RETARDING THE PROGRESSION OF DIABETIC KIDNEY DISEASE BY SGLT2 INHIBITORS

Diabetic kidney disease, which occurs in approximately one third of patients with type 2 diabetes mellitus (T2DM), tends to incur progressive renal functional decline that may culminate in end-stage kidney disease. A fundamental objective in managing patients with T2DM is assessing whether there is renal involvement and, if so, retarding the rate of decline in renal function. Cornerstones in such management include glycemic and blood pressure control and the reduction of proteinuria. A remarkable recent discovery in the field of antihyperglycemic agents (AHAs) is that inhibitors of the sodium glucose cotransporter 2 (SGLT2i) reduce the rate of loss of renal function in patients with T2DM and kidney disease; such findings have been shown in randomized, prospective, placebo-controlled trials and meta-analyses of these trials. In the present issue of Mayo Clinic Proceedings, the retrospective study of Takeuchi et al corroborates these findings with real world data. These investigators compared the effects of SGLT2i and other types of glucose-lowering medications (o-GLM) on the decline in estimated glomerular filtration rate (eGFR) in T2DM. Using the real-world data (RWD) database maintained by the Health, Clinic, Education Information Evaluation Institute (Kyoto, Japan) which compiles patient records from some 160 institutions, this study included matched cohorts of 1433 SGLT2i users and 2739 o-GLM users. Over a 2 to 4 year observation period, the rate of decline in eGFR was slower in SGLT2i users as compared with o-GLM users, and the cumulative incidence of the secondary composite renal endpoint (>40% decline in eGFR and a decline in eGFR to <30 ml/min/1.73 m²) was also less in SGLT2i users. Notable aspects of this study are that SGLT2i were compared with o-GLM, whereas in clinical trials the evaluation of SGLT2i is commonly placebo-controlled; additionally, the nephroprotective effects of SGLT2i were observed despite less effective glycemic control. Several mechanisms may account for this protective effect including the role of tubuloglomerular feedback. In DM, the increased filtered load of glucose in the kidney promotes avid proximal tubular reabsorption of glucose (and sodium), leading to less distal sodium delivery and, accordingly, less sodium reabsorption by the macula densa of the distal convoluted tubule. This signals a vasodilatory response in the neighboring glomerular afferent arteriole, thereby causing glomerular hyperfiltration and glomerular hypertension, both of which are implicated in diabetic glomerulopathy. By inhibiting glucose (and sodium) in the proximal tubule, SGLT2i interrupt this sequence of events, thereby mitigating glomerular hyperfiltration and hypertension; this is one explanation given for the nephroprotective effects of SGLT2i. The story of the introduction of
SGLT2i in clinical practice is an exciting one that shows how basic research drives advances in patient management - the discovery of SGLTs in the mammalian proximal tubule stimulated the search for SGLT2i as AHAs, drugs that not only promote glycemic control, but also, unexpectedly, lessen cardiovascular mortality and renal functional decline. This latter effect is importantly corroborated by real world evidence provided by the study of Takeuchi et al.


