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Chapter 1 : Dietary Strategies: Prevention/Treatment Of Metabolic Syndrome

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 Vascular diseases include cardiovascular and peripheral vascular diseases. For decades, cardiovascular diseases CVD stay the number one mortality worldwide. In more details, coronary heart disease or stroke alone caused around 1 of every 6 deaths or 1 of every 19 deaths in the United States in , respectively [1]. The total direct and indirect cost of CVD remains higher than any other diagnostic groups such as cancer [1]. In contrast to CVD, peripheral vascular diseases suffer lack of attention because most of the affected individuals are asymptomatic. The prevalence of peripheral vascular diseases is increasing which reduces the life quality and exposes the risk of infection and thrombosis. Atherosclerosis serves as the common pathogenesis of peripheral arterial disease and coronary heart disease. Therefore, both types of diseases share the same risk factors. For instance, a recent study demonstrated reduced number of endothelial progenitor cells in patients with CVD [2] and PAD [3]. Patients with vascular diseases are always featured as raised blood pressure, obesity, diabetes, and dyslipidemia, all of which constitute metabolic syndrome. From to , the prevalence of the metabolic syndrome increased from When compared to healthy controls, cardiovascular mortality was 1. Up to date, in vitro and animal studies have consistently illustrated that metabolic disorders disrupt endothelium integrity, promote inflammation and thrombosis, and thus accelerate the progression of vascular diseases [6 â€” 8]. However, in the occurrence of vascular diseases and metabolic disorders, the balance between cell damage and repair is twisted. Because of its fundamental potential in self-renewal and multilineage differentiation capacity, stem cell-related therapy has developed and reformed the manner of remodeling human degenerative diseases, which could be applied for diagnosis, drug screening, and the likelihood for therapy. Among all types of stem cells, mesenchymal stem cells MSCs are one of the most promising ones for translational application. A number of preclinical studies have employed MSC for the treatment of cardiomyopathy, vascular stenosis, and corneal disease [9]. In the special issue, studies from clinical and basic research were selected that presented the current status of vascular diseases and metabolic disorders. Clinical results brought updated findings on Acute Coronary Syndrome as well as peripheral artery disease, aortic aneurysms, and diabetic microvascular complications. We were informed about the effect of stem cell therapy in the treatment of vascular diseases. From the basic research aspect, we got to know more about the physiology of endothelial cells and brown adipocytes.

Chapter 2 : Hypertension in Metabolic Syndrome: Vascular Pathophysiology

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T 2, Dietary Strategies: Metabolic syndrome MetS is established as the combination of central obesity and different metabolic disturbances, such as insulin resistance, hypertension and dyslipidemia. Thus, dietary strategies to treat this heterogenic disease are under continuous study. In this sense, diets based on negative-energy-balance, the Mediterranean dietary pattern, n-3 fatty acids, total antioxidant capacity and meal frequency have been suggested as effective approaches to treat MetS. Furthermore, the type and percentage of carbohydrates, the glycemic index or glycemic load, and dietary fiber content are some of the most relevant aspects related to insulin resistance and impaired glucose tolerance, which are important co-morbidities of MetS. Finally, new studies focused on the molecular action of specific nutritional bioactive compounds with positive effects on the MetS are currently an objective of scientific research worldwide. The present review summarizes some of the most relevant dietary approaches and bioactive compounds employed in the treatment of the MetS to date. Metabolic Syndrome It was during the period between and when it was suggested for the first time that a cluster of associated metabolic disturbances tended to coexist together [1]. Since then, different health organisms have suggested diverse definitions for metabolic syndrome MetS but there has not yet been a well-established consensus. The most common definitions are summarized in Table 1. Obesity consists of an abnormal or excessive fat accumulation, for which the main cause is a chronic imbalance between energy intake and energy expenditure [7,8]. The excess of energy consumed is primarily deposited in the adipose tissue as triglycerides TG [9]. Dyslipidemia encompasses elevated serum TG levels, increased low density lipoprotein- cholesterol LDL-c particles, and reduced levels of high density lipoprotein-cholesterol HDL-c [10]. It usually involves narrowed arteries and is identified as a major cardiovascular and renal risk factor, related to heart and vascular disease, stroke and myocardial infarction [13,15â€”17]. Hyperglycemia, related insulin resistance and type 2 diabetes mellitus are characterized by an impaired uptake of glucose by the cells, that lead to elevated plasma glucose levels, glycosuria and ketoacidosis [18]. Currently, diabetes is considered the leading cause of death in developed countries [22]. Moreover, oxidative stress and low grade inflammation are two important mechanisms implicated in the etiology, pathogenesis, and development of MetS [23]. Oxidative stress is defined as an imbalance between the pro-oxidants and antioxidants in the body [24]. It plays a key role in the development of atherosclerosis by different mechanisms such as the oxidation of LDL-c particles [25] or impairment of HDL-c functions [26]. Inflammation is an immune system response to injury hypothesized to be a major mechanism in the pathogenesis and progression of obesity related disorders and the link between adiposity, insulin resistance, MetS and CVD [27]. Although the prevalence of the MetS varies broadly around the word and depends on the source used for its definition, it is clear that over the last 40â€”50 years the number of people presenting with this syndrome has risen in epidemic proportions [28]. Moreover, the frequency of this syndrome is increased in developed countries, sedentary people, smokers, low socioeconomic status population, as well as in individuals with unhealthy dietary habits [29,30]. For all of this, there is currently a wide concern to find effective strategies to detect, treat and control the comorbidities associated with MetS. This is a complex challenge as MetS is a clinical entity of substantial heterogeneity and therefore, the different cornerstones implicated in its development should be addressed. In this review we compiled and examined different dietary patterns and bioactive compounds that have pointed out to be effective in MetS treatment. Dietary Patterns Several dietary strategies and their potential positive effects on the prevention and treatment of the different metabolic complications associated to the MetS, are described below and summarized in Table 2. Energy-Restricted Diet Strategies Energy restricted diets are probably the most commonly used and studied dietary strategies for combating excess weight and related comorbidities.

