The effect of metformin in the treatment of intractable and late onset acne: a comparison with oral isotretinoin

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Background: Insulin resistance and increased insulin-like growth factor (IGF)-1 with consequent mammalian target of rapamycin complex (mTORC) 1 overexpression is responsible for acne pathogenesis, especially in women with polycystic ovary syndrome (PCOS). Metformin is shown to improve acne as an adjunct therapy in females with PCOS and males with altered metabolic profile. We evaluated the use of metformin in the treatment of resistant and late-onset acne in females, and compared it with isotretinoin.

Methods: Females with late-onset acne or acne resistant to common therapies (n=70) were randomized to receive metformin (n=35) or isotretinoin (n=35) for 6 months. Changes in acne severity were scored by global acne grading system (GAGS) which was the primary outcome. Other endpoints were changes in the components of metabolic profile.

Results: Six-month treatment with metformin and isotretinoin significantly reduced the GAGS from 31.9 to 24.6 and from 34.1 to 13.3, respectively, indicating the superior impact of isotretinoin. Metfromin was more effective in decreasing the GAGS score in those with PCOS (13.5±7.1 vs. 24.2±19.4, P<0.05). Furthermore, patients with hirsutism had a higher reduction score with metfromin compared to patients without hirsutism (21.1±9.1 vs. 30.2±6.4) (P<0.05). Lipid profile and fasting blood sugar were improved following the 6-month treatment with metformin, and isotretinoin increased the levels of liver enzymes and bilirubin (P<0.05).

Conclusion: Metformin is effective in treating late-onset or resistant acne and improving metabolic status, without serious side effects. In patients with altered metabolic profiles such as PCOS, metformin seems to be superior to isotretinoin regarding acne treatment.

Keywords: acne vulgaris, metformin, isotretinoin, IGF-1, mTORC1

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INTRODUCTION

Acne is one of the most common chronic inflammatory skin diseases, affecting approximately 85% of the adolescent population. Prevalence of acne is also rising among post-adolescents in developed nations [1]. Severe cases of acne are reported to be associated with social impairment, reduced global self-esteem, diminished quality of life, and depression [2]. Acne involves pilosebaceous unit with hyperkeratosis and sebaceous hypersecretion, prominently at skin sites, with a high density of sebaceous glands (e.g. the face, back and chest). The pathogenesis of acne is multifactorial and polymorphic, and several factors are believed to have influence on the onset and development

of acne. Basically, the main contributors of acne development are increased sebum production, keratinocyte hyperproliferation, inflammation, and altered bacterial colonization, primarily with propionibacterium acnes [3]. The initiator and the exact sequence of these events are yet to be known; however, androgen-induced altered sebum quality and increased secretion are reported to be the main causative factors [3,4]. There is increasing data on the role of growth-promoting hormones and growth factors, particularly insulin/insulin-like growth factor (IGF)-1 signaling in proliferation and differentiation of sebocytes [5]. Increased insulin and IGF-1 level leads to the inhibition of the hepatic synthesis of sex hormone-binding globulin (SHBG) and the subsequent increased bioavailability of androgens [3,6]. Both IGF-1 and androgens are involved in the development of acne, while IGF-1 deficiency has been observed to prevent acne development [7]. The pathogenesis of polycystic ovary syndrome (PCOS), presenting with acne, obesity, insulin resistance and hyperandrogenism, is a typical example corroborating the relationship between acne and insulin metabolism [8]. Additionally, recent studies have confirmed the role of insulin resistance in the development of acne vulgaris in affected post-adolescent patients, male patients and females independent of hyperandrogenemia [8-12].

Insulin resistance also occurs in other physiological and pathological conditions, such as puberty, pregnancy, aging, physical inactivity, type 2 diabetes, cardiovascular diseases, essential hypertension, nonalcoholic fatty liver disease; or as a side effect of medications such as corticosteroids, certain oral contraceptives and diuretics.The role of nutritional and endocrine factors in acne pathogenesis is documented [8]. Thus, breaking this negative chain can probably influence acne.

Metformin is an oral anti-hyperglycemic agent utilized for over 60 years for controlling diabetes type 2. This agent reduces IGF-1 signaling and hepatic glucose output, and improves insulin sensitivity, which in turn potentiates glucose utilization by muscles and adipose tissue. Accordingly, metformin has been found to ameliorate acne severity in patients with PCOS [13], and is also effective as an adjunct therapy in those without PCOS or androgen excess, suffering from moderate to severe acne vulgaris [14].

Standard therapies for acne are based on disease severity and treatment response, starting with topical treatments (e.g. topical retinoids, benzoyl peroxide and topical antibiotics), and progressing to systemic therapies such as oral antibiotics, and isotretinoin. Having the highest influence on moderate and severe cases with low response to topical therapies, isotretinoin has various side effects which limit its application. Additionally, it is a potent teratogen causing dryness of skin and mucosa, endocrine and metabolic disturbances, and depression [15]. Thus, it is necessary to search for new therapeutic options. In this study, we examined the effectiveness of metformin in treating intractable acne and acne with late-onset, and compared it with oral isotretinoin.

