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Letters

Effects of 2-Year Walnut-Supplemented Diet on Inflammatory Biomarkers

Robust epidemiological evidence suggests that regular nut consumption is associated with lower cardiovascular disease (CVD) risk. As summarized in a recent meta-analysis of 19 prospective studies (1), when comparing extreme quantiles of total nut consumption (2.5 to 28 g/day), total CVD and CVD mortality were 15% and 23% lower, respectively. Walnut consumption independent from other nuts revealed similar inverse associations with CVD in 3 studies.

Nut consumption may be associated with lower CVD risk because nuts have a consistent cholesterol-lowering effect. A meta-analysis of 24 randomized controlled trials (RCTs) concluded that, compared with control diets, walnut-enriched diets resulted in significant weighted mean differences in low-density lipoprotein cholesterol (−5.5 mg/dl), but had no effect on blood pressure or high-sensitivity C-reactive protein (hs-CRP) (2). Nut-enriched diets also affect endothelial function, with weighted mean differences in flow-mediated dilatation of 0.79% in 8 RCTs (3). These modest salutary effects of nut diets, however, cannot fully account for the lower CVD outcomes observed in prospective studies. Given the prevailing theory that inflammation is a major driver of atherosclerosis, 1 potential mechanism linking nut consumption to reduced CVD might be diminished inflammation.

We hypothesized that incorporating walnuts into the usual diet would improve inflammatory biomarkers. Therefore, we assessed changes in circulating inflammatory molecules in the WAHA (Walnuts And Healthy Aging; NCT01634841) study, a dual-center (Hospital Clínic, Barcelona, Spain, and Loma Linda University, Loma Linda, California) RCT designed to evaluate walnut effects on age-related health outcomes in 708 healthy elders (63 to 79 years of age). Walnut consumption affected cognitive function, the main outcome, only in the high-risk subgroup (4). Changes in inflammatory markers were a pre-specified secondary outcome.

The ethics committees of each center approved the study protocol. After providing informed consent, participants were assigned to either a control diet with abstention from walnuts or a diet with walnuts at ≈15% of energy (30 to 60 g/day). After treatment allocation, participants were scheduled to visit the study dietitians once every 2 months for the duration of the study; they received tailored recommendations to follow the allocated diets and maintain their physical activity level. Those assigned the walnut group were provided 8-week allotments of raw pieced walnuts in sachets for daily consumption. At baseline and 2 years, we determined inflammatory biomarkers (**Table 1**) in fasting plasma by the Milliplex MAP assay using Luminex technology for cytokines (Merck Millipore, Darmstadt, Germany) and colorimetric-enzymatic methods for hs-CRP, ensuring rigorous quality control. Two-year differences in between-diet changes of inflammatory markers were analyzed by multivariate-adjusted analysis of covariance.

In this substudy, 634 participants had complete data (90% retention). Participants' clinical characteristics were similar to those of the parent cohort (4). Mean age was 69 years, 66% were women, and 32% were treated with statins. Compliance with the walnut diet was good, and there were no changes in body weight, as reported (4). Baseline and 2-year changes in inflammatory markers by group allocation are depicted in **Table 1**. Compared with the control diet, the walnut diet significantly reduced concentrations of 6 of 10 biomarkers examined. In-trial changes in main food groups were unrelated to changes of inflammatory molecules.

In conclusion, incorporating daily doses of walnuts at ≈15% of energy into the diet of free-living elders for 2 years reduced the concentrations of several inflammatory biomarkers. A recent meta-analysis of 25 RCTs concluded that nuts had no effect on inflammation (3), but most studies had small sample sizes and a short follow-up, whereas the WAHA study is the largest and longest nut trial to date. Concurring with prior meta-analytical data from walnuts (2) and total nuts (3), we found no effect on hs-CRP. However, we observed a beneficial impact on other relevant inflammatory molecules, including interleukin-1β, a

cytokine for which inactivation with the human monoclonal antibody canakinumab resulted in prevention of recurrent coronary artery disease in a landmark RCT (5). The anti-inflammatory effect of long-term consumption of walnuts demonstrated in this study provides novel mechanistic insight for the benefit of walnut consumption on CVD risk beyond that of lipid lowering.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

TABLE 1 Baseline Concentrations and Changes in Circulating Inflammatory Biomarkers by Intervention Group

