atherosclerosis

Atherosclerosis newsletter

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Chronic inflammation is both a pathogenic factor and a characteristic response of atherosclerotic lesions. The inflammation is, therefore, targeted for diagnostics/prognostics, as well as therapy of atherosclerotic cardiovascular diseases. The two August issues of *Atherosclerosis* contain several articles that cover these aspects of inflammation in atherosclerosis.

Polygenic risk score in comparison with C-reactive protein for predicting incident coronary heart disease

Accurate risk prediction for incident coronary heart disease (CHD) remains a cornerstone of preventive cardiovascular care. Recently, polygenic risk scores (PRS) have emerged as important tools for capturing the CHD risk conferred by common genetic variants. These scores use weighted risk associations derived from genome-wide association studies (GWAS) and frequently incorporate millions of single nucleotide polymorphisms (SNPs). Despite the increasing interest in the use of PRS to predict CHD risk, the clinical utility of PRS compared to conventional risk factors has not been demonstrated. Aday et al. compared the performance of PRS with that of high-sensitivity C-reactive protein (hsCRP) in two well-established cohorts.

The study population included individuals of European ancestry free of baseline CHD from the Atherosclerosis Risk in Communities (ARIC) Study and the Framingham Offspring Study (FHS). The primary predictors included a validated PRS consisting of >6.6 million single nucleotide polymorphisms and hsCRP. The outcome was incident CHD, defined as non-fatal or fatal myocardial infarction. The performance of both predictors was compared after adjusting for the Pooled Cohort Equations in multivariable-adjusted Cox regression models. Discrimination and reclassification using C-statistics and net reclassification improvement were assessed.

Incident CHD occurred in 565 ARIC and 153 FHS participants. In multivariable-adjusted models, both PRS and hsCRP were associated with incident CHD. In models incorporating both predictors, strengths of association were similar. Neither predictor significantly increased model discrimination or net reclassification when compared with models containing the Pooled Cohort Equations alone.

In these two independent cohorts, PRS performed similarly to hsCRP for the prediction of CHD risk. These findings suggest that PRS does not function as an effective risk enhancer for coronary heart disease.

Sustained low-grade inflammation in young participants with childhood onset type 1 diabetes: The Norwegian atherosclerosis and childhood diabetes (ACD) study

Although atherosclerosis is a slowly progressive condition, both genetic and environmental risk factors can induce and accelerate the process. It is now well established that atherosclerosis is a chronic low-grade inflammatory disease. Pro-inflammatory proteins, produced by different cells and organs, seem to play an important role in all phases of atherosclerosis development.

Subjects with type 1 diabetes (T1D) have increased mortality from cardiovascular disease. Several studies have shown increased inflammation and increased levels of pro-inflammatory markers reflecting systemic inflammation in T1D. Simeunovic et al. aimed to evaluate whether increased inflammation in subjects with T1D is sustained over a five-year period and whether changes in the extent of inflammation differ significantly from healthy controls.

The Norwegian Atherosclerosis and Childhood Diabetes (ACD) study is a prospective population-based cohort study on atherosclerosis development in childhood-onset T1D compared to healthy controls, with follow-ups every 5th year. The original study cohort consisted of 314 children with T1D on intensive insulin treatment and 120 healthy controls of similar age. Circulating levels of VCAM-1, TNFα, P-selectin, E-selectin, CRP, IL-6, IL-18, MCP-1, MMP-9 and TIMP-1 were measured by ELISAs at baseline and at the five-year follow-up.

The T1D group had mean age 13.7 years, disease duration 5.6 years and HbA1c 68 mmol/mol at baseline. Levels of almost all inflammatory markers were significantly increased in the group with T1D compared to controls, and significant mean-difference between the two groups over the five-year period was observed in four markers: IL-18, P-selectin, E-selectin and TIMP-1.

The early low-grade inflammation present in young individuals with T1D five years after diagnosis is sustained at ten-year disease duration despite intensive insulin treatment.

