International Invention of Scientific Journal
ISSN: 2457-0958

Research Paper

Available Online at http://iisj.in/index.php/iisj September, 2018|Volume 02|Issue 09|

Frequency of Polycystic Ovary Syndrome and Disturbances in Thyroid Gland Function in Women with Acne Vulgaris: Hormone Profiles and Clinical Findings

[1]D.D. Tsvetanova, [2]I.A. Yordanova, [3]D.D. Strateva, [4]K.N. Todorova, [5]P.D. Yordanova-Laleva, [6]P.A. Hristova, [7]D.K. Gospodinov

[1,2,7]Department of Dermatology, Venereology and Allergology, Faculty of Medicine, Medical University Pleven, Bulgaria.
[3]Department of Obstetrics and Gynaecology, Faculty of Medicine, Medical University Pleven, Bulgaria
[4]Department of Cardiology, Pulmonology and Endocrinology, Division of Endocrinology, Medical University Pleven, Bulgaria
[5]Faculty of Pharmacy, Medical University Pleven, Bulgaria
[6]Department of Social Pharmacy, Faculty of Pharmacy, Medical University Pleven, Bulgaria

Correspondence Author: *

Accepted 2018-07-30, Published 2018-09-01

Abstract:

Background: Acne vulgaris is skin disease affecting the pilosebaceous units. It is related to the polycystic ovary syndrome (PCOS), metabolic syndrome and dysfunction of the thyroid gland.

Objective: This study investigated the relationship between acne vulgaris, PCOS, and dysfunction of the thyroid gland in female patients of reproductive age.

Methods: A prospective case-control study was conducted between June 2016 and June 2017 with 70 female patients (age range 14-40 years). They were divided into two groups: group one (n1=35) with acne vulgaris, and group two (n2=35) included women without acne vulgaris. The patients from both groups were assessed for levels of sex hormones, thyroid gland hormones and the presence of antithyroid antibodies, as well as for insulin resistance index.

Results: Our results revealed a statistic difference between the frequency of PCOS in the patients suffering from acne vulgaris (18.57%) and the healthy volunteers (1.43%) - p=0.001. Elevated total testosterone levels were more commonly found in the patients from the first group (12.86%) as compared with the control group (1.43%) - p=0.02. The data showed a difference in the relationship between the thyroid gland dysfunction and thyroid autoimmunity in patients suffering from acne vulgaris (22.86%), as compared with the control group (1.43%) - p=0.0001. A combination of PCOS and autoimmune thyroid disease (AITD) was established in the group of the patients with acne vulgaris.

Conclusion: Our results provide evidence for co-morbidities in patients with acne vulgaris who should be tested for concomitant endocrine and metabolic diseases such as PCOS and AITD.

Key Words: acne vulgaris, polycystic ovary syndrome, hyperandrogenemia, autoimmune thyroid diseases.

Introduction:

Acne vulgaris it is a common chronic inflammatory disease of the pilosebaceous unit. In developed societies, its prevalence in adolescents is between 70% and 87% [1]. The pathogenesis of the disease involves four main mechanisms:

1) increased sebum production,
2) hyperproliferation of keratinocytes,
3) follicular colonization with Propionibacterium acnes,
4) increased secretion of inflammatory mediators.

Recent studies on the pathogenetic, clinical and therapeutic aspects of the disease in Bulgaria were

published in a doctoral thesis of M. Kadurina, 2005 [2]. The number of studies proving the association of acne vulgaris with PCOS has increased [3]. These two conditions are often associated with MetS, which is characterized by increased body mass index, hyperlipidemia, diabetes mellitus, arterial hypertension, visceral obesity, and insulin resistance (IR) [4]. In recent years, studies have been reported on the so-called acne adultorum, whose onset is after puberty with clinical manifestation in the lower third of the face. It is assumed that the development of acne adultorum could be a sign of AITD with thyroid dysfunction [5].

