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ORIGINAL ARTICLE

Insulin resistance and acne: a new risk factor for men?

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Abstract The purpose of this study is to investigate the relationship between acne and insulin resistance as well as other metabolic impairment in young males. Acne is a skin disease that can be influenced by endocrine abnormalities. In females, it is associated with polycystic ovary syndrome, with peripheral insulin resistance and hyperinsulinemia, whereas few data are available in males. For investigating this, 22 young males with acne have been compared to 22 controls of comparable age and gender. Acne was scored using the global acne grading system score. Clinical as well as biochemical parameters of glucose and lipid metabolism, circulating levels of androgens, and IGF-1 were evaluated. Oral glucose tolerance test was performed and homeostasis model assessment of insulin resistance was calculated. The results thus obtained are as follows, patients had higher BMI ($p = 0.003$), WC ($p = 0.002$), WHR ($p = 0.02$), SBP ($p = 0.0001$), DBP ($p = 0.001$), basal ($p = 0.01$) and 120 min. oGTT serum insulin concentrations ($p = 0.002$), basal glucose concentrations ($p = 0.03$), HOMA-IR ($p = 0.016$), and lower HDL-cholesterol than controls ($p = 0.001$). Among the subgroup of subjects with BMI <24.9, HDL-cholesterol ($p = 0.05$) and 120 min. oGTT serum insulin concentrations ($p = 0.009$) resulted to be independent predictors of acne at multivariate analysis. In conclusion, these findings highlight a metabolic imbalance in young males affected with acne. Insulin resistance seems to play the main role for the development of acne in these subjects. Insulin resistance could represent an effective target for therapy in male acne.

KeyWords Acne · Male acne · Insulin · Insulin resistance · HDL-cholesterol

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Introduction

Acne is a common and complex skin disease. It is a chronic inflammation of pilosebaceous unit, which involves hyperkeratosis and sebaceous hypersecretion. It is more prevalent in adolescence and in female gender and is commonly located in face, shoulders, back, and chest. Genetic modeling using acne scores showed that 81 % of the variance of the disease was attributable to additive genetic effects [1].

Sebum production is one of the key factors in the pathogenesis of acne [2]. Sebum production is regulated by androgens, and in few cases androgen excess may influence or aggravate acne in susceptible individuals [3, 4]. Sebum production begins during puberty in correspondence with the peaking levels of growth hormone and insulin-like growth factor 1 (IGF-1) that occur in mid-puberty [5–9].

Acne can be related to some endocrine diseases: the most common in females is polycystic ovary syndrome (PCOS). There are acne symptoms in 70 % of PCOS cases. PCOS is typically characterized by hyperandrogenism, chronic anovulation, and polycystic ovaries. Women with PCOS have abnormalities in the metabolism of androgens and estrogen, and in the control of androgen production. PCOS is also associated with peripheral insulin resistance and hyperinsulinemia, and obesity amplifies the degree of both abnormalities [10–12]. These rates show that there is a

relationship between the metabolic profile and acne. However, this relationship has not been investigated in male gender.

In males, the relationship between acne and insulin resistance has been poorly investigated. Smith et al. [13] showed that a low-glycemic-load diet induced an improvement in acne severity and in parallel in insulin-sensitivity, as expressed by HOMA index, suggesting that nutrition-related lifestyle factors may play a role in the pathogenesis of acne.

The objective of this study was to investigate the relationship between acne and insulin resistance as well as other metabolic abnormalities in a sample of young males with acne.

Subjects and methods

Subjects

Twenty-two males with inflammatory acne were recruited in the Department of Dermatology of Federico II University of Naples. This study included only male subjects aged 15–26 years who were affected with acne resistant to common therapies. We classified as "resistant" those patients affected with acne from a minimum of 1 year, with no improvement during the last 6 months, also if they performed all the strategies suggested by guidelines for acne therapy [14]. We also evaluated 22 healthy subjects without acne who were comparable for age and gender to subjects with acne. There was a family history for type 2 diabetes mellitus in 7 subjects with acne (32 %) and 4 controls (18 %), without significant differences between groups. The study was conducted after obtaining approval from the Guarantee Committee Department for the case–control Studies. A written informed consent was obtained from each participant or guardian (if aged <18 years old).

