RBM Online - Vol 17 No 4. 2008 579-582 Reproductive BioMedicine Online; www.rbmonline.com/Article/3299 on web 20 August 2008

Article

Treatment of hirsutism with myo-inositol: a prospective clinical study

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Abstract

The aim of this study was to evaluate the effects of myo-inositol treatment in hirsute women; changes in lipid pattern and insulin sensitivity were also considered. Forty-six hirsute women were enrolled at the first Institute of Obstetrics and Gynecology and evaluated at baseline and after receiving myo-inositol therapy for 6 months. Body mass index (BMI), hirsutism, serum concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, apolipoprotein B, lipoprotein(a), serum adrenal and ovarian androgens, fasting glucose and insulin concentrations were evaluated. No changes in BMI were observed. The hirsutism decreased after therapy ($P < 0.001$). Total androgens, FSH and LH concentrations decreased while oestradiol concentrations increased. There was a slight non-significant decrease in total cholesterol concentrations, an increase in HDL cholesterol concentrations and a decrease in LDL cholesterol concentrations. No significant changes were observed in serum triglyceride, apolipoprotein B and lipoprotein(a) concentrations. Insulin resistance ($P < 0.01$), analysed by homeostasis model assessment, was reduced significantly after therapy. Administration of oral myo-inositol significantly reduced hirsutism and hyperandrogenism and ameliorated the abnormal metabolic profile of women with hirsutism.

Keywords: *HDL cholesterol, insulin resistance, LDL cholesterol, myo-inositol, total cholesterol, triglycerides*

Introduction

Contraceptive pills have been the mainstay of therapy for hirsute patients for decades because they are considered the simplest, safest and least expensive therapy (Escobar-Morreale *et al.*, 2000). However, contraceptive pills have been associated with several adverse effects, including alteration of glucose and lipid metabolism, in both normal women and women with hyperandrogenism (Azziz, 2003). Women with hyperandrogenism may also have an increased risk for cardiovascular diseases because of their excessive androgen concentrations and increased prevalence of insulin resistance. Therefore, before prescribing contraceptive pills, physicians must consider the possibility that the patient's lipid profile and glucose tolerance might worsen, especially as most hirsute patients require therapy for an indefinite period. In some normal women, contraceptive pills may affect serum lipid values; this therapy may increase serum concentrations of triglycerides and decrease concentrations of high-density lipoprotein (HDL) cholesterol (Krauss and Burkman, 1992). As in hyperandrogenic patients, insulin resistance may increase as a result of contraceptive pill therapy. Many hormonal contraceptives also have a low compliance rate and some women interrupt the therapy owing to side effects, such as water retention, weight gain and headache. For these reasons, it is desirable to find a new method for treating hirsute women.

Myo-inositol is an isomer of a C_6 sugar alcohol that belongs to the vitamin B complex group. Various studies have suggested that myo-inositol plays an important role in cell morphogenesis and cytogenesis, lipid synthesis, the structure of cell membranes and cell growth. Recent studies outlined a deficiency of

myo-inositol in insulin resistance in women with polycystic ovarian syndrome (PCOS). The administration of myo-inositol reduces serum insulin, decreases serum testosterone and enhances ovulation (Nestler and Jacubowicz, 1997; Yoshida *et al*., 2006). The lipid profile and glucose and insulin serum concentrations were studied in unselected hirsute patients before and after 6 months of treatment with myo-inositol. This therapy effectively controlled hirsutism and induced favourable changes in the lipid profile and insulin sensitivity.

Materials and methods

Forty-six patients (mean age ±SD, 24.2 ± 3.1 years) were enrolled in the study, after informed consent was obtained. Conditions such as hyperprolactinaemia, hypothyroidism, adrenal hyperplasia and Cushing's syndrome, were excluded by hormonal tests. Patients who had taken hormonal medications, including contraceptive pills, for the past 6 months, were excluded from the study.