PARTICIPANTS AND METHODS

Study Design and Patients

This is a randomized, assessor and analyst blinded, parallel, 2-group trial, where eligible patients with resistant or late-onset acne were randomized to receive either oral metformin (MET) or isotretinoin (ISO). Of patients who referred to the dermatology clinic of Rasoul Akram Hospital, between March 2017 and October 2018, 70 patients were included in the study. Participants were eligible for inclusion if they met the following criteria: 1) indication for treatment with oral isotretinoin, including severe nodular acne, moderate acne that is treatment-resistant (having history of using a minimum of one systemic drug for an appropriate time) or physical scarring and psychosocial distress, and 2) late-onset acne vulgaris, defined as acne occurring for the first time after the age of 25. Excluding criteria were: 1) history of previous metformin or isotretinoin use, 2) history of any liver, kidney or cardiac diseases, and 3) pregnancy or lactation. Included patients received a full physical examination, followed by the documentation of their medical and drug history as well as acne severity with global acne grading system (GAGS) [16]. Blood samples were collected to be tested for the analysis of fasting blood sugar (FBS), creatinine and lipid profile (triglyceride, cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL)). Next, the patients were assessed if they had PCOS or met metabolic syndrome criteria according to the

NCEP ATP III definition [17].

The study was performed in accordance with the Declaration of Helsinki and the Medical Research Involving Human Subjects [18]. Ethics committee of the Tehran University of Medical Sciences approved the research protocol. Each patient read and signed an informed consent prior to enrolling in the study.

Randomization and Blinding

The patients were randomly assigned to metformin group (Met group) or isotretinoin group (ISO group) using a simple randomization. An expert dermatologist (secondary assessor) other than the main investigators, blinded to the randomization method and treatment assignment, scored the patients based on GAGS and Visio-face photography; the analyst was also blinded regarding data collection and analysis. The laboratory staff was also oblivious to the treatment assignment.

Interventions

All patients enrolled in this trial received topical antibiotics. Patients in the MET group were treated with oral metformin 500 mg, twice daily. Subjects in the ISO group received oral isotretinoin 20 mg, every other day for six months.

Data Collection and Outcome Measures

The primary endpoint was acne severity, documented according to GAGS. Other endpoints were the changes in the components of metabolic syndrome. Data were measured and collected in pre designed sheets, including the clinical and lab findings at months 1, 3 and 6 following the initiation of treatment.

In 1997, Doshi and colleagues developed GAGS to grade acne [16]. This quantitative scoring system divides the acne prone regions into six areas (forehead, each cheek, nose, chin and chest and upper back). Based on the size of each area, a factor of 1-3 is allocated. In addition, a second factor of 0-4 (no lesion = 0, comedone = 1, papule = 2, pustule = 3, and nodule = 4) is given to each area based on the most severe lesion type observed in the assessed region. The multiplication of two factors is the score for each area, and the overall score is the sum of all areas. A score of 1–18 is considered as mild, 19–30 is moderate, 31–38 is severe, and >39 is very severe [16].

Sample Size and Analysis Method

Group sample sizes of 35 in the Met group and 35 in the ISO group were sufficient to achieve an 80% power to detect a difference of 5.3 (14.1 vs. 19.4) between the groups regarding the mean difference of post-treatment acne severity score. The 2-sided Z test with pooled variance was used. A P-value < 0.05 was significant.

The results were expressed as mean ± standard deviation (SD). The qualitative data were presented as percentage. Normally distributed data were analyzed by parametric tests, otherwise analyzed by nonparametric ones via SPSS version 24 (Chicago, Illinois, United States) using parametric and non-parametric tests. To compare the mean of the quantitative variables based on the qualitative variables through time, repeated t-test and one-way Analysis of Variance (ANOVA) were used. Chi-square test was used for the qualitative variables.

The ethical code of this trial was IR.IUMS.FMD.REC.1397.048, and the IRCT number was IRCT2014040624018210N8.

RESULTS

Patients' Characteristics

All the 70 enrolled patients randomized to receive MET (n=35) or ISO (n=35), completed the study. Both groups were well matched with regards to all patient- and acne-related parameters, except hirsutism which was marginally statistically significant. All the participants were female with a mean age of 32.2±4.3 years.

After 6 months of treatment, GAGS was significantly reduced from 31.9 to 24.6 in the MET group, and from 34.1 to 13.3 in the ISO group (P<0.05). The changes in GAGS scores showed that time was significantly effective on acne severity changes, but there was a significant difference between the efficacies of different drugs. The data showed that the GAGS score was more significantly reduced in the ISO group compared with the MET group concerning the whole population (P<0.05). However, MET was more effective in reducing GAGS score in those with PCOS. At 6 months, the

GAGS scores of the patients with PCOS treated with MET and ISO were 13.5±7.1 and 24.2±19.4, respectively. However, ISO was more effective in reducing GAGS score in those without PCOS (11.3±9.2 vs. 26.2±8.4, P<0.05).

