REVIEW

Cardiovascular Therapeutics

Nutraceuticals in Diabetes and Metabolic Syndrome

Giovanni Davì,[1,2] Francesca Santilli,[1,2] & Carlo Patrono[1,2]

1 Center of Excellence on Aging, "G. d'Annunzio" University Foundation, Chieti, Italy
2 Department of Pharmacology, Catholic University School of Medicine, Rome, Italy

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Correspondence
Carlo Patrono, M.D., Department of Pharmacology, Catholic University School of Medicine, Largo F. Vito, 1, 00168 Rome, Italy.
Tel.: +390630154253;
Fax: +39063050159;
E-mail: carlo.patrono@rm.unicatt.it

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SUMMARY

Metabolic syndrome represents a clustering of risk factors related to an elevated risk of cardiovascular disease and type 2 diabetes. Occurrence of both metabolic syndrome and diabetes and their vascular complications share several pathogenetic features including subclinical, low-grade inflammation, altered oxidative/antioxidant status, and persistent platelet activation. Despite the availability of multiple interventions to counteract these metabolic changes, including appropriate diet, regular exercise, weight control and drugs, epidemiological data are witnessing the growing trend of the problem, reflecting both the multifactorial nature of these diseases as well as the scarce compliance of patients to established strategies. Several nutraceuticals used in clinical practice have been shown to target the pathogenesis of diabetes mellitus, metabolic syndrome and their complications and to favorably modulate a number of biochemical and clinical endpoints. These compounds include antioxidant vitamins, such as vitamins C and E, flavonoids, vitamin D, conjugated linoleic acid, omega-3 fatty acids, minerals such as chromium and magnesium, α-lipoic acid, phytoestrogens, and dietary fibers. Several areas of concern exist regarding the use of dietary supplements and nutraceuticals in this setting, including product standardization, definition of optimal dosing regimen, potential side effects, drug interactions, and need for evidence-based indications.

Introduction

The metabolic syndrome is a controversial clinical entity characterized by a number of cardiometabolic risk factors that include obesity, insulin resistance, hypertension, and dyslipidemia. This clustering of risk factors is linked to an increased risk of cardiovascular disease and type 2 diabetes [1].

Although appropriate diets, regular exercise, and weight control have potential for the prevention of type 2 diabetes, a high proportion of at-risk subjects continue to disattend these recommendations. Moreover, although insulin and other pharmacological interventions can control many aspects of diabetes, they inadequately prevent atherothrombosis and microvascular complications affecting the retina, lens, and kidney [2]. On the other hand, the range of nutraceutical compounds that might have potential efficacy in this regard continues to expand [3].

Several areas of concern exist with use of dietary supplements and nutraceuticals in patients with diabetes and/or metabolic syndrome, including product standardization, definition of optimal dosing regimen, potential side effects, drug interactions, and need for evidence-based indications.

The purpose of this review is to discuss these issues and provide a methodological framework for the clinical investigation of nutraceuticals in diabetes and metabolic syndrome.

Diabetes Mellitus and Metabolic Syndrome: Role of Inflammation and Oxidative Stress

Systemic inflammation and oxidative stress may have an important role in the pathogenesis of diabetes

mellitus and metabolic syndrome as well as in their vascular complications [4]. Pancreatic β-cell failure is the common characteristic of type 1 and type 2 diabetes mellitus, with pancreatic islet inflammation as an underlying mechanism. Oxidative stress resulting from increased generation of reactive oxygen species (ROS) is likely involved in pancreatic β-cell dysfunction and insulin resistance, hallmarks of type 2 diabetes [5–7]. Hyperglycemia causes the autoxidation of glucose, glycation of proteins, and the activation of polyol metabolism. These changes accelerate generation of ROS and result in oxidative chemical modification of lipids, DNA, and proteins in various tissues [8]. Oxidative stress may play an important role in the development of complications in diabetes such as lens cataracts, nephropathy, and neuropathy [9].

Human type 1 diabetes at onset represents an interesting paradigm of the interrelationship between inflammatory reaction, lipid peroxidation, and platelet activation. We reported that enhanced lipid peroxidation, as reflected by F_2-isoprostane formation, and platelet activation, as reflected by thromboxane (TX) biosynthesis *in vivo*, represent early events in the development of this disease in children and adolescents [10]. Isoprostanes are a family of bioactive compounds produced from arachidonic acid via a free radical-catalyzed mechanism of lipid peroxidation on cell membrane phospholipids or circulating low-density lipoproteins [11]. Patients with newly diagnosed diabetes had significantly increased urinary excretion of the F2-isoprostane, 8-iso-$PGF_{2\alpha}$, a reliable and sensitive marker of lipid peroxidation [7] and 11-dehydro-TXB_2, a validated marker of thromboxane-dependent platelet activation [12] as well as higher plasma levels of a number of inflammatory markers [10]. In most of these patients, oxidative stress and platelet activation were reduced after 1 year, coincidently with a fall in the systemic levels of IL-6 and TNF-α. Thus, it appears that biochemical signals of oxidative stress and platelet activation can be appreciated early at the onset of type 1 diabetes, and that their variable intensity is, at least in part, driven by IL-6 production and disease duration. These non-invasive indices may help monitoring nutritional interventions aimed at interfering with disease development and progression.

