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The combined therapy myo-inositol plus D-Chiro-inositol, in a physiological ratio, reduces the cardiovascular risk by improving the lipid profile in PCOS patients

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Abstract. – BACKGROUND: Women with Polycystic Ovarian Syndrome (PCOS) present several factors that increase the cardiovascular risk, such as insulin resistance and dyslipidemia. Myo-inositol and D-chiro-inositol have been shown to improve insulin resistance, hyperandrogenism and to induce ovulation in PCOS women. However, their effects on dyslipidemia are less clear. The aim of the present study was to evaluate whether the combined therapy myo-inositol plus D-chiro-inositol (in a in a physiological ratio of 40:1) improve the metabolic profile, therefore, reducing cardiovascular risk in PCOS patients.

PATIENTS AND METHODS: Twenty obese PCOS patients [BMI 33.7 ± 6 kg/m² (mean ± SD)] were recruited. The lipid profile was assessed by measuring total cholesterol, LDL, HDL and triglycerides before and after 6 months treatment with the combined therapy. Secondary end points included changes in BMI, waist-hip ratio, percentage of body fat, HOMA-IR and blood pressure.

RESULTS: The combined therapy myo-inositol and D-chiro-inositol improved LDL levels (3.50 ± 0.8 mmol/L versus, 3 ±1.2 mmol/L $p < 0.05$), HDL (1.1 mmol/L ± 0.3 versus 1.6 mmol/L ± 0.4 $p < 0.05$) and triglycerides (2.3 ± 1.5 mmol/L versus 1.75 ± 1.9 mmol/L $p < 0.05$). Furthermore, significant improvements in HOMA-IR were also observed.

CONCLUSIONS: The combined therapy myo-inositol plus D-chiro-inositol is able to improve the metabolic profile of PCOS women, therefore, reducing the cardiovascular risk.

Key Words:
Lipids, LDL, Biological variation, Polycystic ovary syndrome.

Introduction

Polycystic ovarian syndrome (PCOS) is a common and multifactorial disorder that combines metabolic hormonal and reproductive morbidities in women in childbearing age. Indeed, PCOS women are characterized by several risk factors, such as impaired glucose tolerance, type 2 diabetes (DM2), insulin resistance, hypertension, abnormalities in the coagulation pathways and atherogenic dyslipidemia[1-3]. In particular, alterations of the lipid profile affects up to 70% of the PCOS patients[4]. Several interrelated pathological processes seem to contribute to dyslipidemia instauration: among others, obesity, insulin resistance and hyperandrogenism[5-10].

Therefore, the causes of dyslipidemia in PCOS are again multifactorial. Insulin resistance appears to have a pivotal role mediated in part by stimulation of lipolysis and altered expression of lipoprotein lipase and hepatic lipase[11].

Along side with insulin resistance, metabolic syndrome, impaired glucose tolerance (IGT) and DM2, women with PCOS also have increased level of novel cardiovascular risk factors (inflammation, oxidative stress and impaired fibrinolysis)[12]. In addition, increased early clinical and subclinical markers of atherosclerosis observed in PCOS women (endothelial dysfunction, impaired pulse wave velocity, increased carotid intima media wall thickness, presence of carotid plaque and increased coronary artery calcification)[11,13] are further exacerbated by obesity[6,14,15].

IGT has been found to increase the risk of cardiovascular diseases (CVD), mortality and progression to DM2 in general populations[16]. Recent population based data noted a mortality rate of 5.5% over 5 years for those with IGT versus 1.9% with normal glucose tolerance[16]. Furthermore, lifestyle intervention, metformin and glitazones can prevent IGT progression to DM2 (although several side effects are present)[17], strengthening the argument for early treatment of PCOS women with insulin sensitizers.

Large longitudinal cohort studies have shown that up to 65% of CVD deaths occur in subjects

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with impaired glucose metabolism[18]. Since IGT and DM2 are common PCOS features, the presence of additional risk factors such as dyslipidemia further increases the risk of PCOS women to develop a CVD[19].

In the present study, we aim to evaluate whether the combined therapy myo-inositol (MI) plus D-chiro-inositol (DCI) is able to improve the lipidic profile (one of the risk factors for CVD) in PCOS subjects and therefore reduce the risk of cardiovascular events. PCOS is a complex syndrome and because of this the study was designed in order to guaranty a multidisciplinary approach.

Patients and Methods

Study Design and Subjects

We performed a 24 weeks, longitudinal study. Twenty obese, Caucasian women diagnosed with PCOS according to Rotterdam criteria[20] were enrolled in this study. Exclusion criteria included diabetes mellitus, uncontrolled hypothyroidism and patients on hormonal treatment and antihyperlipidaemic medication. In addition, non-classical 21-hydroxylase deficiency, hyperprolactinaemia and androgen secreting tumours were excluded by appropriate testing[21]. Baseline patients' characteristics are listed in Table I.

Intervention

All the subjects were on unrestrictive diet at the beginning of the trial and were instructed not to modify their usual eating patterns. Patients received a combined therapy myo-inositol plus D-chiro-inositol in soft gel capsule (550 mg myo-inositol, 13.8 mg D-chiro-inositol, Inofolic® Combi, Lo.Li. pharma Roma; patent pending) twice a day for 6 months.

Study Measurements

The percentage of body fat was estimated by a monitor using Bioelectrical Impedance Analysis (BIA, Tanita®).

Venous blood samples, taken before and after the six months treatment period under similar conditions, were separated by centrifugation at 2000 g for 15 minutes at 4 C and the serum obtained was stored at –20°C within one hour of collection. All the serum samples were thawed and thoroughly mixed before the analysis.