Such effect was also found in the patients with hirsutism such that after 6 months, the mean GAGS was lower in the MET group compared to the ISO group in those with and without hirsutism, respectively, (21.1±9.1 vs. 19.5±16.3) and (30.2±6.4 vs. 10.2±7.2) (P<0.05)

The mean level of AST, ALT, and bilirubin was increased after the 6 months of treatment with isotretinoin, compared to the baseline and the MET group (P<0.05). Additionally, the mean level of LDL and FBS were reduced, while the mean level of HDL was increased after 6-month treatment with metformin compared with baseline and the ISO group (P<0.05).

DISCUSSION

The results of our study showed that the six-month treatment with both metformin and isotretinoin alleviated the severity of resistant and late-onset acne, while GAGS was lower in those receiving isotretinoin compared to the metformin-treated group (P<0.05). A closer look at the findings with a particular focus on the PCOS symptoms reveals that metformin was more effective in treating acne among PCOS patients and those with sings of hirsutism. Additionally, 6-month treatment with metformin led to positive metabolic changes such as increase in HDL and reduction in LDL and FBS. However, serum levels of liver enzymes and total bilirubin were significantly increased in the ISO group.

Acne is the result of complex irregularity of hormonal and metabolic circuits. Serum levels of insulin and IGF-1 are shown to have more prominent roles in the pathogenesis of acne than in circulating androgens [19]. Additionally, increased IGF-1 and androgens end in a vicious cycle as IGF-1 stimulates the production of androgens and vice versa [3,6]. High dietary glycemic load in diet leads to insulin resistance and increased biological activity of IGF-I [5,20]. Insulin resistance is a major contributor of mTORC1 over expression [21], which is the most important signaling pathway with regards to acne pathogenesis [22]. Through AMPK activation, metformin suppresses mTORC1/S6K1 signaling pathway [23], which is upregulated in acneic skin [24]. In addition, metformin is known to improve insulin sensivity in PCOS patients and in male patients with acne [14,19,25]. Metformin treatment in PCOS patients has also been reported to reduce androgen levels [25]. Recent investigations have revealed that insulin resistance and the ensuing pathophysiologic process affect post-adolescent patients, males and females independent of hyperandrogenemia [8-12]. As expected, hypoglycemic agents such as metformin conduce to treating acne in such groups [14]. We found that metformin treatment for 6 months significantly reduced GAGS score in females with resistant and late-onset acne, irrespective of PCOS presentations. Additionally, consistent with previous reports, the present results showed that metformin improved FBS and lipid profile in acneic patients [19]. These findings support the involvement of defeated IGF-1/mTORC1 signaling and metabolic status in such patients. However, isotretinoin that induces apoptosis in sebaceous gland cells was the most effective in acne alleviation among the whole study population, highlighting the implication of other pathologic circuits in acne development. On the other hand, the superior therapeutic effect of metformin among the patients with PCOS and hirsutism underscores the more prominent role of insulin resistance, and IGF-1/mTORC1 pathway in acne occurring under such conditions.

Metformin-induced GAGS reduction from 34.8±7.8 to 24.6±6.7 is comparable to other published reports. Fabbrocini et al. demonstrated that 500 mg metformin twice daily combined with hypocaloric diet (1500 – 2000 kcal) significantly reduced GAGS from 25.1±8.9 to 14.1 ±10.4 in males aged 17-24 years, with acne resistant to common therapies such as retinoids [19]. Despite the differences between Fabbrocini's study and ours, we may conclude that metformin per se, or as anadjacent treatment, exerts similar therapeutic effects in males and females with resistant acne. Gabaton et al. revealed that 18-week treatment with lymecycline and adapalene + benzoyl peroxide gel with or without metformin reduced non-inflammatory lesions in moderate to severe acne vulgaris. They found inflammatory and total lesion count to be more significantly reduced in those receiving metformin [14,26]. Later, Robinson and Affandi showed that topical benzoyl peroxide and oral tetracycline combined with daily intake

of metformin 850 mg resulted in more treatment success rate without serious side effects. Only gastrointestinal symptoms were reported in 31.7% of the participants who received metformin [14,27].

Although there are several studies about the routine therapies of serious acnes [28], there exists emerging evidence as to the correlation between acne and components of metabolic syndrome, especially in resistant late-onset acnes, creating a new paradigm for further research [29].

CONCLUSION

Despite limitations such as small sample size and lack of blinding, our study showed that metformin is helpful in treating late-onset or resistant acne.

Although metformin is not as effective as isotretinoin in treating acneic patients, it causes positive changes in the metabolic status. Moreover, it is superior to isotretinoin concerning the improvement of acne in patients with PCOS suffering from altered metabolic profile.

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Conflict of Interest: None declared.

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