

Assessment of Serum Level of Betatrophin in Acne Vulgaris Patient

F.M.Eleswy¹, D.M.El-Habbak¹, R.A.Khashba² and E.E.Zaky¹

¹ Dermatology, Venereology Dept., Faculty of Medicine, Benha Univ., Benha, Egypt

²Clinical and Chemical Pathology Dept., Faculty of Medicine, Benha Univ., Benha, Egypt

E-Mail: E.E.Zaky@gmail.com

Abstract

Acne, also known as acne vulgaris (AV), is a long-term skin disease that occurs when hair follicles are clogged with dead skin cells and oil from the skin. The investigation is expected to evaluate serum level of betatrophin protein in patients with skin break out vulgaris and contrast it with its level in solid control. This is A case-control study, was led on 80 patients isolated into 2 groups:(Group A); 60 patients experiencing skin break out vulgaris, (Group B); 20 obviously sound people of coordinated age and sex. All examined subjects were tried for Serum level of Betatrophin. Higher betatrophin level was altogether connected with higher seriousness higher betatrophin level was fundamentally connected with male sexual orientation, PCOD, hairsuitism, androgenetic alopecia. The betatrophin level in AV bunch was essentially higher when contrasted with control gathering . Betatrophin level was proposed to be autonomous indicator of AV defenselessness and seriousness.

1. Introduction

Acne happens by extreme touchiness of the sebaceous organs to a typical flowing degree of androgens, which are disturbed by P. acnes and aggravation [1].

Propionibacterium acnes, Staphylococcus epidermis, and Malassezia furfur prompt aggravation and instigate follicular epidermal multiplication [2].

The fundamental objective of skin break out treatment is to control and treat existing skin inflammation injuries, forestall lasting scarring quite far, limit the length of the issue and to limit dreariness. The patient ought to be educated on the points associated with forestalling new skin break out injuries while permitting the current ones to mend. Patients should likewise be made mindful that it might take 3 a month and a half until an improvement can be noticed [3].

At first betatrophin was recognized as a tumor-related antigen its part in charge of serum fatty substance levels or its plausible capacity in lipid digestion was described. Betatrophin in beta cell multiplication and lipid digestion stays questionable [4].

Discoveries seem, by all accounts, to be in strife with betatrophin was accounted for to intercede an expansion in beta-cell multiplication because of insulin opposition incited by treatment with the insulin foe S961 [5].

Betatrophin, additionally called refeeding-actuated fat and liver protein (RIFL) or atypical angiopoietin-like protein 8 (ANGPLT8) is a 22kDa hormone, In mice betatrophin is delivered by the liver, white fat tissue (WAT) and earthy colored fat tissue (BAT), while in people, it is primarily created by the liver, It has been demonstrated that betatrophin has a double job: it influences glucose homeostasis and lipid digestion [6].

'Betatrophin' was first named by the Melton bunch betatrophin (otherwise called angiopoietin-like 8 [ANGPLT8], lipasin, TD26, and refeeding incited in fat and liver [RIFL]), which corresponded with β -cell multiplication in the mouse model of

pharmacologically prompted serious insulin obstruction [7].

Distinguishing proof of the hormone betatrophin lead to different human examinations, which intended to clarify its relationship with metabolic states including diabetes. Numerous examinations have demonstrated contrasts in the flowing degrees of betatrophin with regards to diabetes, insulin obstruction, heftiness, metabolic disorder, or dyslipidemia [8].

In spite of disappointing perceptions in creature considers, numerous affiliation concentrates in people recommend a potential function of betatrophin in glucose and lipid digestion. Flowing betatrophin levels were commonly higher in metabolically upset states, for example, type 1 diabetes mellitus, type 2 diabetes mellitus (T2DM), overweight or weight, metabolic condition and nonalcoholic greasy liver sickness [4].

The point of the work was to survey serum level of betatrophin protein in patients with skin inflammation vulgaris and contrast it with its level in solid control.

2. Patient and method

A case- control study was directed on 60 patients experiencing skin inflammation vulgaris (Group A) and 20 clearly solid people of coordinated age and sex as a benchmark (Group B). Patients were selected from the outpatient center of Dermatology and Andrology Department of Benha University Hospitals among [March and June 2020].

Incorporation rules

- Male & female patients with skin break out vulgaris with various clinical assortments and various levels of seriousness as indicated by worldwide skin break out scaling framework

Rejection rules

- Patients with history of hypertension and atherosclerotic CVD.

