Metabolic Syndrome

Chapter 4

Metabolic Syndrome and Dietary Components

***Adryana Cordeiro*[1*]*; Andrea Ramalho*[1]**

Institute of Nutrition Josué de Castro, Federal University of Rio de Janeiro (UFRJ), 21941-590 Rio de Janeiro, RJ, Brazil.

[*]***Correspondence to: Adryana Cordeiro,*** *Institute of Nutrition Josué de Castro, Federal University of Rio de Janeiro (UFRJ), 21941-590 Rio de Janeiro, RJ, Brazil.*

Email: adrynutri@yahoo.com.br

1. Introduction

Metabolic Syndrome (MS) is a silent epidemic that represents a major public health problem worldwide. The syndrome encompasses a set of metabolic disorders such as dyslipidemia, systemic arterial hypertension (SAH) and insulin resistance (IR) which, commonly associated with the accumulation of central fat, make up a predictive set of risk factors for the development of cardiovascular disease (CVD) [1].

MS confers a 5-fold increase in risk of type 2 diabetes mellitus (T2DM), 2-fold increased risk of developing CVD over the next 5 to 10 years, 2-fold to 4-fold increased risk of stroke, 3- to 4-fold increase times the risk of acute myocardial infarct and 2 times the risk of death from another event compared to those without the syndrome [2].

The called "deadly quartet" composed of obesity, glucose intolerance, hypertriglyceridemia and SAH has a multifactorial origin that is not fully understood. However, genetic predisposition and environmental factors assumed leading roles in the establishment and development of MS.

Furthermore, unhealthy diet and sedentary lifestyle can also play a significant role in the development of metabolic disorders and diseases. In particular, the globalization of dietary patterns and increasing levels of sedentary lifestyle play a central role in this context. Establishing healthy eating patterns is a global priority to reduce disease outbreaks [3]. There are many studies that demonstrate the importance of establishing healthy eating patterns for disease prevention [4]. However, knowledge of how these nutrients enhance or promote health

per se is still lacking. First, because there is a range of nutrients and, second, because each one of them can trigger a infinity of effects, at the level of an organ, tissue, cell and even a specific molecule. However, a universal fact is that they all need to be processed into small subunits and metabolized by the mitochondria for energy.

Mitochondria are unique structures in the cell, and proper mitochondrial activity is critical for eukaryotic cell survival. In fact, mitochondrial dysregulation has been described as a trademark underlying many complex diseases, as mitochondrial dysfunction can itself trigger oxidative stress (OS), bioenergetic failure, inflammation, protein accumulation, and cell death [5], common features in metabolic disorders such as MS.

Thus, mitochondrial function is the key for understanding dietary effects on our body and, at the same time, understanding how dietary patterns and nutrients influence mitochondrial function.

In the course of the chapter, we will present recent findings in relation to MS, focusing on its pathophysiology and its relationship with dietary components, mainly in mitochondrial function.

History of Metabolic Syndrome

In 1988, Reaven described Syndrome X as one in which IR and its associated factors (hyperinsulinemia, impaired glucose tolerance, increased triglycerides and decreased high-density lipoprotein [HDL]) were involved in the etiology of T2DM, SAH and disease coronary artery. A few years later, in 1992, central obesity was included as a major component, and the syndrome was renamed Insulin Resistance Syndrome [6]. In 1996, Kaplan named the combination of obesity, T2DM, SAH and dyslipidemia "the deadly quartet" [7]. However, these concepts were expanding, as other abnormalities started to be associated, culminating in the denomination of MS. This term had already been suggested by Chan et al (1996) and, in 1998, its use came to be recommended by the World Health Organization (WHO).

Therefore, this accumulation of multiple cardiovascular risk factors, currently known as MS, was proposed to describe the connection between obesity, IR, SAH, dyslipidemia, T2DM and cardiovascular disease (CVD).

MS then started to represent a complex of factors such as hyperglycemia, SAH, high triglycerides, low serum concentrations of HDL and obesity (particularly central adiposity) related mainly to cardiovascular risk factors. The presence of MS was seen to represent an increase in overall mortality of about 1.5 times and cardiovascular mortality by about 2.5 times [8].

Pathophysiology of Metabolic Syndrome

The pathophysiology proposed for MS is multifactorial and complex, and its mechanisms are still not fully understood. It is believed to involve primarily the dysregulation of metabolic homeostasis. The various proposed mechanisms are related to IR, adipose tissue dysfunction, neurohormonal activation, lifestyle, circadian disruption, microbiota, genetic factors and maternal programming [9,10]. Recently, endothelial dysfunction, chronic OS, systemic inflammation, and atherothrombotic events have also been included as key pathogenic factors [11]. These "current" clinical factors combine with susceptibility to genetic factors and classical pathogenic factors to construct the complex and multifaceted pathophysiology of MS [12].

Visceral adiposity, together with IR prove to be two of the main triggers for most pathways involved in MS. Both of them together seem to be primarily responsible for the beginning, progression and transition from MS to CVD and T2DM. In addition, OS also appears to make an important contribution to CVD progression.

The contribution of visceral adipose tissue (VAT) in the pathogenesis of the syndrome is controversial due to metabolic specificities related to its distribution. A significant body of evidence suggests that IR appears to precede obesity and specifically TAV accumulation, once not all individuals with obesity develop IR [13]. Likewise, although obesity and central fat accumulation are the main risk factors, individuals with a normal or slightly above normal weight in relation to body mass index (BMI) may also have IR. On the other hand, central fat deposition has been recognized as highly metabolically harmful and continuously associated with IR and CVD [14].

Furthermore, visceral adiposity appears to be the main source of free fatty acids (FFA), first for the liver (via the splanchnic circulation) and then for the circulatory system. TAV is also a crucial source of cytokines that actively participate in the induction of metabolic diseases related to the syndrome [15].

Dysfunctional adipose tissue associated with increased TAV results in increased plasma FFA levels and fluxes, which in turn leads to ectopic lipid deposition and lipidic toxicity. Chronic exposure to high circulating levels of FFA plays a crucial role in overall cell dysfunction of the liver, pancreas, and skeletal muscle [16,17].

There is strong evidence that elevated plasma FFA leads to IR by inhibition of glucose transport and/or phosphorylation with a subsequent reduction in rates of glucose oxidation and muscle glycogen synthesis [18,19].

An important point in the pathophysiology of MS is that abdominal obesity correlates with systemic levels of OS biomarkers [20] and defective mitochondrial biogenesis, manifested by impaired mitochondrial dysfunction, which includes alterations in oxidative metabolism, low expression of the mitochondrial gene and reduction of ATP generation. Likewise,

mitochondrial alterations, increased OS and chronic low-grade inflammation contribute to the etiology of SAH [21,22]. Finally, OS is also one of the main triggers for the formation and progression of the atheromatous plaque responsible for cardiovascular events included in MS.

Metabolic Syndrome Classification Criteria

Although the scientific community agrees that obesity and its implications deserve extra attention, there is currently a great deal of discussion about the use of the term MS. Among the controversies are: its diagnostic criteria, whether it represents a syndrome, its importance in clinical practice and whether it actually represents a greater increase in cardiovascular risk factors when compared to its factors alone.