Moreover, we found persistently increased isoprostane formation in the vast majority of type 2 diabetic patients, with a significant correlation between blood glucose and urinary 8-iso-$PGF_{2\alpha}$, suggesting that lipid peroxidation may be, at least in part, related to determinants of glycemic control [13]. Reduced blood glucose levels were associated with a fall in urinary 8-iso-$PGF_{2\alpha}$ excretion [13].

Nutritional Interventions Targeting the Pathogenesis of Diabetes Mellitus, Metabolic Syndrome, and their Complications

Antioxidant Vitamins

Animal studies have shown that an adequate supply of dietary antioxidants may prevent or delay diabetes complications including renal and neural dysfunction by providing protection against oxidative stress [9]. However, clear evidence in humans is lacking [14].

Vitamin C (ascorbic acid) is a chain-breaking antioxidant, scavenging ROS directly, and preventing the propagation of chain reactions that would otherwise lead to a reduction in protein glycation [15]. In animals, vitamin C also reduces diabetes-induced sorbitol accumulation and lipid peroxides in erythrocytes [15]. Vitamin C (800 mg/day) partially replenishes vitamin C levels in patients with type 2 diabetes and low vitamin C levels but does not improve endothelial dysfunction or insulin resistance [16].

Vitamin E (α-tocopherol) (Figure 1), a component of the total peroxyl radical-trapping antioxidant system, reacts directly with peroxyl and superoxide radicals and singlet oxygen and protects membranes from lipid peroxidation [15]. A deficiency in vitamin E is associated with increased peroxides and aldehydes in many tissues. There have been conflicting reports about vitamin E levels in diabetic subjects [7,17,18].

To assess the reversibility of lipid peroxidation and platelet activation in type 2 diabetes, we examined the effects of short-term vitamin E supplementation (600 mg daily for 2 weeks) on the urinary excretion of 8-iso-$PGF_{2\alpha}$ and 11-dehydro-TXB_2 [13]. Vitamin E supplementation was associated with detectable changes in plasma vitamin E levels and caused virtually complete normalization of 8-iso-$PGF_{2\alpha}$ excretion (Figure 2). Moreover, changes in F2-isoprostane formation were accompanied by similar reductions in thromboxane metabolite excretion [13], consistently with a cause-and-effect relation between enhanced lipid peroxidation and persistent platelet activation in this setting [12].

Observational, prospective cohort studies suggest that higher dietary intake or supplementation of antioxidants (vitamins A, C, E, folic acid, niacin, β-carotene, selenium, zinc) is associated with a lower risk of cardiovascular disease and mortality [19]. In view of these findings, the American Heart Association recommended the consumption of a balanced diet with emphasis on antioxidant-rich fruits, vegetables, and whole grains [19]. However, the results of randomized, controlled clinical trials have failed

