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Editorial

Plasma acylcarnitine, risk for heart failure or atrial fibrillation, and effects of the Mediterranean diet or obesity

Acilcarnitina plasmática, riesgo de insuficiencia cardiaca o fibrilación auricular y efectos de la dieta mediterránea o la obesidad

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Heart failure (HF) and atrial fibrillation (AF) are common chronic cardiovascular diseases (CVD) that are often associated and share several predisposing conditions. Patients with HF and AF show structural, functional, inflammatory, and metabolic derangements that contribute to disease progression.[1] One of the best-known phenomena is remodelling of cardiac energy metabolism, particularly of fatty acids (FAs), which causes a switch in energy substrate use and a decrease in energy production.[1,2] A possible cause of metabolic derangement is insulin resistance that develops in early HF stages, limits glucose utilization, and favors the use of free FAs for ketogenesis. Circulating ketone bodies are increased in patients with HF, with a relationship between their plasma levels and the severity of cardiac dysfunction or neurohormonal activation. The reduction in cardiac production of high-energy phosphates leads to a progressive decline in both diastolic and systolic function and to the progression of left ventricular remodelling in a vicious cycle.[2] In some conditions such as diabetes, metabolic derangement with defective energy production may represent the main driver of cardiac dysfunction, contributing to the altered diastolic function observed in patients with HF and preserved ejection fraction. Hence, processes such as structural remodelling and oxidative stress are activated as a consequence of metabolic alterations.[2] Abnormalities in cardiac metabolism in the setting of AF have been less well characterized, but an energy deficit due to mitochondrial dysfunction in atrial myocardium has recently been proposed as a possible mechanism of the frequent association between HF and AF.[3]

A prominent feature of metabolic dysregulation in the failing heart is the increased level of substrates of FA oxidation.[1,4] Acylcarnitines (ACs) are produced from the conjugations of acyl-coenzyme A with carnitine for the transport of long-chain fatty acids, meant to be beta-oxidized, across the inner mitochondrial membrane (ie, the use of FAs for energy production). Several isoforms of ACs (short-, medium-, and long-chain) have been identified.[5] The amount of ACs in plasma is comparable to the heart tissue content of long- and medium-chain ACs[6] and can be easily affected by the metabolic switch from FA to glucose oxidation in the failing heart. Therefore, medium- and long-chain ACs might be seen as biomarkers of the severity of metabolic dysregulation in patients with heart diseases such as HF and possibly AF. Furthermore, circulating levels of the same molecules could identify subclinical cardiac damage before progression to clinically evident HF or arrhythmias such as AF.

The Mediterranean diet (MedDiet) is a traditional eating pattern found among populations living in Mediterranean countries.[6] Its main characteristics are low consumption of meat products, with very low consumption of red meat, and very low or null consumption of processed meats, butter, ice cream, or other whole-fat dairy products. It has a relatively fat-rich profile because of the abundant consumption of olive oil, together with high consumption of minimally processed, locally grown, vegetables, fruits, nuts, legumes, and cereals (mainly unrefined).[6] An important source of protein is moderate consumption of fish and shellfish, which varies depending on proximity to the sea. The main sources of fat and alcohol are primarily extra-virgin olive oil (EVOO) and red wine, respectively. EVOO and red wine contain several bioactive polyphenols with possible anti-inflammatory properties. Proposed antiatherogenic properties of EVOO are attributed to its high content of monounsaturated fat and possibly also bioactive antioxidants (polyphenols, tocopherols, and phytosterols).[6] There is evidence of a protective association between consumption of the MedDiet and the risk of CVD, mainly related to multiple biochemical processes such as lower endothelial dysfunction and atherosclerotic burden, elevated antioxidant capacity, lower insulin resistance, and selective anti-inflammatory and anticoagulant properties.[6]

