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Editorial

Nutrition and cardiovascular disease: Putting a pathogenic framework into focus

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In the last two decades it has become clear that dietary recommendations are a key element in the management of cardiovascular disease (CVD). An expanding body of evidence indicates that certain dietary patterns can influence cardiovascular health and primary prevention of CVD by modifying risk factors such as obesity, dyslipidemia, and hypertension as well as factors involved in systemic inflammation, insulin sensitivity, oxidative stress, endothelial function, thrombosis, and cardiac rhythm [1–3]. In the last century dietary and exercise habits have changed, with greater abundance of refined foods and a more sedentary lifestyle, resulting in the rising prevalence of obesity in Western countries [4,5].

In the present Spotlight Issue, we present a series of review articles and original papers with the aim of investigating the various dietary profiles and pathogenic mechanisms that have emerged in the literature and the major studies that investigated their effectiveness in modifying cardiovascular risk. However, we need to keep in mind that long-term adherence can become a problem with some dietary advice that uses severe restriction of certain food groups. Indeed, in trials that investigated the effectiveness of low-carbohydrate diets in inducing weight loss, the attrition rates ranged between 24% and 39%. In most of these trials, comparable attrition rates were observed in subjects assigned to a low-fat diet [6–8]. More important, when a major change in the proportion of one macronutrient is imposed, compensatory changes in the proportions of other macronutrients will naturally occur. In the case of low-carbohydrate diets, there is a concern that excessive dietary protein intake without appropriate quantity of water and beverages can occur and potentially increase long-term risks for nephrolithiasis [9]. Furthermore, when dietary fat intake is severely restricted, biochemical evidence of essential fatty acid deficiency can result. Some clinical consequences have been reported, including episodic somnolence, visual problems, and tachyarrhythmias, especially when fat intake remains <5% of total calories for several years [10]. Moreover, environmental toxins such as methylmercury, polychlorinated biphenyls, and dioxins are concentrated in the food chain in fresh waters and oceans, making fish a major source of such toxins. Although suggestions have been made that long-term accumulation of these toxins may increase the risk of cancer, a recent meta-analysis did not show an increased risk of cancer with higher intake of n-3 polyunsaturated fatty acids (PUFAs) [11]. Finally, the promotion of severely fat-restricted diets has led many consumers today to resort to fat substitutes in commercially available low-fat or the so-called "fat-free" snacks instead of naturally occurring, low-fat foods such as fruits, vegetables, and whole grains. Thus, we need to gain a more "balanced" point of view in the face of well-proven beneficial effects of integrated dietary restrictions and the adverse consequences of too "severe" restriction including increased consumption of refined carbohydrates.

A number of articles in this Spotlight examine the connection between dietary fats or carbohydrates and

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cardiovascular health. Mundy and co-workers [12] investigated the role of fat intake on responsiveness and receptor expression of vasoconstrictors and their implications for diet-induced obesity in mice. They conclude that changes in dietary fat intake were associated with augmented vascular contractions to angiotensin II and reactive oxygen species but not with endothelin-1 while endothelium-dependent relaxation was unaffected. Currently, a high-carbohydrate/low-fat diet is recommended for patients with hypertension; however, the potential impact of this diet on hypertension and development of left ventricular hypertrophy (LVH) is discussed in depth in this issue by the group of Stanley [13]. LVH can also be triggered by activation of peroxisome proliferators-activated receptors (PPARs), indicating that metabolic alterations may play a pathogenic role in LVH and cardiac remodelling. This latter issue is discussed here by Fink [14]. Dietary intake of fats and carbohydrates also affects insulin levels. Recent studies show that lipids alter intracellular Ca^{2+} handling of cardiac cells differently in normal and insulin-resistant cardiac cells. Here, Fauconnier et al. [15] show that insulin-resistant cardiomyocytes of obese ob/ob mice have decreased lipid diacylglycerol (DAG)-mediated, non-selective cation currents which were associated with decreased expression of transient receptor potential 3 (TRPC3) and defective insulin-mediated trafficking of this protein. Obesity is an important contributor to the risk of developing insulin resistance, diabetes, and CVD. Alterations in tissue levels of malonyl-CoA have the potential to affect the severity of such pathological conditions. Folmes and Lopaschuk [16] discuss hypothalamic and cardiac studies, demonstrating a pivotal role of malonyl-CoA in obesity and CVD. Similarly, Fulop and co-workers [17] review the emerging role of O-linked *N*-acetyl-glucosamine in mediating post-translational cell function in the cardiovascular system. These actions could be involved in the adverse effects of metabolic diseases on cardiovascular activities.