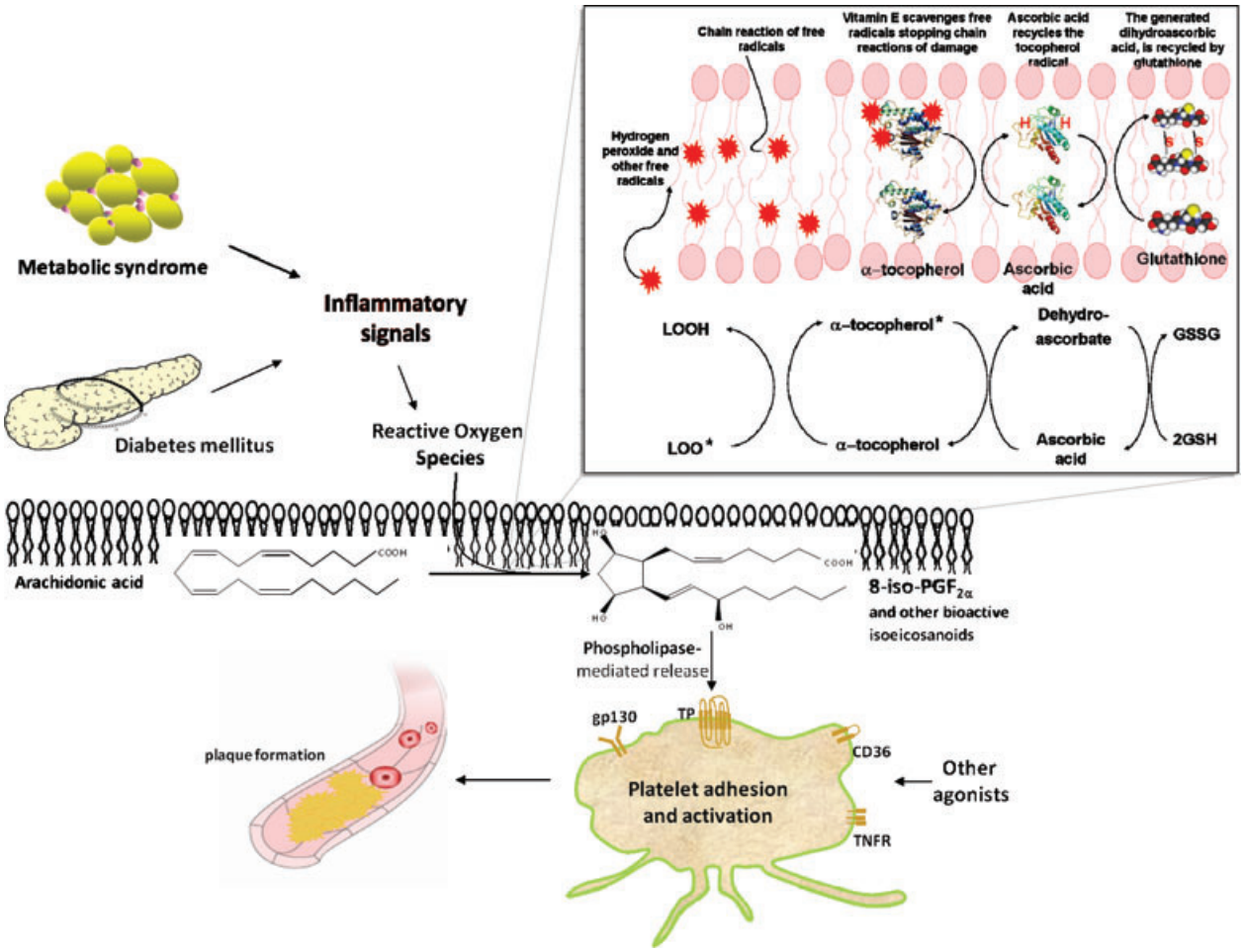

Figure 1 Protective role of vitamins E and C against lipid peroxidation. Vitamin E (α-tocopherol), a component of the total peroxyl radical-trapping antioxidant system, reacts directly with peroxyl (LOO*) and superoxide radicals and singlet oxygen and protects membranes from lipid peroxidation. Vitamin E is reconstituted when ascorbic acid recycles the tocopherol radical; dihydroascorbic acid, which is generated, is recycled by glutathione (GSH), which in turn is converted to its oxidized form glutathione disulfide (GSSG).

to demonstrate a consistent protective effect of any single antioxidant or combination of antioxidants (vitamins C, E, and β-carotene) in the primary or secondary prevention of cardiovascular events [20,21]. Moreover, in some clinical trials the supplementation of vitamins C, E, and/or β-carotene was associated with an increased risk of all-cause mortality [22,23]. Vitamin B supplementation was also associated with a more rapid decrease in glomerular filtration rate and an increase in vascular events as compared to placebo in patients with diabetic nephropathy [24]. Recently, vitamin E proved effective over placebo for the treatment of nonalcoholic steatohepatitis, a disease closely associated with insulin resistance, in non diabetic adults [25].

Studies in healthy subjects [18,26,27] helped identifying the basal rate of lipid peroxidation as a major determinant of the response to vitamin E supplementation. The evidence that the same dose of vitamin E may have variable antioxidant effects in different patient populations characterized by variable rates of lipid peroxidation is consistent with this concept [18]. As shown in Figure 3, we found a linear correlation between the basal rate of 8-iso-$PGF_{2\alpha}$ excretion and the slope of changes in this index of lipid peroxidation as a function of changes in plasma vitamin E associated with short-term dosing with 600 mg/day in different clinical settings [18]. The issues of dose and duration of treatment may also affect the efficacy of vitamin E supplementation [28]. In a dose-ranging study, a significant linear trend has been reported between dose of vitamin E and percent change in plasma concentrations of F_2-isoprostanes, but the magnitude of the reduction was statistically significant only