They consist in personalized regimes that supply less calories than the total energy expended by a specific individual [31]. A hypocaloric diet results in a negative energy balance and subsequently, in body weight reduction [31]. Weight loss is achieved via fat mobilization from different body compartments as a consequence of the lipolysis process necessary to provide energy substrate [32,33]. In people who are overweight or suffering from obesity , as is the case of most people with MetS, weight loss is important as it is associated with improvement of related disorders such as abdominal obesity visceral adipose tissue , type 2 diabetes, CVD or inflammation [32â€”36]. Moreover, as described above, low grade inflammation is associated with MetS and obesity. Therefore, of particular importance is the fact that in obese individuals following a hypocaloric diet, a depletion of plasma inflammatory markers such as interleukin IL -6 has been observed [34]. Thus, caloric restriction in obese people suffering MetS may improve the whole-body pro-inflammatory state. At the same time, body weight reduction is associated with improvements in cellular insulin signal transduction, increments in peripheral insulin sensitivity and higher robustness in insulin secretory responses [32,36]. People with excess body weight who are at risk of developing type 2 diabetes, may benefit from a hypocaloric regime by improving plasma glucose levels and insulin resistance. In addition, different intervention trials have reported a relationship between energy restricted diets and lower risk of developing CVD. Among the different nutritional intervention trials, a reduction of â€” kcal a day of the energy requirements is a well-established hypocaloric dietary strategy, which has demonstrated to be effective in weight reduction [38,39]. However, the challenge lies in maintaining the weight loss over time, as many subjects can follow a prescribed diet for a few months, but most people have difficulty in maintaining the acquired habits over the long term [40,41]. These beneficial effects are thought to be mainly due to the ability of these essential fatty acids to reduce plasma TG levels [43]. These effects are probably mediated by resolvins, maresins and protectins, which are EPA and DHA metabolic products with anti-inflammatory properties [44]. There are some studies that have observed an association between n-3 ingestion and improvements or prevention of type 2 diabetes development. However, other studies found opposite results [44]. Thus, it cannot be made any specific affirmation in this respect. These amounts can be achieved with an ingestion of 1â€”2 fatty fish meals per week [45]. It consists in a ranking on a scale from 0 to that classifies carbohydrate-containing foods according to the postprandial glucose response [47]. The higher the index, the more promptly the postprandial serum glucose rises and the more rapid the insulin response. A quick insulin response leads to rapid hypoglycemia, which is suggested to be associated with an increment of the feeling of hunger and to a subsequent higher caloric intake [47]. There is a theory which states that MetS is a consequence of an elevated intake of high GI foods over time, among others unhealthy dietary habits [49]. In this sense, following a diet rich in high GI CHO has been associated with hyperglycemia, insulin resistance, type 2 diabetes, hypertriglyceridemia, CVD, and obesity [47,50,51], abnormalities directly related to MetS. On the contrary, a low GI diet has been associated with slower absorption of the CHO and subsequently smaller blood glucose fluctuations, which indicate better glycemic control [46]. In patients with type 2 diabetes, diets based on low GI are associated with reductions in glycated hemoglobin HbA1c and fructosamine blood levels, two biomarkers used as key monitoring factors in diabetes management [52,53]. Diets with High Total Antioxidant Capacity Dietary total antioxidant capacity TAC is an indicator of diet quality defined as the sum of antioxidant activities of the pool of antioxidants present in a food [55]. These antioxidants have the capacity to act as scavengers of free radicals and other reactive species produced in the organisms [56]. Taking into account that oxidative stress is one of the remarkable unfortunate physiological states of MetS, dietary antioxidants are of main interest in the prevention and treatment of this multifactorial disorder [57]. Accordingly, it is well-accepted that diets with a high content of spices, herbs, fruits, vegetables, nuts and chocolate, are associated with a decreased risk of oxidative stress-related diseases development [58â€”60]. Moreover, several studies have analyzed the effects of dietary TAC in individuals suffering from MetS or related diseases [61,62]. In the Tehran Lipid and Glucose Study it was demonstrated that a high TAC has beneficial effects on metabolic disorders and especially prevents weight and abdominal fat gain [61]. In the

same line, research conducted in our institutions also evidenced that beneficial effects on body weight, oxidative stress biomarkers and other MetS features were positively related with higher TAC consumption in patients suffering from MetS [63â€”65]. In this sense, the World Health Organization WHO recommendation for fruit and vegetables consumption high TAC foods for the general population is a minimum of g a day [66]. Moreover, cooking with spices is recommended in order to increase the TAC dietary intake and, at the same time, maintain flavor while reducing salt [67]. Two mechanisms have been proposed to explain the potential beneficial effects of high-moderate protein diets: The increment of the thermogenesis is explained by the synthesis of peptide bonds, production of urea and gluconeogenesis, which are processes with a higher energy requirement than the metabolism of lipids or CHO [75]. An increment of different appetite-control hormones such as insulin, cholecystokinin or glucagon-like peptide 1, may clarify the satiety effect [79]. Other beneficial effects attributed to moderate-high protein diets in the literature are the improvement of glucose homeostasis [80], the possibility of lower blood lipids [81], the reduction of blood pressure [82], the preservation of lean body mass [83] or the lower of cardiometabolic disease risk [84,85]. However, there are other studies that have not found benefits associated to a moderate-high protein diet [76]. This fact may be explained by the different type of proteins and their amino acid composition [80], as well as by the different type of populations included in each study [85]. Therefore, more research in the field is needed in order to make these results consistent. In any case, when a hypocaloric diet is implemented, it is necessary to slightly increase the amount of proteins. Otherwise it would be difficult to reach the protein energy requirements, established as 0. High Meal Frequency Pattern The pattern of increasing meal frequency in weight loss and weight control interventions has currently become popular among professionals [87,88]. However, there is no strong evidence about the efficacy of this habit yet [89]. While some investigations have found an inverse association between the increment of meals per day and body weight, body mass index BMI , fat mass percentage or metabolic diseases such as coronary heart disease or type 2 diabetes [71,88,90â€”92], others have found no association [93â€”95]. Different mechanisms by which high meal frequency can have a positive effect on weight and metabolism management have been proposed. An increment of energy expenditure was hypothesized; however, the studies carried out in this line have concluded that total energy expenditure does not differ among different meal frequencies [96,97]. Another postulated hypothesis is that the greater the number of meals a day, the higher the fat oxidation, but again no consensus has been achieved [89,98]. An additional suggested mechanism is that increasing meal frequency leads to plasma glucose levels with lower oscillations and reduced insulin secretion which is thought to contribute to a better appetite control. However, these associations have been found in population with overweight or high glucose levels but in normal-weight or normoglycaemic individuals the results are still inconsistent [93,99â€”]. The Mediterranean Diet The concept of the Mediterranean Diet MedDiet was for the first time defined by the scientific Ancel Keys who observed that those countries around the Mediterranean Sea, which had a characteristic diet, had less risk of suffering coronary heart diseases [,]. The traditional MedDiet is characterized by a high intake of extra-virgin olive oil and plant foods fruits, vegetables, cereals, whole grains, legumes, tree nuts, seeds and olives , low intakes of sweets and red meat and moderate consumption of dairy products, fish and red wine []. There is a lot of literature supporting the general health benefits of the MedDiet. In this sense, it has been reported that a high adherence to this dietary pattern protects against mortality and morbidity from several causes []. Thus, different studies suggested the MedDiet as a successful tool for the prevention and treatment of MetS and related comorbidities [â€”]. Moreover, recent meta-analysis concluded that the MedDiet is associated with less risk of developing type 2 diabetes and with a better glycemic control in people with this metabolic disorder [,,]. Other studies have found a positive correlation between the adherence to a MedDiet pattern and reduced risk of developing CVD [â€”]. In fact, many studies have found a positive association between following a MedDiet and improvements in lipid profile by reduction of total cholesterol, LDL-c and TG, and an increase in HDL-c [â€”]. Finally, different studies also suggest that the MedDiet pattern may be a good strategy for obesity treatment as it has been associated with significant reductions in body weight and waist circumference

