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EDITORIAL

In search of the “metabolic footprint” in cardiovascular disease[☆]



A la búsqueda de la «huella metabólica» en la enfermedad cardiovascular

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A key aspect in the fight against cardiovascular disease is to increase our knowledge of the pathophysiological processes which occur in this complex disease. The so-called “omic” sciences have enabled investigators to obtain a much broader knowledge of the molecular/cellular/functional changes that occur in this disease. Among these sciences, metabolomics is the one dedicated to identifying and quantifying small molecules which reflect the status of an organism at any given time. This means that metabolomics provides an instantaneous image of the metabolic footprint of an organism, capturing the complexity of the metabolic networks. These images may be used potentially as diagnostic and/or prognostic tools to identify systemic or cardiac metabolic disorders, which occur during the development and worsening of the cardiovascular disease, and may help to guide the type and the start time of specific therapies or interventions.¹ In fact, metabolomics and its derivative, lipidomics, which is dedicated to the study of cellular lipids

using a metabolomic approach, are among the most recent strategies in the search for new biomarkers.²

In this issue of *Clinica e Investigación en Arteriosclerosis* [Clinical practice and Research in Arteriosclerosis], a study is presented which evaluates the impact of obesity on cardiac lipomas and its consequences on myocardial damage.³ The presence of obesity is closely related to numerous alterations which impact negatively on the myocardium. In fact, the expansion of adipose tissue in obese individuals releases elevated quantities of free fatty acids, hormones, proinflammatory cytokines and other factors which may affect the myocardium. The increase in circulating fatty acids makes their uptake by different organs, including the heart, easier. These are converted into complex lipids, such as ceramides and diacylglycerol, which are derived from these fatty acids, while the accumulation of triglycerides is considered relatively inert and may even end up being protective by preventing the formation of more harmful lipids.⁴ This

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ectopic lipid accumulation in the heart and other tissues causes cellular metabolic alterations, called lipotoxicity. The authors of this study subjected rats to a high-fat diet for six weeks in order to subsequently analyse the presence of fibrosis and cardiac lipomas, as well as other parameters.

The main findings of the study by Marín-Royo et al. show that the total levels of cardiac diacylglycerols are independent predictors of cardiac fibrosis, while sphingomyelin levels are an independent predictor of glucose transporter GLUT4 levels. The increase in diacylglycerol plays a very important role in the development of conditions such as skeletal muscle and hepatic insulin resistance, and this new study relates it to the onset of cardiac fibrosis. This complex lipid is a second messenger which, according to its fatty acid composition, may activate various isoforms of the protein kinase C, which, ultimately, would be responsible for causing fibrosis in the myocardium. These results suggest that preventing an increase in this complex lipid or modifying its fatty acid composition in the heart could be useful in preventing cardiac fibrosis. The possibility of using cardiac levels of diacylglycerol as a biomarker for the presence of cardiac fibrosis is not feasible for obvious reasons. However, as the composition of diacylglycerol in plasma has been proposed as a biomarker for the onset of metabolic syndrome,⁵ it may be interesting to study whether the changes in plasma diacylglycerol composition following the consumption of a high-fat diet could be a predictor for the presence of cardiac fibrosis.

Furthermore, free fatty acids are the main energy substrate of the adult heart, although glucose or lactate can also be used as additional energy sources. However, in obese patients and states of insulin resistance, GLUT4 levels decrease while the fatty acid transporter CD36 is located preferentially at the sarcolemma, forcing the heart to depend almost exclusively on fatty acids as the only source of energy. The chronic maintenance of this loss of metabolic flexibility predisposes the onset of cardiomyopathies due to the generation of oxidative stress in the heart because of an excess substrate flow, among other reasons.⁶ The results of this study show that the total levels of sphingomyelins are a determiner of GLUT4 cardiac levels. This opens up a new avenue for the study of cardiac metabolic flexibility loss in obese patients and states of insulin resistance. Sphingomyelins are formed by a phosphocholine bound to a ceramide, and exposure to the fatty diet reduced its total cardiac levels, although the sphingomyelin levels which contained arachidonic acid were not modified. Although these results seem to be contradictory to the fact that the increase in sphingomyelin levels has been described as a factor which enhances cardiovascular risk,⁷ it is currently considered that more than the total content of a certain lipid (the

lipids responsible for causing metabolic dysfunction) would be the specific lipid species accumulated in certain sub-cellular locations.⁸ Therefore, more studies are necessary to determine which changes in the composition of sphingomyelins, and in which cellular locations, are responsible for the metabolic alterations in the myocardium.

Ultimately, it is a very interesting study providing greater knowledge of the lipid changes in the myocardium, which can promote fibrosis and cardiac metabolic alterations that occur in obesity. Likewise, the results presented open up the possibility of conducting new studies allowing us to determine the lipid alterations that promote the development of cardiovascular disease in obesity, in order to achieve better and more effective interventions in the prevention and treatment of this condition.

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