All of these deleterious conditions are exacerbated during the late stages of heart diseases represented by chronic heart failure. Here, von Haehling and co-workers [18] discuss this important issue with great clinical implications in the advanced stages of such a pathogenic condition. During heart failure there is both a decrease in food intake and a malabsorption from the gut as a result of bowel wall edema contributing to the progression and devastating prognosis of the disease.

Numerous epidemiologic and intervention studies have been conducted to help provide dietary recommendations for optimal cardiovascular health. The most compelling data appear to come from trials that tested intervention diets rich in fruits, vegetables, MUFAs, and PUFAs, particularly the n-3 PUFAs. In addition, some degree of balance among various food groups appears to be a more sustainable behavioral practice than extreme restriction of a particular food group. In this issue, three different reviews [19–21] provide the scientific rationale of these studies both at the preclinical and clinical stages. Interestingly, although there is a general belief that such compounds have anti-arrhythmogenic effects, Coronel et al. [22] showed that dietary n-3 fatty acids promote late phase of arrhythmogenesis excitability during acute myocardial ischemia in isolated and perfused pig hearts. Overall, these data suggest caution in the clinical use of these supplements during acute myocardial ischemia. Altered Na^{+}–Ca^{2+} exchanger (NCX) activity has been implicated in arrhythmias, hypertension, and heart failure and may be a molecular target for PUFAs. Here, Ander et al. [23] investigated the effects of alpha-linolenic and other fatty acids on the cardiac (NCX1.1) and vascular (NCX1.3) NCX isoforms in isolated rat ventricular cardiomyocytes and rabbit vascular smooth muscle cells in vitro. They discovered that NCX1.3 is more sensitive to inhibition by alpha-linolenic acid, and omega 3-PUFA inhibited NCX.1.1. These data may have clinical applications in CVD if they are confirmed in vivo and in humans.

Similarly, the possible role of dietary polyphenols in the prevention of CVD was investigated intensively in this issue [21,24,25]. These natural compounds possess a well recognized plethora of biological effects; however, their molecular targets are less understood. Overall, polyphenols have antioxidant, anti-inflammatory, and cell-cyle regulatory effects. Here, the beneficial effects on endothelial function and vascular damage of polyphenols contained in Concord grape juice and in pomegranate-derived juices were examined in two exhaustive studies by Anselm et al. [26] and de Nigris et al. [27], respectively. Also, the dietary flavonoid quercetin exerts systemic and coronary vasodilator effects in experimental models, and its consumption is associated with reduced CVD in epidemiological studies. Here, Cogolludo and co-workers [28] show that quercetin increased large conductance Ca^{2+}–activated K^{+} channel (BKCa) currents via production of cytosolic H_2O_2 in isolated rat myocytes, suggesting that this pathway plays a role in the coronary vasodilator actions of quercetin. An effector pathway of polyphenols and other dietary supplements such as L-arginine, citrulline, and antioxidants converging on nitric oxide has been recently clarified to be involved in vascular protection and atherogenesis [29]. Here, Brunini et al. [30] hypothesized also the beneficial role of L-arginine supplementation on nitric oxide synthesis and vascular function in malnourished patients with chronic renal failure.

