Fat-soluble micronutrients and metabolic syndrome

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Purpose of review
Metabolic syndrome (MetS) is associated with increased risk of obesity, type 2 diabetes mellitus and cardiovascular diseases. MetS prevalence has been associated with diet inadequacy. Conversely, the cumulative incidence of MetS has been inversely associated with a Mediterranean-style diet that includes many different health-beneficial nutrients. Adherence to a Mediterranean-style diet could reduce or at least stabilize metabolic risk factors.

Recent findings
Low serum level of fat-soluble micronutrients, such as carotenoids, vitamin (vit) A, D and E, has been linked to MetS. Fat-soluble micronutrients could contribute to prevent MetS thanks to their antioxidant and anti-inflammatory properties (vit E, carotenoids) or to their central role as hormone regulators (vit D) and/or lipid metabolism and glucose homeostasis sensors (vit D and E).

Summary
This review summarizes recent epidemiological studies linking fat-soluble micronutrients to MetS and highlights new evidence on their mechanisms of actions.

Keywords
antioxidant, fat-soluble vitamins, metabolic syndrome, micronutrients

INTRODUCTION

The term metabolic syndrome (MetS) encompasses a cluster of metabolic abnormalities linked to cardiovascular risk factors (hypertension, dysglycemia, dyslipidemia, insulin resistance and android fat) and is associated with an increased prevalence of obesity, type 2 diabetes mellitus and cardiovascular diseases. MetS has a multifactorial cause that includes metabolic, genetic and environmental factors. On the basis of recent recommendations to standardize its diagnosis [1], MetS is defined by the presence of three or more of the following five cardiovascular risk factors: central obesity (waist circumference: men $\geq$102 cm; women $\geq$88 cm), elevated triglycerides ($\geq$150 mg.dl^{-1}), reduced high-density lipoprotein (HDL) cholesterol (men $<$ 40 mg.dl^{-1}; women $<$50 mg.dl^{-1}) (or treated for dyslipidemia), elevated blood pressure ($\geq$130/$\geq$85 mmHg) (or treated for hypertension) and elevated fasting glucose ($\geq$100 mg.dl^{-1}) (or treated for hyperglycemia). According to National Health and Nutrition Examination Survey (NHANES) data from 2003 to 2012, the overall MetS prevalence is 33% among at least 20-year-old adults. Moreover, prevalence is higher among women than men (35.6 vs. 30.3%, respectively, $P < 0.001$) and increases up to 50% among adults aged 60 years or older [2]. This high MetS prevalence, particularly among older people, could be associated with diet inadequacy, which is one of the main environmental risk factors, as well as low physical activity. Therefore, dietary interventions are a key strategy for MetS prevention and stabilization. Among the potential beneficial dietary compounds, fat-soluble micronutrients, such as carotenoids, vitamin (vit) A, D and E, are important research targets.

This article will review findings published in the last 18 months that help to better understand the complex relationship between fat-soluble micronutrients and MetS.

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KEY POINTS

- Low serum levels of fat-soluble micronutrients (vit A, D E and carotenoids) are associated with MetS.
- Food products rich in carotenoids in a well-balanced diet are of interest to prevent MetS.
- Vit D supplementation may have a greater benefit in the early stages of metabolic disease.
- Vit E may indirectly act on MetS risk factors by improving PPAR activity.
- Carotenoids and vit E could prevent inflammation associated with MetS.

CAROTENOIDS AND VITAMIN A

More than 600 different carotenoids have been isolated from natural sources, but only a small number of them are found in blood and human tissues. Fruits and vegetables are the main food sources. All carotenoids are derived from a linear structure ($C_{40}H_{56}$) with many double bonds. The most common carotenoid in plants is β-carotene, also called provit A because, after its absorption, it is hydrolyzed in two vit A molecules. However, not all carotenoids possess vit A activity, as for instance lycopene (a red pigment present especially in tomato and grapefruit), lutein (found in green vegetables, such as spinach, lettuce...) and zeaxanthin (in maize).

