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EDITORIAL COMMENT

Insulin resistance as a predictor of cardiovascular diseases

Resistência à insulina como preditivo das doenças cardiovasculares

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Despite improvements in cardiovascular diseases (CVD) diagnosis and treatment, continuous aging and the sedentary lifestyle of modern societies have led to an increased incidence of heart and blood vessels diseases. The World Health Organization estimates that CVDs account for 31% of all global deaths, increasing to over 50% mortality among individuals with diabetes mellitus.[1] This chronic state of hyperglycemia is normally associated with defects in insulin secretion and insulin action, also known as insulin resistance (IR), or both. Moreover, defects in uptake and oxidation of glucose, glycogen synthesis, and in the ability to suppress lipid oxidation are some of the metabolic alterations due to the IR state. These metabolic events consequently trigger oxidative stress and inflammatory responses that ultimately lead to cell damage. Thus, in hyperglycemia and IR states, metabolic, structural and functional alterations have been shown to affect multiple tissues, including the heart, skeletal muscle, liver, and adipose tissue. In the heart and vasculature, the aforementioned IR-induced changes have been associated with the incidence of diabetic cardiomyopathy, coronary artery disease, myocardial ischemia, and ultimately heart failure. Despite this strong link between IR and increased CVD incidence, the proportion of CVD that can be attributed to IR remains unclear. Through a meta-analysis, IR measured using the homeostasis model assessment (HOMA), a model of glucose-insulin feedback system in the overnight-fasted state,[2] was shown to be a good predictor of CVD.[3] This method has been widely used in clinical practice to measure IR, however due to cost-effectiveness and the instability of insulin in blood, the efficacy of HOMA-IR is questionable. Thus, for clinical practice a simple, robust and accessible marker as a surrogate for IR to address this pathology and predict cardiovascular risk is needed. Triglyceride-glucose index, a product of fasting triglycerides (TG) and glucose, and TG-to-high density lipoprotein cholesterol (HDL) ratio (TG/HDL) have been more recently suggested as an alternative to measure IR with improved efficiency.[4] Moreover, some anthropometric measurements, such as body mass index (BMI) and waist circumference (WC), are also used to identify IR.[5] However, in the current issue, Nunes et al.[6] found that there was a better correlation between lipid accumulation product (LAP) and HOMA-IR than with BMI, neck circumference (NC), waist-hip ratio (WHR) and sagittal abdominal diameter (SAD), in elderly population. Although these measurements are easy to obtain, anthropometric measurements are not comprehensive in reflecting obesity and metabolic abnormalities for each individual. In this scenario, LAP emerges as a result of the correlation between waist measurements and fasting TG levels, thus reflecting

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both anatomic and physiological alterations related to lipid accumulation. The authors therefore suggest LAP as a useful and simple clinical marker to assess cardiometabolic risk factors. Indeed, in a cross-sectional study including non-diabetic subjects, LAP was found to be closely associated with HOMA-IR.[7] Recent studies have also corroborated the direct correlation between LAP and IR, as well as increased incidence of CVD.[8,9] Thus, LAP, a single and inexpensive index, has been suggested as a precise marker that outperforms BMI and WC in identifying IR in a large population range, showing a strong association with CVD risk factors.

Considering the close association between LAP, diabetes and metabolic syndrome, and the fact that this index takes into account TG circulating levels, it is expected to be strongly correlated with an altered circulating lipid profile. Recent studies report that higher LAP is related to abnormal total cholesterol, high density lipoprotein cholesterol (HDL-C) levels, TG to HDL-C ratio and malondialdehyde.[10] Similar results were obtained in the study by Nunes et al., where a positive correlation between low levels of HDL-C as well as high levels of TG and increased levels of LAP was demonstrated. Thus, to gain a deeper knowledge of the etiology of metabolic disorders, considerable efforts have been made to shift CVD research toward the study of dysregulated lipid metabolism by characterizing the circulating lipidome. Very recent data showed, through plasma lipidomic profiling via liquid chromatography-tandem mass spectrometry, that lysoglycerophospholipids and sphingolipids are good lipid biomarkers associated with metabolic risk factors and consequent good biomarkers for CVD.[11] Moreover, work carried out in the Strong Heart Family Study (SHFS), a well-characterized cohort study conducted in a population at high risk of diabetes, demonstrated that higher levels of plasma ceramides were associated with higher fasting plasma insulin and HOMA-IR.[12] Accordingly, due to the complex phenotype and dynamics of chronic metabolic-related diseases, affected by multiple genetic and environmental factors, scientific and clinical communities have made efforts to find the molecular etiology behind these diseases. In this scenario, metabolomics appears as a powerful phenotyping tool, which is described as a comprehensive analysis of all small molecules present in a biological system. These types of approach provide an integrated view of the metabolic profiles due to the sensitive detection of molecular changes over time as result of intrinsic and extrinsic factors.[11] Thus, metabolites, as single molecules or integrated in a comprehensive signature, are promising targets for efficient diagnosis, prognosis and therapeutic approaches, to overcome the limitation of the current conventional clinical markers during risk assessment and stratification. The application of this technology can therefore contribute to decipher molecular mechanisms underlying metabolic diseases. In line with this, recent results obtained from machine learning classifiers, based on the plasma lipidomes, enabled the accurate distinction between different atherosclerosis-related CVD, including ischemic stroke and systemic lupus erythematosus, based on the lipid profile. Notably, this tool was also sensitive to statin treatment, showing a distinct lipid fingerprint from the CVD cohorts.[13]

In conclusion, the work developed by Nunes et al. has contributed to the field of metabolic disorder diagnosis, such as IR, revealing the LAP measurement as a valuable tool for the assessment of IR. Moreover, due to its tight correlation with CVD, this marker can predict cardiometabolism risk in elderly population, thus paving the way for the development of alternative methodologies to accurately measure the odds of cardiovascular events.

Conflicts of interest

The author has no conflicts of interest to declare.

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