by Vergani e*t al*.[45]

The current work showed significant positive correlation between TT and total cholesterol levels and LDL-C levels. It was previously noted that, testosterone supplementation in men with hypogonadotrophic hypogonadism was shown to increase levels of total cholesterol and LDL-C.[45]

In the present study, HDL-C levels were found to be negatively correlated to TT; this adds to the same initial observation by Dhananjay e*t al*.[46]

In the present study, significant positive correlation between E2 and HDL-C and ApoA-1 and significant negative correlation between the hormone and total cholesterol and LDL-C were found. In the previous studies, estrogens have been shown to be associated with a favorable lipid profile.[29] Jerzy *et al*.[47] reported that estrogen increases HDL-C levels and decreases total cholesterol and LDL-C levels.

The demonstrated pattern of abnormal lipid profile in studied cases may underscore the value of dietary intervention in AV management. Previous studies showed the beneficial effect of nutritional alteration on AV outcome. Dietary intervention in acne should decrease total energy and fat intake predominantly provided by increased animal and dairy proteins. This can be achieved by higher consumption of vegetables and fruit and reduction of animal-derived food.[48] The dermatologist should assume the responsibility for dietary education and intervention with his acne patients. Hippocrates of Kós rightly said about 2400 years ago: "your diet should be your medicine and your medicine should be your diet."

In summary, changes in hormone levels and lipid profile should be considered in disease pathogenesis and in treatment prescription to female patients with moderate to severe AV even if they are non-obese and with no apparent signs of androgen excess. These observations should also be considered in all cases that are resistant to therapy. The value of dietary education and intervention is well-documented, but the value of exercise on management of these cases needs to be evaluated.

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Cite this article as: Bakry OA, El Shazly RM, El Farargy SM, Kotb D. Role of hormones and blood lipids in the pathogenesis of acne vulgaris in non-obese, non-hirsute females. Indian Dermatol Online J 2014;5:9-16.

Source of Support: Nil, **Conflict of Interest:** None declared.