- Patients with AV on foundational treatment that influence blood glucose level eg: fundamental retinoids and hormonal treatment.
- Patients with history of diabetes mellitus (DM).
- Pregnant and breastfeeding females.
- Patients with thyroid problems, persistent renal or liver sicknesses.

All read subjects were applied for:

- Full general assessment to reject related foundational sicknesses, for example, thyroid illness, diabetes mellitus, and other immune system infections.
- Detailed dermatological assessment; to assess clinical variation, seriousness of AV and presence of skin inflammation scars.
- Diagnosis of AV was made based on the patient's set of experiences and the average clinical highlights of non-incendiary injuries structure, including shut (whiteheads) and open (clogged pores) comedones, and provocative sores including papules, pustules, knobs or potentially blisters on the face, chest and upper back.

The absolute seriousness score was gotten from the summation of six local subscores. Each was inferred by increasing the factor for every district; (factor for temple and each cheek was 2, jawline and nose was 1 and chest and upper back was 3); by the most vigorously weighted sore inside every locale (1 for comedones, 2 for papules, 3 for pustules and 4 for knobs). A score of (1-18) is viewed as mellow; (19-30) moderate; (31-38) serious; and >39 extreme (9) All studied subjects were tested for:

- Serum level of Betatrophin.
- Serum fasting insulin level.
- Serum fasting blood glucose level.

3. Results

The AV bunch mean age was 19.2 years, they were 29 guys (48.3%) and 31 females (48.3%). Notwithstanding 30 sound benchmark group, their mean age was 17.9 years, they were 11 guys (36.7%) and 19 females (63.3%). Cases and control bunches had coordinated age and sex ($p > 0.05$ for each).

Weight list, SBP and DBP didn't vary altogether among cases and control gatherings ($p > 0.05$ for each).

Complete cholesterol level was essentially higher in situations when contrasted with control gatherings ($p = 0.022$). Where as, blood glucose didn't vary essentially among cases and control gatherings ($p > 0.05$).

Nineteen female cases had Menstrual anomalies (61.3%). Ultrasound assessment uncovered PCOD in 45.2% females. Hirsutism was available in 25.8% females. Androgenic alopecia in 48.3% in completely examined guys and females AV cases.

Numerous destinations were influenced, cheeks were influenced in 96.7%, brow was influenced in 68.3%, chest was influenced in 45%, back was influenced in 43.3%, jaw was influenced in 16.7%,

nose was influenced in 3.3%. Mean Global skin break out reviewing framework was 30.1, and went from 8 to 47; 35% were gentle, 36.7% were moderate, 16.7% were extreme and 11.7% were serious.

The betatrophien level in AV bunch was essentially higher when contrasted with control gathering (mean=5295.5 versus 3671.3, $p = 0.024$).

Collector working trademark (ROC) bend of betatrophien level was led for segregation between AV cases and control gatherings. Betatrophien demonstrated AUC of 0.651. At cut off estimation of 7779.2, affectability was 43.3%, explicitness was 90%, PPV was 89.6%, NPV was 44.2%, and precision was 58.9%.

ROC bend of betatrophien level was directed for separation between mellow to direct versus extreme to exceptionally serious AV cases. Betatrophien demonstrated AUC of 0.923. At cut off estimation of 8162.7, affectability was 94.1%, particularity was 88.4%, PPV was 76.2%, NPV was 97.4%, and exactness was 90%.

Higher betatrophien level was altogether connected with male sexual orientation, PCOD, hairsuitism, androgenic alopecia, degree ($p = 0.030, 0.003, < 0.001, < 0.001, < 0.001$ separately). No critical affiliations were found with respect to Betatrophien level as per feminine abnormalities in AV gathering ($p > 0.05$ for each).

Levels of betatrophien expanded progressively with expanded seriousness grades. Concerning cases, mean betatrophien level was 2998.7, gone from 1188.3 to 8231.1, with respect to direct cases, mean betatrophien level was 4903.4, gone from 1085.1 to 11073, with respect to extreme cases, mean betatrophien was 9052.2, gone from 8274.7 to 10564, in regards to serious cases, mean betatrophien was 8051.5, gone from 2068.8 to 11073. Higher betatrophien level was altogether connected with higher seriousness ($p = < 0.001$).

