Metabolic Syndrome From Adolescence to Early Adulthood: Effect of Infancy-Onset Dietary Counseling of Low Saturated Fat: The Special Turku Coronary Risk Factor Intervention Project (STRIP)

Metabolic syndrome is a cluster of cardiometabolic risk factors, typically comprising waist circumference, blood pressure, serum glucose, triglyceride, and high-density lipoprotein cholesterol concentrations. To date, there is no uniform definition for pediatric metabolic syndrome. In adults, metabolic syndrome predicts type 2 diabetes mellitus and cardiovascular diseases, and it is linked to cardiovascular and all-cause mortality. Having metabolic syndrome in adolescence is associated with future risk of type 2 diabetes mellitus and subclinical atherosclerosis. Importantly, resolving metabolic syndrome by adulthood can normalize these risks. This study is the first longitudinal trial to report the effect of repeated, infancy-onset dietary intervention on adolescent metabolic syndrome. In the randomized Special Turku Coronary Risk Factor Intervention Project (STRIP), individualized dietary counseling was given to introduce a healthy diet to the intervention children and subsequently to reduce their risk of atherosclerosis. The main target of the counseling, maintained until participants were 20 years of age, was to replace dietary saturated fat with unsaturated fat. The counseling has led to lower low-density lipoprotein cholesterol concentrations and blood pressure, improved insulin sensitivity, and increased ideal cardiovascular health in the intervention group. This study shows that the intervention given in STRIP decreased substantially, by 41%, the risk of metabolic syndrome in healthy adolescents studied repeatedly between 15 and 20 years of age. The intervention effect was similar regardless of the metabolic syndrome criteria used. An important message to clinicians is that dietary counseling in childhood and adolescence may protect against the development of risk profiles that predict future cardiovascular disease and type 2 diabetes mellitus. See p 605.

Sex Differences in Perceived Stress and Early Recovery in Young and Middle-Aged Patients With Acute Myocardial Infarction

Because self-perceived stress is inversely associated with advancing age, it is particularly important to understand the role of stress in influencing recovery after acute myocardial infarction (AMI) in younger patients. Findings from this study provide additional insights to help enhance clinical care for young and middle-aged patients with AMI. First, we demonstrated a negative association between baseline psychological stress and multiple health outcomes 1 month after AMI among patients 18 to 55 years old. Helping patients develop positive attitudes and coping skills for stressful situations not only may improve their psychological well-being but also may help recovery after AMI. Interdisciplinary approaches may be particularly beneficial because physical, mental, and psychosocial (eg, intrafamily conflict and caregiving demands) factors were all associated with patients’ stress levels. Second, we found that women perceived greater psychological stress than men at baseline, which partially explained women’s worse recovery after AMI. This offers another opportunity for narrowing sex disparities in recovery. If the relationship between mental stress and 1-month recovery is causal, stress management interventions may help decrease sex-based differences in outcomes. Even if the association does not involve a causal relationship, the strong linkage suggests that baseline stress may be a useful prognostic marker for predicting health outcomes in young and middle-aged patients with AMI. Third, we showed that male and female patients are burdened by different stressors and that some stressors exert different effects on men compared with women. Interventions that recognize and address sex-specific sources of stress are likely more effective than those that do not. See p 614.

Cardiac Sarcoidosis: Epidemiology, Characteristics, and Outcome Over 25 Years in a Nationwide Study

Cardiac sarcoidosis (CS) is a rare and difficult-to-diagnose disease that challenges clinicians with its heterogeneous manifestations and potentially fatal outcome. In the present nationwide study, we evaluated the epidemiology, characteristics, and long-term outcome of clinically manifest and histologically confirmed CS over the 25-year period from 1988 to 2012 in Finland. A total of 110 patients (64% female; mean age, 51 years) fulfilled the diagnostic criteria and were included in our retrospective work. The annual number of new cases grew >20-fold during the study period. At presentation to the cardiology services, two thirds of patients had clinically isolated CS, indicating that they had neither past history of sarcoidosis nor symptoms or signs of extracardiac involvement at the clinical examination or in routine laboratory tests or chest x-rays. Nearly 80% of the patients presented acutely as a result of either a high-grade atrioventricular conduction block or serious ventricular tachyarrhythmias, most of the rest presenting with heart failure. During the median follow-up of 6.6 years, 10 patients died of a cardiac cause, 11 underwent transplantation, and another 11 experienced an aborted sudden arrhythmic cardiac death. Transplantation-free cardiac survival was 97%, 90%, and 83% after 1, 5, and 10 years of follow-up, respectively. Heart failure as the first manifestation predicted worse outcome. The 2012 prevalence of clinically manifest CS in Finland was 22 patients per 1 million adult population. According to our latest data, 5.3 new cases of CS per 1 million adults are diagnosed and need treatment each year. See p 624.

