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Original Research

Omentin Val/Val genotype increases predisposition to acne vulgaris without changing omentin serum level

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Abstract: Acne vulgaris is the most frequent and multifactorial inflammatory skin disorder in all races. Obesity is considered to be a risk factor for acne due to its contribution to inflammation. The involvements of inflammatory (leptin and resistin) and anti-inflammatory (adiponectin) adipokines in the pathogenesis of acne were reported. Omentin resembles adiponectin in terms of having inhibitory effect on tumor necrosis factor-α (TNF-α) induced inflammation, a vital process in the acne formation. This study was designed to investigate the putative involvement of omentin in acne formation. The genotyping was performed by restriction fragment length polymorphism (RFLP) method. Serum omentin protein levels were analyzed by enzyme-linked immunosorbent assay (ELISA). Serum omentin level was not significantly changed between groups. However, the decreased serum omentin level was observed as the mean value of BMI increased. The Asp/Asp, Val/Asp and Val/Val genotypes distributions for control and patient groups (19[17.4%], 22[20.2%], and 3[2.8%] respectively, vs. 31[28.4%], 25[22.9%], and 9[8.3%], respectively) were obtained. The Val/Val (mutant homozygote) genotype was found nearly 1.8 times more in the patient group (p=0.403, OR=1.839 (0.442-7.653)). This is the first time to clarify a linkage between anti-inflammatory omentin and acne vulgaris. Omentin Val109Asp polymorphism affects the overall function of the protein. In conclusion, omentin Val/Val (mutant homozygote) genotype increases predisposition to acne vulgaris by probably disrupting overall protein function of omentin.

Key words: Omentin; Acne vulgaris; Inflammation; Obesity; Adipokines.

Introduction

Acne vulgaris is the most observed chronic inflammatory skin disease in all races. The symptoms of acne vulgaris mostly seem in adolescence and teenagers, but they may also be observed in forties and fifties of some people. So, acne vulgaris has potential to cause psychological and social problems not only in teenagers but also in adults (1, 2). Although several factors including androgen level, bacteria and genetics are accused to cause acne, the etio-patogenesis is still unclear. Typical definition of acne vulgaris is a formation of scar as a result of excessive accumulation of sebum produced by gland when follicles get blocked. Then, sebaceous gland response to Propionibacterium acnes localized in sebum by producing cytokines like interleukin-1β (IL-1β). Up to date, the involvement of inflammation in all kinds of acne vulgaris has been demonstrated (3).

Obesity is a risk factor for acne due to increasing sebum production by secreting adipokines. An association between high Body Mass Index (BMI) and acne vulgaris was demonstrated before (2). The adipocytes in visceral obesity make contribution to inflammation by inducing mammalian target of rapamycin complex 1 (mTORC1) production (driver of inflammation) as in the sebum production.

The putative involvement of adipokines in the pathogenesis of acne vulgaris has been identified recently (4). The adipose tissue has been assumed as an endocrine organ since characterization of the first adipokines called leptin in 1994. Then, the researchers have paid great attention to investigate new adipokines and its putative function in disorders. Nowadays, we clearly knew that adipokines take important roles in immunology and inflammatory processes (5-7). Omentin discovered in 2003, is the one of the latest characterized adipokine. The gene of omentin consists of 8 exons and 7 introns, and it is located in the first chromosome. Omentin with anti-inflammatory characteristic has been linked to several inflammatory disorders (8-10). However, the putative involvement of omentin in the formation of acne vulgaris has not been investigated yet. The genotyping has been done via molecular methods in many researches (11-14). In this research, the purpose, serum level of omentin and Omentin Val109Asp polymorphism were analyzed and compared between patients with acne vulgaris and healthy control groups.