First, there are several definition criteria for MS and there is still no consensus on the best criterion to be used, which even compromises the comparison of studies on the subject. In 1999, the WHO was the first to propose a diagnosis for MS based on laboratory assessments of IR, bringing difficulties to clinical practice [23]. The following year, in 1999, the WHO definition was modified by the European Group for the Study of Insulin Resistance (EGSIR), but remained focused on IR [24]. In 2001, the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII) published its proposal, with more reproducible clinical measures. The proposal aimed to guide therapy for low-density lipoprotein (LDL) to reduce coronary heart disease. In addition to reducing LDL, MS was seen as an additional goal, which could result in a reduction in the risk of heart disease [25]. In 2003, the American Association of Clinical Endocrinologists (AACE) proposed its definition, which was focused on IR, as well as those of WHO and EGSIR [26]. An update to the NCEP/ATPIII occurred in 2005, provided by the American Heart Association (AHA) and National Heart Lung and Blood Institute (NHLBI), lowering the fasting blood glucose threshold as recommended by the American Diabetes Association (ADA), and including patients already undergoing treatment for dyslipidemia or SAH [27]. In 2006, it was the turn of the International Diabetes Federation (IDF), which reduced the cutoff points for waist circumference (WC), with specific ethnic values, and promoted it as a mandatory criterion [28].

The different definitions have some similarities, such as the recognition of obesity, abdominal adiposity, IR, impaired glucose metabolism, SAH and dyslipidemia as components of MS. On the other hand, there are disagreements as to how the components are clinically detected. Furthermore, in some cases, the presence of a specific component is mandatory to meet the definition [29]. In this way, efforts have been made to unify the definition of SM.

In 2009, representatives from the IDF, AHA, National Institutes of Health, International Atherosclerosis Society, World Heart Federation and International Association for the Study

of Obesity came up with a proposal called “Metabolic Harmonization Syndrome”, containing five components. None of them should be mandatory, while three abnormal findings out of five of them qualify a person for SM. All components have defined cutoff points, except for CC, where national or regional cutoff points can be adopted [30].

Among the most used diagnostic criteria are the NCEP/ATPIII and the IDF. What can be extracted from the two criteria is that they are in agreement in relation to risk factors for MS, as they include changes in glucose metabolism, obesity, dyslipidemia and SAH. However, the cut points adopted for some components are not the same recommended by the most recent specific Guidelines.

Metabolic Syndrome: Risk Factors

Several risk factors seem to be involved with the development of MS, such as a positive family history; smoking; increasing age; obesity; low socioeconomic status; ethnicity; postmenopausal status; physical inactivity; dietary patterns (mostly Western); excessive alcohol consumption; low cardiorespiratory fitness; and use of some medications (antiretrovirals, antipsychotic drugs, among others) [31]. Thus, some guidelines draw attention to the contribution of genetic predisposition, inadequate nutrition, and physical inactivity [32,33].

Physical inactivity seems to be related to the Western lifestyle, with increased use of cars, decreased daily steps and longer screen time (television, video games, cell phones, among others), associated with low physical exercise. This sedentary lifestyle, low cardiorespiratory fitness and low muscle strength are related to the increased prevalence of MS [32,34].

With regard to diet, a Western dietary pattern, characterized by high intake of red and processed meat, eggs, refined grains, sugars and sweets, processed foods and saturated fatty acids, is associated with an increased risk of MS [35, 36]. These foods have pro-inflammatory characteristics, increasing the release of inflammatory cytokines that can contribute to IR and lipid changes, conditions often observed in individuals with MS.

Metabolic Syndrome and its relationship with physical exercises

Physical activity and physical exercise contribute to negative energy balance and, consequently, to weight loss, which is usually the therapeutic target in the prevention and treatment of MS. However, the role of physical activity, mainly physical exercise, goes far beyond increasing energy expenditure. With its constant practice, the chronic effect leads to muscle structural changes, stimulates mitochondrial biogenesis, angiogenesis, increases vagal tone and stimulates the secretion of metabolically beneficial hormones and myokines, such as irisin, which contributes to the decrease of muscular IR and reduction of postprandial hepatic

lipogenesis [37]. Furthermore, these modifications lead to an increase in cardiorespiratory fitness, which is associated with an increase in the function of pancreatic β-cells in individuals with MS, and is also a protective factor against CVD ([38]. Thus, improving cardiorespiratory fitness can be a strategy to control MS.

In general, physical activity and exercise should be individualized based on the individual's physical fitness and comorbidities. A minimum daily duration of 30 minutes is recommended, ranging from 30 to 60 minutes, including aerobic exercise or work-related aerobic activities and muscle strengthening. In addition, there must be an improvement in lifestyle habits, including the reduction of passive leisure time, such as watching television, playing video games, using cell phones and computers, among others.

Metabolic Syndrome and its relationship to dietary components

The impact of diet on mitochondrial function has been widely studied due to its role as a cell powerhouse and its involvement in nutrient metabolism. In fact, mitochondria are essential in a maintenance metabolic flexibility, in efficient changes in metabolism depending on environmental demand (feeding/fasting cycles) [39]. In addition, the amount of intake of certain nutrients, such as high fat and/or sugars in the diet, affects mitochondrial function [40]. Vitamins, minerals, fatty acids and amino acids, in addition to bioactive compounds, must be considered in a balanced way in the diet to obtain an optimal function of the cell-mitochondria-metabolism axis.

Furthermore, redox reactions generate reactive oxygen species (ROS). And when there is a reduction in ROS production there can be healthy physiological responses, activating complex transcriptional cascades of stress resistance, cell proliferation and cell differentiation pathways [41]. However, when cells produce excessive ROS they can trigger pathological consequences, promoting cellular compound damage, thus impairing cell proliferation, differentiation and apoptosis, among others [42]. Furthermore, mitochondria can trigger or amplify by their own cell death signals triggered by an alternative source of damage. All these effects can have a profound impact on mitochondrial dysregulation and related diseases such as MS.

Therefore, one of the best options to avoid, delay or minimize the risk factors that contribute to MS is to change lifestyle routines, including a balanced and nutrient-rich diet. Next, we present the nutrients that act positively in minimizing risk factors in the development of MS.

1. Vitamins

Vitamins are essential micronutrients for the proper functioning of metabolism. However,

there are vitamins that cannot be synthesized by the body, or not in sufficient quantities, so they must be obtained through the diet. Vitamins can be classified into water-soluble (vitamins B and C) and fat-soluble (vitamins A, D, E and K). And its biological properties will be discussed below in the context of SM.

1.1. Complex B vitamins

B-complex vitamins comprise a set of molecules found in a wide variety of food groups, such as dairy (B2, B3, B5), eggs (B1, B3, B7, B12), fish and meat (B1, B3, B5, B6, B12) or herbal foods (B1, B5, B6, B9). B-complex vitamins are essential in the Krebs cycle, so deficiencies in some of these vitamins will lead to impaired mitochondrial metabolism, increased levels of mitochondrial ROS production, and decreased total energy production [43].

- Vitamin B1 (thiamine) is a cofactor of several enzymes, such as cytosolic pyruvate dehydrogenase or mitochondrial ketoglutarate dehydrogenase; in vitro models demonstrate that its deficiency is linked to increased ROS formation [44].

- Vitamin B2 (riboflavin) is essential as a prosthetic group for several enzymes that catalyze redox reactions; different studies have shown that its deficiency is associated with loss of mitochondrial complex IV and induced OS [45].

- Vitamin B3 (niacin) is an important cofactor involved in mitochondrial respiration, glycolysis, or lipid oxidation reactions; B3 has also been shown to have important antioxidant activity.

- Vitamin B5 (pantothenic acid) is an important prosthetic group involved in the Krebs Cycle and lipid metabolism; Cell models have also shown an important role in enzymatic activity and in the antioxidant defense system that promotes catalase (CAT), glutathione reductase (GR) and glutathione peroxidase (GPx).

- Vitamin B6 (pyridoxal) has several functions in different metabolic pathways, such as one-carbon reactions, gluconeogenesis or lipid metabolism, among others; it also has an important antioxidant role through its activity in the glutathione pathways.