Methods

At the dermatological examination, acne was classified according to the degree of disease in mild-moderate-severe acne by a global acne grading system (GAGS) >15. The GAGS considers six locations on the face and chest/upper back, with a factor for each location based toughly on surface area, distribution, and density of pilosebaceous units. The global score is the summation of all local scores (0 = None, 1–18 = Mild, 19–30 = Moderate, 31–38 = Severe, >39 = Very severe) [15].

Height, weight, body mass index (BMI), waist circumference (WC), waist to hip ratio (WHR), and measurements of systolic (SBP) and diastolic blood pressure (DBP) were evaluated by standard methods. BMI was measured as the ratio between the weight and the square of the height. A BMI between 25 and 30 was considered as index of overweight while >30 as index of obesity [16]. WC was measured as the smallest torso circumference between the twelfth rib and the iliac crest. WHR was measured as the ratio between the WC and the circumference of the hip, considered as the maximal extension of the buttocks. The measurements were performed with the patients in standing position with relaxed abdomen, arms at sides, and joined feet. WHR >0.8 in females and WHR >0.95 in males are considered abnormal values [17]. Blood pressure was measured in the right arm, with the subjects in relaxed sitting position. The average of six measurements (three taken by each of two examiners) with a mercury sphygmomanometer was used. Hypertension was diagnosed when DBP values were >90 mmHg and SBP values were >140 mmHg. Hypertension was graded as grade 1 when DBP is between 90 and 99 mmHg and SBP between 140 and 159 mmHg, grade 2 when DBP is between 100 and 109 mmHg and SBP between 160 and 179 mmHg and grade 3 when DBP is >110 mmHg and SBP >180 mmHg [18].

To make the diagnosis of Metabolic Syndrome at least two of the following criteria are required: the presence of abdominal obesity which is defined with different cut-offs of the WC according to ethnic group of the patients (for Europeans >94 cm in men and >80 cm in females); serum triglycerides >150 mg/dl, cholesterol levels HDL < 40 mg/dl (in men) and <50 mg/dl (in female) or lipid-lowering therapy, blood pressure >130/85 mmHg or antihypertensive treatment, and fasting glucose >100 mg/dl or previous diagnosis of diabetes mellitus Type 2 [19–22].

In all subjects, serum blood samples were obtained by standard methods to measure total (total-cholesterol; <200 mg/dl) and high density lipoprotein cholesterol (HDL-cholesterol; >45 mg/dl), triglycerides (<180 mg/dl), glycemia (60–110 mg/dl), insulin (5–20 μU/ml), and glycated hemoglobin (<6 %). An oral glucose tolerance test (oGTT) was also performed (75 g of glucose diluted in 250 ml of saline solution, measuring blood glucose every 30 min for 2 h). The homeostasis model assessment of insulin resistance (HOMA-IR; 0.23–2.5) was calculated as fasting glucose × fasting insulin/405 [23].

The hormonal work-up included free testosterone (15–40 μg/ml), total testosterone (10.4–34.7 nmol/l), dehydroepiandrosterone sulfate (DHEAS; 35–430 μg/dl), sex hormone-binding globulin (SHBG; 6–50 nmol/l), and Insulin-like Growth Factor 1 (IGF-1; 90–280 mg/ml), which were evaluated by standard methods using commercially available kits.

Statistical analysis

Statistical analyses were performed by using SPSS 17.0 for WINDOWS (SPSS Inc, Chicago, IL). The comparison

between numerical data was performed by the Wilcoxon test. The correlation study was performed by the linear regression analysis calculating the Pearson's coefficient. The multiple regression analysis was performed among the variables correlated at the linear correlation. A ROC analysis (receiver operator characteristic) was performed by a non-parametric model to test that/those parameter/s significantly distinguishing subjects with acne and controls to determine the best cutoff in differentiating the two groups. Data were reported as Mean ± SEM. p values <0.05 were considered significant.