Materials and Methods

Study participants and Measurements

The study population comprised 109 subjects (49 males and 60 females). Among them, 65 subjects aged 18 to 25 years were diagnosed with acne vulgaris in the

Dermatology Department of Duzce University Hospital and 44 age-compatible healthy volunteers as a control group. Full history of all participants was obtained, and the cases with systemic disorders (Diabetes, hypothyroidism or hyperthyroidism), dermatological disorders, acne lesions, pregnancy, malignancy and systemic drug or alcohol abuse were excluded from control group. This study conformed to the Declaration of Helsinki and approved by the Ethical Committee of Medical Faculty, University Duzce. Written informed consent was obtained from all individuals, after the main goal of this study had been informed. The demographic and biochemical characteristics of individuals were recorded. Body mass index (BMI) was calculated as the body mass divided by the square of the body height and expressed in units of kg/m^2. The laboratory parameters including High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), triglyceride and testosterone were measured enzymatically using spectrophotometric methods.

Genotyping

2 mL venous blood was taken from all individuals. DNA extraction was done as explained previously (15-17). Briefly, PureLink DNA isolation kit (Invitrogen, Carlsbad, CA) was used to obtain genomic DNA according to the manufacturer's instructions. Then, the samples were used to amplify target region including Val109Asp polymorphism site by the polymerase chain reaction (PCR). For this purpose, 1 µL (10 pmol) forward 5′-GAGCCTTTAGGCCATGTCTCT-3′ and reverse 5′-CTCTCCTTCTTCTCCAGCCCAT-3′ primers were used in a 25 µL total volume with 0.5 µL Taq DNA polymerase (Fermantas, Lithuania) to generate a 471 base-pair (bp) amplicon. 25 µL PCR mixture was exposed to 5 min at 94°C for pre-denaturation followed by 35 cycles of 1 min at 94 °C, 1 min at 58 °C, and 1 min at 72 °C, with a final step at 72 °C for 10 min by using Bioneer My GenieTM 96 Gradient Thermal Block (Daejeon, Korea).

The genotyping was performed by Restriction Fragment Length Polymorphism (RFLP) method. The amplicon were incubated with Xmil (AccI) restriction enzyme (NEB, UK) at 37 °C for overnight and analyzed on agarose gel stained with ethidium bromide. The genotypes were determined according to band profile on agarose gel as shown in Figure 1. The Asp/Asp homozygote genotype has no digestion site and show only one visualized band with 471 bp. Val/Asp heterozygote individuals show three bands with 471, 274 and 197 bp. Val/Val mutant homozygote individuals show two bands with 274 and 197 bp.

Serum omentin level and clinical measurement

Serum omentin concentrations were measured using a commercially available Omentin-1 enzyme-linked immunosorbent assay (ELISA) kit (Bio Vendor, Brno, Czech Republic) as described before. ELISA method was conducted according to manufacturer instruction. Body mass index was calculated as kg/m^2 for all participants.

Statistical Analysis

PASW 15.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses after collection of enough cases on the basis of statistical power analysis results. Descriptive parameters were presented as mean ± standard deviation (SD). For comparison of continuous variables in the two groups, independent sample *t*-test and Mann-Whitney U tests were used and the results were given as mean ± SD. Genotype was compared by using a Chi-square test, and the results were expressed as frequency and percentage. Binary logistic regression analyses were performed to identify independent predictors for acne vulgaris disease. A statistically significant criterion was accepted as a less than 0.05.

Results

The characteristics and laboratory parameters of patient and control groups within the study populations were summarized in Table 1. Patient with acne vulgaris and control groups consist of 65 individuals with mean age of 19.55±4.16 and 44 individuals with mean age