The NHANES study that enrolled 13 196 adults (≥20 years of age) found that higher serum concentrations of lycopene are associated with reduced MetS prevalence, but only in participants with normal weight or overweight, and not in those with obesity [3]. Among the 2499 participants with MetS, higher serum lycopene concentration was associated with longer survival [4]. Moreover, among the 40- to 70-year-old participants, higher concentrations of carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein and zeaxanthin, trans-lycopene and total lycopene), which reflect healthy eating behaviors, were significantly associated with lower MetS risk and higher physical activity (walking), which also contributes to the overall health benefits [5].

The meta-analysis by Leermakers *et al.* [6▪] included data on lutein and cardiometabolic status from six cross-sectional studies that involved 8133 participants among whom 1773 had MetS. The authors found that MetS risk was reduced by 25% [Relative risk: 0.75; 95% confidence interval (CI): 0.60, 0.92] in the highest lutein intake or concentration quantile compared with the lowest one. Conversely, they did not highlight any association with blood pressure, adiposity and triglycerides, but this could be explained by the inclusion of exclusively cross-sectional studies.

In a subsample of participants in the Women's Health Initiative aged 50–79 years and followed for 6 years, the serum concentration of carotenoids was inversely associated with anthropometric parameters (BMI, waist circumference, waist circumference-height and waist-hip ratio), with the strongest association between serum β-carotene and waist circumference [7]. Conversely, serum retinol level (positively associated with lutein and zeaxanthin, lycopene and α-tocopherol) was positively associated with the waist-hip ratio.

Recent clinical trials on carotenoid efficacy in MetS are scarce. Silveira *et al.* [8] reported that a daily intake of 750 ml of red orange juice during 8 weeks in overweight volunteers improves diastolic blood pressure (−5%, $P < 0.05$ OU 83–79 mmHg) and the lipid profile by reducing total cholesterol (−7%, $P < 0.05$ OU 217–202 mg/dl) and LDL-cholesterol (−10.6%, $P < 0.05$ OU 121–126 mg/dl). They also report the reduction of C-reactive protein levels (−29%, $P < 0.05$ OU 0.38–0.25 mg/dl) suggesting decreased inflammatory status and increased serum antioxidant capacity. Red orange juice is a source of provit A carotenoids (β-cryptoxanthin and β-carotene) and of other antioxidant molecules, such as vit C and polyphenols, which could contribute to improve metabolic parameters, as reviewed by Amiot *et al.* [9]. Tabeshpour *et al.* [10] reviewed clinical studies on the benefits of avocado, which is a source of carotenoids (lutein), mono and polyunsaturated fatty acids (oleic, linoleic and linolenic acids), minerals (iron, potassium and magnesium), polyphenols and phytosterols. All these micronutrients could contribute to the observed improvement of the anthropometric and lipid parameters.

To better understand the possible mechanisms of actions of carotenoids, experiments have been performed in cells or animal studies. In mice supplemented with dry tomato peels (DTP) (containing either 46 or 84 mg of lycopene per kg of food vs. placebo) to test lycopene antioxidant and anti-inflammatory activities, plasma lycopene levels increased with 10.9 ± 2.8 μg/l and 26.0 ± 6.9 μg/l after low and high DTP supplementation, respectively, against nondetectable amounts in control mice, whereas plasma lipid peroxidation, insulin resistance and glucose intolerance decreased [11]. These results are in agreement with previous in-vitro and animal experiments showing that carotenoids have antioxidant properties, by quenching singlet oxygen

species and scavenging free radicals, and counteract inflammatory processes, by decreasing cytokine and chemokine expression via the nuclear factor-κB signaling pathway [12].

