atherosclerosis

Atherosclerosis newsletter

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The present issue contains several articles presenting results of clinical or population studies on the associations of biomarkers of obesity, metabolism, or kidney function with preclinical measures or clinical endpoints of atherosclerotic cardiovascular diseases.

Modest decrease in severity of obesity in adolescence associates with low arterial stiffness

Childhood obesity tracks into adulthood and is associated with premature mortality and morbidity, largely due to cardiovascular disease (CVD). The duration and severity of obesity throughout childhood predict the acquisition of traditional cardiovascular risk factors (CVRF), and subclinical cardiovascular phenotypes including carotid intima-media thickness (cIMT), pulse-wave velocity (PWV), and carotid elasticity. In this longitudinal study, Saner et al. aimed to investigate associations between changes in adiposity and CVRF in early adolescence and subclinical cardiovascular phenotypes in late adolescence.

Participants had adiposity measures (%>95th body mass index (BMI)-centile), waist circumference (WC), percentage total body fat (%BF) and CVRF (systolic blood pressure (SBP), glycoprotein acetyls (GlycA), and low-density lipoprotein cholesterol) assessed in early and late adolescence. Subclinical cardiovascular phenotypes were assessed in late adolescence. Multivariable regression analysis was performed.

The results showed that maintaining or decreasing the severity of obesity over 5.5 years from early to late adolescence was associated with higher carotid elasticity in females, and with lower PWV in males in late adolescence compared to those who further increased the severity of obesity; ageing and change in all adiposity measures were associated with arterial stiffness, and male sex was the only factor associated with higher cIMT compared to the female counterparts.

Impact of sarcopenic obesity on long-term clinical outcomes after ST-segment elevation myocardial infarction

Abnormal body composition, such as skeletal muscle disorder and specific abdominal fat distribution (i.e., increased ratio of abdominal visceral fat to subcutaneous fat: increased V/S fat ratio), has been receiving considerable attention as an emerging risk factor for cardiovascular disease. However, the combined impact of these 2 components on long-term outcomes remains unclear, especially in patients with ST-segment elevation myocardial infarction (STEMI). Sato et al. aimed to

investigate whether the combined assessment of skeletal muscle volume and abdominal fat distribution could add incremental prognostic value to the standalone evaluation of skeletal muscle volume or abdominal fat distribution in patients with STEMI, and to explore the possible impact of age on its prognostic value.

In 303 patients with STEMI, low appendicular skeletal muscle index (ASMI) and V/S fat ratio were assessed using dual-energy X-ray absorptiometry and abdominal computed tomography. Based on the criteria of the Asian Working Group for Sarcopenia and median of V/S fat ratio, sarcopenic obesity (SO) pattern was defined as low ASMI with high V/S fat ratio. The primary endpoint was composite outcomes of all-cause death, myocardial infarction, ischemic stroke, hospitalization for heart failure and unplanned revascularization.

During a median follow-up of 3.9 years, primary endpoint occurred in 67 patients. Patients with an SO pattern showed significantly lower event-free survival rate compared with those without. Notably, when stratified by median age, this trend was particularly prominent in the younger-age group, but not significant in the older-age group. In the younger-age group, multivariate analysis revealed that patients with SO pattern had a higher risk for primary endpoints compared with those without.

SO was associated with poor prognosis after STEMI, particularly in younger-age patients. The combined assessment of skeletal muscle with abdominal fat distribution may help stratify the risk among patients with STEMI, rather than each component alone.

These results are further discussed in the editorial by Guaraldi et al.

Glucose as a modifiable cause of atherosclerotic cardiovascular disease: Insights from type 1 diabetes and transplantation

While the association of elevated blood glucose levels and cardiovascular disease is not in question, establishing a causal role for glucose has been difficult. Senior reviews how glucose is a modifiable cause of atherosclerotic cardiovascular disease giving insights from type 1 diabetes and transplantation.

