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A New Oral Formulation based on D-Chiro-Inositol/Monacolin K/Bergamot Extract/Methylfolate and Vitamin K2 in Prevention and Treatment of Metabolic Syndrome in Perimenopausal Women with a BMI>25 Kg/m^2

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Abstract

Background: Insulin resistance is characteristic of patients with metabolic syndrome and it's more pronounced in overweight patients. In the long term there may be cardiovascular and pressor consequences. Lifestyle and diet changes may partly improve these aspects. The use of insulin-sensitizing drugs such as metformin gives good results, although side effects limit its use. Recently, new molecules exerting a similar effect without side effects have been put on the market, such as the d-chiro-inositol, a new insulin-sensitizing molecule. Have been proposed various associations between inositol and ingredients able to potentiate its therapeutic effect.

Materials and methods: This was a prospective study. 40 women were recruited aged>40 years in perimenopause with metabolic syndrome with insulin resistance, altered lipid parameters and with a BMI>25. Were evaluated: BMI, insulin levels and fasting plasma glucose, lipid profile (total cholesterol, HDL, triglycerides). The patients were divided into 2 groups: group A treated with a new oral product containing d-chiro-inositol 100 mg, monacolin-K 3 mg, bergamot extract 250 mg, methylfolate 200 mcg and natural vitamin K2 45 mcg (Mesix®) in tablets for 6 months, one tablet per day. Group B not treated and followed for 6 months.

Results: The results demonstrated a significant reduction in the levels of almost all parameters in the group treated with this new supplement, without any side effect.

Conclusions: This innovative natural supplement, thanks to the synergy of action of its components, can be a new effective alternative in prevention and treatment of metabolic syndrome in perimenopausal women.

Keywords: Metabolic syndrome; Inositol; Natural supplement; Perimenopause

Abbreviations

MS: Metabolic Syndrome; HOMA: Homeostatic Model Assessment; BMI: Bone Mineral Index

Introduction

Metabolic Syndrome (MS) is defined as a disease characterized by the presence of different variable clinical manifestations such as hypertension, abnormal glucose metabolism, abdominal fat distribution, dyslipidemia, and alterations of coagulation. The definition of the International Diabetes Federation (IDF) in 2005 attributed to the abdominal circumference a determining value for the diagnosis [1,2]. In Italy, the prevalence of this syndrome in the general population appears to be approximately 34%, with a peak in the age group between 65 and 74 years [1]. In type 2 diabetics, however, we arrive at a prevalence of 80-90% [1,2]. A high percentage of women after the age of 40 tend to develop hormonal changes that are reflected in an altered metabolic trim. The estrogen deficiency that occurs with advancing age may be a risk factor for the development of insulin resistance; in fact, physiologically estrogen increases the sensitivity of adipose tissue and striated muscle tissue at insulin action and can affect insulin secretion by increasing circulating levels of growth hormone and cortisol [3,4]. Can also be realized that an increase in blood pressure due to several factors: increase in body weight, increase in plasma insulin levels, whose action can be mediated by sympathetic activation, by a saline retention and/or by a hypertrophy, and finally increased vasomotor reactivity to the stimulations. Even the haemocoagulative structure undergoes significant changes to coincide with the decline of ovarian activity that results in a tendency to hypercoagulability and increased risk of thrombotic events [5]. It's therefore established the framework best defined as metabolic syndrome, characterized by: fasting plasma glucose > 110 mg/dl; blood pressure ≥ 130/85 mm Hg; triglycerides ≥ 150 mg/dl; HDL cholesterol < 50 mg/dl in women, associated with a waist circumference>88 cm in women or a waist-hip ratio [WHR] ≥ 0.81 with minor differences related to age and race [6-8].

