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A Nutritional Approach to the Metabolic Syndrome

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Abstract

Poor diet and sedentary lifestyle contribute to the development of metabolic syndrome (MetS); addressing both is crucial for its management. A diet featuring the Mediterranean dietary pattern or low glycemic load has been shown to prevent and ameliorate MetS. Plant compounds, including soy protein and phytosterols, have been associated with reduced cardiovascular disease (CVD) risk. Recently, phytochemicals from hops and *acacia* were identified as lipogenic, anti-inflammatory compounds that reduced serum insulin and glucose levels in animals. A 12-week, randomized lifestyle intervention study in overweight and obese women with LDL ≥3.37 mmol/L (130 mg/dL) compared a Mediterranean-style, low-glycemic-load diet and soy/phytosterol-based medical food to an AHA low-fat diet. The modified Mediterranean diet with medical food was superior in reducing markers of MetS and CVD risk. A subsequent, randomized 12-week study in men and women with MetS and LDL ≥3.37 mmol/L (130 mg/dL) showed that supplementation with soy/phytosterol-based medical food plus phytochemicals enhanced the benefits of a Mediterranean-style low-glycemic-load diet and aerobic exercise. At the completion of the study, 43% of participants receiving medical food and phytochemicals exhibited net resolution of MetS compared with only 22% of those on diet and exercise alone. A

subanalysis of participants at high risk (MetS + LDL ≥4.14 mmol/L [160 mg/dL]) indicated minimal benefit from lifestyle change alone but marked benefits with the addition of medical food and phytochemicals. Case studies illustrate long-term benefits of this supplemented lifestyle change program. In conclusion, institution of a phytochemical-enhanced lifestyle intervention promises to be a clinically useful approach in MetS management.

Key words: metabolic syndrome, low-glycemic-load diet, rho iso-alpha acids, Acacia nilotica, Humulus lupulus, lifestyle modification, medical food, phytosterol, phytochemicals

Introduction

Metabolic Syndrome (MetS) is a cluster of interrelated clinical factors including insulin resistance, dyslipidemia, excess body weight, and elevated blood pressure. Together, these components increase an individual's risk for several chronic diseases, including type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). In 2004, it was estimated that 34% of adults in the US met criteria for MetS [1]. As the prevalence of MetS increases dramatically with age [1], and the mean age of the US population is rising, further increase in MetS incidence appears inevitable. Also, the associated healthcare costs are projected to increase to unsustainable levels in 10-20 years, not only in the US, but in Europe and Asia as well [2, 3].

An AHA and National Heart, Lung, and Blood Institute (NHLBI) scientific statement concluded "Lifestyle interventions are the initial therapies recommended for treatment of the metabolic syndrome. If lifestyle change is not sufficient, then drug therapies for abnormalities in the individual risk factors may be indicated" [4]. Lifestyle management consists of diet and exercise modification. The following research review demonstrates that lifestyle interventions with specific dietary changes and supplemental phytonutrients provide a feasible approach to managing patients with MetS.

Nutritional Aspects

Mediterranean-style diet. The Mediterranean-style diet has been associated with a reduced prevalence of MetS [5, 6]. The traditional Mediterranean diet is comprised of foods such as fruits and vegetables, olives and olive oil, fish and seafood, legumes and nuts, herbs and spices, whole grains, and moderate amounts of wine. Benefits of this food plan have been studied widely; for a detailed review, please see the companion paper in this supplement by Dr. Maria Luz Fernandez, "Metabolic Syndrome and the Mediterranean Diet".

Low-glyemic-load diet. Glycemic load describes the quantity and the quality of carbohydrates in a food, taking into account the glycemic index. High glycemic index foods such as white bread, chips, and soft drinks may lead to fluctuations in serum glucose and insulin levels with resultant increase in appetite and subsequent weight gain [7, 8]. Increased dietary glycemic load has been

associated with increased risk for CVD [9] and diabetes [10]. Modification of the Mediterranean diet to exclude high glycemic index foods and to limit the use of alcohol and grains may provide even greater advantage for reducing risk factors for CVD and T2DM.

Soy protein and plant sterols. Consumption of soy protein reduces serum cholesterol and risk for coronary heart disease [11-14]. Short-term soy consumption was found to reduce inflammatory markers and to increase plasma nitric oxide levels in postmenopausal women with MetS [15]. Plant sterols also have been shown to reduce cholesterol [11, 12] and heart disease risk [16]. In MetS patients, plant stanol esters were found to lower both triglycerides (TG) and non-HDL cholesterol [17]. In the PROCAM study of men and women with MetS, TG were found to improve in relationship to the sitosterol/cholesterol ratio (inversely related). Also, the sitosterol/cholesterol ratio was negatively associated with BMI. However, the ratio was positively related to HDL cholesterol [18]. Plant sterols occur naturally in small amounts in foods such as vegetables, grains, nuts, and seeds, but most people do not consume enough from diet alone. Consumption of margarine products fortified with plant sterols reduces cholesterol [19]. According to the FDA [20], the amount of plant sterol esters required to reduce risk of CHD is at least 1.3 g/day. Thus, incorporation of soy protein and plant sterols into a lifestyle change program promises to be a valuable intervention for reducing heart disease risk.

