atherosclerosis

Atherosclerosis newsletter

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The two final issues of 2021 contain several articles on the interaction between inflammation and cardiovascular diseases. Most of them describe diagnostic approaches to unravel these pathogenic pathways.

Heightened splenic and bone marrow uptake of ^{18}F-FDG PET/CT is associated with systemic inflammation and subclinical atherosclerosis by CCTA in psoriasis: An observational study

Atherosclerosis is a multifactorial disease being recognized as an inflammatory process. Psoriasis is a hyperproliferative cutaneous skin disorder associated with increased cardiovascular risk and is a reliable model to study inflammatory atherogenesis. Preclinical studies in psoriasis models show an association between chronic inflammation and immune cell proliferation in the spleen and bone marrow (BM). Patel et al. tested the hypothesis that splenic and BM ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake is heightened in psoriasis and that higher uptake associates with systemic inflammation and subclinical atherosclerotic disease measures.

Multimodality imaging and biomarker assays were performed in 240 participants (210 with psoriasis and 30 healthy). Splenic and BM uptake was assessed using ^{18}F-FDG positron emission tomography/computed tomography (PET/CT). Coronary artery plaque characteristics, including non-calcified burden (NCB) and lipid rich necrotic core (LRNC), were quantified using a dedicated software for CT angiography.

Splenic and BM ^{18}F-FDG uptake was increased in psoriasis and significantly associated with proatherogenic lipids, immune cells and systemic inflammation. Higher splenic ^{18}F-FDG uptake associated with higher total coronary burden, NCB, and LRNC in fully adjusted models. Similar associations were seen for BM ^{18}F-FDG uptake in adjusted models.

Heightened splenic and BM uptake of ^{18}F-FDG is associated with proatherogenic lipid profile, immune cells, inflammatory markers and coronary artery disease. These findings provide insights into atherogenic mechanisms in psoriasis and suggest that immune cell proliferation in the spleen and BM is associated with subclinical atherosclerosis.

Sex-specific platelet activation through protease-activated receptor-1 in patients undergoing cardiac catheterization

Antiplatelet therapy is a cornerstone of the treatment of atherosclerotic cardiovascular disease. Thrombin is a potent platelet agonist activating human platelets via protease-activatedeceptor (PAR)-1 and PAR-4. PAR-1-mediated platelet activation may vary according to sex and clinical situation. To investigate sex-specific platelet activation through PAR-1, Gremmel et al. assessed platelet response to thrombin receptor-activating peptide (TRAP) in 562 patients undergoing cardiac catheterization without (Group 1A) and with (Group 1B) acute coronary syndrome (ACS). Subsequently, they confirmed the findings in 287 patients undergoing elective (Group 2A) or acute (Group 2B) percutaneous coronary intervention.

TRAP-stimulated platelet surface expression of P-selectin and activated glycoprotein IIb/IIIa (GPIIb/IIIa) were measured by flow cytometry in Group 1. Light transmission aggregometry (LTA) and multiple electrode aggregometry (MEA) in response to TRAP were assessed in Group 2.

In Group 1A, platelet activation in response to TRAP was significantly higher in women compared to men. In contrast, in Group 1B, TRAP-stimulated P-selectin and activated GPIIb/IIIa were similar in men and women. TRAP-stimulated platelet aggregation was significantly higher in female patients in Group 2A, while men and women in Group 2B had similar platelet aggregation. The occurrence of ischemic endpoints did not differ significantly between men and women in Group 1A and Group 1B.

Platelet PAR-1 signaling is more pronounced in women than in men without ACS. In patients with ACS, however, platelet PAR-1-stimulated responses are similar between women and men.

Association of inflammatory markers and lipoprotein particle subclasses with progression of coronary artery calcium: The multi-ethnic study of atherosclerosis

A significant association of lipoprotein particles and inflammatory markers with coronary atherosclerosis has been shown. However, there is heterogeneity in studies evaluating the association of lipoprotein particles and markers of inflammation with coronary artery calcium (CAC) that represents calcified atherosclerosis. Zeb et al. assessed association of nuclear magnetic resonance (NMR) lipid variables and inflammatory markers with incident CAC and CAC progression among participants with baseline CAC ≥0.

