

Increased Insulin Sensitivity by Metformin Enhances Intense-Pulsed-Light-Assisted Hair Removal in Patients with Polycystic Ovary Syndrome

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Key Words

Polycystic ovary syndrome · Metformin · Intense pulsed light · Hirsutism

Abstract

Background: Polycystic ovary syndrome (PCOS) is an insulin-resistant state with hirsutism as a common manifestation. **Objective:** We hypothesized that treatment with metformin would improve the cosmetic effects of intense pulsed light (IPL) therapy for hair removal in PCOS patients. **Methods:** In a prospective randomized controlled trial, 70 PCOS patients randomly received metformin (1,500 mg daily) + IPL therapy or IPL therapy alone for 5 IPL sessions during a 6-month period, followed by an additional 6 months of observation. Hirsutism score, homeostasis model assessment for insulin resistance (HOMA-IR), free androgen index (FAI) and patient satisfaction were evaluated at every visit. **Results:** Fifty-two patients finished the study. Hirsutism was significantly better controlled in the metformin group ($p = 0.009$). Patient satisfaction was significantly better in the metformin group at the end of the observation period (52.9 vs. 34.1%, $p = 0.019$). HOMA-IR and FAI scores improved after metfor-

min + IPL treatment ($p < 0.05$). **Conclusion:** Adding metformin to IPL in women with PCOS results in a significant improvement in insulin sensitivity and hirsutism.

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Introduction

Hirsutism, a common distressing symptom, is usually a challenging clinical dilemma as well as an endocrine and cosmetic problem [1, 2]. Permanent treatment modalities such as lasers and intense pulsed light (IPL), which have been shown to target melanin in hair follicles, are usually most appreciated [3, 4]. Hair removal is easier with these methods and causes fewer adverse effects [4]. The reported laser efficacy is 50–75% hair reduction after 3–4 sessions with some degrees of hair regrowth after cessation [4].

Determination of the underlying cause of hirsutism would be beneficial in its management and might improve the laser efficacy. In approximately 90% of women with hirsutism, the underlying disorder is either polycystic ovary syndrome (PCOS), or it is idiopathic [1].

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PCOS is the most common endocrinopathy affecting young women that involves 6–10% of women at the reproductive age [5]. It is characterized by 2 or more of the following features: chronic anovulation, hyperandrogenism, polycystic ovaries [6, 7] and a form of insulin resistance [8, 9]. The background abnormality is considered insulin resistance and ensuing hyperinsulinemia. This may even be observed in men. A part of the men with premature androgenic alopecia could be considered a male equivalent of the PCOS of women. These prematurely balding men, mostly brothers of women with polycystic ovaries, represent a risk group for the development of impaired glucose tolerance or type 2 diabetes mellitus [10, 11].

Although androgens are required for sexual hair and sebaceous gland development, pilosebaceous unit growth and differentiation require the interaction of androgens with numerous other biological factors. Many other hormones such as growth hormone, insulin-like growth factors (IGFs), insulin, glucocorticoids, estrogen and thyroid hormone play important roles in their growth and development.

Insulin can directly stimulate ovarian androgen production that is independent from its glucose transport [8, 9]. Insulin stimulates the ovarian production of androgen by activating its homologous receptor (IGF receptor), and the ovaries of women with PCOS appear to remain sensitive to insulin, or perhaps hypersensitive to it, even when classic target tissues such as muscle and fat manifest resistance to insulin action [6]. It can also augment luteinizing-hormone-stimulated ovarian androgen biosynthesis [12, 13] and also indirectly change the responsiveness of hair follicles to androgens [14, 15].

In addition, hyperinsulinemia inhibits the hepatic production of sex-hormone-binding globulin, further increasing circulating free testosterone levels [16]. Insulin-sensitizing agents, like metformin, can suppress both hyperinsulinemia and hyperandrogenemia in patients with PCOS [5, 17, 18]. Its application is a logical pharmacological modality in PCOS patients as it affects hirsutism [1, 7, 19], obesity and irregularity of menstrual cycles [5]. Several studies have introduced metformin as an appropriate first-choice treatment for PCOS with great success [20–25].

