

Nutritional Supplements Modulating Metabolic Syndrome Risk Factors and the Prevention of Cardiovascular Disease

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Abstract: Metabolic syndrome risk factors (MSRF) can lead to cardiovascular disease (CVD) and its prevalence is increasing at an alarming rate in the United States and worldwide. Pathways leading directly from visceral adiposity to the genesis of free fatty acids and lipid accumulation are mediators of insulin resistance and hypertension. These conditions lead to a proinflammatory and prothrombotic state that can potentiate cardiovascular disease. Metabolic syndrome risk factors are interrelated and associated with predisposition to diabetes, obesity, hypertension and dyslipidemia and, thus, ultimately can lead to CVD. In this review, the authors focused on seven research-supported nutrients available as dietary supplements that offer potential benefits for people with MSRF. For the past two decades, a number of studies have evaluated the role of nutritional supplementation in the prevention of atherogenic and abnormal glucose risk factors. It is, therefore, important to identify strategies that favorably impact MSRF and disease conditions. This review focuses on nutritional compounds such as policosanol, soy proteins, plant stanols, plant esters and isoflavones, omega-3 fatty acids and chromium. These ingredients can beneficially modulate MSRF and, thus, potentially improve disease risk factors and related sequelae. Although the benefits of dietary supplements in general have not been comprehensively elucidated or established, it seems plausible, given available data, that non-pharmacological compounds exhibit the ability to measurably reduce MSRF and, consequently, provide potential protection against CVD and its associated complications.

Keywords: Metabolic syndrome, insulin resistance and cardiovascular disease.

INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of death in the United States (U.S.). According to prevalence data from the National Health and Nutrition Examination Survey III [NHANES III 1988-94, CDC/NCHS], 64,400,000 Americans have one or more types of CVD, of whom 25,300,000 are aged 65 years and older [1]. In 2001, one in every five deaths in the U.S. was caused by coronary heart disease (CHD) or some form of CVD. In fact, CVD accounted for 38.5% of all deaths or one of every 2.6 deaths in the U.S. Hurst [2] reported that the lifetime risk for development of CHD after age 40 is 49% for men and 32% for women.

Metabolic syndrome (MS), also called insulin resistance syndrome, is a metabolic abnormality associated with dyslipidemia and increased secretion of very low-density lipoprotein (VLDL) particles, and is marked by increased triglycerides (TG), hypertension, abdominal obesity, low levels of high density lipoprotein cholesterol (HDL-C) and impaired glucose tolerance (IGT). The prevalence of metabolic syndrome risk factors (MSRF) is prominent and predisposing in individuals and populations with CVD, with its incidence increasing at an alarming rate worldwide [1]. It is estimated that over 47 million Americans have metabolic syndrome comprised of three or more of the following risk factors: body mass index (BMI) greater than 25 kg/m² (or waist circumference greater than 40 inches in men and 35 inches in women), elevated serum TG (150 mg/dL or

higher), low HDL-C (<40 mg/dL in men and 50 mg/dL in women), elevated blood pressure (130/85 mm Hg or higher) and elevated fasting blood glucose levels (110 mg/dL or higher) [2-4]. The mechanisms leading to metabolic syndrome and the accelerated risk of cardiovascular disease are shown in (Fig. 1).

Ford *et al.* (5) reported that 22% of US adults (24% men and 23.4% women) have metabolic syndrome and found it especially prevalent among Mexican Americans (31.9%), whites (23.8%) and African Americans (21.6%). The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) estimated that there are 95 million Americans with some degree of insulin resistance, in addition, it was further estimated that approximately one in four U.S. adults (50 million) has high blood pressure (32.8%), 11.1 million Americans have physician-diagnosed diabetes (5.5%) and 5.9 million Americans are estimated to have undiagnosed diabetes (2%). In addition, other prevalence rates are as follows: pre-diabetes (14.5 million); CHD (13.2 million) myocardial infarction (7.8 million), angina pectoris (6.8 million); new and recurrent heart attacks and fatal CHD (1.2 million); overweight (130.8 million), obesity (62 million), HDL-C < 40 mg/dL (53 million), LDL-C >130 mg/dL (93 million) and total cholesterol (TC) >240 mg/dL (37 million), respectively. Mokdad *et al.* [6] and Ford *et al.* [7] reported that for every kg of weight gain, the risk of diabetes is increased by 4.5 to 9%. Hence, a weight loss of to 11% of body weight is associated with a 25% reduction in CVD and diabetes mortality [8].

Two-thirds to three-fourths of Americans with diabetes die of cardiovascular disease. Insulin resistance is an additional, independent risk factor that is linked to oxidative