Aim of the study:

To find the relation between acne vulgaris, PCOS and thyroid dysfunction in patients aged 14 to 40 years. To achieve that goal, we set the following tasks:

1. To determine the severity of acne vulgaris in patients aged 14 - 40 years according to GAGS.
2. To perform a screening for endocrine diseases (thyroid gland, ovarian dysfunction and for MetS) among patients with acne vulgaris and control group patients without acne vulgaris by consultations with specialists in obstetrics, gynecology and endocrinology at the University Hospital in Pleven.
3. To investigate serum levels of ovarian hormones in both groups during the two phases of menstruation, as follows:
- levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2) and prolactin (Prol) in the follicular phase;
- levels of dehydroepiandrosterone-sulfate (DHEA-S), total testosterone (TTest) and progesterone (Prog) in the luteal phase

Thyroid stimulating hormone (TSH), free Thyroxin (FT4), Thyroglobulin antibodies (TAT) and Anti-thyroid peroxidase autoantibodies (TPO-ab) was measured irrespectively of menstrual phases.

4. To evaluate Insulin Resistance in the two groups by calculating HOMA-IR.
5. To analyze and interpret the results from the study statistically.

Materials and methods:

Study population: The study included patients with acne vulgaris treated in the University Hospital in Pleven, in the Clinic of Endocrinology and Metabolic Diseases, diagnosed with MetS, as well as patients hospitalized in the Clinic of Dermatology and Venereology. Outpatients with Acne vulgaris referred to the Clinic of Dermatology and Venereology from the outpatient practices of Obstetrics and Gynecology, Endocrinology and Dermatology were also included.

Design of study: A prospective, case: control study was conducted among 70 female patients aged 4 to 40 years, divided into two main groups: with acne vulgaris (gr1=35) and without acne vulgaris (gr2=35).

Considerations: the severity of acne was evaluated by a dermatologist and stratified according to GAGS as described by Doshi et al. [6]. (Table 1). There is a factor (1 to 3) that corresponds to each of the affected areas, as indicated in Table 1. Each area was evaluated according to the severity of the lesions calculated as points (p) as follows: lack of lesions = 0, comedones = 1, papules = 2, pustules = 3 and nodules = 4. The so-called "local score" was calculated for each area, according to the formula: local score = factor × degree of severity lesions (0-4). After that, the so-called Global score was calculated as a sum of the results for the areas. Following the obtained results, the severity of acne vulgaris is was determined as follows: mild acne vulgaris (1 to 18 points), moderate acne vulgaris (19 to 30 points), severe acne vulgaris (31 to 38 points) and very severe acne vulgaris (more than 39 points).

Table. 1 Description of Global Acne Grading System (GAGS)

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

In all patient's hormonal analyses were performed as follows: in the follicular phase (day 3 to 5) of the menstrual cycle, investigation of FSH, LH, E2 and Prol were investigated. TTest, Prog and DHEA-S

were investigated in the luteal phase (day 21 to 23) of the menstrual cycle. TSH, fT4, TAT and TPO-Ab, fasting blood glucose and fasting basal insulin were measured irrespectively of menstrual phases.

Laboratory Methods: Automatic immunological analyzer Cobas E 411 was used for all hormonal analyses. The assay included an immunological determination by antibodies marked with biotin-streptavidin, and with electrochemiluminescence detection (ECLIA). Assessment of the IR was done according to the HOMA-IR calculation formula: HOMA-IR = Fasting Insulin (μIU/mL) X Fasting Glucose (mmol/L) /22.5 [7,8]. Interpretation of the results was as follows: normal IR (HOMA-IR <2.5), mild IR (HOMA-IR from 2.5 to 5.0) and moderate (IR HOMA-IR>5.0). We focused on the results of HOMA-IR over 2.5. When necessary, additional consultations were carried out with an obstetrician-gynecologist.

Clinical examinations: Ultrasound examinations of the ovaries and thyroid gland were performed in all patients with deviations in the levels of sex and thyroid hormones, antibodies and IR index. Patients were diagnosed with PCOS according to the Rotterdam criteria (2003). We chose 2 out of 3 criteria out of the following: hyperandrogenemia (presented by clinical and/or biochemical signs), oligo-or amenorrhea and 12 or more follicles with a size of 2 to 9 mm and/or an ovary volume of more than 10 cm3 estimated ultrasonographical. Statistical analysis of the results was performed with STATGRAPHICS plus, SPSS version and EXCEL for Windows by using Student's t-test. All data in the text are presented as mean values and their standard deviations (±SD). Results from the assessment of the relationship between PCOS, autoimmune and hormonal disturbances of the thyroid gland in patients with acne vulgaris and the control group were described by graphics and numerals, structure indicators, frequency, correlation coefficients (Pierson and Contingency empirical coefficient). The levels of significance of results and conclusions were determined at empirical value p <0.05.

