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Biomarkers of the Metabolic Syndrome: Influence of Caloric Intake, Various Food Groups and Vitamins

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Abstract Influences of caloric intake, various food groups and vitamins on the concentration of biomarkers of the metabolic syndrome (MetS) are reviewed. Since food is a complex mixture of caloric compounds and essential non-caloric food components with multiple interactions and varying bioavailability, it is hard to separate or identify the effect of one single component in a total meal or diet on the biomarkers. Literature data should be studied in detail to conclude whether a component is related to a reduction of MetS-related symptoms or whether its influence is merely affecting a biomarker. Moreover the diet contains various biologically active components, which may add some beneficial characteristics. Therefore, conclusions on the effect of a component on the various biomarkers of MetS are sometimes quite contradictory.

Keywords: *biomarkers, metabolic syndrome, food groups, vitamins*

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1. Introduction

Metabolic syndrome (MetS), also called "insulin resistance syndrome" [1], "deadly quartet" [2], or "syndrome X" [3], is characterized by abdominal obesity, hypertriglyceridemia, relatively low high-density lipoprotein (HDL) cholesterol concentration, increased blood pressure, and elevated glucose level [4].

Although the exact aetiology of MetS has not yet been completely elucidated, many cross-sectional or longitudinal studies have shown that MetS is strongly associated with insulin resistance [5], oxidative stress [6], inflammation [7], endothelial dysfunction [8] and risk of cardiovascular diseases [9].

Most research groups use a mixture of biomarkers for MetS [10]. Metabolic overload (high caloric intake) evokes oxidative stress, which can lead to a low-grade of inflammation and result in a cardiovascular risk. Therefore, due to this sequence of actions, dividing the biomarkers of MetS into four groups (dyslipidemias, markers of oxidative stress and inflammation, and cardiometabolic markers) seems quite logic. The biochemical action and clinical significance of these markers is discussed in an extensive review article [11].

Here we intend to review the influences of caloric intake, various food groups and vitamins on the concentration of biomarkers, while influence of biologically active components, with function beyond their nutritional activity, will be discussed in a second paper [12].

Literature is screened up to the end of 2015, by doing a search, using a combination of the various food groups, "biomarkers" and "metabolic syndrome". We have tried to limit ourselves to "metabolic syndrome", but that was not always that obvious, since accurate description was not present and related syndromes exist.

2. Caloric Intake

The increased prevalence of obesity and a parallel rise in MetS incidence, which is related to increased BMI, focused research on caloric reduction to treat MetS. A 2-year treatment program with low-calorie, low-fat diet altered indicators of MetS in obese, nondiabetic patients presenting the syndrome [13].

High-fat, energy-dense, fast-food-style breakfast results in an increase of oxidative stress in MetS [14,15]. However, high caloric breakfast versus a reduced intake at dinner proved to be beneficial and might be a useful alternative for the management of MetS [16].

A hypocaloric diet was not reflected in significant changes of serum cytokines or obesity markers in comparison with baseline values in obese children [17].

Patients with MetS, who also tend to have a greater degree of oxidative stress, demonstrated a less favorable biochemical profile in their blood [14,17].

However, not only the total caloric intake is related to the development of MetS, more specifically total diet and type of diet, with various essential food components, are also important. This is reviewed somewhere else [18].

3. Food Components

3.1. Fat, Fish and ω-3 Fatty Acids

a) Fat

Consumption of fat and certain fatty acids can lead to cardiovascular problems in MetS, via enhanced oxidative stress and subclinical inflammation [19].

A sufficient number of studies suggests that total and saturated fat intake increases the risk of having unfavorable characteristics of the MetS and that higher intake of MUFAs and PUFAs have a beneficial effect in reducing this risk [20,21].

It is clear that dietary fat, both total fat as specific fat types, can effect MetS. Therefore research on plasma fatty acid components can give some indications on the risk of the MetS [22]. An energy-restriction trial proved that reduction of total dietary fat and not calcium or dairy products improved plasma lipid profile [23].

Diets relatively high in unsaturated fatty acids are associated with a low prevalence of coronary heart diseases and type 2 diabetes in MetS patients [24].

Not only total fat intake or type of fatty acids [25], but also the food source had an influence on the incidence of MetS and related biomarkers.

