CLINICAL STUDY

The effect of metformin on hirsutism in polycystic ovary syndrome

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Abstract

Objective: Polycystic ovary syndrome (PCOS) is a common reproductive disorder characterised by insulin resistance and often associated with hirsutism. Insulin sensitising agents, such as metformin, improve both the biochemical and reproductive parameters; however, no study has been designed to specifically assess the effect of metformin on hair growth.

Design and patients: Sixteen women with PCOS and hirsutism were enrolled into a 14 month (two 6 month phases with a 2 month washout) double-blind placebo-controlled cross over study.

Measurements: Hirsutism was assessed using the Ferriman and Gallwey (F-G) score, patient self-assessment and growth velocity. Weight, height and waist–hip ratio were recorded. Gonadotrophins, androgens, plasma glucose and lipids were also measured.

Results: Ten women completed the full 14 month study. There was a significant improvement in hirsutism at the end of the metformin phase compared with placebo: F-G score 15.8 ± 1.4 vs 17.5 ± 1.2 ($P = 0.025$) and patient self-assessment 2.4 ± 0.1 vs 3.3 ± 0.3 ($P = 0.014$). Growth velocity, in millimetres per day at the end of each phase also improved (0.67 ± 0.17 vs 0.77 ± 0.11 ; $P = 0.03$). There was a non-significant improvement in both sex hormone binding globulin (SHBG) and free androgen index (FAI), although there was a significant difference between baseline and metformin treatment for SHBG ($P = 0.023$) and FAI ($P = 0.036$). Metformin treatment also reduced weight significantly (91.5 ± 7.6 vs 94.0 ± 9.8 kg; $P = 0.009$) and led to a significant improvement in cycle frequency (0.53 ± 0.12 vs 0.35 ± 0.08 cycles per month; $P = 0.008$).

Conclusion: We have demonstrated that metformin treatment in a group of women with PCOS results in a clinically and statistically significant improvement in hair growth compared with placebo.

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Introduction

Polycystic ovary syndrome (PCOS) is a common reproductive endocrine disorder affecting about 5% of premenopausal women and characterised by hyperandrogenism and chronic anovulation (1–3). It is now recognised to have a metabolic component consisting of hyperinsulinaemic insulin resistance; women with PCOS have a similar decrease in insulin sensitivity to that seen in subjects with type 2 diabetes mellitus (between 30 and 40%) (4, 5).

This observation has led to the use of insulin sensitising drugs, particularly metformin, in the treatment of PCOS (6–21). The majority of studies have reported improvements in biochemical and reproductive parameters. Few, however, have commented on the effect of insulin sensitisation on hirsutism (14, 18). Hirsutism is a common problem for women with PCOS and one with potentially serious psychosocial sequelae (22).

While it can be managed by mechanical means it is none the less an important consideration when considering pharmacological treatment in PCOS.

This pilot study was designed to assess the effect of metformin on hirsutism in a population of women with PCOS. Hirsutism was assessed subjectively using both the Ferriman and Gallwey (F-G) score and a patient self-evaluation score and objectively by measuring plucked hair length.

Materials and methods

All subjects gave their written informed consent prior to entering the study, which was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki.

PCOS was defined as androgen excess (total testosterone > 3.6 nmol/l or a free androgen index (FAI) $\geq 9\%$) with ovulatory dysfunction (less than 6

menstrual cycles per year) once specific disorders, such as adult onset congenital adrenal hyperplasia, hyperprolactinaemia and androgen secreting neoplasia had been excluded. Hirsutism was defined as an F-G score > 8 (23). In brief hair distribution is assessed at 11 sites and scored (scale 0–4) in accordance with a validated marking system. Subjects were recruited from women with PCOS referred with hirsutism to the endocrinology clinic at Stobhill hospital. Patients were eligible for the study if they had previously noted no improvement in hirsutism following 6 months of oral Dianette (ethinylestradiol 35 µg, cyproterone acetate 2 mg). As this was a pilot study it was deemed unethical to enrol patients prior to a trial of treatment with Dianette. No subjects were on treatment for their hirsutism, and all active treatments had been stopped for 6 months. Body weight was measured using analogue scales to within 500 g in light clothes; height was measured barefoot using a stadiometer to within 0.5 cm. Body mass index was calculated as follows: weight (kg)/height² (m). Anthropometric measurements were made using standard techniques; waist circumference was obtained as the minimum value between the iliac crest and the lateral costal margin, whereas hip circumference was determined as the maximum value over the buttocks, using a 1 cm wide measure.