- Vitamin B7 (biotin) is an important cofactor for some carboxylase enzymes involved in lipid metabolism; reduced levels of B7 have been associated with increased ROS formation and impaired mitochondrial respiration [46].

- Vitamin B9 (folic acid) exerts different effects on biological functions such as nucleotide synthesis or modification of mitochondrial transfer RNA (tRNA), among others; folate contributes to cellular redox states by indirectly preventing EO [47].

- Vitamin B12 (cobalamin) is essential for nucleotide synthesis or succinyl-CoA

generation; its deficiency is related to an indirect increase in ROS levels due to glutathione dysregulation [48].

1.2. Vitamin C

Vitamin C, or ascorbic acid, is found primarily in pepper (and other vegetables) and fruits (mostly in kiwi, guava, and citrus fruits). This molecule is a potent antioxidant that activates sirtuin 1(Sirt1), triggering a signaling cascade that decreases ROS and apoptosis and also acts as an ROS inhibitor. Furthermore, it is also involved in the biosynthesis of carnitine, the key factor in β-oxidation. Thus, vitamin C deficiency can lead to impaired ATP production, oxidation deficiency and ROS formation [49] and therefore mitochondrial dysfunction.

1.3. Vitamin A

Vitamin A or retinol is found mainly in carrots, sweet potatoes or spinach, as well as in beef liver, which concentrates the greatest amounts. This vitamin affects mitochondrial function as it increases levels of mitochondrial transcription factor A (mtTFA), a key transcription factor for mitochondrial function, and plays a key role in glycolytic energy generation. Thus, vitamin A deficiency has been associated with decreased respiration and ATP synthesis [50].

1.4. Vitamin D

The main source of vitamin D is through cutaneous synthesis under the incidence of ultraviolet B sunlight. And the food sources are salmon, sardines and shellfish, egg yolks, milk, liver, cheese and mushrooms.

Many biological functions of vitamin D are mediated by the control of the vitamin D receptor (VDR) in nuclear transcription. The main function of the VDR is to regulate Ca2+ homeostasis through the upregulation of calcium transporters. Furthermore, VDR protects from excessive respiratory activity and limits the production of ROS, controlling the mitochondrial and nuclear transcription of proteins involved in ATP synthesis and in the mitochondrial respiratory chain [51].

1.5. Vitamin E

Vitamin E is found primarily in avocados, leafy vegetables like spinach and broccoli, sunflower seeds, walnuts and olive oil. Vitamin E is the most important antioxidant in cell membranes. It protects the mitochondrial structure and function, maintaining the integrity of the mitochondrial membrane, allowing the recovery of the respiratory function and reducing the oxidation of lipids and proteins. This protective function would be, in part, explained by the inhibition of lipid peroxidation and the increase in CAT, superoxide dismutase (SOD), GR and GPx activity demonstrated in experimental studies with rats that had T2DM.

Action of Vitamins Against MS

The role of vitamins in mitochondrial metabolism and their antioxidant properties suggest that they may play a role in the prevention of MS. In a case-control study it was shown that plasma levels of vitamins A, C, E and D were significantly lower in individuals with MS compared to healthy individuals [52].

Different animal studies have suggested that vitamin A supplementation improves obesity through uncoupling protein 1 (UPC1) mediated thermogenesis and delays the onset of T2DM by increasing mtTFA. Biotin deficiency has been associated with impaired glucose tolerance, hyperglycemia, and decreased glucose oxidation in animal studies [53] and a cross-sectional study showed that high levels of vitamin B12 are protective against MS [54].

Regarding vitamin C, different studies have suggested that ingestion or supplementation decreases the risk of MS and improves the quality of life of individuals with MS [55], especially when combined with regular physical exercise [55,56]. In addition, a cross-sectional study of more than 2,000 individuals demonstrated that vitamin C deficiency was associated with an increased likelihood of MS.

Several epidemiological studies have established a strong association between vitamin D deficiency and SAH, abdominal obesity and dyslipidemia, criteria related to MS [57,58]. In a randomized clinical trial with patients with MS, vitamin E had beneficial effects on cytokines and lipid profile [59]. Furthermore, different studies have found that vitamin E can improve pathological conditions associated with MS, such as hyperglycemia or obesity [59,60].

However, when it comes to vitamins, over-consumption can be just as bad as scarcity. For example, an excess intake of vitamin A (with a tolerable upper intake level for adults of 3000 g/day) promotes OS and mitochondrial death [61] and is associated with an increased likelihood of MS. A high intake of vitamin B3 (niacin) can result in niacin-induced IR, and when vitamins C and E are consumed in excess, they promote pro-oxidant activity rather than antioxidant function [44].

2. Monounsaturated Fatty Acids (MUFAs)

MUFAs are fats with an unsaturation in their carbon chain. Dietary MUFAs can have different origins, therefore, in Western diets, the contribution is made through foods of animal origin, and the main sources of MUFAs are extra virgin olive oil containing oleic acid [62]. Other sources of MUFAs are other vegetable oils and nuts, such as macadamia nuts, hazelnuts or walnuts [63].

2.1. Oleic acid

Some cell model studies have reported that oleic acid may have a positive role in mitochondrial function. An in vitro modeling study of pancreatic cells showed that oleic acid increased antioxidant defense [64]. Furthermore, alternative studies have shown that oleic acid supplementation reduced the generation of ROS and protected mitochondria from OS or apoptosis [65, 66]. Oleic acid has also been reported as an anti-inflammatory modulator through the activation of AMP-activated protein kinase (AMPK) and its activity between different targets such as the inhibition of nuclear factor kB (NF-kB) and, consequently, the decrease in secretion of cytokines such as tumor necrosis factor alpha (TNF-α) [67,68].

In turn, oleic acid also increases fatty acid oxidation through the AMPK response and the interaction with Sirt1 and the peroxisome proliferator-activated receptor gamma 1-alpha PGC-1 coactivator [69], the master gene regulator of mitochondrial remodeling and biogenesis. Finally, oleic acid has been shown to increase the level of carnitine palmitoyl transferase 1 (CPT-1), promoting acid transport to the mitochondria for β-oxidation [70].

Therefore, consumption of oleic acid seems to reduce MS risk factors, such as SAH and LDL-c. It also plays a role in improving insulin sensitivity and the inflammatory response. In addition, it can reduce central obesity and abdominal fat [71]. Other components of olive oil may also play a beneficial role in MS. This is the case of olive pomace, rich in triterpenes, which can reduce postprandial triglyceride-rich lipoproteins [72].

Action of MUFAs against SM

Systematic review and meta-analysis of cohort studies demonstrated the positive effects of oleic acid in decreasing mortality risk (11%) and cardiovascular risk (12%) [73]. Focusing on the main theme of this chapter, MS, dietary MUFAs have shown similar results. In fact, clinical trials have shown a reduction in MS risk factors such as blood pressure or total LDL-c. Furthermore, also an improvement in insulin sensitivity and inflammatory response has been demonstrated using oleic acid in cell models [74] and randomized clinical trials. Finally, a recent systematic review of human intervention studies with oleic acid-enriched diets demonstrated that this intervention can reduce central obesity and abdominal fat [75].

3. Polyunsaturated Fatty Acids (PUFAs)

PUFAs are fats with more than two unsaturations in their carbon chain that can be divided into two main groups. Omega-3 fatty acids (linoleic acid, eicosapentaenoic acid, and docosahexaenoic acid) found primarily in salmon, herring, sardines, tuna, flaxseed, chia seed, and walnuts. In turn, the omega-6 group (linoleic acid, arachidonic acid and docosapentaenoic acid) are found mainly in vegetable oils such as sunflower, soybean, corn and canola.