Diabetes is a major risk factor for cardiovascular (CV) disease. In contrast to the clear benefits from treatments, which reduce blood pressure and lipids, clinical trials targeting blood glucose have not shown clear CV benefits. Interventions to intensify glycemic control early in the course of diabetes may have benefits in long-term observational studies (DCCT-EDIC/UKPDS), but may not be helpful if introduced late in the course of type 2 diabetes (ACCORD, ADVANCE, VA-DT). More recent cardiovascular outcome trials (CVOT) in high-risk subjects suggest that the benefits of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon like peptide 1 receptor agonists (GLP1-RA) are glucose-independent. Type 1 diabetes provides a “cleaner” model to study the links between glucose

and cardiovascular disease. Abnormalities of glucose regulation in type 1 diabetes are not restricted to hyperglycemia, but include glycemic variability and hypoglycemia. The mechanisms linking glycemic variability and hypoglycemia as key mediators of cardiovascular complications are being understood more and more. Furthermore, data from pancreas and islet transplantation showing reduced cardiovascular mortality and regression of intima-media thickness supports a causal role for glucose in the pathogenesis of atherosclerosis, but suggests that restoration of normal glucose regulation may be required to demonstrate substantial impact on CV risk accrued over decades of type 1 diabetes. Considering the limited organ supply and risks of immunosuppression, advances in biology (stem cell derived beta cells) or technology (automated insulin delivery systems) will be required to provide a scalable solution to deliver optimal glucose control and reduce CV risk for people with type 1 diabetes.

Association of plasma trimethylamine *N*-oxide levels with atherosclerotic cardiovascular disease and factors of the metabolic syndrome

Trimethylamine N-oxide (TMAO) derives from dietary precursors phosphatidylcholine, choline, l-carnitine, and betaine, which are metabolized by gut microbial enzymes, forming trimethylamine (TMA). TMA is enterally absorbed, excreted into the blood circulation and oxidized to TMAO in the liver. Plasma TMAO is eliminated almost exclusively by renal excretion. TMAO plasma levels are therefore determined by diet, gut microbial composition, drug administration, and renal function. The association of TMAO with atherosclerotic cardiovascular disease (ASCVD), diabetes mellitus (DM) and its determinants, as well as the role of TMAO as a predictor for short and long-term mortality, is still under discussion. Ringel et al. investigated associations between four plasma metabolites of the TMAO pathway and different clinical manifestations of atherosclerosis, diabetes determinants, and risk of short and long-term mortality in patients with stable ASCVD, acute myocardial infarction (AMI), cardiogenic shock (CS), and DM in three independent cohorts.

TMAO and its dietary precursors were simultaneously quantified by liquid chromatography-tandem mass spectrometry in a total of 2655 participants of the German Leipzig Research Center for Civilization Diseases (LIFE)-Heart study, LIFE-Adult study, and the European Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) multicenter trial. Associations with ASCVD manifestations, metabolic syndrome, 30-day mortality of patients with AMI and CS, and long-term mortality of subjects with suspected coronary artery disease (CAD) were analyzed.

TMAO plasma levels were not independently associated with stable ASCVD. Elevated TMAO plasma concentrations were independently associated with obesity and DM. No association of TMAO plasma levels with short-term mortality in patients with AMI and CS was observed. However, TMAO plasma levels were independent predictors of long-term mortality in patients with suspected CAD.

Potential proatherogenic mechanisms of TMAO seem to have no short-term effect in AMI. Presented associations with diabetes mellitus and obesity suggest that TMAO might have a functional role in metabolic syndrome.

The metabolomic profile of carotid artery intima-media thickness and echogenicity

Nuclear magnetic resonance (NMR)-based metabolomics analyses have defined the lipoprotein profile of carotid artery intima-media thickness (IMT) in detail. In this study, Lind aimed to use multi-modal mass spectroscopy (MS) to relate multiple metabolites from different chemical classes to IMT and also to the echogenicity of the intima-media complex (IM-GSM).

