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Mediterranean diet and cardiovascular disease: A step closer to mechanisms using a precision animal model?

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Coronary heart disease (CHD), the leading cause of mortality in the U.S. and other western countries, is a multifactorial disease. As a result of extensive investigations spanning several decades, many contributing factors, such as age, sex, smoking, hypertension, obesity and a high cholesterol level have been identified, and these factors are now known as well-established or traditional risk factors for CHD. Novel factors, including biomarkers of vascular endothelial dysfunction, inflammation, genetics, and dyslipidemia [e.g. small dense low-density lipoprotein and lipoprotein(a)], have emerged recently and their association with CHD, as well as their potential for predicting future risk have been tested in many studies with some showing considerable promise. The diet-heart theory described more than six decades ago by Dr. Ancel Keys, the founder of “The Seven Countries Study” (SCS), has remained central in shaping the efforts to reduce global risk of CHD based on lifestyle modification. The SCS was the first epidemiological longitudinal study systematically investigating the relationship between lifestyle, diet, CHD and stroke risks in multiple populations representing different regions of the world with contrasting dietary patterns [1]. Dr. Keys and his colleagues demonstrated a direct and independent association between the serum total cholesterol level and the risk and rates of heart attack and stroke both at the population and at the individual level across diverse cultures. Through studies like these, the importance of the Mediterranean diet in modulating CHD risk, the impact of changes in lifestyle and diets of populations in the Mediterranean region on the rates of heart disease, and associations between food composition (e.g., saturated fatty acids, mono- and polyunsaturated fatty acids, etc.) and coronary death rate have been explored [2-4].

The traditional Mediterranean style diet has been associated with a low risk of CHD in previous studies [5, 6]. The diet is high in monounsaturated fat, such as olive oil and in cereal products, legumes, fruits and vegetables. The diet is also characterized by a moderate fish consumption and a low intake of dairy and meat products, as well as a moderate wine consumption. A recent large prospective cohort study confirmed an inverse association between adherence to the Mediterranean diet and the incidence of fatal and non-fatal CHD in initially healthy middle-aged individuals [7]. Another recent large randomized intervention trial (the PREDIMED Study) among individuals at high cardiovascular risk

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showed that a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events [8]. Together these studies provide strong support for a beneficial effect of the Mediterranean diet. This effect is thought to be mediated through multiple mechanisms in a variety of systems, including blood lipids and lipoproteins, vascular endothelium and modulation of inflammation. The positive effects are thought to be driven from the nutritional components of the diet, including fibers, plant sterols and stanols, flavonoids, antioxidants and polyunsaturated fatty acids, particularly omega 3 fatty acids. It is notable that a protective effect with regard to cardiovascular disease has been seen in the absence of any changes in levels of lipids and lipoproteins [5].

In this context, the study by Vilahur et al. published in this issue of Translational Research [9], offers some opportunities for additional mechanistic insight. The authors systematically analyzed the effects of supplementing the diet with cooked tomato sauce (CTS) in Mediterranean style (sofrito) on coronary endothelial dysfunction, molecular pathways and lipoprotein properties. The authors, using an animal model (i.e. pigs), demonstrated that dietary supplementation with 100 g CTS per day, a level within the consumption range of tomatoes in Europe, can prevent diet-induced impairment of receptor- and non-receptor operated endothelial-dependent coronary vasodilation. The design of the study illustrates some important key principles. First, the authors used an animal model allowing detailed physiological assessment where the cardiovascular system mirrors human conditions. This approach fits well into the emerging concept of using precision animal models to more carefully reflect naturally occurring conditions in humans. Second, the measurements undertaken reflected physiological conditions going beyond isolated measurements of individual markers. Further, this was supplemented by molecular characterization of candidate pathways. Third, the intervention was based on a comprehensive food product, being a part of the human food pattern, rather than a single component or a nutritional supplement of the most plausible, but perhaps not the only, active ingredient (lycopene). Fourth, the authors were able to link HDL functional properties to proteomic characterization. Altogether, the approach was mechanistic going beyond a characterization of individual markers, which gives the study a translational focus.

In keeping with the physiological focus, the animals were fed an atherogenic diet containing 20% saturated fat, 2% cholesterol, and 1% cholic acid for 10 days, which led to hyperlipidemia closely resembling that of humans. In these hyperlipidemic animals, CTS supplementation providing 21.5 mg lycopene per day resulted in marked improvements of coronary vasodilatory capabilities assessed by responses to intracoronary delivery of endothelium-dependent (acetylcholine and calcium ionophore agonists) and endothelium-independent (sodium nitroprusside) vasodilators. It should be noted that the authors undertook the study using female pigs and that any potential gender-specific effects were beyond the scope of the current study.

Lycopene, the main carotenoid of tomato, is a potent scavenger of reactive oxygen species, which cause oxidative damages to cellular components of cardiovascular system. Indeed, the authors, in support of likely mechanisms underlying the CTS-induced preservation of vascular function, showed an enhanced eNOS transcription and activation, and diminished DNA damage in the coronary arteries. Despite a lack of change in lipid levels, CTS-

supplemented animals exhibited lower lipid peroxidation and a higher HDL-antioxidant potential with a protein profile change of two main apolipoproteins (Apo A-I and Apo J). The authors conclude that their findings identified CTS as a natural dietary antioxidant capable of providing cardiovascular protection by reducing oxidative stress, acting on coronary eNOS transcription and activity and promoting HDL functionality by ameliorating its apolipoprotein profile. However, the systems addressed in the study are complex and many contributory mechanisms may be in play. The role of HDL is well established with regard to protection against cardiovascular disease, but beyond this, detailed mechanisms underlying the anti-atherogenic effect of HDL in any given condition remains somewhat elusive. The relative contribution of each of the likely suspects, being enhanced reverse cholesterol transport, antioxidative effects, anti-inflammatory effects or other possibilities have been challenging to characterize in a conclusive fashion. Therefore, although the authors were able to associate proteomic HDL changes with functional aspects, more studies are needed to firmly establish this relationship. The need to translate these findings to a clinical setting (i.e. human subjects) as well as utilization of CTS and/or other tomato-based products as preventive tools to improve overall cardiovascular health warrants further investigation. Through the elegant studies undertaken by Vilahur and colleagues [9], the authors have provided a promising foundation for well-designed large-scale future studies needed to shed further lights into this important question.

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