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Serum Levels of Fetuin- A in Patients with Acne Vulgaris

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Abstract
Background: *Acne vulgaris is a common cutaneous disorder involving dysfunction of the pilo-sebaceous unit. Acne vulgaris affects up to 80% of Americans at some point in their lives. Though prevalent most frequently in adolescents, it may persist well into adulthood in some individuals*
Aim of Work: *The aim of this study is to evaluate the serum levels of Fetuin-A in patients with acne vulgaris and to assess it relation to the clinical severity of disease.*
Methods: *This case-control study was conducted in Outpatient Clinic of Dermatology and Andrology, Department of Benha University. The study included 80 participants; 60 patients suffering from acne vulgaris, in addition to 20 apparently healthy, age and sex matched individuals as control group, serum level of fetuin A was be assessed in all participants,*
Results: *the result of the study revealed there was negative non-significant correlation between Serum Fetuin A and sex, course of disease, Stress, Sun Exposure, Relation to Smoking ,Post Acne Scar , the age and GAGS score,*
Conclusion: *Serum fetuin-A levels are detected higher in patients with acne. Also, there are no statistically significant relation between it and gender, age, Duration of disease, course of disease and in terms of stress, Sun Exposure, Smoking, Post Acne Scar, Family History, Diet & PIH.*
Keywords: *Acne vulgaris, fetuin-A, case-control, Outpatient.*

Introduction

Acne vulgaris is a common cutaneous disorder involving dysfunction of the pilosebaceous unit. Acne vulgaris affects up to 80% of Americans at some point in their lives. Though prevalent most frequently in adolescents, it may persist well into adulthood in some individuals(1).

The traditional paradigm of acne has generally consisted of four components, often presented in a sequential fashion. Androgen excess leads to increased sebum production, along with follicular hyperkeratinization which results in plugging of the follicle. This allows the bacterium Propionibacterium acnes to grow within the follicle, eventually culminating in an inflammatory cascade and clinically evident disease(2).

Serum Fetuin-A (also called α-2 heremanschmid glycoprotein) is a multifunctional glycoprotein predominantly secreted by the liver and mainly involved in promoting insulin resistance(3).

Accumulating experimental and epidemiological studies reported that it was associated with a spectrum of cardiometabolic disorders, such as

metabolic syndrome , nonalcoholic fatty liver disease , type 2 diabetes, and cardiovascular diseases (CVD)[4].

It has been currently recognized as one of the most significant hepatokines regulating human metabolism[5].

Fetuin-A protein is Alpha 2-Heremans Schmid glycoprotein (AHSG) of 62 kilo Dalton (KD). It belongs to the class of cysteine proteinase inhibitors, which are responsible for bone resorption[6].

It acts as a negative acute phase reactant synthesized by the liver cells, it is responsible for preventing calcium and phosphate precipitation in the blood by increasing their solubility and inhibiting calcium crystal growth[7].

Fetuin-A is participating in macrophage deactivation by being as anti-inflammatory mediators[8].

Patients and Methods

Subjects: This case-control study was conducted in Outpatient Clinic of Dermatology and Andrology, Department of Benha University. The study included 80 participants; 60 patients suffering from acne vulgaris, in addition to 20 apparently healthy, age and sex matched individuals as control group. A written informed consents were obtained from all participants. The study was approved by the Local Ethics Committee on Research involving human subjects of Benha Faculty of Medicine.

Studied Groups

A. Patients Group: included sixty patients with different presentations of acne vulgaris classified according to the global acne grading system (GAGS) into three groups:

- **a. Group A:** 20 patients with mild acne vulgaris**.**
- **b. Group B*:*** 20 patients with moderate acne vulgaris.
- **c. Group C:** 20 patients with severe acne vulgaris.

B. Control Subjects Group: included twenty apparently healthy subjects of matched age and sex served as a control group.

Exclusion Criteria: Subjects with any of the following conditions were excluded from the study:

- Patients with infectious, inflammatory or autoimmune cutaneous or systemic diseases.
- Malignancy.
- Pregnancy and lactation.
- Patients with liver or kidney disease.

Inclusion Criteria

- Patients with acne vulgaris.
- Age between 12 and 25 years ago.

