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Effects of Myo-inositol, D-chiro-inositol and Glucomannan in PCOS Women: Prospective Observational Multicentric Cohort Study

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Abstract

Objective: Polycystic Ovary Syndrome (PCOS) is one of the most common endocrinopathies of the reproductive age in women. PCOS is an endocrine-metabolic disorder characterized by insulin resistance. Aim of the study was to evaluate the efficacy of natural substances such as inositol and glucomannan, and their combination in reducing glucose levels and improving insulin sensitivity in PCOS patients.

Methods: 100 PCOS insulin-resistant women were enrolled for the administration of myo-inositol 1,75 g, D-chiro-inositol 0,25 g, and glucomannan 4 g a day for 90 days.

Plasma levels of glucose and insulin, BMI, menstrual cycles, Ferriman Gallwey score, and acne were evaluated before and after treatment.

Results: There was a significative reduction of glucose, insulin, acne and Ferriman Gallwey score.

Conclusion: Present results show that the association-inositol glucomannan may represent a good therapeutic strategy in the treatment of PCOS women with insulin resistance.

Keywords: PCOS; Insulin resistance; Inositol; Glucomannan; Glucose; Endocrinopathies; Reproductive age

Introduction

Polycystic Ovary Syndrome (PCOS) represents the most common female endocrinopathy [1] and manifests itself through oligomenorrhea, anovulation, hirsutism, and ultrasonography micro-polycystic ovaries [2,3].

Insulin resistance is a characteristic of PCOS patients and is more pronounced in obese patients, but it is present in a moderate percentage in normal weight patients. Moreover, insulin resistance and consequent hyperinsulinemia are related to further hormonal alterations such as hyperandrogenism and decrease in Sex Hormone Binding Globulin (SHBG). It is well known that a therapeutical approach based on a decrease in insulin levels should have a fundamental effect on metabolic, hormonal and reproductive features of the syndrome.

PCOS, as a metabolic dysfunction, has both a significant effect on the reproductive life of the patients, induces a higher risk for common pathologies to include type II diabetes, metabolic syndrome, cardiovascular disease, endometrial carcinoma, and many gestational complications, compared to the healthy population [4]. Therefore, it is also important to consider PCOS morbidity and it is associated with high social impact, both economic and in healthcare.

Nowadays, a standardized treatment of PCOS patients doesn't exist, which aims either to treat the weight loss in obese patients or to restore menstrual cycle/fertility or to cure clinical hyperandrogenism [5]. In this way, the attention of specialists has turned in the last years to the research of drugs and nutraceutical substances able to improve glucose metabolism in these women.

Metformin has an insulin-sensitizing activity and it is currently used to reduce blood sugar levels in patients with diabetes mellitus since it improves the peripheral utilization of glucose, acting on the liver by increasing insulin sensitivity and inhibiting glucose production, whereas it improves glucose storage and utilization in skeletal muscle cells.

This drug is not accepted by all patients due to its side effects on the gastrointestinal system, which often forces practitioners to interrupt its prescription. For these reasons, alternative therapeutic options have been studied in recent years.

For example, Inositol Phosphoglycans (IPGs) are putative mediators in non-classical insulin signaling cascade for glucose uptake and use, they play an important role in cell development and morphogenesis, moreover in the cell IPGs exert their metabolic effect.

Like, Myo-Inositol (MI) and D-Chiro Inositol (DCI) are the two most important isomers able to interact with the insulin receptor to activate IPGs way. Low levels of D-chiro inositol are associated with glucose tolerance reduction, insulin resistance, iperinsulinemia, metabolic syndrome and type II diabetes.

In PCOS women D-chiro inositol levels are always reduced and it has been demonstrated that the administration of D-chiro inositol restores gonadal function, reduces free testosterone and triglycerides and improves insulin sensitivity. Similar results have been shown with Myo-inositol therapy, which lowered insulin resistance in both lean and obese PCOS. Further Myo-inositol effect was observed in obese PCOS women, where significant weight reduction was registered [6,7]. Additionally, Myo-inositol has relatively low costs and remarkably lower side effects, especially when compared to metformin.

Another molecule of interest is Glucomannan (GM), which is a soluble, fermentable, and highly viscous dietary fiber. It is derived from the root of the elephant yam or konjac plant, which is native to Asia. Glucomannan consists of a polysaccharide chain of beta-D-glucose and beta-D-mannose with attached acetyl groups in a molar ratio of 1 : 1.6 with beta 1-4 linkages. Since human salivary and pancreatic amylase cannot split beta 1, 4 linkages, glucomannan passes relatively unchanged into the colon, where it is highly fermented by colonic bacteria [8].