Results:

There was a non-significant difference in the mean age of the participants in the groups: g1 - 23.28 ±6.44 years, g2 -24.0± 7.41 years; p >0.05.

According to GAGS, patients with acne vulgaris were classified in the following subgroups: mild form - sg1=2 patients (5.71%), moderate form - sg2=6 patients (17.14%), severe form - sg3=18 patients (51.43%) and very severe form - sg4=9 patients (25.71%). (Fig.1).

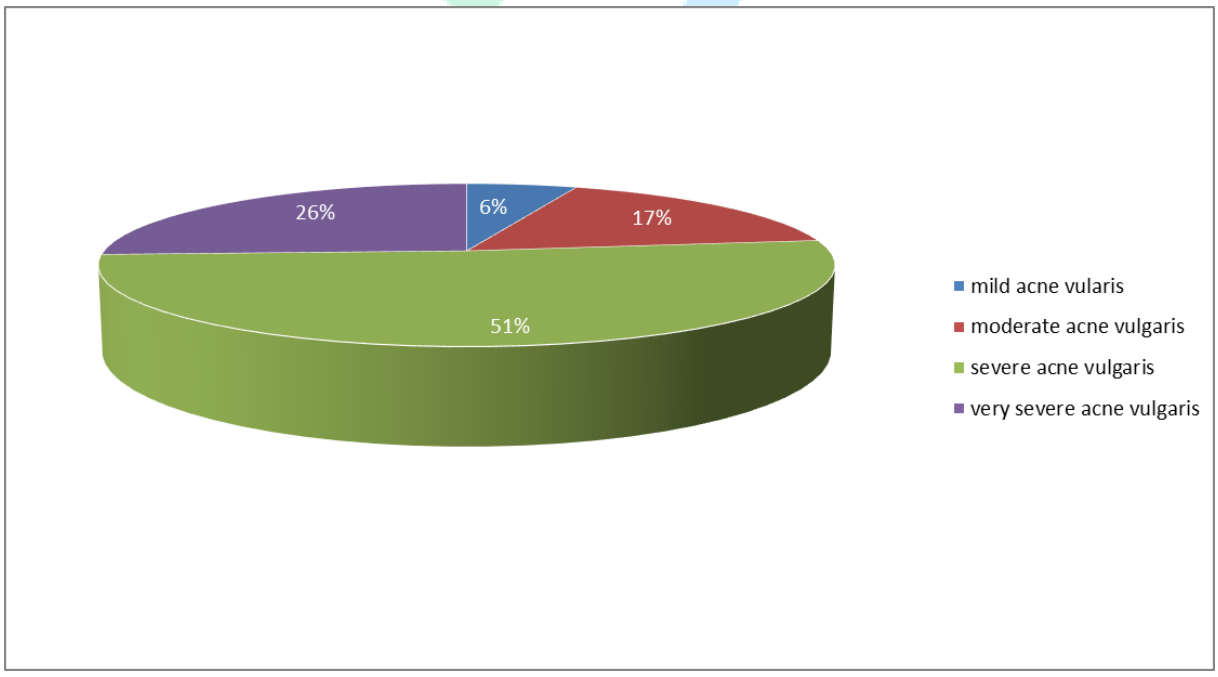

Figure. 1 Distribution of patients with acne vulgaris according Global Acne Grading System (GAGS)

Polycystic ovary syndrome was diagnosed with a significantly higher frequency in patients with Acne vulgaris - n=13 (18.57%) as compared to the healthy controls, n=1 (1.43 %); (p = 0.001), respectively. (Fig. 2).