Insulin resistance was defined as a state (of a cell, tissue or organism) in which is necessary a quantity of higher than normal insulin to quantitatively produce a normal response [9]. This leads to an increased insulin secretion from β cells and to a compensatory hyperinsulinemia. As long as hyperinsulinemia exceeds insulin resistance, glucose levels remain normal; if the compensatory response of the β cells decreases, a relative or absolute insulin deficiency develops that can lead to glucose intolerance and diabetes type 2.

Insulin resistance diagnosis is based on several tests, the simplest is the determination of blood insulin and sugar levels calculated by the HOMA index (HOMA=glucose (mmol/l) × insulin (mU/ml)/22.5). Values>2.5 indicate insulin resistance [10].

Unfortunately there is not a single treatment to treat MS, the approach is to deal with each symptom separately through the administration of various drugs or nutraceuticals as berberine, resveratrol, urosolic acid [11-13]. With regard to insulin-sensitizing drugs the most often used in women of this age group it's undoubtedly metformin but with side effects. In 30% of cases are reported gastro intestinal side effects such as diarrhea, nausea, bloating, loss of appetite, anorexia, metallic taste in the mouth.

In order to reduce the incidence of these side effects, in recent times it has been used inositol, either in the form of myo-inositol that in that of d-chiro-inositol.

While intracellular inositol is almost all (>99%) myo-inositol, in most of the tissues there are signi icant differences in the concentrations of myo-inositol and d-chiro-inositol, another important stereoisomer present in fat, in muscles and liver. This distribution reflects the different functions that probably the two isomers play in different tissues, and their proportions are maintained thanks to the action of the NAD, NADH-dependent enzyme epimerase that converts myo-inositol in d-chiro-inositol [14]. Some actions of insulin are performed by inositolphosphoglycan (IPG) mediators that are released by cells after stimulation by insulin [15,16]. It was found that a deficiency in a specific d-chiro-inositol-containing IPG (DCI-IPG) may contribute to IR in individuals with impaired glucose tolerance or type 2 diabetes mellitus [17].

Inositol has been associated to other natural substances in order to potentiate the therapeutic effects [18,19]. The aim is to have a unique formulation in a single daily dosing; thanks to the synergic action of its natural components it may help to stabilize the different altered parameters of MS in order to combine efficacy, safety and compliance.

On this bases we have developed a new formulation based on d-chiro-inositol for insulin-resistance along with monacolin k for hypercolesterolemia, bergamot extract for dyslipidemia, natural vitamin K2 for cardiovascular protection and methylfolate for hyperomocisteinemia.

Monacolin K acts on the regulation of the lipid profile. The monacolins are a group of molecules produced by the fermentation of red yeast rice by *Monascus purpureus*. All monacolins and, in particular, the monacolin K, play an important action in the control of cholesterol levels; in particular, they are involved in hepatic metabolism of cholesterol by competing structurally with the 3-hydroxy-3-methyl-CoA-reductase (HMG-CoA-reductase) active site. In this way the metabolic pathway is interrupted and the endogenous cholesterol production is reduced. Numerous clinical studies conducted on the fermented red yeast rice have highlighted the significant reduction of serum cholesterol, in particular LDL cholesterol, with increase, instead, of HDL [20].

The bergamot juice has been recently studied for its important action on dyslipidemia. Pharmacological studies have confirmed the activities already known in folk medicine, cholesterol lowering action and lipid lowering action. These actions are mainly due to the flavonoids. Clinical studies have shown that the activity of individual flavonoid compounds doesn't have the same power of action of the entire plant complex. The lipid-lowering action carried out by the main bioactive compounds (flavonoids) contained in bergamot juice was further confirmed in a major clinical RCT study conducted on 237 patients with hypercholesterolemia either associated to hyperglycemia or not. The results obtained after 30 days have confirmed that treatment with bergamot extract results in a significant reduction of total and LDL-cholesterol, and a significant increase in HDL-cholesterol values [21]. The plant complex of bergamot has demonstrated in vivo to lower triglyceride levels [22-24].