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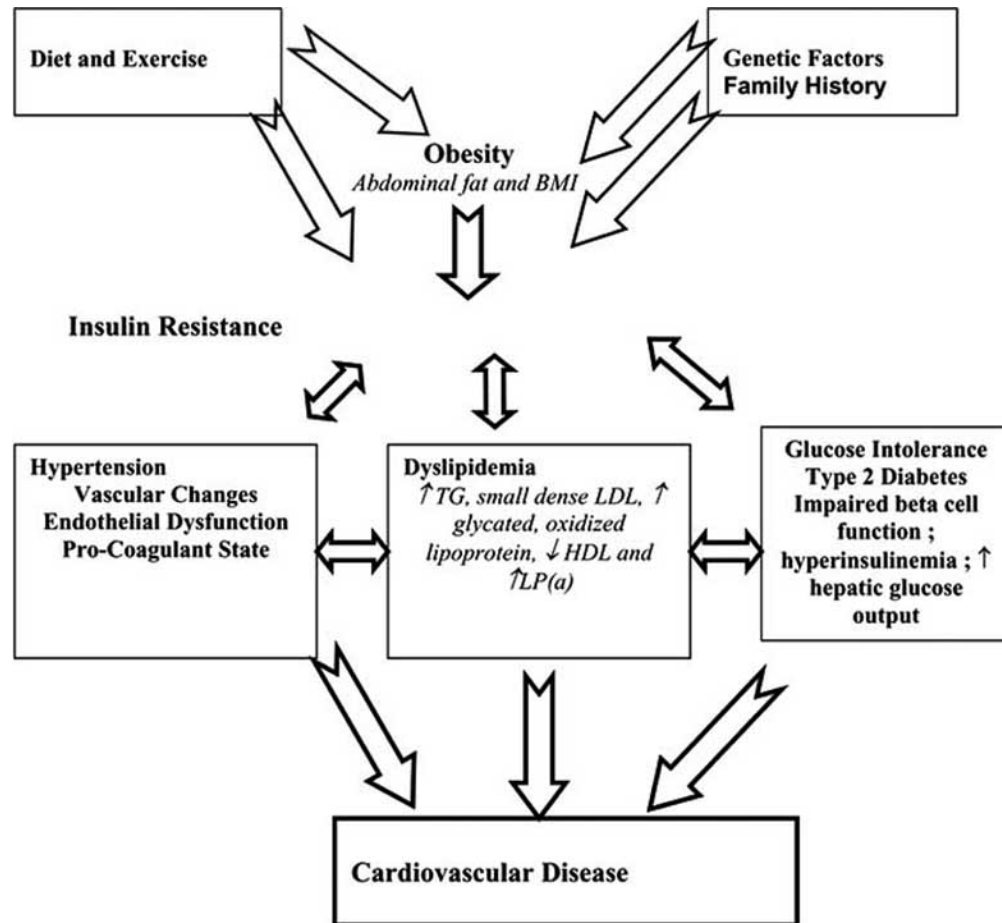


Fig. (1). Mechanism leading to metabolic syndrome and the accelerated risk of cardiovascular disease.

stress, dyslipidemias and prothrombic/hypofibrinolytic states in cardiovascular disease. Insulin resistance, as assessed by elevated fasting insulin concentrations without other markers of metabolic syndrome, increases cardiovascular risk by 1.5 to 2-fold over that of subjects with normal insulin sensitivity [2,3]. An atherogenic lipid profile is a common feature of the dyslipidemia components of diabetes and increases the risk by 2 to 4 fold in people with diabetes to develop CVD than in people without diabetes. The interaction between glucose, lipid and lipoprotein metabolism and CVD is illustrated in (Fig. 2).

It was observed that inflammatory markers, such as C-reactive protein, adipokines, tumor necrosis factor alpha (TNF α), interleukin 2 (IL-2), interleukin 6 (IL-6) and thrombosis are integral components of the metabolic syndrome (MS), diabetes mellitus (DM), obesity and hypertensive conditions which may, in turn, enhance the progression of atherosclerosis. The accelerated macro- and micro-vascular complications due to MSRF are related, in part, to the increased incidence of CVD including coronary artery disease (CAD), cerebrovascular disease and peripheral vascular disease (PVD). Advanced glycation end products, glycoxidised and oxidized low-density lipoproteins and reactive oxygen species (ROS) linked to hyperglycemia have all been identified in CVD. Endothelial dysfunction associated with MSRF, and marked by diabetic macro- and

micro-angiopathy, reduces blood circulation to the heart due to reduction in the size of coronary artery diameter [4].

Epidemiological, clinical and observational studies have predicted CHD in individuals with diabetes who also have increased TG and TC levels and decreased HDL-C levels (but neither increased LDL nor non-HDL-C) [9,10]. Diabetic dyslipidemia is preceded by hyperinsulinemia resulting from insulin resistance (IR). Identification criteria associated with metabolic syndrome differ among recognized public health and policy-setting bodies (Table 1). Furthermore, in large-scale clinical trials (e.g., Scandinavian Simvastatin Survival Study [4S] and the Cholesterol and Recurrent Events [CARE] study), it has been demonstrated that MSRF can appreciably reduce cardiovascular events [11]. There is strong evidence of a pre-diabetic state along with increased inflammatory markers associated with MSRF, predicting increased risk of CVD. Several clinical trials suggested that lowering MSRF reduces the risk of CVD and associated complications [12-14]. Overall, these MSRF and metabolic disturbances lead to increased risk of CVD morbidity and mortality and are strongly predictive for premature CVD events, stroke and premature death.