Another important issue is represented by the complex interplay of physical exercise and nutrition in the pathogenesis of CVD. Here, we have attempted to address this topic [21]. It is well established that resistance exercise training (RT) and subsequent increases in muscle mass may reduce multiple CVD risk factors [21,31]. The inclusion of RT as part of an exercise program for promoting health and preventing disease has been endorsed by the American Heart Association, the American College of Sports Medicine, the European Society of Cardiology, and the American Diabetes Association. To date, however, the evidence that RT reduces CV risk factors and at which degree concurrent nutritional habits can contribute to this effect remains equivocal. The quantitative relationship

between these risk factors and CV events has been elucidated by the early Framingham Heart Study [32] and other studies. However, the joint safety and effectiveness of RT and dietary advice in other populations of CVD patients (eg, women, older patients with low aerobic fitness, patients with heart failure) have not been well studied. Moreover, there is only a limited literature assessing the independent benefits of RT on CVD risk factors in patients with established CVD. Studies in cooperation with comprehensive cardiac rehabilitation programs typically include the confounding influences of aerobic activity, initiation of vasoactive and lipid-lowering drugs, and nutritional education with subsequent dietary modifications.

Changes in dietary habits are generally cost-effective, and the means are widely available. Through heightened attention of health professionals and the public to current data on appropriate nutritional practices, better measures can be adopted to help reduce CVD risk at the public health level, both for youths and adults. The association between nutritional and genetic factors will be clarified, as well as the forecast that in the future it may be possible to tailor dietary and physical exercise advice on preventing CVD more precisely to the individual's particular risk profile. The prevention of vascular damage and CVD should start earlier than previously assumed (i.e., in children) with special medical attention to maternal hypercholesterolemia during pregnancy (Ref. [3] and reviewed in [33]). Furthermore, many emerging studies indicate that maternal over-nutrition is deleterious to the health of offspring and can result in a phenotype of the offspring that is characteristic of metabolic syndrome (reviewed in [34] and [35]). It is clear that dietary modifications need to start very early in life to produce significant results in the prevention and natural history of CVD. The clinical perspectives in this Spotlight Issue are crucial because translation of any preclinical strategy into the clinical arena is a validation of its importance as a therapy in man.

References

[1] Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. JAMA 2002;288:2569–78.

[2] Parikh P, McDaniel MC, Ashen MD, Miller JI, Sorrentino M, Chan V, et al. Diets and cardiovascular disease: an evidence-based assessment. J Am Coll Cardiol 2005;45:1379–87.

[3] Napoli C, Lerman LO, de Nigris F, Goessl M, Balestrieri ML, Lerman A. Rethinking primary prevention of atherosclerosis-related diseases. Circulation 2006;114:2517–27.

[4] Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. JAMA 2002;288: 1723–7.

[5] Seidell JC. Epidemiology of obesity. Semin Vasc Med 2005;5:3–14.

[6] Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, et al. A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med 2003;348:2082–90.

[7] Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Ann Intern Med 2004;140:778–85.

[8] Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. J Clin Endocrinol Metab 2003;88:1617–23.

[9] Reddy ST, Wang CY, Sakhaee K, Brinkley L, Pak CY. Effect of low-carbohydrate high-protein diets on acid–base balance, stone-forming propensity, and calcium metabolism. Am J Kidney Dis 2002;40: 265–74.

[10] Gould KL. Diagnosing essential fatty acid deficiency. Circulation 1998;97:2581–3.

[11] Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. Br Med J 2006;332:752–60.

[12] Mundy AL, Haas E, Bhattacharya I, Widmer CC, Kretz M, Hofmann-Lehmann R, et al. Fat intake modifies vascular responsiveness and receptor expression of vasoconstrictors: implications for diet-induced obesity. Cardiovasc Res 2007;73:368–75.

[13] Sharma N, Okere IC, Duda MK, Chess DJ, O'Shea KM, Stanley WC. Potential impact of carbohydrate and fat intake on pathological left ventricular hypertrophy. Cardiovasc Res 2007;73:257–68.

[14] Finck BN. The PPAR regulatory system in cardiac physiology and disease. Cardiovasc Res 2007;73:269–77.

[15] Fauconnier J, Lanner JT, Sultan A, Zhang SJ, Katz A, Bruton JD, et al. Insulin Potentiates TRPC3-mediated cation currents in normal but not in insulin-resistant mouse cardiomyocytes. Cardiovasc Res 2007;73: 376–85.

[16] Folmes CDL, Lopaschuk GD. Role of malonyl-CoA in heart disease and the hypothalamic control of obesity. Cardiovasc Res 2007;73: 278–87.

