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Call for original research papers on
"THE LINK BETWEEN DIABETES AND CARDIOVASCULAR DISEASE"

The most recent observations from pathophysiological, epidemiological, and genetic studies are increasing substantially our knowledge on the close link between diabetes and cardiovascular disease.

Atherosclerosis, the journal of the European Atherosclerosis Society (EAS), is now **calling for the submission of Original Research Papers for a dedicated theme issue on "The link between diabetes and cardiovascular disease"**. Submissions are encouraged from all fields related to the topic including clinical, translational, and basic research.

The submitted Original Research Articles will be handled by Jan Borén, Alberico Catapano, and Katariina Öörni, Co-Editors of *Atherosclerosis*. All papers will be reviewed following standard reviewing procedures for the Journal. **Accepted manuscripts will be published with promotional open access for a one-year period, free of charges for the authors, together with invited reviews on the topic.**

For preparation of the Original Research manuscripts please see the "Guide for authors"

Deadline for submission of the first draft of the Original Research Papers is April 30, 2023. This call is only open for Original Research Articles and no review articles are allowed. Please select "Special issue: Diabetes and CVD" as article type at submission.

To submit your paper go to: Editorial Manager®

Atherosclerosis newsletter

Simona Negrini and Arnold von Eckardstein

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Beyond cholesterol in plasma, low-density lipoprotein (LDL) or nonHDL and high-density lipoprotein (HDL), as well as triglycerides in plasma LDL, other biomarkers of lipid and lipoprotein metabolism get more and more attention. Among them, lipoprotein(a) (Lp(a)) has the strongest evidence of clinical utility and its clinical use for risk assessment is supported by guidelines. Others, such as remnants and subfractions of LDL, are intensively investigated in cohort studies. Mass spectrometry helps measure other lipid classes such as glycerophospholipids and sphingolipids. Their clinical validation has only started. Issues 363 and 364 contain several articles on Lp(a), as well as lipid determinants of LDL features or atherosclerosis.

Relationship of low-density lipoprotein-cholesterol and lipoprotein(a) to cardiovascular risk: The Multi-Ethnic Study of Atherosclerosis (MESA)

Plasma low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) (Lp(a)) are both associated with coronary heart disease (CHD). Rikhi et al. investigated whether elevated plasma Lp(a) concentration was associated with increased CHD risk when LDL-C was low in individuals not on statin therapy.

Participants from the Multi-Ethnic Study of Atherosclerosis (MESA) were categorized into four groups: Group 1: LDL-C ≤ 100 mg/dL, Lp(a) < 50 mg/dL; Group 2: LDL-C > 100 mg/dL, Lp(a) < 50 mg/dL; Group 3: LDL-C ≤ 100 mg/dL, Lp(a) ≥ 50 mg/dL; and Group 4: LDL-C > 100 mg/dL, Lp(a) ≥ 50 mg/dL. The relationship of Lp(a) and LDL-C with time to CHD events was assessed with Kaplan Meier curves and multivariable Cox proportional hazard models.

Participants were followed for a mean of 13.4 years and a total of 315 CHD events occurred. Compared to participants with LDL-C ≤ 100 mg/dL and Lp(a) < 50 mg/dL, those with LDL-C > 100 mg/dL and Lp(a) < 50 mg/dL (Group 2) demonstrated no increased risk for CHD events. However, participants with LDL-C ≤ 100 mg/dL and Lp(a) ≥ 50 mg/dL (Group 3) and those with LDL-C > 100 mg/dL and Lp(a) ≥ 50 mg/dL (Group 4) exhibited significantly increased risk of CHD events compared to Group 1 and Group 2, respectively.

When Lp(a) was elevated, risk of CHD events increased, regardless of baseline LDL-C. Lp(a) is an important risk marker in primary prevention, even when LDL-C is optimal.

Lipoprotein(a), high-sensitivity C-reactive protein, and cardiovascular risk in patients undergoing percutaneous coronary intervention

In patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), the effects of high-sensitivity C-reactive protein (hsCRP) on Lipoprotein(a) (Lp(a))-associated cardiovascular risk remains unclear. Yuan et al. hypothesize that individuals with dual elevation of Lp(a) and hsCRP levels may have worse clinical outcomes. This study aimed to investigate the independent and joint association of Lp(a) and hsCRP with long-term outcomes in patients with CAD based on a large secondary prevention cohort.