Results

Of the 22 subjects with acne, 7 had mild, 12 moderate, and 3 severe acne. Among these subjects, the biochemical work-up identified a condition of impaired glucose tolerance in 4.5 %, diabetes mellitus in none, while hypercholesterolemia was in 22 %. Grade 1 arterial hypertension was in 18 % of subjects with acne, while grade 2 and grade 3 in none. Overweight was in 36 %, obesity in 4.5 %, increased WC in 18 %, and WHR in 10 %. Metabolic syndrome was in 36 % of subjects with acne and in none of controls. At the linear correlation study, there was a significant correlation between family history for type 2 diabetes mellitus and BMI ($r = 0.7$, $p = 0.0001$), WC ($r = 0.5$; $p = 0.01$), and WHR ($r = 0.5$, $p = 0.016$) and an inverse correlation between acne score and age of the subjects ($r = -0.49$, $p = 0.02$). As compared to controls, the subjects with acne had higher BMI ($p = 0.003$), WC ($p = 0.002$), WHR ($p = 0.02$), SBP ($p = 0.0001$), DBP ($p = 0.001$), HOMA-IR ($p = 0.016$), and lower HDL-cholesterol ($p = 0.001$). Total cholesterol, triglycerides, serum IGF-1, and androgen levels were similar in subjects with acne and controls (Table 1). Baseline serum insulin and glucose concentrations were significantly higher in subjects with acne ($p < 0.05$). In parallel, oGTT curves were significantly different between subjects with acne and controls (Figs. 1, 2). At 120 min. oGTT, serum glucose levels were similar between subjects with acne and controls, while serum insulin levels were significantly higher in subjects with acne than in controls ($p = 0.002$) (Table 1).

A subgroup analysis was then performed by excluding subjects with overweight/obesity (BMI >24.9). At the linear correlation study, among the 13 subjects with acne and BMI ≤24.9, there was a significant correlation between acne score and HOMA-IR ($r = 0.50$, $p = 0.04$), 120 min. oGTT serum glucose levels ($r = 0.56$, $p = 0.05$), serum IGF-1 levels ($r = 0.60$, $p = 0.03$), a correlation between family history for type 2 diabetes mellitus and BMI ($r = 0.5$, $p = 0.04$), and an inverse correlation persisted between acne score and age ($r = -0.70$, $p = 0.008$). By comparing the 13 subjects with acne and BMI ≤24.9 with 13 age-matched controls, SBP ($p = 0.0001$), DBP

Table 1 Clinical and metabolic characteristics of subjects with and without acne: whole population

	Subjects with acne ($n = 22$)	Subjects without acne ($n = 22$)	p (Wilcoxon test)
Age	18.6 ± 2.5	20.2 ± 3	0.06
BMI (Kg/m^2)	24 ± 2.8	20.1 ± 1.5	0.003
WC (cm)	86.8 ± 9.8	83.4 ± 8	0.002
WHR	0.8 ± 0.1	0.7 ± 0.1	0.02
SBP (mmHg)	128.1 ± 7.9	112.5 ± 9	0.0001
DBP (mmHg)	80.9 ± 6.4	72.9 ± 7.8	0.001
Fasting serum glucose (mg/dl)	88.9 ± 7.8	84.3 ± 5.9	0.03
Fasting serum insulin (μU/mL)	10.6 ± 8.4	5.5 ± 1.4	0.01
120 min oGTT serum glucose (mg/dl)	86.5 ± 19.4	85.4 ± 8.3	0.8
120 min oGTT serum insulin (μU/mL)	30.1 ± 30.4	7.6 ± 1.2	0.002
HOMA-IR	1.7 ± 0.8	1.1 ± 0.3	0.016
Total cholesterol (mg/dl)	168.9 ± 33.1	166.7 ± 17.6	0.78
HDL cholesterol (mg/dl)	46.5 ± 8	57.3 ± 8	0.001
Triglycerides (mg/dl)	83 ± 3.2	78.5 ± 22.3	0.4
Serum IGF1(nmol/L)	338.8 ± 81	308 ± 58	0.15
Free testosterone (pg/ml)	16.8 ± 11.6	20 ± 14	0.82
Total testosterone (ng/dl)	5.1 ± 1.5	5.3 ± 1.3	0.92
DHEAS (μg/dl)	232.5 ± 142.7	211.7 ± 163.5	0.7
SHBG (nmol/L)	30.1 ± 8.1	31.6 ± 9.4	0.3

BMI body index mass, *WHR* waist/hip ratio, *HOMA-IR* homeostasis model assessment of insulin resistance, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *DHEAS* dehydroepiandrosterone sulfate, *SHBG* sex hormone-binding globulin, *WC* waist circumference, and *oGTT* oral glucose tolerance test