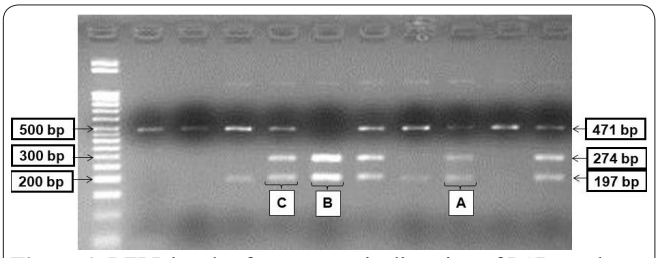

Figure 1. RFLP bands after enzymatic digestion of PCR products. The genotyping for omentin Val109Asp SNP was conducted with RFLP method. After amplification of target sequence, the products of PCR were digested with AccI restriction enzyme and run into 2% agarose gel. A) Asp/Asp homozygote genotype (just one band). B) Val/Asp heterozygote genotype (three bands). C) Val/Val homozygote genotype (two bands).

Table 1. Comparison of characteristics and laboratory parameters in patient and control groups.

Variables	Total (109)	Acne (65)	Control (44)	p
Age (Year)	19.86±3.74	19.55±4.16	20.31±3.00	0.297
BMI (kg/m^2)	22.44±3.19	22.41±3.06	22.48±3.41	0.912
Glucose (mg/dL)	90.71±10.40	90.96±8.83	90.34±12.40	0.767
HDL (mg/dL)	50.67±14.30	52.91±14.43	47.44±13.62	0.053
LDL (mg/dL)	91.25±29.42	88.14±26.54	95.44±32.78	0.220
Triglyceride (mg/dL)	107.35±51.73	93.11±44.53	128.39±62.37	0.001
Testosterone (ng/mL)	225.19±248.48	243.10±262.89	199.79±227.08	0.384
Omentin (ng/mL)	641.00±217.78	657.53±203.69	611.16±241.30	0.308

BMI: Body Mass Index, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein.

Table 2. Omentin Val109Asp SNP genotypes distributions in the patient and control groups

Genotypes	Total (109)	Control (44)	Acne (65)	p (χ2)	OR* (95% Cl)	P*
Asp/Asp n (%) (Ref)	50 (45.9)	19 (17.4)	31 (28.4)		Ref	-
Val/Asp n (%)	47 (43.1)	22 (20.2)	25 (22.9)	0.349	0.696 (0.310-1.564)	0.381
Val/Val n (%)	12 (11)	3 (2.8)	9 (8.3)		1.839 (0.442-7.653)	0.403
Val/Asp+Val/Val n (%)	59 (54.1)	25 (23)	34 (31.2)	0.643	0.834 (0.386-1.800)	0.643

Val/Val=GTC/GTC, Val/Asp=GTC/GAC, Asp/Asp=GAC/GAC, OR: odds ratio, Cl: confidence interval, * for logistic regression.

Table 3. Comparison of characteristics and laboratory parameters in Omentin Val109Asp genotypes.

Variables	Val/Val (12)	Val/Asp (47)	Asp/Asp (50)	p
Age (Year)	22.42±6.30	19.85±3.19	19.26±3.22	0.03
BMI (kg/m^2)	23.36±3.34	22.14±3.20	22.51±3.18	0.49
Glucose (mg/dL)	91.33±8.48	90.18±11.65	91.04±9.80	0.90
HDL (mg/dL)	53.75±8.92	50.22±14.34	50.33±15.45	0.73
LDL (mg/dL)	75.73±24.73	99.83±34.12	86.76±22.90	0.01
Triglyceride (mg/dL)	78.17±24.15	112.27±44.76	110.50±66.79	0.14
Testosterone (ng/mL)	173.10±243.74	230.69±259.81	233.18±242.63	0.74
Omentin (ng/mL)	668.93±180.10	656.89±216.34	619.14±229.23	0.64

BMI: Body Mass Index, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein.

of 20.31±3.00 respectively. In the comparison of these groups in terms of the characteristics and laboratory parameters, no statistically significant variables including omentin serum level were observed except triglyceride level.