3.1. Omega-3 vs. Omega 6

Omega-3 PUFAs have been reported to act as mitochondrial protectors as they reduce ROS production and inflammation through AMPK activation. PGC-1 triggers different signaling pathways that promote mitochondrial biogenesis, β-oxidation, glucose utilization, antioxidant detoxification, and activation of uncoupling proteins, which lead to a decrease in lipid accumulation and a reduction in ROS [76]. All of these actions decrease the expression of pro-inflammatory cytokines and attenuate the inflammasome, which is an oligomeric protein complex implicated in the innate immune system, which improves insulin sensitivity [77]. Decreasing the omega-6 / omega-3 balance and the incorporation of omega-3 into mitochondrial membranes increases their viscosity. This situation improves mitochondrial function and prevents cell dysfunction and cell death [78]. However, the unbalanced omega-3/omega-6 ratio at the expense of omega-6 can also lead to adverse consequences, since excess omega-3 can eventually trigger pro-oxidant and pro-inflammatory environments. Thus, maintaining the balance of the omega-3/omega-6 ratio is essential to avoid harmful effects.

Action of PUFAs against SM

It is still controversial whether omega-6 PUFAs have pro-inflammatory action or anti-inflammatory effects, per se [79]. However, an unbalanced omega-6/omega-3 ratio in favor of omega-6 PUFAs is known to be highly pro-thrombotic and pro-inflammatory. The high amounts of omega-6 PUFAs present in Western diets, along with the very low amounts of omega-3 PUFAs, lead to a harmful omega-6/omega-3 ratio that can reach a ratio of 20:1 (rather than of expected 1:1) [80], contributing to atherosclerosis, obesity and T2DM. Furthermore, animal studies have shown that omega-3 improves insulin sensitivity and reduces visceral fat storage [81]. Different randomized clinical trials have proven that omega-3 supplementation produces favorable lipid-lowering effects, reduced pro-inflammatory cytokine production and improved blood glucose [82].

4. Trace Elements

Trace elements are minerals present in small amounts in living tissue. Some of them are nutritionally essential and therefore need to be incorporated through the diet, such as selenium or zinc, and others are considered non-essential (or there is no consistent evidence to consider them essential).

4.1. Selenium and Zinc

Selenium and zinc are mainly present in nuts, mushrooms, fish and meat, with antioxidant and mitochondrial properties. Selenium promotes mitochondrial biogenesis through the stimulation of PGC-1a, while the generation of nuclear redox factor 1 (NRF-1)

plays its antioxidant role by activating the enzymes GPx and GR. Some of these positive effects would be modulated by the impact of selenium on the microRNA (miRNA) profile preventing OS and inflammation [83]. On the other hand, zinc exerts its antioxidant power, promoting the activation of SOD and CAT, inhibiting important pro-oxidant enzymes such as NADPH oxidase and competing with redox-active transition metals such as iron and copper for certain binding sites (cell membranes, proteins), prohibiting them from catalyzing the formation of ROS and initiating lipid peroxidation [84].

Action of trace elements against SM

Some studies have shown that adequate intake of these trace elements is associated with an attenuation of MS risk factors. In vivo and human studies have found that the recommended doses of selenium (1-2 g/kg/day) act as an insulin mimetic, alleviating diabetes [85, 86] and have cardio protective effects (increase antioxidant capacity in plasma and decrease lipid peroxidation and LDL-c. Furthermore, a cross-sectional study including more than 2.600 patients showed that dietary selenium intake was negatively associated with MS.

Regarding zinc, this trace element is involved in different protection mechanisms against obesity, IR, SAH and dyslipidemia, which suggests a potential role in the prevention and treatment of MS. However, current scientific evidence in humans regarding associations between zinc status and the occurrence of MS is still inconsistent [87].

Despite these health and wellness properties of minerals, as with vitamins, an excess of these elements is as bad as a deficiency. Fortunately, the severe impact of vitamins and minerals on human health is only achieved at very high concentrations. For example, doses of selenium 100 times higher than expected had adverse effects than recommended doses, increasing the risk of T2DM and promoting cardiovascular disease [88].

5. Polyphenols

Polyphenols are bioactive compounds with antioxidant properties found mainly in plant foods. According to their molecular structure, polyphenols can be categorized into two main groups: flavonoids (such as catechins) and non-flavonoids, including phenolic acids (such as elegiac acids), stilbenes (such as resveratrol), lignans (such as pinoresinol) and others (in which we find oleuropein and hydroxytyrosol). Many of them show mitochondrial effects and have been reported to modulate MS [89].

5.1. Catechins

Within the flavonoid family, we find catechin molecules, present mainly in green tea (with a minimum total catechin content of 8%), but also in a wide variety of fruits such as blackberries, apricots, black grapes and strawberries. It has been shown that catechins can work

directly as ROS scavengers and metal ion chelators and activate some antioxidant enzymes such as CAT and SOD. In addition, they can also inhibit some pro-oxidant enzymes such as NADPH oxidase and suppress stress-related signaling pathways.

Some in vitro studies have also demonstrated an anti-inflammatory effect of catechins by altering the miRNA profile. Together, these effects contribute to decreased OS and improved mitochondrial function [90].

5.2. Resveratrol

Resveratrol is another antioxidant, found mainly in black grapes. Resveratrol is a mitochondrial protective agent. Activates Sirt1, which triggers different signaling pathways that promote antioxidant and anti-inflammatory effects, and in parallel activates PGC-1, the master regulator of mitochondrial biogenesis. Activation of Sirt1 increases β-oxidation and glucose utilization, promotes mitochondrial biogenesis, antioxidant detoxification and expression of uncoupling proteins [91]. Furthermore, some of the anti-inflammatory effects of resveratrol are triggered by changing miRNA profiles, as demonstrated in cell models and human clinical trials [92].

5.3. Oleuropein, Hydroxytyrosol and Pinoresinol

Olive oil has a high content of polyphenols, such as oleuropein (OL), hydroxytyrosol (HT) and pinoresinol. Olive oil polyphenols are mitochondrial protective agents due to their antioxidant property. Recently, it was discovered that olive oil polyphenols, particularly HT, are able to induce Sirt1 expression.

Furthermore, Sirt1 interaction with nuclear redox factor 2 (NRF2) signaling, responsible for the transcriptional activation of anti-stress target genes, exerts a protective effect against OS. Furthermore, OL and HT can also eliminate ROS and olive oil polyphenols have been shown to activate antioxidant enzymes such as GPx and CAT.

Action of polyphenols against MS

Several studies have proven the beneficial effects of polyphenols in the prevention of MS. Animal studies have shown that green tea catechins lower blood pressure, reduce ROS and have lipid-lowering activities. In addition, catechins have been shown to improve glucose tolerance and decrease IR-related events in animal and human studies [93].

The cardio protective functions have been attributed to resveratrol, thanks to their ability to neutralize inflammation and reduce LDL-c oxidation [93,94].

In humans, a meta-analysis of 20 randomized controlled trials, with a total of 1536 participants who received green tea regularly, showed a slight decrease in systolic blood pressure

and a moderate decrease in LDL-c [95]. Another study of 48 patients with MS demonstrated that dietary doses of blueberries significantly lowered blood pressure.

Regarding resveratrol, a meta-analysis including 16 studies, 10 human-based and 6 in vivo studies, showed that resveratrol intake significantly reduced body weight, waist circumference, triglycerides and glucose level [96]. In addition, a meta-analysis including 28 randomized controlled trials also documented an improvement in obesity measures with resveratrol supplementation [97].

6. Lycopene with Oleic Acid

Lycopene is a carotenoid found primarily in tomatoes, but also found in other fruits such as watermelon, papaya or red grapefruit. The lycopene content increases during the different stages of fruit ripening, therefore, the highest lycopene content is found in ripe tomatoes [98].