Evidence That Links Loss of Cyclooxygenase-2 With Increased Asymmetric Dimethylarginine: Novel Explanation of Cardiovascular Side Effects Associated With Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs are the most common over-the-counter medications worldwide and the mainstay therapy for those with chronic inflammatory conditions such as rheumatoid arthritis. The COX-2 enzyme is critical for the production of prostaglandins. Inhibition of COX-2 by NSAIDs has been linked with cardiovascular adverse effects, including cardiovascular death. Recent evidence suggests that inhibition of COX-2 may be linked to elevated asymmetric dimethylarginine (ADMA), which is an inhibitor of the enzyme guanylyl cyclase. ADMA plays a role in the regulation of blood pressure, and elevated levels of ADMA are associated with cardiovascular disease. This study demonstrated a link between decreased COX-2 activity and increased ADMA levels in human cardiovascular cells, providing a potential mechanism for the cardiovascular side effects associated with COX-2 inhibitors. See p 618.
as arthritis. Cyclooxygenase (COX)-2 is the therapeutic target of nonsteroidal anti-inflammatory drugs, but these drugs also inhibit the constitutive form COX-1, potentially causing serious gastrointestinal side effects. COX-2 selective drugs, such as celecoxib and rofecoxib, were introduced to reduce gastrointestinal side effects. However, it is now clear that COX-2 selective anti-inflammatory drugs and older-style nonsteroidal anti-inflammatory drugs like ibuprofen and diclofenac increase the risk of cardiovascular events. These side effects are relatively rare, but concern over them has meant that there has been a return to prescribing older style drugs, which generally carry a similar risk of heart attacks and strokes but with the added disadvantage of increased gastrointestinal side effects. Currently there is no accepted unifying mechanism to explain how COX-2 inhibitors cause cardiovascular side effects, and, consequently, there are no biomarkers or rescue strategies to identify or treat those few individuals who might be at risk. Our study shows methylarginines, which block cardioprotective endothelial nitric oxide synthase in vessels, are elevated when COX-2 is inhibited. Methylarginines are elevated in a range of cardiovascular diseases and as such are considered risk factors. Our work suggests methylarginines may also be biomarkers of the risk associated with COX-2 inhibition. If these findings are validated in a larger patient group, a simple test for methylarginines could be used to identify those individuals most at risk for cardiovascular events while taking COX-2 inhibitors. See p 633.

**NADPH Oxidase 4 Induces Cardiac Fibrosis and Hypertrophy Through Activating Akt/mTOR and NFκB Signaling Pathways**

Left ventricle remodeling is a common response to acute and chronic cardiac injury that eventuates in heart failure. Activation of the renin-angiotensin system and enhanced generation of reactive oxygen species by NADPH oxidases have been implicated in cardiac remodeling. The role of NADPH oxidase 4 (Nox4) in cardiac remodeling has been controversial. Moreover, little is known about the downstream effector signaling pathways activated by Nox4-derived reactive oxygen species. In this study, we demonstrate that myocardial-specific overexpression of human Nox4 increases reactive oxygen species production and induces cardiac remodeling through activation of the Akt-mTOR and NFκB pathways. The effects of the Nox4 transgene were potentiated by angiotensin II. Treatment of angiotensin II-infused myocardial Nox4 transgenic mice with Nox4/Nox1 inhibitor GKT137831 abolishes the increase in oxidative stress, suppresses Akt-mTOR and NFκB pathways, and markedly attenuates cardiac remodeling. In addition, the mTOR inhibitor, rapamycin, or an inhibitor of NFκB, significantly inhibits the expression of cardiac remodeling markers in tissue explant cultures of left ventricles of Nox4 transgenic mice infused with angiotensin II. Because other mechanisms besides angiotensin II may increase Nox4 and reactive oxygen species production, and because Nox4 is upstream of the mTOR/NFκB signaling pathway, inhibition of Nox4 may afford superior protection to blockade of angiotensin II. GKT137831 has passed phase 1 clinical trials and is currently being evaluated in a phase 2 clinical trial in patients with type 2 diabetes mellitus and albuminuria (clinical trials.gov unique identifier NCT02020242). Clinical trials of Nox4 inhibitors to prevent cardiac remodeling and the progression of heart failure are warranted. See p 643.

**Dual-Specificity Phosphatase 3 Deficiency or Inhibition Limits Platelet Activation and Arterial Thrombosis**

A limitation of current antiplatelet therapies is their inability to separate thrombotic events from bleeding occurrences. The present study demonstrates that dual-specificity phosphatase 3 (DUSP3) phosphatase deficiency in mice does not cause bleeding but still protects against arterial thrombosis and collagen-induced thromboembolism. This protection is at least partially attributable to the selective inhibition of glycoprotein VI– and C-type lectin-like receptor 2–dependent signaling. Furthermore, ex vivo, a selective inhibitor of DUSP3 limits glycoprotein VI– and C-type lectin-like receptor 2–mediated aggregation of human platelets. Our findings pave the way for further preclinical studies in animal models and future validation in humans toward the development of a novel, DUSP3-based therapeutic strategy in arterial thrombosis. See p 656.