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The May issues of *Atherosclerosis* contain several articles that address the effects of diversity in sex, race, age, and body composition on the course or treatment efficacy of atherosclerotic vascular diseases or atherogenic dyslipidemias

Risk of peripheral artery disease according to race and sex: The Atherosclerosis Risk in Communities (ARIC) study

Previous community-based studies have demonstrated sex and race-based disparities in the risk of cardiovascular disease. Hicks et al. examined the association of sex and race with incident peripheral artery disease (PAD-) and critical limb ischemia (CLI-) related hospitalizations.

In 13,451 Black and White ARIC participants without prevalent PAD at baseline, the cumulative incidence of PAD- and CLI-related hospitalization over a median follow-up of 26 years was evaluated. Hazard ratios (HRs) using Cox models across four sex- and race-groups were calculated and PAD and CLI were defined by hospitalization discharge codes.

The cumulative incidence of PAD-related hospitalization was higher in males than females in Whites but not in Blacks. The cumulative incidence of CLI-related hospitalization differed significantly by race more than sex, occurring in 3.1% Black males, 3.1% Black females, 1.4% White males, and 0.8% White females. After risk factor adjustment, the risk of incident PAD-related hospitalization was similar for White males *vs.* White females, and slightly higher for Black males and Black females compared to White females. The adjusted risk of incident CLI-related hospitalization was similar for White males *vs.* White females, and significantly higher for Black males and Black females compared to White females.

These data suggest that there are both sex- and race-specific patterns of PAD-related hospitalization that lead to differences in clinical disease risk and presentation.

Sex related differences in therapy and outcome of patients with intermittent claudication in a real-world cohort

Lower extremity artery disease (LEAD) belongs to atherosclerotic induced vascular diseases leading to stenoses or occlusions of the arteries in the lower limbs (LL). The resulting peripheral malperfusion causes progressive symptoms from intermittent claudication (IC), to rest pain and

chronic ischemic ulcers. The prevalence of LEAD is increasing worldwide and sex-related differences are a current matter of debate.

Makowski et al. analysed claims data on unselected patients with in-patient treatment for LEAD with intermittent claudication from January 2014 to December 2015. Data files included diagnostic and procedural information from two years before index, and a five-year follow-up.

The analysis comprised 42,197 IC patients, 28,520 male. Male patients were younger but presented with higher frequency of cardiovascular risk factors such as diabetes, atrial fibrillation, chronic coronary syndrome, chronic heart failure, or chronic kidney disease). Revascularisation applied in 80% of patients. Concomitant pharmacotherapy with statins and platelet inhibitors were long lasting, under-use being more pronounced in women. Two years after index, one-third of IC patients had subsequent revascularisation, one-quarter progressed to chronic limb threatening ischemia (CLTI), and 2% underwent amputation. Male sex was an independent risk factor for long-term mortality and CLTI during follow-up.

The majority of in-patient treated patients for IC were male, presenting with worse cardiovascular risk profiles. In view of a general under-supply with statins and platelet inhibitors, women received somewhat less often preventive medication. Despite low LEAD stages at index, serious prognosis was observed in the long term. Male patients were at high risk for all-cause mortality and the combined endpoint CLTI and death.

Inferior control of low-density lipoprotein cholesterol in women is the primary sex difference in modifiable cardiovascular risk: A large-scale, cross-sectional study in primary care

Cardiovascular disease (CVD) is the leading cause of death and loss of quality-adjusted life years in women and men alike. Cardiovascular risk is driven by both non-modifiable risk factors, particularly age, and modifiable risk factors. Sex differences in cardiovascular prevention have been reported, yet the role of sex with regard to different modifiable risk factors such as low-density lipoprotein cholesterol (LDL-C), systolic blood pressure (BP), and glycated hemoglobin (HbA1c) in primary care settings is unclear. Rachamin et al. studied sex differences in the assessment and measured values of LDL-C, BP, and HbA1c in primary and secondary cardiovascular prevention delivered by general practitioners.

The study was based on electronic medical records of 59,092 primary care patients aged 40–79 years in Switzerland. Multilevel regression was used to model associations of sex with assessment and measured values of LDL-C, BP, and HbA1c in 2018.

In both primary and secondary prevention, women had lower LDL-C assessment rates, and higher measured LDL-C values than men. Compared with men, women in primary prevention displayed lower BP and HbA1c assessment frequencies, while there was no sex difference in secondary

prevention. Age-dependent increases in measured values of LDL-C, BP, and HbA1c were greater in women than men.

Improvement in LDL-C management in women is key to reduce sex-based inequalities.

In their editorial, Farukhi and Mora comments on how misperceptions and management of risk are ongoing challenges in women's cardiovascular health.