The addition of methylfolate ensures the control on plasma total homocysteine in women with defects in the methylene tetrahydrofolate reductase (MTHFR) as well [25,26], and natural vitamin K2 helps to improve vascular functionality [27].

The aim of this study was to show as the synergic action of nutritional components and plant extracts of this new supplement may help to control the various altered functional states of MS. We have evaluated changes of lipid profile (total cholesterol, HDL, triglycerides), the reduction of BMI and insulin resistance assessed by HOMA index, after taking this new natural product based on d-chiro-inositol/monacolin K/bergamot extract/natural vitamin K2 and methylfolate.

Materials and Methods

After careful clinical and physical evaluation, 40 women were enrolled aged 40-50 years with metabolic syndrome, BMI>25 kg/m^2 and insulin resistance, with HOMA index>2.5. The women have been introduced to our surgery for menstrual irregularities problems ranging from oligomenorrhea to a real amenorrhea with absences of the menstrual cycle for 60-90 days. Five women had a shortened cycle with a flow rate between 20 and 23 days.

The women were divided into two groups of 2 0 each and treated respectively as follows:

- Group A: treated with a natural supplement based on: bergamot extract 250 mg; d-chiro-inositol 100 mg; vitamin K2 45 mcg, methylfolate 200 mcg; monacolin K 3 mg (Mesix®, PharmaSuisse, Italy) at a dose of 1 tablet per day for 6 months.

- Group B: control, not treated and followed for 6 months.

All the women were subjected to gynecological examination, transvaginal ultrasound and blood sampling at baseline, after 3 months and after 6 months. Patients have been analyzed for those parameters which are typical of MS: insulin, glucose (HOMA index), total cholesterol, HDL cholesterol and triglycerides and has been also rated their BMI. It was also carried out a determination of basal levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, prolactin, thyroid stimulating hormone (TSH) to make a diagnosis of perimenopause resulting FSH levels>20 mIU/ml and, at the same time, to exclude pituitary and thyroid pathologies. Pelvic ultrasonography had excluded the presence of uterine fibromatosis and ovarian cysts, therefore, from the gynecological point of view, enrolled women could be considered dysfunctional patients. The patients were not allowed to assume other treatments (drugs or nutraceuticals), to make changes in diet nor life style in order not to affect the results of the study.

Statistical analysis

Data were reported as mean and standard deviation (SD). The comparison between the parameters before and after treatment for each variable was performed by Wilcoxon Signed Ranks test and

between the two different groups through the Mann-Whitney test. The data were considered statistically significant for values of $p < 0.05$. All analyses were performed using SPSS statistical software version 17 (SPSS Chicago, IL, USA).

Results

All patients completed the study and any particular side effects have not been reported.

The baseline characteristics of the patients are reported in Table 1. There are no statistical significant differences between group A and group B.

	Group A	Group B	p
Age	41 ± 1.8	42 ± 2.0	ns
Insulin (mIU/l)	24.5 ± 2	23 ± 3	ns
Blood glucose (mg/dl)	104 ± 3	106 ± 5	ns
HOMA index	6.3 ± 1.2	6.1 ± 1.4	ns
Triglycerides (mg/dl)	128 ± 15	133 ± 14	ns
Total cholesterol (mg/dl)	255 ± 16	248 ± 15	ns
HDL cholesterol (mg/dl)	47 ± 3	45 ± 2	ns
BMI (kg/m^2)	30 ± 2	29.2 ± 1.8	ns
FSH (mIU/ml)	25 ± 4	23 ± 4.5	ns
LH (mIU/ml)	19.2 ± 3.1	18 ± 2.7	ns
E2 (pg/ml)	35 ± 12	39 ± 8	ns
TSH (mIU/ml)	1.3 ± 0.7	1.5 ± 0.9	ns
PRL (ng/ml)	12.1 ± 4	10.3 ± 3.5	ns

Table 1: Patients baseline characteristics (Mean ± SD). Group A: 20 women treated with d-chiro-inositol/monacolin K/bergamot extract/ natural vitamin K2 and methylfolate. Group B: 20 women untreated.