Glucomannan has a high molecular weight and can absorb up to 50 times its weight in water, making it one of the most viscous dietary fibers known. In the stomach, the glucomannan turns into gelatine and induces a sense of satiety. Thus, glucomannan inhibits the absorption of cholesterol and fats and reduce sugar absorption; it prevents the blood glucose peak by reducing the release of insulin from the pancreas and thus prevents hypoglycemia.

It has been shown that glucomannan long-term supplementation reduces fasting glucose and LDL cholesterol plasmatic levels in diabetic patients [9].

This observational multicenter study wants to evaluate the efficacy of an association between myo-inositol, D-chiro inositol and glucomannan in overweight PCOS women on fasting glucose and insulin plasmatic levels, on insulin sensitivity and clinical parameters such as irregular menses, anovulatory cycles, overweight, hirsutism and acne. The choice of an observational study was based on the possibility to evaluate efficacy and tolerability of the association between two inositols (myo-inositol and D-chiro inositol) and glucomannan out of conditions of clinical randomized studies, to observe the "real life" clinical condition.

Materials and Methods

The design of the study was observational, cohort, prospective, multi-centric.

Inclusion criteria

- Age between 18 and 35 year
- Diagnosis of PCOS (based on Rotterdam Consensus, 2013) [2]
- BMI ≥ 25 (kg/m)
- Current treatment with myo-inositol 1.75 g, D-chiro inositol 0.25 g, glucomannan 4 g for no more than 30 days
- Informed consent was obtained from all patients before participation in the study

Our sample size included 100 women under treatment with myo-inositol 1.75 g, D-chiro inositol 0.25 g, glucomannan 4 g divided into two administrations before main meals. The observational period was 90 days.

Before the beginning of the treatment and after 90 (± 15) days were collected for every woman anthropometric data (age, ethnic origin, work activity, marital status) and were evaluated in all patients ultrasonography, insulin-glucose metabolism (with oral administration of 75 g glucose and evaluation of plasmatic levels of glucose and insulin at time 0, 30, 60, 90, 120 and 180 minutes) [2,10], hirsutism (evaluated in accordance with Ferriman Gallwey score) and acne (evaluated in accordance with Global evaluation scale [11]), expected in clinical routine.

Global evaluation scale provides

Grade 0: clean, without inflammatory or not inflammatory lesions.

Grade 1: almost clean, rare not inflammatory lesions, no more than one papule/pustule.

Grade 2: Slight, some inflammatory lesions, a small number of papules or pustules, no nodules.

Grade 3: moderate, a lot of not inflammatory lesions, some inflammatory lesions and no more than one nodule.

Grade 4: severe, many non-inflammatory and inflammatory lesions, a small number of nodules.

Ferriman Gallwey score is a useful clinical scoring system that analyses the presence of terminal hairs in androgen-dependent areas in women and provides [12]:

- Score <8: no hirsutism
- Score 8-15: slight hirsutism
- Score 16-25: moderate hirsutism
- Score >25: severe hirsutism

During the first study visit (V0), the experimenter verified inclusion criteria and informed every woman about targets of the study. Every woman signed informed consent.

Moreover, all women compiled a sheet about general information, clinic history, BMI (calculated from weight (kg)/ height (m^2)), menstrual cycle data.

During the control visit (V1) were checked the correct therapy administration, clinical symptoms and adverse events. In every woman were evaluated menstrual cycles, Progesterone dosage in 22° menstrual day and acne and hirsutism; moreover, were conducted ultrasonography and glucose-insulin metabolism (plasmatic levels of glucose and insulin after 75 g glucose administration at time 0', 30', 60',90',120',180').

Statistical Analysis

The normal distribution of data was evaluated thought Kolgomorov-Smirnov test. Normal variables were expressed as Media (M) and Standard Deviation (SD). Demographic data are presented as percentage (%).

Differences between insulin and glucose during the study were evaluated using t-Test.

FDA values during the study were divided into 2 groups (FDA lesions between 2 and 4 and FDA lesions between 0 and 1) and were evaluated the different percentage with confidential limit 95%.

Ferriman Gallwey index [12] ≥ 8 indicates the presence of clinical hirsutism; the difference between V0 e V1in every woman with initial value ≥ 8 was evaluated with a confidential interval of 95%.

Values were significative if $p<0.05$.

Statistical analysis was conducted using NCSS 2007 and PASS (Power Analysis and Sample Size) Hintze J, NCSS and PASS Number Cruncher Statistical System Kaysville, Utah. Age, anthropometric data, marital status, BMI, work activity and menstrual cycle characteristics were explained in Table 1.