[,,]. The high amount of fiber which, among other beneficial effects, helps to weight control providing satiety; and the high antioxidants and anti-inflammatory nutrients such as n-3 fatty acids, oleic acid or phenolic compounds, are thought to be the main contributors to the positive effects attributed to the MedDiet []. For all these reasons, efforts to maintain the MedDiet pattern in Mediterranean countries and to implement this dietary habits in westernized countries with unhealthy nutritional patterns should be made. Single Nutrients and Bioactive Compounds New studies focused on the molecular action of nutritional bioactive compounds with positive effects on MetS are currently an objective of scientific research worldwide with the aim of designing more personalized strategies in the framework of molecular nutrition. Among them, flavonoids and antioxidant vitamins are some of the most studied compounds with different potential benefits such as antioxidant, vasodilatory, anti-atherogenic, antithrombotic, and anti-inflammatory effects []. Table 3 summarizes different nutritional bioactive compounds with potential positive effects on MetS, including the possible molecular mechanism of action involved. Ascorbate Vitamin C, ascorbic acid or ascorbate is an essential nutrient as human beings cannot synthesize it. It is a water-soluble antioxidant mainly found in fruits, especially citrus lemon, orange , and vegetables pepper, kale []. Several beneficial effects have been associated to this vitamin such as antioxidant and anti-inflammatory properties and prevention or treatment of CVD and type 2 diabetes [â€”]. This dietary component produces its antioxidant effect primarily by quenching damaging free radicals and other reactive oxygen and nitrogen species and therefore preventing molecules such as LDL-c from oxidation []. It can also regenerate other oxidized antioxidants like tocopherol []. Moreover, it has been described that ascorbic acid may reduce inflammation as it is associated with depletion of CRP levels []. This is an important outcome to take in consideration in the treatment of MetS sufferers, as they usually present low grade inflammation [27].

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Chapter 3 : Vascular Diseases and Metabolic Disorders

A metabolic disorder occurs when the metabolism process fails and causes the body to have either too much or too little of the essential substances needed to stay healthy.

Received Jul 28; Accepted Jul This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. This article has been cited by other articles in PMC. Vascular diseases include cardiovascular and peripheral vascular diseases. For decades, cardiovascular diseases CVD stay the number one mortality worldwide. In more details, coronary heart disease or stroke alone caused around 1 of every 6 deaths or 1 of every 19 deaths in the United States in , respectively [1]. The total direct and indirect cost of CVD remains higher than any other diagnostic groups such as cancer [1]. In contrast to CVD, peripheral vascular diseases suffer lack of attention because most of the affected individuals are asymptomatic. The prevalence of peripheral vascular diseases is increasing which reduces the life quality and exposes the risk of infection and thrombosis. Atherosclerosis serves as the common pathogenesis of peripheral arterial disease and coronary heart disease. Therefore, both types of diseases share the same risk factors. For instance, a recent study demonstrated reduced number of endothelial progenitor cells in patients with CVD [2] and PAD [3]. Patients with vascular diseases are always featured as raised blood pressure, obesity, diabetes, and dyslipidemia, all of which constitute metabolic syndrome. From to , the prevalence of the metabolic syndrome increased from When compared to healthy controls, cardiovascular mortality was 1. Up to date, in vitro and animal studies have consistently illustrated that metabolic disorders disrupt endothelium integrity, promote inflammation and thrombosis, and thus accelerate the progression of vascular diseases [6 â€” 8]. However, in the occurrence of vascular diseases and metabolic disorders, the balance between cell damage and repair is twisted. Because of its fundamental potential in self-renewal and multilineage differentiation capacity, stem cell-related therapy has developed and reformed the manner of remodeling human degenerative diseases, which could be applied for diagnosis, drug screening, and the likelihood for therapy. Among all types of stem cells, mesenchymal stem cells MSCs are one of the most promising ones for translational application. A number of preclinical studies have employed MSC for the treatment of cardiomyopathy, vascular stenosis, and corneal disease [9]. In the special issue, studies from clinical and basic research were selected that presented the current status of vascular diseases and metabolic disorders. Clinical results brought updated findings on Acute Coronary Syndrome as well as peripheral artery disease, aortic aneurysms, and diabetic microvascular complications. We were informed about the effect of stem cell therapy in the treatment of vascular diseases. From the basic research aspect, we got to know more about the physiology of endothelial cells and brown adipocytes. Heart disease and stroke statisticsâ€” update: Circulating progenitor cells identify peripheral arterial disease in patients with coronary artery disease. Prevalence of the metabolic syndrome in the United States, â€” The Journal of the American Medical Association. Recent changes in the clinical outcome of papillary thyroid carcinoma with cervical lymph node metastasis. Map4k4 signaling nodes in metabolic and cardiovascular diseases. USF1 deficiency activates brown adipose tissue and improves cardiometabolic health. Rebuilding the damaged heart:

