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Low glycaemic diet and metformin therapy: a new approach in male subjects with acne resistant to common treatments

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Summary

Acne is a common and complex skin disease, with a very complex pathogenesis. Although in women the relationship between acne and insulin resistance is well known, in particular in women with PCOS, in males this relationship has been poorly investigated. In total, 20 subjects with an altered metabolic profile were considered for this study and randomized as follows: 10 patients were treated with metformin plus a hypocaloric diet for 6 months (group A), while 10 patients did not receive any treatment with metformin and were only followed up (group B). All patients of group A, after 6 months of metformin therapy, had a statistically significant improvement compared with patients in group B. Our study reveals the importance of diet and insulin resistance in acne pathogenesis, and underlines the possible use of metformin and diet as possible adjuvant therapy for male patients with acne.

Acne is a common and complex skin disease. It is a chronic inflammation of the pilosebaceous unit, which involves hyperkeratosis and sebaceous hypersecretion. Sebum production, regulated by androgens, is one of the key factors in the pathogenesis of acne.[1] Sebum production starts during puberty in line with the peaking levels of growth hormone and insulin-like growth factor (IGF)-1 that occur in mid-puberty.[2–4]

The association between acne and insulin resistance is well known in females with polycystic ovary syndrome (PCOS),[5] but this association has been poorly investigated in males. Smith *et al.*[6] showed that a low glycaemic-load diet induced an improvement in acne severity and in insulin sensitivity. Del Prete *et al.*[7] investigated the association between metabolic abnormalities and acne in a sample of male patients affected by inflammatory acne resistant to common therapies (common topical retinoids, topical antibacterials, and oral retinoids and antibiotics after >1 year of treatment) and found that these had an impaired metabolic profile and decreased insulin sensitivity. One hypothesis is that metabolic impairment in these subjects can influence on key pathogenesis factors of acne, such as the proliferation of basal keratinocytes in the pilosebaceous unit.[8]

These modifications can aggravate the abnormal desquamation of follicular corneocytes that is often seen in patients with acne. In fact, IGF-1 stimulates the production of androgens by gonadal and adrenal glands, and consequently the growth of sebocytes of the hair follicle. It is also responsible for the comedogenic effects of androgens, growth factors and corticosteroids. Insulin induces hepatic secretion of IGF-1, amplifying these effects.[8]

These data suggest that in male patients with acne not responsive to common therapies, insulin resistance might play an important role in acne

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pathogenesis, as happens in the pathogenesis of PCOS, in which the presence of insulin resistance plays a key role.

The literature contains only studies demonstrating the benefits of diet alone in the treatment of acne. Therefore, in this study we aimed to evaluate the synergistic effect of metformin with a hypoglycaemic diet in the treatment of patients with acne resistant to common treatments, who have an altered metabolic profile.

Report

The study was approved by the institutional human research review committee of University of Naples Federico II. All patients gave written informed consent to treatment, and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki.

We assessed 42 consecutive young male patients with acne resistant to common standard therapies. Inclusion criteria were: age 17–24 years, male sex and presence of acne for at least 1 year that was resistant to common therapies. Exclusion criteria were: presence of other dermatological diseases or presence of endocrinological diseases.

Of the 42 patients, 22 had a normal metabolic profile, while 20 had an altered metabolic profile (defined as impaired fasting glucose, raised levels of total and low-density lipoprotein cholesterol, reduced levels of high-density lipoprotein cholesterol, and waist circumference and body mass index (BMI) at the upper limit of normal. These 20 young male subjects were enrolled in the study and randomly assigned by simple randomization as follows: 10 patients to group A (metformin treatment) and 10 patients to group B (symptomatic treatment only). The two groups were matched for Global Acne Grading System (GAGS); BMI; metabolic profile based on the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), which is used for the estimation of insulin resistance; and the type of symptomatic anti-acne therapies used.

The 10 patients in group A received metformin 500 mg twice daily, in association with a hypocaloric diet (1500–2000 kcal, rich in fruits, vegetables and fish, low in carbohydrates) for 6 months. All patients continued to use the symptomatic anti-acne treatment (bland detergent and a sebostatic cream based on azelaic acid and nicotinamide) that they had been using before entering the study. For the 10 patients in group B, only this symptomatic anti-acne therapy was used; no metformin or change in diet was prescribed.

