A New Supplement for the Treatment of Metabolic Syndrome in Postmenopausal Women

Annamaria Giacobbe1, Alessandra Bitto2, Vincenzo Arcoraci2, Roberta Granese1, Rosario D’Anna1*

1Department of Human Pathology, University of Messina, Messina, Italy
2Department of Experimental Medicine of Messina, Messina, Italy
Email: *rdanna@unime.it

Abstract

Background: Metabolic Syndrome (MS) is considered a cluster of metabolic abnormalities whose pathogenesis is principally attributable to insulin resistance. Lack of estrogens occurs in postmenopausal women and worsening insulin resistance and lipid profile, predispose to MS. The aim of the study was to show whether a new supplement containing cinnamon, corosolic acid and glycyrrhizic acid may counteract MS manifestations. Methods: A total of 60 postmenopausal women were enrolled in a randomized, controlled trial; the active treatment group was taking the new supplement for 3 months and was on a hypocaloric diet, control group was only on diet. At the beginning and after 3 months, metabolic variables were evaluated. Results: After 3 months, a significant difference in the treated group was observed for glucose, HOMA, total cholesterol and HDL-cholesterol; whereas, in the control group, a significant difference was shown only for glucose. After 3 months, a significant difference between groups was highlighted only for HDL-cholesterol. Conclusion: This study has shown the naturally occurring components of this new supplement may improve insulin resistance and lipid profile in a small sample of postmenopausal women.

Keywords
Metabolic Syndrome, Postmenopause, Insulin Resistance, Cinnamon, Corosolic Acid, Glycyrrhizic Acid

1. Introduction
Metabolic Syndrome (MS) is considered a cluster of metabolic abnormalities and
a complex condition which predicts future development of type 2 diabetes mel-
litus (DM) and cardiovascular disease [1]. It is defined by four clinical mani-
festations: central obesity, glucose intolerance, dyslipidemia and high blood pres-
sure. Several risk factors have been identified, mainly excessive calorie intake,
sedentary lifestyle and genetic predisposition. Pathogenesis of MS is largely at-
tributable to insulin resistance [2] while the onset of complications like cardio-
vascular diseases is closely linked to chronic, systemic pro-inflammatory and
pro-coagulation state [3]. Menopausal transition may predispose to MS being
usually associated with changes in body composition, due to the prevalence of
androgens over estrogens, and a reduction in physical activity. Furthermore, lack
of estrogens increases insulin resistance and changes in lipid profile predispose
to atherogenesis [4]. Adipose tissue, in particular visceral fat, is an important
source of inflammatory markers, which contributes to the development of a
pro-inflammatory state. Conversely, it has been ascertained that high levels of
physical activity and exercise have an anti-inflammatory effect [5]. MS is usually
treated with statins and/or metformin, but these drugs taken for long periods
may cause tiresome side effects. There is actually an increased request of natural
compounds to prevent or to treat metabolic disorders too. Some of these sub-
stances are Corosolic Acid, Glycyrrhizic Acid and Cinnamon. These supple-
ments were already individually used in oriental traditional medicine as a reme-
dy for various illnesses and ailments, particularly for lowering blood glucose le-
vels, reducing body weight and treating metabolic diseases, such as DM. Coroso-
lic Acid (CA) has been identified from the red leaves of Lagerstroemia speciosa,
commonly known as Banaba; it grows widely in tropical countries, including
Philippines, India, Malaysia, China and Australia [6]. Glycyrrhizic Acid (GA), a
triterpenoid saponin found in abundance in the root of genus Glycyrrhiza
glabra, commonly known as liquorice, has shown some compelling therapeutic
activities in counteracting MS [7]. Extracts of cinnamon contained consistent
amounts of procyanidin that has insulin-potentiating properties and may be in-
volved in the alleviation of the signs and symptoms of diabetes and cardiovas-
cular disease-related to insulin resistance and MS [8]. A large number of studies
have demonstrated that MS correlates with chronic and low-grade inflammation
with massive secretions of pro-inflammatory cytokines [9]. High Mobility
Group Box 1 (HMGB1) is a new potential biomarker of inflammation, acting as
a “danger signal” that positively correlates with insulin resistance [10]. Based on
literature reports, this study aims to show if the association of the above supple-
ments could improve MS in post-menopausal women.

2. Materials and Methods

A prospective, randomized, controlled, open-label study was carried out in the
Obstetrics and Gynaecology Unit, University Hospital of Messina. A total of 60
women were selected from a cohort of postmenopausal outpatient women af-
ccted by MS. All subjects gave their informed consent for inclusion before they
participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Messina (project identification code n. 64/17). Inclusion criteria were: a) amenorrhea for at least 12 months, b) an age between 45 and 65 years old, c) women affected by MS, diagnosed in accordance with the National Cholesterol Educational Program Adult Treatment Panel III 2015 criteria which are: fasting glucose ≥ 110 mg/dl; triglycerides ≥ 150 mg/dl; blood pressure ≥ 130/85 mmHg; abdominal obesity (waist circumference > 88 cm); HDL-cholesterol < 50 mg/dl. For diagnosing MS at least 3 of the above criteria were needed. Exclusion criteria were principally current treatments with hypoglycaemic (metformin) or anti-cholesterol drugs (statins).