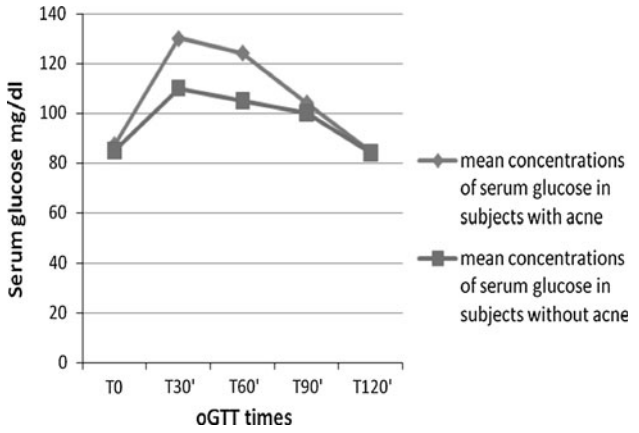

Fig. 1 Comparison of mean concentrations of serum glucose for each time of OGTT in subjects with acne and subjects without acne

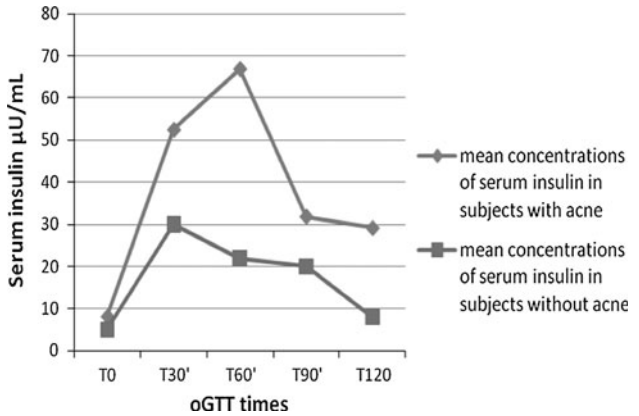

Fig. 2 Comparison of mean concentrations of serum insulin for each time of OGTT in subjects with acne and subjects without acne

($p = 0.03$) and 120 min. oGTT serum insulin levels ($p = 0.009$) were significantly higher in subjects with acne than controls, while HDL-cholesterol was higher in controls than in subjects with acne ($p = 0.05$) (Table 2). At the multivariate analysis, there were two independent predictors of acne: HDL-cholesterol ($t = -2.6$, $p = 0.02$) and 120 min. oGTT serum insulin levels ($t = 2.1$, $p = 0.04$). At the ROC analysis, a cut-off of HDL-cholesterol of 48.5 mg/dl significantly distinguished subjects with and without acne with sensitivity 61 % and specificity 92 % ($p < 0.003$), while a cut-off of 120 min. oGTT serum insulin levels of 9.6 µU/ml significantly distinguished subjects with and without acne with sensitivity 85 % and specificity 100 % ($p < 0.002$).

Discussion

This study investigated the relationship between metabolic abnormalities and acne in a sample of males affected with acne. In females with acne and PCOS, insulin resistance is a well known etiopathogenetic factor, while poor data are available in males. Acne incidence has been related to changes in insulin and IGF-1 circulating levels rather than to changes in androgen levels. During puberty and adolescence, there is a reduction in insulin sensitivity, combined with an increase in IGF-1 and insulin serum levels and a decrease in SHBG and IGFBP-1 serum levels. In particular, insulin and IGF-1 levels peak during late puberty and gradually decline until the third decade. Acne begins about the same time as the preadolescent increase in plasma insulin, IGF-1, and BMI, and generally resolves by the end of puberty despite circulating androgens remain unchanged [24]. Smith et al. [13, 24, 25] suggest that increases in dietary glycemic load may augment the biological activity of IGF-1 as well as of sex hormones, suggesting that dietary regimens rich in carbohydrates may stimulate factors potentially involved in acne development.

In the current study, two groups of male subjects with resistant acne and paired controls were considered regardless from the type of dietary regimen. All subjects with acne had a significant increase in BMI, WC, WHR, SBP, DBP, HOMA-IR and 120 min. oGTT, and serum insulin levels, and a significant reduction of HDL-cholesterol values. The subgroup of young males with acne showed in the majority of cases an impaired metabolic profile and decreased insulin sensitivity, resulting in a condition of metabolic syndrome in 36 % of them, while a family history for type 2 diabetes mellitus also occurred in 32 % of them, indicating an imbalance in glucose/insulin metabolism in this population.