Targeted phytochemicals. Consumption of plant foods has been associated with reduced incidence of chronic diseases such as diabetes, CVD, and cancer. Phytochemicals from plants may be responsible for such benefits, possibly due to their effects on insulin signaling and inflammation. At the molecular level, chronic activation of protein kinase C (PKC) has been implicated in dysregulated insulin signaling [21]. Adipocytes release cytokines that induce an inflammatory response involving a host of intracellular protein kinases such as phosphoinositide 3 kinase (PI3K), glycogen synthase kinase 3 (GSK-3), and PKC [22-26]. Pharmaceutical research has targeted protein kinases, but has been hampered by adverse effects associated with these therapies. Little work has been done on development of protein kinase inhibitors from natural products for attenuating inflammation and regulating insulin signaling.

Recently, more than 200 botanical compounds with a history of safe use have been evaluated for their effects on lipogenesis and inflammation in 3T3-L1 adipocytes [27]. Lipogenic indices and adiponectin secretion, both indicators of insulin sensitivity, were compared in cells treated with either natural products or conventional pharmaceuticals such as metformin and thiazolidinediones. These experiments revealed that *rho* iso-alpha acids (RIAA) extracted from hops (*Humulus lupulus*) and an extract from the bark and heartwood of *Acacia nilotica*, a tree native to Africa and India, were among the most potent of the tested compounds [27]. *Acacia* extract has a high concentration of proanthocyanidins (PAC) [27]. PAC also are found in tea,

apple, and grape seed, and have been shown to have antioxidant, anti-inflammatory, and hypolipidemic properties (reviewed in [28]).

In lipogenic assays, RIAA and PAC were more potent than metformin, troglitazone, or pioglitazone [27]. Both botanical compounds selectively inhibited protein kinases in vitro. RIAA inhibited the activity of PI3K, GSK-3, and PKCβ in cell-free assays, and PAC inhibited GSK-3, IKKβ, and PKCβ [29]. When RIAA and PAC were combined in a defined ratio of 5:1 (w/w), an enhanced effect was observed on inhibition of tumor necrosis factor (TNF)-α induced free fatty acid release from adipocytes, suggesting a reduction in lipolysis. In a *db/db* diabetic mouse model, RIAA and PAC administered at a ratio of 5:1 for 7 days synergistically decreased serum glucose and insulin levels to the same order of magnitude as were observed with metformin or rosiglitazone (unpublished data; personal communication with Dr. Matthew Tripp). These studies suggest that selectively acting natural compounds have the potential to be effective in the management of insulin resistance.

Dietary interventions in clinical settings

The following are summaries of two clinical studies; the first suggesting that a soy and phytosterol-containing medical food may be an appropriate clinical approach for individuals with MetS, and the second testing that hypothesis. In addition, two case reports of participants in the second study provide evidence supporting long-term benefits of a lifestyle management program that includes a low-glycemic-load Mediterranean-style diet, medical food, specific phytochemicals and aerobic exercise.

Low-glycemic-load diet with medical food

In a 12-week, randomized, controlled study, the AHA Step 1 low-fat diet (AHAD) [30] was compared to a modified Mediterranean-style, low-glycemic-load diet (MED) along with a medical food providing 30 g of soy protein and 4 g of phytosterols per day [31]. CVD risk factors were measured in overweight or obese postmenopausal women with serum LDL ≥3.37 mmol/L (130 mg/dL). Both study arms followed an individually-planned, hypocaloric diet and ~150 min/week of aerobic exercise calculated to achieve a weight loss goal of about one pound per week [31].

While all women lost weight and experienced reductions in blood pressure and TG after 12 weeks, only those in the MED/medical food arm experienced significant reductions from baseline in total cholesterol and LDL, as well as increased HDL [31]. Elevated TG/HDL ratio is a marker for MetS [32]. Women in the MED/medical food arm had significantly lower TG/HDL ratios, with a mean reduction of 42% from baseline compared with 17% in the AHAD arm [31], suggesting that subjects with MetS would be good targets for MED/medical food intervention. However, this study did not address whether benefits were due to MED and/or the medical food.