Betatrophien level demonstrated critical positive relationship with GAGS, seriousness and degree yet not with age, BMI, SBP, DBP, glucose, TC in AV gathering.

Calculated relapse examination was led for forecast of AV advancement utilizing age, sex, BMI, SBP, DBP, glucose, TC, PCOD and betatrophien level as confounders. Presence of PCOD, higher BMI, TC and betatrophien were related with AV danger in Univariable investigation. Notwithstanding, taking huge covariates into multivariate investigation uncovered that lone more significant level of betatrophien was recommended to be free danger indicator for AV advancement ($p = 0.035, OR = 1.058$).

Straight relapse examination was directed for expectation of AV seriousness utilizing age, sexual orientation, BMI, SBP, DBP, glucose, TC, PCOD and betatrophien level as confounders. Presence of PCOD and higher betatrophien were recommended to be free danger indicators for AV severity.

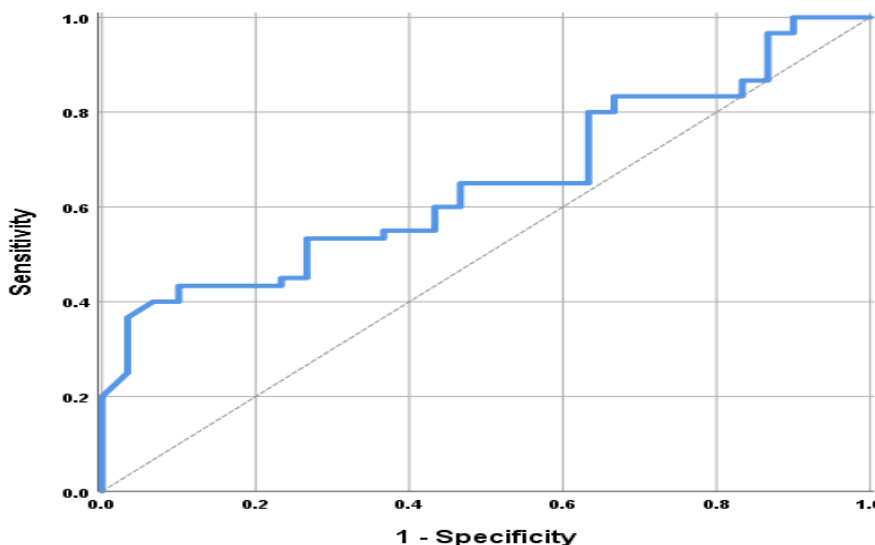


Fig (1) ROC curve of betatrophin level for discrimination between cases and control groups.

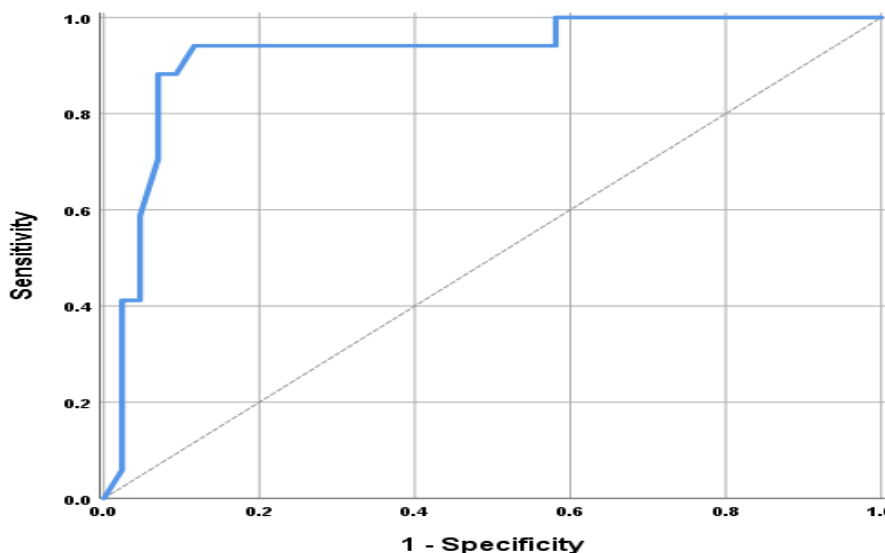


Fig (2) ROC curve of betatrophin level for discrimination of AV severity.