The present investigation examines the hypothesis that addition of metformin treatment to laser-assisted hair removal provides a higher efficacy in the treatment of hirsute patients with PCOS.

Patients and Methods

This study was a prospective randomized controlled clinical trial. Women with PCOS and hirsutism who were visited at the dermatology clinic of St. Al-Zahra Hospital, Isfahan, Iran, were invited to the study. The diagnosis of PCOS was based on the presence of at least two of the following criteria: (1) oligoanovulation, (2) clinical and/or biochemical signs of hyperandrogenism and (3) observation of polycystic ovaries by an ultrasound technique [26]. Hirsutism was defined based on the Ferriman-Gallwey score (FGS) >8 [27].

Patients with renal and liver dysfunction, a history of significant congestive heart failure or alcohol abuse, hyperprolactinemia, ovarian or adrenal tumors, diabetes and congenital adrenal hyperplasia and known Cushing's syndrome were excluded from the study. Participation in any hair removal program in the previous 3 months was also a criterion for exclusion. Patients were advised not to use any hair removal method (waxing, plucking or depilatory cream) for 1 month before participation, but shaving the region was allowed until 1 week before the IPL session. Informed consent was obtained, and the patients were advised to use barrier contraception if randomized to metformin.

Patients were randomly divided into two groups based on the random numbers table. The intervention group (group IPL/metformin, $n = 35$) received combined therapy (IPL+ metformin), while the control group (group IPL, $n = 35$) received IPL alone. Five IPL sessions were administered with a 45-day interval between each session, to both groups. Group IPL/metformin received metformin 500 mg 3 times daily, in addition to IPL therapy. IPL-treated regions were the lower face areas, including the chin, upper lip, submental and preauricular areas if there was any unwanted hair.

An IPL system, Ellipse Relax Light 1,000, Danish Dermatologic Development, Hoersholm, Denmark, with a 600-nm filter was used. A thin layer of cooling gel was applied as cooling system. The pulse duration was adjusted between 5 and 40 ms to match the thermal relaxation time of both thin and thick hair follicles. The filtered light was guided to the skin surface by a 48×10 mm light-conducting crystal with an optical design that partly recycles backscattered photons from the skin surface. A thin layer of optical-index-matching hydrogel optimized the optical coupling between the crystal and the skin. Nonselective absorption in superficial cutaneous blood vessels was reduced by applying a firm mechanical pressure to the skin surface with the IPL system's optical light guide causing blood being pushed from the treatment area during treatment. The fluencies used for treatment of the individual patients (17 – 21.5 J/cm²) were selected according to a pretreatment clinical evaluation of skin color followed by a series of test shots and inspection of the immediate physiological reaction.

Both treatments were stopped after 5 laser sessions (7.5 months), and the patients were followed up for a further 6 months (end of the study).

Assessment Program

After giving informed consent, the patients underwent clinical and hormonal assessments, including body mass index (BMI), FGS, hair diameter, hair count, free androgen index (FAI) and homeostasis model assessment for insulin resistance (HOMA-IR) at the start of the study, at the end of the treatment periods (phase

1) and 6 months later (phase 2). The main outcome was the reduction of the hair count, and this was used for the sample size calculation. Plasma glucose, insulin, testosterone and sex-hormone-binding globulin concentrations were measured on fasting blood samples. Glucose was measured by an enzymatic method (Liasys, Rome, Italy). Insulin was measured by immunoradiometric assay (Iran Kavoshyar kits, Tehran, Iran; inter- and intra-assay coefficient of variation: 2.8%). Testosterone and sex-hormone-binding globulin were measured by enzyme-linked immunosorbent assay. Samples of hair were also collected from each area on the face.

Self-Assessment Score

Patients assessed their own hirsutism and the degree of improvement at baseline, i.e. before treatment, after IPL/metformin (phase 1) treatment and 6 months later at the end of the study (phase 2), using a visual analog sliding scale. It was made as a scale from 0 to 100% for the evaluation of the degree of the patient's impression of her improvement regarding hirsutism.

