The high homeostatic model assessment of insulin resistance as risk factor for acne vulgaris

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ABSTRACT

Background: Acne vulgaris (AV) is a common chronic skin disease involving blockage and or inflammation of pilosebaceous glands which usually affects teenagers and young adults. Elevated sebaceous gland secretion, Propionibacterium acne colonization and inflammation, high androgen effects, and follicular hyperproliferation are the main pathogenic factors of AV. IGF-1 and insulin were studied to stimulate sebaceous lipogenesis. In the skin, besides inducing lipid production in human sebocytes IGF-1 also induces keratinocyte proliferation in vitro and in vivo. HOMA-IR is an examination to determine insulin activity in the basal state.
Objective: To prove that high HOMA-IR value is a risk factor for the occurrence of acne vulgaris.

Methods: This study is a case control analytic study by comparing HOMA-IR in subjects with AV (case group) and non AV (control group). AV is diagnosed based on clinical predilection. Insulin testing was carried out by the immulite 2000 device through the immunochemiluminescent method.
Results: Mean HOMA-IR of case group is 2.63 ± 0.29 meanwhile in the control group was 1.71 ± 0.26 (p <0.001). Subjects with high HOMA-IR had 4.8 times higher risk to experience AV compared to patients with normal HOMA-IR values (p <0.001; 95% CI 2.765-8.332).
Conclusion: HOMA-IR values in acne patients were higher than controls. A high HOMA-IR value is an AV risk factor.

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INTRODUCTION

Acne vulgaris (AV) is a chronic inflammatory disease of pilosebaceous follicle, characterized by blackheads, papules, pustules, nodules and often scarring that usually affects adolescents and young adults.[1] Acne vulgaris affects 40-50 million people in United States with peak incidence during adolescence . Acne also affected 85% of people in age ranged 12 to 24 years.[2] Study conducted by Suryadi showed that prevalence of AV was 40-80% in Southeast Asia, whereas in Indonesia, according to Indonesian cosmetics dermatology study reported the prevalence of AV is 60% in 2006, 80% in 2007, and 90% in 2009. The highest prevalence is in the age of 14-17 years, around 83-85% in women and around 95-100% in men aged 16-19 years.[3]

Elevated in sebaceous gland secretion, high androgen effects, Propionibacterium acne colonization, inflammation, and follicular hyperproliferation,[1,4] androgen triggers sebum production, sebaceous gland growth and hyperkeratinization[4] are the main pathogenic

factors of acne. Insulin and IGF-1 stimulate sebaceous lipogenesis. This is shown in sebocytes SEB-1 and by sterol induction response element-binding protein-1 (SREBP-1).[5] Insulin receptors are structurally as same as IGF-1 receptors and insulin can bind to IGF-1 receptors. At very high doses, insulin increases the expression of sebocyte growth hormone receptors.[5,6] In the skin, besides inducing lipid production in human sebocytes, keratinocyte proliferation in vivo and in vitro induced by IGF-1. In acne lesions compared to healthy skin, IGF-1 and IGF-1R were overexpressed. In acne lesions, excessive expression IGF-1 and IGF-1R were associated with increased expression of Ki-67 and filagrin in the epidermis, thus confirming that the IGF-1 / IGF-1R system was associated with modulation of keratinocyte differentiation and proliferation.[7]

HOMA-IR (homeostatic model assessment of insulin resistance) is an examination to determine insulin activity in the basal state.[8] Based on the cut-off point of Yamada's study (2011) in Japan it was stated insulin resistance if the HOMA-IR value ≥

2.5.[9] This study aims to prove that a high HOMA-IR value as a risk factor for acne vulgaris occurence.

MATERIAL AND METHODS

This is an analytical case control study which compared HOMA-IR in AV patients (case group) and non-AV patients (control group). Affordable populations were all patients with AV aged 12 - 55 years old who visited Dermato-venerology Polyclinic of Cosmetic Subdivision Sanglah Hospital Denpasar from July 2017 until August 2017.

Sampling method in this study is consecutive sampling to collect sample in affordable population. The inclusion criteria for the case group were all patients with acne vulgaris, male or female aged between 12 to 55 years, willing to be included in the study and signed the informed consent. Subjects with isotretinoin treatment, hormonal therapy (such as cyproterone acetate, ethinyl estradiol and drosiprenon), drugs that affect insulin metabolism (such as metformin and pioglitazone) or corticosteroids in the last 1 month and have conditions related to hormonal imbalances such as pregnancy, breastfeeding, ovarian tumors and diabetes mellitus were excluded from the case group. Each sample subjects then paired by one control that met the criteria and age-matched matching. The inclusion criteria of the control group were non-AV patients who visited the Dermato-Venerology Polyclinic of Cosmetic Subdivision Sanglah Hospital Denpasar, aged 12 to 55 years, both male or female, and willing to be included in this study by signed an informed consent.