Relationship between muscle mass index and LDL cholesterol target levels: Analysis of two studies of the Korean population

Aging is associated with metabolic, physiologic, and functional impairments. Important changes include a decrease in skeletal muscle mass, centralization of body fat, and accumulation of intra- and intermuscular adipose tissue. Maintaining the optimal low-density lipoprotein (LDL) cholesterol level is crucial for the prevention of cardiovascular diseases (CVD). Previous studies found that high skeletal muscle mass is closely associated with lower risk of CVD. However, studies evaluating the effect of skeletal muscle mass on low-density lipoprotein (LDL) cholesterol level are limited. Lee et al. investigated whether muscle mass was associated with dyslipidemia defined as LDL cholesterol level based on CVD risk level.

Data of 17,546 adults from the 2008–2011 Korean National Health and Nutrition Examination Survey (KNHANES) and 5126 adults from the Korean Genome and Epidemiology Study (KoGES) were analysed. Participants were classified into lower skeletal muscle mass index (LSMI) group and normal group. LSMI was defined as body mass index (BMI)-adjusted appendicular skeletal muscle mass <0.789 (men) and <0.512 (women) in the KNHANES, and as sex-specific lowest quintile of the BMI-adjusted total skeletal muscle mass in the KoGES. Participants were defined as having dyslipidemia when the serum LDL cholesterol levels were higher than their LDL cholesterol management targets based on their CVD risk level.

The odds ratio with 95% confidence interval for dyslipidemia of the LSMI group was 1.230 after adjusting for confounding variables compared to the normal group in the 2008–2011 KNHANES. In the KoGES, the hazard ratio with 95% CI for incident dyslipidemia of the LSMI group compared to the normal group was 1.225.

LSMI was associated with dyslipidemia regardless of abdominal obesity. Maintaining adequate muscle mass may be an effective strategy for maintaining the optimal LDL cholesterol levels.

The gut microbiota is associated with clinical response to statin treatment in patients with coronary artery disease

The structure and composition of the gut microbiota influence patients' response to therapeutic interventions. It is also known that the response to statin treatment can vary greatly from

one patient to another, suggesting a possible connection between microbiome composition and response to statins. In this study, Wang et al. explore the influence of the microbiome on the response to statin treatment among patients with coronary artery disease (CAD).

A prospective cohort of 836 CAD patients enrolled from January 2016 to December 2017 was used to perform a nested case-control study. One-hundred ten CAD patients were divided into two groups according to their response to statins: good response group (GR) and poor response group (PR), and their gut microbiota was compared.

No significant difference in microbiome between the two groups was observed. However, significant differences were found in the relative proportion of numerous genera between GR and PR groups. Most remarkably, a poor response to statin treatment correlated to a significant decrease in the abundance of beneficial bacteria for the lipid metabolism (*Akkermansia muciniphila* and *Lactobacillus*) and a significant increase in the abundance of bacteria *Holdemanella* and *Facecallibacterium*.

Gut microbiota structure is associated with the response to statin. Manipulation of the gut microbiota composition can be an interesting and effective treatment strategy to blood lipid control among CAD patients.

Adiposity and the development of dyslipidemia in APOE ε2 homozygous subjects: A longitudinal analysis in two population-based cohorts

Familial dysbetalipoproteinemia (FD), characterized by remnant lipoprotein accumulation and premature cardiovascular disease, occurs in homozygous carriers of the *APOE* ε2 allele, but genetic predisposition alone does not suffice for the clinical phenotype. Cross-sectional studies suggest that a second metabolic hit – notably adiposity or insulin resistance – is required, but the association between these risk factors and development of FD has not been studied.

Heidemann et al. evaluated 18,987 subjects from two large prospective Dutch population-based cohorts (PREVEND and Rotterdam Study) of whom 118 were homozygous *APOE* ε2 carriers. Of these, 69 subjects were available for prospective analyses. Dyslipidemia – likely to be FD – was defined as fasting triglyceride (TG) levels >3 mmol/L in untreated subjects or use of lipid lowering medication. The effect of weight, body mass index (BMI), waist circumference, type 2 diabetes mellitus and non-TG metabolic syndrome on development of dyslipidemia was investigated.

Eleven of the 69 ε2ε2 subjects (16%) developed dyslipidemia – likely FD – during follow-up. Age-, sex- and cohort-adjusted risk factors for the development of FD were BMI, waist circumference and presence of non-TG metabolic syndrome at baseline. Change in adiposity during follow-up was not associated with development of dyslipidemia.

Adiposity increases the risk of developing an FD-like lipid phenotype in homozygous *APOE* ε2 subjects. These results stress the importance of healthy body weight in subjects at risk of developing FD.