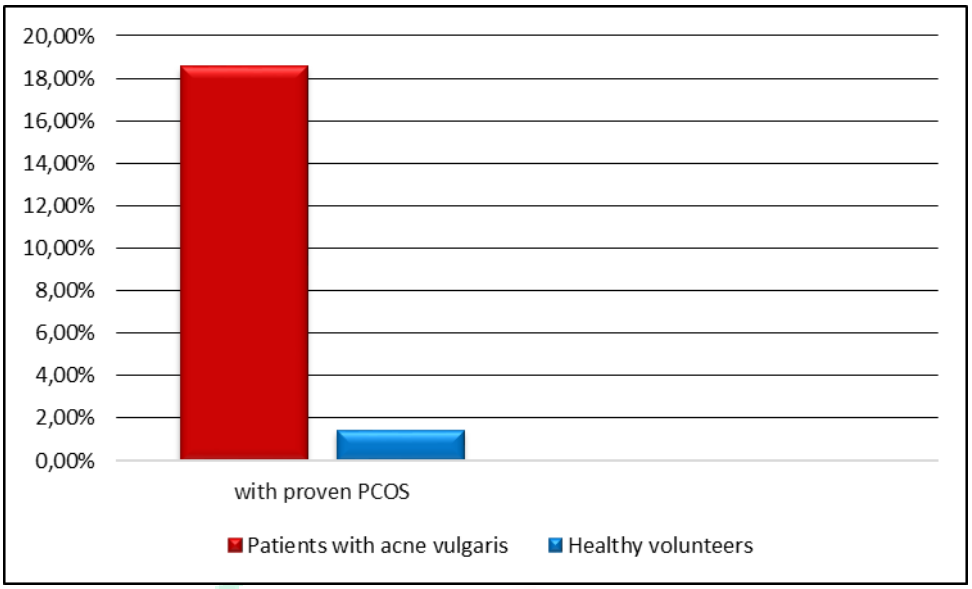

Figure.2 Frequency of polycystic ovary syndrome among the patients with acne vulgaris and healthy volunteers

We found a statistically significant difference in the frequency of hyperandrogenemia proven by elevated levels of TTest and DHEA-S. There were statistically significant differences between the levels of TTest in the two groups: n1=9 (12.86%) vs. n2=1 (1.43%); p =0.02. We did not find significant differences in the levels of DHEA-S in the groups n1=8 (11.43%) vs. n2=5 (7.14%); (p =0.25). The patients with acne vulgaris had significantly elevated levels of prolactin n1=11 (15.71%) in comparison with the healthy volunteers n2=3 (4.29%); p = 0.04. (Table 2).

Table.2 Data about statistic differences of the frequency of the laboratory and clinical parameters tested in the group of patients with Acne vulgaris and those in the group of healthy volunteers.

Indicators	Patients with acne vulgaris	Healthy volunteers	Significance (p values)
Elevated levels of Prol.	n=11(15.71%)	n=3 (4.29%)	p=0.04
Elevated levels of TTest.	n=9 (12.86%)	n=1 (1.43%)	p=0.02
Diseases of thyroid gland	n=16 (22.86%)	n=1 (1.43%)	p=0.0001
Elevated levels of TPO - ab	n=9 (12.86%)	n=0 (0.00%)	p=0.004
Elevated levels of TAT	n=7 (10.00%)	n=1 (1.43%)	P=0.01
Elevated levels of DHEA-S	n=8 (11.43%)	n=5 (7.14%)	P=0.25
Patients with IR above 2.5	n=10 (14.29%)	n=7 (10.00%)	P=0.53

Clinically diagnosed thyroid diseases with hormonal or autoimmune dysfunction were more frequently seen in patients with acne vulgaris than in patients without acne, and the differences between them were significant: n1=16 (22.86%) vs. n2=1 (1.43%); p = 0.0001. The results showed that 18.5% of the women in g1 suffered from AITD. The majority of patients (17.1%) were with Autoimmune Hashimoto's Thyroiditis, and only one woman (1.4%) had Graves' disease. Nodular goiter was found in one woman (1.4%) and subclinical hypothyroidism - in two patients (2.9%). According to the functional

activity of the thyroid gland in patients with AITD, we found that the majority of women were euthyroid. Thyroid dysfunction was found in a small number of patients. We established a higher frequency of AITD, especially in cases with Hashimoto's Thyroiditis in group 1, as compared to group 2 [n1=12 (17.1 %) vs. n2 = 1 (1.4%); (p = 0.001)] (Fig.3).