In addition, pharmacological management typically prescribed for diabetes, obesity, CHD, depression and birth-control--such as oral hypoglycemic agents, including sulfonylureas, nateglinides, biquanides, alpha glucosidase

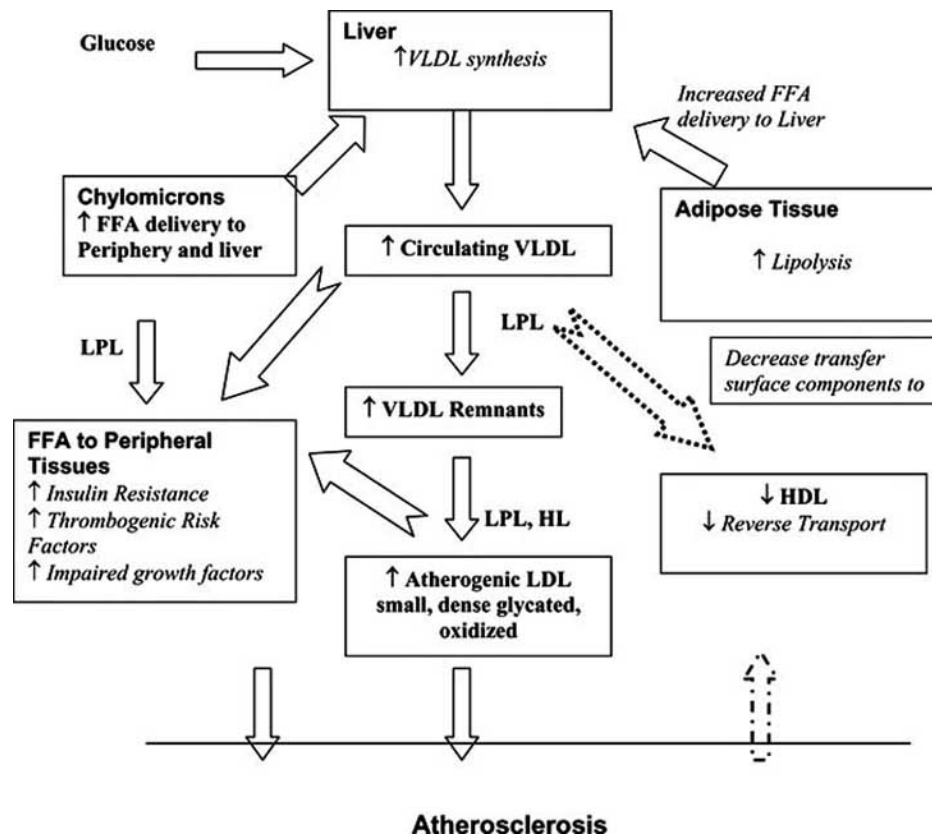


Fig. (2). Interrelationship between glucose, lipid and lipoprotein metabolism. Abbreviations: LPL: Lipoprotein Lipase; HL: Hepatic Lipase

inhibitors, thiazolidinediones, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, chlorpromazine, clozapine, amitriptyline, valproate-related products (anti-convulsants), mirtazapine and olanzapine - is often associated with weight gain [15] and is linked to potential side effects that initiate metabolic syndrome.

Recent epidemiological studies and clinical trials suggest that certain biologically active compounds available as dietary supplements can reduce MSRF and may prevent CVD. These components offer the beneficial effects of lowering MSRF including LDL-C, LDL oxidation, platelet aggregation, endothelial damage, and smooth muscle cell proliferation. The body's stores of essential nutrients such as chromium appear to drop with age [16], decreasing by 50 to 57 percent over time, depending on the tissue analyzed. The Food Guide Pyramid and Recommended Dietary Allowances (RDAs) of essential nutrients were recently adapted into Dietary Reference Intakes (DRIs) that have separate nutrient value ranges for different age groups. The DRIs attempt to factor in the physiological changes of aging and acknowledge nutrients' potential roles in preventing age-related chronic disease [17]. However, current consumption patterns of nutrients from the diet suggest that Americans may require nutritional supplementation in order to meet the requirement of essential nutrients in aging. The increased incidence of MSRF with aging suggests that the elderly, in particular, may be at increased risk for essential nutrients.

Treating MSRF begins with lifestyle changes. Weight management, exercise, reducing the amount of dietary fat and cholesterol in the diet and smoking cessation will reduce the risk of CVD. However, some people will also require lipid-lowering therapy in order to reduce their risk of CVD problems.

The purpose of this article is to review the clinical significance of biologically active components of dietary supplements--such as policosanol, plant stanols and esters/soy proteins and isoflavones, omega - 3 fatty acids and chromium--that appear to have the potential to convey a MSRF-lowering effect in humans. The possible mechanisms by which these components may affect glucose and lipid metabolism will also be briefly addressed. In this context, it is important to note that National Cholesterol Education Program (NCEP) studies have shown that for every 10 percentage points of cholesterol lowering achieved CHD mortality is decreased by 13% and total mortality by 10%.