However, lycopene undergoes photo-oxidation and degradation with light, which produces a decrease in bioavailability. Incorporating lycopene into an oil phase overcomes photo-oxidation. An interesting option is the association of lycopene with olive oil, which prevents the degradation of lycopene and enriches its healthy properties with oleic acid, a monounsaturated fatty acid with antioxidant properties, as mentioned earlier [99].

Action of lycopene action against MS

Based on the potent antioxidant and lipid-lowering properties of lycopene, different studies have evaluated it as a beneficial nutrient for the prevention and treatment of MS. As lycopene is a powerful antioxidant and anti-inflammatory molecule, it acts as a scavenger of ROS and nitrogen species [100], decreases DNA damage, and modulates SOD and GPx production [101,102]. Regarding its anti-inflammatory effects, lycopene also reduces apoptosis as the expression of inflammatory cytokines, exerts lipid-lowering properties through the induction of Sirt1 activity.

Based on experimental and human studies it has been shown that lycopene reduces blood pressure [103], atherosclerotic burden [104] and improves the antioxidant capacity of the blood, in addition to playing a role anti-obesity [105], improves insulin sensitivity, reduces hyperglycemia [106] and lipid profile [107]. In addition, a retrospective study of 2.500 patients with MS showed that higher serum levels of lycopene are associated with a reduced risk of death [108].

Final Considerations

The prevention and treatment of MS should focus on changing the individual's lifestyle. The early adoption of a lifestyle related to health maintenance, including physical activity

and adequate nutrition, is a basic component for the prevention of MS. And, although there are pharmacological and surgical treatments for MS components, such as SAH, T2DM, dyslipidemia and obesity, these do not modify the underlying causes. Thus, some authors claim that the most effective treatments are the adoption of physical exercise and diet changes [109].

Different types, volumes and intensities of physical exercises can be used in these cases. As well as different dietary patterns, foods and nutrients can have positive effects in the prevention and treatment of MS. Another important factor is the control of body weight, related to both MS and obesity.

The nutrients and bioactive compounds reviewed above are just one example of the benefits and impact of some dietary patterns to prevent the onset and development of MS and its associated complications. They exert a huge healthy actions, some of them through the modulation of mitochondrial functions. All this evidence confirms that a balanced diet represents a valuable therapeutic strategy to improve overall metabolic status.

For this, eating habits must focus on the quality and quantity of what you eat. It is not the ingestion of any of these isolated compounds on their own, such as dietary supplements, but the synergistic action of all of them in foods and meals that makes the difference. This means a predominance of vegetables, fruits and fish, typical of the Mediterranean diet. Studies increasingly prove that a healthy eating pattern is a protective factor for MS [110].

Likewise, the excess of most of them on a diet is as bad as their absence. This is the case with the antioxidant paradox, since most antioxidants, at the threshold, become pro-oxidant compounds. Balance is truly the key to getting healthy effects within a diet.

However, several additional factors must be considered to achieve a healthy lifestyle in order to minimize elements that have a negative effect on health, and particularly on MS, such as tobacco, alcohol consumption or physical inactivity [111].

7. References

1. Gurka MJ, Guo Y, Filipp SL et al. Metabolic syndrome severity is significantly associated with future coronary heart disease in Type 2 diabetes. Cardiovasc Diabetol 2018; 17: 17.

2. Lopez-Candales A, Hernández Burgos PM, Hernandez-Suarez DF et al. Linking chronic inflammation with cardiovascular disease: From normal aging to the metabolic syndrome. J Nat Sci 2017; 3: e341.

3. Imamura, F.; Micha, R.; Khatibzadeh, S.; Fahimi, S.; Shi, P.; Powles, J.; Moza_arian, D. Dietary quality among men and women in 187 countries in 1990 and 2010: A systematic assessment. Lancet Glob. Heal. 2015, 3, e132–e142.

4. Cena, H.; Calder, P.C. Defining a healthy diet: Evidence for the role of contemporary dietary patterns in health and disease. Nutrients 2020, 12, 334.

5. Bullon, P.; Marin-Aguilar, F.; Roman-Malo, L. AMPK/Mitochondria in metabolic diseases. EXS 2016, 107,129–152.

6. Zafar U, Khaliq S, Ahmad HU, Manzoor S, Lone KP. Metabolic syndrome: an update on diagnostic criteria, pathogenesis, and genetic links. Hormones (Athens). setembro de 2018;17(3):299–313.

7. Nilsson PM, Tuomilehto J, Rydén L. The metabolic syndrome – What is it and how should it be managed? Eur J Prev Cardiolog. 1o de dezembro de 2019;26(2_suppl):33–46.

8. Magalhães, H; Magalhães, P; Segundo, L; Bomfim, M. Manual de Prevenção da Síndrome Metabólica. Editora Mais Saúde, Primeira Edição, 2018, p (38).

9. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. Ther Adv Cardiovasc Dis. agosto de 2017;11(8):215–25.

10. Xu H, Li X, Adams H, Kubena K, Guo S. Etiology of Metabolic Syndrome and Dietary Intervention. Int J Mol Sci [Internet]. 31 de dezembro de 2018 [citado 7 de fevereiro de 2021];20(1).

11. Campbell, A.P. DASH eating plan: An eating pattern for diabetes management. Diabetes Spectr. 2017, 30, 76–81.

12. Jayarathne, S.; Koboziev, I.; Park, O.H.; Oldewage-Theron, W.; Shen, C.L.; Moustaid-Moussa, N. Anti-inflammatory and anti-obesity properties of food bioactive components: E_ects on adipose tissue. Prev. Nutr. Food Sci. 2017, 22, 251–262.

13. Cardinali, D.P.; Vigo, D.E. Melatonin, mitochondria, and the metabolic syndrome. Cell. Mol. Life Sci. 2017, 74, 3941–3954.

14. Zhao, R.Z.; Jiang, S.; Zhang, L.; Yu, Z. Bin Mitochondrial electron transport chain, ROS generation and uncoupling (Review). Int. J. Mol. Med. 2019, 44, 3–15.

15. Monteith, G.R.; Prevarskaya, N.; Roberts-Thomson, S.J. The calcium-cancer signalling nexus. Nat. Rev. Cancer. 2017, 17, 367–380.

16. Meyer, J.N.; Leuthner, T.C.; Luz, A.L. Mitochondrial fusion, fission, and mitochondrial toxicity. Toxicology 2017, 391, 42–53.

17. Gómez-Valadés, A.G.; Gonzalez-Franquesa, A.; Gama-Perez, P.; Claret, M.; Garcia-Roves, P.M. Emerging concepts in diabetes: Mitochondrial dynamics and glucose homeostasis. Curr. Diabetes Rev. 2017, 13.

18. Sliter, D.A.; Martinez, J.; Hao, L.; Chen, X.; Sun, N.; Fischer, T.D.; Burman, J.L.; Li, Y.; Zhang, Z.; Narendra, D.P.; et al. Parkin and PINK1 mitigate STING-induced inflammation. Nature 2018, 561, 258–262.

19. Kerr, J.S.; Adriaanse, B.A.; Greig, N.H.; Mattson, M.P.; Cader, M.Z.; Bohr, V.A.; Fang, E.F. Mitophagy and Alzheimer's Disease: Cellular and Molecular Mechanisms. Trends Neurosci. 2017, 40, 151–166.

20. Fujita, K.; Nishizawa, H.; Funahashi, T.; Shimomura, I.; Shimabukuro, M. Systemic Oxidative Stress is Associated With Visceral Fat Accumulation and the Metabolic Syndrome. Circ. J. 2006, 70, 1437–1442.