Multi-modal MS with 791 annotated non-xenobiotic metabolites was measured in two different population-based samples in which carotid IMT and IM-GSM were assessed by ultrasound.

Four metabolites were significantly related to IMT in a meta-analysis of the Prospective InVestigation of Uppsala Seniors (PIVUS) study and the Prospective investigation of Obesity, Energy and Metabolism (POEM) study. The top finding was adenosine 3',5'-cyclic monophosphate (cAMP), being inversely related to IMT. Fifty metabolites were significantly related to IM-GSM in a meta-analysis of POEM and PIVUS. The top findings were branched-chained amino acids (BCAA), fructosyllysine, metabolonic lactone sulfate, a ceramide together with some sphingomyelins and phosphatidylcholines. All these top findings represented inverse relationships. Two metabolites identified by lasso regression in PIVUS increased discrimination of an echolucent IM-GSM by 3.3% in POEM compared to traditional cardiovascular risk factors.

IMT, especially IM-GSM, was related to multiple metabolites from different chemical classes. Although such metabolites improved the discrimination of an echolucent IM-GSM, it remains to be investigated if any of those metabolites are involved in the pathogenesis of carotid arteriopathy.

Chronic kidney disease measures for cardiovascular risk prediction

Chronic kidney disease (CKD) affects 15–20% of adults globally and causes various complications, one of the most important being cardiovascular disease (CVD). CKD has been associated with many CVD subtypes, especially severe ones like heart failure, independent of potential confounders such as diabetes and hypertension. There is no consensus in major clinical guidelines as to how to incorporate the two key measures of CKD (glomerular filtration rate and albuminuria) for CVD risk prediction. This is a critical missed opportunity to appropriately refine predicted risk and personalize prevention therapies according to CKD status, particularly since these measures are often already evaluated in clinical care. In this review, Mok et al. provide an overview of CKD definition and staging, the subtypes of CVD most associated with CKD, major pathophysiological mechanisms, and the current state of CKD as a predictor of CVD in major clinical guidelines. The authors also introduce

the novel concept of a “CKD Add-on”, which allows the incorporation of CKD measures in existing risk prediction models, and the implications of taking into account CKD in the management of CVD risk.

The difference between cystatin C- and creatinine-based eGFR is associated with adverse cardiovascular outcome in patients with chronic kidney disease

The risk of premature death and cardiovascular disease (CVD) is substantially higher in patients with chronic kidney disease (CKD) than in those without. However, assessing risk of CVD may be difficult when there is a gap between creatinine- and cystatin C-based estimated glomerular filtration rate (eGFR). Kim et al. studied the association of the difference in eGFRs with major adverse cardiovascular events (MACE) in patients with CKD.

This prospective cohort study was conducted in 2076 patients with CKD stages based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. The difference in eGFR ($eGFR_{diff}$) was calculated by subtracting the cystatin C-based eGFR ($eGFR_{cys}$) from the creatinine-based eGFR ($eGFR_{creat}$). The primary outcome was MACE, defined as non-fatal acute myocardial infarction and unstable angina, stroke, congestive heart failure, symptomatic arrhythmia, and cardiac death.

During a median follow-up of 4.1 years, MACE occurred in 147 patients (incidence rate, 15.0 per 1000 patient-years). When patients were categorized into baseline $eGFR_{diff}$ tertiles, the highest tertile was associated with a significantly higher risk of MACE than the lowest tertile when adjusted for $eGFR_{creat}$, $eGFR_{cys}$, or eGFR based on both creatinine and cystatin C. Patients in the highest tertile had more baseline coronary artery calcification (CAC) than those in the lowest tertile. In addition, 978 patients had data for both baseline and follow-up CAC at year 4. In this subgroup, baseline $eGFR_{diff}$ was significantly associated with accelerated CAC progression (≥50/year).

A large positive difference between $eGFR_{creat}$ and $eGFR_{cys}$ was associated with a higher risk of MACE and faster CAC progression in patients with CKD.