4. Discussion

Acne vulgaris is a typical persistent skin infection including blockage and additionally irritation of pilosebaceous units (hair follicles and their going with sebaceous organ). Skin break out can present as noninflammatory sores, fiery injuries, or a combination of both, influencing generally the face yet additionally the back and chest [9]. Skin inflammation vulgaris has a multifactorial pathogenesis, of which the key factor is hereditary qualities. Skin break out creates because of an exchange of the accompanying four elements: follicular epidermal hyperproliferation with resulting stopping of the follicle, overabundance sebum creation, the presence and movement of the commensal microbes *Propionibacterium acnes*, and irritation [10].

Androgens and insulin add to an expansion in sebum creation in the pathogenesis of skin

inflammation vulgaris. Likewise, a relationship between's insulinlike development factor-1 (IGF-1) and facial sebum levels has been appeared [11]

Betatrophin, a recently recognized peptide hormone emitted basically by liver and fat tissue, is an individual from a group of angiotensin-like proteins and is embroiled in the guideline of lipid and glucose digestion. As the peptide was found freely by various gatherings, it is known by different names that incorporate 're-taking care of instigated fat and liver (RIFL) protein,' 'lipasin,' 'angiotensin-like 8 protein' (ANGPLT8), and 'hepatocellular carcinoma-related protein' (TD26) [12]. Initially, betatrophin was determined to function in lipid digestion by diminishing fatty oil leeway through lipoprotein lipase hindrance. It has been ensnared that the hormone is a critical go between of the postprandial dealing of fatty substance

unsaturated fats to fat tissue [13]. What's more, betatrophin succession varieties were accounted for in lipid digestion [14]. The gathering exhibited that discharge of betatrophin increments in light of insulin obstruction in mice, which animates beta cell replication and development. Organization of betatrophin was appeared to improve glucose homeostasis in these mice [15].

The point of the current examination was to evaluate serum level of betatrophin protein in patients with skin inflammation vulgaris and contrast it with its level in solid control.

The current examination was led more than 60 member separated into two gatherings Group I:sixty patients griping of skin inflammation vulgaris and Group II:Twenty evident sound age and sex coordinated people as control gathering. In this examination we found that The Acne vulgaris (AV) bunch mean age was 19.2 years, they were 29 guys (48.3%) and 31 females (51.7%). Notwithstanding 30 solid benchmark group, their mean age was 17.9 years, they were 11 guys (36.7%) and 19 females (63.3%). Cases and control bunches had coordinated age and sexual orientation.

This was in concur with El-Tonsy et al., [2] examined the qualities of skin inflammation vulgaris in Egyptian populace show that they female percent was higher than guys as 33 guys (33.0%) and 67 females (67.0%), mean age of the contemplated cases was 23.36. Bagatin et al., [16] 452 youths matured somewhere in the range of 10 and 17 years are remembered for his investigation 62.4 % of them were females. Ismail et al., [17] found the equivalent in his examination on included 510 patients (173 guys and 337 females) with a male: female proportion of 0.41:1. Collier et al., [18] detailed that grown-up ladies in various age classes have a fundamentally higher pervasiveness of skin inflammation than grown-up men.

In negate with Al Kubaisy et al., [19] who made a cross-sectional investigation led in the Syrian International University for Science and Technology, an example of 500 understudies was picked and discovered that guys have higher predominance of skin break out contrasted with females (42.9% versus 23.6%).Sobhan et al., [20] uncovered that the male to female proportion was about 1:2, however this was not factually huge ($P=0.5$). Li et al., [21] confirmed in their a meta-examination which was directed in terrain China found a higher pervasiveness pace of skin inflammation in guys than females, because of contrasts in way of life, skincare schedules, and androgen levels.Well, [22] uncovered that Over 90% of guys and 80% of females have encountered skin inflammation by the time of 21.Tan and Bhate, [23] study results uncovered that male patients were all the more oftentimes influenced, especially with more serious types of acne.This doesn't imply that skin inflammation is more normal in female yet it implies that young ladies are more mindful about their facial

appearance than young men, and they look for treatment.

In this examination we found that Total cholesterol level was essentially higher in situations when contrasted with control gatherings ($p=0.022$). While, blood glucose didn't vary altogether among cases and control gatherings ($p>0.05$).

This was in concur with Sobhan et al., [20] who found that for cholesterol, a huge distinction was seen between male patients and solid partners (173.9 ± 0.13 and 150.3 ± 0.33 for patients and controls, separately, $p=0.04$).