Omentin Val109Asp genotypes distributions in patient and control groups were summarized in Table 2. The Asp/Asp genotype was found in 19 (17.4%), Val/Asp genotype in 22 (20.2%), and Val/Val genotype in 3 (2.8%) individuals in the control group. In the patient group, Asp/Asp genotype was found in 31 (28.4%), Val/Asp genotype in 25 (22.9%), and Val/Val genotype in 9 (8.3%) individuals. The total of Val/Asp and Val/Val genotypes were calculated in 25 (23%) and 34 (31.2%) individuals in the control and patient groups respectively. No statistical significance was determined for all genotypes (p>0.05). However, Val/Val genotype was found nearly 1.8 times more in the patient group than in the control group (p=0.403, OR=1.839 (0.442-7.653)).

The characteristics and laboratory parameters of Omentin Val109Asp genotypes were summarized in Table 3. The Val/Val, Val/Asp, and Asp/Asp genotypes were consisted of 12 individuals with mean age 22.42±6.30, 47 individuals with mean age 19.85±3.19, and 50 individuals with mean age 19.26±3.22 respectively. When comparing the groups in terms of the variables, age and LDL were found to be statistically significant between groups. Omentin serum level was not significantly changed.

Discussion

Acne vulgaris is the most prevalent skin disorder causing psychological problem, especially in juvenile. Although acne vulgaris was known to be a multifactorial disorder, it was well identified that genetics and inflammation are key components in the formation of acne vulgaris. (18). Adipose tissue has been considered as an endocrine organ due to secreting several functional adipokines like omentin. However, the linkage between adipokines and acne vulgaris has not been widely studied yet. An identification of biomarkers for acne vulgaris might be very helpful to establish new treatment methods, and the adipokines has potential to be biomarker for acne vulgaris (19, 20). For this purpose, the putative involvement of the omentin with anti-inflammatory property in acne vulgaris was investigated. The omentin serum level was not significantly changed between groups. The aspartic acid at the position 109 is less conserved when compared the alanine at the position 108 which is completely conserved. The potential effects of the SNP at position 109 (Val109Asp) on the overall function of omentin protein were put forward in the literature (21). So, we investigated the Val109Asp genotypes distributions to compare between groups. The frequency of Val/Val genotype was found to be nearly 1.8 times more in the patient group than in control group (p=0.403, OR=1.839 (0.442-7.653)). It can be speculated that the Val/Val genotype might be a risk factor for acne vulgaris development.

The increment of BMI is considered as a risk factor for acne vulgaris, but the relationship between them remains uncertain. So, the putative effects of dietary factors were taken great attention by researchers. As well as a specific dietary, the accumulated adipose tissue might cause acne vulgaris. The adipose tissue by secreting adipokines contributes to the chronic inflammation occurring in many inflammatory disorders like acne vulgaris (22, 23). So, the adipokines became target due to having potential to be a marker for acne vulgaris. Leptin is the first characterized adipokine, the linkage between leptin and inflammatory processes has already been established (24). Similarly, the increased serum level of leptin in acne was also reported by *Abulnaja et. al.* (25). In this research, the serum level of leptin in obese acne patients (0.9 ± 0.2) was found higher than non-obese acne patient (0.4 ± 0.12), obese healthy subjects (0.6 ± 0.15) and non-obese healthy subjects (0.29 ± 0.1). According to results, serum leptin level was increased obesity-related acne vulgaris cases. In this case, leptin with inflammatory characteristics may contribute to acne formation by increasing inflammation. Isotretinoin