Phytochemicals as part of nutritional intervention

Using a similar design to the previous study, a second randomized controlled trial was initiated to investigate whether the medical food along with RIAA/PAC would enhance the metabolic benefit of the MED [33]. Participants were overweight and obese men and women with MetS, diagnosed according to ATP III criteria, with elevated LDL ≥3.37 mmol/L [130 mg/dL]. Both arms in the study followed the same lifestyle program consisting of the MED without imposed caloric restriction and participation in ~150 min/week of aerobic exercise. The control arm followed the lifestyle change program only; the phytochemical-enriched diet (PED) arm additionally received the soy/phytosterol medical food and a tableted nutraceutical combination of RIAA:PAC twice daily.

Participants in both arms lost a similar amount of weight (approximately 13 pounds) over the 12-week study. Waist circumference, fasting serum insulin levels, LDL, total cholesterol, non-HDL cholesterol, the ratio of apolipoprotein B to apolipoprotein A1 (ApoB/ApoA1), and hemoglobin A1c (HbA1c) values were reduced significantly at 12 weeks in both arms. Those in the PED arm experienced greater reductions in total cholesterol, TG/HDL, and non-HDL cholesterol, compared with controls. Reductions in LDL and VLDL particle number (by NMR) were seen only in the PED arm. Notably, 43% of participants in the PED arm experienced net resolution of MetS, compared with only 22% in the control arm [33].

Interestingly, cravings for fast food, sweets, carbohydrates, and fats decreased after 2 weeks in all participants, and remained low for the duration of the study [33]. Likewise, between-meal hunger was decreased at 8 and 12 weeks. However, between the evening meal and bedtime, hunger decreased only in the PED arm at 8 and 12 weeks.

Both elevated LDL and MetS are major independent CVD risk factors that carry comparable relative risk [34]. When elevated LDL coexists with MetS, the risk for CVD is magnified [35, 36]. ATP III guidelines define LDL ≥4.14 mmol/L (160 mg/dL) as high risk for cardiovascular events [37]. To examine the benefit of nutritional intervention in high risk subjects, subgroup analysis of study participants with baseline LDL ≥4.14 mmol/L (160 mg/dL) was performed [38]. Participants in the PED arm had a 26.5% reduction in LDL levels, compared with a reduction of 10.9% in the diet and exercise only control arm. At 12 weeks, LDL levels in all participants in the PED arm were below the high risk range, compared with approximately 40% in the control arm. Half of those in the PED arm had LDL <3.37 mmol/L (130 mg/dL), while everyone in the control arm had LDL ≥3.37 mmol/L (130 mg/dL). In tandem with lowering of LDL, greater reductions of total cholesterol, non-HDL cholesterol, and ApoB/ApoA1 were observed in the PED compared with the control arm. Participants in the control arm had little improvement in CVD risk factors. In contrast, administration of soy and phytosterol-based medical food with RIAA/PAC led to a significantly greater improvement in multiple CVD risk factors. These results indicate that a lifestyle program alone is inadequate in

these high risk individuals and underscore the beneficial effects of the myriad nutritional factors provided by the medical food and the RIAA/PAC nutraceutical.

Case Studies

Two study participants were followed after study conclusion, and their case studies demonstrate long-term benefit. A 40 year-old male had gained 55 kg (121 lbs) over about 20 years since high school; he ate a standard American diet and was not physically active. He was randomly allocated to the control (MED) arm, receiving instructions to eat a low-glycemic-load, Mediterrranean-style diet and initiate an aerobic exercise program. At the end of the 12-week study period, the patient lost 10.8 kg (24 lbs), and experienced improvements in blood pressure, cholesterol, LDL, TG, and TG/HDL (**Table 1**). However, HDL remained low and the patient still met all 5 criteria for MetS. He was followed for individual case management (ICM) and began supplementation with the soy/phytosterol medical food and RIAA/PAC nutraceutical at the same dose given to participants in the intervention arm of the study. After 7 months on this supplementation regimen, the patient lost an additional 17.1 kg (38 lbs) and experienced marked improvements in practically every variable (Table 1). As a result, the patient no longer met the criteria for MetS.

Another study participant, an obese, 73 year-old female with a history of hypercholesterolemia and hypertriglyceridemia experienced a significant weight gain postmenopausally. Her weight increased about 14 kg (31 lbs) between ages 50 and 63, and another 14 kg (31 lbs) over the 15 months prior to her first study visit. She normally ate a standard American diet without fast food and did not smoke nor drink. Her physical activity was limited due to knee osteoarthritis. She was randomized to the PED arm with soy/phytosterol medical food and RIAA/PAC nutraceutical, and lost 10.7 kg (24 lbs) over 12 weeks (**Table 2**). At study completion, she no longer met the criteria for MetS. She then became an ICM patient and continued to receive the medical food and nutraceutical. Over 15 months, she lost an additional 6.8 kg (15 lbs), for a total weight loss of 17.5 kg (39 lbs) (approximately 18% of initial body weight) over 18 months. The patient continued to exhibit net resolution of MetS with remarkable improvements in HDL, TG and TG/HDL (Table 2). These two case studies indicate that MetS can be reversed and improvement sustained with lifestyle modification including nutritional supplementation with soy/phytosterol based medical food and RIAA/PAC nutraceutical.

