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Effects of Supplemented Mediterranean Diets on Plasma-Phospholipid Fatty Acid Profiles and Risk of Cardiovascular Disease after 1 Year of Intervention in the PREDIMED Trial

Article:
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Guests: Dr. Cristina Razquin is a Senior Research Associate at the University of Navarra, Spain. Dr. Miguel Martínez-González, a Medical Epidemiologist and Professor of Public Health, is also from the University of Navarra.

Bob Barrett: This is a podcast from the journal *Clinical Chemistry*, a production of the American Association for Clinical Chemistry. I am Bob Barrett.

Cardiovascular disease is by far the leading cause of death worldwide, with increasing incidents since the year 2000. To tackle this public health problem, substantial effort is focused on disease prevention. And one such study, the PREDIMED trial, found that the Mediterranean diet reduced the risk of cardiovascular events by 30% relative to a low-fat diet. While undoubtedly an exciting finding, the mechanism responsible for this risk reduction is largely unknown. Initial findings from the PREDIMED trial, suggested that certain phospholipids were more strongly associated with cardiovascular disease. Could the differences in phospholipid concentrations be explained by differences in diet? If so, is it possible to determine the phospholipid profile that protects against cardiovascular disease and link that profile to the composition of the Mediterranean diet?

A new article appearing in the March 2023 issue of *Clinical Chemistry* explores exactly these questions. Two researchers with extensive experience in epidemiology, high throughput OMICS technologies, and the contribution of diet to chronic disease focus their attention on the mechanism responsible for the cardiovascular benefits of the Mediterranean diet.

In this podcast, we are pleased to be joined by the lead and senior authors of that study. Dr. Christina Razquin is a Senior Research Associate at the University of Navarra in Spain. She is joined by her colleague, Dr. Miguel Martinez-Gonzalez, a Medical Epidemiologist and Professor of Public Health, also from the University of Navarra. The main aim of this paper was to explain the reduced cardiovascular risk in individuals following a Mediterranean diet in the PREDIMED trial. So, Dr. Martinez-Gonzalez, do you think that this aim was achieved,

and if so, what are the main conclusions of your study and what do these results mean for public health?

Miguel Martinez: Well, to put this question in perspective, it may be useful to give a short explanation of what PREDIMED is. It was the first randomized primary prevention trial showing that a Mediterranean diet reduces the risk of cardiovascular heart events. This study was conducted in Spain with 7,447 participants doing a median follow up of 4.8 years. Participants were randomized to three groups, a Mediterranean diet supplemented with extra virgin olive oil in the first group. In the second one, the same Mediterranean diet that supplemented with nuts. And the third was the control group, advised to reduce all types of dietary fat.

The study showed a significantly, roughly 30%, reduction in the combined endpoint of myocardial infarction, stroke, and cardiovascular death, each of the two Mediterranean diets compared to the control group. However, the mechanisms explaining in this reduction in cardiovascular risk are not completely understood. So we hypothesized that the high fat intake in both Mediterranean diet groups may change the circulating profile of fatty acids and more specifically, of fatty acids in the circulating phospholipid fraction. We also hypothesized that those changes in the fatty acid profile may lead to changes in cardiovascular events. As a result of testing this hypothesis, we found that both Mediterranean diet intervention significantly change the plasma phospholipid fatty acid profile. And these changes were especially marked in the Mediterranean diet plus nuts groups. Particularly for linoleic and alpha linolenic acids, that they significantly were raised by this intervention in plasma phospholipids.

And this increase, especially linoleic acid, was associated with a reduction in subsequent cardiovascular events. So for this aim, we had repeated measurements of the phospholipid fatty acids and also, a follow-up with the cardiovascular events.

Bob Barrett: Your study specifically measured fatty acids in the phospholipid fraction. Dr. Razquin, what benefit does this provide over the measurement of free fatty acids?

Christina Razquin: The reason to measure tissue or blood fatty acids in dietary intervention studies is to find biological markers of fat intake. The incorporation of dietary fatty acids into different lipid classes and tissues occurs at different rates. The study of the fatty acid composition of adipose tissue, which reflects long term intake, is very interesting in long trials. However, accessing a sample of adipose tissue is complicated.

Regarding blood lipids, there are also differences between fractions. Erythrocytes are reported to reflect midterm fat

intake--few weeks. And plasma lipids, short to midterm fat intake. Among plasma lipids, there are also specific differences between fractions, and for example, free fatty acids, or non-esterified fatty acids, are very dependent on the fasting state. Fatty acids of the plasma phospholipid fraction do not only reflect dietary fatty acid intake, but they also reflect endogenous metabolism, including digestion, interaction with the gut microbiota, enteropathic circulation, absorption, nutrient interactions, tissue fatty acid use, and other factors.

In PREDIMED, it was observed how the changes in dietary pattern may change the metabolism, and may interact with the microbiota. This was very important, as this may shed light on the CVD protective mechanisms of the Mediterranean diet. In addition to this, in a previous article, we found that plasma phospholipids were associated, depending on their content of double bounds with cardiovascular disease in the PREDIMED trial. These results suggested a potential role of fatty acids esterified to plasma phospholipids in mediating cardiovascular risk. These were the reasons for choosing the phospholipid fraction of plasma to measure changes in its fatty acid profile.

Bob Barrett: I see. Okay. So, Dr. Martinez-Gonzalez, what specific changes do you see in the fatty acid profiles of individuals following the two types of Mediterranean diet?

Miguel Martinez: Yes. As I said before, very important changes related to the fat intake were seen in two fatty acids: in linoleic acid and alpha-linolenic acid, both especially in the group supplemented with nuts. So we give the interpretation that this was an effect of the high intake of nuts. And also, in the other group, in the Mediterranean diet plus extra virgin olive oil group, we saw a sizable increase in eicosatrienoic acid and omega nine acid that cannot be directly related to the fat intake in that group but to endogenous metabolism. There was also in both groups, in both Mediterranean diet groups, an important reduction in palmitoleic acid that has been related to a high cardiovascular risk. So, this is also a likely explanation of the findings regarding the reduction in cardiovascular heart clinical events with our intervention.

Bob Barrett: Okay. So finally, Dr. Razquin, what other work are you planning within the PREDIMED Trial or other similar studies?

Christina Razquin: Yeah. These results open a door to a study of the biological mechanisms by which the Mediterranean diet has a protected effect, not only in cardiovascular disease, but also in other relevant chronic diseases. In this sense, a next step would be to see if these results can be replicated in other cohorts with other population characteristics. But it also opens the door to try to find, within the PREDIMED trial, whether

changes in the fatty acid profile led to a change in the risk of other diseases, such as type 2 diabetes or cancer. It seems also important to deepen into the analysis of how the Mediterranean diet affect endogenous metabolism and its interactions with the gut microbiota.

Bob Barrett: That was Dr. Christina Razquin and Dr. Miguel Martinez-Gonzalez from the University of Navarra, Spain. They studied changes in plasma fatty acids in order to understand why individuals who follow the Mediterranean diet have a reduced risk of cardiovascular disease. They published their findings in the March 2023 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.