VITAMIN D

Vit D is a fat-soluble vit mostly known for its role in calcium metabolism. However, it is also actively involved in several metabolic pathways, especially in the cardiovascular system and insulin resistance. Despite vit D crucial role, it is estimated that 30–50% of the worldwide population has vit D deficiency. According to the US Endocrine Society guidelines, vit D deficiency is defined as a circulating 25-hydroxyvit-D (25(OH)D) level less than 20 ng/ml (50 nmol/l). The latest vit D guidelines recommend a target 25(OH)D concentration of 30 ng/ml (75 nmol/l) to ensure vit D pleiotropic effects [13▪].

Several cross-sectional studies have shown an inverse relationship between serum 25(OH)D levels and MetS or one of the five cardiovascular risk factors associated with MetS [14–18]. In the cross-sectional study by Vigna *et al.* [14] on 385 Italian adults with a BMI more than 25 kg/m^2, the overall MetS prevalence was 39.48% and serum 25(OH)D was inversely associated with BMI and the insulin resistance index (HOMA-IR). An Australian study investigated the association between 25(OH)D serum levels and all MetS-associated cardiovascular risk factors (adiposity, glucose intolerance, insulin resistance and blood pressure) in 111 healthy non-diabetic adults with obesity. Univariate analysis found an association between 25(OH)D serum level and body fat-mass ($r = -0.27$; $P = 0.005$), as well as 2-h glucose level at the end of an oral glucose tolerance test (OGTT) ($r = -0.21$; $P = 0.03$), pulse pressure ($r = 0.26$; $P = 0.006$) and insulin sensitivity ($r = 0.20$, $P = 0.04$). However, after adjustment for age, sex and body fat percentage, vit D serum level remained associated only with fasting glucose and pulse pressure, suggesting that associations between vit D and cardiometabolic risk factors among healthy individuals are largely mediated by adiposity [15]. Similarly, a health survey on 1790 Japanese workers with vit D deficiency (40.8%) or insufficiency (51.4%) and MetS (12.2%) showed a stronger inverse association between serum 25(OH)D level and MetS among individuals with overweight/obesity than among those with normal weight. Interestingly, in the fully adjusted model (for age, sex, smoking, alcohol drinking, physical activity, calcium intake and BMI), the odds of having any of the five MetS components were lower in the vit D sufficient than in the vit D-deficient group (by 23% for high fasting plasma glucose, by 13% for high triglycerides and low HDL-cholesterol, by 48% for high blood pressure and by 8% for high waist circumference); however, none of these associations was statistically significant [16]. Another cross-sectional study on 1205 Qatari individuals reported an overall MetS prevalence of 28%. In this population, 64% had vit D deficiency, and 25(OH)D level was 8% lower in participants with MetS. Multivariate linear regression analyses found a significant positive association between vit D deficiency and waist circumference, HDL and high triglyceride level. Furthermore, elevated blood pressure was slightly and inversely associated with 25(OH)D level, particularly among participants with vit D deficiency [17]. A large Korean survey evaluated 180 918 individuals with an obesity prevalence of 39.4% [18]. In men, after multiple adjustments, individual in the third and the highest quartiles for serum 25(OH)D level had the lowest odds ratio (OR) values for MetS (0.92, 95% CI: 0.87–0.97; and 0.81, 95% CI: 0.76–0.86, respectively) compared with those in the lowest quartile (probability value for the linear trend < 0.001). Similarly, vit D serum level was inversely associated with the OR values for MetS and insulin resistance in both men and women. The authors concluded that maintaining 25(OH)D above a certain level in Korean population ($\geq$21.4 and $\geq$17.2 ng/ml in men and women, respectively) may have a protective effect against metabolic diseases, including MetS and insulin resistance.

