SEX DIFFERENCES IN MEDICINE: PAIN IN THE OLDER INDIVIDUAL

Pain in life is inescapable and ubiquitous, and its severity ranges from transient, self-remitting episodes to chronic pain syndromes refractory to virtually all therapeutic interventions. A perhaps underappreciated issue is that sensitivity to and sensation of pain are sex-dependent, generally being heightened in female as compared with male subjects, a propensity recognized no more than some 20 years ago. Preclinical studies of this phenomenon demonstrate that the biologic basis for nociception differs between males and females in that microglial cells are critical modulators in relevant neural networks in males whereas T cells are involved in females, with additional modulation provided by sex hormones (Dance A. Nature. 2019;567:448). Additional discoveries in this field are that the perception and intensity of pain are influenced not only by sex but also by personal attributes pertaining to gender (as distinct from biologic sex) and by the nature of the surrounding milieu including the sex of nearby individuals. Such considerations have significant implications for the treatment of pain syndromes and the development of novel therapies for pain. In this issue of Mayo Clinic Proceedings, Garcia-Esquinas et al significantly advance this field by prospectively evaluating pain and sex differences in community-dwelling older individuals, demonstrating that the relative risk ratio for pain was significantly higher (two-fold) in women as compared with men aged 63 years and older. This increased risk of pain in females was associated with more frequent musculoskeletal disease, greater impairment in functional activity and mobility, and higher rates of depression, psychological stress, and disturbance of sleep. As pointed out by Garcia-Esquinas et al, the association between pain and these conditions may be bidirectional, with chronic pain promoting their occurrence and/or exacerbation, and these conditions, in turn, preventing the remittance of pain. The importance of the paper by Garcia-Esquinas et al resides in several considerations. First, it highlights that there are sex differences in the risk of pain in older subjects. Second, it uncovers several factors that may drive the persistence of pain. Third, these findings suggest that strategies designed to promote functionality and activity and/or to ameliorate chronic conditions associated with pain may significantly decrease this increased risk of pain. The importance of sex differences in medicine is clearly recognized beyond pain perception to diverse fields including, for example, the fact that female as compared with male subjects have an increased risk for autoimmune diseases including systemic lupus erythematosus, but generally exhibit a reduced sensitivity to acute kidney injury and a slower rate of progression of chronic kidney disease. Mayo Clinic Proceedings emphasizes the importance of sex differences in medicine by dedicating one of its Sections, under the editorial leadership of Dr. Vesna Garovic, entirely to this field.

**BURNING FAT DURING CARDIAC REHABILITATION**

Cardiac rehabilitation programs for patients recovering from myocardial infarction seek to recruit reparative cardiovascular processes, to improve cardiopulmonary fitness, to reduce mortality, and to enhance the quality of life for these patients. Such programs integrate, among other approaches, exercise training; strategies targeting secondary prevention for cardiovascular risk factors; education pertaining to pharmacologic therapy, diet, and dealing with stress; and counseling that underscores the need for compliance with such goals, and that their core principles should be followed long into the future. A key component is exercise training as this is of proven value in patients with cardiovascular disease, as it is in healthy subjects. Among the various types of exercise training, high-intensity interval training (HIIT) has received considerable recent attention, and, indeed, is considered by some to provide greater health benefits in the general population as compared with aerobic exercise; this raises the question of the relative benefits of either form of exercise in cardiac rehabilitation programs in cardiovascular diseases. This topic is addressed in the present issue of Mayo Clinic Proceedings by Dun et al who retrospectively compared outcomes in patients in cardiac rehabilitation undergoing either HIIT or moderate-intensity continuous training (MICT) following myocardial infarction. The findings demonstrate that the HIIT group as compared with the MICT group evinced greater reduction in fat mass and abdominal fat, serum cholesterol, LDL, and triglycerides, and, after adjusting for exercise indices and energy expended, HIIT still achieved greater reduction in fat mass, body fat percentage, and abdominal fat. The greater reduction in abdominal fat is of particular pathogenetic and clinical interest. Setting aside the perplexing and contested Obesity Paradox (which holds that for certain types of cardiovascular disease obesity, in a certain range, is cardioprotective), the evidence is quite clear that fat mass in general, and abdominal fat in particular, are risk factors for cardiovascular disease. Abdominal (visceral) fat produces a range of cytokines and humoral factors inimical to the cardiovascular system because these factors cause endothelial dysfunction, inflammation, neointimal hyperplasia, oxidative stress, and a procoagulant milieu. The occurrence of such vasculopathic processes in the coronary circulation may be especially damaging in patients who previously experienced myocardial infarction. Thus the finding by Dun et al that incorporation of HIIT rather than MICT into cardiac rehabilitation programs was attended by greater reduction in abdominal fat invites the speculation that the risk for future cardiovascular disease, including acute coronary events, may be less with such programs. Recent studies have indicated that, using cardiopulmonary fitness as an outcome, HIIT generally exerts either superior or comparable effects as compared with MICT in cardiac rehabilitation, and that HIIT is generally considered safe in post-myocardial infarction patients. The present study by Dun et al is the first to demonstrate that HIIT, as compared with MICT, is attended by a greater reduction in fat mass and abdominal fat, effects that may be of particular cardiovascular benefit, especially in patients undergoing cardiac rehabilitation.