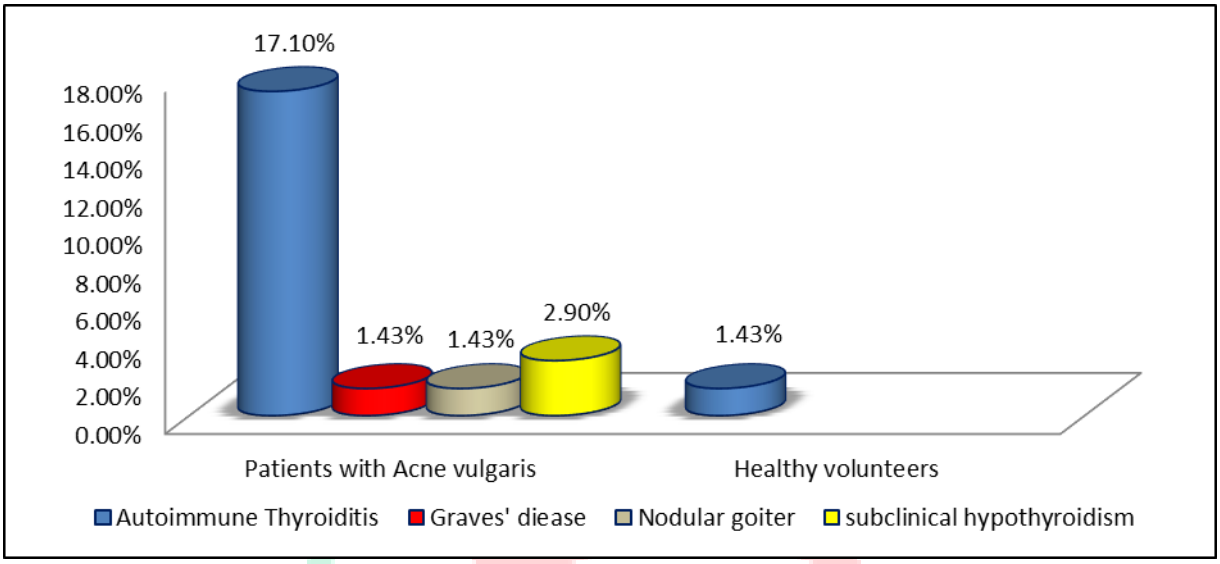

Figure.3 Frequency of thyroid diseases in combination with disorders in thyroid function and autoimmunity

Changes in thyroid autoimmunity were accompanied by finding antithyroid antibodies in the majority of women with AITD. The estimation of thyroid autoimmunity showed significantly higher levels of both TPO in patients with acne vulgaris, as compared with the control group [n_1=9 (12.8%) vs. n_2 = 0 (0%); p = 0.004, and TAT [n_1=7 (10%) vs. n_2=1 (1.43%); (p=0.01)]; (Tabl.2). A combination of AITD and PCOS was established in 20.00 % of the patient suffering from Acne vulgaris. We took a special interest in evaluating IRI in patients with acne. Ten patients in group one n_1= 10 (14.2%) had HOMA-IR above 2.5 (the so-called risk area), as compared to the group of healthy volunteers n_2=7 (10 %);(p=0.53). This result tended to be significant, and an association was revealed between of the values of HOMA-IR above 2.5 and existence of thyroid gland diseases in 17.14% of the patients with acne vulgaris.

Discussion:

The results from our study showed that the investigated patients with acne vulgaris also had PCOS and AITD. That combination has not been reported in the literature. First, we examined the relationship between combinations of IR, thyroid autoimmunity and skin changes. While attempting to explain why acne vulgaris is more common in female patients with AITD, we found out that some patients with autoimmune Hashimoto's Thyroiditis had insulin resistance. All of them had clinical features for MetS with a different degree of IR. Insulin resistance contributes but is not an isolated factor for the occurrence of acne. The causes are complex. IR is the major cause for hyperandrogenemia and hyperprolactinemia, and this complex relationship is involved in the pathogenesis of acne. Although we did not establish a statistically significant difference between IR and acne, we assume that in a larger scale study, a statistically significant relationship could be established. We supposed that IR with possible thyroid autoimmunity could be a key factor for the development of acne. We found acne vulgaris in 14.2% patients with HOMA-IR above 2.5, and 17.1% with of HOMA-IR above 2.5 in combination with AITD. We are aware that our hypothesis was based on a small number of participants and further investigations are necessary. The clinical significance of such combinations is that they are related to the occurrence of acne, its severity and response to treatment. Our data about the higher incidence of PCOS in the group of patients with acne vulgaris and the healthy control group were similar to that reported by Maluki (2010), who investigated 123 women aged 17 to 40 years with resistant to treatment for acne vulgaris and found PCOS in 51.2% of them [9]. Our results are supported by those from Zandi's study (2010). This study revealed a statistically significant relationship between the presence of PCOS and acne vulgaris [10]. Lee at al. suggested that acne vulgaris, hirsutism and androgenic alopecia can be considered as a dermatological expression of PCOS [11,12,13]. There