At enrolment (t0) and after 3 months (t1), blood pressure, waist circumference, weight and BMI were recorded for each participant. Moreover, a modified life-style, such as moderate aerobic physical activity (duration ranging from 20 to 50 minutes at least three times per week) and a hypocaloric diet (1400 kg/cal divided in 50% carbohydrates, 30% lipids and 20% proteins) was strongly suggested to all women. A blood sample to evaluate glycaemic (fasting glycaemia and insulin) and lipid profile, total cholesterol (TC), HDL-cholesterol (HDL-C), triglycerides, was taken to confirm diagnosis of MS. Insulin-resistance was evaluated as Homeostasis Model Assessment (HOMA) index. In addition, thyroid function was evaluated (TSH, Ft3, Ft4, AbTg, AbTPO) as well as an inflammatory marker as serum HMGB1 too. Participants were then randomly divided into two groups using a computer-generated randomization. Two soft gel capsules per day were administered to each participant of the treated group (TG) before lunch and dinner, for 3 months. Each capsule contained corosolic acid 480 mcg, glycyrhizic acid 38 mg and procyanidin (methyl hydroxicalcone) 2.4 mg. No supplements were administered to the control group (CG), only a modified life-style and diet as for the other group. After 3 months (t2), blood pressure, waist circumference, weight and BMI, glycaemic and lipid profiles, HOMA Index, HMGB1 and thyroid pattern were re-evaluated.

CLINICAL TRIAL REGISTRATION: https://www.clinicaltrials.gov/, NCT 03813914.

Statistical Analysis

Data are expressed as mean (standard deviation) for continuous variables and as percentages for categorical variables. The means of independent groups were compared using the Student’s t-test after checking for normal distribution. For parameters that did not have normal distribution, we used the Mann-Whitney test. Intra-group differences were evaluated with the Wilcoxon test. A p-value of 0.05 or less was considered statistically significant. All analyses were performed using SAS software, version 9.1 (SAS Institute, Inc., Cary, NC, USA).

3. Results

A total of 56 women completed the study and were considered for the final evaluation; all reported a good adhesion to the hypocaloric diet suggested. In
each group 2 drop-outs (lack at the control after 3 months) have been recorded. The two groups were comparable for age: 55.8 ± 5.5 (TG) vs. 56.9 ± 5.6 years in the CG (p = 0.5), and time elapsed from the last period: 81.4 ± 61 months in the TG and 95.6 ± 66.7 months in the CG (p = 0.4). At baseline, there were no differences between groups for each measure considered (Table 1). At the end of the study, no statistically significant differences were found in the two groups regarding anthropometric variables, such as BMI and waist circumference, and for some metabolic measures such as insulin, triglycerides, but also blood pressure and thyroid profile (Table 1). After 3 months, a significant difference in the TG was highlighted for glucose (Figure 1), HOMA-IR (Figure 2), TC (Figure 3) and HDL-C (Figure 4).

In the control group, a significant difference was shown only for glucose. Furthermore, a significant difference between groups at the end of the study was highlighted only for HDL-cholesterol (Figure 4). HMGB1 values were comparable at the beginning of the study (TG 4.6 ± 2.2 vs. CG 4.4 ± 2.1 ng/ml, p = 0.7), but significantly different at the end of it (TG 2.6 ± 1.3 vs. CG 3.6 ± 1.7 ng/ml, p = 0.01); in the TG, the difference (T0 vs. T3) was significant (p < 0.001); instead, no difference between T0 vs. T3 in the CG (p = 0.1).

4. Discussion

This study has shown that an association of three natural substances (cinnamon, corosolic acid, glycirrhizic acid) well known by some eastern populations since ancient times may decrease fasting blood glucose, triglycerides and insulin resistance, increase HDL-cholesterol and thus improve the metabolic syndrome. One of the limitations of this study may be the time of treatment (3 months), probably too short to obtain resounding results. Furthermore, the substances used were natural compounds which usually need more time to show an appreciable effect. However, recent studies have demonstrated that cinnamon at high doses may determine similar results in a similar period of treatment: 2 and 4 months respectively [11] [12]. A possible mechanism of action for cinnamon may involve the reduction of post-prandial intestinal glucose absorption by inhibiting the activity of enzymes involved in carbohydrate metabolism [13], promoting cellular glucose uptake by membrane translocation of GLUT-4, stimulation of glycogen synthesis and inhibition of gluconeogenesis [14]. Furthermore, methylchalcone which is a procyanidin component of cinnamon enhances the triacylglycerol lipase activity that hydrolyzes dietary fat, the effect that may explain the decrease of body weight and fat body mass in subjects with type 2 DM [15]. All these experimental results have been confirmed by very recent small trials performed in humans [11] [12]. Commonly used anti-diabetic drugs up-regulate both glucose transport and lipid biosynthesis in adipocytes: weight gain is a frequent side effect, damaging the psycho-physical wellness of women in menopause; therefore, drugs with glucose-lowering activity with lacking adipogenic activity are highly desirable. An improvement of glucose and lipid profile (cholesterol and triglycerides) could be also the effect of the anti-adipogenic property
Table 1. General characteristics and outcomes measures.