Chapter 4 : Metabolic Syndrome: Proven Diet & Natural Treatment Plan - Dr. Axe

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Their body weight was monitored throughout the study, and an echocardiography was performed at the end of the treatment. Blood and tissues were collected for biochemical and functional analysis, including nitric oxide and oxidative stress measurement. Vascular reactivity and liver mitochondrial complexes activity were also analyzed. In western diet-fed mice, GSE reduced adiposity, plasma triglycerides, and oxidative stress in the heart, liver, adipose and skeletal tissues; but did not improve the vascular dysfunction. This report highlights the therapeutic potential of polyphenols, and especially extract enriched in procyanidin dimers, against the metabolic disorders associated with excessive energy intake. Introduction Obesity represents a major health challenge in developed countries Flegal et al. Lifestyle modification remains the primary point of intervention for obesity management. However, pharmacological and dietary interventions represent promising strategies for both weight reduction and improving associated cardiometabolic risk Ahluwalia et al. Among these dietary approaches, the use of nutraceuticals, has attracted great interest in the recent years Magrone et al. Different in vitro and in vivo studies have demonstrated a broad range of protective effects of polyphenols in the context of metabolic and cardiovascular diseases Andriantsitohaina et al. We previously demonstrated in Zucker fatty rats that the red wine polyphenol RWP extract ProvinolsTM improves glucose and lipid metabolism, as well as endothelial and cardiac functions without affecting the body weight gain Agouni et al. ProvinolsTM is mainly composed of the flavonoids flavanols and anthocyanins, which are described as the most effective classes of polyphenols Chalopin et al. They correct lipid abnormalities associated with obesity Quesada et al. Anthocyanins limit weight gain, and improve lipid profiles, hepatic function Wu et al. They also have antioxidant Chiang et al. We have previously identified the molecular mechanisms involved in the regulation of vascular reactivity by RWP and anthocyanins. We tested this hypothesis in diet-induced obese mice supplemented with a grape seed extract GSE enriched in procyanidin dimers, flavanols described to be the most effective RWP on the endothelium Aldini et al. With regard to western diet, it contains The concentration of extract used in present study was comparable with that described in our previous studies Diebolt et al. Also, it was consistent with a human consumption of one to two glasses of red wine per day and was in the range of that able to provide healthy effects on oxidative damage in humans Covas et al. Upon 1 week of acclimatization, mice were ovariectomized to avoid the cofounding effect of circulating estrogens in the effect of polyphenols. Seven days later, both strains were randomized divided into four groups standard diet, western diet data concerning these mice have previously published by Leonetti et al. Mice were allowed ad libitum access to water and diets. Mouse weight was measured weekly. One week before sacrifice, mice underwent an echocardiography. The adiposity was calculated as the total adipose tissue weight the sum of the visceral and subcutaneous adipose tissues vs. It was centrifuged for 15 min at g and room temperature to obtain plasma. Briefly, a two-dimensional short axis view of the left ventricle was obtained in order to record M-mode tracings. The maximal contractile capacity of the vessel was tested by challenging the artery with the combination of depolarizing solution, [i. Obtained signals were expressed in A. Values were expressed in nmol of product formed per minute and per mg of protein in homogenates as previously described Mingorance et al. The statistical software GraphPad Prism 6. It was assessed that data follow a normal distribution by Shapiroâ€”Wilk test. When random effects are supposed in our analyses, we performed a linear mixed model. This kind of model allows us to take into account both variabilities inter and intra observation. These analyses are performed using package lme4 from R statistical software. If coefficient associated with the variable of interest is significant, then we will realize post hoc analyses followed by Sidak correction. The final body weight was increased in western diet-fed mice compared to standard diet-fed mice. This was associated with

higher adiposity Table 1. Interestingly, GSE supplementation partially prevented the fat accumulation induced by western diet Table 1 without affecting the body weight gain Figure 1A. Animal characteristics following 12 weeks of diets. The body weight was recorded twice a week. This was also associated with an increased adiposity index Table 1. The liver and heart weights were not significantly modified independently of diets in the two strains. Blood was collected by cardiac puncture at sacrifice. Taken together, the experimental model of obesity used in this study is associated with vascular function alterations: The treatment of GSE was not able to correct these vascular alterations. Cardiac function following 12 weeks of diets. GSE supplementation tended to enhance the mitochondrial complexes activity of mice fed with western diet and significantly increased complex II activity. However, it did not have any effect in the mice fed with standard diet. This was not affected by GSE supplementation. GSE supplementation did not modify the ROS level in standard diet mice; in contrast it significantly reduced that of mice fed with western diet. GSE supplementation did not modify oxidative stress in mice fed with standard diet, however, it tended to decrease ROS level in western diet group Figure 6G. Discussion In the present study, we provide evidence that the supple mentation of GSE significantly improved obesity-associated vascular and metabolic disorders. Although the GSE did not affect the increased body weight induced by western diet, it was able to partially prevent the fat accumulation and displayed antioxidant protection in the subcutaneous and visceral adipose tissues. In the liver, this effect was associated with an improvement of hepatic enzyme activities. In accordance with previous report Leonetti et al. However, the western diet did not affect cardiac and endothelial functions but induced vascular hypo-reactivity in response to 5-HT. The main objective of this study was to investigate the effects of oral administration of GSE enriched the flavanols procyanidin dimers in an experimental model of obesity. Here, we showed that GSE was not able to decrease the weight gain in response to the western diet, in line with previous studies using RWP in mice fed with western diet Leonetti et al. Although GSE supplementation did not affect the body weight gain, it partially reduced fat accumulation induced by western diet. Adipose tissue plays a critical role in the regulation of energy balance. Its primary metabolic role is to store nutrients in the form of triglycerides and to mobilize fatty acids according to metabolic needs. In the present study, we found that the inhibition of fat deposition by GSE was associated with a reduction of plasma triglyceride levels. Similar results were observed in mice fed with western diet and supplemented with a RWP Leonetti et al. Since both extracts are rich in flavanols, these observations highlight a potential role of this class of polyphenols in correcting hypertriglyceridemia, an independent risk factor for the development of cardiovascular diseases. In accordance with these results, it has been previously reported that the use of grape seed procyanidin extract improves plasma lipid profile and reduces plasma triglyceride levels Pinent et al. In particular, the in vivo hypotriglyceridemic effect of dietary procyanidins involves the activation of the farnesoid X receptor, the subsequent upregulation of the nuclear receptor small heterodimer partner expression and the downregulation of SREBP1 expression Del Bas et al. Beside its effect on lipid content, GSE also reduced the oxidative stress induced by western diet in both visceral and subcutaneous adipose tissues. Finally, the treatment of adipocytes with flavanol-rich fruit extract has been shown to decrease ROS production and the gene expression of adipokine in adipocytes. These results were similar to our previous study using RWP under the same experimental condition Leonetti et al. Consequently, the ability of GSE to improve oxidative stress in the heart may be linked either to the capacity of procyanidins to scavenge free radicals or to their ability to reduce the expression of pro-oxidant enzymes. Interestingly, the antioxidant effects of GSE in the liver were associated with an improvement of complexe II activity in WT western diet-fed mice. In the liver, the obese state promotes lipogenesis and elicits mitochondrial dysfunction resulting in hepatic fatty acid and lipid overload. In the long term, these alterations in lipid homeostasis can promote oxidative stress and lipid peroxidation, leading to inflammation and fibrosis Diebolt et al. Obesity may interfere with mitochondrial bioenergetics by affecting cellular respiratory functions and oxidative pathways. In the present study, we provided evidence that supplementation with GSE increased mitochondrial complex II activity in the liver of WD-induced obese mice. This could in turn improve the mitochondrial respiratory