To assess the effects of vit D supplementation in individuals with metabolic diseases, Mousa *et al.* [19] carried out a double-blind, randomized, placebo-controlled trial in which 65 individuals with BMI classified as overweight or obesity ($\geq$25 and $\geq$30 kg/m^2, respectively) and vit D deficiency received either a bolus oral dose of 100 000 IU followed by 4000 IU/day of cholecalciferol, or a matching placebo for 16 weeks. The study was completed by 54 participants. As expected, vit D serum level increased in the vit D supplementation compared with the placebo group. However, insulin sensitivity or first-phase insulin secretion did not differ between groups and this remained unchanged after various adjustments. A randomized control trial by Yin *et al.* [20] included 126 individuals with MetS and vit D deficiency (serum level < 20 ng/ml) who were categorized as obese or nonobese, using a BMI cutoff of 28 kg/m^2. At baseline, the obese group had significantly lower serum vit D ($P < 0.05$), fasting plasma insulin and HOMA-IR. After the 1-year intervention (700 IU/day of vit D, or placebo), MetS risk factors did not improve in treated participants, despite the significant increase in serum vit D level

in both the obese (from 11.4 to 26.8 ng/ml, $P < 0.05$) and nonobese groups (from 17.4 to 38.7 ng/ml, $P < 0.05$). A meta-analysis of 10 randomized controlled trials investigated the effect of vit D over periods ranging from 2 months to 7 years on insulin resistance and glycemic control in individuals displaying a prediabetes. No measurable improvement in insulin resistance and 2-h plasma glucose was found after systematic exposure to vit D. However, vit D supplementation significantly reduced fasting plasma glucose and HbA1c levels [21▪]. Finally, another randomized placebo-controlled trial enrolled 96 healthy Japanese individuals (BMI = 22.1 kg/m^2 ± 3.0) who received vit D supplementation (420 IU/day vit D_3) or a placebo; 81 individuals completed the 1-year study. At the end, serum vit D was increased from 13.2 to 24.4 ng/ml ($P < 0.01$) and parathyroid hormone (PTH) level was significantly reduced in the treated group; of interest, fasting glucose concentration decreased by 3.0 mg/dl and HOMA-IR from 1.17 to 0.84 ($P < 0.01$) in the treated group [22].

Different mechanisms have been proposed to explain the link between low serum 25(OH)D levels and MetS risk factors. Specifically, serum vit D concentration is inversely associated with the renin–angiotensin–aldosterone system activity and vit D improves endothelial function and prevents secondary hyperparathyroidism. In addition, high PTH levels are commonly observed in vit D deficiency and are associated with myocardial hypertrophy and high blood pressure levels [23▪▪]. Lower vit D levels in individuals with obesity could result from insufficient exposure to sunlight, too low vit D intake, decreased vit D intestinal absorption and/or vit D adipose tissue sequestration due to the presence of vit D receptors in adipocytes [23▪▪]. Among potential mechanisms, Fu *et al.* [24▪▪] assessed, in a cohort of 559 young individuals at risk of MetS, whether vit D levels regulated β-trophin. Betatrophin is primarily involved in lipid metabolism through an inhibition of lipoprotein lipase and may also play a role in glucose homeostasis by inducing β-cell proliferation as shown in mice [25]. Fu *et al.* [24▪▪] found that, in the entire population, β-trophin levels were negatively correlated with vit D, and positively correlated with total cholesterol, triglycerides, LDL-cholesterol, HbA1c and adiponectin. Interestingly, in the vit D-deficient group (25(OH)D serum level ≤15 ng/ml), β-trophin level was also positively correlated with high blood pressure, dyslipidemia and hyperglycemia. Conversely, in the vit D group, vit D showed a negative association only with fasting insulin, 2 h insulin-level post-OGTT and insulin resistance.

All these studies suggest that vit D supplementation could potentially be beneficial at least on one of the five cardio-vascular risk factors associated with MetS, with a more pronounced effect in healthy individuals. vit D supplementation may be more advantageous in the early stages of metabolic disease. This suggests that a well-balanced diet with an adequate vit D intake (from fish, mushrooms and enriched oil) could be beneficial for MetS prevention at all ages.

VITAMIN E

Vit E is a fat-soluble vit with antioxidant capacity. The eight isomers (α, β, γ, δ-tocopherol and α, β, γ, δ-tocotrienol) are distinguished by the position and degree of methylation. Nuts, vegetable oils and seeds are among the best sources of α-tocopherol, but green leafy vegetables and fortified cereals also provide substantial amounts.