Medical nutrition therapies or adjunct complementary nutrition therapies may emerge from the aggressive pursuit of newer molecular therapeutic targets that have the potential to prevent or treat metabolic syndrome and its risk factors. Data from U. S. government sources show that the great majority of Americans get less essential nutrients in the diet than the amount recommended by nutrition experts [18]. Some of these nutrients are involved in carbohydrate, lipid and protein metabolism as co-factors. The food sources of the essential nutrients are typically denatured and, therefore

Table 1. Defining Metabolic Syndrome Based on Metabolic Factors

| Characteristics | NCEP/ATP III | AAACE* | WHO [#] |
|--|-------------------------------------|---------------------|-----------------------------------|
| Plasma glucose, mg/dL Fasting 120 min post-glucose challenge † | 110-125 140-200 | >140 | >110 and <126 140 and < 200 |
| Triglycerides, mg/dL | 150 | 150 | 150 |
| HDL-C, mg/dL Men Women | <40 <50 | <40 <50 | <35 <39 |
| Blood pressure, mm Hg | 130/85 | 130/85 [‡] | 160/90 |
| Abdominal obesity or waist circumference Men Women | >102 cm (>40 in) >88 cm (>35 in) | - | WHR Men: >0.90 Women: >0.85 |
| Microalbuminuria urinary albumin excretion rate, mg/g | - | - | 20 |

[#] Syndrome present if two or more of the other components met; † Current use of antihypertensive medication; ‡ After a 75 g glucose load; * Absence of diabetes—fulfillment of 2 of the risk factors.

largely lost during processing and *via* interaction with dietary fiber, phytates and other nutrients.

As a result, insufficiently bioavailable levels of micronutrients such as chromium, magnesium, zinc, copper and B vitamins, including folic acid, may contribute to clinical or sub-clinical nutritional deficiency and may enhance MSRFs. For example, epidemiological studies and observational data have reported that omega-3 fatty acids and chromium (Cr) status are significantly associated with relative risk of CVD [19-22]. These macro- and micro-nutrient deficiencies may predispose the heart and render it more susceptible to injury due to inflammation, thrombosis, dyslipidemia, hyperinsulinemia and hypertension. This review specifically assesses the beneficial effects of policosanol, plant stanols, omega-3 fatty acids and chromium on metabolic syndrome risk factors and prevention of CVD.

ESSENTIAL ALCOHOLS: POLICOSANOL

Policosanol is a mixture of essential alcohols isolated from sugar cane wax (*Saccharum officinarum L.*) and consists of different components such as octacosanol (66%), hexacosanol (7%), triacontanol (12%) and eicosanol, tetracosanol, nonacosanol, dotriacontanol, tetratriacontanol and heptacosanol (15%). It was not clear whether policosanol inhibits 3-hydroxyl-3 methyl glutaryl CoA (HMG-CoA) reductase and, in fact, if it increases receptor-mediated uptake of LDL-C by the liver that may improve LDL metabolism [23,24].

Cholesterol-lowering effects were observed in healthy volunteers, patients with type II hypercholesterolemia (HC), type 2 diabetes mellitus (Type 2 DM) with hypercholesterolemia (HC), postmenopausal women with HC, and patients with combined HC and abnormal liver function tests. Short-

term (8 weeks) and long-term (12 months and 2 years) double blind clinical trials in patients with type II HC [24-26] have shown a significant decrease in TC (17-18%) and LDL-C (25%) and a very significant increase in HDL-C (21-28%). Castano *et al.* [27] reported that, after 24 weeks, 20 and 40 mg/day of policosanol significantly lowered LDL-C by 27.4% and 28.1%, TC by 15.6% and 17.3%, and LDL-C/HDL-C ratio by 37.2% and 36.5%, respectively. The ratio of TC/HDL-C was lowered by 27.1% and 27.5%, while HDL-C levels increased by 17.6% and 17.0%, respectively. In a recent study, Mas *et al.* [28] reported that policosanol lowered LDL-C (29.5 %), TC (21.9 %), TG (16.9 %) and raised HDL-C (12.4 %) in older patients with type 2 DM. In addition, a few short-term studies indicated that the cholesterol-lowering effect of policosanol was better than that of statins such as simvastatin, pravastatin, lovastatin, probucol, or acipimox and with fewer side effects in patients with type II HC [27-30]. Prat *et al.* [31], Crespo *et al.* [32] and Noa *et al.* [33] reported that policosanol reduces intermittent claudication [27,34], platelet aggregation [35,36], diastolic blood pressure [DBP] and systolic blood pressure [SBP] [37,38] in older patients with hypertension and type II HC and dyslipidemia in type 2 DM [27,39]; and cerebral ischemia in animals [40]. Policosanol decreased progression and increased regression of CVD as assessed by thallium-labeled myocardial perfusion scintigraphy (TL-MPS) and Doppler-ultrasound, and decreased symptoms of CVD [41-43].

In terms of safety profile, no studies are available for policosanol interacting with other antiplatelet or anticoagulant drugs, such as clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox) other low molecular weight heparins (LMWH), heparin and coumadin. Side effects were equal to placebo in 12 trials and less than placebo in 2 trials. Studies in type 2 DM with HC reported

no significant effect in reducing LDL-C, TG and increasing HDL-C; glucose levels and glycosylated hemoglobin (HbA1C) values remained unchanged [32,39]. Crespo *et al.* [32] reported a significant change in DBP but not SBP. In another study [38], SBP in older patients with hypertension and type II HC was significantly reduced but not DBP; in addition, no significant effect on body weight reduction was noted in any of the reported studies.

Overall, policosanol has been well tolerated in numerous clinical trials in Cuban populations (over 1,200 people), with doses up to 40 mg per day, and has been more effective in lipid lowering than other agents with no significant effects on blood glucose, glycosylated hemoglobin A1c (HbA1c), blood pressure, abdominal obesity or body weight. Further research is needed to determine the effects in other population groups including glycemic control, MSR, relative risk (RR) of CVD and cardiac events.