AV is diagnosed based on efflorescence of polymorphic chronic eruptions; in the form of blackheads, then become papules, pustules, nodes or cysts in the predilection sites such as face, neck, chest, upper back, shoulders and upper arms. Insulin testing was conducted by the immulite 2000 device through the immunochemiluminescent method. HOMA-IR calculated by this formula: fasting insulin level (μU / ml) X fasting glucose (mg / dL) / 405 plasma. The collecting data then examined by statistical tests of SPSS program, version 16.0. This study has ethical permits with ethical clearance numbers 747/UN.14.2/KEP/2017 issued by Research Ethic Commission of Udayana University/Sanglah General Hospital.

RESULTS

The study was conducted at Dermato-Venerology Outpatient Clinic of Sanglah Hospital Denpasar from 8th July to 31th August 2017. Total number of subjects who fulfilled the inclusion and exclusion criteria were 76 subjects consisting of 38 acne subjects and 38 controls with age-based matching. The baseline characteristics of the research sample according to the descriptive analysis presented in Table 1.

Table 2 shows that the case group had higher mean of HOMA-IR (2.63 ± 0.29) than the control group (1.71 ± 0.26) with p value < 0.001. This shows that there is a significant difference of HOMA-IR in cases group compared with control group.

HOMA-IR is said to be high if ≥2.5 and normal if <2.5. From the crosstabulation table, there is an absolute 0 value in one column, so that the odds ratio cannot be calculated in this study. The role of high HOMA-IR value as risk factor for acne is proven through the proportion ratio which can be seen in Table 3.

In this population the proportion ratio is 4.8. It can be concluded that patients with high HOMA-IR have 4.8 times higher chance to experience acne compared with patients with normal HOMA-IR values. These results were statistically significant with p <0.001 and 95% CI (2.765-8.332).

DISCUSSION

In this study we found that the highest incidence of acne was in the age group of 15-24 years as many as 18 people (47.4%) and none in the age ≥ 45 years as shown in Table 1. This results also found in previous research by Ayudianti who identified acne patients in Dr. RSUD Sutomo Surabaya which acne was most often found in the age group 15-24 years (64.3%) and is rarely aged ≥ 45 years (0.8%).[10] Other studies also revealed that age groups suffering from AV in the age with a range of 17-21 year.[11]

The frequency of acne vulgaris was higher in the female, which was 28 people or 73.7%. This results also found in previous research by Pratiwi at the Derma Sakura Dermatology and Venereology Specialist Clinic in Bandung with the highest number of acne sufferers was female as many as 74 people (79.65%).[12] In women, a sudden increase in LH following the ovulation event triggers an increase in sebaceous gland activity.[13] Another possible reason is the use of cosmetics which can be one of the causes of acne in the female population.[14]

The most severe degree of acne was a mild degree of 22 people or 57.9%, followed by a moderate degree was 15 people or 39.5% and a severe degree was 1 person or 2.6%. This results also found in the previous study by Sutanto, namely that the most severe degree of acne was a mild degree of 37.5%, followed by a moderate degree of 35.9% and a severe degree of 26.6%.[15] The study by Shen in China showed the most was mild 68.4%, moderate 26% and only 5.6%.[16] Acne predilection area on the face, shoulder, upper arm, chest, and back.[17] Because

Tabel 1   Baseline characteristics of subjects

Characteristics	Group	
	Case N = 38 (%)	Control N = 38 (%)
Age (years old)		
≤14	4 (10.5)	2 (5.3)
15-24	18 (47.4)	23 (60.5)
25-34	14 (36.8)	10 (26.3)
35-44	2 (5.3)	3 (7.9)
≥45	0 (0)	0 (0)
Mean ± SD	23.71 ± 7.42	24.37 ± 7.31
Sex		
Male	10 (26.3)	10 (26.3)
Female	28 (73.7)	28 (73.7)
Body mass index (BMI)		
Underweight	8 (21.1)	9 (23.7)
Normal	24 (63.2)	22 (57.9)
Overweight	5 (13.2)	6 (15.8)
Obese I	1 (2.6)	1 (2.6)
Obese II	0 (0)	0 (0)
Mean ± SD	21.32±3.83	21.62±3.99
Severity of acne vulgaris		
Mild	22 (57.9)	
Moderate	15 (39.5)	-
Severe	1 (2.6)	
Family history		
Yes	28 (73.7)	22 (57.9)
No	10 (26.3)	16 (42.1)
Fasting blood glucose (mg/dL)		
Mean ± SD	117.65±6.29	99.48±9.61
Fasting blood insulin (µU/ml)		
Mean ± SD	9.07±0.79	6.9±0.53
HOMA-IR		
Mean ± SD	2.63±0.29*	1.71±0.26**

*Normality test of HOMA-IR in case group p=0.304
**Normality test of HOMA-IR in control group p=0.100

Tabel 2   Comparison of HOMA-IR value between case and control group

	Mean± SD	Difference± SD	95% CI	P value
HOMA-IR case	2.63±0.29	0.92±0.33	0.81-1.02	<0.001*
HOMA-IR control	1.71±0.26			

*Significancy if p<0.05

Tabel 3   High HOMA-IR value as the risk factor of acne vulgaris

Variable	Group		PR	CI 95%	P value
	Case n=38 (%)	Control n=38 (%)			
HOMA-IR					
High (≥2.5)	28 (73.7)	0 (0)	4.8	2.765-8.332	<0.001*
Normal (<2.5)	10 (26.3)	38 (100)			

*Significancy p<0.05; PR = proportion ratio

most acne lesions occur on the face, so often due to cosmetic and psychological problems for sufferers so they tend to seek treatment immediately when experiencing mild degrees of acne. This is what is likely to cause the acquisition of mild degrees as the most frequent degree of acne vulgaris in this study.