In the landmark Spanish *Prevención con Dieta Mediterránea* (PREDIMED) trial, enrolling 7447 high-risk participants initially free from CVD, a 5-year intervention with a MedDiet significantly reduced the incidence of a composite major CVD endpoint including nonfatal stroke, nonfatal coronary heart disease, and fatal CVD events. The MedDiet was also associated with lower N-terminal pro-B-type natriuretic peptide[7] levels, a decreased risk of new-onset HF,[8] and a lower risk of AF.[9]

In a new analysis of the PREDIMED cohort, Ruiz-Canela et al. focused on the relationship between circulating AC levels and the risk of new-onset HF or AF in patients with high cardiovascular risk, and the effect of MedDiet + EVOO in individuals with high baseline AC levels.[10] Patients were followed up from 2003 to 2017, with registration of 326 cases of incident HF, 509 of incident AF, and 108 combined cases. Medium- and long-chain ACs were correlated with a higher risk of HF (odds ratio [OR], 1.27; 95% confidence interval [95%CI], 1.08-1.49; $P = .003$ and OR, 1.22;

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95%CI, 1.09-1.38; $P = .001$, respectively), whereas only long-chain ACs appeared significantly associated with AF development (OR, 1.20; 95%CI, 1.06-1.36; $P = .005$). After adjustment for total AC levels, medium-chain ACs were strongly associated with incident HF while long-chain ACs were only associated with incident AF. Notably, the risk of new-onset HF was 27% higher per each standard deviation of medium-chain AC levels. In individuals with high levels of long-chain ACs, the risk of AF was reduced by the MedDiet + EVOO and was increased by obesity. No other significant interactions were found.[10]

Accurate prediction of cardiovascular disease in participants from the general population remains an unmet need, despite the availability of many risk prediction tools including the revised score systems proposed by latest European Society of Cardiology guidelines.[11] Another important issue is the management of individuals with a high predicted cardiovascular risk, following the neutral or negative findings of trials assessing aspirin therapy for primary prevention, including in diabetic or elderly patients.[12] ACs were first considered as tools to screen for inborn errors of metabolism with defective carnitine biosynthesis.[13] Because of the relationship between plasma and tissue AC levels and the proposed interplay between circulating ACs, the severity of metabolic derangement and final outcomes, ACs are attractive biomarkers for the diagnosis and management of HF. A further step is to assess if plasma ACs can identify subclinical cardiac dysfunction (stage B HF) in individuals with risk factors for HF (stage A HF), such as those with a high cardiovascular risk enrolled in the PREDIMED cohort. The results of Ruiz-Canela et al. support the notion that ACs predict the risk for HF and suggest a predictive value for new-onset AF. Nonetheless, clinical translation of these findings does not seem very likely. The first limitation is that clinical application would be difficult, given the absence of absolute quantification of ACs and reference cutoffs. Most notably, accurate measurement of ACs is far beyond the possibility of most laboratory facilities, as opposed to cardiac biomarkers such as high-sensitivity troponins or natriuretic peptides. The latter have been investigated fairly extensively in participants from the general population and individuals at higher cardiovascular risk, demonstrating a good predictive value for clinical HF.[14] On the other hand, preventive strategies (ie, the measures to be taken based on risk stratification) are unclear, as therefore is the cost-effectiveness profile of any biomarker-based cardiovascular risk stratification, including a strategy based on AC measurement.

Another significant study limitation should be considered. The prevalence of traditional risk factors, such as hypertension and dyslipidemia (showing a percentage of at least 80% and 60% respectively) was listed, but the authors did not show whether these factors were well controlled, nor did they specify baseline blood pressure values or low-density lipoprotein levels. Starting from a condition of intensive control of these traditional risk factors would be advisable to study the added value of additional dietary interventions.

Finally, the effects of obesity and the MedDiet on the relationship between AC levels and the risk of HF or AF seemed limited or absent. Although these results are far from conclusive, given the relatively small number of participants and events, they suggest that dietary interventions alone are unlikely to change the natural history of individuals with high cardiovascular risk. Intensive treatment of cardiovascular risk factors according to current guidelines[11] thus remains the mainstay of primary prevention.

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CONFLICTS OF INTEREST

None declared.

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