Study population	No. (%)
Age (M, DS, range)	26.7 (6.4, 15-42)
Ethnic origin	
Caucasian	96 (97.0)
Other	3 (3.0)
Empty data	21
BMI	
Normal weight	38 (31.7)
Overweight	62 (51.7)
Underweight	20 (16.7)
Work activity	
Student	38 (53.5)
Professional	6 (8.4)
Housewife	8 (11.3)
Shop assistant	5 (7)
Farmer worker	4 (5.6)
Dealer	1 (1.4)
Nurse	1 (1.4)
Employee	8 (11.3)
Other or not specified	49
Marital status	
Maiden	58 (81.9)
Conjugated	12 (16.9)
Separate	1 (1.4)
Not specified	49
Menstrual cycle	
Hypomenorrhea	27 (26)
Eumenorrhea	66 (63.5)
Hypomenorrhea	11 (10.6)
Not specified	16

Table 1: Age, anthropometric data, marital status, BMI, work activity and menstrual cycle characteristics.

Time	Pre-treatment	Post-treatment
0	16 ± 5,1	8,1 ± 3,0
30’	85,4 ± 11,3	51 ± 13,2
60’	103,1 ± 17,7	62 ± 15
90’	68,4 ± 11,9	43 ± 8,8
120’	55 ± 9,3	30 ± 7,3
180’	39,6 ± 7,2	21,1 ± 3,1

Table 2: Insulin plasmatic levels during the glucose tolerance test before and after treatment. Data are presented as Mean (M) ± Standard Deviation (SD). Values are significative if $p<0.05$.

Time	Pre-treatment	Post- treatment
0	98 ± 7,8	85 ± 6
30’	138 ± 15,2	122 ± 8,1
60’	159 ± 12	140 ± 9,4
90’	130 ± 16,7	109 ± 12
120’	105,3 ± 7,1	97 ± 6,2
180’	94 ± 8,9	90 ± 2,5

Table 3: Glucose plasmatic levels during the glucose tolerance test before and after treatment. Data are presented as Mean (M) ± Standard Deviation (SD). Values are significative if $p<0.05$.

	Pre-treatment	Post- treatment
Acne	2 ± 0,8	0,9 ± 0,6
Ferriman gallwey score	12 ± 3	7 ± 2
Ovary volume	18 ± 3	12 ± 2
Antral follicular count	16 ± 4	8 ± 3

Table 4: Acne values (reported as slight, moderate and severe, score 1-4), Ferriman Gallwey score. Data are presented as Mean (M) ± Standard Deviation (SD). Values are significative if $p<0.05$.

Results

Data analyzed refer to 100 women from 6 Italian centers.

Fasting glucose and insulin and weight significate improved through 3 months of study observation (paired test; $p<0.0001$).

Glucose and insulin after 75 g glucose administration and evaluation after 30’, 60’, 90’, 120’ and 180’ resulted significative reduced in every evaluation.

Tables 2 and 3 and Figures 1 and 2 explained basal values and after 3 months of treatment data.

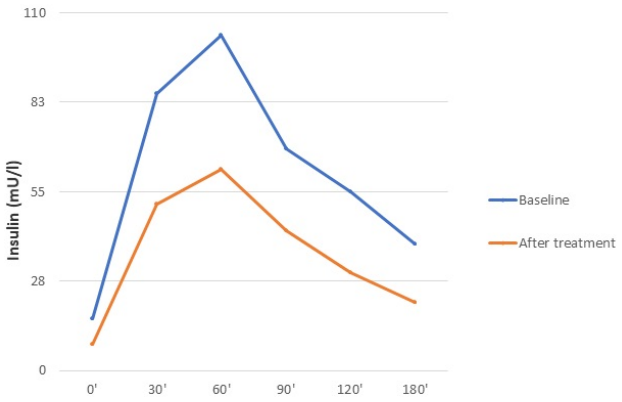

Figure 1: Insulin plasmatic level during glucose tolerance test before and after treatment.

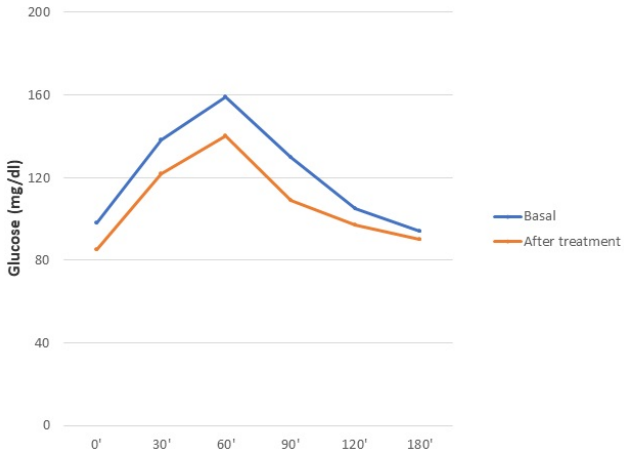

Figure 2: Glucose plasmatic level during glucose tolerance test before and after treatment.