Biomarker	Walnut Diet (n = 324)	Control Diet (n = 310)	p Value*
GM-CSF, pg/ml			
Baseline	18.2 (16.4 to 20.0)	17.9 (16.0 to 19.9)	0.837
Change	−2.10 (−2.89 to −1.31)	−0.002 (−0.81 to 0.82)	<0.001
Percent change	−11.5 (−15.9 to −7.2)	−0.01 (−4.5 to 4.6)	
IFN-γ, pg/ml			
Baseline	16.2 (15.4 to 17.0)	15.2 (14.3 to 16.0)	0.083
Change	−1.35 (−1.81 to −0.89)	−0.09 (−0.55 to 0.38)	<0.001
Percent change	−8.3 (−11.2 to −5.5)	−0.6 (−3.6 to 2.5)	
IL-1β, pg/ml			
Baseline	1.19 (1.12 to 1.26)	1.14 (1.08 to 1.21)	0.354
Change	−0.12 (−0.16 to −0.08)	−0.02 (−0.06 to 0.02)	<0.001
Percent change	−10.1 (−13.4 to −6.7)	−1.8 (−5.3 to 1.8)	
IL-6, pg/ml			
Baseline	2.26 (2.09 to 2.44)	2.16 (1.98 to 2.33)	0.395
Change	−0.19 (−0.30 to −0.08)	−0.01 (−0.12 to 0.10)	0.021
Percent change	−8.4 (−13.3 to −3.5)	−0.5 (−5.6 to 4.6)	
TNF-α, pg/ml			
Baseline	6.09 (5.89 to 6.29)	5.86 (5.64 to 6.08)	0.135
Change	−0.40 (−0.57 to −0.24)	−0.09 (−0.26 to 0.08)	0.009
Percent change	−6.6 (−9.4 to −3.9)	−1.5 (−4.4 to 1.4)	
sE-selectin, ng/ml			
Baseline	49.4 (46.4 to 52.4)	47.1 (44.1 to 50.0)	0.277
Change	−1.66 (−2.67 to −0.65)	0.91 (−0.13 to 1.95)	0.001
Percent change	−3.5 (−5.6 to −1.5)	1.8 (−0.4 to 4.0)	
sICAM-1, ng/ml			
Baseline	1.37 (1.27 to 1.46)	1.24 (1.18 to 1.30)	0.037
Change	0.01 (−0.05 to 0.07)	0.03 (−0.03 to 0.09)	0.674
Percent change	1.5 (−2.9 to 5.1)	3.2 (−1.6 to 8.1)	
sVCAM-1, ng/ml			
Baseline	9.38 (9.14 to 9.63)	9.20 (8.96 to 9.44)	0.302
Change	−0.07 (−0.22 to 0.08)	0.04 (−0.11 to 0.20)	0.305
Percent change	−0.6 (−2.2 to 1.0)	0.7 (−1.1 to 2.3)	
SAA, ng/ml			
Baseline	106.9 (94.1 to 119.7)	106.6 (96.0 to 117.2)	0.970
Change	−2.40 (−11.12 to 6.31)	3.23 (−5.68 to 12.14)	0.377
Percent change	−2.2 (−10.4 to 5.9)	3.0 (−5.3 to 11.4)	
hs-CRP, mg/l			
Baseline	2.91 (2.22 to 3.60)	3.25 (2.62 to 3.88)	0.471
Change	−0.01 (−0.06 to 0.04)	−0.003 (−0.05 to 0.05)	0.903
Percent change	−2.8 (−19.6 to 14.1)	1.9 (−13.2 to 17.2)	

Values are mean (95% confidence interval). *Obtained by analysis of covariance of the change variables, adjusting for center, age, sex, hypertension, diabetes, education years, smoking, baseline statin use, in-trial statin changes, baseline body mass index, in-trial body mass index change, baseline physical activity, in-trial physical activity changes, and baseline cytokine values.

GM-CSF = granulocyte-monocyte colony stimulating factor; hs-CRP = high-sensitivity C-reactive protein; IFN = interferon; IL = interleukin; SAA = serum amyloid A; sE-selectin = soluble E-selectin; sICAM = soluble intercellular adhesion molecule; sVCAM = soluble vascular cell adhesion molecule; TNF = tumor necrosis factor.