Analysis of the results showed a significant reduction in the levels of all individual parameters in the group treated with the supplement. A result to be emphasized is the body weight reduction measured by the BMI (Kg/m^2), which reduced from 30 ± 2 to 24 ± 1 ($p<0.05$) after 6 months of treatment with the supplement (Group A) with a 20% BMI reduction; in the control group BMI was instead mostly unchanged (Figure 1).

Even insulin levels were significantly reduced in Group A passing from baseline values of 24.5 ± 2 mIU/l to 18.2 ± 4 mIU/l after 3 months up to 15 ± 1.8 mIU/l after 6 months ($p<0.05$), while in group B the insulin levels were not significantly altered, rather they are slightly increased (Figure 2). Insulin values were reduced by 37.5% in the group treated with the supplement.

Blood glucose levels in Group A decreased (no statistically significant) from 104 ± 3 mg/dl to 93 ± 4 mg/dl after 3 months to achieve the concentration of 90 ± 2 mg/dl after 6 months of treatment compared to group B where levels remained virtually unchanged (106 ± 5 mg/dl; 108 ± 4 mg/dl; 104 ± 5 mg/dl at baseline time, after 3 months and 6 months, respectively). Blood sugar values in group A have, therefore, been decreased of 14% compared to a reduction of 2% in the group B.

A similar trend was observed for lipid pro ile; total cholesterol in group A decreased from 255 ± 16 mg/dl to 220 ± 8 mg/dl after 3 months up to 212 ± 9 mg/dl after 6 months of treatment ($p<0.05$) compared to group B, whose concentrations were not significantly changed (Figure 3).

The total cholesterol is therefore decreased by 16% in the group A. The baseline blood levels of HDL cholesterol increased significantly from 47 ± 3 mg/dl to 66 ± 5 mg/dl after 6 months of treatment ($p<0.05$) in the group A, with an increase of 40%. In this case also the group B showed no significantly changes (Figure 4). Another interesting parameter is triglycerides value reduced in the group A from 128 ± 15 mg/dl to 112 ± 6 mg/dl (no statistically significant). In the group B this parameter has, instead, increased changing from 133± 14 mg/dl to 138 ± 12 mg/dl after 6 months. Group A showed a decrease in triglycerides values of 12.5%, while in the group B there was a slight increase of 3%.

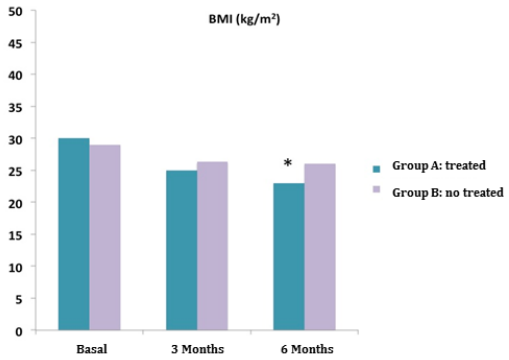

Figure 1: BMI changes during the study period. Values are statistically significant (*) for $p<0.05$.

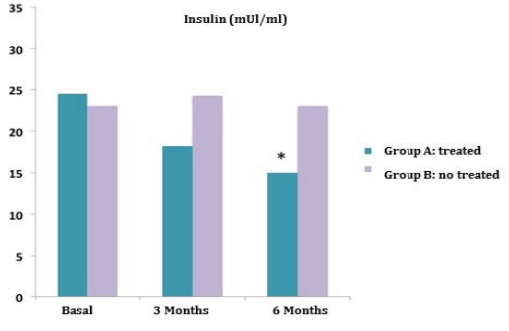

Figure 2: Insulin changes during the study period. Values are statistically significant (*) for $p<0.05$.