I. **Methods:** Patients under study were subjected to the following:

1. **Full History Taking Including**
   - Personal history, course and duration of acne vulgaris in the patients and various demographic and lifestyle factors were recorded, including age, gender, any relation to stress, sun exposure, smoking and diet.
   - Family history of acne vulgaris: family histories were obtained from all patients.
2. **General Examination:** Complete general examination was performed for all patients with emphasis on the Body Mass Index (BMI). The BMI is defined as the body mass (weight) divided by the square of the body height and is universally expressed in units of kg/m2, resulting from weight in kilograms and height in meters. BMI ranges are underweight: under 18.5, normal weight: 18.5 to 25, overweight: 25 to 30, obese: over 30
3. **Dermatological Clinical Examination:** The patients were examined carefully to detect acne lesions and to determine their types, distribution and grading. The grading of acne lesions was assessed according to the global acne grading system (GAGS)[9].

Results

Sociodemographic Data

There was insignificant difference between patients and controls regarding age, BMI and sex, the mean age of cases was18.833±2.924 versus 19.350± 3.438in control, with BMI 24.637± 4.005 in cases versus 25.570±4.560 in control group. The majority was female 90 % & 80% in cases and control group respectively. There was insignificant difference between patients and controls regarding age, BMI and sex (p= 0.515, 0.386 and 0.242 respectively) (Table 2).

Table 1: Sociodemographic data of the studied groups

		Groups						T-Test or Chi-square	
		Patients			Controls			T	P-value
Age	Range	13	-	24	15	-	25	-0.655	0.515
	Mean ±SD	18.833	±	2.924	19.350	±	3.438		
BMI	Range	16.33	-	34.51	18.02	-	33.59	-0.871	0.386
	Mean ±SD	24.637	±	4.005	25.570	±	4.560		
Sex	Male	6		10.00	4		20.00	1.371	0.242
	Female	54		90.00	16		80.00		

BMI: body mass index, SD: standard deviation, P<0.05 is significant.

Clinical Data

In current study: 55% of cases had positive family history, 66.67% with positive relation to stress, 93.33% had positive relation to sun exposure, 13.33% with positive relation to smoking and 86.67 with positive relation to diet.

Table 2: History findings in the patients group

History Parameters		N	%
Course	Progressive	15	25.00
	Stationary	45	75.00
Positive Family History		33	55.00
Positive Relation To Stress		40	66.67
Positive Relation To Sun Exposure		56	93.33
Positive Relation To Smoking		8	13.33
Positive Relation To Diet		52	86.67

Table 3: Clinical findings in the patients group

Clinical aspects	N	%
GAGS. (Mean± SD)	21.950± 8.903	
Positive Post Acne Scar	23	38.33
Positive PIH	56	93.33

GAGs: global acne grading system, SD: standard deviation,
PIH: post inflammatory hyperpigmentation.

The mean value of global acne grading system (GAGS) was 21.950± 8.903.

In current study, 93.33% of cases had post inflammatory hyperpigmentation and 38.33 % had Positive Post Acne Scar.

Laboratory Investigations

The mean serum level of fetuin A in patients group (164.485±91.432) was significantly higher than that in the control group (109.381±40.127) as p=0.011.

Fig 1: Serum levels of fetuin A in the studied groups

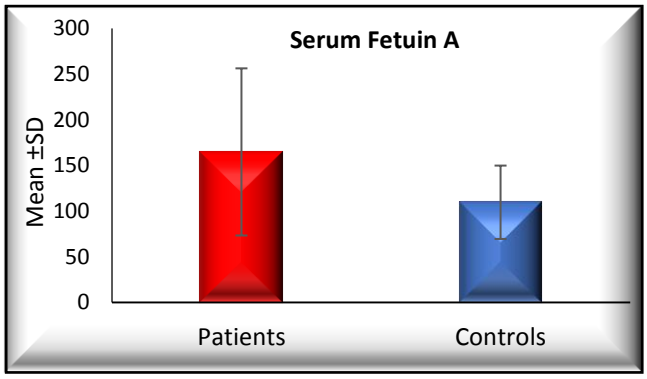

Table 4: Relation between serum fetuin A and studied variables

		Serum Fetuin A				T-Test	
		N	Mean	±	SD	T	P-value
Sex	Male	6	144.658	±	34.443	-0.557	0.580
	Female	54	166.688	±	95.629		
Course	Progressive	15	157.391	±	41.014	-0.344	0.732
	Stationary	45	166.849	±	103.207		
Family History	Positive	33	176.141	±	114.650	1.094	0.279
	Negative	27	150.238	±	49.086		
Relation To Stress	Positive	40	151.359	±	45.052	-1.593	0.117
	Negative	20	190.737	±	143.894		
Relation To Sun Exposure	Positive	56	160.717	±	93.263	-1.199	0.235
	Negative	4	217.238	±	31.209		
Relation To Smoking	Positive	8	140.684	±	42.012	-0.788	0.434
	Negative	52	168.146	±	96.574		
Relation To Diet	Positive	52	168.447	±	95.091	0.854	0.397
	Negative	8	138.729	±	60.894		
Post Acne Scar	Positive	23	146.359	±	38.249	-1.216	0.229
	Negative	37	175.752	±	111.653		
PIH	Positive	56	165.217	±	93.421	0.230	0.819
	Negative	4	154.235	±	65.240		

PIH: post inflammatory hyperpigmentation, P<0.05 is significant, SD: standard deviation, Fetuin A.