PLANT STEROLS AND STANOLS, SOY PROTEIN, ISOFLAVONES

Sterols and Stanols

Plant sterols and stanols are naturally present in small quantities in many fruits, vegetables, nuts, seeds, cereals, legumes, vegetable oils and other plant sources. Dietary plant stanols and sterols have been found to inhibit the absorption of cholesterol in the small intestine by 50% and decrease LDL-C by 14%. Stanols and sterols have been well tolerated in numerous clinical trials involving over 1,800 people, with doses up to 25 g per day. In general, a maximum cholesterol-lowering effect has been achieved at doses of at least 1 to 25 g/day. In these studies it was reported that TC was decreased by 10-12%, LDL-C was lowered by 9-14%, with no effect observed in HDL-C [44]. Intakes greater than 25 g/d do not appear to confer any additional TC and LDL-C lowering benefits. Miettinen and Gylling [45] reported that plant stanols and sterols taken concomitantly with statins further enhances the cholesterol lowering effects by 20%.

Soy Protein and Isoflavones

Other plants proteins, such as soy protein and isoflavones (*e.g.*, genistein and daidzein) have been studied for their cholesterol-lowering effects in humans. The proposed improvements associated with these nutrients include increases in LDL receptor activity, increases in the synthesis and fecal excretion of bile acids, and a suppression of cholesterol absorption.

In 38 clinical trials (n=743) an average consumption of 47g/d soy protein (range 18-124 g/day), in place of animal protein, lowered TC (~9%, 0.60 mmol/L), LDL-C (13%, 0.56 mmol/L) and TG concentrations (11%, 0.15 mmol/L). No changes were found in serum HDL-C. The changes in serum total and LDL cholesterol concentrations depended on the initial serum TC concentration. The effects of isoflavones on CHD risk factors were inconclusive. Overall, TC was decreased by 5 to 9% and LDL-C was lowered by 6-8% at active doses of >20 g/d of soy protein and >27 mg/d isoflavones [46,47]. Overall, there were significant effects on TC, TGs and LDL-C, but no effect on HDL-C and no significant effects on glycemic control and hypertension. It is

not clear whether isoflavones in the soy are responsible for the proposed hypocholesterolemic effects. The significance of inconsistent findings regarding the effects of isoflavones on lipids and lipoproteins remain uncertain.

A recent meta-analysis of eight randomized controlled trials [48] reported that serum LDL-C decreased by 0.15 mmol/L in subjects who consumed 50g/day of soy protein isolate with a mean daily intake of 96 mg/day of high isoflavone content. However, in October 1999, the FDA approved a health claim for foods that contain 6.25 g of soy protein, or more, allowing manufacturers to state that 25 g per day soy protein may reduce the risk of heart disease. Further studies are recommended to evaluate the effect of stanols and soy protein on cardiac events, relative risk (RR) of CVD and metabolic syndrome risk factors (MSRFs).

OMEGA-3 FATTY ACIDS

Omega-3 fatty acids are a unique class of fatty acids characterized by a long straight chain length with a double bond at either the third carbon atom from the terminal carbon (omega-3) or at the sixth carbon (omega-6), respectively. Omega-3 fatty acids have significant cardioprotective effects *via* multiple mechanisms that relate to arrhythmic actions, thrombosis, growth of atherosclerotic plaque, lipogenesis and hypertension. Omega-3 fatty acids inhibit monocyte migration into atherosclerotic plaque and enhance production of endothelial-derived relaxation factor (*i.e.*, nitric oxide), both of which: inhibit the atherogenic process; reduce damage to the vessel wall and intimal thickening in response to trauma to the intima; inhibit atherosclerotic plaque formation *via* a significant reduction in platelet-derived growth factors [49,50]. Placebo-controlled randomized clinical trials RCTs trials (study duration varying from 1 yr to 3.5yrs, N =223 to 11,324; dose: 850-882 mg/d of ethyl esters of EPA and DHA) suggest that omega-3 fatty acid supplements can reduce cardiac events by 15 percent (*e.g.*, death, non-fatal myocardial infarction [MI], nonfatal stroke) and decrease progression of atherosclerosis in coronary patients [51-54], beneficially reduce blood pressure [55,56] and lower TG [57,58].

Several prospective controlled randomized studies have evaluated the use of omega-3 fatty acids at doses of 2.25 to 7.2 g/d for preventing restenosis following coronary angioplasty [59-62]. Overall, restenosis was reduced by 14 to 29% [63].

Most of the intervention studies that measured blood lipids, both in general and in diseased populations, reported no significant differences in LDL-C or increases in LDL-C in response to intake of omega-3 fatty acids [51,58,64-68]. Thus, most of the intervention studies that measured LDL-C did not support a relationship between omega-3 fatty acids and reduced risk of CHD either in diseased or general populations.