Table 1. Summary of Case Study 1. A male participant in the control arm of the 12-week metabolic syndrome study initiated a phytochemical-enriched diet intervention after study completion. Table is original to this manuscript.

	Study start	End of 12-week study	7 months post-study
Weight (lb)	256.3	232.5	194.9
Waist circumference (in)	50.0	47.5	40.5
Blood pressure (mm Hg)	128/93	120/89	124/79
BMI (kg/m^2)	39.5	35.9	30.1
Cholesterol (mg/dL)	257.1	208.1	174.9
Triglycerides (TG) (mg/dL)	472.6	187.6	87.6
HDL (mg/dL)	30.1	30.1	39.0
LDL (mg/dL)	161.0	140.2	118.1
TG/HDL	15.8	6.3	2.3
Fasting insulin (µU/mL)	12.7	11.6	2.8
Fasting glucose (mg/dL)	93.7	95.5	88.3
Hemoglobin A1c (%)	5.9	5.7	5.5
Apolipoprotein-A1 (mg/dL)	150	160	140
Apolipoprotein-B (mg/dL)	140	130	90
Apo-B/Apo-A1	0.9	0.8	0.7
LDL particles (nmol/L)	1308	1181	1144

Conversion factors to SI units: lb to kg, ÷ 2.2; in to cm, x 2.54; mg/dL to mmol/L for total, HDL and LDL cholesterol, x 0.0259; µU/mL to pmol/L for insulin, x 7.175; mg/dL to mmol/L for glucose, x 0.0555; mg/dL to mmol/L for TG, x 0.0113; mg/dL to g/L for Apolipoprotein-A1, B, x 0.01.

Table 2. Summary of Case Study 2. A female participant was randomized to the phytochemical-enriched diet arm for the 12-week metabolic syndrome study, and continued the intervention after study completion. Table is original to this manuscript.

	Study start	End of 12-week study	11 months post-study	14 months post-study	15 months post-study
Weight (lb)	220.9	197.3	180.4	185.5	182.4
Waist circumference (in)	47.0	45.0	N/A	44.0	N/A
Blood pressure (mm Hg)	140/77	114/72	130/79	144/82	120/79
BMI (kg/m^2)	37.3	33.4	30.6	31.3	30.9
Cholesterol (mg/dL)	235.1	191.1	208.9	230.9	N/A
Triglycerides (TG) (mg/dL)	192.0	123.9	125.7	91.2	N/A
HDL (mgl/dL)	35.9	40.9	51.0	66.0	N/A
LDL (mg/dL)	161.0	125.1	132.8	147.1	N/A
TG/HDL*	5.3	3.0	2.5	1.4	N/A
Fasting insulin (µU/mL)	18.2	17.2	11.1	N/A	N/A
Fasting glucose (mg/dL)	109.0	98.9	101.1	85.0	N/A
Hemoglobin A1c (%)	5.7	5.7	5.6	N/A	N/A

Conversion factors to SI units: lb to kg, ÷ 2.2; in to cm, x 2.54; mg/dL to mmol/L for total, HDL and LDL cholesterol, x 0.0259; µU/mL to pmol/L for insulin, x 7.175; mg/dL to mmol/L for glucose, x 0.0555; mg/dL to mmol/L for TG, x 0.0113.

Conclusions

Diet and exercise are core ingredients of a healthy lifestyle. The studies reviewed indicate that lifestyle change including moderate exercise and a low-glycemic-load modified Mediterranean-style diet was effective in the management of MetS. Addition of a soy/phytosterol containing

medical food and RIAA/PAC nutraceutical to this lifestyle change program significantly enhanced its effectiveness in reducing cardiometabolic risk factors and led to greater net resolution of MetS. This effect occurred despite equal weight loss in both study arms. Further, patients at high CVD risk with both MetS and LDL ≥4.14mmol/L (160 mg/dL) experienced greater benefit with addition of the medical food and nutraceutical. Case studies demonstrated prolonged improvement. Lifestyle intervention with targeted phytochemicals provides a rational clinical approach to the management of MetS.

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Conflict of interest

RH Lerman is the Director of Medicine & Extramural Clinical Research of Metagenics, Inc. This review was not sponsored by any funding agency.

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