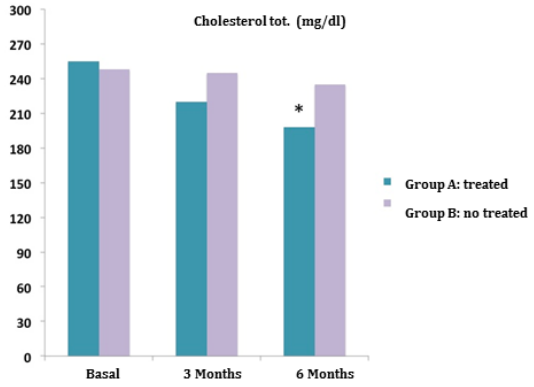

Figure 3: Total cholesterol changes during the study period. Values are statistically significant (*) for p<0.05.

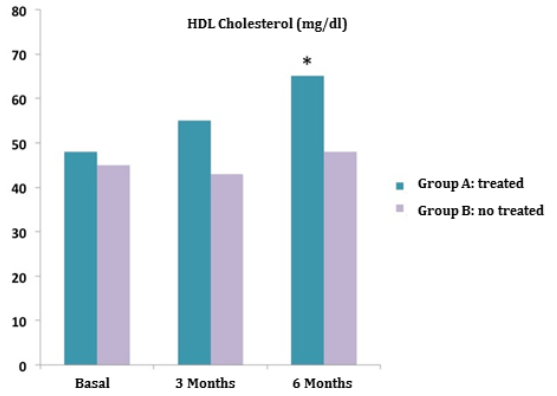

Figure 4: HDL cholesterol changes during the study period. Values are statistically significant (*) for p<0.05.

The HOMA index evaluation has changed significantly in the group of women treated with the supplement (group A) with values that decreased from 6.3 ± 1.2 to 4.1 ± 1.1 after 3 months (p<0.05) and to 3.3 ± 0.6 after 6 months with a variation at the end of the study of 48% from baseline; in the untreated group (Group B), instead, the values increased after 3 months (6.1 ± 1.4 at baseline and 6.48 ± 1.3 at 3 months) and reduced, however not significantly, at the end of study with values that are passed from 6.1 ± 1.4 to 5.9 ± 0.5 with a change of 4% (Figure 5).

Discussion

These data demonstrate that treatment with d-chiro-inositol, monacolin k, bergamot extract, methylfolate and vitamin K2 in perimenopausal overweight women, suffering from metabolic syndrome, improves lipid parameters, insulin resistance, HOMA index and reduces the BMI after 6 months of therapy.

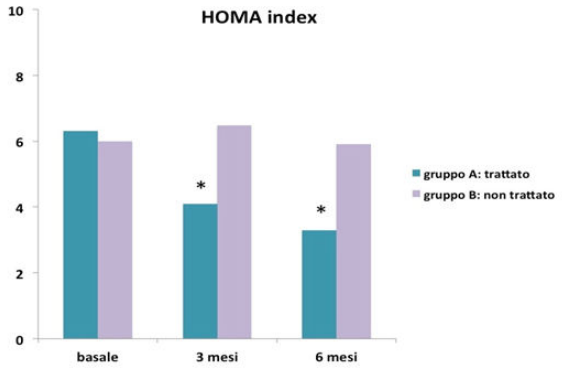

Figure 5: HOMA index changes during the study period. Values are statistically significant (*) for p<0.05.

The BMI was significantly reduced after 6 months in women treated with the supplement and this result has certainly affected the improvement of glucose and lipid metabolism parameters. Regarding the lipid profile, total cholesterol and triglycerides showed a significant decrease while HDL levels have increased. This study demonstrated that the association between d-chiro-inositol, monacolin-K, bergamot extract, methylfolate and vitamin K2 is not limited only to the reduction of total cholesterol, but may increase HDL production that is universally recognized as the most powerful protection factor of cardiovascular risk.