Dual elevated remnant cholesterol and C-reactive protein in myocardial infarction, atherosclerotic cardiovascular disease, and mortality

Remnant cholesterol is the cholesterol content of triglyceride-rich lipoproteins including very low-density lipoproteins and intermediate-density lipoproteins in the fasting state, and additionally chylomicron remnants in the nonfasting state. Elevated remnant cholesterol and low-grade inflammation each cause atherosclerotic cardiovascular disease (ASCVD); however, it is unknown whether joint elevation of both factors confers the highest risk.

Using data from The Copenhagen General Population Study that randomly recruited white Danish individuals aged 20–100 years in 2003–2015 and followed them for a median 9.5 years, Doi et al. tested the hypothesis that dual elevated remnant cholesterol and low-grade inflammation, marked by elevated C-reactive protein (CRP), are associated with the highest risk of myocardial infarction, ASCVD, and all-cause mortality.

In 103,221 individuals, the authors observed 2,454 (2.4%) myocardial infarctions, 5,437 (5.3%) ASCVD events, and 10,521 (10.2%) deaths. The hazard ratios increased with each of stepwise higher remnant cholesterol and stepwise higher C-reactive protein. In individuals with the highest tertile of both remnant cholesterol and C-reactive protein compared to individuals with the lowest tertile of both, the multivariable adjusted hazard ratios were 2.2 for myocardial infarction, 1.9 for ASCVD, and 1.4 for all-cause mortality. Corresponding values for only the highest tertile of remnant cholesterol were 1.6, 1.4, and 1.1, and those for only the highest tertile of C-reactive protein were 1.7, 1.6, and 1.3, respectively. There was no statistical evidence for interaction between elevated remnant cholesterol and elevated C-reactive protein on risk of myocardial infarction, ASCVD, or all-cause mortality.

Dual elevated remnant cholesterol and C-reactive protein confer the highest risk of myocardial infarction, ASCVD, and all-cause mortality compared to either of these two factors individually.

Anti-inflammatory therapies were associated with reduced risk of myocardial infarction in patients with established cardiovascular disease or high cardiovascular risks: A systematic review and meta-analysis of randomized controlled trials

Atherosclerosis is now considered as a chronic inflammatory disease. Therefore, anti-inflammatory therapies may serve as another independent therapeutic method for atherosclerotic cardiovascular disease (ASCVD) in addition to traditional lipid-lowering treatments. Lin et al. aimed to evaluate the association between anti-inflammatory therapies and the incidence of cardiovascular events in patients with established cardiovascular disease (CVD) or high cardiovascular risks.

The authors conducted literature retrieval in PubMed, Medline, Embase, the Cochrane Central Register of Controlled Trials and Clinicaltrial.gov website from the inception to December 2022. Randomized controlled trials comparing anti-inflammatory therapies with placebo in patients with established CVD or high cardiovascular risks were included. The results of the meta-analysis were computed as risk ratio (RR) with 95% confidence interval (CI).

Compared with placebo, anti-inflammatory therapies were associated with decreased incidence of myocardial infarction (MI), which was mainly driven by therapies targeting central IL-6 signaling pathway. IL-1 inhibitors treatment was associated with reduced risks of heart failure while lower incidence of stroke was observed in patients with colchicine treatment. MI events were less

frequent in patients over 65 years of age or with follow-up duration over 1 year when comparing anti-inflammatory therapies with placebo.

Anti-inflammatory therapies, especially those targeting the central IL-6 signaling pathway, may serve as promising treating strategies to ameliorate the risk of MI. IL-1 inhibitor and colchicine were associated with decreased risks of heart failure and stroke, respectively. MI risk reduction by anti-inflammatory therapies seemed to be more prominent in older patients with long follow-up duration.