The women had mild to moderate hirsutism, evaluated using a modification of the Ferriman–Gallwey score (Ferriman and Gallwey, 1961) that quantified terminal hairs in nine body areas. Non-classic congenital adrenal hyperplasia was ruled out by normal 17-hydroxyprogesterone and 11-deoxycortisol responses to adrenocorticotrophic hormone. Ten of the patients had oligomenorrhoea, while no patients had evidence of Cushing's syndrome, acromegaly, hyperprolactinaemia or thyroid disorders.

The women had similar body mass index (BMI) except for three patients who were obese. General recommendations about healthy dietary and lifestyle habits were made to obese patients, but no specific intervention was directed towards weight reduction.

For the present study, hirsutism scores and fasting blood samples were obtained during the follicular phase of the menstrual cycle. Serum concentrations of total cholesterol, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, apolipoprotein B, lipoprotein(a), glucose, insulin, testosterone, sex hormone-binding globulin (SHBG), Δ4-androstenedione, cortisol, dehydroepiandrosterone sulphate (DHEA-S), LH, FSH and E_2 were measured within the first 5 days of the menstrual cycle.

Measurement of these substances was repeated after 6 months of treatment with myo-inositol (Inofolic®, LO.LI. Pharma, Rome, Italy) 2 g twice a day. Insulin resistance was measured using homeostasis model assessment. Serum samples were obtained after 6 months of treatment to avoid any direct acute pharmacological effect of the medication and to compare its effects adequately with baseline measurements.

Statistical analysis

Results are expressed as means; the mean of the difference of each value before and after treatment ± SE is also reported in **Table 1**. The Kolmogorov–Smirnov statistical test with a

Table 1. Clinical and biochemical variables in 46 hirsute patients at baseline and after six months of treatment with myo-inositol.

Variable	*Baseline*	*After treatment*	*Difference ± SE*	P-*value*
BMI (kg/m²)	27.5	25.5	–2.0 ± 1.0	NS
Hirsutism score	13.1	10.8	–2.3 ± 0.9	<0.001
Testosterone (ng/dl)	72	59	–13 ± 2.6	<0.002
Free testosterone (ng/ml)	1.8	1.0	–0.8 ± 0.4	<0.001
Free androgen index	7.3	2.3	–5.0 ± 1.7	<0.001
SHBG (μg/dl)	378	373	–5.0 ± 42	NS
Δ4-androstenedione (ng/ml)	3.2	2.5	–0.7 ± 0.2	<0.010
DHEA-S (ng/ml)	3152	2590	–562 ± 197	<0.050
LH (mIU/ml)	6.5	3.9	–2.6 ± 1.8	<0.005
FSH (mIU/ml)	6.7	5.6	–1.1 ± 0.4	NS
Oestradiol (pg/ml)	50	54	4 ± 16	NS
Cortisol (μg/dl)	20.2	31.4	11.2 ± 0.8	<0.001
Fasting glucose (mg/dl)	80	82	2 ± 1.6	NS
Insulin (μIU/ml)	12.2	8.3	–3.9 ± 1.8	NS
Insulin resistance	3.07	1.3	–1.77 ± 0.71	<0.010
Total cholesterol (mg/dl)	174	170	–4 ± 11	NS
HDL cholesterol (mg/dl)	61	70	9 ± 1.2	<0.001
LDL cholesterol (mg/dl)	98	79	–19 ± 7.8	<0.005
HDL:LDL ratio	0.62	0.89	0.25 ± 0.04	NS
Apolipoprotein B concentration (mg/dl)	84	89	5 ± 2.5	NS
Lipoprotein(a) (mg/dl)	22	30	8 ± 2.8	NS
Triglyceride (mg/dl)	65	66	1 ± 14	NS

BMI = body mass index; DHEA-S = dehydroepiandrosterone sulphate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NS = difference not significant; SHBG = sex hormone-binding globulin.

Lilliefors significance level for testing normality was applied to continuous variables. Logarithmic transformation was used to ensure a normal distribution as needed. Paired *t*-tests were used to identify the differences between variables at baseline and after 6 months of treatment with myo-inositol. A P-value < 0.5 was considered statistically significant.