The study lasted for 14 months and was a randomised double-blind, placebo-controlled cross over design. The pharmacist randomised the subjects by coin tossing in batches of four in a four square design to metformin or an identical placebo (BMS, Hounslow, UK). Once randomised the subjects received oral metformin or placebo for 6 months. There then followed an 8 week washout and patients then crossed over treatments. The study drug was increased stepwise from 500 mg (1 tablet) to 500 mg three times daily, over 3 weeks. The subjects were reviewed every 8 weeks.

Prior to commencing the study and at each subsequent visit the following were carried out: (i) assessment of menstrual history (time between cycles); (ii) physical examination for weight, waist–hip ratio and blood pressure recorded by an oscillometric technique using a Dinamap Critikon (Johnson and Johnson, UK); and (iii) compliance (this was assessed by counting the remaining tablets).

The measures of hair growth, biochemistry and self-assessment were performed on four occasions – at the start and end of each phase.

Hair measurement

We used a modified version of the methods described by Azziz (24) and Heiner (25). Hair measurements were obtained prior to commencing each phase of the study and at the end of both phases. Subjects were instructed not to shave an identical area on the chin

up to 72 h prior to attending the clinic. Samples were plucked from the shaved area and time between shaving and sampling was recorded to establish the shaving interval. Growth was derived by averaging the length of up to five hairs removed from the chin, which were mounted on a glass slide using double sided tape. The slides were examined using a Zeiss Stemi 2000 dissecting microscope with micrometer eyepiece. Growth velocity was calculated by dividing the mean length of the hairs by the shaving interval (number of days) giving a rate in millimetres per day. The same observer (CJGK) performed all measurements at one sitting.

A semi-quantitative clinical evaluation was performed using the F-G score, and the patient's objective opinion of the therapy was obtained using an analogue scale (1 much improved, 2 improved, 3 no difference, 4 worse, 5 much worse). A score of 3 was recorded at the start of each phase and patients asked to compare the effect of each treatment phase with their score at the start of that phase.

Reproducibility

Hair velocity The same observer (CJGK) carried out all measurements at one sitting. An intra-measure coefficient of variance was determined by measuring five hairs, ten times at one sitting.

F-G score CJGK again carried out all observations. An inter-measure coefficient of variance was determined by assessing eight of the women on three separate days within the same 4 week period prior to the start of the study.

Biochemistry

Fasted venous blood sampling for glucose, gonadotrophins, androgens (total testosterone, dehydroepiandrosterone sulphate (DHEAS) and androstenedione), sex hormone binding globulin (SHBG) and lipids (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides). FAI was calculated from total testosterone and SHBG.

Statistics

Statistical analysis was carried out using Minitab 13.1 on a PC. Data are expressed as means $\pm$ S.E. or as the median (Q1, Q3) if not normally distributed. The comparison of differences between the groups was analysed using the paired *t*-test for normally distributed data and the Mann–Whitney test for non-parametric data. The significance level was set at $P < 0.05$.

Results

A total of 16 women were recruited for the study. Ten women completed the full 14 month study. Three were excluded because of non-compliance, while three withdrew because of a lack of effect (all three were in the first phase and on placebo). Of the ten patients who completed the study four consented to go without shaving and be included in the objective assessment of hair growth velocity.

