ORIGINAL ARTICLES

Intake of cooked tomato sauce preserves coronary endothelial function and improves apolipoprotein A-I and apolipoprotein J protein profile in high-density lipoproteins

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Intake of tomatoes has been linked with healthy diets (eg, Mediterranean diet). However, it remains unknown whether tomato intake exerts protective effects on the vasculature. The aim of this study was to determine whether medium-term supplementation with cooked tomato sauce (CTS) Mediterranean style (sofrito) attenuates diet-induced coronary endothelial dysfunction in an animal model with clinical impact and explore the mechanisms behind the effects. Pigs (N = 18) were fed a 10-day hypercholesterolemic diet. Half of the animals were given a supplement of 100 g/d of CTS (21.5 mg lycopene per day). Coronary responses to escalating doses of vasoactive drugs (acetylcholine, calcium ionophore, and sodium nitroprusside) and L-NG-monomethylarginine (endothelial nitric oxide synthase (eNOS) inhibitor) were measured using flow Doppler. In the coronary arteries, we investigated eNOS gene expression and activation, monocyte chemoattractant protein 1 (MCP-1) expression, and oxidative DNA damage. In the circulation, we investigated lipoprotein resistance to oxidation and the differential proteomic protein profile. In dyslipidemic animals, CTS intake prevented diet-induced impairment of receptor-operated and nonreceptor-operated endothelial-dependent coronary vasodilation. These beneficial effects were associated with enhanced eNOS transcription and activation and diminished DNA damage in the coronary arteries. CTS-fed animals showed lower lipid peroxidation, higher high-density lipoprotein (HDL) antioxidant potential and plasma lycopene levels of 0.16 mg/L. Interestingly, improved HDL functionality was associated with protein profile changes in apolipoprotein A-I and apolipoprotein J. Lipids levels and MCP-1 expression were not affected by CTS. We report that CTS intake protects against low-density lipoprotein–induced coronary endothelial dysfunction by reducing oxidative damage, enhancing eNOS expression and activity, and improving HDL functionality. (Translational Research 2015;166:44–56)

Abbreviations: CHD = coronary heart disease; CTS = cooked tomato sauce; CV = cardiovascular; HDL = high-density lipoprotein; LDL = low-density lipoprotein

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AT A GLANCE COMMENTARY

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Background

Intake of tomatoes has been linked with healthy diets (eg, Mediterranean diet). However, it remains unknown whether tomato intake exerts protective effects on the vasculature.

Translational Significance

We provide evidence that medium-term supplementation with cooked tomato sauce Mediterranean style (sofrito) attenuates diet-induced coronary endothelial dysfunction in an animal model with clinical impact. These beneficial effects are associated with enhanced endothelial nitric oxide synthase transcription and activation, lower vascular DNA oxidative damage and improved high-density lipoprotein functionality (protein profile changes in apolipoprotein A-I and apolipoprotein J).

INTRODUCTION

Healthy diets have shown to play a significant role in the prevention of coronary heart disease (CHD), the leading cause of death in the Western countries.[1] Several epidemiologic and prospective studies have provided convincing evidence that a diet rich in a variety of fruits and vegetables (eg, the Mediterranean diet) results in a lower risk of developing CHD.[2-5] In this regard, dietary intake of tomatoes and tomato-based products has been associated with lower risk of CHD and myocardial infarction.[6-8] However, the mechanisms behind such cardiovascular (CV) beneficial effects remain unclear. Despite the fact that tomatoes are a valuable source of micronutrients, tomato-related health benefits have been mainly ascribed to the presence of lycopene, the main tomato carotenoid.[7] The European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer (EURAMIC) multicenter case-control study reported that high lycopene levels in adipose biopsy specimens were found to be protective against myocardial infarction.[3] The protective effects of tomato ingredients have been mainly attributed to their capacity to prevent atherogenesis by their antioxidant properties, which play a crucial role. Indeed, lycopene has been found to protect lymphocyte DNA, plasma proteins, and low-density lipoprotein (LDL) against oxidative damage.[9,10] Moreover, few in vitro studies have also documented other lycopene-related antiatherogenic effects including anti-inflammatory properties and prevention of vascular smooth muscle cell migration and proliferation.[11,12] Human studies are inconclusive, however, regarding the potential benefits of tomato over the endothelium, a key determinant of CV health. Some studies report vascular improvements, whereas others report no effects.[12-14] Noteworthy, all studies conducted so far have been carried out on healthy subjects. Therefore, the effect of tomatoconsumption in the presence of comorbid conditions (eg, hyperlipemia) known to result in endothelial impairment remains to be investigated. Indeed, endothelial dysfunction is considered one of the earliest markers of atherosclerosis[15,16] and is associated with an increased risk of CV events.[17,18]

With all this in mind we have assessed, in a well-characterized preclinical animal model, whether a 10-day intake of a commercially available cooked tomato sauce (CTS; 100 g/d sofrito) protects against hypercholesterolemia-induced coronary endothelial dysfunction. Moreover, we have further explored the mechanisms behind such potential beneficial effects by histological, molecular and serum proteomic approaches.

MATERIALS AND METHODS

The study protocol was approved by the institutional ethics committee (Consejo Superior de Investigaciones Científicas- Instituto Catalán de Ciencias Cardiovasculares [CSIC-ICCC]) and all animal procedures performed conformed to the guidelines from Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes or the National Institutes of Health guidelines. In addition, we have followed the animals in research: reporting in vivo experiments (ARRIVE) guidelines.[19]

Study design. Eighteen crossbred commercial female swine were fed a high-fat diet (Western-type hypercholesterolemic diet [WT-diet], 20% saturated fat [beef tallow], 2% cholesterol, and 1% cholic acid) for 10 days. This hyperlipemic diet contains 20.2% proteins, 35.33% carbohydrates, 24.02% fats, 5% fiber, 6% minerals, and 9% water resulting in 20441 ± 372 kJ/kg. We have already reported that intake of this fat-rich diet (1.5 kg/d) for 10 days raises cholesterol to levels comparable with that found in dyslipidemic humans and induces endo-thelial dysfunction.[20] Half of the WT-diet animals were supplemented with CTS (WT + CTS; 100 g/d; 21.5 mg per lycopene). This dose was chosen based on previous studies on peripheral vascular reactivity studies carried out on healthy subjects and on the total