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Letters

Effect of Lifestyle Modification and Green Mediterranean Diet on Proximal Aortic Stiffness

Proximal aortic stiffness (PAS), reflecting the aortic stiffness from the ascending to the proximal descending thoracic aorta, is a distinct marker of vascular aging and a sensitive early predictor of cardiovascular morbidity and mortality risk.[1] Beyond aging, and similarly to atherosclerosis, PAS is sensitive to obesity-related metabolic conditions, specifically metabolic syndrome.[1]

Lifestyle modification is the first and most widely taken intervention for treating obesity and its metabolic complications. Although intense physical activity (PA) intervention reduces PAS,[2,3] the effect of weight loss interventions on PAS remains uncertain. The Mediterranean diet is the most substantiated dietary intervention for cardiometabolic risk reduction and cardiovascular disease prevention. However, the effects of the Mediterranean diet on PAS are unclear.

Recently, we reported that hypocaloric-green-Mediterranean (hGreen-Mediterranean), enriched with plant-based polyphenols and lower in red/processed meat and simple carbohydrates, might offer benefits beyond hypocaloric-Mediterranean (hMediterranean) and healthy dietary guidelines (HDG) to improve cardiometabolic risk,[4] to optimize microbiome signatures, and to regress intrahepatic fat and visceral adiposity.[5] In this study, we aimed to address the effects of distinct lifestyle interventions on PAS, a secondary outcome of the DIRECT-PLUS (Effects of Green-MED Diet Via the Gut-fat-brain Axis) trial.

What is the clinical question being addressed?
What are the effects of long-term dietary interventions on proximal aortic stiffness?

What is the main finding?
Healthy dietary intervention promotes regression of proximal aortic stiffness independent of weight loss.

In the 18-months DIRECT-PLUS (Effects of Green-MED Diet Via the Gut-Fat-Brain Axis; NCT03020186) study, we randomized participants aged ≥30 years with abdominal obesity/dyslipidemia to 1 of 3 diets: HDG, hMediterranean, or hGreen-Mediterranean. All study groups were instructed to engage in PA. Both hMediterranean diets were similarly hypocaloric (men: 1,500-1,800 kcal/day; women: 1,200-1,400 kcal/day) and included 28 g/day of walnuts. The hGreen-Mediterranean dieters further consumed green tea (3 to 4 cups/day) and a *Wolffia globosa* (Mankai) plant green shake and were guided to avoid processed and red meat. PAS was expressed by aortic arch pulse wave velocity using vector cardiac-gated magnetic resonance imaging (MRI) at baseline and after 18 months. The cardiac cycle was retrospectively reconstructed into 40 phases, resulting in an effective temporal resolution of 20 to 38 ms. PAS was expressed by aortic arch pulse wave velocity, which was calculated by dividing the aortic path (the distance between the ascending and descending aorta) by the temporal shift (measured by the least-square estimate of the systolic upslope of the ascending and descending aorta optimal sigmoid flow curves). Soroka University Medical Center Ethics Committee and Institutional Review Board approved the study protocol.

Because ΔPAS did not distribute normally, ln-transformed PAS values for evaluating between-group differences were used in univariate analysis of covariance models and were adjusted for baseline ln(PAS), age, sex, Δweight, dyslipidemia, hypertension, diabetes, and baseline and changes in mean arterial pressures. Analyses were performed in an intention-to-treat manner for the primary outcome variables. Missing data occurred among 63 participants (22.3%) who dropped out from the trial or did not have follow-up PAS measurements; these participants had similar characteristics. Missing data were completed using multiple-imputation techniques based on age, sex, baseline PAS, baseline weight, and $\Delta\text{weight}_{18\text{-months}}$.

Of 294 participants (age 51 ± 10.6 years, body mass index 31.3 ± 4.0 kg/m^2), 281 had valid baseline PAS measurements. The baseline PAS (6.1 ± 2.7 m/s) was similar across intervention groups (P = 0.20). Increased PAS was associated with aging, hypertension, dyslipidemia, diabetes, and visceral adiposity