21. Mansego, M.L.; Solar, G.D.M.; Alonso, M.P.; Martínez, F.; Sáez, G.T.; Escudero, J.C.M.; Redón, J.; Chaves, F.J. Polymorphisms of antioxidant enzymes, blood pressure and risk of hypertension. J. Hypertens. 2011, 29, 492–500.

22. Togliatto, G.; Lombardo, G.; Brizzi, M.F. The future challenge of reactive oxygen species (ROS) in hypertension: From bench to bed side. Int. J. Mol. Sci. 2017, 18, 1988.

23. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. julho de 1998;15(7):539–53.

24. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med. maio de 1999;16(5):442–3.

25. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 16 de maio de 2001;285(19):2486–97.

26. Einhorn D. American College of Endocrinology Position Statement on the Insulin Resistance Syndrome. Endocrine Practice. 1o de setembro de 2003;9:5–21.

27. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 25 de outubro de 2005;112(17):2735–52.

28. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med. maio de 2006;23(5):469–80.

29. Samson SL, Garber AJ. Metabolic syndrome. Endocrinol Metab Clin North Am. março de 2014;43(1):1–23.

30. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 20 de outubro de 2009;120(16):1640–5.

31. McCracken E, Monaghan M, Sreenivasan S. Pathophysiology of the metabolic syndrome. Clin Dermatol. fevereiro de 2018;36(1):14–20.

32. I Diretriz Brasileira de Diagnóstico e Tratamento da Síndrome Metabólica. Arq Bras Cardiol. abril de 2005; 84:3–28.

33. De Sousa SM, Norman RJ. Metabolic syndrome, diet and exercise. Best Pract Res Clin Obstret Gynaecol. 2016. Nov:37-140-151.

34. Myers J, Kokkinos P, Nyelin E. Physical Activity, Cardiorespiratory Fitness, and the Metabolic Syndrome.Nutrients. 2019 Jul 19;11(7):1652.

35. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. Curr Hypertens Rep [Internet]. 2018 [citado 17 de fevereiro de 2021];20(2). Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5866840/.

36. Pérez-Martínez P, Mikhailidis DP, Athyros VG, Bullo M, Couture P, Covas MI, et al. Lifestyle recommendations for the prevention and management of metabolic syndrome: an international panel recommendation. Nutr Rev. maio de 2017;75(5):307–26.

37. Fabiani R, Naldini G, Chiavarini M. Dietary Patterns and Metabolic Syndrome in Adult Subjects: A Systematic Review and Meta-Analysis. Nutrients. 2 de setembro de 2019;11(9):2056.

38. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. Curr Hypertens Rep [Internet]. 2018 [citado 17 de fevereiro de 2021];20(2). Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5866840/

39. Xu H, Li X, Adams H, Kubena K, Guo S. Etiology of Metabolic Syndrome and Dietary Intervention. Int J Mol Sci [Internet]. 31 de dezembro de 2018 [citado 7 de fevereiro de 2021];20(1). Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6337367/.

40. Smith, R.L.; Soeters, M.R.; Wüst, R.C.I.; Houtkooper, R.H. Metabolic flexibility as an adaptation to energy resources and requirements in health and disease. Endocr. Rev. 2018, 39, 489–517.

41. Leckey, J.J.; Ho_man, N.J.; Parr, E.B.; Devlin, B.L.; Trewin, A.J.; Stepto, N.K.; Morton, J.P.; Burke, L.M.; Hawley, J.A. High dietary fat intake increases fat oxidation and reduces skeletal muscle mitochondrial respiration in trained humans. FASEB J. 2018, 32, 2979–2991.

42. Ristow, M. Unraveling the truth about antioxidants. Nat. Med. 2014, 20, 709–711.

43. Hamanaka, R.B.; Chandel, N.S. Mitochondrial reactive oxygen species regulate cellular signaling and dictate biological outcomes. Trends Biochem. Sci. 2010, 35, 505–513.

44. Wesselink, E.; Koekkoek, W.A.C.; Grefte, S.; Witkamp, R.F.; van Zanten, A.R.H. Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence. Clin. Nutr. 2019, 38, 982–995.

45. Manzetti, S.; Zhang, J.; van der Spoel, D. Thiamin function, metabolism, uptake, and transport. Biochemistry 2014, 53, 821–835.

46. Ashoori, M.; Saedisomeolia, A. Riboflavin (vitamin B2) and oxidative stress: A review. Br. J. Nutr. 2014, 111, 1985–1991.

47. Moretti, R.; Peinkhofer, C. B Vitamins and fatty acids: What do they share with small vessel disease-Related dementia? Int. J. Mol. Sci. 2019, 20, 5797.

48. Fan, J.; Ye, J.; Kamphorst, J.J.; Shlomi, T.; Thompson, C.B.; Rabinowitz, J.D. Quantitative flux analysis reveals folate-dependent NADPH production. Nature 2014, 510, 298–302.

49. Pastore, A.; Martinelli, D.; Piemonte, F.; Tozzi, G.; Boenzi, S.; Di Giovamberardino, G.; Petrillo, S.; Bertini, E.; Dionisi-Vici, C. Glutathione metabolism in cobalamin deficiency type C (cblC). J. Inherit. Metab. Dis. 2014, 37, 125–129.

50. Peng,W.; Xu, S.; Zhang, J.; Zhang, Y. Vitamin C attenuates sodium fluoride-induced mitochondrial oxidative stress and apoptosis via Sirt1-SOD2 pathway in F9 cells. Biol. Trace Elem. Res. 2019, 191, 189–198.

51. Hammerling, U. Vitamin A as PKC co-factor and regulator of mitochondrial energetics. Subcell. Biochem. 2016, 81, 201–230.

52. Ricca, C.; Aillon, A.; Bergandi, L.; Alotto, D.; Castagnoli, C.; Silvagno, F. Vitamin D receptor is necessary for mitochondrial function and cell health. Int. J. Mol. Sci. 2018, 19, 1672.

53. Godala, M.; Materek-Kusmierkiewicz, I.; Moczulski, D.; Rutkowski, M.; Szatko, F.; Gaszyñska, E.; Tokarski, S.; Kowalski, J. The risk of plasma Vitamin A, C, E and D deficiency in patients with metabolic syndrome: A case-control study. Adv. Clin. Exp. Med. 2017, 26, 581–586.

54. Kanagasabai, T.; Alkhalaqi, K.; Churilla, J.R.; Ardern, C.I. The Association between metabolic syndrome and serum concentrations of micronutrients, inflammation, and oxidative stress outside of the clinical reference ranges: A cross-sectional study. Metab. Syndr. Relat. Disord. 2019, 17, 29–36.

55. Wei, J.; Zeng, C.; Gong, Q.Y.; Li, X.X.; Lei, G.H.; Yang, T.B. Associations between dietary antioxidant intake and metabolic syndrome. PLoS ONE 2015, 10, e0130876.

56. Farag, H.A.M.; Hosseinzadeh-Attar, M.J.; Muhammad, B.A.; Esmaillzadeh, A.; Bilbeisi, A.H. El Comparative_ects of vitamin D and vitamin C supplementations with and without endurance physical activity on metabolic syndrome patients: A randomized controlled trial. Diabetol. Metab. Syndr. 2018, 10, 80.

57. Prasad, P.; Kochhar, A. Interplay of Vitamin D and metabolic syndrome: A review. Diabetes Metab. Syndr. Clin. Res. Rev. 2016, 10, 105–112.

58. Wimalawansa, S.J. Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. J. Steroid Biochem. Mol. Biol. 2018, 175, 177–189.