Calculations and Statistical Analysis

The BMI was calculated by weight (in kilograms) divided by height squared (in square meters). The FAI was calculated as the ratio of total testosterone (in nanomoles per liter) \times 100/sex-hormone-binding globulin concentration (in nanomoles per liter). The HOMA-IR index was calculated as fasting plasma glucose (in millimoles per liter) \times fasting insulin/22.5. For measurements of hair diameter, a minimum of 5 terminal hairs were collected from the chin. The diameters of their widest portion were assessed by microscopy, using a 0.05-mm micrometer (under 40×10 magnification), and the mean value was calculated. The terminal hairs of 2 square areas of 1 cm^2 in the chin area were also counted, and the mean value was determined. The degree of hair reduction is reported as percentage of decrease from baseline. According to our dermatologist's consensus, improvement was defined as reduction of 50% in hair count and 30% in hair diameter.

Statistical Analysis

Data are presented as means \pm SD. Numeric variables between the two groups were compared by t test and within each group during the two trial phases by repeated-measure ANOVA. Improvement rate and incidence of side effects between the two groups were compared by the χ^2 test. p values less than 0.05 were considered significant. Statistical analyses were carried out by SPSS version 15.

Results

Seventy patients participated in the present study. Fifty-two patients finished the study programs, 22 in the group IPL + metformin and 30 in the group IPL alone. Eighteen patients did not follow the study protocol (13 in the group IPL/metformin and 5 in the group IPL). The reasons were either metformin intolerance (1 patient), misbelief about adverse effects of metformin (by the pa-

Table 1. Baseline characteristics in the two groups

	Group 1	Group 2
BMI	25.2 \pm 5.0	24.5 \pm 4.7
Age, years	27.6 \pm 6.1	26.6 \pm 5.5
Hirsutism degree (FGS)	16.9 \pm 4.6	15.8 \pm 4.2
Hair count, n/cm ²	50.5 \pm 9.7	46.9 \pm 15.6
Hair thickness, μm	103 \pm 35	125 \pm 52
Duration of disease, years	7.81 \pm 4.1	6.5 \pm 4.1
HOMA-IR	2.83 \pm 1.7	3.13 \pm 1.65
FAI	7.2 \pm 5.4	8.1 \pm 4.6

For all parameters, p values were not significant.

tient or her relatives), use of alternative hair removal programs during the study, immigration/relocation or unmentioned. All the patients had skin types 3–5 based on the Fitzpatrick scale.

Baseline characteristics of the participants were not significantly different between the two groups at the beginning of the study (table 1). The patients who did not follow the study protocol were not different regarding baseline characteristics from the remaining participants either. The BMI did not change during the study. At the end of the treatment period, 15 of 22 (68.2%) in group IPL/metformin and 7 of 30 (33.3%) in group IPL were improved ($p = 0.013$; table 2). After 6 months of follow-up, 59.9% of patients in group IPL/metformin and 23.3% in group IPL remained improved ($p = 0.009$).

Hair count decreased in both groups after the treatment phases 1 and 2 (fig. 1). Hair count decreased more significantly in group IPL/metformin than group IPL. After phase 1, hair count was 19.84 ± 5.50 versus $25.20 \pm 11.98/\text{cm}^2$ ($p = 0.044$) in groups IPL/metformin and IPL, respectively. Similarly, after phase 2, hair count was 22.14 ± 10.52 versus $29.7 \pm 14.67/\text{cm}^2$ ($p = 0.044$).