A cross-sectional study by Godala *et al.* [26] included 182 adults with MetS ($n = 91$) and healthy controls ($n = 91$). Vit E levels were significantly lower in patients with MetS than healthy controls. Moreover, vit E levels were inversely correlated with diastolic blood pressure and positively correlated with HDL-cholesterol in patients with MetS. In contrast, vit E levels were not associated with systolic blood pressure, total cholesterol, LDL or triglycerides. In the NHANES cohort, among the 13 348 adults, sedentary behavior was significantly associated with higher risk of MetS, whereas γ-tocopherol serum levels (but not the level of other vits) were inversely correlated with the number of daily steps. This is a surprising result and it can be hypothesized that the lower γ-tocopherol levels in the active group are an adaptive response to oxidative stress induced by aerobic exercise, such as walking and running [5]. Similar results were reported by Traber *et al.* [27] who found higher plasma γ-tocopherol levels at baseline in individuals with MetS ($n = 10$) than in healthy controls ($n = 10$) (3.70 and 2.27 μmol/l, respectively; $P = 0.004$). In this interventional study, participants coingested nonfat, reduced-fat, whole or soy milk with 15 mg hexadeuterium-labeled RRR-α-tocopherol (d_6-α-T), and their urine excretion of α-tocopherol catabolites [α-carboxyethyl hydroxychromanol (α-CEHC) and α-carboxymethylbutyl hydroxy-chromanol (α-CMBHC)] was monitored during 72 h. It was previously reported that α-CEHC urine concentration is correlated with increasing amounts of dietary and plasma α-tocopherol concentrations. Individuals with MetS excreted significantly less labeled and unlabeled α-tocopherol catabolites and had significantly lower plasma d_6-α-T concentrations. They

also had higher levels of oxidative stress and inflammation biomarkers, suggesting that individuals with MetS need higher vit E amounts than healthy individuals.

Among the mechanisms behind vit E requirement in MetS, a review article reported the central role of peroxisome proliferator-activated receptors α and γ (PPAR-α and PPAR-γ) that are key players in the regulation of insulin sensitivity and lipid metabolism. Therefore, by promoting PPAR expression and activity, vit E may indirectly modulate MetS risk factors [28▪▪].

CONCLUSION

Recent findings suggest that the different fat-soluble micronutrients might contribute to MetS prevention. However, these results are based mainly on cross-sectional studies that do not allow drawing cause–and–effect relationships. Additional prospective studies and clinical trials are needed to demonstrate the protective roles of fat-soluble micronutrients on MetS risk factors. Lutein, which has beneficial effects on vision and eye health, could also have a protective role against MetS. This carotenoid has still no Dietary Reference Intake and further research is needed to determine its adequate daily intake. Vit A and vit E nutritional requirements are relatively easy to reach with a diversified diet. Conversely, this is not the case for vit D mainly because of insufficient sun exposure, which is required for its biosynthesis, and the limited number of foodstuff that provide it (fat fish and dairy products). Supplementation is particularly important for vit D because a large part of the population has a deficit. However, vit excess has been observed with fat-soluble vits because they are stored in adipose tissue and liver. Therefore, caution should be exercised particularly with food supplements containing vit A, because overdose is reached with concentrations that are only three times higher than the Recommended Dietary Allowance. This is particularly dangerous for pregnant women because it can lead to fetal malformations. Moreover, consuming too much vit E also is not insignificant, although it is considered to be an antioxidant. Indeed, it was reported that supplementation of vit E and β-carotene (vit A precursor) given to smokers in doses much higher than the usual doses has oxidizing effects, with an increased risk of developing cancer [29]. Although dietary supplements could be useful in specific situations and during a limited period, the ideal is to have a well-balanced diet. Accordingly, a new meta-analysis showed that a prudent/healthy dietary pattern is a protective factor for MetS [30].

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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