59. Wong, S.K.; Chin, K.Y.; Suhaimi, F.H.; Ahmad, F.; Ima-Nirwana, S. Vitamin E as a potential interventional treatment for metabolic syndrome: Evidence from animal and human studies. Front. Pharmacol. 2017, 8, 444.

60. Goncalves, A.; Amiot, M.J. Fat-soluble micronutrients and metabolic syndrome. Curr. Opin. Clin. Nutr. Metab. Care

2017, 20, 492–497.

61. De Oliveira, M.R. Vitamin A and retinoids as mitochondrial toxicants. Oxid. Med. Cell. Longev. 2015, 2015, 140267.

62. Linseisen, J.; Welch, A.A.; Ocké, M.; Amiano, P.; Agnoli, C.; Ferrari, P.; Sonestedt, E.; Chajès, V.; Bueno-de-Mesquita, H.B.; Kaaks, R.; et al. Dietary fat intake in the european prospective investigation into cancer and nutrition: Results from the 24-h dietary recalls. Eur. J. Clin. Nutr. 2009, 63, S61–S80.

63. Gillingham, L.G.; Harris-Janz, S.; Jones, P.J.H. Dietary monounsaturated fatty acids are protective against metabolic syndrome and cardiovascular disease risk factors. Lipids 2011, 46, 209–228.

64. Sargsyan, E.; Artemenko, K.; Manukyan, L.; Bergquist, J.; Bergsten, P. Oleate protects beta-cells from the toxic e_ect of palmitate by activating pro-survival pathways of the ER stress response. Biochim. Biophys. Acta Mol. Cell Biol. Lipids 2016, 1861, 1151–1160.

65. Yuzefovych, L.; Wilson, G.; Rachek, L. Di_erent e_ects of oleate vs. palmitate on mitochondrial function apoptosis, and insulin signaling in L6 skeletal muscle cells: Role of oxidative stress. Am. J. Physiol. Endocrinol. Metab. 2010, 299.

66. Nakamura, S.; Takamura, T.; Matsuzawa-Nagata, N.; Takayama, H.; Misu, H.; Noda, H.; Nabemoto, S.; Kurita, S.; Ota, T.; Ando, H.; et al. Palmitate induces insulin resistance in H4IIEC3 hepatocytes through reactive oxygen species produced by mitochondria. J. Biol. Chem. 2009, 284, 14809–14818.

67. Sacks, D.; Baxter, B.; Campbell, B.C.V.; Carpenter, J.S.; Cognard, C.; Dippel, D.; Eesa, M.; Fischer, U.; Hausegger, K.; Hirsch, J.A.; et al. Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke. Int. J. Stroke 2018, 13, 612–632.

68. Castellano, J.M.; Garcia-Rodriguez, S.; Espinosa, J.M.; Millan-Linares, M.C.; Rada, M.; Perona, J.S. Oleanolic acid exerts a neuroprotective e_ect against microglial cell activation by modulating cytokine release and antioxidant defense systems. Biomolecules 2019, 9, 683.

69. Lim, J.H.; Gerhart-Hines, Z.; Dominy, J.E.; Lee, Y.; Kim, S.; Tabata, M.; Xiang, Y.K.; Puigserver, P. Oleic acid stimulates complete oxidation of fatty acids through protein kinase A-dependent activation of SIRT1-PGC1_ complex. J. Biol. Chem. 2013, 288, 7117–7126.

70. Henique, C.; Mansouri, A.; Fumey, G.; Lenoir, V.; Girard, J.; Bouillaud, F.; Prip-Buus, C.; Cohen, I. Increased mitochondrial fatty acid oxidation is su_cient to protect skeletal muscle cells from palmitate-induced apoptosis. J. Biol. Chem. 2010, 285, 36818–36827.

71. García-García FJ, Monistrol-Mula A, Cardellach F, Garrabou G. Nutrition, Bioenergetics, and Metabolic Syndrome. Nutrients. 11 de setembro de 2020;12(9):2785.

72. Pérez-Martínez P, Mikhailidis DP, Athyros VG, Bullo M, Couture P, Covas MI, et al. Lifestyle recommendations for the prevention and management of metabolic syndrome: an international panel recommendation. Nutr Rev. maio de 2017;75(5):307–26.

73. Schwingshackl, L.; Ho_mann, G. Monounsaturated fatty acids, olive oil and health status: A systematic review and meta-analysis of cohort studies. Lipids Health Dis. 2014, 13, 154.

74. Perdomo, L.; Beneit, N.; Otero, Y.F.; Escribano, Ó.; Díaz-Castroverde, S.; Gómez-Hernández, A.; Benito, M. Protective role of oleic acid against cardiovascular insulin resistance and in the early and late celular atherosclerotic process. Cardiovasc. Diabetol. 2015, 14.

75. Tutunchi, H.; Ostadrahimi, A.; Saghafi-Asl, M. The e_ects of diets enriched in monounsaturated oleic acid on the management and prevention of obesity: A systematic review of human intervention studies. Adv. Nutr. 2020, 11, 864–877.

76. Lorrente-Cabrián, S.; Bustos, M.; Marti, A.; Martinez, J.A.; Moreno-Aliaga, M.J. Eicosapentaenoic acid stimulates

AMP-activated protein kinase and increses visfatin secretion in cultured murine adipocytes. Clin. Sci. 2009, 117, 243–249.

77. Lepretti, M.; Martucciello, S.; Aceves, M.A.B.; Putti, R.; Lionetti, L. Omega-3 fatty acids and insulin resistance: Focus on the regulation of mitochondria and endoplasmic reticulum stress. Nutrients 2018, 10, 350.

78. Yin, J.; Peng, M.; Lin, W. Visualization of mitochondrial viscosity in inflammation, fatty liver, and cancer living mice by a robust fluorescent probe. Anal. Chem. 2019, 91, 8415–8421.

79. Tortosa-Caparrós, E.; Navas-Carrillo, D.; Marín, F.; Orenes-Piñero, E. Anti-inflammatory e_ects of omega 3 and omega 6 polyunsaturated fatty acids in cardiovascular disease and metabolic syndrome. Crit. Rev. Food Sci. Nutr. 2017, 57, 3421–3429.

80. Simopoulos, A.P. An increase in the Omega-6/Omega-3 fatty acid ratio increases the risk for obesity. Nutrients 2016, 8, 128.

81. Lionetti, L.; Mollica, M.P.; Donizzetti, I.; Gifuni, G.; Sica, R.; Pignalosa, A.; Cavaliere, G.; Gaita, M.; De Filippo, C.; Zorzano, A.; et al. High-lard and high-fish-oil diets di_er in their e_ects on function and dynamic behaviour of rat hepatic mitochondria. PLoS ONE 2014, 9, e92753. 143.

82. O'Mahoney, L.L.; Matu, J.; Price, O.J.; Birch, K.M.; Ajjan, R.A.; Farrar, D.; Tapp, R.;West, D.J.; Deighton, K.; Campbell, M.D. Omega-3 polyunsaturated fatty acids favourably modulate cardiometabolic biomarkers in type 2 diabetes: A meta-analysis and meta-regression of randomized controlled trials. Cardiovasc. Diabetol. 2018, 17, 98.

83. Alehagen, U.; Johansson, P.; Aaseth, J.; Alexander, J.; Wågsäter, D. Significant changes in circulating microRNA by dietary supplementation of selenium and coenzyme Q10 in healthy elderly males. A subgroup analysis of a prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens. PLoS ONE 2017, 12, e0174880.

84. Koekkoek, W.A.C.; van Zanten, A.R.H. Antioxidant vitamins and trace elements in critical illness. Nutr. Clin. Pract. 2016, 31, 457–474.