(13-cis-Retinoic acid) is the most effective and widely used medicine in severe acne treatment due to reducing sebum production and inflammation. A study conducted to reveal putative effect of isotretinoin on leptin level was demonstrated that isotretinoin significantly decreased the serum level of leptin (26). Adiponectin is relatively recently characterized adipokine and considered to involve in the pathogenesis of acne vulgaris. The decreased serum level of adiponectin in acne patients was reported before (27). In addition, the significantly elevated adiponectin level in acne patients after isotretinoin treatment was reported by several groups. Even if it is controversial, adiponectin was accepted to show anti-inflammatory property in most cases. The reason for elevated serum adiponectin level might be the suppression effect of isotretinoin on inflammation (26, 28). The inflammatory features of resistin as an adipokine has already characterized (29), the involvement in the formation of acne vulgaris was investigated by *Harrison et. al.* They showed that resistin was expressed from basal sebocytes, indicating the linkage to inflammatory skin disorder like acne vulgaris (30). In addition, strong association between acne vulgaris and resistin SNPs (-420 C/G and +299 G/A) were demonstrated by researchers (31, 32). Visfatin is also another inflammatory adipokine (33), and a hypothesis of its involvement in the skin disorders was put forward by Kovács D et al (34). They showed that the high level of visfatin is founded in sebocytes. With the inflammatory characteristics, visfatin might take an inflammatory role in the formation of dermatological disorders.

Several cytokines including interleukins (IL) and Tumor Necrosis Factor-α (TNF-α) take central place in the pathogenesis of inflammatory pathological processes like acne vulgaris due to involving in inflammatory biological pathways (35, 36). The mutations in these genes might play critical roles in the pathogenesis of acne vulgaris (37). The increased serum levels of IL-1β and IL-8 in acne vulgaris were reported by several groups (25, 38). *Hussain et al.* (39) reported not only elevated serum level of IL-8 but also the association between the IL-8-251T>A polymorphism and acne vulgaris. Acne vulgaris was also associated with IL-6-572 G/C and IL-1A-889 C/T polymorphism (40). IL-1A-889 C/T polymorphism was also linked to acne vulgaris by Ibrahim et al (41). They speculated that the triggering or exacerbating effect of diet on acne may be related to IL-1A-889 C/T gene polymorphism. Another important systematic pro-inflammatory cytokine is TNF-α. TNF-α is also one of the most important agent and takes central role in the inflammatory response by initiating and regulating the cytokine cascades. The importance of the TNF -308 G>A in acne vulgaris pathogenesis was showed by both experimental and meta-analysis (42, 43). TNF-α has also vital position in the pathogenesis of acne vulgaris by regulating matrix metalloproteinases (MMPs) expression level. MMPs play decisive roles by degradation of extracellular cell components. Its activity is regulated by tissue inhibitors of metalloproteinases (TIMPs), and the ratio between MMPs and TIMPs has vital importance for hemostasis. TNF-α can induce atrophic or hypertrophic scars in acne patients by disrupting this balance (44).

Unlike other adipokines, omentin in the pathogenesis of acne vulgaris has not been studied before. Omentin resembles to adiponectin in terms of many respects including the inhibitory effect on TNF-α induced inflammation and decreased serum level in obesity. Although the exact mechanism is not clear, the involvement of adiponectin in the formation of acne vulgaris was demonstrated. In addition, omentin was involved in other skin disorders including psoriasis (45) and behcet (46). These findings took our attention to investigate whether omentin takes any role in the pathogenesis of acne vulgaris. According to our results, serum omentin level and genotypes distributions were not statistically significant. However, the mutant homozygote genotype (Val/Val) was found nearly 1.8 times more in the patient group than the control group. Omentin Val109Asp polymorphism affects the overall function of the protein. In conclusion, omentin Val/Val genotype may increase predisposition to acne vulgaris by disrupting overall protein function of omentin. However, to be an attractive target for new treatment methods, the exact mechanism of omentin in the pathogenesis of acne should be explored further. However, our main limitation is the limited number of study population. Therefore, it might be better to repeat this research using a larger study population.

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Interest conflict
The authors have no conflict of interest to declare.

Author's contribution
KOY and HT designed the study. HS, EY, and EK performed the experiments and generated the data. KOY, HT and EK analyzed and interpreted the data. HS, EY and EK wrote the manuscript. KOY revised the final version of manuscript.

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