Results

The hirsutism score decreased by 2.3 ± 0.9 after 6 months of therapy. The total androgens evaluated decreased (**Table 1**). There was a non-significant decrease in SHBG concentrations after treatment while FSH and oestradiol concentrations were similar to those at the beginning of the trial. The cortisol concentration increased slightly (**Table 1**).

Fasting glucose concentrations were normal (<110 mg/dl) in all patients before and after treatment. There was a decrease in insulin concentration and insulin resistance after therapy. At baseline, nine hirsute women presented fasting insulin concentrations >20 μIU/ml, which is the upper limit of the normal range of the assay used and 29 patients had elevated androgen concentrations. Increased insulin concentrations normalized in all nine patients after 6 months of myo-inositol treatment (**Table 1**).

Serum total cholesterol concentrations decreased after myo-inositol therapy but not statistically significantly. HDL cholesterol concentrations increased and LDL cholesterol concentrations decreased (**Table 1**). In all patients, total cholesterol concentrations were <240 mg/dl at baseline and after 6 months of treatment with myo-inositol. Seventeen patients (37.0%) presented with HDL cholesterol concentration <60 mg/dl; in 14 patients, these concentration normalized after myo-inositol treatment. Concentrations of LDL cholesterol were <160 mg/dl in all patients throughout the study.

The serum lipoprotein(a) and triglyceride concentrations did not change significantly from the baseline value; an apparent but non-significant increase in apolipoprotein B concentrations was seen. Only one of the 46 patients had increased serum triglyceride concentrations (209 mg/dl) at baseline; these concentrations decreased to 179 mg/dl after 6 months of treatment. At baseline, 12 patients had lipoprotein(a) concentrations >30 mg/dl (which is considered a cardiovascular risk factor); one of these patients also had a low HDL cholesterol concentration. The increased lipoprotein(a) concentrations persisted after myo-inositol treatment in only two patients. There were no reported side effects during the period of treatment with myo-inositol.

Discussion

Women with hyperandrogenism, especially those affected by PCOS, have an increased prevalence of risk factors for cardiovascular diseases, including dyslipidaemia and insulin resistance (Papaleo *et al*., 2007; Proctor *et al*., 2007). The European Society for Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM) consensus on diagnosis, nomenclature and long-term health risks of polycystic ovarian syndrome (PCOS) (conference in Rotterdam, Netherlands, March 2003) is still being debated following the publication by Azziz in 2004. The long-term health risks and the importance of early treatment for PCOS have recently been discussed by Geisthövel and Rabe (2007).

A high proportion of women with PCOS have insulin resistance and hyperinsulinaemia. A defect in insulin action has been suspected, particularly as a consequence of a deficiency of D-chiro-inositol, a component of inositol phosphoglycan. Insulin-lowering medications represent novel therapies for restoring spontaneous ovulation (Cheang and Nestler, 2004; Baillargeon, 2005). D-chiro-inositol administration increases the action of insulin in patients with PCOS, thereby improving ovulatory function and decreasing serum testosterone concentration (Nestler *et al*., 1999; Gerli *et al*., 2003; Baillargeon *et al*., 2006;). Myo-inositol, a precursor of D-chiro-inositol, is widely distributed in nature whereas D-chiro-inositol is relatively rare (Iuorno *et al*., 2002).

The changes in lipid concentrations among hirsute women in the present study suggest an overall beneficial effect of myo-inositol on the lipid profile. Six months of therapy with myo-inositol significantly improved insulin sensitivity (P < 0.01) without producing changes in weight or BMI. These results agree with those of Papaleo *et al*. (2007), who found that treatment with myo-inositol in women with PCOS prevented the insulin resistance found in untreated women and increased HDL cholesterol concentrations.

Finally, myo-inositol effectively controlled hyperandrogenism and hirsutism in the study patients, producing substantial reductions in the hirsutism score and serum androgen concentrations of ovarian and adrenal origin.

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Declaration: The authors report no financial or commercial conflicts of interest.

Received 16 November 2007; refereed 19 December 2007; accepted 11 June 2008.