Hair assessment

In the ten women who completed the study there was no difference in the F-G score between baseline and the end of the placebo phase (17.7 ± 1.4 vs 17.5 ± 1.2 ; $P > 0.9$). There was a significant improvement in the F-G score at the end of the metformin phase compared with both baseline (15.8 ± 1.4 vs 17.7 ± 1.4 ; $P = 0.02$) and placebo (15.8 ± 1.4 vs 17.5 ± 1.2 ; $P = 0.025$) (Fig. 1). There was a significant improvement in patient self-assessment between the end of the metformin phase and placebo (2.4 ± 0.1 vs 3.3 ± 0.3 ; $P = 0.014$). There was no difference between the growth velocity at baseline and the end of the placebo phase (0.76 ± 0.15 vs 0.77 ± 0.11 ; $P > 0.9$). There was, however, an improvement in growth velocity at the end of the

metformin phase compared with both baseline (0.67 ± 0.17 vs 0.76 ± 0.15 ; $P = 0.03$) and placebo (0.67 ± 0.17 vs 0.77 ± 0.11 ; $P = 0.03$).

The inter-measure coefficient of variance for the F-G score was 4.3% and the intra-measure coefficient of variance for velocity was 0.6%.

Biochemistry

No significant difference was noted between the placebo and metformin phase for SHBG (23.8 ± 1.8 vs 37 ± 5.8 nmol/l; $P = 0.054$) or FAI (14.7 ± 2.1 vs 10.6 ± 1.7 ; $P = 0.07$). However, there was a significant difference between baseline and metformin treatment for SHBG (20.5 ± 1.2 vs 37 ± 5.8 nmol/l; $P = 0.02$) and FAI (15.5 ± 1.4 vs 10.6 ± 1.7 ; $P = 0.036$). There was no change in total testosterone, DHEAS, androstenedione or lipids between the placebo and metformin phase, nor between phases and baseline (Table 1).

Anthropomorphic details

There was no significant change in weight between baseline and placebo (94.3 ± 9.1 vs 94.0 ± 9.8 kg; $P > 0.8$). There was, however, a significant reduction in weight with metformin treatment compared with placebo (91.5 ± 7.6 vs 94.0 ± 9.8 kg; $P = 0.009$) and

Figure 1 Change in hirsutism as assessed by the F-G score. Baseline 17.8 ± 1.6 vs placebo 17.5 ± 1.23 vs metformin 15.8 ± 1.4 . Metformin phase compared with placebo: F-G score (15.8 ± 1.4 vs 17.5 ± 1.2 ; $P = 0.025$). Mean in bold.

Table 1 Results between phases of the study. Data are means $\pm$ s.e.

	Baseline	Metformin	Placebo	P value
Testosterone (nmol/l)	3.2 $\pm$ 0.3	3.2 $\pm$ 0.3	3.4 $\pm$ 0.5	—
SHBG (nmol/l)	20.5 $\pm$ 1.2	37 $\pm$ 5.8	23.8 $\pm$ 1.6	*P = 0.02; **P = 0.054
Free androgen index	15.5 $\pm$ 1.4	10.6 $\pm$ 1.7	14.7 $\pm$ 2.1	*P = 0.04; **P = 0.07
Androstenedione (nmol/l)	9.9 $\pm$ 1.9	9.1 $\pm$ 1.3	8.9 $\pm$ 1.4	—
DHEAS (μ mol/l)	6.0 $\pm$ 0.9	5.8 $\pm$ 0.8	5.8 $\pm$ 0.8	—
LDL (mmol/l)	2.4 $\pm$ 0.3	2.4 $\pm$ 0.6	2.8 $\pm$ 0.5	—
Triglyceride (mmol/l)	2.3 $\pm$ 0.3	2.5 $\pm$ 0.4	2.6 $\pm$ 0.3	—
Ferriman–Galwey score	17.7 $\pm$ 1.4	15.8 $\pm$ 1.4	17.5 $\pm$ 1.2	*P = 0.025; **P = 0.02
Self-assessment	3	2.4 $\pm$ 0.1	3.3 $\pm$ 0.3	*P = 0.014
Weight (kg)	94.3 $\pm$ 9.1	91.5 $\pm$ 7.6	94.0 $\pm$ 9.8	*P = 0.009; **P = 0.005
Growth velocity (mm/day)	0.76 $\pm$ 0.2	0.67 $\pm$ 0.2	0.77 $\pm$ 0.1	*P = 0.03; **P = 0.03

* Metformin vs. Baseline.