In healthy non-smoking men, dietary supplementation with 3.8 g EPA/d, 3.6 g DHA/d, or 4.0 g corn oil/d (placebo) for seven weeks reduced serum TG by 26% in the DHA group and 21% in the EPA group compared with controls. Serum HDL-C was increased by 0.06 mmol/L in the DHA group and TC was decreased by 0.15 mmol/L in the EPA group. In addition, apolipoprotein A- I was decreased by

0.04 g/L in the EPA group [58]. This study suggests that even though there was a decrease in TG, there were differential effects on lipoprotein and fatty acid metabolism. In another study, TG was reduced with 9 to 13 g/d of fish oil (*i.e.*, 1.1 to 7 g/d of omega-3 fatty acids) by 20 to 25% in normo-triglyceridemic individuals and 26 to 33% in hypertriglyceridemic individuals. These levels of fish oil exhibited a modest LDL-C raising effect (*i.e.*, 4 to 5%); in addition TC levels increased by 2% in normo-triglyceridemic individuals. In comparison, LDL-C was elevated approximately 5 to 11%, but no change was observed in TC or HDL-C in hypertriglyceridemic individuals. It is important to note, however, that in some individuals with familial hyperlipidemia (Type IV/V) the elevation of coronary risk lipids is more pronounced (*e.g.*, 30%) [57].

In a meta-analysis of 31 randomized controlled trials (RCTs, n =1356; length of treatment: 3- 24 weeks), Morris *et al.* [69,70] reported that omega-3 fatty acids from fish oil reduced blood pressure (-3.0/1.5 mm Hg) and that the omega-3 fatty acid dose response was statistically significant (-1.3/-0.7 mm Hg, -2.9/-1.6 mm Hg and -8.1/-5.8 mm Hg) at doses of < or = 3 g/d, 3.3 to 7 g/d and 15 g/d, respectively.

In eight studies, healthy subjects did not respond to omega-3 fatty acids (mean dose of 4.2g). Significant effects were, however, observed in hypercholesterolemic patients (4 g/d) and a non-significant decrease in blood pressure was observed in atherosclerotic CVD.

This beneficial lowering of TG levels has often been accompanied by an increase in LDL-C levels and the effects on glucose tolerance have been inconsistent, with significant differences in the reports of patients with type 2 DM and type 1 DM. A recent meta-analysis of 26 studies concluded that fish oil had no adverse effects on glycemic control, as assessed by HbA1C/ levels, and decreased TG levels by almost 30%. However, a slight increase in LDL-C concentration has accompanied these changes [71]. Recently, the FDA [72,73] approved qualified health claims for dietary supplements and conventional foods containing EPA and DHA omega-3 fatty acids and the reduced risk of CHD. The FDA recommended that consumers not exceed more than a total of 3 grams per day of EPA and DHA omega-3 fatty acids, with no more than 2 grams per day from a dietary supplement. Overall, omega-3 fatty acids have demonstrated significant effects on TC, TG and significant beneficial effects in reducing cardiac events. Further studies are required to determine their effects on glycemic control and other metabolic risk factors.

CHROMIUM

Chromium is an essential mineral and a co-factor of insulin in the insulin-signaling pathway and enhances glucose transport and metabolism in the body. Chromium is a trace element that exerts a beneficial effect on atherosclerosis [74-78]. Chromium deficiency is associated with a disturbance in lipid metabolism and may lead to elevated TC, LDL-C and decreased HDL-C [79,80]. Newman and Simonoff [81] reported that coronary artery disease was most prevalent in persons with plasma Cr levels less than 0.006 mcg/L. Recent studies further support that tissue chromium levels in serum, hair and toenails are

significantly associated with the relative risk of CVD and diabetes with CVD [82,83]. Swapnil *et al.* [85] reported that, in the Health Professionals Follow-up Study, the mean toenail Cr levels were significantly lower in diabetic men and diabetes with prevalent CVD than they were in healthy controls and that low Cr levels were associated with a relative higher risk of MI with higher BMI [86].

The chromium ion binds to an oligopeptide in order to become biologically active and then binds to an insulin receptor, also involving the activity of tyrosine kinase [87]. Trivalent chromium activates insulin to move glucose into cells. Chromium is either involved with the binding of insulin to its receptor or with initial receptor site activation (post-receptor events). Chromium plays a major role in cell sensitivity and insulin-regulating activities. In addition to the early interest in glucose tolerance factor (GTF), Evans and Bowman [88] demonstrated an interaction between Cr and the insulin receptor and the specific effect of Cr on the insulin receptor complex internalization.

Chromium supplementation in the form of chromium picolinate [CrPic] can enhance glycogen synthesis in an *in vivo* model; this provides a mechanistic basis for the enhanced insulin resistance seen *in vivo*. In insulin-stimulated skeletal muscle, glucose uptake was enhanced and glycogen production was also increased in human skeletal muscle cells [89, 90]. Recent studies on the mechanism of action strongly suggest chromium as CrPic may enhance intracellular insulin signaling such as insulin receptor mediated tyrosine kinase activities. Wang *et al.* [91] evaluated the effect of CrPic on IRS-1 associated phosphoinositide 3-kinase (PI3K) activity and observed increased deoxy-2D-glucose uptake when CrPic was incubated with insulin (47%, 73%, 62% and 71% , p<0.05) than with insulin alone (2, 20, 200 and 2000 nM respectively). CrPic incubated with insulin significantly increased glycogen accumulation and the IRS-1 associated PI3-kinase activity of skeletal muscle cells dose-dependently increased by 48%, 172% and 233%, respectively (p<0.001). These studies suggest that Cr as CrPic may enhance insulin action *via* increased glucose uptake and glycogen synthesis in human skeletal muscle. In another study, Wang *et al.* [91] identified genes that may be involved in enhanced insulin action by Cr, resulting in 18 selected down-regulated genes, including two genes postulated to play a role in insulin action, *e.g.* tumor necrosis factor alpha-induced protein 6 (TNFAIP6) and F-box only protein 5 (ubiquitin-protein ligase and ubiquitin-conjugating enzyme). These study results demonstrated that gene expression of TNF in CrPic or CrPic insulin-treated cells was significantly lower (p<0.01). In another study, Cefalu *et al.* [92] suggested that there is a growing body of evidence that CrPic is involved in the early and intermediate steps of the insulin-signaling pathway, and have identified the insulin receptor, IRS-1, PI3-kinase and Akt as candidates for defects contributing to insulin resistance in skeletal muscle. Cefalu *et al.* [92] reported that treatment with CrPic enhances insulin-stimulated Akt phosphorylation activity in skeletal muscle. Possible explanations for the enhancement of Akt by CrPic is that the activation in skeletal muscle may occur through effects on gene expression. Based on these results, improvements in glycemic control could be expected in type 2 DM subjects.