Utami and his colleagues [24] saw a huge connection between's serum lipids (LDL-C, HDL-C, and TC) and AV seriousness.

This can be legitimized by that it is realized that HMG-CoA reductase is directed by the cholesterol levels in the sebaceous organ climate so the expansion of blood cholesterol levels may impact squalene levels in the sebum. It likewise can be found in the blood as a result of lipid spillage from the cholesterol biosynthesis. Nonetheless, squalene levels in sebum are more bountiful than those in blood. Likely, sebocyte has advanced a component that intrudes on the cholesterol biosynthesis and advances squalene aggregation. The presence of six twofold chains in the substance structure permits squalene to effortlessly go through photograph oxidation measure delivering squalene mono-hydroperoxide as the primary item which has favorable to provocative action [3].

On the negate El-Akawi et al., [25] announced that there was no huge contrast in cholesterol levels in patients with every one of the three skin break out evaluations (gentle, moderate and serious) contrasted and those of solid controls.Also Finzi et al., [26] didn't locate any huge contrasts in the fatty substance and all out cholesterol levels among patients and controls.

In the current examination we found that nineteen female cases had feminine inconsistencies (61.3%). Ultrasound assessment uncovered PCOD in 45.2% females. Hirsutism was available in 25.8% females. Androgenic alopecia in 48.3% in totally considered guys and females A.V cases.

This was in concur with Al-Kubaisy et al., [19] who checked around 80 % of the females expressed hyperandrogenicity during the feminine cycle may have added to the skin break out development. Lee et al., [27] revealed hirsutism and alopecia found in ladies with skin break out because of hyperandrogenism. As indicated by Zahida Baqai et al., [28] skin inflammation was highly connected with 11 hirsutism in 5% ladies. Carmina et al., (2006) noticed higher level of PCOS ladies with skin inflammation, hirsutism alopecia and stoutness. Koivunen et al., [29] announced that polycystic ovaries by sonography are considerably more typical in ladies with 35 years of age or more youthful (21.6%) commonness than in more established than 36 years. Soodabeh Zandi et al., [30] detailed that in 5.5 of skin inflammation cases, PCOS could be noticed .According to Seirafi et al., [31] the

commonness of PCO in ladies with skin break out was about 40%. Chuan and Chang, [32] investigated skin break out as conceivable danger factors for PCOS. Late examination shows 80% of PCOS bunch were found to have skin break out, and having skin inflammation was found to build danger to create PCOS by multiple times. Fraser and Kovacs et al., [34] in their examinations found that 45.37% skin break out patients had PCOS. The recurrence of PCOS all in all populace is more which shows that skin break out patients are multiple times more inclined to have PCOS and was analyzed in about 60% of patients experiencing skin inflammation.

On the negate El-Tonsy et al., [2] exhibited that set of experiences of feminine abnormality was available in 28.4% of A.V cases.

In our investigation we found that numerous locales were influenced, cheeks were influenced in 96.7%, temple was influenced in 68.3%, chest was influenced in 45%, back was influenced in 43.3%, jaw was influenced in 16.7%, nose was influenced in 3.3%. Mean Global skin break out reviewing framework was 30.1, and went from 8 to 47; 35% were mellow, 36.7% were moderate, 16.7% were serious and 11.7% were extreme.

This was in concordant with El-Tonsy et al., [2] who detailed that as indicated by skin inflammation circulation face was influenced in 51% of cases, back and chest in 18% and face and different locales in 31% of cases, 16% of cases had mellow, 82% had moderate and 2% had extreme skin inflammation.

Bagatin et al., [16] study detailed that the most usually influenced site was the face (97.5%) or the face and trunk (2.3%).

Utami and his colleagues in [24] revealed that the majority of study members had moderate AV (56.5%), trailed by mellow (35.5%) and extreme AV (8.1%)

In our investigation we saw that the betatrophin level in AV bunch was essentially higher when contrasted with control gathering (mean=5295.5 versus 3671.3, $p=0.024$).

Crujeiras and his partners in [35] expressed in their investigation that betatrophin level was fundamentally higher in people with metabolic condition, weight, and disabled lipid profile and glucose resistance.

This can be connected to our outcomes as skin inflammation appears to lie at the point of hormone activity and lipid digestion in sebocyte separation. Skin inflammation won't create without sebum, and sebum won't be delivered without androgenic incitement of sebocytes. Basic incendiary skin break out possibly happens when androgens ascend at adolescence. Essential exploration proposes that the compensatory insulin overabundance autonomously disturbs the skin inflammation [36].