As shown in this table, there was negative non-significant correlation between Serum Fetuin A and sex, course of disease, Stress, Sun Exposure, Relation to Smoking, Post Acne Scar, the age and GAGS score

On the other hand, there was positive non-significant correlation between Serum Fetuin A and Family History (r=1.094&p=0.279), Relation to Diet (r=0.854 &p=0.397), PIH (r= 0.230 &p=0.819), BMI (r=0.123 &p=0.351) and Duration of acne (r=0.159 &p=0.224), and shown in the below graph.

Table 5: Correlation between serum fetuin A and studied variables.

	Serum Fetuin A	
	r	P-value
Age	-0.024	0.857
BMI	0.123	0.351
GAGS.	-0.158	0.228

BMI: body mass index, , P<0.05 is significant,
GAGS: global acne grading system.

Table (6)

ROC curve between Patients and Controls						
	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
Serum Fetuin A	>138.57	68.33	80.00	91.1	45.7	77.2%

ROC: receiver operating characteristic, PPV: positive predictive value,
NPV: negative predictive value.

In current study, at cut off >138.57 ng/ml, serum fetuin A had 68.33% sensitivity and 80 % specificity for discrimination between Patients and Controls with 91.1% PPV, 45.7% NPV and 77.2% Accuracy.

Discussion

Acne is a chronic dermatosis that affects the pilosebaceous follicles. The physiopathogenesis of this condition involves periglandular dermal inflammation mechanisms, sebum hyperproduction, follicular hyperkeratosis, an

increase of colonization of Propionibacterium acnes *(P. acnes)*, and hormones[10].

It was observed that many of these pathogenic mechanisms are governed by a bio-immuno-molecular phenomena that serves as the basis for research on and the future development of possible individual treatments for this dermatosis. [11].

Fetuin-A is a glycoprotein produced primarily in the liver and secreted into circulation in high concentrations in humans with fatty liver disease; it binds the insulin receptor and inhibits hepatic and muscle insulin signaling resulting in insulin resistance. In humans, high levels of fetuin-A have been associated with greater risks for type 2 diabetes (T2D) and with features of the metabolic syndrome; paradoxically, increased fetuin-A concentrations prevent vascular calcification and exert a protective role in systemic inflammation, suggesting that fetuin-A secretion can be divergently regulated in different pathological conditions[12].

The aim of this study was to evaluate the serum levels of fetuin-A in 60 patients with acne vulgaris and 20 apparently healthy age/sex and BMI matched persons as a control subjects group and to assess its relation to the clinical severity of disease.

To the best of our knowledge, this is the first study to compare fetuin-A levels in fetuin A in pathogenesis of acne. In current study, the mean serum level of fetuin A in patients group (164.485±91.432) was significantly higher than that in the control group (109.381±40.127) as p=0.011. This elevation may be explained by absence of active infection or inflammation in our cases as all patients with acne usually received multiple treatment line and in our study we don't documented the used treatment and time science last dose of it.

There was debate about its role in inflammation and clear role in inflammatory disease still matter of debate

Despite its abundance, the functions of fetuin-A remain poorly understood. A wide range of biological functions have been proposed for fetuin-A based on its structural similarities to other proteins or physical interactions with biogenic molecules.

Fetuin-A in inflammation

Acute phase response: Fetuin-A had early been described as an anti-acute phase protein in sepsis, yet it can act as a positive or negative acute phase protein depending on the respective stimulus [13]: early proinflammatory mediators (TNF-alpha, IL-1, IL-6, Interferon-gamma) down regulate fetuin-A, thus allowing for a strong inflammatory response and excess accumulation of late mediators (e.g., High-Mobility-Group-Protein B1, HMGB1); late pro-inflammatory mediators (such as HMGB1) stimulate hepatic fetuin-A expression, thereby restoring circulating fetuin-A levels in late stages of sepsis [14].

Seemingly, the mode of inflammation (infection or injury) may contribute to the ensuing (positive or negative) acute phase reactions and effects of fetuin-A. Fetuin is a prerequisite of anti-inflammatory protective actions of cationic polyamines (e.g., spermine)[15].