One hypothesis is that metabolic impairment in these subjects can influence one of the key pathogenesis factor of acne, such as the proliferation of basal keratinocytes in the sebaceous-pilosebaceous unit. These modifications can aggravate the abnormal desquamation of follicular corneocytes that is often altered in patients with acne. These data suggest that insulin resistance might play an important role in the development of acne in males that are no responders to common therapies. With respect to females with PCOS, who have hyperinsulinemia and hyperandrogenism [26, 27], in all males with acne here evaluated, the androgenic profile was found to be normal, suggesting that acne in these patients can be influenced by hyperinsulinemia but not by androgen activity. This finding is supported by the fact that even in subjects with acne and BMI <24.9 there is an independent relationship between acne and hyperinsulinemia.

Beyond insulin, HDL cholesterol seems to be another metabolic parameter influencing the development of acne in males. In the current study, HDL-cholesterol resulted to be an independent predictor of acne at the multivariate analysis. A relationship between low HDL cholesterol values and insulin resistance has been reported in females

Table 2 Clinical and metabolic characteristics of subjects with and without acne: only subjects with BMI < 24.9

	Subjects with acne ($n = 13$)	Subjects without acne ($n = 13$)	p (Wilcoxon test)
Age	18.6 ± 3	20 ± 3.1	0.1
BMI (Kg/m^2)	22.2 ± 2.1	20.7 ± 1.7	0.1
WC (cm)	83.3 ± 10	79.4 ± 7.6	0.02
WHR	0.8 ± 0.05	0.7 ± 0.07	0.04
SBP (mmHg)	128.1 ± 7.9	112.5 ± 9	0.0001
DBP (mmHg)	80.9 ± 6.4	72.9 ± 7.8	0.03
Fasting serum glucose (mg/dl)	87.3 ± 8.6	84.3 ± 6.3	0.3
Fasting serum insulin (μU/mL)	10.3 ± 9.2	5.2 ± 1.2	0.09
120 min oGTT serum glucose (mg/dl)	84.3 ± 21.6	83.3 ± 9.7	0.05
120 min oGTT serum insulin (μU/mL)	20.5 ± 14.7	7.6 ± 1.2	0.009
HOMA-IR	1.5 ± 0.7	1.1 ± 0.3	0.05
Total cholesterol (mg/dl)	179.5 ± 32.2	165. ± 19.4	0.2
HDL cholesterol (mg/dl)	47.1 ± 7.2	58.8 ± 8.3	0.05
Triglycerides (mg/dl)	85.1 ± 19.5	83.6 ± 15.3	0.83
Serum IGF1(nmol/L)	325.3 ± 97.2	318.3 ± 67	0.03
Free testosterone (pg/ml)	22.6 ± 19.8	21 ± 18.8	0.8
Total testosterone (ng/dl)	5.4 ± 1.6	5.4 ± 1.4	0.9
DHEAS (μg/dl)	222.6 ± 116.5	180.5 ± 167.9	0.46
SHBG (nmol/L)	32.4 ± 8.9	32.8 ± 7.8	0.9

BMI body index mass, *WHR* waist/hip ratio, *HOMA-IR* homeostasis model assessment of insulin resistance, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *DHEAS* dehydroepiandrosterone sulfate, *SHBG* sex hormone-binding globulin, *WC* waist circumference, and *oGTT* oral glucose tolerance test

with acne [28, 29]. In male with acne, insulin resistance seems to play a major role in the development of this skin abnormality, while low HDL cholesterol likely influences indirectly acne development through the metabolic syndrome, of which represents a well known risk factor.

Both these abnormalities might influence each other and results in the induction of acne. On the other hand, increased BMI as well as all other characteristics of metabolic syndrome affecting males with acne would be likely a consequence of insulin resistance and low HDLcholesterol.

Finally, a cut-off of HDL-cholesterol of 48.5 mg/dl and of 120 min. oGTT serum insulin levels of 9.6 μU/ml significantly predict the presence of acne and should be used to adopt a life-style intervention based on proper diet and appropriate physical activity to improve lipid profile and decrease insulin resistance.

Our study highlights a close relationship between inflammatory acne and insulin resistance in males. In fact, these findings show a worse metabolic profile in male subjects affected with acne than in controls, consistent with an increase in insulin resistance and decrease of HDL cholesterol serum levels. These factors, as already seen in female gender, are suggested such as a risk factor for resistant acne in males. These preliminary data can suggest that young males with acne can be investigated for insulin sensitivity and lipid profile, to start the best dietary and/or pharmacological treatment options.

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Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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