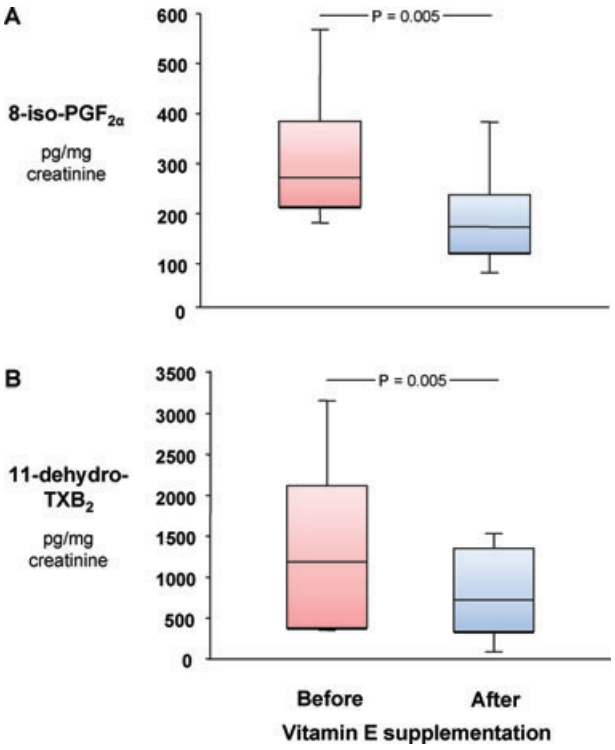

Figure 2 Effects of vitamin E supplementation on the urinary excretion of 8-iso-PGF_{2a} and 11-dehydro-TXB_2 in type 2 diabetic patients. Box and whisker plots of urinary 8-iso-$PGF_{2\alpha}$ (panel A) and 11-dehydro-TXB_2 (panel B) before and after 2-week vitamin E supplementation (600 mg/die) in 10 type 2 diabetic patients.

at doses of 1600 I.U./day and 3200 I.U./day. Moreover, a time-course study revealed that maximum suppression of plasma F_2-isoprostane concentrations did not occur until 16 weeks of supplementation [28]. Taken together, all these factors may have implications for the study of vitamin E in diabetic subjects as well as for the design and interpretation of clinical trials of antioxidant intervention.

Vitamin D

Observational studies have described a link between geographical latitude and the incidence of type 1 and type 2 diabetes and have shown that glycemic control in patients with diabetes has a seasonal variation, suggesting an inverse correlation between the incidence of diabetes and the effective exposure to sunlight [29]. This variation may be explained, at least in part, by fluctuations in vitamin D concentrations as a result of fluctuations in the exposure to ultraviolet radiation [29]. Vitamin D may modulate the pathogenesis of type 1 diabetes through its immunomodulatory and anti-inflammatory actions, reducing the inflammatory reaction in the pancreatic islets and decreasing the autoimmune insulinitis. Vitamin D may also decrease insulin resistance and increase insulin secretion in type 2 diabetes [30], by altering the balance between intracellular and extracellular calcium in β cells [31].

Vitamin D deficiency is often associated with obesity and type 2 diabetes, probably due to deposition of vitamin D in the fat stores where it becomes less bioavailable. Vitamin D-deficient obese subjects have elevated PTH levels, which can decrease insulin sensitivity, through disproportionate increase in Ca^{2+} [29].

Increased vitamin D intake by infants may reduce the risk of developing type 1 diabetes. A 33% reduction in the risk of developing childhood-onset type 1 diabetes was found in children who received vitamin D supplementation compared with nonsupplemented children [32]. In adult patients with recent onset type 1 diabetes, an open-label randomized trial also found a benefit of supplementation with calcitriol, which temporarily reduced the required insulin dose [29].

Two large randomized controlled trials that used combined calcium and vitamin D treatment found that it may lower the risk of type 2 diabetes [29]. This suggests that calcium, vitamin D, or both may have a role in the prevention of the disease [29].

In vitamin D-deficient populations with impaired glucose tolerance (IGT) or type 2 diabetes, vitamin D replacement may improve insulin secretion and glucose tolerance as well as $HbA1_C$ levels [29]. However, there are few randomized, controlled trials specifically testing vitamin D as a modifier of type 2 diabetic risk. Also, an independent role of calcium itself on insulin resistance can influence the results. Nonetheless, a recent meta-analysis suggested that vitamin D and calcium may promote β-cell function and insulin sensitivity. It remains unclear whether these effects are additive or synergistic [33].

Flavonoids

Flavonoids are polyphenols found in fruits, vegetables, legumes, herbs, spices, stems, flowers as well as tea and red wine. They are prominent components of citrus fruits and other food sources and are in many countries regularly consumed in a healthy diet [34]. The anti-inflammatory properties of flavonoids have been studied, to evaluate their potential utility as therapeutic agents in the treatment of inflammatory diseases [35].