are few reports in the literature on the role of Prol and its association with acne vulgaris. Our results may confirm the role of prolactin in the development of acne vulgaris. We report a higher frequency of hyperprolactinemia (15.7%) in a small group of 35 patients. Makhecha et al. (2016) reported a lower incidence (8%) of hyperprolactinemia in a group of 50 patients with acne vulgaris. [14]. Hyperprolactinaemia is a hormonal feature for PCOS and contributes to ovarian hormonal dysfunction and maintenance the hyperandrogenic production. Another hypothesis about the role of Prolactin in major pathogenic mechanisms of Acne vulgaris is discussed by Chukwu et al. (2017). These authors suggest that Prolactin is involved in the process of subclinical skin inflammation through synthesizing and activating inflammatory cytokines [15]. We also report a significantly higher frequency of increased TTest levels and non-significantly higher levels of DHA-S in the group of patients with acne vulgaris. Similar results have been presented by Bakry et al. (2014) and Rahman et al. (2012) [16,17]. Androgens are a major factor in the pathogenesis of acne vulgaris. They increase sebum production and lead to follicular hyperkeratosis. Other studies have also shown elevated levels of TTest and DHEA-S in patients with Acne vulgaris, who which suffer from hirsutism, alopecia or menstrual disorders [18,19]. Our results support the hypothesis of Melnik et al. (2009) that insulin levels are involved in the pathogenesis of Acne vulgaris. Insulin acts on metabolism by controlling the levels of blood glucose. In a condition associated with chronic inflammation, such as acne vulgaris, high levels of proinflammatory cytokines activate p36MAPK - a mitogen activating protein kinase p36. It, in turn, induces an inflammatory response, resulting in the development of insulin resistance and blocking the differentiation and increasing the proliferation of basal keratinocytes [20,21]. Insulin resistance itself leads to hyperandrogenemia, whose clinical manifestations include hirsutism, alopecia, seborrhoea, acne vulgaris and signs of virilization [20]. The data we obtained about the relationship between HOMA-IR values in the group of patients with acne vulgaris over 2.5 was similar to that described by Emiroglu (2015) [22].

Our study established a higher frequency of autoimmune thyroiditis in the group of patients with acne vulgaris than in the healthy controls. These results are identical with the data described by Vergou et al. (2012) [23]. They revealed a significantly higher risk for elevated levels of TAT in patients with acne vulgaris, as compared to the group of healthy controls. However, their results are not associated with the age of the patients, as in our study. Vergou et al. (2012) reported that elevated levels of TAT cause autoimmune inflammation with subsequently induced cytokine synthesis of interleukin 1 (IL1), interferon alpha (INF alpha), interferon gamma (INF gamma), interleukin 2 (IL 2). Proinflammatory cytokines, in turn, activate the sebaceous gland function. However, in his article the authors proved statistically significant relationships between elevated TAT, but not in TPO-Ab levels. In our study, we emphasize the presence of both anti-thyroid antibodies TAT and TPO-Ab and give convincing evidence for their role in the pathogenesis of autoimmune inflammation in acne vulgaris.

Conclusion:

The data we obtained about this problem are the first reported in Bulgaria and the literature we studied. We found a statistically significant correlation, which has not been reported in the literature. This correlation is concerns the simultaneous combination of autoimmune thyroiditis and PCOS in the group of patients with acne vulgaris. Autoimmune thyroiditis in young women may be the cause of acne vulgaris, MetS including IR, and reproductive disorders in cases of PCOS. This relation should be further explored in further studies on a larger number of women.

Acknowledgement: This publication was funded by Project BG05M2OP001-2.009-0031-C01.