NONCOMMUNICABLE DISEASE IN YOUNG ADULTS WITH CHILDHOOD-ONSET DISABILITIES

Noncommunicable diseases is a term used to describe a group of diseases by what they are not: they are not transmissible among individuals and generally not infectious in nature. Such inauspiciously named diseases represent, ironically, the dominant cause of mortality and disability in the United States and worldwide; their major constituents include cardiovascular diseases, cancer, chronic pulmonary diseases, and diabetes. These diseases usually occur later in life, their pathogenesis is commonly protracted rather than acute, and there is generally a slow tempo to their clinical course. Noncommunicable diseases often reflect the adverse and chronic effects of unhealthy lifestyles and diet, and underpin much of the multimorbidity observed in aging populations. The appearance of such diseases in young adults thus raises the question—what predisposes to this prematurity in their onset? To this end, and in the present issue of Mayo Clinic Proceedings, Whitney et al examined whether young adults (age 18 to 40 years) with pediatric-onset disabilities (PoDs) had an increased prevalence of noncommunicable diseases. Using the Optum Clinformatics Data Mart, the authors examined the prevalence of 10 categories of diseases (for example, ischemic heart disease, cerebrovascular disease, type 2 diabetes, cancer, chronic respiratory disorders, among others) in these adults with PoDs, the latter grouped into 9 categories (musculoskeletal, neurodevelopmental, and circulatory systems, among others). The data demonstrate that the prevalence of all noncommunicable diseases was increased in young adults with PoDs, as was the prevalence of multimorbidity, which was defined as two or more noncommunicable diseases. Not unexpectedly, PoDs in a given system predisposed to noncommunicable diseases in young adults in the same system; for example, developmental defects in the genitourinary tract predisposed to chronic kidney disease in young adults. However, there was a higher prevalence of the various categories of noncommunicable diseases and multimorbidity when analyzed for a given category of PoDs. This is remarkable because it shows that the adverse effects of specific PoDs are broad-based as any one PoD is attended by noncommunicable diseases involving multiple systems. A central implication and call emanating from these findings, as emphasized by the authors, are two-fold: first, the need for increased recognition of these distant and broad-based adverse effects of PoDs; and, second, the need for clinical practice and health care policies that more effectively screen and detect noncommunicable diseases occurring prematurely in young adults.


ULTRAVIOLET EXPOSURE AND SEX DIFFERENCES IN THE RISK FOR HERPES ZOSTER

A potent stimulus to vitamin D production, sunlight is salutary in small/moderate amounts, as it benefits numerous systems (endocrine, musculoskeletal, immune, among others), promotes circadian rhythms and sleep patterns, and cushions against disturbances in mood. Sunlight, in
large amounts and/or with direct exposure to it, however, can be harmful by causing sunburn, skin senescence, and skin cancer, in large part because of its content of ultraviolet radiation (UVR). Underpinning the adverse effects of UVR are the cellular generation of reactive oxygen species, damage to lipid bilayers and cellular macromolecules such as DNA, and immune suppression. Immunosuppression by UVR can silently abrogate innate and adaptive immune processes that effectively hold in check the evolution of a given disease. In this regard, the reactivation of varicella zoster virus—lying quiescent for years in the sensory ganglia after an episode of chickenpox infection has resolved—as painful, dermatome-aligned, blistering lesions of herpes zoster has been linked to exposure to sunlight and UVR, a thesis supported by epidemiologic and clinical observations. In the present issue of Mayo Clinic Proceedings, Kawai et al rigorously examine the association between the risk of herpes zoster and UVR by utilizing 3 prospective cohorts, one of which involved male participants, while the other two involved female participants, the total number for all 3 cohorts exceeding 200,000 participants. UVR exposure was estimated by a sophisticated high spatiotemporal resolution model that predicted UVR exposure based on geocoded addresses, while herpes zoster was a self-reported clinician diagnosis. The data demonstrate that UVR exposure was associated with an increased risk for herpes zoster in males, but not in females, whereas a history of severe sunburn was attended by a higher risk of herpes zoster in both men and women. Women, in general, have more vigorous innate and adaptive immune responses and are less susceptible to UVR-induced immunosuppression—this may explain the observed sex differences with regard to the risk of herpes zoster with UVR exposure. Kawai et al also suggest that women may be more attentive to the hazards of direct sunlight and more likely to adopt a sun protection strategy. The lack of observable sex differences in the risk for herpes zoster following severe sunburn may reflect the fact that such UVR-induced skin injury is more intense and immediate, thereby overwhelming any sex-dependent differences in immune responses. While lesions of herpes zoster usually heal without significant complications, postherpetic neuralgia may occur in 10% or more of affected individuals, and eye, ear, and neurologic complications may occur in a quite small subset of patients. The study by Kawai et al underscores the association between sunshine exposure and the risk for herpes zoster and the need for protective behavioral responses that can mitigate such risks.


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