Fenzl and his partners in [6] have indicated a huge connection between's betatrophin level and plasma atherogenic lipids in bleak corpulent patients and patients with type 2 DM, be that as it may, no connection was resolved with control gathering.

Espes et al., [8] could also show that betatrophin flowing levels were essentially expanded in long standing sort 1 diabetes patients versus the protein.

5. Conclusion

Betatrophin level was significantly higher in AV cases when compared to control group. Higher betatrophin level was significantly associated with male gender, PCOD, hirsutism, androgenetic alopecia, severity and extent. Betatrophin level was significantly correlated with GAGS score, severity and extent. Betatrophin level was suggested to be independent predictor of AV susceptibility and severity. Betatrophin ability to detect severity was better than that for diagnosis (AUC=0.923 versus AUC=0.651).

References

- [1] A. Bienenfeld, S. Azarchi, K. L. Sicco, Androgens in women: Androgen-mediated skin disease and patient evaluation. *Journal of the American Academy of Dermatology*, Vol.80(6), PP. 1497-1506, 2019.
- [2] T. M. K. El-Tonsy, M. A. Mohammed, Y. A. E. E. Hamed, Bacteriological study of Acne Vulgaris in Cairo Egypt. *The Egyptian Journal of Hospital Medicine*, Vol.72(9), PP.05203-5209, 2018.
- [3] E. Camera, M. Picardo, Lipids in Serum and Sebum. In *Pathogenesis and Treatment of Acne and Rosacea* Vol.21, PP. 305-313, 2016.
- [4] Y. Zhang, S. Li, W. Donelan, Angiopoietin-like protein 8 (betatrophin) is a stress-response protein that down-regulates expression of adipocyte triglyceride lipase. *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids*, Vol.1861(2), PP. 130-137, 2016.
- [5] H. Hu, W. Sun, S. Y. u, Increased circulating levels of betatrophin in newly diagnosed type 2 diabetic patients. *Diabetes care*, Vol.37(10), PP. 2718-2722, 2014.
- [6] A. Fenzl, B. K. Itariu, L. Kosi, Circulating betatrophin correlates with atherogenic lipid profiles but not with glucose and insulin levels in insulin-resistant individuals. *Diabetologia*, Vol.57(6), PP.1204-1208, 2014.
- [7] A.R. Cox, O. Barrandon, E.P. Cai, Resolving discrepant findings on angptl8 in β -cell proliferation: a collaborative approach to resolving the betatrophin controversy. *PLoS one*, Vol.11(7), PP.210-225, 2016.
- [8] D. Espes, J. Lau, P. O. Carlsson, Increased levels of irisin in people with long-standing Type 1 diabetes. *Diabetic medicine*, Vol.32(9), PP. 1172-1176, 2015.
- [9] M. A. E. H. Habib, Assessment of serum Desnutrin levels in patients with acne vulgaris, Vol.50(8), PP. 2015-230, 2017