References:

1) Thappa D. Epidemiology of Acne. Ind J Dermatol Venereol Leprol. 2009; 75:1-3.
2) Kadurina M.I., Acne - pathogenetical, clinical and the rapeutical aspects. Dis, PhD degree. Clinic of Dermatovenereology, Military Medical Academy Sof., 2004
3) Chuan SS, Chang RJ. Polycystic Ovary Syndrome and Acne. Skin Therapy Lett. 2010; 10:1-4.
4) Saxena P., Prakash A., Nigam A. et al. Polycystic ovary syndrome: Is obesity a sine qua non? A clinical, hormonal, and metabolic assessment in relation to body mass index. Indian J Endocrinol Metab. 2012; 16:996–999.
5) Dreno B., Thiboutot D., Layton AM. Et al., Large-scale international study enhances understanding of an emerging acne population: adult females. J Eur Acad Dermatol Venereol. 2015; 29:1096–1106.

6) Adityan B, Kumari R, Thappa D. M et al. Scoring systems in acne vulgaris. Indian J Dermatol Venereol Leprol. 2009; 75:323-326.
7) Qu HQ., Li Q., Rentfro AR. et al. the Definition of Insulin Resistance Using HOMA-IR for Americans of Mexican Descent Using Machine Learning. PLoSONE. 2011:6;1-4.
8) Matthews DR., Hosker JP.,Rudenski AS.et al. Homeostasis model assessment: insulin resistance and b-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985:28;412–419.
9) Maluki AH. the frequency of polycystic ovary syndrome in females with resistant acne vulgaris. J Cosmet Dermatol. 2010; 9:142-148.
10) Zandi S., Farajzadeh S., Safari H. Prevalence of polycystic ovary syndrome in women with acne: hormone profiles and clinical findings. JPAD. 2010; 20:194-198.
11) Lee AT., Zane LT. Dermatological manifestations of polycystic ovary syndrome. Am. J Clin Dermatol, 2007;8:201-219.
12) Lujan ME., Jarrett BY., Brooks ED. et al, Updated ultrasound criteria for polycystic ovary syndrome: reliable thresholds for elevated follicle population and ovarian volume. Hum Reprod. 2013; 5:1361–1368.
13) Ramanand SJ., Ghongane BB., Ramanand JB. et al. Clinical characteristics of polycystic ovary syndrome in Indian women. Indian J Endocrinol Metab.2013;17:138–145.
14) Makhecha M, Gonsalves N, Singh T. Acne vulgaris - Associated Cutaneous Findings, PCOS and Hormonal Changes. Sch J App Med Sci. 2016; 4:4164-4170.
15) Chukwu EO., Ifeoma JO, Chia T. Et al. Comparative Study of Prolactin Levels in Acne and Non-Acne Individuals Among Students of College of Health Sciences, Nnamdi Azikiwe University, Nnewi, Nigeria. Int J Biomed Engineer Clin Sci 2017; 3:25-31.
16) Bakry OA., Azmi EL Shazly RM., Mahamoud El Farargy S. Et al. Role of hormones and blood lipids in the pathogenesis of acne vulgaris in non-obese, non-hirsute females. Ind Dermatol On J 2014;5: S9-S16.
17) Rahman M, Sikder AU.,Rashid MM et al. Association of Serum Testosterone with Acne vulgaris in Women. BSMMU J. 2012:5;1-5.
18) Pavicic BD., Skrgatic L., Bukvic MZ. et al. Hyperandrogenemia association with Acne and Hirsutism Severity in Croatian Women with Polycystic Ovary Syndrome. Acta Dermatovenerol Croat.2013;21:105-112.
19) Cinar N., Cetinozman F., Aksoy DY. et al. Comparison of adrenocortical steroidogenesis in women with post-adolescent severe acne and polycystic ovary syndrome. J Eur Acad Dermatol Venereol. 2015;29:875-880.
20) Napolitano M.,Megna M., Monfrecola G. Insulin Resistance and Skin Diseases. ScientificWorldJournal. 2015; 4:1-11.
21) Melnik BC, Schmitz G. Role of insulin, insulin-like growth factor-1, hyperglycaemic food and milk consumption in the pathogenesis of acne vulgaris. Exp Dermatol. 2009; 18:833-841.
22) Emiroglu N., Cengiz FP., Kemeriz F. Insulin resistance in severe acne vulgaris. Postepy Dermatol Alergol. 2015; 32:281–285.
23) Vegou T., Mantzou E., Tseke P. Et al. Association of thyroid autoimmunity with acne in adult women. J Eur Acad Dermatol Venereol. 2012; 26:413-416.