Hair thickness changed significantly in both groups after treatment phase 1 ($p < 0.05$ in both groups) without any significant change in phase 2. After adjustment for baseline hair thickness by ANCOVA, there was no significant difference between the two groups regarding hair thickness change (fig. 2). The difference of visual analog scale values between groups was not significant after phase 1 (51.1 ± 21.8 vs. $40.8 \pm 28.6\%$, $p = 0.16$) but it was significantly higher in group IPL/metformin than in group IPL at the end of the study (52.9 ± 26.3 vs. $34.1 \pm 28.1\%$, $p = 0.019$). The HOMA-IR decreased significantly in group IPL/metformin after phase 1 ($p < 0.05$) and remained decreased until the final evaluation (phase 2) but

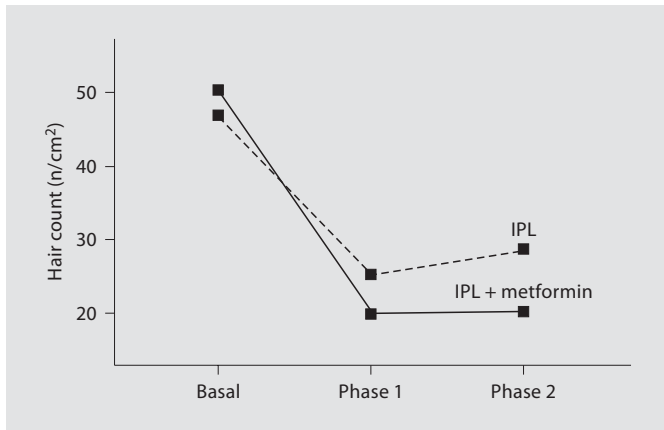


Fig. 1. Mean hair count in the two groups during the study.

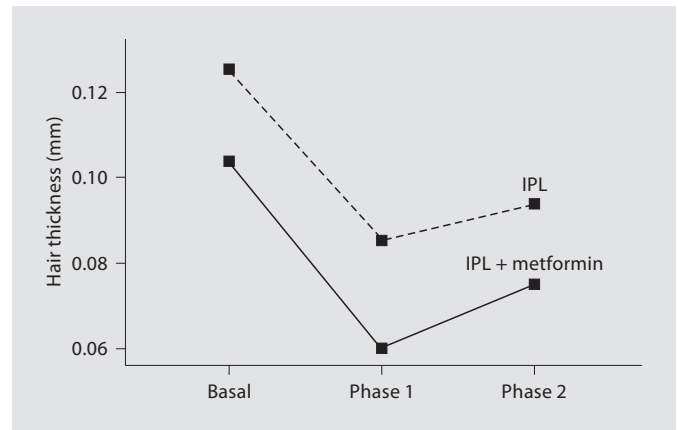


Fig. 2. Mean hair thickness in the two groups during the study.

Table 2. Changes in parameters of hirsutism in both groups

	Group 1 (IPL + metformin)	Group 2 (IPL alone)	p value
Improvement, %			
After treatment	68.2	33.3	0.013
End of study	59.9	23.3	0.009
Hair count, n/cm ²			
Basal	50.5 ± 9.7	46.9 ± 15.6	0.33
After treatment	19.89 ± 5.50	25.20 ± 11.98	0.044
End of study	22.14 ± 10.52	29.7 ± 14.67	0.044
Hair thickness, mm			
Basal	0.103 ± 0.035	0.125 ± 0.052	0.12
After treatment	0.060 ± 0.022	0.085 ± 0.038	0.013
End of study	0.075 ± 0.069	0.093 ± 0.0496	0.30
VAS, %			
After treatment	51.13 ± 21.87	40.83 ± 28.68	0.165
End of study	52.95 ± 26.35	34.13 ± 28.15	0.019
HOMA-IR			
Basal	2.83 ± 1.7	3.13 ± 1.65	0.59
After treatment	2.28 ± 1.13	3.14 ± 1.60	0.016
End of study	2.28 ± 1.35	3.13 ± 1.84	0.023
FAI			
Basal	7.2 ± 5.4	8.1 ± 4.6	0.54
After treatment	4.8 ± 3.6	7.9 ± 4.4	0.020
End of study	4.9 ± 4.5	8.0 ± 5.7	0.032
FGS change			
After treatment vs. basal	-2.27	-1.03	0.001
End of study vs. basal	-2.04	-1.01	0.002
BMI			
Basal	25.25 ± 5.02	24.59 ± 4.7	0.67
After treatment	24.95 ± 5.00	24.50 ± 4.7	0.6
End of study	24.84 ± 4.9	24.53 ± 4.74	0.65