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Pulmonary Artery Endovascular Device Compensates for Loss of Vascular Compliance in Pulmonary Arterial Hypertension

In pulmonary arterial hypertension (PAH), the resistance-compliance relationship of the pulmonary circulation shows an early loss of pulmonary arterial compliance (C_{PA}) (1), that is changed only modestly by currently available pharmacological treatments (2). We hypothesized that a distensible balloon within the main pulmonary artery (PA) augments C_{PA}.

On the basis of favorable results from in vitro desktop modeling and an in vivo experience with a prototype device implanted in calves during normobaric hypoxia (3), we tested the device in 10 PAH patients stable on multidrug therapy undergoing clinically indicated right heart catheterization. The objective was to evaluate device safety, its performance characteristics during rest and exercise, and its impact on pulmonary hemodynamics.

The ethics committee of the Medical University of Vienna approved the study, and all patients signed informed consent (#1046/2017). The Aria endovascular device system (Aria CV, St. Paul, Minnesota) consists of the Aria balloon catheter, a 14-F introduction catheter through the femoral vein, and a closed system, gas-filled reservoir that connects to the balloon catheter. The balloon catheter consists of a 15-ml Pellethane balloon (Catheter Research Incorporated, Indianapolis, Indiana) on a 4-lumen catheter. One lumen allows for gas cycling to and from the reservoir in response to cyclic PA pressure (PAP) changes. Another provides access for a 0.35-inch guide wire to facilitate device delivery and positional stability. The remaining 2 lumens accommodate pressure wires positioned proximal and distal to the balloon. The reservoir is a glass container with 2 connection ports, 1 for the balloon catheter and 1 to monitor reservoir pressure (**Figure 1A**). The device was placed in the main PA under fluoroscopic monitoring and systemic heparinization. During systole, intrinsic PAP is greater than the pressure in the reservoir and consequently forces gas flow from the balloon into the reservoir, mimicking the capacitance effect of normally distensible PAs. During diastole, intrinsic PAP falls below the pressure in the reservoir, and gas flow reverses, moving back into the balloon during diastole. Balloon inflation increases PAP and restores diastolic pulmonary blood flow into the lung capillary bed. Balloon inflation and deflation were monitored under fluoroscopy. Changes in hemodynamics were assessed using the paired samples Student's *t*-test, with significance inferred at $p < 0.05$.

PAP and right ventricular pressures were assessed using the pressure wires under the following 4 conditions, in sequence: 1) rest device off; 2) rest device on; 3) exercise device off; and 4) exercise device on. Pulmonary and systemic arterial blood gases were analyzed under each condition, and oxygen consumption was measured via expired gas analysis (Vyntus CPX, Vyaire Medical, Chicago, Illinois) continuously throughout the whole study to assess cardiac output (CO) with the direct Fick method. Right ventricular-to-PA coupling was assessed using the simplified single-beat approach (4).

The mean age of patients was 52 ± 17 years (range 21 to 75 years); 4 patients were female. Eight patients were in World Health Organization functional class III, the remaining were in functional class II. Six patients had idiopathic PAH, 2 had drug- and toxin-induced PAH, and 2 had PAH associated with congenital heart disease (1 corrected ventricular and 1 open atrial septal defect). At the time of the intervention, the mean PAP was 48.8 ± 11.9 mm Hg, CO was 7.1 ± 1.7 l/min, and pulmonary vascular resistance was 6.0 ± 2.6 WU. Total procedural time was 59.8 ± 29.5 min. Handgrip exercise hemodynamics were assessed in 6 patients. No complications or adverse events occurred within 30 days.

At rest, pulse pressure decreased acutely (47.6 ± 12.1 mm Hg to 44.1 ± 11.6 mm Hg), and CO (6.8 ± 1.7 l/min to 7.5 ± 2.2 l/min), C_{PA} (2.1 ± 1.0 to 2.5 ± 1.2) (**Figure 1B**), and end-systolic elastance (E_{es})/effective arterial elastance (E_a; 1.01 ± 0.25 to 1.27 ± 0.21) increased significantly with the device on (all $p < 0.01$). During exercise, the same changes occurred as when the balloon was activated at rest, yet with a greater magnitude (CO 8.5 ± 2.9 l/min to 10.3 ± 2.9 l/min; C_{PA} 1.7 ± 0.7 to 2.3 ± 1.0; E_{es}/E_a 1.01 ± 0.37 to 1.26 ± 0.24; all $p < 0.05$).