Several mechanisms have been proposed to explain flavonoid anti-inflammatory properties, including antioxidant and radical scavenging activities, modulation of platelet activation and of the activity of eicosanoid generating enzymes (phospholipase A2, cyclooxygenase,

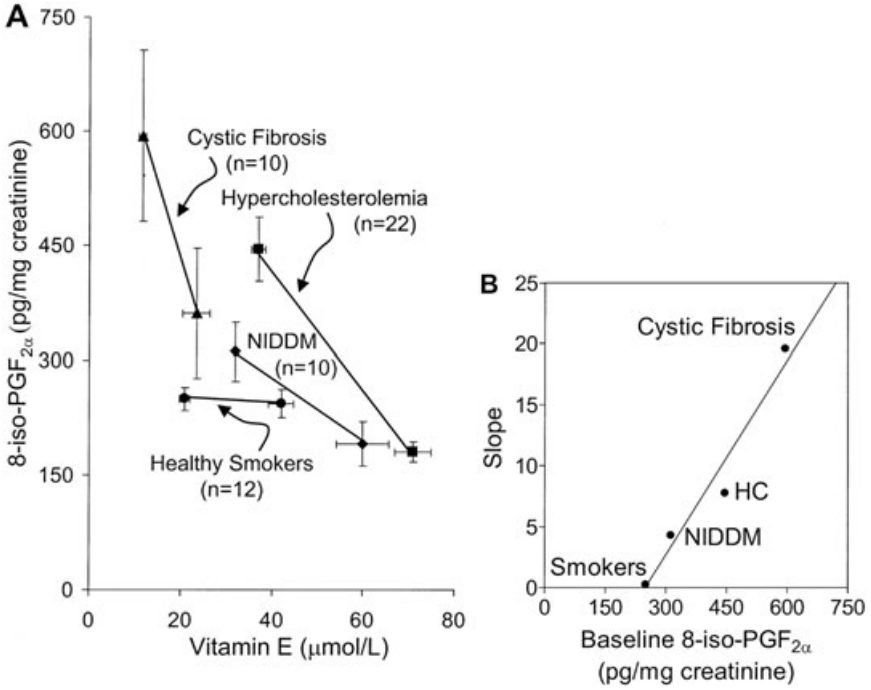

Figure 3 (**A**) Changes in plasma vitamin E levels and urinary 8-iso-$PGF_{2\alpha}$ excretion associated with vitamin E supplementation (600 mg/day for 2 weeks) in patients with cystic fibrosis [12] hypercholesterolemia [12] (HC), and type 2 diabetes mellitus [12] and in healthy cigarette smokers [18]. Each solid line connects mean (±SEM) values measured before and after vitamin E supplementation. (**B**) Slope of these lines is linearly correlated with mean basal rate of 8-iso-$PGF_{2\alpha}$ excretion measured in each clinical setting ($r = 0.976$, $P = 0.023$).

lipoxygenase) and nitric oxide synthase in inflammatory cells, and modulation of proinflammatory gene expression [34–36].

Moreover, polyphenols have also been shown to have antioxidant and radical scavenging properties and to modulate the function of cellular components involved in the process of thrombosis [37,38].

Several prospective studies have reported inverse associations between flavonoid intake and cardiovascular disease (CVD) incidence or mortality [39–42]. A systematic review [43] of the effectiveness of different flavonoid subclasses and flavonoid-rich foods on CVD concluded that some flavonoid-rich foods, including chocolate or cocoa, red wine or grape, and black tea may have some measurable effects on CVD risk factors, including a reduction in blood pressure, and a favorable influence on endothelial function.

In the general population, a significant reduction in vascular events is associated with moderate versus no wine consumption [37,38]. An overall beneficial effect of alcohol consumption in decreasing the risk of death due to CVD in people with older-onset diabetes has been demonstrated [44]. Similarly, moderate alcohol consumption is associated with reduced CVD risk in women with diabetes [45].

Studies exploring the association between alcohol intake and the risk for type 2 diabetes have reported conflicting results. Several large-scale epidemiological studies have suggested an inverse association between moderate alcohol consumption and reduced risk for type 2 diabetes, whereas others have reported null or even positive associations. Among participants in the Physicians' Health Study followed for an average period of 12.1 years, apparently healthy men who self-selected for light to moderate alcohol consumption had a decreased risk of developing type 2 diabetes [46].

Diabetes-Preventive Nutraceuticals

There is considerable need for safe agents that can reduce the risk for diabetes in at-risk subjects. Although certain drugs—including metformin, acarbose, and orlistat—have shown diabetes-preventive activity in large randomized studies, nutraceuticals have potential in this regard as well [47].