Of note, at least 43 human clinical studies have tested specific chromium compounds on insulin resistance and risk factors associated with patients with type 2 DM. Several forms of chromium (chromium picolinate, n=16, chromium chloride, n=15, chromium yeast, n = 5 and chromium nicotinate, n = 4; combination of chromium yeast and chromium chloride, n =3) have been studied with respect to glucose metabolism; however, studies of CrPic supplementation have evidenced greater effects on metabolic syndrome risk factors.

Chromium picolinate supplementation has demonstrated significant beneficial effects on HbA1c, glucose, insulin and cholesterol variables in subjects with type 2 DM. Controlled clinical trials (number of patients in 16 clinical trials: 1,664; randomized clinical trials, N = 9; non-randomized clinical trials, N =7) evaluating efficacy for CrPic supplementation in people with DM or impaired glucose showed statistically significant benefits, including increased insulin sensitivity and improved glycemic control as assessed by reductions in fasting insulin (16 –74 pmol/L) and/or glucose (5 – 32 mg/dL), HbA1c levels (0.1- 1.9 units) and coronary risk lipids and lipoproteins.

The effect of Cr supplementation (200-1,000 mcg Cr/day) on blood lipid profiles has been tested in six placebo-controlled, double blind, clinical trials (N= 357 and study duration: 3-16 wks). Five studies showed significant decreases in TC (20 –30 mg/dL) and/or LDL -C (22-26 mg/dL) [93-97] . In two studies, reductions of serum TG (16 -35 mg/dL) were observed in type 2 DM (97,98). Levels of apo lipoprotein B were significantly reduced (25 mg/dL) and levels of apolipoprotein A were increased (16mg/dL); the levels of HDL-C were increased by 1 mg/dL (not significant) in type 2DM [96].

Studies have shown that Cr improves insulin sensitivity, and reduces elevated blood sugar and glycosylated hemoglobin levels. In addition, six studies have shown significant effects on postprandial glucose levels in type 2 DM and in normal healthy subjects given a glucose load [93,99-102]. The reduced blood sugar levels and insulin improvements achieved may reduce the risk of macro- and micro-vascular complications. Therefore, chromium supplementation may help reduce the risk of early onset of coronary heart disease by reducing the associated coronary risk complications.

Thus, in the majority of studies, supplementation with 200-1,000 mcg of Cr as CrPic has resulted in improvements in MSR risk factors [89,93,96-109]. Only two studies with chromium chloride [110,111], three studies with chromium yeast [112-114] noted improvement in glucose homeostasis. A reduction in insulin requirements due to chromium supplementation has important implications for management of blood glucose concentrations and coronary risk factors [107].

The management of blood glucose and lipid profile is essential for strict glycemic control and LDL-C and requires anticipatory adjustments in insulin dosage in response to major changes in dietary chromium intake. In another study [102], it was observed that supplementation with 400 and 800 mcg Cr as CrPic lowered the incremental area under the curve (AUCg) for capillary glucose (23%, p<0.053 and 20%,

p<0.054 respectively) after a white-bread meal. Ten responders in this study significantly reduced AUCg by 36 and 30%, respectively. In another study (115), six healthy subjects were given 14.5 oz of carrot juice for seven consecutive days to increase baseline blood glucose levels; the subjects were concomitantly supplemented with 200 mcg Cr as CrPic for the same seven days. Four out of six subjects showed a 20 to 54% reduction in AUCg. In another study, 10 of 13 subjects responded to CrPic supplementation after a 75 g glucose load [102]. Although these are small studies, they suggest that Cr may be beneficial for lowering blood glucose in response to a carbohydrate load.

It is interesting to focus the effect of CrPic on abnormal EKG of QTc interval prolongation, which is a predictor of future stroke and cardiovascular morbidity and mortality in the general population and in patients with nephropathy, type 1 DM and type 2 DM. Vrtovec *et al.* [116] reported that CrPic supplementation at 1,000 mcg daily for 12 weeks shortens QTc interval duration in patients with type 2 DM. These effects were significant in patients with type 2 DM who had a higher BMI. This study suggests that improving glucose homeostasis might have potential effects on cardiac arrhythmias.