High dietary fat intake and IL-6 were associated with MetS in Korean men [26]. Hydrogenated trans fatty acid intake was positively associated with several metabolic risk factors among Japanese women with relative low intake [27]. Fat intake from vegetables was inversely associated with the risk of hypertriglyceridemia in Korean adults [28].

b) Fish

A systematic review on fish consumption and its possible role in the development and prevalence of metabolic syndrome proved that in four studies (one follow-up and three cross-sectional) an inverse association between fish consumption and MetS was found [29]. The protective role might be related to gender, since men seem to benefit more from the consumption of fish. Fish intake was independently related to lower odds of MetS and its features [30].

Fish oil consumption increased serum adiponectin and NO in women with MetS and resulted in a blood pressure decrease [31], increased values of HDL-cholesterol [32] and decreased triglycerides [33,34]. In general, lipid metabolism is improved [34,35], oxidative stress is blocked and inflammation ameliorated [34].

Another study proved that increased dietary ω-3 PUFAs (via fish oil) and extra virgin olive oil had beneficial effects on lipid metabolism and oxidative stress in patients with MetS [36].

On the other hand, salutary effects of fish oil ω-3 fatty acids on arterial health, inflammation, and MetS could not be observed in small studies [37,38]. Relatively low doses with a small sample size, and a weak dietary compliance [37] or a short period of administration in an overweight, but healthy young adult cohort [38] may be responsible for the lack of significant improvement.

Also the population sampled has to be carefully checked. Pedersen et al. [32] studied normotensive and normolipidemic slightly overweight adolescent boys and effect of fish oil supplementation on markers of MetS.

Sometimes krill oil is used as a source of PUFAs [37], which metabolic effects are similar to those of fish oil, even at lower dose of EPA and DHA [39].

Supplementation of botanical oils and fish oil improved biomarkers associated with MetS. Lipid profiles, inflammation markers, as well as metabolic markers have been measured [40].

Fatty fish intake can be monitored by the highly specific biomarker CMPF (3-carboxy-4-methyl-5-propyl-2-furanpropionic acid) [41].

Fish intake is one of the examples, where various factors may play additional or synergistic roles: the type of fish, the fatty acid composition and the content of ω-3 fatty acids.

c) ω-3 fatty acids

The benefit of increasing unsaturated fatty acids as a substitute for dietary saturated fat is deserving considerable attention for already a relatively long time now [42,43,44]. In a review on the role of ω-3 fatty acids in obesity, metabolic syndrome, and cardiovascular diseases however, it was concluded that more clinical trials are necessary to recommend the most effective dosages and formulas (type of ω-3; EPA/DHA ratio) for specific pathologies [45]. Another review assessed current understanding of the effect of actions of ω-3 fatty acids on multiple risk factors of MetS [46]. Often studies are not only related to a variation in PUFA, but also other beneficial components are included, like fish oil [47], fibers [48] or a Mediterranean diet [49,50].

A combination of fish and ω-3 fatty acids was significantly associated with a lower risk of MetS among men, but not among women [47]. Levels of IL-18 were significantly reduced by Mediterranean-like diet and ω-3 PUFA supplementation [49]. The changes correlated only weakly to triglycerides, fatty acids, and anthropometric measures [49].

Fractalkine, a chemokine associated with atherosclerosis, was reduced after 3 years of dietary intervention and ω-3 PUFA supplementation [51].

3.2. Carbohydrates

a) Total carbohydrate

Diets high in carbohydrates negatively impact the biomarkers of MetS [52] by influencing blood glucose, triglyceride, and HDL-cholesterol levels [53,54]. High-carbohydrate (and low fat) diet did not change ghrelin secretion, but significantly decreased leptin levels and increased adiponectin concentrations in obese children [55] and resulted in improvement of serum cholesterol [56].

Increasing dietary carbohydrate across a range of intakes resulted in higher levels of plasma palmitoleic acid, a biomarker consistently associated with adverse healthy outcome [57].

Consumption of sugar-sweetened beverages was associated with unfavourable biomarker concentrations of the MetS in Taiwanese adolescents [58]. Malik and coworkers [59] therefore argued that intake of this type of beverages should be limited or substituted by homemade fruit juice [60].