capacity. In line with these findings, it has been previously observed that the intake of procyanidin-rich extracts improves mitochondrial function in the skeletal muscle and brown adipose tissue in an experimental model of obesity Pajuelo et al. It is also described that the activity of the respiratory chain complexes is closely associated with mitochondrial ROS production Le Lay et al. Accordingly, we observed that GSE-induced improvement of mitochondrial function was associated with a reduced of WD-induced oxidative stress in the liver. The antioxidant effect of GSE in the liver may also be due to the ability of the extract to modulate the expression and activity of antioxidant enzyme systems, as previously reported Puiggros et al. One can hypothesize that the increased activity of the mitochondrial complex chain could also increase the oxidation of lipids and therefore prevent the rise of hepatic disorders such as steatosis. In accordance with our data, a recent study reported that the administration of grape polyphenols in a mouse model of chronic high-grade inflammation reduces muscle atrophy and prevents ROS damage through the reduction of oxidized mitochondrial proteins, an improvement of mitochondrial function and a significantly reduction of caspases-9 and 3 activation Lambert et al. Despite strong antioxidant effects, GSE supplementation did alter neither the endothelial function, nor the vascular reactivity, independently of the diet used. Conclusion The present report highlighted the ability of a GSE enriched with the flavanols procyanidin dimers to attenuate obesity-associated disorders Figure 7. Additional studies are required to understand the molecular mechanisms involved in these beneficial effects. This study is a good starting point to promote the therapeutic potential of GSE against the cardiovascular and metabolic disorders associated with obesity. All authors read and approved the final manuscript. Conflict of Interest Statement The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Acknowledgments We thank M. Riou University of Angers for support in data analysis. Supplementary Material The Supplementary Material for this article can be found online at:

Chapter 5 : Joint Support â€“ Metabolic Diet

Up to date, in vitro and animal studies have consistently illustrated that metabolic disorders disrupt endothelium integrity, promote inflammation and thrombosis, and thus accelerate the progression of vascular diseases [].

This is an open access article distributed under the Creative Commons Attribution License , which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Abstract Metabolic syndrome is a cluster of metabolic and cardiovascular symptoms: Hypertension and vascular disorders are central to this syndrome. After a brief historical review, we discuss the role of sympathetic tone. Subsequently, we examine the link between endothelial dysfunction and IR. NO is involved in the insulin-elicited capillary vasodilatation. The insulin-signaling pathways causing NO release are different to the classical. There is a vasodilatory pathway with activation of NO synthase through Akt, and a vasoconstrictor pathway that involves the release of endothelin-1 via MAPK. IR is associated with an imbalance between both pathways in favour of the vasoconstrictor one. We also consider the link between hypertension and IR: Next we discuss the importance of perivascular adipose tissue and the role of adipokines that possess vasoactive properties. Finally, animal models used in the study of vascular function of metabolic syndrome are reviewed. This one suffers macro- and microvascular malfunction due to a failure in the NO system and an abnormally high release of vasoconstrictor prostaglandins, all this alleviated with glitazones used for metabolic syndrome therapy. Introduction The metabolic syndrome is a cluster of metabolic and cardiovascular symptoms that are strongly associated with type II diabetes mellitus. In this kind of diabetes, rather than prolonged high levels of glycemia, there is insulin resistance with secondary hyperinsulinemia, both very frequently associated with, hypertension, dyslipemia, atherosclerosis, and, most importantly, obesity Figure 1 [1]. Vascular disorders are central to this condition. For these reasons, it is also known as cardiometabolic syndrome [1], and hypertension plays a pivotal role. There is a clear association between body mass index and arterial pressure even in nonobese, lean people [4 â€” 6]. Still, some obese people are not hypertensive. For example, the North American Pima Indians, who have a high prevalence of obesity, but do not have corresponding high rates of hypertension [7]. Two ways to conceptualize metabolic syndrome and the position hypertension and the other symptoms occupy. According to the WHO definition, insulin resistance is central to any other symptom a. Others define metabolic syndrome as a cluster of symptoms where none has a central position b. In these articles, the two physicians described for the first time the coexistence of hypertension and diabetes mellitus in adults and proposed a common mechanism for the development of these disorders. In , Reaven, hypothesized that insulin resistance is the common etiological factor of a group of disorders, such as high blood pressure, hyperinsulinemia, high levels of low density lipoproteins LDL , triglycerides, and cholesterol, and low levels of high density lipoproteins HDL. A year later, Kaplan added to the pathologies described by Reaven a very important factor, central adiposity increase in splanchnic and subcutaneous fat depots in the abdominal region [10]. Since then, abdominal obesity has been considered one of the typical components of the syndrome. Both type 2 diabetes mellitus and metabolic syndrome are reaching epidemic proportions. Considering that million people worldwide are diabetic, this disease has become a serious epidemiological problem [11]. Metabolic syndrome is, probably, the most important challenge for health authorities in developed and developing countries [11 , 12]. In Europe there is a clear North-South gradient in almost all cardiovascular risk factors related with metabolic syndrome. For example, mortality from coronary heart disease, expressed as a mortality ratio, presented in men aged 30â€”69 the following geographical indices: However, there is no doubt that the paradigm of overdevelopment-overweight is the United States. A diet that is as excessive as inadequate has yielded these epidemiological figures in less than 20 years: This is the equivalent to an increment of 10 calories per year [14]. Role of the Sympathetic Nervous System There are 3 conditions, typical of metabolic syndrome, that may cause an exacerbation of sympathetic tone. Namely, hyperinsulinemia, hyperleptinemia, and

