

MAYO CLINIC
PROCEEDINGS

In the Limelight: October 2022



This month's feature highlights four articles that appear in the current issue of *Mayo Clinic Proceedings*. These articles are also featured on the *Mayo Clinic Proceedings*' YouTube Channel (<https://youtu.be/tj-vwUQ00C0>).

ACTIVITY, INACTIVITY, AND THE AILING HEART

With such cardinal symptoms as fatigue, lassitude, and exertional dyspnea and tiredness, heart failure (HF) predisposes to a sedentary lifestyle. In the evolution of the management of HF, such sedentary behavior was even considered by some in the past as beneficial as it avoided the supposed hemodynamic stress imposed by physical activity (PA). However, abundant and growing evidence now attests to the adverse cardiovascular effects of a sedentary lifestyle, and in the present issue of *Mayo Clinic Proceedings*, Kim et al address this issue in patients with HF. These investigators examined the so called "displacement hypothesis" which posits that increased sedentary time (ST) largely occurs at the expense of PA, and such displacement may underlie adverse outcomes in patients with HF. Kim et al studied all-cause and cardiovascular disease (CVD)-specific mortality in 265 patients with heart failure who participated in the National Health and Nutrition Examination Survey from 2003 to 2006. Activity or lack thereof was assessed by an accelerometer, the latter used to quantitate ST, time spent in light-intensity PA (LPA), and time spent in moderate and vigorous intensity PA (MVPA). The data demonstrate that, for a given 24-hour period, ST accounted for 70% of time while awake, but LPA and MVPA accounted for only 29% and 1% of such time, respectively.

Importantly, replacing just 10 minutes of ST by LPA was attended by a significant reduction in all-cause and CVD-specific mortality. Furthermore, there was a graded risk reduction in mortality as ST was progressively replaced by LPA. Replacement of ST with MVPA tended to decrease such risks, but the findings were not significant, likely reflecting, as the authors suggest, the very low occurrence of MVPA in these patients. While the data of Kim et al support the displacement hypothesis, it should be noted that sedentary behavior - in particular, sitting - *per se*, as distinct from decreased PA, may exert adverse CV effects, including increased blood pressure, impaired peripheral blood flow, impaired glycemic control, proinflammatory effects, and the blunting of the acute beneficial responses to exercise (*Nat Rev Cardiol.* 2021;18:637-648.). Intrinsic, adverse effects of ST may thus conspire and summate with decreased PA in underpinning the mortality observed in patients with HF. These important findings of Kim et al demonstrate inactivity as a risk factor for mortality in patients with heart failure, and the salutary effects that may attend exchanging inactivity by activity, even when such exertional activity is relatively limited in duration and low grade in its intensity.

Kim Y, Canada JM, Kenyon J, et al. Effects of replacing sedentary time with physical activity on mortality among patients with heart failure: National Health and Nutrition Examination Survey follow-up study. *Mayo Clin Proc.* 2022;97(10):1897-1903. doi.org/10.1016/j.mayocp.2022.05.009

DIABETIC KIDNEY DISEASE: AN UPDATE

Both nationally and globally, diabetic kidney disease (DKD) is the most common cause of