Carbohydrate restriction on the other hand improves the features of MetS [61,62,63]. Correction of the dyslipidemias occurred, together with a decrease of inflammatory markers and an increase in adiponectin [58].

b) Fructose

High dietary intake of fructose seemed to be an important causative factor in the development of MetS [64,65,66,67,68]. The level of fructose intake provided by fruits and vegetables is limited and should not be of concern [67].

The influence of fructose consumption on an increase of total triglyceride and lipoprotein distribution was observed already quite long ago [69].

Uric acid, a byproduct of the fructose metabolism, is a key factor in the development of MetS and hypertension [67,69,70,71,72]. Increased uric acid concentration can lead to inhibition of the endothelial function [70].

3.3. Whole Grains, Dietary Fibers and Legumes

a) Whole grains, dietary fibers and legumes

Whole grain intake is associated with a lower prevalence of MetS [73,74,75], largely due to the cereal fiber in combination with high PUFAs [76].

Total dietary fiber (soluble and insoluble) is associated with a protective effect against MetS [77]. Especially fruit fiber has a noticeable effect [78], which is further discussed somewhere else [79].

The consumption of a whole-grain diet lowers LDL-cholesterol and total cholesterol levels, but has no influence on HDL-cholesterol or triglyceride. Whole-grain oat appears to be the most effective whole grain for lowering cholesterol [80]. In combination with whole wheat increased omentin concentration and decreased C-peptide levels and insulin resistance were observed [81].

Plasma alkylresorcinols can be used as a biomarker of whole-grain food consumption [82,83,84,85], although some researchers have remarks [86]. Nevertheless intake of these phenolic lipids of the bran fraction of whole-grain, wheat, rye, and barley revealed an inverse relationship with BMI in older adults [87].

A minimum fiber intake of 25 g/day based on a diet rich in whole grains will probably decrease the risk of MetS [88].

Different mechanisms related to its dietary source, specific chemical structure and physical properties, or fermentability in the gut are reviewed by Galisteo and coworkers [89].

b) Legumes

Dietary legume intake is inversely associated with the risk of having MetS and its related biomarkers as published in various studies in Iran [90-96], even after adjustment for confounding factors [93]. Another study [94] indicated beneficial effects of hypocaloric legumes on metabolic features.

Legume consumption is inversely associated with serum concentrations of adhesion molecules and inflammatory biomarkers among Iranian women [95]. Non-soy legume consumption reduced the hs-CRP concentrations, but did not change the serum level of adiponectin [96].

3.4. Protein

Literature data on influence of protein consumption on MetS and its biomarkers are quite scarce.

Heart-healthy weight-loss dietary patterns that emphasize either animal or plant protein improve MetS markers (LDL-cholesterol and TC) similarly [97]. The reductions in total cholesterol, triacylglycerol, LDL-c, total cholesterol-to-HDL-c ratio, HOMA-IR and the increased HDL-c were not statistically different between a weight-loss diet with either normal protein or high protein content [98].

In a MetS treatment study by combination of physical activity and diet, a lower threshold intake for protein must be set at 1.2 g/kg/day to maintain blood protein homeostasis (albuminemia) [99].

3.5. Alcohol Consumption

The relation of alcohol consumption and MetS, epidemiological evidence for alcohol's putative vascular protective effects and plausible underlying biological mechanisms are reviewed by Fujita and Takei [100].

A meta-analysis of observational studies revealed that "moderate alcohol intake" appears to be associated with a reduced prevalence of MetS [101]. The favorable metabolic effect seems to be restricted to alcohol consumption of less than 20 g/day among women and less than 40 g/day among men [101,102,103,104]. The protective effect of this low to moderate alcohol consumption was more prominent among individuals with stricter adherence to the Mediterranean diet [105]. For others the relationship still remains vague [106].

Some research groups claim that this observation was irrespective of the type of beverage [107], while others pretend to find an association especially with beer and wine consumption [108].

The observed dose-response relation between alcohol consumption and odds ratio for MetS [109,110] was especially registered for liquor drinkers [111].

The protection by low/moderate alcohol amounts could be working via the influence on cardiovascular risk parameters [102,111], others think that this is more effective in preventing fatty liver instead of MetS [113]. The combination of smoking and drinking is associated with higher prevalence of MetS [114].