- [10] P. A. Jadhav, Formulation And Evaluation Of Anti-Acne Face Wash Gel, Vol.25(8),pp415-425,2016.
- [11] G. Plewig, B. Melnik, W. Chen, Acne Pathogenesis. In Plewig and Kligman's Acne and Rosacea, Vol.8, PP. 45-61,2019
- [12] S. Aydin, Three new players in energy regulation: preptin, adropin and irisin. Peptides, Vol.56, PP.94-110,2014.
- [13] M. Calan, O. Yilmaz, T. Kume, G.U. Kocabas, Elevated circulating levels of betatrophin are associated with polycystic ovary syndrome. *Endocrine*, Vol. 53(1), PP.271-279,2016.
- [14] H. Ghasemi, J. Karimi, I. Khodadadi, Association between rs2278426 (C/T) and rs892066 (C/G) variants of ANGPL8 (betatrophin) and susceptibility to type2 diabetes mellitus. *Journal of clinical laboratory analysis*, Vol.33(1),PP. e22649,2019.
- [15] D. Liu, H. Qu, H. Wang, Relationship between serum betatrophin levels and the first-phase of glucose-stimulated insulin secretion. *Obesity research & clinical practice*, Vol.12(1),PP. 9-15,2018.
- [16] E. Bagatin, D. L. Timpano, L. R. D. S.Guadanhim, Acne vulgaris: prevalence and clinical forms in adolescents from São Paulo, Brazil. *Anais brasileiros de dermatologia*, Vol.89(3), PP.428-435,2014.
- [17] K. H Ismail, K. B. Mohammed-Ali, Quality of life in patients with acne in Erbil city. *Health and Quality of life Outcomes*, Vol.10(1), PP.60,2015.
- [18] C. N. Collier, J. C. Harper, W. C. Cantrell, The prevalence of acne in adults 20 years and older. *Journal of the American Academy of Dermatology*, Vol.58(1),PP. 56-59,2018.
- [19] W. Al-Kubaisy, N. N. Abdullah, S. M.Kahn, Sociodemographic characteristics of acne among university students in Damascus, Syria. *Epidemiology Research International*, Vol.70,PP.242-255, 2014.
- [20] M.Sobhan, M. A. S.Rabiei, M. Amerifar, Correlation between lipid profile and acne vulgaris. *Clinical, Cosmetic and Investigational Dermatology*, Vol. 13,PP. 67,2020.
- [21] D. Li, Q.C hen, Y.Liu, The prevalence of acne in Mainland China: a systematic review and meta-analysis. *BMJ open*, Vol.7,PP. e015354,2017.
- [22] D. Well, Acne vulgaris: A review of causes and treatment options. *Journal of the Dermatology Nurses' Association*, Vol.6, PP.302-309,2014.
- [23] J. K. Tan, K. Bhate, A global perspective on the epidemiology of acne. *British Journal of Dermatology*, 172, 3-12,2015.
- [24] O. C. Utami, Y. Kurniawati, S. Diba, Correlation between serum lipid profile and acne vulgaris severity. In *Journal of Physics: Conference Series*, Vol. 1246, PP. 012066,2019.
- [25] Z. El -Akawi, N. Abdel-Latif, K. Abdul-Razzak, The relationship between blood lipids profile and acne. *Journal of health science*, Vol. 53(5), PP.596-599,2007.
- [26] C. Vergani, A. F. Finzi, P. D. Pigatto, Low level of HDL in severe cystic acne. *N. Engl. J. Med*, Vol. 307, 1151–1152,1982.
- [27] A.T. Lee, A.T. Zane, Dermatological manifestations of polycystic ovary syndrome. *Am. J Clin Dermatol*, Vol.8,PP.201-219,2007.
- [28] Zahida Baqai, Majidah Khanam, Sajida Parveen, Prevalence of PCOS in infertile patients. *Reproductive Health*, Vol.60,PP.437-440,2010.
- [29] E. Carmina, F. Rosato, A. Janni, Relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. *Endocrinol Metab*, Vol. 91,PP. 2-6,2006.
- [30] R. Koivunen, T.Laatikainen, C.Tomas, The prevalence of polycystic ovaries in healthy women. *Acta Obstet Gynecol Scand*, Vol. 78,PP.137-141,1999.
- [31] Soodabeh Zandi, Saeideh Farajzadeh, Hamideh Safari, Prevalence of polycystic ovary syndrome in women with acne: hormone profiles and clinical findings. *Journal of Pakistan Association of Dermatologists*, Vol.20,PP. 194-198,2010
- [32] H. Seirafi, F. Farnagh, A. Vasheghani- Farahani, Assessment of androgens in women with adult-onset acne. *Int J Dermatol*, Vol.46,PP.1188-1191,2007
- [33] S.S. Chuan, R.J. Chang, Polycystic Ovary Syndrome and Acne. *Skin Ther Lett*, Vol. 15,PP.1–4,2010.
- [34] I.S. Fraser, G. Kovacs, Current recommendations for the diagnostic evaluation and follow-up of patients presenting with symptomatic polycystic ovary syndrome. *Best Pract Res Clin Obstet Gynaecol*, Vol.18,PP.813-823,2004.
- [35] A. B. Crujeiras, M. A. Zulet, I. Abete, Interplay of atherogenic factors, protein intake and betatrophin levels in obese–metabolic syndrome patients treated with hypocaloric diets. *International Journal of Obesity*, Vol. 40(3), PP.403-410,2016.
- [36] W. Chen, B.Obermayer Pietsch, J.B. Hong, Acne-associated syndromes: models for better understanding of acne pathogenesis. *Journal of the European Academy of Dermatology and Venereology*, Vol.25(6),PP. 637-646,2011