The STOP-NIDDM trial [48] has demonstrated that, in subjects with glucose intolerance at baseline, acarbose—an α-glucosidase inhibitor—reduces the subsequent incidence of diabetes over a 4-year follow-up by about 25%. Natural agents which slow carbohydrate absorption may

mimic the protective effect of acarbose; these include: soluble fiber—most notably glucomannan; chlorogenic acid—likely responsible for the reduction in diabetes risk associated with heavy coffee intake; and legume-derived α-amylase inhibitors [47].

The favorable effects of metformin on insulin sensitivity and on hepatic glucose output reflect activation of AMP-activated kinase; there is preliminary evidence that certain compounds in barley malt brewers' yeast can indeed activate AMPK, and the first clinical trial with these extracts in type 2 diabetics is currently underway [47].

Conjugated linoleic acid (CLA) and the natural rexinoid phytanic acid, activating the RXR receptor that forms a heterodimer with PPAR-γ, appear to be PPAR-γ agonists. Both have shown insulin-sensitizing activity in diabetes-prone rats but not in clinical trials [47].

Recommendations from the American Heart Association [49] state that randomized trials have convincingly demonstrated that *omega-3 fatty acids* can significantly reduce the occurrence of CVD events in patients with coronary artery disease. The strongest evidence to date is from studies in which marine-derived omega-3 fatty acids have been consumed as supplements or fish [49]. A food-based approach to increasing omega-3 fatty acids is preferable, although supplements are a suitable alternative (see Chapter by De Caterina in this volume).

Omega-3 fatty acids supplementation in type 2 diabetes has a favorable impact in lowering triglycerides and VLDL-cholesterol, and reducing blood pressure and inflammatory markers [50]. Omega-3 fatty acids supplementation has no statistically significant effects on glycemic control or fasting insulin, but may prevent or revert insulin resistance [51].

Protective Minerals

Chromium is a trace element that may be deficient in persons with diabetes [52]. It has been suggested that chromium supplements may increase insulin sensitivity and improve glucose tolerance in patients with type 2 diabetes [52]. A meta-analysis [53] of randomized controlled trials investigating the effects of chromium supplementation on glucose and insulin response in healthy individuals and those with diabetes showed a modest but significant improvement in glycemic control in the latter, but not in the former. The American Diabetes Association's official position is that there is inconclusive evidence for the benefit of chromium supplementation in diabetes [54].

Prospective epidemiology links *magnesium*-rich diets to decreased risk for diabetes, with an inverse correlation between magnesium intake and fasting insulin levels, suggesting an improvement in insulin sensitivity [47]. This view is supported by limited clinical data, as well as by animal studies demonstrating that magnesium helps preserving adipocyte insulin sensitivity [55].

The retina is particularly vulnerable to oxidative damage because of its abundance of polyunsaturated fatty acids, predominantly found in photoreceptor outer membranes, which are readily oxidized [8,56]. Nutritional supplementation for age-related macular degeneration (AMD) has been investigated in the Age-Related Eye Disease Study, that reported a 25% reduction in the risk of progression to advanced AMD in people who had later stages of AMD and were supplemented with a high-dose zinc plus antioxidants formulation [56].

α-Lipoic Acid

α-Lipoic acid is a naturally occurring antioxidant with potent ROS-scavenging activity. It has the unusual property of being a ROS scavenger in its oxidized state, quenching several radicals. α-Lipoic acid and dihydrolipoic acid work in a redox couple (an electron donating molecule and its oxidized form), and together have other antioxidant properties including chelation of transition metals and the regeneration of other antioxidants such as glutathione, vitamin C, and vitamin E [9,57].

α-Lipoic acid has been shown to protect the retina against ischemia-reperfusion injuries *in vivo* and *in vitro*. Ischemic injury to the retina is considered to be one of the major causes of visual loss and occurs in diabetic retinopathy [9].

α-Lipoic acid increases insulin sensitivity by approximately 18–20% in patients with type 2 diabetes [57].

A review of the clinical trials of α-lipoic acid in the treatment of diabetic neuropathy reported beneficial effects on acute symptoms and disease progression [58].

Phytoestrogens and Glucose Metabolism

Of any plant, soy contains the largest concentration of isoflavones, a class of phytoestrogens [47]. Phytoestrogens are structurally similar to estradiol and mimic its effects. Soy and phytoestrogens have received increasing attention due to the health benefits associated with their consumption [59]. In animal studies, soy and phytoestrogens are effective at reducing adipose tissue and improving glucose uptake. However, available data from human studies do not offer clear evidence for the benefits of soy and phytoestrogens in adiposity control and glucose metabolism [59].