Other researchers observed an inverse relation between the incidence of MetS and alcohol at all levels of consumption [115]. This effect was more pronounced in men [116].

Biomarkers related to alcohol consumption are serum lipids, waist circumference and fasting insulin [108]. Moderate alcohol intake is associated with higher adiponectin [117].

All alcoholic beverages increased HDL-cholesterol; red wine decreases triglyceride level and blood glucose levels, while excessive liquor consumption resulted in hypertension and central obesity in Chinese men [118]. Moderate wine drinking did not increase serum uric acid concentration [119].

Table 1 summarizes most important effects of food groups on biomarkers of Met S.

Table 1. Effect of various food groups on biomarkers of MetS

Nutrient component	Specification	Risk on MetS	Biomarkers	Ref.
Fat		enhanced	IL-6↑	[26]
	fish	lowered		[29]
	fish oil	inflammation ↓	adiponectin↑	[31]
			HDL-c↑	[32]
			triglycerides↓	[33]
	ω-3 fatty acids	lowered	IL-18↓	[49]
			fractalkine↓	[51]
Carbohydrates	Restriction	lowered	inflammatory markers↓	[58]
			correction of dyslipidemias	[58]
			adiponectin ↑	[55,58]
			leptin ↓	[55]
	fructose	increased	triglycerides	[69]
			uric acid↑	[67,69,70,71,72]
Whole grains	fibers	lowered	correction of lipoprofiles	[80]
			omentin	[81]
	legumes		inflammatory markers ↓	[95]
			cell adhesion molecules ↓	[95]
			hs-CRP	[96]
Proteins	scarce data			[97,98]
Alcohol consumption	various types	contradictory	HDL-cholesterol ↑	[118]
	red wine		triglycerides ↓	[118]
	moderate intake		adiponectin↑	[117]
	moderate intake		no effect on uric acid	[119]

3.6. Vitamins.

3.6.1. Vitamin D

Vitamin D deficiency is a common problem worldwide. Dietary vitamin D was inversely associated with prevalence of MetS.

Several cross-sectional and prospective studies have shown an association between vitamin D deficiency and the increased risk of metabolic syndrome and hypertension [120-138]. Since vitamin D and calcium are quite well interrelated it is sometimes hard to separate these two food components in their influence on MetS [139].

Serum 25-hydroxyvitamin D is independently associated with HDL-cholesterol [140], and determines hsCRP and plasma glucose [125].

Higher serum levels of the vitamin are inversely associated with adiposity, triglycerides and triglyceride/HDL-c ratio [126,141-146]. However, serum concentrations of 25-hydroxyvitamin D do not predict insulin action or secretion [147].

Lee et al. [131] showed an inverse relationship between BMI and serum vitamin D levels.

Randomized controlled trials of vitamin D supplementation addressing aspects of the metabolic syndrome have yielded inconsistent results [148,149,150]. Although some are promising [149], many of them suffer from methodological limitations. Until definitive results from such studies are available, caution should be taken towards the use of vitamin D-supplementation for other than musculoskeletal disorders. Efficacy and safety of different doses have to be evaluated [150,151,152,153].

3.6.2. Vitamin E

Alpha-tocopherol, the major form of vitamin E, is one of the antioxidant vitamins in the human body [154]. Supplementation studies have revealed a significant decrease of biomarkers of oxidative stress and inflammation [154,155,156]. Supplementation of the alpha-form in combination with gamma-tocopherol appears to be superior in this action [156].

Several studies reported that serum vitamin E concentration is lower in patients with MetS than in controls, showing unbalanced serum redox status with decreased lipid antioxidant capacity [157,158,159]. In a study in Taiwan the higher concentrations of vitamin E in subjects with MetS were not significant after normalizing for triglyceride level [158].

In Chinese women with MetS, receiving vitamin E supplements, reduced oxidative stress and improved lipid status was observed [160].

3.6.3. Vitamin C

Literature data on this vitamin and the risk for MetS are scarce and deals most of the time with comparing vitamin C levels in patients already developed MetS with serum levels in healthy controls.

Moreover, other food components and vitamins (e.g. vitamin E) are also considered [159,161].