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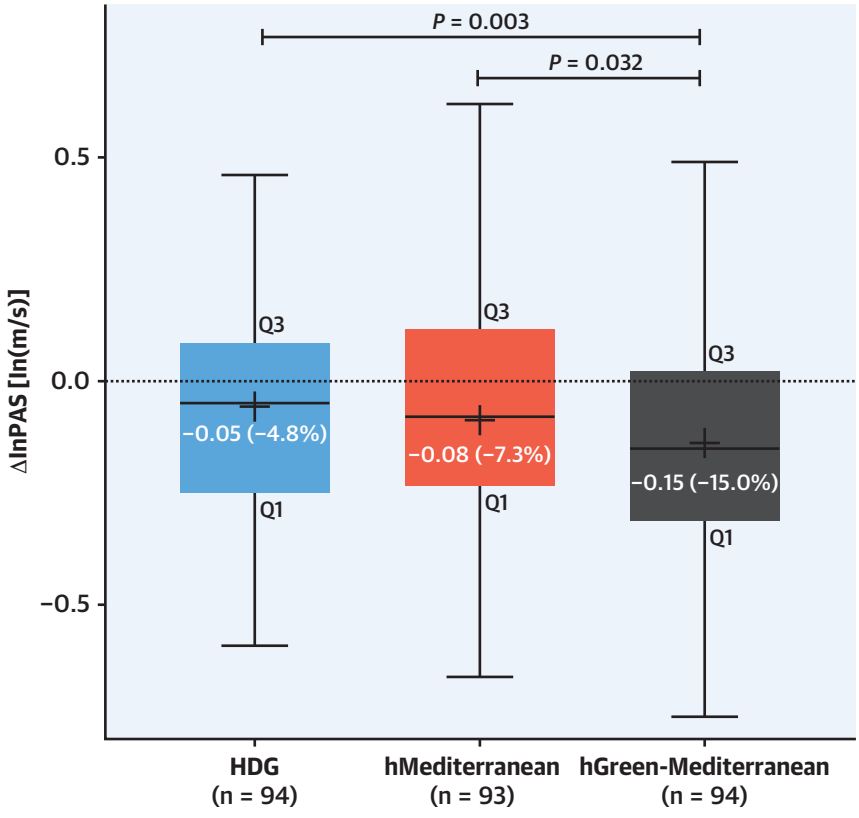
FIGURE 1 PAS Changes Across Intervention Groups



Comparison of proximal aortic stiffness (PAS) changes among 3 interventions: healthy dietary guidelines (HDG), hypocaloric-Mediterranean diet (hMediterranean), and hypocaloric-green-Mediterranean (hGreen-Mediterranean). Data are presented as raw natural logarithmic (ln) transformed PAS changes by Tukey's boxplots. Q denotes quartile, + denotes the group's mean, and corresponding medians of proportional PAS changes are denoted in parentheses. Between-group differences in ln(PAS) were compared using analysis of covariance models adjusted for age, sex, ln(baseline PAS), Δweight%, hypertension, dyslipidemia, diabetes, and baseline and changes of mean arterial pressures. Although all interventions were associated with lowering of PAS, hGreen-Mediterranean dieters had greater reduction in PAS compared with hMediterranean and HDG dieters ($P = 0.032$ and $P = 0.003$, respectively). These results suggest that hGreen-Mediterranean diet may promote greater PAS regressions than hMediterranean and HDG diets, irrespective of weight loss.

($P < 0.05$). After 18 months' intervention (retention rate 89.8%), all diet groups showed significant PAS reductions (Figure 1): HDG −0.05 ln(m/s) (IQR: −0.25 to 0.08 ln[m/s]) (−4.8%); hMediterranean −0.08 ln(m/s) (IQR: −0.23 to 0.11 ln[m/s]) (−7.3%); hGreen-Mediterranean −0.15 ln(m/s) (IQR: −0.31 to 0.02 ln [m/s]) (−14.0%); $P < 0.05$ for within-group changes. The hGreen-Mediterranean dieters had greater PAS reduction than HDG and hMediterranean dieters ($P = 0.003$ and $P = 0.032$, respectively; multivariable model).

This study, to our knowledge, is the first to show that PAS might be regressed by maintaining a healthy lifestyle. Namely, and beyond weight loss, the hGreen-Mediterranean diet may have greater influence on PAS regression, a predictor of lower risk of cardiovascular disease, compared with the HDG diet, which was marginally evident and compared with the hMediterranean diet. Two previous studies showed that PAS might be regressed through lifestyle intervention,[2,3] involving, however, intense PA interventions ranging from 20 weeks to 6 months.

Some limitations should be considered. The study population comprised mostly men, reflecting the unique workplace where the study was performed. During the MRI, we did not measure blood pressure, to which PAS may be sensitive. However, analyses were adjusted for baseline and changes in office mean arterial pressure. The DIRECT-PLUS study had multiple endpoints; thus, this exploratory post hoc analysis might be sensitive to type I statistical error and should be considered hypothesis-generating by

nature. The study's major strengths are the highly supervised conditions, the long intervention duration, the use of MRI that allows highly accurate estimation of PAS, the high retention rate, and the intervention-implementation feasibility in real life.

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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 Author Center.

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