The specific soy protein components that may lead to metabolic improvement have yet to be determined. Comparisons between different animal or clinical studies are hampered by the lack of standardization of soy

Table 1 Overview of clinical studies on nutraceuticals in diabetes mellitus and metabolic syndrome

Reference	Intervention	Participants (n)	Duration of intervention	Outcome measures	Main results
Vitamin C (ascorbic acid)					
Chen et al. (2006)	Vitamin C (800 mg/day)	Type 2 DM subjects with low plasma vitamin C (<40 μM) (32)	4 weeks	FPG Fasting plasma insulin Forearm blood flow	No significant effect
Vitamin E (α-tocopherol)					
Davì et al. (1999)	Vitamin E (600 mg daily)	Type 2 DM subjects (10)	2 weeks	8-iso-$PGF_{2\alpha}$ and 11-dehydro-TXB_2 urinary excretion	Significant reduction in urinary 8-iso-$PGF_{2\alpha}$ and 11-dehydro-TXB_2
Sesso et al. (2008)	Vitamin E (400 IU every other day) vs. placebo or Vitamin C (500 mg daily) vs. placebo	US male physicians (14,641)	10 years	A composite end point of major CV events	Neither vitamin E nor vitamin C supplementation reduced the risk of major CV events
Vitamin D					
Borissova et al. (2003)	Cholecalciferol 1332 IU	Type 2 DM females (10)		IR Insulin secretion	Increase in first phase of insulin secretion Decrease in IR
Pittas et al. (2007)	Calcium citrate 500 mg + vitamin D_3 700 IU daily	Non diabetic Caucasian adults aged > 65 years (314)	3 years	FPG IS	In healthy adults with IFG supplementation may attenuate increases in glycemia and IR
Flavonoids					
Knekt et al. (2002)	24.2 ± 26.7 mg/day (quercetin, Kaempferol, myricetin, naringemin, hesperetin)	Both sex random population (10,054)	1 year (preceding the baseline examination)	CV disease, hospitalization, death	Lower risk of chronic diseases as DM at higher dietary flavonoid intakes Decrease in ischemic heart disease Lower incidence of CV disease leading to hospitalization or death
Mink et al. (2007)	Total flavonoids intake 0.6–133.1 mg/day 133.2–201.8 mg/day 201.9–281.9 mg/day 282.0–425.2 mg/day 425.3–3524.4 mg/day	Postmenopausal women (34,489)	16 years	All-cause an CV mortality in postmenopausal women	Reduced risk in death due to CV and all causes
Mukamal et al. (2002)	<14 cups of tea/weekly >14 cups of tea/weekly	Patients with AMI, retrospectively assessed (1019)	1 year (before AMI)	All-cause CV mortality after AMI	Lower mortality after AMI
Omega-3 fatty acids					
Mostad et al. (2006)	17.6 mL fish oil/day (5.9 g total n-3 fatty acids)	DM without hyper-triglyceridemia (26)	9 weeks		Moderate increase of blood glucose Decrease in IS
Tsitouras et al. (2008)	Fatty fish 720 g/week+sardine oil 15 mL/day (4–5 g n-3) or olive and corn oil	Healthy men and women (12)	8 weeks	FPG Insulin concentration	No change in FPG and insulin Improved IR in 3 h OGTT

Table 1 Continued

Reference	Intervention	Participants (n)	Duration of intervention	Outcome measures	Main results
Chromium					
Wilson et al. (1995)	220 μg/day elemental Cr(III)	Healthy young adults (15)	90 days	IS	Improvement of IS
Bagchi et al. (2004)	300 μg/day elemental Cr(III) or placebo	Type 2 DM subjects (20)	3 months	FPG Triglycerides HbA_{1c}	Mean fasting glucose levels lowered Blood triglycerides and HbA_{1c} reduced
Kleefstra et al. (2006)	500 or 1000 μg/day chromium picolinate or placebo	Type 2 DM subjects with HbA_{1c} $\geq$8%, and age <75 years (46)	6 months	HbA_{1c} Weight, BP, lipid profile	No differences between the three groups
Magnesium					
Paolisso et al. (1992)	Magnesium pidolate 4.5 g /day equivalent to 16.2 mmol/day	Aged (12) vs. young (25) healthy subjects	4 weeks	Glucose handling	Improvement of Glucose handling
Zinc plus antioxidants formulation					
Evans JR 2006	Zinc sulfate 200 mg daily	Subjects from the general population with AMD at different stages (969)		Reduction in the risk of progression to advanced AMD	Modest benefit of treatment
α-Lipoic acid					
Jacob et al. (1995)	1000 mg α-lipoic acid or 500 mL NaCl	Type 2 DM subjects (7)		IS	Increase in IS
Jacob et al. (1999)	600 mg/day 1200 mg/day 1800 mg/day	Type 2 DM subjects (72)	4 weeks	FPG IS	Increase in IS 600 mg/day may be the maximum effective dose
Phytoestrogens					
Ikeda et al. (2006)	Fermented Soy Bean 40 g of *natto*	Pre- and postmenopausal women (944)	3 years	Weight BMI	No effects
Dietary fiber supplements (soluble)					
Wolf et al. (2003)	OGTT 50 g of available carbohydrate from maltodextrin and white bread or the same meal with either 5 g of guar gum (3.6 g galactomannan), 5 g of fructose, or 5 g guar gum + 5 g of fructose	Healthy subjects (30)		Baseline-adjusted peak glucose response	Guar gum reduces whereas fructose increases the peak glucose response
Dietary fiber supplements (insoluble)					
Gruendel et al. (2007)	200 mL water w/50 g glucose and 5, 10, or 20 g carob fiber	Healthy subjects aged 22–62 years (20)		Plasma glucose Serum insulin	Increase in postprandial plasma glucose and insulin response after carob fiber up to 10 g (no further increase with 20 g)

BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; DM, diabetes mellitus; CV, cardiovascular; IR, insulin resistance; IS, insulin sensitivity; AMI, acute myocardial infarction; AMD, age-related macular degeneration.

nomenclature, the different formulations, doses, routes of administration, time, and duration of exposure [59].

Dietary Fiber Supplements

The term "dietary fiber" characterizes a heterogeneous group of natural food sources, processed grains, and commercial supplements. It includes polysaccharides, oligosaccharides, lignin, and associated plant substances [47,60].

There are several studies showing that the general population and diabetic patients in the United States do not meet adequate daily fiber intake in their diets [60]. Observational studies suggest an inverse association between dietary fiber intake from natural food sources and CVD risk [60]. This protective effect appears mostly related to consumption of cereals and whole grain [60].

Several forms of dietary fiber have been used as complementary or alternative agents in the management of the metabolic syndrome. Epidemiologic studies suggest an inverse relation of dietary fiber intake and body weight. However, randomized controlled studies suggest only minor effects on weight loss for commonly used dietary fiber supplements [60].

Soluble dietary fiber is associated with lower postprandial glucose levels and increased insulin sensitivity in diabetic and healthy subjects, effects that are generally attributed to the viscous and/or gelling properties of soluble fiber [47,60]. Insoluble dietary fiber exerts negligible effects on postprandial glycemia. However, soluble dietary fiber consumption did not reduce the risk of type 2 diabetes mellitus [60]. In contrast, the consumption of insoluble fibers demonstrated the strongest associations with decreased risk of diabetes [60]. Increased consumption of cereal dietary fiber significantly reduced the risk of diabetes and a meta-analysis of six prospective studies indicates that a 2-serving-per-day increment in whole grain consumption may reduce the risk of diabetes by 21% [60].

Conclusions

Most of the nutraceuticals used in clinical practice are known to modulate one or more pathogenic mechanisms underlying the development of diabetes mellitus, metabolic syndrome, and their complications thus providing the target and outcome measures to test their efficacy and safety in randomized clinical trials (Table 1).

The strength of the association between dietary antioxidant consumption and the prevention of coronary events is strongest in observational studies, which are confounded by self-selection of patients and co-consumption of other nutrients in whole foods. Nutrition is a very complex research topic and it is not clear whether an individual component of the diet or a combination of nutrients and dietary habits may be responsible for any cardioprotective effects. Animal studies and observational cohort studies are largely consistent with the concept that dietary supplementation with antioxidant nutrients reduces the progression of atherosclerosis [19]. However, firm recommendations to take antioxidant supplements to treat or prevent coronary artery disease or metabolic diseases require evidence derived from randomized controlled trials. Several large, well designed, randomized, placebo-controlled studies powered to detect differences in clinical events have failed to show a benefit of vitamin E supplementation in preventing cardiovascular events in different high-risk groups, including diabetic patients [7].

A striking feature of these and other trials of antioxidants is the absence of a biochemical basis for patient inclusion or, indeed, dose selection. Patients with high levels of oxidant stress or depletion of natural antioxidant defense systems may be the most likely to benefit from antoxidant therapy [18]. If this is the case, then reliable, quantitative indices of *in vivo* oxidant stress, such as urinary isoprostane excretion, should be considered as an inclusion criterion for patient selection. Furthermore, the dose of the antioxidant should be chosen based on dose-finding studies relying on the same biomarker [18,26–28].

Conflict of Interest

The authors have no conflict of interest.

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