Vitamin C and E, as natural antioxidants, may prevent MetS by reducing oxidative stress [159,162].

A vegetarian diet, containing more vitamin C, seems to exert beneficial effects on biomarkers of micro-inflammation (CRP, leukocytes, neopterin) in MetS [163].

Patients with symptoms of the MetS are recommended to practice regular exercises, resulting in a decrease in plasma antioxidant level [164]. Therefore a diet rich in vitamin C [165] or vitamin C supplementation [164] is recommended there.

3.6.4. Other Vitamins

Studies show that high vitamin K status is associated with a lower occurence of MetS [166,167]. This occurs probably through an overall more heart-healthy dietary pattern [166].

Decreased folate concentrations may influence susceptibility to MetS [168].

Folate supplementation seems to improve insulin resistance and endothelial dysfunction, along with decreasing homocysteine levels in patients with MetS [169,170]. Homocysteine is a key molecule in a lot of biochemical pathways, but the association between MetS and homocysteine levels are showing conflicting results [8,171,172,173,174]. Frequently MetS patients show elevated homocysteine levels, which are not associated with an increased risk for cardiovascular events. On the other hand there is an increased risk in patients without MetS [8].

Only a few publications could be traced that related the other B group vitamins with MetS [175,176,177,178,179].

A beneficial effect of some of them on the prevention of MetS was published [167], but this could not be found for vitamin B12 [177]. This vitamin is only negatively associated with body mass index. Others [175,178] found no relationship between vitamin B1, B2, B6, B12, and folate on one hand and MetS on the other.

Intake of thiamine (vitamin B1), a coenzyme for various enzymes, in obese individuals was higher than in subjects without MetS [179].

Vitamin A belongs to the group of the carotenoids, which are compounds derived primarily from plants and several have shown to be potent antioxidants. The effects of these biological components will be discussed in another review paper [12].

4. Conclusion

MetS is a concept rather than a diagnosis. It can be defined by a constellation of interconnected physiological, biochemical, clinical, and metabolic factors that directly or indirectly increase the risk of cardiovascular diseases, diabetes type 2, and other mortalities [180].

A plethora of unhealthy body measurements and abnormal laboratory test results are associated with MetS and include atherogenic dyslipidemia, hypertension, glucose intolerance, enhanced oxidative stress, proinflammatory state, and a prothrombotic state [181]. Biomarkers of these processes (biochemical background and clinical significance) are discussed in a previous review [11].

In this review various food groups and essential food components are discussed in their relation with changes in biomarkers.

Since food is a complex mixture of caloric compounds, and essential food components with various interactions and varying bioavailability, it is very difficult to isolate or identify one single component in the total meal or diet. The example of calcium, vitamin D, and dairy products is quite illustrative. Therefore it is very hard to draw definite conclusions.

Literature data should be studied in detail to evaluate whether a food component is related to a lowered or increased risk of MetS development or rather influences a certain biomarker of the syndrome.

In contrast to total caloric intake, the diet type, with various essential food components is more important. However, also the definitions of diet types (e.g. Mediterranean type, Nordic style, Korean) or nutrition pattern (e.g. Western style, “fast food”) are quite confusing and details should be checked quite well.

Moreover, the diet may contain various biological active components, which do add some beneficial characteristics. The Mediterranean diet can be taken as illustrative here.

Also the degree of dietary adherence rather than diet type seems to be of importance on biomarker concentration as was proven by various lifestyle intervention programs.

Fat, type of fat and carbohydrate content are quite well related to MetS and biomarkers. Literature data on influence of protein content are scarce.

For a lot of essential food components conclusions are quite contradictory and can partly be explained by the above mentioned interactions and combinatory effects, and differences in total diet composition.

List of Abbreviations

-CRP: C-reactive protein
-DHA: docosahexaenoic acid (C22:6 n-3)
-EPA: eicosapentaenoic acid
- HOMA-IR: homeostasis model assessment of insulin resistance
-HDL-c: high-density lipoprotein-cholesterol
-IL: interleukin
-LDL-c: low-density lipoprotein-cholesterol
-MetS: metabolic syndrome
-MUFA: monounsaturated fatty acids
-NO: nitric oxide
-PUFA: polyunsaturated fatty acids
-TC: triglycerides

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