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal cohort study of 6,814 participants. 3,115 had CAC = 0 and 2,896 had CAC>0 at baseline. Repeat CAC measurements were obtained during a mean follow up of 6.5 years.

Interleukin-6 (IL-6) and fibrinogen were associated with a higher relative risk (RR) of incident CAC (HU). Small low-density lipoprotein (LDL) and log large very low-density lipoprotein (VLDL) were associated

with higher risks, whereas large high-density lipoprotein (HDL) was associated with an inverse risk of incident CAC in a model adjusted for follow up time, age, gender and race. Among participants with baseline CAC>0, progression of CAC was positively associated with high sensitivity C-reactive protein (hsCRP), IL-6, fibrinogen, large VLDL, and small LDL in a model adjusted for scanner type, age, gender and race.

Inflammatory markers and specialized lipoprotein particles were associated with CAC incidence and progression in minimally adjusted models, but not after adjustment for traditional risk factors. Traditional risk factors were strongly associated with both CAC incidence and progression with the exception of cholesterol parameters not associated with CAC progression in adjusted model.

Copeptin as a marker of atherosclerosis and arteriosclerosis

Even though a link between copeptin, the precursor peptide of vasopressin, and several cardiovascular conditions has been established, a possible association between copeptin and objective measures of subclinical cardiovascular disease (CVD) has not been investigated. Schill et al. aimed to determine whether copeptin is associated with markers of atherosclerosis and arteriosclerosis measured by coronary artery calcium score (CACS) and carotid-femoral pulse wave velocity (c-f PWV).

CACS, c-f PWV, and fasting plasma copeptin were measured in 5303 individuals in the Swedish cardiopulmonary bioimage study (SCAPIS). Multivariable logistic regression models were used to analyze the associations between copeptin and high CACS and high c-f PWV, respectively.

The number of individuals with high CACS and c-f PWV increased across increasing tertile of copeptin. The top tertile of copeptin was, compared with reference tertile 1, significantly associated with high CACS and high c-f PWV after adjustment for age, sex, hypertension, diabetes mellitus, high-density lipoprotein, triglycerides, body mass index, smoking status, creatinine and high sensitive C-reactive protein.

Copeptin is associated with both coronary atherosclerosis and increased arterial stiffness in the general population. Copeptin may be a useful marker in the assessment of cardiovascular risk.

Associations of adipokine levels with the prevalence and extent of valvular and thoracic aortic calcification: The Multi-Ethnic Study of Atherosclerosis (MESA)

Cardiovascular disease (CVD) is the leading cause of death worldwide. Increased focus has been directed towards preventing the development and progression of CVD through the modification of risk factors. Obesity has been clearly implicated as one such risk factor, however, the mechanisms by which risk is conferred are complex and not fully understood. One potential contribution comes from dysregulation of endogenous hormones secreted by adipose tissue, called adipokines. A putative mechanism by which adipokine dysregulation would influence CVD is via atherosclerosis. Extra-

coronary calcification (ECC) is a marker of atherosclerosis and independently associated with cardiovascular disease (CVD). However, the relationship between adipokines and ECC is not well established. Sweeney et al. examined the associations of the adipokines leptin, resistin and adiponectin with ECC in a diverse community-based cohort.

They performed a cross-sectional analysis of 1897 adults without clinical CVD in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. Serum adipokine levels and non-contrast cardiac CT scans were obtained at Exam 2 or 3 (randomly assigned). ECC was quantified by Agatston score and included calcification of the mitral annulus (MAC), aortic valve (AVC), ascending thoracic aorta (ATAC), and descending thoracic aorta (DTAC). Multivariable regression was used to evaluate the associations between leptin, resistin and adiponectin with ECC prevalence and extent.

The mean age of participants was 65 ± 10 years; 49% were women. After adjusting for demographic factors, adiponectin was inversely associated with AVC prevalence and extent, leptin positively associated with MAC prevalence and extent, and resistin positively associated with ATAC prevalence and extent and DTAC extent. After adjustment for BMI and other CVD risk factors, adiponectin remained inversely associated with AVC prevalence, and resistin remained associated with greater ATAC prevalence and extent. Leptin was not associated with measures of ECC after full adjustment. No adipokine was associated with MAC after full adjustment.
These results show the complex interplay between obesity, adipokine levels, and atherosclerosis.