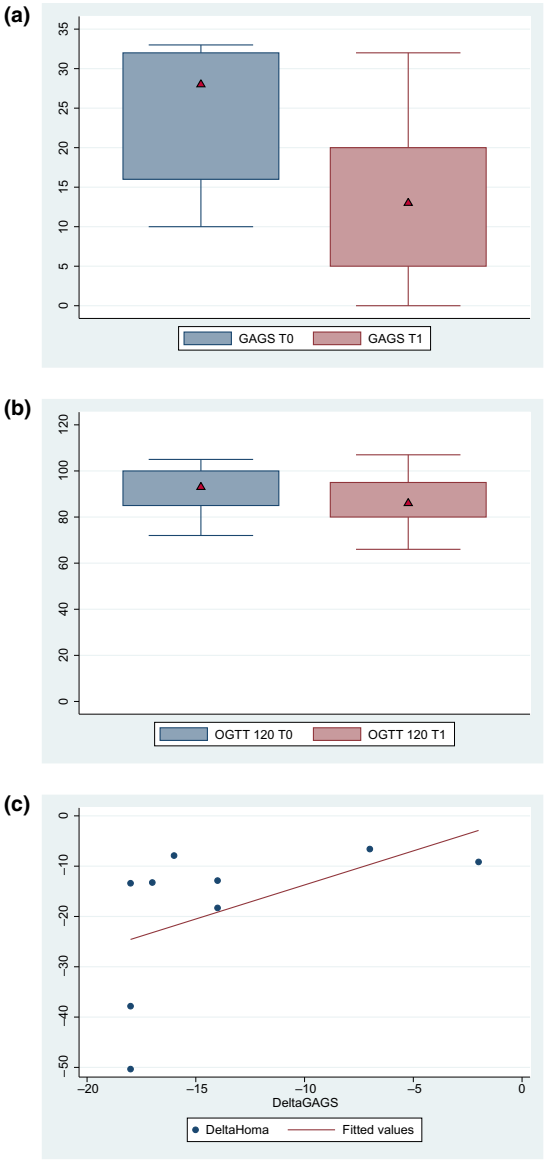

Figure 1 Groups A: comparison of (a) Global Acne Grading System (GAGS) at T0 (25.1 ± 8.9) and T1 (14.1 ± 10.4) ($P < 0.03$); and (b) oral glucose tolerance test (OGTT) at 120 min at T0 (88.2 ± 8.1) and T1 (79.2 ± 6.8) ($P = 0.04$). (c) Correlation between the differences in Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) (T1 to T0) and GAGS (T1 to T0) ($P = 0.03$, $\rho = 0.72$).

All patients were photographed by digital camera (Reveal® Imager; Canfield Imaging Systems, Fairfield, NJ, USA) and acne severity was rated by four observers (GF, RI, CM ad MD) using GAGS, which evaluates six locations on the face and trunk (front face, left

cheek, right cheek, nose, chin, chest and back). A score is assigned to each side, and this score is multiplied by a number corresponding to the presence of a specific type of lesion, such as comedones, papules, pustules or nodules. The summation of the scores is indicative of the severity of the acne (1–18 = mild, 19–30 = moderate; 31–38 = severe and > 39 = very severe).

BMI, waist circumference, hip circumference and waist to hip ratio (WHR) were evaluated by standard methods. Serum blood samples were obtained from all patients to measure total and HDL cholesterol, glycaemia and insulin by standard methods. Oral glucose tolerance test (OGTT) was also performed on blood samples drawn at baseline and at 30, 60, 90 and 120 min. HOMA-IR (0.23–2.5) was calculated as [fasting glucose × fasting insulin]/22.5. All these evaluations were performed at baseline (T0) and after 6 months of therapy (T1).

Statistical analysis was performed using SPSS IBM software (Naples, Italy). Student *t*-test was performed to evaluate differences between mean GAGS, BMI and WHR before starting treatment and after 6 months of therapy in the case and control groups. For correlation between the variables examined, we used Spearman regression and correlation, with the line of least squares and goodness of fit. $P < 0.05$ was considered significant.

All patients completed the study, and no side effects related to metformin were reported.

In group A, after 6 months of treatment with metformin, GAGS was statistically significantly reduced from 25.1 ± 8.9 at T0 to 14.1 ± 10.4 at T1 ($P < 0.03$) (Fig. 1a; Table 1), whereas in group B, GAGS did not significantly decrease (from 24.9 ± 7.6 at T0 to 19.4 ± 7.4 at T1; $P = 0.06$). As expected, the 120 min OGTT glucose serum levels were also significantly reduced after treatment ($P = 0.04$) in group A (Fig. 1b).