In this study found the mean fasting blood glucose level as higher in case group (117.65 ± 6.29 mg/dL) than the control group (99.48 ± 9.61 mg/dL) and was statistically significant (p<0.001). Likewise, the mean insulin level was higher in the case group (9.07 ± 0.79 µU/ml) than the control group (6.97 ± 0.54 µU/ml) which was statistically significant (p<0.001). This results also found in Del Prete's study which found that acne patients had higher fasting blood glucose and insulin levels than controls with p=0.03 and p=0.01 which were statistically significant.[18] Besides, Emigrolu's study found that fasting insulin levels in acne patients was significantly higher than control (p <0.001).[4]

Evidence shows that consumption of foods with high glycemic load can lead to acne by inducing compensatory hyperinsulinemia.[19] Foods with a high glycemic load cause increased response to glucose and higher blood insulin.[20] Prolonged high blood glucose levels decrease the response of ß cells to glucose stimulation and cause hyperglycemia which in turn will increase blood insulin concentration, thus affecting the levels of androgens and IGF-1, causing uncontrolled tissue growth and increased androgen synthesis which can aggravate acne.[5,21]

In this study, the HOMA-IR value of the case group was different (higher) than the control and was statistically significant. The difference was seen from the mean HOMA-IR case group of 2.63 ± 0.29 and in the control group was 1.71 ± 0.26 and the p value was <0.001. This shows that there is indeed a difference in the value of HOMA-IR which is statistically significant in the higher cases compared to the control with a value of p<0.001. This shows that there was significant differences between the HOMA-IR values of the two groups where the higher values was obtained in case group. The study by Emiroglu, in 243 acne patients found a significantly higher HOMA-IR value than 156 control patients with a p<0.001.[4] study by Del Prete, who compared 22 male acne patients and 22 controls that matched sex and age, it was found that acne patients had higher HOMA-IR values than controls (p-value 0.016).[18] Research by Maffeis, which compared 7 patients with acne and control, obtained higher HOMA-IR values than controls with p<0.05.[7] HOMA-IR values higher in acne patients is caused by hyperinsulinemia which can be caused by a diet with high glycemic load or some

systemic diseases or syndromes associated with insulin resistance.[4,6]

The calculation of proportion ratio obtained a value of 4.8, which means that patients with high HOMA-IR risk 4.8 times to experience acne compared to patients with normal HOMA-IR values. These results were statistically significant with p<0.001 and 95% CI 2.765-8,332. In the study of insulin resistance in acne by Emiroglu and friends, the HOMA-IR value was significantly higher in the case group (2.87 ± 2.56) than controls (1.63 ± 0.65) (p <0.001) which indicates that insulin resistance can play a role in the pathogenesis of acne.[4] Moreover, the Del Prete study found a significant increase in HOMA-IR in acne patients compared to controls.[18] The results obtained can be influenced by various factors such as samples, research sites and variables used in research, as well as the sensitivity of the equipment used.

The increased HOMA-IR value is thought to be due to its role in the pathogenesis of acne which involves an increase in blood glucose which triggers the insulin response. High insulin concentrations can cause exacerbations of acne by increasing the proliferation of basal keratinocytes in the ducts of the pilosebacea unit causing failure of terminal differentiation in follicular corneocytes, thereby demonstrating their involvement in the pathogenesis of acne. Furthermore, insulin also stimulates the synthesis of adrenal and gonadal androgens, androgen receptor signal transduction, sebocyte proliferation, sebum production, and sebaceous gland lipogenesis, thus affecting the development of acne.[6]

Higher HOMA-IR values was found in acne patients than the controls. A high HOMA-IR value is a risk factor for acne. Insulin reactivity can occur via cross-receptor signal transduction via the IGF-1 receptor. Activation of IGF-1 receptors can increase 5a reductase, synthesis of adrenal and gonad androgens, androgen receptor signal transduction, sebocyte proliferation, sebum production, and lipogenesis. Insulin growth factor-1 stimulates lipogenesis through the induction of SREBP-1 proteins that regulate fatty acid gene synthesis.[6,22]

CONCLUSION

In AV patients, HOMA-IR were higher than subjects without acne. It can be concluded that high HOMA-IR value is an independent risk factor for Acne Vulgaris.

CONFLICT OF INTERESTS

There is no personal or institutional interest regarding this article.

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AUTHOR CONTRIBUTION

All of authors are equally contributed to the study from the study framework, data gathering, data analysis, until reporting the result of study.

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