Evidence of an anti-inflammatory effect of PCSK9 inhibitors within the human atherosclerotic plaque

Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) is an enzyme promoting the clearance of low-density lipoprotein (LDL) receptors in the liver, raising the circulating levels of LDL-cholesterol (C). Preclinical evidence suggests that PCSK9 inhibitors hold anti-inflammatory properties independently of their ability to lower LDL-C. However, whether PCSK9 inhibitors exert anti-inflammatory effects within the atherosclerotic plaque in humans is unknown. Marfella et al. explored the impact of PCSK9 inhibitors, used as monotherapy, compared with other lipid-lowering drugs (oLLD) on the expression of inflammatory markers within the plaque, assessing also the subsequent incidence of cardiovascular events.

In this observational study, the authors recruited 645 patients on stable therapy for at least six months and undergoing carotid endarterectomy, categorizing patients according to the use of PCSK9 inhibitors only or oLLD. The expression of NLRP3, caspase-1, IL-1β, TNFα, NF-kB, PCSK9, SIRT3, CD68, MMP-9, and collagen within the plaques was measured in the two groups through immunohistochemistry, ELISA, or immunoblot. A composite outcome including non-fatal myocardial infarction, non-fatal stroke, and all-cause mortality was assessed during a 678 ± 120 days follow-up after the procedure.

Patients treated with PCSK9 inhibitors had a lower expression of pro-inflammatory proteins and a higher abundance of SIRT3 and collagen within the plaque, a result obtained despite comparable levels of circulating hs-CRP and observed also in LDL-C-matched subgroups with LDL-C levels <100 mg/dL. Patients treated with PCSK9 inhibitors showed a decreased risk of developing the outcome compared with patients on oLLD, also after adjustment for multiple variables including LDL-C. The expression of PCSK9 correlated positively with that of pro-inflammatory proteins, which burden was associated with a higher risk of developing the outcome, independently of the therapeutic regimen.

The use of PCSK9 inhibitors is accompanied by a beneficial remodelling of the inflammatory burden within the human atheroma, an effect possibly or partly independent of their LDL-C lowering ability. This phenomenon might provide an additional cardiovascular benefit.

Nuclear FAK in endothelium: An intrinsic inhibitor of NF-κB activation in atherosclerosis

Atherosclerosis is a progressive disease characterized by excess accumulation of lipids in the vessel wall that contributes to multiple cardiovascular diseases. One of the primary risk factors for atherosclerosis is hyperlipidemia that leads to the accumulation of oxidized low-density lipoprotein (oxLDL) within the vessel wall where it causes chronic inflammation in endothelial cells (ECs) and drives atherosclerotic lesions. Focal adhesion kinase (FAK) is a protein tyrosine kinase that has been implicated in vascular inflammation and atherosclerosis progression. Although FAK is critical in proinflammatory NF-κB activation in ECs, it is unknown if hyperlipidemia alters FAK-mediated NF-κB activity *in vivo* to affect atherosclerosis progression.

Murphy et al. investigated changes in EC FAK and NF-κB activation using *Apoe*$^{-/-}$ mice fed a Western diet (WD). Pharmacological FAK inhibition and EC-specific FAK inhibited mouse models were utilized. FAK and NF-κB localization and activity were also assessed in human atherosclerotic samples.

ECs of hyperlipidemic mice showed higher levels of FAK activation in the cytoplasm, which was required for subsequent activation of NF-κB while FAK was mostly localized in the nucleus and inactive in ECs under healthy conditions, which presented a low NF-κB activity. Both pharmacological and EC-specific genetic FAK inhibition in WD fed *Apoe*$^{-/-}$ mice lead to a significant decrease in FAK activity and cytoplasmic localization, NF-κB activation, macrophage recruitment, and atherosclerotic lesions compared to the vehicle or FAK wild-type groups. Analyses of human atherosclerotic specimens revealed a positive correlation between increased active cytoplasmic FAK within ECs and NF-κB activation in the lesions.

Hyperlipidemic conditions activate NF-κB pathway by increasing EC FAK activity and cytoplasmic localization in mice and human atherosclerotic samples. As FAK inhibition can efficiently reduce vascular inflammation and atherosclerotic lesions in mice by reversing EC FAK localization and NF-κB activation, these findings support a potential use for FAK inhibitors in treating atherosclerosis.