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The widespread consumption of energy-rich food and lack of physical activity have led to a steady increase in the prevalence of overweight and obesity, as well as ectopic fat accumulation. As such, diabetes mellitus, non-alcoholic fatty liver diesases (NAFLD) and atherosclerotic cardiovascular diseases have become frequent clinical consequences in many countries worldwide. Several articles in the April and May issues of *Atherosclerosis* describe novel data from basic, clinical and population research on the interdependencies of these diseases.

Sitagliptin attenuates the progression of coronary atherosclerosis in patients with coronary disease and type 2 diabetes

Type 2 diabetes mellitus (T2DM) increases the risk for atherosclerosis and cardiovascular disease, which is one of the major causes of morbidity and mortality in these patients. Li et al. aimed to investigate the effects of a new class of oral hypoglycemic agents, sitagliptin, on the prevention of coronary atherosclerosis progression assessed by three-dimensional quantitative coronary angiography (3D-QCA) in T2DM patients with coronary artery disease (CAD).

In this prospective, randomized, double-center, open-label, blinded end point, controlled 18-month study of patients with CAD and T2DM, 149 patients who had clinically indicated coronary angiography or percutaneous coronary intervention (PCI), with at least 1 atherosclerotic plaque with 20%–80% luminal narrowing in a coronary artery that had not undergone intervention, were randomized to sitagliptin group or control group. Atherosclerosis progression was measured by repeat 3D-QCA examination in 88 patients at study completion. The primary outcome was changes in percent atheroma volume (PAV) from baseline to study completion measured by 3D-QCA. Secondary outcomes included change in 3D-QCA-derived total atheroma volume (TAV) and late lumen loss (LLL).

The primary outcome of PAV increased of 1.69% with sitagliptin and 5.12% with conventional treatment. The secondary outcome of change in TAV in patients treated with sitagliptin increased of

6.45 mm^3 and of 9.45 mm^3 with conventional treatment, however, no significant difference between groups was observed. Patients treated with sitagliptin had similar LLL as compared to those treated with conventional antidiabetics.

In patients with type 2 diabetes and coronary artery disease, treatment with sitagliptin resulted in a significantly lower rate of progression of coronary atherosclerosis compared with conventional treatment. This study may have important implications for defining the optimal strategy for management of patients with type 2 diabetes and coronary atherosclerosis.

An oxide transport chain essential for balanced insulin action

Patients with overnutrition, obesity, the atherometabolic syndrome, and type 2 diabetes typically develop fatty liver, atherogenic dyslipoproteinemia, hyperglycemia, and hypertension. These features share an unexplained origin – namely, imbalanced insulin action, also called pathway-selective insulin resistance and responsiveness. To control glycemia, these patients require hyperinsulinemia that then overdrives extracellular signal-regulated kinase (ERK) and hepatic *de-novo* lipogenesis. Wu et al. previously reported that NADPH oxidase-4 (NOX4) regulates balanced insulin action, but the model appeared incomplete. Therefore, the authors conducted structure-function studies in liver cells to search for additional molecular mediators of balanced insulin action.

They found a new pathway of insulin signaling in hepatocytes “NSAPP” (after its five major proteins: NOX4, superoxide dismutase-3 (SOD3), aquaporin-3 (AQP3) and phosphatase and tensin homolog deleted on chromosome 10 and protein-tyrosine phosphatases (PTEN/PTPases)). The NSAPP pathway is an oxide transport chain that begins when insulin stimulates NOX4 to generate superoxide (O_2•–). NOX4 forms a novel, tight complex with SOD3, to efficiently transfer O_2•– for quantitative conversion into hydrogen peroxide. The pathway ends when AQP3 channels H_2O_2 across the plasma membrane to inactivate PTEN. Accordingly, AQP3 forms a novel complex with PTEN in McArdle hepatocytes and in unpassaged human primary hepatic parenchymal cells. Molecular or chemical disruption of any component of the NSAPP chain, from NOX4 to PTEN, leaves PTEN persistently active, thereby recapitulating the same deadly pattern of imbalanced insulin action seen clinically.

The NSAPP pathway functions as a master regulator of balanced insulin action via ERK, phosphatidylinositol 3’-kinase (PI3K)-AKT, and downstream targets of AKT. Dysfunction of the NSAPP pathway may explain the molecular cause of the atherometabolic syndrome and type 2 diabetes.

Relationship of fibroblast growth factor 21 levels with inflammation, lipoproteins and non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is defined as ≥5% hepatic steatosis in the absence of a secondary cause (e.g. excessive alcohol consumption, infection or autoimmune disease). As such, NAFLD encompasses a spectrum of pathologies ranging from uncomplicated hepatic lipid accumulation (simple steatosis) to non-alcoholic steatohepatitis (NASH) and cirrhosis. NAFLD is associated with inflammation and atherogenic lipoprotein abnormalities. Previous studies suggest an association of fibroblast growth factor 21 (FGF21) with NAFLD. Therefore, Tucker et al. assessed the association of circulating FGF21 levels with inflammatory markers, lipoprotein profile and NAFLD in the Multi-Ethnic Study of Atherosclerosis (MESA), a multi-center, multi-ethnic prospective cohort study designed to investigate the prevalence, risk factors and progression of subclinical cardiovascular disease.