**INTENSIVE GLUCOSE-LOWERING THERAPY AND THE RISK FOR SEVERE HYPOGLYCEMIA**

In health, hypoglycemia is relatively uncommon because effective homeostatic mechanisms safeguard plasma levels of glucose, the latter representing the brain’s indispensable metabolic fuel. These mechanisms include, among others, suppression of insulin secretion, increased secretion of glucagon and epinephrine with attendant
increase in hepatic glucose production, and increased sympathetic output that drives the seeking of food. These responses are impaired in diabetic patients undergoing treatment with insulin or oral insulin secretagogues; diabetic patients are thus at risk for hypoglycemia as well as the acute and chronic complications of hyperglycemia. In addition to its acute—and potentially lethal—effects, hypoglycemia, in particular when recurrent, may cause cognitive decline and cardiovascular events. Glycemic control thus requires a fine balance: on the one hand, such control exerts abundant beneficial effects including the reduction in macrovascular and microvascular complications; on the other hand, if glycemic control is too strict, or patients are treated with an intensive glucose-lowering regimen, hypoglycemia may ensue. Practice guidelines broadly recommend a level of glycated hemoglobin (HbA1c) of equal to or less than 7.0% for nonpregnant adults. However, this threshold is increased in circumstances when the benefits of such control are uncertain and/or the risks for hypoglycemia are increased; such circumstances include older age, the presence of clinical complexity, and reduced life expectancy. In the current issue of Mayo Clinic Proceedings, Mahoney et al examined the prevalence and significance of intensive glucose-lowering therapy in diabetic patients in the United States. Intensive glucose-lowering therapy was determined as an HbA1c of 5.6% or less, as achieved by one agent, or an HbA1c ranging from 5.7% to 6.4%, as achieved by 2 or more agents. Clinically complex was defined by age 75 years or older, end-stage kidney disease, impairment in 2 or more daily living activities, and the presence of 3 or more chronic disorders. Using data from NHANES 2011-2014, these authors demonstrate that approximately 49% of diabetic patients in the United States had an HbA1c less than 7%, with approximately 32% of these patients being clinically complex. Approximately 22% of both clinically complex and the non-clinically complex patients were intensively treated. Drawing upon prior data by McCoy et al regarding severe hypoglycemia event risk (JAMA Intern Med. 2016;176:969) with intensive therapy, Mahoney et al calculated that intensive treatment led to approximately 5000 hospitalizations and approximately 5000 visits to the Emergency Department over a 2-year period. This important study by Mahoney et al emphasizes two essential considerations: First, it highlights the potentially life-threatening risks of hypoglycemia induced by intensive treatment, especially so in the clinically complex diabetic patient; and, second, it underscores the need for individualized, evidence-driven, nuanced care for diabetic patients, and, in particular, the need to moderate glucose-lowering therapy and accept a higher HbA1c level in the older, clinically complex patient.


UNDERSTANDING DISEASE: PARANEOPLASTIC NEUROLOGIC AUTOIMMUNITY

Autoimmunity can be triggered by diverse causes including therapeutic agents such as immune checkpoint inhibitors (ICIs). Immune checkpoint inhibitors, agents that promote T cell activation, represent a pivotal advance in the treatment and management of malignancies. T cells are kept in relative inactivity when T cell checkpoint molecules such as PD-1 and CTLA-4 (both representing “off-switches” for T cells) bind, respectively, to PD-L1 and B7-1/B7-2 on other cells. As cancer cells may copiously express PD-L1, cancers can keep T cells quiescent, and thereby elude immune surveillance and removal. Immune checkpoint inhibitors are antibodies that currently target and inhibit either PD-1, PD-L1, or CTLA-4, thereby enabling T cell activation and the killing of cancer cells. Not unexpectedly, these agents may cause immune-related adverse events. These far-ranging toxicities of ICIs were comprehensively reviewed in the July issue of Mayo Clinic Proceedings by Marin-Acevedo et al. In the current issue Zekeridou and...
Lennon masterly use the backdrop of ICIs in current cancer therapy, and their attendant risk of inducing autoimmune processes, to provide an in-depth, insightful, and comprehensive review of neurologic autoimmunity driven by paraneoplastic processes. Their review discusses onconeural proteins and how immune responses to these proteins can target, collaterally, shared autoantigens in the nervous system; the key underlying immunologic participants and mechanisms involved in paraneoplastic autoimmunity; the different pathways whereby neurologic autoimmune processes target intracellular or plasma membrane-residing antigens; the range of IgG paraneoplastic neural antibodies associated with cancers and their accompanying neurologic syndromes; and clinical-serologic correlations for assorted neoplasms. The authors then return to mechanisms underlying ICI-induced autoimmunity in the nervous system and clinical manifestations of this complication including exacerbation of demyelinating disease, peripheral nerve disorders, aseptic meningitis, myasthenia gravis, and hypophysitis. The review concludes by calling for vigilance for autoimmune complications in the nervous system in the setting of ICIs, especially in light of their increasing use in oncology. This contribution is the first in a new type of article entitled “Understanding Disease,” a review that provides a clear discussion of relevant pathobiology/cell biology intended for the generalist and written by the specialist. Mayo Clinic Proceedings is deeply appreciative of this inaugural contribution by Zekeridou and Lennon and invites other experts to consider submitting articles in their respective areas of expertise to Mayo Clinic Proceedings for consideration in the “Understanding Disease” category of articles.