85. Zhou, J.; Huang, K.; Lei, X.G. Selenium and diabetes-Evidence from animal studies. Free Radic. Biol. Med. 2013, 65, 1548–1556.

86. Bahmani, F.; Kia, M.; Soleimani, A.; Mohammadi, A.A.; Asemi, Z. The e_ects of selenium supplementation on biomarkers of inflammation and oxidative stress in patients with diabetic nephropathy: A randomised, double-blind, placebo-controlled trial. Br. J. Nutr. 2016, 116, 1222–1228.

87. Ruz, M.; Carrasco, F.; Rojas, P.; Basfi-fer, K.; Hernández, M.C.; Pérez, A. Nutritional e_ects of zinc on metabolic syndrome and type 2 diabetes: Mechanisms and main findings in human studies. Biol. Trace Elem. Res. 2019, 188, 177–188.

88. Wang, X.; Zhang, W.; Chen, H.; Liao, N.; Wang, Z.; Zhang, X.; Hai, C. High selenium impairs hepatic insulin sensitivity through opposite regulation of ROS. Toxicol. Lett. 2014, 224, 16–23.

89. Chiva-Blanch, G.; Badimon, L. E_ects of polyphenol intake on metabolic syndrome: Current evidences from human trials. Oxid. Med. Cell. Longvity 2017

90. Bernatoniene, J.; Kopustinskiene, D.M. The role of catechins in cellular responses to oxidative stress. Molecules 2018, 23, 965.

91. Diaz-Gerevini, G.T.; Repossi, G.; Dain, A.; Tarres, M.C.; Das, U.N.; Eynard, A.R. Beneficial action of resveratrol: How and why? Nutrition 2016, 32, 174–178.

92. Bigagli, E.; Cinci, L.; Paccosi, S.; Parenti, A.; D'Ambrosio, M.; Luceri, C. Nutritionally relevant concentrations of resveratrol and hydroxytyrosol mitigate oxidative burst of human granulocytes and monocytes and the production of pro-inflammatory mediators in LPS-stimulatedRAW264.7 macrophages. Int. Immunopharmacol. 2017, 43, 147–155.

93. Finicelli, M.; Squillaro, T.; di Cristo, F.; di Salle, A.; Melone, M.A.B.; Galderisi, U.; Peluso, G. Metabolic syndrome, Mediterranean diet, and polyphenols: Evidence and perspectives. J. Cell. Physiol. 2019, 234, 5807–5826.

94. Madreiter-Sokolowski, C.T.; Sokolowski, A.A.; Graier, W.F. Dosis facit sanitatem-Concentration-dependente_ects of resveratrol on mitochondria. Nutrients 2017, 9, 1117.

95. Onakpoya, I.; Spencer, E.; Heneghan, C.; Thompson, M. The e_ect of green tea on blood pressure and lipid profile: A systematic review and meta-analysis of randomized clinical trials. Nutr. Metab. Cardiovasc. Dis. 2014, 24, 823–836.

96. Asgary, S.; Karimi, R.; Momtaz, S.; Naseri, R.; Farzaei, M.H. E_ect of resveratrol on metabolic syndrome components: A systematic review and meta-analysis. Rev. Endocr. Metab. Disord. 2019, 20, 173–186.

97. Mousavi, S.M.; Milajerdi, A.; Sheikhi, A.; Kord-Varkaneh, H.; Feinle-Bisset, C.; Larijani, B.; Esmaillzadeh, A. Resveratrol supplementation significantly influences obesity measures: A systematic review and dose–response meta-analysis of randomized controlled trials. Obes. Rev. 2019, 20, 487–498.

98. Saini, R.K.; Zamany, A.J.; Keum, Y.S. Ripening improves the content of carotenoid, _-tocopherol, and polyunsaturated fatty acids in tomato (Solanum lycopersicum L.) fruits. 3 Biotech 2017, 7, 43.

99. Mishra, S.; Chattopadhyay, A.; Naaz, S.; Ghosh, A.K.; Das, A.R.; Bandyopadhyay, D. Oleic acid ameliorates adrenaline induced dysfunction of rat heart mitochondria by binding with adrenaline: An isothermal titration calorimetry study. Life Sci. 2019, 218, 96–111.

100. Kong, K.W.; Khoo, H.E.; Prasad, K.N.; Ismail, A.; Tan, C.P.; Rajab, N.F. Revealing the power of the natural red pigment lycopene. Molecules 2010, 15, 959–987.

101. Zhao, B.; Ren, B.; Guo, R.; Zhang, W.; Ma, S.; Yao, Y.; Yuan, T.; Liu, Z.; Liu, X. Supplementation of lycopene attenuates oxidative stress induced neuroinflammation and cognitive impairment via Nrf2/NF-B transcriptional pathway. Food Chem. Toxicol. 2017, 109, 505–516.

102. Li, W.; Jiang, B.; Cao, X.; Xie, Y.; Huang, T. Protective e_ect of lycopene on fluoride-induced ameloblasts apoptosis and dental fluorosis through oxidative stress-mediated caspase pathways. Chem. Biol. Interact. 2017, 261, 27–34.

103. Han, G.M.; Liu, P. Higher serum lycopene is associated with reduced prevalence of hypertension in overweight or obese adults. Eur. J. Integr. Med. 2017, 13, 34–40.

104. Chiva-Blanch, G.; Jiménez, C.; Pinyol, M.; Herreras, Z.; Catalán, M.; Martínez-Huélamo, M.; Lamuela-Raventos, R.M.; Sala-Vila, A.; Cofán, M.; Gilabert, R.; et al. 5-CIS-, trans-and total lycopene plasma concentrations inversely relate to atherosclerotic plaque burden in newly diagnosed type 2 diabetes subjects. Nutrients 2020, 12, 1696.

105. Guerendiain, M.; Mayneris-Perxachs, J.; Montes, R.; López-Belmonte, G.; Martín-Matillas, M.; Castellote, A.I.; Martín-Bautista, E.; Martí, A.; Martínez, J.A.; Moreno, L.; et al. Relation between plasma antioxidante vitamin levels, adiposity and cardio-metabolic profile in adolescents: E_ects of a multidisciplinary obesity programme. Clin. Nutr. 2017, 36, 209–217.

106. Zeng, Z.; He, W.; Jia, Z.; Hao, S. Lycopene improves insulin sensitivity through inhibition of STAT3/Srebp-1c-Mediated lipid accumulation and inflammation in mice fed a high-fat diet. Exp. Clin. Endocrinol. Diabetes 2017, 125, 610–617.

107. Zidani, S.; Benakmoum, A.; Ammouche, A.; Benali, Y.; Bouhadef, A.; Abbeddou, S. E_ect of dry tomato peel supplementation on glucose tolerance, insulin resistance, and hepatic markers in mice fed high-saturated-fat/high-cholesterol diets. J. Nutr. Biochem. 2017, 40, 164–171. 216.

108. Han, G.M.; Meza, J.L.; Soliman, G.A.; Islam, K.M.M.;Watanabe-Galloway, S. Higher levels of serum lycopene are associated with reduced mortality in individuals with metabolic syndrome. Nutr. Res. 2016, 36, 402–407.

109. Priest C, Tontonoz P. Inter-organ cross-talk in metabolic syndrome. Nat Metab. dezembro de 2019;1(12):1177–88.

110. Rodríguez-Monforte, M.; Sánchez, E.; Barrio, F.; Costa, B.; Flores-Mateo, G. Metabolic syndrome and dietary patterns: A systematic review and meta-analysis of observational studies. Eur. J. Nutr. 2017, 56, 925–947.

111. Sun, K.; Liu, J.; Ning, G. Active smoking and risk of metabolic syndrome: A meta-analysis of prospective studies. PLoS ONE 2012, 7, e47791