hyperlipidemia. In , it was reported that hyperinsulinemia, independently of changes in glycemia, caused a substantial increase in circulating noradrenaline concentration accompanied by an increase in blood pressure [15]. These sympathoexcitatory effects of insulin appear to be centrally mediated, since they are apparent only during systemic insulin infusion but not local infusion [16]. In addition, high levels of insulin increase sodium reabsorption [17] favouring expansion of extracellular fluid volume, which may predispose to hypertension [18]. Furthermore, obesity impairs renal-pressure natriuresis and causes sodium retention. Obese subjects require increased arterial pressure to maintain sodium balance, indicating impaired renal-pressure natriuresis [19]. In addition to insulin, leptin can also be a link between obesity and increased sympathetic activity. Besides its effect on appetite and metabolism, leptin acts in the hypothalamus to increase blood pressure through activation of the sympathetic nervous system [20]. High circulating levels of leptin are reported to explain much of the increase in the renal sympathetic tone observed in obese human subjects [21]. Leptin-induced increases in renal sympathetic activity and blood pressure are mediated by the ventromedial and dorsomedial hypothalamus [22]. Finally, high circulating levels of free fatty acids in visceral obese individuals may participate in the activation of the sympathetic nervous system. The increased release of free fatty acids into the portal vein from lipolysis in visceral fat depots could explain the strong association between visceral obesity and increased sympathetic nerve outflow [23]. Role of Insulin 3. Insulin Resistance and Endothelial Dysfunction In , Himsworth postulated that type 2 diabetes mellitus was not only an insulin deficiency state but also a disease in which cells are unresponsive to insulin. Insulin resistance is clinically defined as the inability of a known quantity of insulin exogenous or endogenous to increase glucose uptake and utilization in an individual as much as it does in a normal population [26]. There is a clear link between endothelial dysfunction and insulin resistance [27 , 28] but the mechanism by which insulin resistance leads to endothelial dysfunction is complex and involves the action of mediators of inflammation in the visceral fat, liver, and muscle [29]. It is well known that insulin resistance and compensatory hyperinsulinaemia, besides activating the mechanisms mentioned above, have also a vascular toxicity effect, mainly at the endothelial level. This, partly because insulin resistance impairs the production of NO, favors the production of endothelin-1 and the vasoconstrictive and mitogenic responses on the vascular wall [30]. Role of NO in Insulin Resistance King and Johnson reported in that the endothelial cell membrane displays insulin receptors [31]. Functional studies indicate that endothelium-derived NO is involved in the insulin-elicited increase in blood flow and recruitment of capillaries that physiologically links hemodynamics to the metabolic action of insulin on the tissues [32 â€” 34]. Insulin resistance is associated with impaired NO synthase activity [35] and an abnormal basal NO-mediated dilation in the forearm arterial bed [36]. The insulin-induced increase of microvascular endothelium-dependent vasodilation is abolished in insulin resistance conditions such as obesity [37]. Moreover, insulin has been shown to constrict rather than dilate forearm resistance arteries in obese patients [38]. On the other hand, inhibition of NO synthesis or endothelium removal reveals a vasoconstrictor effect of insulin on isolated arterioles [39]. Definitive proof of the relationship between NO and insulin sensitivity has been provided by knock-out mice that are homozygous null for the eNOS gene. These peculiar animals display an expected hemodynamic phenotype of increased basal blood pressure but also are insulin resistant [40]. Therefore, insulin has indeed a hemodynamic component, albeit small compared to the metabolic one. But both are coupled in such a manner that endothelial dysfunction can cause insulin resistance, and this, in a vicious circle, aggravates endothelial function. Interestingly, insulin-signaling pathways in vascular endothelium leading to the activation of endothelial NO synthase are completely independent and distinct from classical calcium-dependent mechanisms used by G-protein-coupled receptors, such as the acetylcholine receptor [34]. The messenger pathway that is activated when insulin binds insulin receptor appears to be as follows [41]: The signalling pathway from insulin branches at IRS One of the branches involves the activation of phosphoinositide 3 kinase PI-3K , leading to phosphatidylinositol-3,4,5-triphosphate as well as to phosphorylation and activation of phosphoinositide-dependent kinase 1 PDK Remarkably, the vascular actions of insulin that stimulate the

production of NO possess remarkable similarities to metabolic insulin-signaling pathways. For instance, activation of Akt is also a common step for glycogen synthase kinase inhibition and GLUT-4 transporter translocation [41]. Later, it was shown that insulin can modulate circulating ET-1 levels [44] and increased plasma levels of ET-1 were observed in type II diabetic patients [45]. An additional work in the skeletal muscle circulation reported that insulin stimulates both NO activity already known as we showed before and ET-1 [46]. The authors then suggested that an imbalance between the release of both substances may be involved in pathophysiology of hypertension and atherosclerosis in insulin-resistant states associated with endothelial dysfunction [46]. Following research has shown that insulin induces endothelin-mediated vasoconstriction only when NO synthase or phosphatidylinositol-3 kinase PI3K is inhibited [47]. This proved previous proposals that insulin exhibits a dual and opposite action on blood vessels: NO-mediated vasodilation and ETmediated vasoconstriction. It is known that MAPK activation by IRS-1 causes the release of endothelin-1, which promotes insulin resistance by reducing blood supply to the skeletal muscle , increases oxidative stress, reduces the bioavailability of NO, and promotes a proatherogenic state [49]. Hyperglycaemia and Vascular Function Regardless of the evidence linking the vascular dysfunction of type II diabetes mellitus with failures in the vascular biology of insulin, there are many reports that attribute these dysfunctions to the very fact of the existing hyperglycaemia. We wish to draw attention to the functional effects of the acute excess in glucose occurring in a particular moment. In this regard, it has been reported that glucose favours vasoconstriction [50] and impairs vasodilation [51]. In arteries of diabetic rats, Taylor et al. Most interesting is the finding that in healthy subjects, acute hyperglycaemia impairs endothelium-dependent vasodilation in both the microcirculation and the macrocirculation when assessed in the brachial artery [53]. More precise data on the mechanisms involved in hyperglycaemia was released by Sobrevia et al. This would be good news if they did not find as well that insulin treatment downregulated the elevated activity of the L-arginine transport system and that of NO synthase in the cells exposed to hyperglycaemia. They concluded that the modulation of the human endothelial cell L-arginine-NO pathway by insulin is influenced by predisposing hyperglycaemic clinical conditions [54]. In a later study, Renaudin et al. Insulin Actions on Blood Pressure: The Insulin Hypothesis of Hypertension So far we have focused on the cardiovascular effects of insulin at a local level. However, it cannot be forgotten that insulin has systemic actions affecting the sympathetic nervous system and kidney. The surge of epidemiological reports relating insulin resistance and hyperinsulinemia has fueled the idea of the so-called insulin hypothesis of hypertension. There is no question that insulin resistance is epidemiologically linked with hypertension [1]. The insulin hypothesis of hypertension proposes that the compensatory hyperinsulinemia that occurs with insulin resistance increases sodium reabsorption and sympathetic activity, which combine to cause elevated arterial pressure. Support for this hypothesis comes from various lines of evidence. First, the correlation between insulin resistance and high blood pressure [56], which is emphasized by the fact that, even lean individuals with essential hypertension, display insulin resistance and hyperinsulinemia. Second, as explained before, insulin has multiple actions on the sympathetic nervous system, the kidney, and the vasculature which can lead to hypertension. Third, the observation that drugs which improve insulin resistance and decrease hyperinsulinemia, are reported to be antihypertensive. For instance, Landin et al. Another remarkable example is the well-known blood pressure lowering effects of insulin sensitizers glitazones [59]. For review, see [60].