Recent metanalysis reported that chromium appears to have no effect on blood glucose and endogenous insulin levels in normal healthy people [117]. Nevertheless, overall it was observed that Cr as CrPic helps to improve glycemic control. In addition, Cr may increase HDL-C and decrease TG in people with type 2 DM and may reduce AUCg after glucose load. There is increasing evidence that events in the post-prandial state are important contributing factors for CVD; most CVD factors are modified by hyperglycemia in the post-prandial phase. It is especially during this state that enhanced production of free radicals is noted. Increased oxidative stress during this phase contributes to the development of endothelial dysfunction and pro-thrombotic and pro-inflammatory conditions that may lead to CVD. Further long-term studies are required to study the association of Cr status and relative risk of CVD, postprandial response to glucose, lipids and cardiac events. Studies need to explore the effects of CrPic supplementation on the progression and regression of atherosclerosis and CVD relative risk.

RECOMMENDATIONS

Public health efforts should focus on reducing each individual metabolic syndrome risk factor and aim at preventing specific manifestations of cardiovascular disease. Educating healthcare professionals and consumers is the highest priority; encouraging healthy diet and physical activity in schools and improving the National School Lunch Program are important. Also important are: early prediction of metabolic syndrome risk factors based on family history, diet and lifestyle and encouraging regular blood pressure, blood glucose and lipid monitoring in adults aged 30 years and over. Table 2 summarizes the biological effects of nutritional supplements in managing MSRF in the prevention of CVD.

Table 2. Effects of Dietary Supplements on Metabolic Syndrome Risk Factors

| Primary Effect | Dietary Supplements | Observed Biological Effects |
|-------------------------------------|--|---|
| LDL-C or total cholesterol lowering | Policosanol, plant stanols/soy protein, omega-3 fatty acids, chromium picolinate | Lowers TC and LDL-C; binds bile acids; may inhibit key enzymes in cholesterol biosynthesis. |
| TG-lowering | Policosanol, plant stanols/soy protein and chromium picolinate | Decreases triglyceride synthesis, inhibits FFA release from adipose tissue |
| Raises HDL-C | Chromium picolinate, policosanol, | Raises HDL-C |
| Anti-diabetic | Chromium picolinate | Delays glucose absorption; decreases fasting and post-prandial hyperglycemia and improves glycemic control; inhibits key enzymes in insulin-signaling pathway and enhances PI3 kinase and Akt phosphorylation and helps in GLUT 4 translocation; may stimulate insulin release from pancreatic beta cells, increase glucose uptake and glycogen synthesis, decrease hepatic glucose production and insulin sensitivity; may decrease body weight and decrease triglycerides and HbA1c, improve glucose tolerance, inhibit PTP1B activity, and lower circulating insulin levels. |
| Anti-hypertensive | Policosanol; omega-3 fatty acids; chromium picolinate | Improves endothelial function; inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle; improves coronary vascular circulation and reduces coronary constriction, resulting in reduction in systolic and diastolic blood pressure. |
| Anti-obesity | Chromium picolinate | Decreases body weight and body fat; increases lean body mass; decreases insulin resistance and may inhibit digestion and absorption of dietary triglycerides; improves lipid profile and insulin sensitivity; suppresses carbohydrate cravings and improves glycemic control |

Costs of Cardiovascular Disease

The rising costs associated with MSRF are raising concerns among health officials who are becoming increasingly interested in nutritional therapeutic approaches (as adjunct therapies or monotherapy) for the early prevention and treatment of CVD. It is currently estimated that the direct and indirect costs of CVD are \$368.4 billion. It is imperative for us to identify nutritionally based therapeutic approaches to the management of MSRF in order to reduce costs, improve quality-of-life and prevent the clinical complications associated with MSRF to ultimately prevent the end-disease condition of CVD.

Safety of Dietary Supplements

In vitro, *in vivo* and human clinical trials have shown no adverse events with these nutritional supplements. However, it is recommended that, in future long-term clinical trials, records of adverse events for the safe use of these nutritional supplements in reducing metabolic syndrome risk factors and for the long-term prevention of CVD are needed.

CONCLUSIONS

Nutritional therapies can potentially prevent or treat MSRF and CVD. Considerable experimental evidence suggests that nutritional supplements can potentiate insulin sensitivity, including impaired glucose tolerance. Clinical manifestations of hyperglycemia, relative insulin resistance,

obesity, hypertension and dyslipidemia have been reversed *via* targeted application of these essential nutrients as nutritional supplements. Long-term consumption of these supplements needs to be studied, along with an effective combination of pharmaceutical therapies, in beneficially modulating the clinical manifestations of CVD.

Therefore, it is important to document the putative mechanisms of action of these supplements, under various conditions, both in combination with lipid-lowering diets or drugs, and in different population groups. Further studies are needed to explore the long-term health benefits and safety of dietary supplements in individuals with MSRF. Prevention of MSRF can reduce the fatal risk of CVD. The nutritional supplements used should be high quality, manufactured under good manufacturing practices (GMPs), bioavailable, stable and safe if they are to be broadly recommended for the prevention of CVD risk. In conclusion, the control of all modifiable metabolic syndrome risk factors to prevent transition to metabolic syndrome and cardiovascular disease should be considered as the ultimate goal.

ABBREVIATIONS

LPL = Lipoprotein lipase
HL = Hepatic lipase

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