The results are means ± SD. VAS = Visual analog scale.

did not change in group IPL. In group IPL/metformin, the FAI was lower at the end of the study, compared to before treatment ($p = 0.02$). The FAI values did not differ significantly in group IPL at the end of the study ($p > 0.05$). The FGS decreased in group IPL/metformin after phase 1 and at the end of the study with no change in group IPL.

Twelve patients in group IPL/metformin experienced mild side effects (transient nausea, diarrhea and abdominal pain/discomfort) with metformin, but only 1 patient stopped metformin due to intolerance.

Discussion

The results of our study demonstrate that the addition of metformin (500 mg t.i.d.) to IPL therapy provides better long-term results of hair removal than IPL alone. The beneficial effects of this addition were the clearance of unwanted hair in 59.9% of participants of the intervention group compared with 23.3% of the control group at the end of the study. Although 25% of patients being lost to follow-up is a strong limitation to the interpretation of the trial results, if confirmed by future studies, the study may provide useful evidence for using metformin in hair removal programs.

Patients were followed up to 6 months without any intervention. Patients who received IPL therapy alone showed some degrees of hair count increment at the end of the study, which could be due to telogen induction in follicles by IPL. The results demonstrated that the efficacy of metformin on hirsutism was not transient, and it

is unlikely to be due to telogen induction in hair follicles. It would be advisable not to evaluate IPL efficacy immediately after cessation of therapy.

The efficacy of metformin on the reduction of serum androgen levels and improvement of hirsutism in PCOS has been demonstrated previously [5, 7, 8, 17, 18], but this is the first comparative, randomized, controlled trial to assess the beneficial effects of a combination therapy over the mechanical method (IPL) alone.

Subjective evaluations may be influenced by many factors. Applying an objective scale to measure hair growth (count and diameter) was an important aspect of our assessment method. In both groups, the hair diameter and count decreased as the study progressed, so therapeutic outcomes could be improved by increasing treatment duration. Further studies are required to define the appropriate treatment duration to achieve an acceptable steady state.

The reduction of HOMA-IR and FAI by metformin suggests that increasing insulin sensitivity and decreasing serum free androgen levels help to improve hirsutism in the intervention group. The beneficial effects of metformin may be mediated by at least 3 mechanisms. First, metformin improves insulin action and so leads to a decrease in hyperinsulinemia. As stated, hyperinsulinemia decreases sex-hormone-binding globulin, leading to increased serum free testosterone levels. Metformin counteracts this effect and decreases free testosterone, the substrate for dihydrotestosterone production. Hyperinsu-

linemia may also stimulate IGF-1 receptors of the ovarian parenchyma leading to an increased testosterone production by the theca cells.

In addition, beneficial effects of metformin might be caused by mechanisms involving local growth factor action at the dermal papilla [1]. IGF-1 and its receptor have important antiapoptotic and anabolic effects on hair follicles [14]. It is also possible that IGF-1 stimulates the activity of 5 α -reductase in the skin, which increases the local production of dihydrotestosterone from testosterone [28]. Decreasing hyperinsulinemia by metformin may also have beneficial effects by these additional mechanisms.

Most of the participants who received metformin showed no adverse reaction and tolerated metformin well, which helped the patient's compliance during treatment. In patients with side effects of metformin, we first reduced the prescribed dose of metformin and gradually increased it to 500 mg 3 times daily. This was usually effective to ameliorate any side effects [6].

In summary, metformin has long-lasting therapeutic effects and exhibits additive effects on laser therapy besides self-satisfaction in hirsute PCOS patients. Future studies are required to determine the optimal dose and duration of both IPL (and laser sources) and metformin. After identifying such a regimen, randomized placebo-controlled studies involving a large sample size would provide more reliable evidence.

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