Total cholesterol, triglycerides, HDL cholesterol and glucose were measured using a Synchron LX20 analyser (Beckman-Coulter, High Wycombe, UK). LDL was calculated with the Friedewald equation ((LDL cholesterol)=(total cholesterol)-(HDL cholesterol)-(triglycerides)/5). Serum insulin was assayed using DPC Immulite 2000 analyser (Euro/DPC, Llanberis, UK). Insulin resistance was calculated using the Homeostasis Model Assessment (HOMA).

Statistical Analysis

Outcome measures in the two treatment groups were compared by paired t test using GraphPad Prism software (La Jolla, CA, USA).

Results

LDL levels after 6 months treatment with the combined therapy significantly improved compared

Table I. Metabolic profile of the enrolled subjects at baseline and after 6 months treatment (means ± SD).

	Baseline	After 6 months treatment with myo-inositol plus D-chiro-inositol	*p* value
Age (years)	26.8 ± 5.1		
BMI	33.71 ± 6.1	33.1 ± 5.3	
Waist-hip ratio (cm)	0.92 ± 0.05	0.91 ± 0.09	
Tanita (% fat)	47.8 ± 4.4	47.1 ± 4.4	
BP systolic (mmHg)	121 ± 9.6	119 ± 8	
BP diastolic (mmHg)	71 ± 3.9	69 ± 8.5	
F. insulin (μU/ml)	18.2 ± 8.1	15 ± 8.7	= 0.05
F. glucose (mmol/L)	5.6 ± 0.5	4.7 ± 0.5	= 0.05
HOMA	5.8 ± 1.7	3.5 ± 1.1	= 0.05
T. cholesterol (mmol/L)	6.0 ± 1.8	5.01 ± 0.9	= 0.10
LDL (mmol/L)	3.5 ± 0.8	3.0 ± 0.8	= 0.03
TG (mmol/L)	2.0 ± 1.2	1.75 ± 1	= 0.24
HDL (mmol/L)	1.2 ± 0.2	1.3 ± 0.2	= 0.05

BMI: body mass index, BP: blood pressure, T. cholesterol: total cholesterol, LDL: low density lipoprotein, TG: triglycerides, HDL: high density lipoprotein, F. Insulin: fasting insulin, F. Glucose: fasting glucose.

with baseline levels (3.5 ± 0.8 versus 3.0 ± 1.2, p = 0.03); significant changes were observed for HDL (1.1 mmol/L ± 0.3 versus 1.3 mmol/L ± 0.4 $p < 0.05$) and triglycerides (2.0 ± 1.5 mmol/L versus 1.75 ± 1.9 mmol/L $p < 0.05$). Furthermore, it was possible to observe a significant reduction of the HOMA index and glucose and insulin levels (Table I).

Discussion

In the present study we show that the combined therapy myo-inositol plus D-chiro-inositol is able to improve the metabolic profile of obese PCOS women thus reducing the risk of CVD.

Among the comorbidities that affect PCOS women, there are several factors that contribute to increase the cardiovascular risk. Indeed, PCOS women have an increased risk of CVD compared to BMI matching women[6,19,22-24].

A recent study performed by the Women's Ischemia Evaluation Study (WISE)[19] highlighted that PCOS women undergo through an increased number of cardiovascular events. In particular, a cardiovascular event was observed in 32% of PCOS women compared with 25% of non-PCOS, resulting in an odds ratio of 1.7, meaning that PCOS women have almost twice the chance of developing a CVD. Furthermore, the event free survival (including fatal and non-fatal events) was found to be significantly lower in PCOS compared to non-PCOS women. Looking at the cerebrovascular events, the difference between PCOS and non PCOS was higher, further confirming the association of PCOS with stroke[25].

In 2010 Wild et al[26] already proposed a protocol to assess CVD risk in PCOS, highlighting the importance of prevention strategies in young PCOS women.

Following the guidelines provided by the American Heart Association[27], women with PCOS were classified at risk or at high risk according to the following criteria:

1. At risk – PCOS women with any of the following risk factors:
- Obesity (especially increased abdominal adiposity)
- Cigarette smoking
- Hypertension
- Dyslipidemia (increased LDL-C and/or non-HDL-C)
- Subclinical vascular disease
- IGT
- Family history of premature CVD (55 yr of age in male relative, 65 yr of age in female relative).

2. At high risk – PCOS women with:
- MBS
- T2DM (type 2 diabetes mellitus)
- Overt vascular or renal disease

In the present study we have shown that several of the risk factors identified by the American Heart Association and translated by Wild et al[26] on PCOS women, were indeed reduced by the administration of a combined therapy myo-inositol plus D-chiro-inositol.

Total cholesterol, LDL and triglycerides were significantly reduced as well as fasting insulin, fasting glucose and HOMA index. Furthermore, HDL significantly increased.

Taking together literature and present data, we can conclude that the combined therapy myo-inositol plus D-chiro-inositol (in a in a physiological ratio of 40:1) is able to reduce the cardiovascular risk in PCOS women.

These striking results obtained by the combined treatment are likely linked to the fact that the administration of both stereoisomers is able to regulate glucose metabolism in a physiological way. While DCI is able to promote glycogen synthesis, MI is able to promote glucose cell intake[28]. The different inositol functions are directly transferred to body tissues; indeed, DCI is present at high concentrations (although always lower than MI) in glycogen storage tissues, such as liver, muscles and fat[29]. On the other hand, DCI is present at low concentrations in those tissues that must have a high energy status (i.e. use high amount of glucose) such as brain, ovary, hearth[29].

In conclusion, the improvement of the glucose metabolism in PCOS women will in turn improve the lipid profile thus reducing the cardiovascular risk.

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