A total of 10,424 patients with measurements of both Lp(a) and hsCRP were included in this prospective cohort study. Cox proportional hazards models and Kaplan-Meier analysis were performed to evaluate the relationship between Lp(a), hsCRP and adverse cardiac and cerebrovascular events (MACCE; all-cause death, myocardial infarction, ischemic stroke and revascularization).

During 5 years of follow-up, 2140 MACCE occurred. Elevated Lp(a) and hsCRP levels were associated with increased risks of MACCE. Notably, there might be a significant interaction between Lp(a) and hsCRP. In the setting of hsCRP≥2 mg/L, significant higher risk of MACCE was observed with Lp(a) 15–29.9 mg/dL and Lp(a) ≥30 mg/dL, whereas such association was attenuated when hsCRP was <2 mg/L with Lp(a) 15–29.9 mg/dL and Lp(a) ≥30 mg/dL. Moreover, when Lp(a) and hsCRP were combined for risk stratification, patients with dual elevation of these two biomarkers had a significant higher risk of MACCE compared with the reference group (Lp(a) < 15 mg/dL and hsCRp<2 mg/L).

In patients with CAD undergoing PCI, high Lp(a) level was associated with worse outcomes, and this association might be stronger in those with concomitantly elevated hsCRP. Evaluation of Lp(a) and hsCRP together may help identify high-risk individuals for targeted intervention in clinical utility.

Lipoprotein (a) and long-term outcome in patients with peripheral artery disease undergoing revascularization

Despite recent advances in secondary prevention of cardiovascular (CV) disease, the residual risk for future CV events remains high. This particularly extends to patients with peripheral artery disease (PAD), a CV disease that can be seen as a manifestation of systemic and advanced atherosclerotic disease and burden. Lipoprotein (a) (Lp(a)) is a known risk factor for PAD incidence, but little is known regarding the outcome in patients with symptomatic PAD. Thus, Zierfuss et al. investigated Lp(a) and CV mortality in PAD after endovascular repair.

A total of 1222 patients with PAD in two cohorts according to Lp(a) assay in nmol/L (Lip-LEAD-A) or mg/dl (Lip-LEAD-B) were followed up for 4.3 or 7.6 years. Lp(a) was measured before endovascular repair for either intermittent claudication (IC) or critical limb ischemia (CLI). Outcome information was obtained from the federal death registry.

After adjustment for traditional CV risk factors, Lp(a) was not associated with cardiovascular mortality in either cohorts. No specific pattern of lesion site (iliacal, femoral, below the knee, multivessel) for endovascular repair was detected with elevated Lp(a) levels.

In this large-scale cohort of symptomatic PAD no association of elevated Lp(a) with CV mortality was found over a median observation period of 5 years. Thus, an even longer study including asymptomatic patients is warranted.

The human liver lipidome is significantly related to the lipid composition and aggregation susceptibility of low-density lipoprotein (LDL) particles

The main cause of atherosclerotic cardiovascular disease (ASCVD) is accumulation of cholesterol carried in low density lipoprotein (LDL) particles to the arterial wall. A high concentration of LDL-cholesterol is the major risk factor for ASCVD, but the quality of LDL particles, including their aggregation susceptibility, also contributes. LDL aggregability predicts independently ASCVD events and mortality, but does not seem to correlate with known ASCVD risk factors such as age, sex, body mass index (BMI), or the concentration of serum LDL cholesterol. The reason(s) for the interindividual variation in LDL aggregability remain poorly understood. Lahelma et al. examined whether the lipid composition and aggregation susceptibility of LDL reflect the lipid composition of the human liver.

Liver biopsies and blood samples for isolation of LDL particles were obtained from 40 obese subjects. LDL was isolated using sequential ultracentrifugation and lipidomic analyses of liver and LDL samples were determined using ultra-high performance liquid chromatography–mass spectrometry. LDL aggregation susceptibility *ex vivo* was analyzed by inducing aggregation by human recombinant secretory sphingomyelinase and following aggregate formation.

The composition (acyl carbon number and double bond count) of hepatic triglycerides, phosphatidylcholines, and sphingomyelins (SMs) was closely associated with that of LDL particles. Hepatic dihydroceramides and ceramides were positively correlated with concentrations of the corresponding SM species in LDL as well with LDL aggregation. These relationships remained statistically significant after adjustment for age, sex, and body mass index.