Fetuin-A as an anti-inflammatory protein

For instance, fetuin-A shares amino acid sequence homology to type II anti-inflammatory cytokines (TGF-β) receptors[16] , and has been proposed as an inhibitor of the TGF-β signaling pathway. Similarly, fetuin-A exhibits amino acid sequence similarity to insulin receptor tyrosine kinases[17], and can bind to the insulin receptor, thereby inactivating (rather than activating, as in the case for insulin) the receptor tyrosine kinase[18].

This may partly explain why higher fetuin-A levels were associated with insulin resistance in some patients with type 2 diabetes[19].

As a glycoprotein, fetuin-A carries two N-linked and three O-linked oligosaccharide chains that terminate with sialic acid residues, enabling the binding of cationic Ca^{2+} ions. Accordingly, fetuin-A has been proposed as an endogenous inhibitor of pathological mineralization or calcification in soft tissues[20].

Specifically, fetuin-A forms protein-mineral colloids with calcium and phosphate (Jahnen-Dechent et al., 2011), thereby preventing uncontrolled mineralization that may otherwise occur under pathological conditions[21].

As aforementioned, fetuin-A also functions as an opsonin for cationic spermine, and its availability to immune cells may be critical for regulating the innate immune response[22].

Indeed, levels of fetuin-A in macrophage cultures was decreased by 40% after stimulation with LPS (100 ng/ml, 2 h). Supplementation of LPS-stimulated macrophages with fetuin-A (100 μg/ml) conversely elevated cellular fetuin-A levels by 30–50%[23], confirming the notion that macrophages can 'adopt" fetuin-A from the environment [22].

Intriguingly, exogenously administered fetuin-A was predominantly localized in LC3-containing cytoplasmic vesicles - possibly autophagosomes or amphisomes - in LPS-stimulated macrophages [23].

At higher concentrations (e.g., 3.5 mg/ml), even crude fetuin-A (> 98%) can almost completely abrogated endotoxin-induced release of IL-1 and nitric oxide in macrophage cultures[24].

Following gel filtration and ion-exchange chromatography, the highly purified fetuin-A almost completely abrogated proinflammatory mediators (e.g., TNF, IFN-γ, and HMGB1) or LPS-induced HMGB1 release even when given at relative lower doses (e.g., 100 μg/ml) , suggesting fetuin-A as an effective anti-inflammatory APP [15].

So we depends on other studies evaluated the level of fetuin in many disease. For example.

Psoriasis

[25] Reported that serum fetuin A levels were elevated in patients with psoriasis in comparison with the healthy individuals.

In disagreement with current results,[26] found significant decreased fetuin A levels in all patients with psoriasis compared to controls. They suggest that inflammation may cause this reduction because fetuin A as it was known as a negative acute phase protein

In study by[27] The mean serum fetuin-A level was 12.0 ± 2.2 ng/ml in the psoriasis group and 14.6 ± 2.4 ng/ml in the healthy control group, and this difference was significant ($p < 0.001$) which in contrast to our observation**.** Probably, these discrepancies may be related to differences in level of insulin resistance and other yet undefined metabolic factors

Psoriasis arthiritis (SpA)

In[28] study, the serum fetuin-A levels were lower in psoriasis arthiritis (SpA) patients than in controls. Additionally, compared to controls, SpA patients had an increased risk of decreased serum fetuin-A levels.

And their explanation because the serum fetuin-A is regulated as a negative acute phase protein (anti-inflammatory) and its serum concentration falls during the acute inflammatory response and normalizes when the infection is successfully treated[13].

Polycystic ovary syndrome

In the paper by[29] mean serum fetuin-A concentrations were considerably elevated in polycystic ovary syndrome compared to healthy controls.

But[30] finding of lower levels of fetuin-A in PCOS girls than healthy was unexpected and could be derived—at least in part—from the status of low-grade inflammation associated with this entity, since it is known that proinflammatory cytokines and proteins such as CRP—which are increased in PCOS—down-regulate fetuin-A expression in the liver .

Whereas in the study by[31] there was no difference between women with PCOS and healthy subjects with regard to fetuin-A levels.

Probably, these discrepancies may be related to differences in age and BMI

SLE

SLE patients have multi-organ involvement related to their chronic inflammatory, autoimmune disease. Calciphylaxis and calcinosis are

manifestations of SLE that may be associated with significant morbidity and mortality[32].