After excluding participants with excessive alcohol consumption, 3446 participants were included in the analysis. NAFLD was defined using non-contrast cardiac computed tomography with a liver-to-spleen ratio (LSR) < 1 or liver attenuation <40 Hounsfield units (HU).

The mean age of the participants was 63.5 years with 54% females, 36% Caucasian, 10% Chinese American, 31% African American and 23% Hispanic. 17% of the participants had NAFLD. After adjustment for demographic, socioeconomic and other confounders, a 1-SD increment in ln-transformed FGF21 level was associated with a 5.1% higher IL-6 level, a 0.31 nm larger very-low-density lipoprotein particle diameter, a 0.014 nm smaller high-density lipoprotein particle diameter, and a 5.25 nmol/L lower intermediate-density lipoprotein particle concentration. A 1-SD increment in ln-transformed FGF21 level was associated with LSR<1 and liver attenuation <40 HU, even after adjusting for the aforementioned inflammation and lipoprotein parameters.

This study suggests an association between FGF21 and NAFLD, independent of inflammation and atherogenic lipoprotein abnormalities. Further studies are needed to assess FGF21 as a biomarker for future NAFLD risk.

Association between liver fibrosis scores and the risk of mortality among patients with coronary artery disease

Fatty liver diseases are highly prevalent in patients with coronary artery disease (CAD) and might progress to irreversible liver fibrosis. Whether baseline liver fibrosis (LF) scores are associated with long-term mortality among patients with CAD is currently unknown. Chen et al. assessed the association of LF scores with mortality risk in CAD patients by conducting an analysis on 3263 patients with CAD in China.

Cox models were used to assess the association of baseline levels of LF scores, including non-alcoholic fatty liver disease fibrosis score (NFS), fibrosis 4 score (FIB-4), aspartate aminotransferase to platelet ratio index (APRI), gamma-glutamyltransferase to platelet ratio (GPR), and Forns score, with the risk of all-cause and cardiovascular mortality among CAD patients.

During a median follow-up period of 7.56 years, 538 deaths occurred, 319 of which due to cardiovascular diseases. Compared with patients with lowest score levels, multivariable-adjusted HRs for those with highest levels of NFS, FIB-4, APRI, GPR and Forns score were 2.89, 2.84, 1.77, 1.47 and 3.10 for all-cause mortality and 3.02, 3.34, 1.99, 1.80 and 2.43 for cardiovascular mortality, respectively. These associations were consistent when the authors excluded those who died within the first year of follow-up or stratified patients by different sex, age, BMI, diabetes status, metabolic syndrome status, CAD type and hsCRP level.

Higher LF scores are associated with increased risks of all-cause and cardiovascular mortality among CAD patients. LF scores might play a potential role in CAD prognosis prediction.

Advanced fibrosis of non-alcoholic steatohepatitis affects the significance of lipoprotein(a) as a cardiovascular risk factor

Lipoprotein(a) [Lp(a)] is an important cardiovascular risk factor, independent of traditional risk factors such as high low density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), hypertension, diabetes mellitus, obesity, sedentary lifestyle, and smoking. Lp(a) levels are lower in patients with chronic liver disease than in healthy subjects. Furthermore, Lp(a) levels decrease as residual liver function declines. Although non-alcoholic fatty liver disease (NAFLD), especially advanced non-alcoholic steatohepatitis (NASH), increases the risk of cardiovascular diseases, the relationship between serum Lp(a) level and NASH is unknown. Konishi et al. examined the relationship between serum Lp(a) levels and biopsy-proved NAFLD and clarified the significance of Lp(a) measurements for cardiovascular disease screening in patients with NAFLD.

A total of 176 patients with NAFLD were enrolled. Comprehensive blood chemistry tests and histological examinations of liver samples were conducted. The relationship between serum Lp(a) levels and NAFLD was analyzed.

Serum Lp(a) levels in advanced fibrosis (stage 3–4) were lower than those in non-advanced fibrosis (stage 0–2). After adjustment for age, sex, body mass index, alanine aminotransferase (ALT), creatinine (Cre), HbA1c level, HDL-C, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and the use of lipid-lowering agents, the significant inverse association between advanced fibrosis and serum Lp(a) levels remained present. Although Lp(a) levels were inversely associated with an NAFLD Activity Score (NAS) of 5–8, there was no significant association between Lp(a) levels and NAS adjusted

for age, sex, body mass index, ALT, Cre, HbA1c level, HDL-C, LDL-C, TG, and the use of lipid-lowering agents.

Advanced NASH is associated with low serum Lp(a) levels; therefore, Lp(a) levels may not be useful in evaluating cardiovascular risk.