See also pages
1771, 1780, 1897,
1904



Scan code to view
video

chronic kidney disease (CKD) and endstage kidney disease (ESKD). The development of DKD in type 1 or 2 diabetes imparts added morbidity and mortality: DKD worsens cardiovascular and other complications of diabetes, challenges glycemic and blood pressure control, and increases the risk that death occurs before CKD progresses to ESKD. However, the outlook for patients with diabetes has markedly improved with the introduction of new glucose-lowering agents that reduce cardiovascular morbidity and mortality, and diminish the risk for progressive CKD. In this issue of *Mayo Clinic Proceedings*, Alicic and Nicholas provide a comprehensive and masterful synthesis which incorporates an in-depth discussion of these newer agents within the broader context of the overall management of DKD. The authors begin by discussing key considerations in diagnosing DKD (a clinical diagnosis) and diabetic nephropathy (a tissue diagnosis), and the significance of albuminuria and eGFR. Then drawing upon guidelines from various societies (American Diabetes Association; Kidney Disease: Improving Global Outcomes; and others) and a comprehensive review of the relevant literature, Alicic and Nicholas review key recommendations pertaining to lifestyle interventions, glycemic targets, glycemic monitoring, antihyperglycemic therapeutic options, control of blood pressure (especially by angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), and lipid management. Helpful tables summarize the guidelines from various societies and committees regarding screening and monitoring for DKD, blood pressure management, and HbA1c targets. Special attention is directed to sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs), and for each member of each class of drug, the authors discuss the route and frequency of administration, approved indications, recommended dosing for glycemic control, and drug dosing in the setting of reduced kidney function; also provided is an algorithm of glucose-lowering therapy for cardiorenal benefit.

Salient clinical concerns for SGLT2 inhibitors and GLP-1 RAs are reviewed and strategies to address them discussed. Alicic and Nicholas are to be commended for providing this lucid, timely, and instructive review on the current management of diabetic kidney disease.

Alicic R, Nicholas SB. Diabetic kidney disease back in focus: management field guide for health care professionals in the 21st century. *Mayo Clin Proc.* 2022;97(10):1904-1919. doi.org/10.1016/j.mayocp.2022.05.003

RESISTING COVID-19

Two articles address the issue of how resistance to COVID-19 may be conferred, the first being the efficacy of the COVID-19 booster, the second being the importance of eliciting mucosal immunity. Using Medicare claims from January 1, 2020, to December 31, 2021, Mehta et al matched almost 4 million subjects who received or did not receive the booster over a maximum follow-up of 130 days so as to determine hospitalization rates in either group. The data demonstrate that the booster was associated with 81% efficacy in reducing hospitalization; and that the booster could prevent almost 70,000 hospitalizations in the currently nonboosted 15 million individuals aged 65 years or older. Factors that reduced the booster's efficacy included certain comorbidities, such as hematologic and other malignancies, diabetes, renal failure, and autoimmune diseases; the efficacy of the booster was also reduced in Black and Hispanic enrollees, and in enrollees with prior hospitalizations. In those subjects older than 65 years, the reductive effect in hospitalization rates with boosting significantly increased with age. Boosters were more effective when given between 6 and 9 months after the vaccination, and less effective if given at 5 to 6 months or less than 5 months after vaccination. This study by Mehta et al provides compelling evidence regarding the efficacy of the COVID-19 booster in preventing severe COVID-19. The *Perspective* by Adashi and Gruppuso, also in this issue, highlights the significance of eliciting mucosal IgA-based immunity as a preventive strategy in COVID-19. Parenteral vaccines

are effective in reducing the risk for severe COVID-19 and attendant mortality, but breakthrough infections may occur despite being vaccinated. As pointed out by these authors, a relevant consideration is that while parenteral COVID-19 vaccines promote humoral IgG-based immunity, such vaccines generally do not achieve mucosal IgA-based immunity; the latter is important in enabling resistance to breakthrough infections and in potentially impeding the spread of COVID-19. An effective and safe intranasal COVID-19 vaccine will thus be an important advance, either administered in concert with, or supplanting, a parenteral vaccine. A number of relevant initiatives and studies, as summarized

by Adashi and Gruppuso, are currently exploring these exciting prospects for intranasal vaccines.

Mehta HB, Li S, Goodwin JS. Effectiveness of COVID-19 booster on the risk of hospitalization among Medicare beneficiaries. *Mayo Clin Proc.* 2022;97(10):1780-1793. doi.org/10.1016/j.mayocp.2022.06.029

Adashi EY, Gruppuso PA. SARS-CoV-2 vaccines: the mucosal immunity imperative. *Mayo Clin Proc.* 2022;97(10):1771-1773. doi.org/10.1016/j.mayocp.2022.07.002

Karl A. Nath, MBChB
Editor-in-Chief