[33] Found and found no significant difference in fetuin-A level between cases and control. As this cases may evaluated during the relapse remission phase of diseases with suppressed inflammation

Course of calciphylaxis

[34]Found the Fetuin-A inhibits arterial calcification in vitro as it interacts with calcium and phosphorus, increasing their solubility and inhibiting precipitation so prevent calcification

[19]found in relatively high concentrations in human blood, and are believed to exert its inhibitory effects on arterial calcification within the bloodstream, blood fetuin-A concentrations represent an attractive candidate marker of arterial calcification

[35]Found Fetuin-A is a potent regulator of extracellular matrix mineralization and the major serum-based inhibitor of calcium phosphate precipitation. Dysregulation of Fetuin-A levels has been associated with increased systemic inflammation and pro-calcifying cytokine production. Indeed, pro-inflammatory cytokines are considered important promoters of vascular smooth muscle cell osteochondrocytic transformation and mineralization

And [32] found the Fetuin A, a systemic inhibitor of calcification, facilitates the formation of soluble calciprotein particles and limits the formation and expansion of hydroxyapatite crystals

Gender

In current study, there was negative non-significant correlation between Serum Fetuin A and **sex**.

In agreement to current study,[26] did not find any influence of sex on fetuin A.

Also,[36] found Serum fetuin A levels did not correlate significantly with gender which against us.

In disagreement with us, a study by[37] of patients with pseudoxanthoma elasticum, higher fetuin-A levels were determined in women. From here, the authors have been suggested that fetuin-A levels could be changed by gender.

And their study was conducted on different sample size and this may the cause of discrepancy

Scar

In current study, there was negative non-significant positive correlation between Serum Fetuin A and Post Acne **Scar.**

Against our results, in the[14] **study**, their results indicate that high levels of fetuin-A may partially contribute to less scar formation in newborn**.** And this may be the different studied group as they conducted their study on infants.

BMI

On the other hand, there was positive non-significant correlation between Serum Fetuin A and **BMI**.

In agreement with us, according to[38] there was no significant difference in serum fetuin-A levels between lean and obese subjects so it was not significantly associated with BMI

Also,[39] examined the association between circulating fetuin-A levels, and subclinical atherosclerosis in 290 subjects. In all study participants, fetuin-A levels were positively non significantly associated with BMI

[36] Studied the relationship between serum fetuin A and clinical diabetes. Serum fetuin A levels did not correlate significantly with body mass index (BMI).

[26] Did not find any significant influence of BMI on fetuin A.

Age

In current study, there was negative non-significant positive correlation between Serum Fetuin A and the **age**.

In agreement with us, [36] studied the relationship between serum fetuin A and clinical diabetes. Serum fetuin A levels did not correlate with age.

[26] did not find any influence of age a on fetuin A.

As reported by[31] There was no difference between the groups with regard to Fetuin-A, before and after adjustment for age.

[27] They could not determine a statistically significant relationship between age and fetuin-A levels and they suggested that age is an ineffective factor on fetuin-A levels in patients with psoriasis.

In contrary, It has been shown previously by[19] that younger age was strongly associated with higher fetuin-A levels in patients with diabetes mellitus and this difference can be contributed to different diseases studied in their study.

Severity score

In current study, there was negative non-significant correlation between Serum Fetuin A and **GAGS score**.

Similar data was reported by[40] as they found there were no significant correlations among fetuin-A levels and PASI which measured the severity of psoriasis**.**

[27] Study revealed that patients with psoriasis were assessed by the PASI score; it was not observed a significant correlation between PASI scores and fetuin-A levels.

In contrast,[41] results showed that fetuin-A levels were significantly correlated with PASI score.

Moreover, according to[25] study, PASI score values were positively correlated with fetuin-A levels. But we found the negative correlation in acne**.**

Stress

In current study, there was negative non-significant correlation between Serum Fetuin A and **Stress**.

Similarly[42] found there was no significant correlation between fetuin-A levels and stress parameters

Smoking

In current study, there was negative non-significant correlation between Serum Fetuin A and **Smoking**.

Similarly [43] found no significant correlation was observed between serum fetuin A levels and smoking

PIH

On the other hand, there was positive non-significant correlation between Serum Fetuin A and **postinfilmmatory hyperpigmentation (PIH)**.

No study evaluated its role in skin pigmentation till this time. So we recommended more studies to found its role and effect on melanine content of skin and postinflimmatory pigmentation.

Conclusion

Serum fetuin-A levels are detected higher in patients with acne. Also, there are no statistically significant relation between it and gender, age, course of disease and in terms of stress, Sun Exposure, Smoking, Post Acne Scar, Family History, Diet & PIH.

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