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Plasma Branched-Chain Amino Acids and Incident Cardiovascular Disease in the PREDIMED Trial

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Guest: Dr. Miguel Ruiz-Canela is an Associate Professor of the Department of Preventive Medicine and Public Health at the University of Navarra in Spain.

Bob Barrett: This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett.

We've all heard, or maybe even tried, the so-called "Mediterranean diet." Although there is considerable evidence that adherence to the Mediterranean diet is effective for primary cardiovascular disease prevention, the biological mechanisms for such effects are not well understood. Recently, metabolomics applied to the field of nutrition have offered great potential to provide new insights into such underlying mechanisms.

Several studies have found an association between the concentrations of selected small molecule metabolites in peripheral blood, and cardiovascular risk. Among these, branched chain amino acids have been found to predict obesity, insulin resistance, diabetes and cardiovascular disease outcomes.

Branched chain amino acids include leucine, isoleucine, and valine. The relevance of the metabolism of these amino acids to coronary heart disease remains poorly understood, but increased circulating concentrations of those amino acids maybe explained by an obesity-related decline in their catabolism in adipose tissue. The April 2016 issue of *Clinical Chemistry* published a paper examining if plasma branched chain amino acid concentrations predict future risk of cardiovascular disease and the role of a Mediterranean diet in that process.

Dr. Miguel Ruiz-Canela is the senior author of that case cohort study, and he joins us in this podcast. He is an Associate Professor at the Department of Preventive Medicine and Public Health at the University of Navarra in Spain.

Doctor, what is PREDIMED?

Miguel Ruiz-Canela: Yes, PREDIMED means prevention with Mediterranean diet. In Spanish, "prevención con dieta mediterránea" and this PREDIMED study is the first randomized primary prevention

trial. And it showed that the promotion of a Mediterranean diet reduces cardiovascular risk. This study was conducted here in Spain with 7,447 participants. The median follow-up was 4.8 years. Participants were randomized, one of three groups.

The first was a Mediterranean diet with supplemental extra virgin olive oil. The second, also Mediterranean diet but supplemented with nuts. The third was a controlled diet group, and it consisted of just advice to reduce all types of dietary fat.

This study showed a significant reduction in roughly 30% in the combined end-point, that was a myocardial infarction, stroke, and cardiovascular death, when comparing each of the two Mediterranean diets with a control group.

Bob Barrett: Which are the potential applications of LC-MS metabolomics methods on the PREDIMED study?

Miguel Ruiz-Canela: We know that metabolomic profiling techniques have a great potential to advance our understanding of the metabolic pathways, through which dietary interventions may influence cardiovascular risk. And we have a rich deposit from the PREDIMED trial.

Specifically, we have stored plasma samples collected every one or two years from participants, as well as a plethora of information, diet, lifestyle, CVD biomarkers. So, I think this is a great opportunity to address our goal in this project. It is to examine the effect of the PREDIMED dietary interventions on plasma levels of metabolites, and also to determine whether this metabolites profiles, where mediating or not, the benefits of the Mediterranean diet on cardiovascular risk.

Bob Barrett: What's the advantage of using case cohort study design?

Miguel Ruiz-Canela: I think the main advantage is efficiency. We can get similar results with a lower cost. In this case cohort design, we have used samples from 970 participants including all incident cases of cardiovascular disease and also a representative selection of the PREDIMED participants. Roughly, it's a random sample of 10%.

So, just to have an idea, we have analyzed about 300 metabolites at the Broad Institute of MIT and Harvard. And in a rough estimate, just the cost of the metabolite profiling is $300 per sample. So, the total cost is more or less $500,000 but it could more or less $5 million if we're using the samples from all the participants in the PREDIMED study. So, this is the -- I think the main advantage.

Bob Barrett: Doctor, what is the relevance of branched chain amino acids regarding cardiovascular risk?

Miguel Ruiz-Canela: I think the branched chain amino acids, those essential amino acids, leucine, isoleucine, and valine, these are critical for human life because they are involved in stress, energy, and muscle metabolism. And there are several studies that have already shown that high levels of baseline BCAA or branched chain amino acids in blood are associated with a variety of metabolic disorders such as diabetes, obesity, or insulin resistance.

And a couple of studies have also shown this association in patients with cardiovascular diseases.

Bob Barrett: What does this research add to previous studies? And what would you say is the main contribution of the research?

Miguel Ruiz-Canela: One important strength of our study is the viability of not only using baseline samples, but also samples taken at a one year follow-up. This is very important. First, to assess the longterm effects of diet, and second, to evaluate if a change in BCAA's level may mediate the effect of the Mediterranean diet.

Regarding our results, our main contribution, we have shown an association between high levels of baseline BCAAs and an increased risk of CVD, cardiovascular disease. Also, a higher risk was observed when repeated the analysis only for stroke as the outcome.

We have also seen that a Med diet reduces the risk of this high levels of BCAAs at baselines, and especially in the group enriched with nuts, when you compare it with the control group.

Bob Barrett: Did the Mediterranean diet have some effect on branched chain amino acid metabolism?

Miguel Ruiz-Canela: We have found that the Mediterranean diet had a negligible effect on one year changes in BCAA. And we concluded that the cardioprotective's effect of a Mediterranean diet may occur through alternative mechanism. Our results also suggest that high values of baseline concentrations of branched chain amino acids can be just a biomarker of an underlying metabolic dysfunction, and this happened independently of the quantity of BCAA ingested with diet.

Bob Barrett: Which other candidate metabolites are you studying in your research?

Miguel Ruiz-Canela: We're including in our analysis almost 300 metabolites. We are following first a hypothesis-driven approach. We focused on several candidate metabolites that have already been implicated with cardiometabolic risk. Apart from the branched chain amino acids, we are analyzing the association between glutamine/glutamate ratio, carnitines, gut flora metabolites, urea cycle metabolites, and also several lipid metabolites.

Bob Barrett: And why do you think it's relevant to publish these results in *Clinical Chemistry*?

Miguel Ruiz-Canela: So far, many results from the PREDIMED study have been published in clinical or nutritional journals. And I think we are taking an important step into a new phase of our research. The connection we feel in the field of laboratory medicine, through their Broad Institute, I think that it has a great potential to advance in our understanding of metabolic pathways. And moreover, I think that this collaboration may have also important clinical and public health implications.

Bob Barrett: Finally doctor, let's look ahead. What is the next step to be taken in this research?

Miguel Ruiz-Canela: I think that apart from the analysis of the targeted metabolites, a relevant step in this research is the known targeted metabolites analysis. There are thousands of [inaudible] of potentially single metabolites without known name at the moment. And this approach requires a more complex statistical analysis, and we are working on these with several colleagues from the Harvard School of Public Health under their own institute.

On the other hand, we want to know if the association between the Mediterranean diet, and over cardiovascular diseases such as heart failure, atrial fibrillation, peripheral artery disease, maybe are also related to some metabolic pathways that can be identified through metabolomic techniques.

Bob Barrett: That was Dr. Miguel Ruiz-Canela. He is an Associate Professor of the Department of Preventive Medicine and Public Health at the University of Navarra in Spain. He's been our guest in this podcast from *Clinical Chemistr*y on the Mediterranean diet and branched chain amino acids. His paper on that topic appeared in the April 2016 issue of *Clinical Chemistry*.

I'm Bob Barrett. Thanks for listening!