This study confirms the results of previous studies conducted with some of the individual components and, at the same time, gives the evaluated product specific therapeutic characteristics related to the synergistic action of all substances.

A lot of study demonstrated that oral nutritional supplementation with inositol enhances insulin sensitivity and improves the clinical and hormonal characteristics of PCOS patients [28-30].

Recently an International Consensus on Myo-Inositol and d-Chiro-Inositol studied the link between inositol and metabolic syndrome [31].

De Leo et al. demonstrated that the association between monacolin k and inositol improves hormonal and metabolic profiles of women with altered blood value of TG, HDL, LDL and total cholesterol [32].

The endocrine changes that occur in women after age 40, with the reduction in estrogen levels, may contribute to the development of some clinical features of the metabolic syndrome as the different distribution of body fat. In the period of transition from the fertile period to menopause, women are subject to a weight gain with a redistribution of body fat that causes an accumulation of it on the abdomen. In addition to the changes characteristic of the metabolic syndrome such as increased LDL, triglycerides and very low density lipoproteins (VLDL), we observed reduced HDL levels and increased glucose and insulin levels as well. These risk factors may be the result of menopause hormonal deficiency or, alternatively, of the metabolic status due to the redistribution of fat at the central level.

Metabolic syndrome is a condition in which coexist different risk factors and predisposing to the development of diabetes and cardiovascular problems. Risk factors consist of: abdominal obesity, increased triglycerides levels, low HDL cholesterol levels, glucose intolerance, hypertension. In women, a weight gain is achieved with a fat distribution, central or android type, which correlates with a major alteration in blood lipid levels and an increased risk of insulin resistance with compensatory hyperinsulinemia. The latter determines a worsening of atherogenic mechanisms, increasing the risk of cerebrovascular and cardiovascular diseases. Hormonal changes cause, in fact, an increase in total cholesterol, LDL cholesterol, apolipoprotein AI, apolipoprotein B and triglycerides and a decrease in HDL cholesterol plasma concentrations. Lipid alterations, most often associated with the metabolic syndrome, are characterized by elevated levels of triglycerides (>150 mg/dl), low HDL (<50 mg/dl), and LDL levels borderline or high (130/159 mg/dl). This syndrome shows as well significant amounts of small, dense LDL particles with an increased residence time in the circulation for a lower affinity with their receptor and exercising histolesive and inflammatory action on the endothelial tissue.

The synergic action of nutritional components and plant extracts of this new supplement demonstrated to effectively rebalance the altered functional states of the gluco-lipid metabolism and vascular system. The d-chiro-inositol is the most active isomer of inositol. It is an insulin-sensitizing agent, involved in the successful activation of second messenger systems and the insulin receptor. The d-chiro-inositol has contributed, in patients enrolled in this study, to normalize insulin resistance and has been crucial in bringing back the body weight within normal limits. The monacolin K is a phytostatin, for chemical structure and properties very similar to the synthetic statins. It acts as an inhibitor of the HMG-CoA reductase enzyme, involved in the endogenous cholesterol synthesis, exerting cholesterol lowering action with a high degree of clinical evidence, safety and efficacy. The bergamot extract showed multilevel action on the lipid profile (cholesterol, HDL, LDL and triglycerides) and glucose with a mixed mechanism of action, due to the action statin-like and complementary mechanisms of action of the plant complex flavanones. Vitamin K2 (MK-7) biological role is to remove calcium from arteries and soft tissues and help to deposit it on bone tissue, contributing to reduce the risk of cardiovascular diseases. The methylfolate is the active form of folic acid and it doesn't require metabolic transformation by the body. It has shown greater efficacy than folic acid in reducing homocysteine values. Hyperhomocysteinemia is an important cardiovascular factor risk. Based on these results, it can be said that the administration of this innovative natural supplement, Mesix®, thanks to the synergy of action of its components, can be a new and effective alternative in prevention and treatment of metabolic syndrome in perimenopausal women.

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