In both groups, the regression and correlation data showed that BMI and WHR positively correlated with GAGS at T0; the higher the BMI and WHR value, the higher the GAGS. In the total population of 20 patients, the correlation between GAGS at T0 and BMI, evaluated by linear regression, was 0.72 ($P = 0.02$, $r^2 = 0.36$); this correlation was also statistically significant with the Spearman test ($\rho = 0.65$, $P = 0.01$). The correlation between GAGS at T0 and WHR by linear regression was 48.5 ($P = 0.041$, $r^2 = 0.30$), and again, with the Spearman test, a statistically significant result was found ($\rho = 0.55$, $P = 0.04$).

When the correlation between fasting glycaemia and GAGS at T0 and at T1 was analysed, the angular coefficient of T1 was more negative ($\rho = -0.18$) than that of T0 ($\rho = -0.18$), and the goodness of fit to the linear regression line was improved at T1 from T0, indicating that treatment with metformin is more effective than no treatment.

In group A, there was also a statistically significant positive correlation between T1 and T0 for both HOMA-IR and GAGS ($P < 0.03$, $\rho = 0.72$) (Fig. 1c). In addition, the difference in mean pretreatment and post-treatment HOMA-IR between the two groups was statistically significant ($P< 0.001$). Figure 2a,b shows the results of a patient before and after metformin plus diet treatment.

Onset of acne is related to the pre-adolescent increase in BMI, but it seems to be more closely related to the levels of insulin and IGF-1 rather than

Table 1 Main parameters at T0 and T1 in groups A and B.

	T0		T1	
Parameter	Group A (n = 10)	Group B (n = 10)	Group A (n = 10)	Group B (n = 10)
Mean age, years	19.5	19.5		
BMI, kg/m^2	24.8 ± 3	24.5 ± 2.5	22.9 ± 3.5	24.1 ± 2.5
WHR	0.83 ± 0.02	0.83 ± 0.04	0.74 ± 0.02	0.81 ± 0.07
GAGS	25.1 ± 8.9	24.9 ± 7.6	14.1± 10.4	19.4 ± 7.418
HOMA-IR	1.7 ± 0.8	1.5 ± 0.2	1.5 ± 0.1	1.5 ± 0.8
Fasting glucose, mg/dL	91	87	85	88
Fasting insulin, IU/mL	11 ± 7.9	10.2 ± 1.7	9.6 ± 7.5	10.4 ± 1.6
oGTT glucose @ 120 min, mg/dL	88.2 ± 8.1	86.4 ± 7.3	79.2 ± 6.8	84.4 ± 5.2
Total cholesterol, mg/dL	170 ± 9.8	165 ± 16.5	165 ± 4.8	166 ± 14.5
HDL cholesterol, mg/dL	45.8 ± 0.8	49 ± 0.4	49.5 ± 0.5	50 ± 0.4

GAGS, Global Acne Grading System; HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; OGTT, oral glucose tolerance test; WHR, waist to hip ratio.