Moreover, follicles number and ovary volume were significative reduce after 3 months treatment (paired t-test; $p<0.001$ and $p<0.0001$ respectively). Also, acne lesions ($p=0.014$) and Ferriman Gallwey score ($p=0.0002$) were reduced (Table 4).

Adverse events

We reported 9 adverse events in 2 centers, in particular, 8 cases of moderate abdominal bloating, 1 case of slight abdominal bloating. These cases generally manifested themselves during the first week of treatment. In the other 4 centers, no adverse events were reported.

Discussion and Conclusion

Despite the significant scientific progress in diagnosis and therapy, PCOS remains the first female endocrinopathy during reproductive age, which commonly manifests with anovulation, hyperandrogenism, and polycystic ovaries in ultrasonography scan.

Hyperinsulinemia is one of the most predominant features of the syndrome, and it can be present in up to 70% PCOS patients. It is well known that PCOS is an endocrine-metabolic syndrome with the possible negative sequel not only on fertility but also on the increased risk of diabetes and cardiovascular diseases in the medium and long term.

Moreover, PCOS can manifest itself with cutaneous disorders such as seborrhea, acne, hirsutism, alopecia. These symptoms can worsen PCOS patient's quality of life.

Metabolic aspect represents a key issue in the pathogenesis of the syndrome and long-term sequelae.

This study was designed to evaluate real practice effects of an association containing myo-inositol 1,75 g, D-chiro inositol 0,25 g e galactomannan 4 g daily in overweight PCOS women.

Inositol is a 6-carbon carbohydrate compound belonging to the vitamin B group, is present in various isoforms and it is helpful in PCOS because of its action in activation of insulin signaling. In fact, when insulin binds to its receptor, through hydrolysis of glycosphosphatidylinositol lipids present on cell membranes, some mediators are produced and internalized in the cytoplasm and contribute as second messengers to the activity of enzymes that regulate the oxidative and non-oxidative metabolism of the glucose. One of these mediators would be identified in D-chiro inositol. A publication by Nesler and collaborators (REF), showed that D-chiro inositol use improve insulin sensitivity in PCOS women, with the reduction of the area under the insulin curve, with consequent improve in ovulation rate and SHBG levels, decrease of androgens plasmatic levels (testosterone, androstenedione, DHEAS), triglycerides and expression values [13].

D-chiro inositol derived from the intracellular conversion of myo-inositol, this process is mediated by a specific enzyme called epimerase [14]. Also, Myo-inositol is an intracellular insulin mediator and it has proved to be effective in the control of glucose metabolism and hyperandrogenism, favoring the ovulatory function [15].

Glucomannan is a highly viscous dietary fiber, with a high molecular weight and can absorb up to 50 times its weight in water. In the stomach, the glucomannan turns into gelatine and induces a sense of satiety. it also inhibits the absorption of cholesterol and fats and reduces sugar absorption; it prevents the blood glucose peak by reducing the release of insulin from the pancreas and thus prevents hypoglycemia [8,16].

The mechanism by which glucomannan performs its function in the context of weight loss can be based on various components: it is presumed to be due to the mechanical effect due to the formation of a gelatinous mass which slows gastric emptying and induces a sense of satiety, associated with the metabolic effect linked to the marked slowing of the absorption of fats and sugars [17].

This last aspect, in particular, would represent the improvement of lipid and insulin resistance, important objectives in the control of the metabolic syndrome [18,19].

A meta-analysis and review showed [20] that glucomannan can reduce total cholesterol, LDL, triglycerides, fasting glucose and basal weight (with a not significative improvement of HDL). European Food Safety Authority (EFSA) [21] recognized that glucomannan has positive effects on many parameters of metabolic syndrome such as weight and glucose during its administration (1 g three times a day

with 1-2 glass of water before meals) in association with a hypocaloric diet. With the administration of 4 g of glucomannan, it can modulate cholesterol levels.

De Leo and collaborators [22] studied a group of 40 PCOS women (age between 20 and 30 years); data results showed that the group treated with inositol and glucomannan had a significative better improvement in glucose and insulin levels during the curve compared with the group treated with inositol alone.

Data reported in this observational, multi-centric study demonstrate how the association between inositol and glucomannan determines a good glucometabolic effect that can provide a valid therapeutic response to many of the problems of PCOS women, particularly in overweight/obese patients, with an improvement also of body weight, factors most involved in the pathogenesis and maintenance of PCOS.

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