|                  | suppl t0 | placebo t0 | suppl t3 | placebo t3 |
|------------------|----------|------------|----------|------------|
|                  | p1       | p2         | p3       | p4         |
| BMI              | 26.8 ± 3.7 | 26.7 ± 3.7 | 26.3 ± 3.9 | 26.9 ± 3.7 |
| WC               | 100.1 ± 10.9 | 99.6 ± 10.7 | 98.2 ± 10.5 | 98.2 ± 10.3 |
| Glucose          | 102.5 ± 19.3 | 104.9 ± 22.3 | 90.1 ± 9.4 | 97 ± 14.2 |
| Insulin          | 11.1 ± 5.6 | 9.8 ± 3.9 | 8.6 ± 4.8 | 8.6 ± 4.8 |
| HOMA             | 2.8 ± 1.4 | 2.5 ± 1.1 | 1.9 ± 1.1 | 1.9 ± 0.8 |
| Triglycerides    | 171.0 ± 58.4 | 169.6 ± 59.0 | 134.4 ± 48.7 | 149.4 ± 57.3 |
| Total-chol       | 222.8 ± 34.1 | 221.8 ± 34.3 | 195.3 ± 37.4 | 204.8 ± 39.3 |
| HDL-chol         | 49.8 ± 11.3 | 49.6 ± 10.7 | 71.5 ± 31 | 57.7 ± 11.3 |
| TSH              | 1.1 ± 0.6 | 1.2 ± 0.6 | 1.4 ± 0.8 | 1.5 ± 0.8 |
| FT3              | 3.6 ± 1.3 | 3.3 ± 0.7 | 3.7 ± 1.4 | 3.3 ± 0.9 |
| FT4              | 1.2 ± 0.6 | 1.2 ± 0.6 | 1.1 ± 0.5 | 1.1 ± 0.5 |
| AbTG             | 44.2 ± 45.5 | 28.0 ± 40.2 | 45.5 ± 91.2 | 30.1 ± 43 |
| AbTPO            | 8.3 ± 9.1 | 9.2 ± 10 | 6.2 ± 4.6 | 6.5 ± 5.2 |

P1: supplement t0 vs. placebo t0. P2: supplement t3 vs. placebo t3. P3: supplement t0 vs. t3. P4: placebo t0 vs. t3.

of corosolic acid which has shown anti-obesity effect inhibiting adipocyte differentiation [16] and a stimulating activity on glucose transport and glucose uptake in adipocytes [17]. Experimental studies have shown that also glycyrrhizic acid may improve insulin sensitivity and lipid metabolic disorders by reducing circulatory stress hormones, normalizing gluconeogenesis and increasing muscular lipid uptake [7]. Furthermore, glycyrrhizic acid may inhibit the expression of High Mobility Group box 1 (HMGB1), an important mediator of the inflammatory response, improving renal injury in diabetic rats [18]. This last report
might be the reason for which a significant reduction of HMGB1 has been evidenced in the treated group; the statistically significant reduction of HMGB1 values in the treated group suggest that these natural compounds may decrease the oxidative stress status characteristic of MS, procrastinating the onset of complications such as cardiovascular diseases and diabetes. HMGB1 could be considered a new, effective tool for monitoring metabolic profile in MS. This is the first study which deals with this emergent biomarker of inflammation in menopausal women suffering by MS, treated with natural supplements.

In conclusion, our study suggests an association of three natural compounds as a new therapeutic approach for MS in a peculiar target of patients: women in
post-menopause. As already known the study underlines the importance of a modified lifestyle and this was strongly recommended in both groups. The data obtained show that the association of these natural compounds determines metabolic effects, ameliorating some characteristics of MS, with benefits achieved only after 3 months of treatment. The association of corosolic acid, glycyrrhizic acid and cinnamon may represent an alternative choice to antidiabetic drugs to induce glucose uptake. Our data highlight the effectiveness of these ancient supplements with insulin-like and anti-adipogenesis, antioxidant and anti-inflammatory properties, to evaluate a possible application in medical practice. Further studies appear necessary in this field, and a larger study sample for a longer time is required to confirm our results.
Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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