[17] Fülöp N, Marchase RB, Chatham JC. Role of protein O-linked *N*-acetyl-glucosamine in mediating cell function and survival in the cardiovascular system. Cardiovasc Res 2007;73:288–97.

[18] von Haehling S, Doehner W, Anker SD. Nutrition, metabolism, and the complex pathophysiology of cachexia in chronic heart failure. Cardiovasc Res 2007;73:298–309.

[19] von Schacky C, Harris WS. Cardiovascular benefits of omega-3 fatty acids. Cardiovasc Res 2007;73:310–5.

[20] Den Ruijter HM, Berecki G, Opthof T, Verkerk AO, Zock PL, Coronel R. Pro- and antiarrhythmic properties of a diet rich in fish oil. Cardiovasc Res 2007;73:316–25.

[21] Ignarro LJ, Balestrieri ML, Napoli C. Nutrition, physical activity and cardiovascular disease: an update. Cardiovasc Res 2007;73:326–40.

[22] Coronel R, Wilms-Schopman FJG, Den Ruijter HM, Belterman CN, Schumacher CA, Opthof T, et al. Dietary n-3 fatty acids promote arrhythmias during acute regional myocardial ischemia in isolated pig hearts. Cardiovasc Res 2007;73:386–94.

[23] Ander BP, Hurtado C, Raposo CS, Maddaford TG, Deniset JF, Hryshko LV, et al. Differential sensitivities of the NCX1.1 and the NCX1.3 isoforms of the Na^+–Ca^{2+} exchanger to α-linolenic acid. Cardiovasc Res 2007;73:395–403.

[24] Halliwell B. Dietary polyphenols: good, bad, or indifferent for your health? Cardiovasc Res 2007;73:341–7.

[25] Stangl V, Dreger H, Stangl K, Lorenz M. Molecular targets of tea polyphenols in the cardiovascular system. Cardiovasc Res 2007;73: 348–58.

[26] Anselm E, Chataigneau M, Ndiaye M, Chataigneau T, Schini-Kerth VB. Grape juice causes endothelium-dependent relaxation via redox-sensitive Src- and Akt-dependent activation of eNOS. Cardiovasc Res 2007;73:404–13.

[27] de Nigris F, Ignarro-Williams S, Sica V, Lerman LO, D'Armiento FP, Byrns RE, et al. Effects of a pomegranate fruit extract rich in punicalagin on oxidation-sensitive genes and eNOS activity at sites of perturbed shear–stress and atherogenesis. Cardiovasc Res 2007;73:414–23.

[28] Cogolludo A, Frazziano G, Briones AM, Cobeno L, Moreno L, Lodi F, et al. The dietary flavonoid quercetin activates BKCa currents in coronary arteries via production of H_2O_2. Role in vasodilatation. Cardiovasc Res 2007;73:424–31.

[29] Napoli C, de Nigris F, Williams-Ignarro S, Pignalosa O, Sica V, Ignarro LJ. Nitric oxide and atherosclerosis: an update. Nitric Oxide 2006;15:265–79.
[30] Brunini TMC, Mendes-Ribeiro AC, Ellory JC, Mann GE. Platelet nitric oxide synthesis in uremia and malnutrition: a role for L-arginine supplementation in vascular protection? Cardiovasc Res 2007;73: 359–67.
[31] Fletcher GF, Balady G, Blair SN, Blumenthal J, Caspersen C, Chaitman B, et al. Statement on exercise: benefits and recommendations for physical activity programs for all Americans: a statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. Circulation 1996;94:857–62.
[32] Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–47.
[33] Napoli C, Palinski W. Maternal hypercholesterolemia during pregnancy influences the later development of atherosclerosis: clinical and pathogenic implications. Eur Heart J 2001;22:4–9.
[34] Armitage JA, Taylor PD, Poston L. Experimental models of developmental programming: consequences of exposure to an energy rich diet during development. J Physiol 2005;565:3–8.
[35] Poston L. Intrauterine vascular development: programming effects of nutrition on vascular function in the new born and adult. Nutr Health 2001;15: 207–12.