** Metformin vs. Placebo.

baseline (91.5 $\pm$ 7.6 vs 94.3 $\pm$ 9.1 kg; $P = 0.009$) (Table 1). Despite this there was no significant change in waist–hip ratio or blood pressure.

Menstrual history

There was no significant difference in cycle frequency between baseline and placebo (0.3 $\pm$ 0.1 vs 0.4 $\pm$ 0.1 cycles per month; $P > 0.8$). Metformin treatment led to a significant increase in cycle frequency compared with placebo (0.53 $\pm$ 0.12 vs 0.35 $\pm$ 0.08 cycles per month; $P = 0.008$) and baseline (0.53 $\pm$ 0.12 vs 0.30 $\pm$ 0.08 cycles per month; $P = 0.005$).

Discussion

We have demonstrated that metformin treatment in a group of women with PCOS results in a significant clinical improvement in hair growth compared with placebo. We have also confirmed that metformin leads to improvements in both weight and menstrual frequency.

Previous studies with metformin in PCOS have shown improvement in reproductive function and this has been associated with reduced insulin resistance, independent of weight loss (8, 9, 11–21). However, the majority of studies with metformin in PCOS have been of too short a duration to comment on hair growth. This study was designed to assess the effect of 6 months of metformin on hair growth as a primary end point. While we are aware of no published studies designed to assess hirsutism as a primary end point, two recent publications on prolonged metformin use in women with PCOS comment on hirsutism in their final analysis (14, 18). The study of Pasquali *et al.* (18) described a significant improvement in hirsutism, while Moghetti *et al.* (14) found no improvement. The most likely explanation for this is the different baseline characteristics of the groups. Moghetti *et al.* studied a group of women referred with menstrual disturbance who had low levels of hirsutism, while Pasquali *et al.* described a group of women from their endocrine

clinic with significantly greater baseline hirsutism as assessed by the F-G score. The latter study should be interpreted with caution, as hirsutism was assessed using a subjective scoring system with no methodological and reproducibility data reported.

Studies of hirsutism often have considerable shortcomings (26, 27). This study was designed to record both subjective (F-G score and self-assessment) and objective (plucked hair velocity) measures of response. The major limitation of the objective method in the current study was the fact that the majority of the subjects were reluctant to go for any length of time without depilatory treatment and as such it made statistical interpretation of this outcome potentially unsound.

Understandably, women expect a global improvement in appearance. However, the subjective scoring systems used to record this exhibit considerable observer variation, even when carried out by the same person (26, 27). We addressed this by using a single blinded observer and combined subjective and objective assessments of hair growth. The results demonstrate that in our hands the subjective assessment (F-G score) was reproducible and in keeping with both the objective measurement and patient self-assessment.

The assessment of menstrual abnormalities was not a primary end point for this study, however we did find an improvement in cycle frequency, with an increase from 0.35 to 0.53 cycles per month ($P = 0.008$). Indeed six women had started cycling monthly by the end of the metformin phase. This finding is not new and confirms previous studies particularly those of Nestler *et al.* (17).

While this study demonstrates an improvement in hirsutism there are limitations to the work. The numbers recruited for the study were low and the study design could have been more robust. The study was, however, designed as a pilot to investigate if metformin had any effect over placebo prior to comparing metformin to existing treatments. We feel this has been achieved and while overall changes in F-G score were modest (15.8 $\pm$ 1.37 vs 17.5 $\pm$ 1.23 (10% reduction)), they are in keeping with studies using gonadotrophin releasing hormone agonists (24, 25) but less impressive

than a larger study using cyproterone acetate (28) which demonstrated a 20% improvement. The latter study was, however, carried out in women with higher F-G scores.

In summary, we have shown for the first time that metformin treatment, in addition to its well-reported benefit on menstrual function, has significant additional benefit in reducing hair growth in a population of hirsute women with PCOS. It is now necessary to conduct a larger study comparing metformin with, for example, Dianette (ethinylestradiol 35 µg, cyproterone acetate 2 mg) and if possible assessing the response using both subjective and objective measures.

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