Impact of a lifestyle intervention program with energy-restricted Mediterranean diet on cardiovascular risk factors, blood biomarkers of inflammation and plaque instability in elderly subjects with metabolic syndrome after one year

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Background and objectives: Cardiometabolic diseases and obesity are major contributors to morbimortality. Long-term adherence to an *ad libitum* Mediterranean diet (MedDiet) has a protective impact on the progression of atherosclerosis and inflammatory biomarkers. Thus, the aim of this study was to assess the effect of an energy-reduced Mediterranean diet in cardiovascular risk factors and biomarkers of inflammation and plaque instability in elderly subjects with metabolic syndrome (MetS) after 12 months.

Methods: This substudy of the PREDIMED-Plus, a randomized parallel controlled trial, was conducted in subjects with obesity or overweight with MetS (55-75 years). The intervention group followed an energy-restricted MedDiet (erMedDiet) focused on weight loss, plus physical activity and behavioral support. Control group followed an *ad libitum* MedDiet. Anthropometric, biochemical, and 10 inflammatory and plaque instability blood biomarkers were assessed at baseline and after 1 year follow-up by Luminex® and Enzyme-Linked Immunosorbent Assay. Data were analyzed by repeated-measures 2-factor ANOVA.

Results: 150 Spanish subjects (47% women, mean age: 66.2 ± 4.4) were randomized: 75 to the erMedDiet and 75 to the control MedDiet, with no-significant differences among groups at baseline. After 12 months the erMedDiet group showed a significant improvement in cardiovascular risk factors: body weight, waist circumference, BMI, systolic and diastolic blood pressure, fasting blood glucose, HbA1c, triglycerides, total cholesterol to HDL cholesterol ratio and HDL cholesterol; and reduced their serum levels of inflammation and plaque instability biomarkers: ICAM-1, IL-6, IL-18, MMP-9, Endothelin-1, MCP-1 and SST-2. While the control MedDiet group improved waist circumference, systolic and diastolic blood pressure. Compared to the control MedDiet, the erMedDiet had a greater reduction in body weight [-2.9 kg (95% CI -3.8, -2.0), *P*-value between groups <0.001], waist circumference [-3.0 cm (-4.0, -2.0), *P*=0.03], BMI [-1.0 kg/m^2 (-1.3, -0.6), *P*<0.001], fasting glucose [-5.4 mg/dL (-8.9, -1.9), *P*=0.04] and HDL cholesterol [2.9 mg/dL (1.0, 4.8), *P*<0.01], as well as in IL-6 [-0.6 mg/mL (-1.3, 0.003) *P*=0.01] and MPC-1 [-8.6 mg/mL (-15.8, -1.5), *P*=0.02].

Discussion and Conclusion: After one year, both Mediterranean diets demonstrated a protective effect on cardiometabolic parameters in the elderly; however, only the erMedDiet seemed to modulate inflammation and plaque instability biomarkers.

Summarized CV of the first author: Ana Maria Ruiz-Leon graduated in Human Nutrition and Dietetics in 2014 is currently a PhD student at the University of Barcelona (Spain). She is part of the research team on Cardiovascular Risk, Nutrition and Ageing at the biomedical research institute '*Instituto de Investigaciones Biomédicas August Pi i Sunyer*' (IDIBAPS) and at the Mediterranean Diet Foundation (Barcelona, Spain). Her research is focus on cardiometabolic health, Mediterranean diet. lifestyle interventions, inflammation and atherosclerosis. She has been involved in national and international research projects. Publications: 24, N Citations: 951, h-Index: 11 (WoS 02/2025).

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