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NC Med J March/April , Volume 66, Number 2 Book Review: Scientific Publications by Walter Kempner, MD: Volume II. Radical Dietary Treatment of Vascular and Metabolic.

Caloric restriction CR has proved to be the most effective and reproducible dietary intervention to increase healthy lifespan and aging. A reduction in cardiovascular disease CVD risk in obese subjects can be already achieved by a moderate and sustainable weight loss. Other dietary strategies changing specific macronutrients, such as altering carbohydrates, protein content or diet glycemic index have been also shown to decrease the progression of CVD in obese patients. In this review, we will focus on the positive effects and possible mechanisms of action of these strategies on vascular dysfunction. Introduction Obesity is a chronic disease due to an energetic imbalance in which caloric intake is higher than energetic expenditure. It is closely associated with insulin resistance and type 2 diabetes T2D , leading to several manifestations of cardiovascular disease CVD , such as hypertension, coronary artery disease, myocardial infarction, heart failure and stroke [1]. In obese individuals, the earliest indication of vascular dysfunction preceding the development of prehypertension and hypertension is the impairment of endothelial function [2]. The primary goal to reduce CVD risk in subjects who are overweight and obese is a moderate and sustainable weight loss. Since pharmacological approaches for body weight BW reduction have, at present, a poor long-term efficacy, other strategies such as caloric restriction CR , exercise programs, or bariatric surgery are of great interest [3 , 4]. CR is defined as a state in which energy intake is reduced below usual ad libitum intake without malnutrition, independently of its duration. It is one of the most common and cost-effective interventions used to induce BW reduction and CV risk factor amelioration. Other dietary strategies changing specific macronutrients have also been shown to decrease progression of CVD. It is important to note that the induction of a negative energy balance is mandatory for achieving the metabolic benefits of weight loss since the sole reduction in fat mass alone by surgical procedures does not improve CV risk factors in obese patients [5 , 6]. Taking into consideration the complex and vast literature regarding dietary strategies, in this review, we will focus on the positive effects on vascular dysfunction, CV risk factors and CVD exerted by CR and macronutrients intake modification. CR Reduces CV Risk Factors Benefits on CV risk factors by reducing the daily caloric intake have been widely described in overweight and obese patients [7 , 8 , 9 , 10 , 11 , 12 , 13 , 14 , 15 , 16 , 17 , 18 , 19]. CR induces reductions in BW, waist perimeter, total fat, serum triglycerides TG , or low-density lipoprotein LDL -cholesterol concentrations [12 , 14 , 20]. It is also associated with a reduction of circulating insulin levels together with an increase in insulin sensitivity [12 , 14 , 18 , 20]. In obese patients with or without associated hypertension, weight loss enhances flow-mediated vasodilation FMD, which determines endothelial function in vivo [8 , 11], and induces a reduction in blood pressure BP [7 , 20]. Interestingly, benefits of CR are not only observed in obese subjects. A decrease in the inflammatory state is reflected by the extremely low levels of high-sensitivity C-reactive protein CRP detected in these subjects [20]. Since CV risk factors increase with age, CR reveals as a promising strategy to prevent the development of CVD in both obese and non-obese individuals. A comparison of several approaches is shown in Table 1. There is no agreement on how severe a CR must be in order to confer benefits in different organs and systems. However, numerous protocols include an alternate-day fasting, in which caloric intake reduction will be intermittent [22 , 23]. Most of the CR protocols reduce very intensively the energetic consumption for a long time. Others use comparable approaches but only for four or five weeks, obtaining similar effects [26]. This suggests that a CR does not need to be prolonged for a long time to be effective, with the advantage that short-term CR is easier to include in clinical practice. In this context, a genomic analysis revealed that the results obtained after CR during four weeks were similar to those from longer CR 28 weeks. However, other authors report different findings in other tissues, such as in white adipose tissue [28], probably due to variations in responding to fasting cycles. Overall, we feel that most of the studies do not reflect a realistic intervention since they include

