Can changes in the plasma lipidome help explain the cardiovascular benefits of the Mediterranean diet?

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The influence of diet on cardiovascular disease (CVD) risk has long been a question of interest in the scientific community. The Seven Countries Study, established in 1958 by Ancel Keys, first suggested a link between the local diet and a reduction in CVD prevalence and death in Mediterranean populations (1). The "Mediterranean diet," as described at the time, was notable in that a higher proportion of fat calories were supplied by olive oil, which is high in monounsaturated fats and oleic acids compared with diets in other regions. The PREDIMED (PREvención con Dleta MEDiterránea) study, which was initiated in 2013, is the first randomized controlled trial to test the hypothesis that intervention with a Mediterranean diet is associated with reductions in CVD in a primary prevention setting. The trial enrolled 7447 Spanish men and women without a previous history of CVD but with risk factors such as type 2 diabetes (2). Participants were randomly assigned to 1 of 3 groups: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with nuts, or a control group who were educated to follow a low-fat diet. Although the trial was scheduled to follow participants for 6 y, interim analyses showed conclusive evidence of a reduction of $\sim 30\%$ in the risk of CVD events and death in both groups who were randomly assigned to receive the Mediterranean diet compared with the control arm, prompting early termination of the trial at 4.8 y (2).

The natural questions that followed these results were related to elucidating the molecular pathways that were altered by the Mediterranean diet and may have affected the progression of atherosclerosis or cardiovascular events. Studying alterations in lipid function and metabolism was an obvious focus for investigation in an attempt to tease apart this complex relation between diet and disease risk. As early as 3 mo after the intervention, PREDIMED investigators noted favorable changes in lipid profiles in the groups who were randomly assigned to receive the Mediterranean diet compared with the control arm. There were reported reductions in LDL-cholesterol concentrations (3), increased HDL-cholesterol concentrations (3), significant decreases in oxidized LDL concentrations (4), and reductions in apolipoprotein B with increased apolipoprotein A-I concentrations (5) in the Mediterranean diet groups. More recent work that used nuclear magnetic resonance spectroscopy on samples from participants at baseline and after 1 y showed that lipoprotein subfractions were shifted to lessatherogenic patterns in the Mediterranean diet groups—specifically, significant reductions in very small LDL particles, decreased LDL particle number, and an increase in large LDL concentration and LDL size (6). In addition, the results showed increased cholesterol efflux capacity and an increase in HDL particle size in the 2 intervention arms after 1 y of follow-up (7).

In this issue of the Journal, Toledo et al. (8) report the use of lipidomic techniques in a subset of PREDIMED participants ($n = 983$) to extend on this previous work. They used mass spectrometry to measure $>200$ plasma lipid metabolites at baseline and after 1 y of follow-up in participants. With the use of the baseline data, the study authors found a higher risk of CVD associated with shorter mean acyl carbon chain number and higher saturation in triacylglycerols, phosphatidylcholines, and lysophosphatidylethanolamines. As the study authors note, these findings extend on work from other populations in whom similar associations with these metabolites and CVD risk factors, such as type 2 diabetes, have been shown. When comparing the 1-y changes in the metabolites between the 3 study groups, Toledo et al. found significant changes in cholesteryl ester concentrations in the group randomly assigned to receive the Mediterranean diet supplemented with nuts compared with the control arm. They also found that lipids with a longer mean acyl chain length showed greater increases than lipids with shorter acyl chain length in the group randomly assigned to receive the Mediterranean diet supplemented with olive oil compared with the control arm. These results signify that there are measurable changes in the plasma lipidome induced by the diet. However, the study authors did not find a significant association between the 1-y change in lipid metabolites and CVD outcomes.

It is difficult to conclude from these results whether a causal relation exists between the changes in the lipid metabolites induced by the Mediterranean dietary intervention and the development of CVD. The results suggest that although there are
observed changes in lipid concentrations—changes that differ in magnitude between the intervention arms and the control arm—these 1-y changes are not associated with event outcomes. However, the study by Toledo et al. is likely limited in power to address this question. The changes for each of these metabolites over the 1-y period were very small in magnitude for all 3 study groups, and after correction for multiple testing (which was necessary, given the 202 metabolites that were examined), many observed associations were no longer significant. Although the study authors reference previous work (9, 10) that indicates that changes in metabolites may stabilize after the initial period of several weeks to a few months, these earlier trials were shorter in duration (3–6 mo) and were limited by dietary compliance through the follow-up period. Conceivably, longer-term adherence to a dietary intervention would result in more-significant changes in lipid metabolites.

The impressive expanse of work that has emerged from the PREDIMED trial has provided greater insight into the mechanisms by which dietary intervention alter the course of disease. Certainly, the Mediterranean diet may affect CVD risk through pathways other than by affecting lipid metabolism, such as by reducing inflammation (11, 12). However, given the changes in various lipid classes and markers of lipid function that have been shown with the Mediterranean diet intervention in PREDIMED (3–7), and the well-established association between lipid metabolism and atherosclerosis, it remains plausible that products of lipid metabolism, and changes in these products, are mediators on the pathway between diet and CVD outcomes. It will be interesting to see future analyses on the lipidome from the PREDIMED trial, which has several years of follow-up on its participants with a validated tool for measuring dietary adherence (13). Defining the circulating lipidome is a novel technique that provides greater insight into lipid metabolism and atherogenesis and will aid in determining new pathways to target for CVD prevention and management in the future.

The authors had no conflicts of interest to declare.

REFERENCES