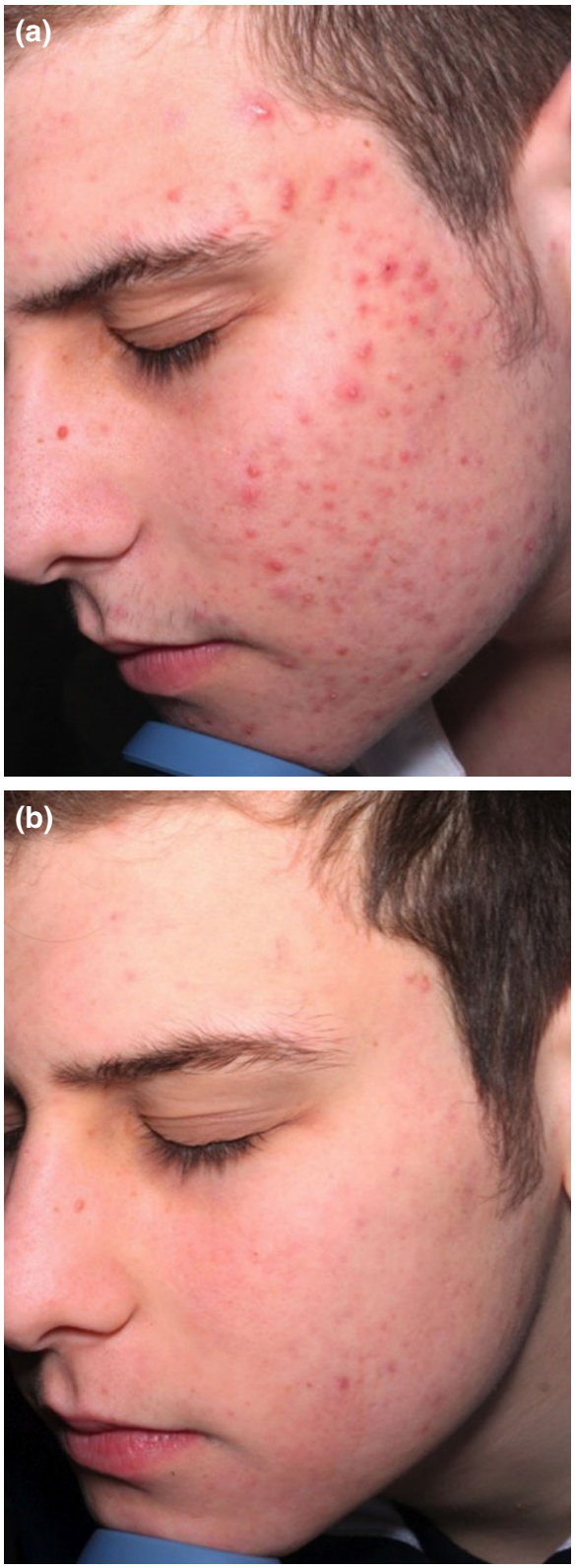

Figure 2 Patient in group A (a) before and (b) after 6 months of treatment with metformin plus diet. Global Acne Grading System (GAGS) 28 and 10, respectively.

to the levels of circulating androgens.[9] Increases in dietary glycaemic load are positively correlated with an increase in the biological activity of insulin and IGF-I, suggesting that carbohydrate-rich diets may aggravate potential factors involved in acne development. This also explains why hypoglycaemic agents may be of benefit.[9] Several studies, such as those by Smith *et al.*[6] and Kwon *et al.*,[10] have shown a significant improvement in acne lesions after 10/12 weeks of dietary intervention, demonstrating a linear correlation between improvement in acne and reduction in glycaemic load. Metformin has a hypoglycaemic effect, but we also treated our patients with a hypoglycaemic diet to amplify the effect; however, because of the study design, we cannot accurately quantify the benefits obtained by this synergistic therapy compared with treatment with diet alone, as group B was not treated with diet.

The improvement in acne and insulin sensitivity after metformin therapy seen in our study suggests a new possible approach to acne therapy, particularly in male subjects with acne resistant to common therapies. This is because metformin decreases hepatic glucose output and acts as an insulin sensitizer by increasing glucose utilization by muscles and adipocytes, thereby reducing serum insulin concentration and its effects. In addition, metformin has antioxidant and platelet antiaggregating effects. Because of these pharmacological properties, metformin has been proposed as a treatment for many nondiabetic conditions, including cutaneous conditions such as hirsutism, acne, hidradenitis suppurativa, acanthosis nigricans, psoriasis and skin cancer.[11]

Our data suggest that an accurate evaluation of metabolic profile is essential in both female and male patients affected by acne. We propose the following diagnostic algorithm for patients with mild to moderate (GAGS 1–18 and 19–30, respectively) acne resistant to 6 months of conventional therapy. First, serum glucose and insulin levels should be evaluated, followed by evaluation of HOMA-IR derived from these data, and finally OGTT measurement. If these parameters are altered, this would necessitate endocrinological counselling to evaluate the benefits of prescribing a low glycaemic diet or metformin administration.

Our study, although limited because of its small sample, shows that patients with an altered metabolic profile and insulin resistance can obtain a significant improvement in acne severity with metformin therapy and diet reduction.

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Learning points

- A low glycaemic-load diet induces an improvement in acne severity and in insulin sensitivity.
- IGF-1, by stimulating androgen production from the gonadal and adrenal glands, is responsible for the comedogenic effects of androgens, growth factors and corticosteroids.
- Young male patients with acne resistant to common therapies may have an impaired metabolic profile and decreased insulin sensitivity.
- Metformin can reduce GAGS score and insulin resistance in patients with an impaired metabolic profile and with acne resistant to common treatments.
- In male patients with acne resistant to common therapies, a possible diagnostic/therapeutic algorithm is the following: evaluate serum glucose and insulin levels, then HOMA-IR, and finally OGTT.
- If metabolic parameters are altered, an endocrinological consultation should be carried out to evaluate prescription of a low glycaemic diet or metformin administration.

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