Associations of maternal angiogenic factors during pregnancy with childhood carotid intima-media thickness and blood pressure

Placental vascular development and function are major determinants of fetal cardiovascular development. Abnormalities in such processes may lead to long-term alterations in childhood vasculature. Placental growth factor (PlGF), a pro-angiogenic factor, and its soluble receptor fms-like tyrosine kinase (sFlt-1), an anti-angiogenic factor, are produced by placental cytotrophoblasts during pregnancy and are among the most important circulating angiogenic factors in pregnancy. Reduced maternal PlGF and higher sFlt-1 concentrations in pregnancy may have persistent effects on offspring vasculature. Bongers-Karmaoui et al. hypothesized that suboptimal maternal angiogenic factors in pregnancy may adversely affect fetal vascular development, leading to an increased risk of adverse atheriosclerotic adaptations and higher blood pressure in offspring.

To test this hypothesis, they examined the associations of maternal serum PlGF and sFlt-1 concentrations in the first half of pregnancy with offspring vascular development, in a population-based prospective cohort study among 4565 women and their offspring. They measured childhood blood pressure and obtained childhood carotid intima media thickness (IMT) and carotid distensibility through ultrasonography at 9 years.

After adjustment for maternal sociodemographic and lifestyle characteristics, no associations were present between maternal first and second trimester angiogenic factors and childhood blood pressure, IMT or distensibility in the total population. In preterm born children only, higher maternal second trimester PlGF concentrations, but not sFlt-1 concentrations, were associated with a lower childhood diastolic blood pressure. No associations among children born small-for-gestational age were present.

In a low-risk population, maternal angiogenic factors in the first half of pregnancy are not associated with childhood blood pressure, carotid IMT or carotid distensibility after considering maternal socio-demographic and lifestyle factors. Only in children born preterm, lower maternal second trimester PlGF concentrations are associated with higher childhood diastolic blood pressure, but not with other vascular outcomes.

PRMT4 inhibitor TP-064 impacts both inflammatory and metabolic processes without changing the susceptibility for early atherosclerotic lesions in male apolipoprotein E knockout mice

Atherosclerotic cardiovascular disease is a metabolic and inflammatory disorder. *In vitro* studies have suggested that protein arginine methyltransferase 4 (PRMT4) may act as a transcriptional coactivator to modulate inflammatory and metabolic processes. Zhang et al. investigated the potential anti-atherogenic effect of the PRMT4 inhibitor TP-064 *in vivo*.

Male apolipoprotein E knockout mice fed a high cholesterol/high fat Western-type diet were intraperitoneally injected three times a week with 2.5 mg/kg (low dose) or 10 mg/kg (high dose) TP-064 or with DMSO control.

TP-064 induced a dose-dependent decrease in lipopolysaccharide-induced *ex vivo* blood monocyte tumor necrosis factor α (Tnfα) secretion in the context of unchanged blood monocyte concentrations and neutrophilia induction. A dose-dependent decrease in gonadal white adipose tissue expression levels of proliferator-activated receptor γ (PPARγ) target genes was detected, which translated into a reduced body weight gain after high dose TP-064 treatment. TP-064 treatment also dose-dependently downregulated gene expression of the glycogen metabolism related protein glucose 6-phosphatase catalytic subunit (G6pc) in the liver. In addition, a trend towards lower plasma insulin and higher blood glucose levels was observed, which was paralleled by a reduction in hepatic mRNA expression levels of the insulin-responsive genes fatty acid synthase (*Fasn*) and glucokinase (*Gck*) in high dose-treated mice. Plasma triglyceride levels were reduced by high dose TP-064 treatment. However, no change was observed in the size or composition of aortic root atherosclerotic lesions.

The PRMT4 inhibitor TP-064 impacts both inflammatory and metabolic processes without changing atherosclerosis susceptibility of male apolipoprotein E knockout mice.