really severe protocols. Initially, it was thought that benefits appeared only after long periods of CR [46]. Nevertheless some of the beneficial effects promoted by CR, such as plasmatic glucose levels decrease, show up within the first week of the diet [47]. Important protection of endothelial function occurs in vascular aging models even under CR protocols for less than three weeks [35 , 48]. Other vascular aged-related complications, such as aortic stiffening and artery wall hypertrophy, need longer dietary treatments to be prevented [29]. Regarding the starting point of a CR, its effects on lifespan are higher if it is initiated at the weaning [49 , 50 , 51]. This suggests that CR protocols might be more beneficial at early stages of vascular disease [32]. The different phases in which a CR can be subdivided play a substantial role in the achievements can be reached. In multiphase dietary interventions, the pattern of adipokine expression, secretion rate, and plasma levels is different with respect to the phase of the intervention, and to the cellular origin of the respective adipokine [42]. Adipocyte-derived adipokines adiponectin, leptin, serum amyloid A, or haptoglobin decrease except for adiponectin , during the initial very low-calorie diet VLCD , whereas they increase toward prediet levels during the weight stabilization phase. Similar results have been observed with low-calorie diets [52]. During the various phases of a dietary weight loss program, adipose tissue macrophages and adipocytes show distinct patterns of gene regulation and association with insulin sensitivity, the regulation of gene expression being dependent on the severity and duration of CR [43]. In conclusion, the optimal CR protocol for each specific situation remains to be determined and standardization will be necessary to allow comparison of the beneficial effects of different dietary approaches on CVD. Mechanisms by Which CR Exerts Vascular Protection in Metabolic Disorders The improvement of vascular dysfunction associated with metabolic disorders might be due to changes in endothelial function, in the arterial wall structure, or in the paracrine effects of perivascular adipose tissue PVAT. Effects of CR on Endothelial Function CR leads to an improvement of endothelial function in arteries from several models of aged [24 , 29 , 33 , 34 , 36 , 53] and obese rodents [38 , 39 , 40]. CR triggers endothelial AMPK activation leading to i normalization of endothelial function and systolic BP reduction in Zucker obese rats [39]; ii an improvement of vascular compliance and BP reduction in hypertensive rats [32]; or iii revascularization in response to ischemia [26]. Moreover, activation of AMPK by CR reduces lipotoxicity associated with high-fat diets HFD , insulin resistance, and obesity by decreasing the excessive exposure of the endothelium to free fatty-acids FFAs [61 , 62], thus exerting a protective effect on endothelial cells [61 , 62]. Obese patients subjected to CR that reported systolic BP reduction, as well as FFA and inflammatory marker level decrease, showed an increase of AMPK phosphorylation in peripheral blood mononuclear cells [19]. The fact that these changes are observed even with a moderate reduction in BW supports the predominant role of the negative energy balance to achieve CV benefits of CR. Activation of the cellular sensing protein sirtuin-1 SIRT1 is another mechanism proposed as key mediator of vascular benefits of CR [29 , 34]. There are, however, very few studies assessing the vascular role of SIRT1 activation by CR in obesity, and further research needs to be performed in this line. Effects of CR on Arterial Wall Structure and Remodeling Subclinical organ damage, such as vascular remodeling, precedes the occurrence of CV events in individuals with obesity and hypertension [64]. Life-long CR significantly reduces large elastic artery wall hypertrophy and prevents aortic stiffening in mice [29] due to a suppression of collagen production [29] and elastin fiber degradation [53]. Increases in elasticity after CR have also been described in arteries from young, but not from aged SHR [32]. This suggests that reversal of early changes in the arterial wall structure, at a time when vascular remodeling is emerging and still reversible, is essential for the prevention of vascular dysfunction. Mechanisms underlying CR-induced changes in vascular remodeling have been mainly analyzed in models of aging. Whether the same mechanisms underlie the effects of CR on metabolic arterial wall remodeling remains to be further analyzed. Both intervention and cross-sectional studies in humans demonstrate that short-term CR and reduced BW are associated with lower BP and carotid wall thickness [15 , 16 , 20 , 65]. However, other parameters, such as augmentation index, strain, augmentation pressure and pulse pressure were not significantly improved with weight loss [66]. All of these results demonstrate that an intensive dietary intervention at a time when

vascular remodeling has only been initiated and is not irreversibly established might significantly reverse some of the key adverse vascular structural changes associated with excess weight in severely obese adults. It might be white or brown adipose tissue and produces a number of vasoactive factors, adipokines and cytokines. A large body of evidence supports the paracrine influence of PVAT for the maintenance of vascular resistance under physiological and pathophysiological conditions [67]. PVAT releases a number of adipokines, inflammatory cytokines, and other vasoactive factors, which are variable in quantity and pattern depending on the PVAT amount [67]. In fact, obesity triggers an increase in PVAT throughout the vasculature [68 , 69], accompanied by an unbalance in favor of vasoconstrictor and pro-inflammatory substances, which leads to endothelial dysfunction and vascular damage [70 , 71 , 72]. An interesting issue, which deserves future investigation, is the impact of the diet composition on oxidative stress in PVAT. A fructose-rich diet, which decreases polyunsaturated FAs and increases saturated and monounsaturated FAs in PVAT impairs vascular function by a decrease in antioxidant enzymes and a reduction in glutathione content [76]. Altogether, these results indicate that obesity and the diet composition induce a switch in PVAT to a more pro-inflammatory, pro-oxidant and vasoconstrictor phenotype. Since the beneficial or deleterious paracrine influence of PVAT is directly dependent on its amount [77 , 78], a key question is whether the proportion of adipose tissue loss induced by CR is uniform overall adiposity or predominant in specific adipose depots i. Significant reduction in the thickness of epicardial fat surrounding coronary arteries has been described both in severely obese patients who underwent substantial weight loss after bariatric surgery [79], as well as after a short-term VLCD program [41]. Interestingly, the decrease of epicardial fat is substantially higher than changes in overall BW loss body mass index and waist circumference, and correlates with the improvement in both left ventricular mass and diastolic function. We believe that these studies open a new approach for the management of vascular damage and CV risk associated with PVAT dysfunction in metabolic related disorders. Effects of CR on Vascular Actions of Leptin and Adiponectin Obesity is associated with hyperleptinemia and hypoadiponectinemia, both playing a key role in the pathogenesis of endothelial dysfunction [81]. On the other hand, hypoadiponectinemia is closely associated with endothelial dysfunction in humans and adiponectin knock-out mice show a decrease in eNOS phosphorilation levels. Different CR protocols in rats, markedly changes the adipokine production pattern leading to an increase in circulating levels of adiponectin, whereas leptin levels profoundly decrease in adipose tissue [85 , 86]. A role for adipokine levels in PVAT and their paracrine influence on the vascular wall might not be discarded. These studies again stress the concept that PVAT-vessel interaction is a promising therapeutic target for the prevention of vascular complications of metabolic disorders. The effect of CR and dietary approaches on this interaction deserves future investigation. Dietary Strategies Based on Macronutrients Modification Not only the amount but also the quality of the nutrient intake contributes to benefits on vascular function [89 , 90 ,