Lipid composition of LDL reflects that of the human liver in obese patients. Changes in hepatic sphingolipid metabolism may contribute to interindividual variation of LDL lipid composition and susceptibility to aggregation.

Spatial metabolomics identifies lipid profiles of human carotid atherosclerosis

Carotid atherosclerosis is an important cause of ischemic stroke. Lipids play a key role in the progression of atherosclerosis. Spatial metabolomics is an emerging omics that can map the spatial distribution of small molecules, such as lipids, and correlate with pathological findings *in situ* without

chemical labels or antibodies.To date, the spatial lipid profile of carotid atherosclerotic plaques related to histology has not been systematically investigated. In this study, Li et al. employed desorption electrospray ionization-mass spectrometry imaging (DESI-MSI) on carotid atherosclerosis samples from 12 patients (classified into four classical pathological stages (preatheroma, atheroma, fibroatheroma and complicated lesion)) to investigate the spatial lipid profile distribution in human carotid plaques at different stages of atherosclerosis, and correlate MSI data with histological information, aiming to delineate metabolic profiles and provide deep insights into spatial metabolic mechanism of human carotid atherosclerosis.

A total of 55 lipids (26 throughout cross-section regions [TCSRs], 13 in lipid-rich regions [LRRs], and 16 in collagen-rich regions [CRRs]) were initially identified in carotid plaque from one patient. Subsequently, 32 of 55 lipids were further screened in 11 patients. Pathway enrichment analysis showed that multiple metabolic pathways, such as fat digestion and absorption, cholesterol metabolism, lipid and atherosclerosis, were enriched in TCSRs; sphingolipid signaling pathway, necroptosis pathway were enriched in LRRs; and glycerophospholipid metabolism, ether lipid metabolism pathway were mainly enriched in CRRs.

This study comprehensively showed the spatial lipid metabolism footprint in human carotid atherosclerotic plaques. The lipid profiles and related metabolism pathways in three regions of plaque with disease progression were different markedly, suggesting that the different metabolic mechanisms in these regions of carotid plaque may be critical in atherosclerosis progression.

Temporal lipid profiling in the progression from acute to chronic heart failure in mice and ischemic human hearts

Epidemiological studies have established several risk factors for heart failure (HF). HF after myocardial infarction (MI) is a primary cause of late morbidity and mortality. Advanced atherosclerosis leads to an MI event that results in irreversible damage to the myocardium due to a lack of oxygen, leading to impairment in systolic function. At present, increased levels of plasma markers, such as creatinine kinase and cardiac troponin I, are used to determine the extent of myocardial injury. However, more recent research interest has shifted toward identifying the temporospatial and prognostic biomarkers of HF progression in the early stages of cardiac injury and late cardiac remodeling. In this study, Gowda et al. aimed to obtain sequential lipid profiling from acute to chronic HF.

The comprehensive lipidome of the hearts from diseased and healthy subjects was reported. To induce heart failure in mice, a non-reperfused model of coronary ligation was used, and MI was confirmed by echocardiography and histology, then temporal kinetics of lipids in different tissues (heart, spleen, kidney), and plasma was quantitated from heart failure mice and compared with naïve controls. For

lipid analysis in mouse and human samples, untargeted liquid chromatography-linear trap quadrupole orbitrap mass spectrometry (LC-LTQ-Orbitrap MS) was performed.

In humans, multivariate analysis revealed distinct cardiac lipid profiles between healthy and ischemic subjects, with 16 lipid species significantly downregulated by 5-fold, mainly phosphatidylethanolamines (PE), in the ischemic heart. In contrast, PE levels were markedly increased in mouse tissues and plasma in chronic MI, indicating possible cardiac remodeling. Further, fold change analysis revealed site-specific lipid biomarkers for acute and chronic HF. A significant decrease in sulfatides (SHexCer (34:1; 2O)) and sphingomyelins (SM (d18:1/16:0)) was observed in mouse tissues and plasma in chronic HF.

Overall, a significant decreased lipidome in human ischemic LV and differential lipid metabolites in the transition of acute to chronic HF with inter-organ communication could provide novel insights into targeting integrative pathways for the early diagnosis or development of novel therapeutics to delay/prevent HF.