

MAYO CLINIC
PROCEEDINGS

In the Limelight: December 2021



This month's feature highlights three 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/cNPtMz9vDtk>).

THE EFFECT OF SENOLYTICS ON GLYCEMIC CONTROL IN TYPE 2 DIABETES MELLITUS

Several clinical observations indicate that improved glycemic control may attend the use of tyrosine kinase inhibitors (TKIs), agents introduced some 20 years ago for the treatment of Philadelphia chromosome-positive chronic myelogenous leukemia. In the present issue of *Mayo Clinic Proceedings*, Salaami et al present a retrospective analysis of glycemic control assessed after 1 year in patients maintained on either one of the following TKIs, dasatinib or imatinib. This study involved the interrogation of Mayo Clinic's Informatics for Integrating Biology at the Bedside database from January 1994 through December 2019, and had as inclusion criteria the continuous use of either TKI for at least 12 months and the diagnosis of type 2 diabetes mellitus (T2DM) prior to the introduction of either TKI. As compared with imatinib, patients on dasatinib exhibited a 43.6 mg/dL reduction in glucose concentration, a mean 0.80 absolute point reduction in hemoglobin A1c, and tended to require less daily insulin units. While patients on dasatinib (relative to imatinib) exhibited a 4.8 kg relative weight loss, linear regression analyses demonstrated that such weight loss may account for less than 20% of the reduction in blood glucose associated with dasatinib. These findings are particularly important as they relate to the

recognition that T2DM may be a consequence of and a catalyst for cellular senescence, and that dasatinib is a senolytic, a class of compounds that destroys senescent cells. Cellular senescence describes a specific type of cell fate wherein afflicted cells become cell cycle-arrested and resilient to cell death pathways; importantly, they also exhibit a senescence-associated secretory phenotype (SASP), which refers to their production of a plethora of inflammatory and potentially cytotoxic species. These species may exert adverse effects on neighboring cells, and once these species have gained access to the systemic circulation, they may adversely affect cells in distant tissues and organs. Cellular senescence underlies various aging syndromes and predisposes to assorted chronic diseases including T2DM. Age and obesity, conditions in which senescent cells gather in increasing numbers, are risk factors for T2DM. In 2015, Kirkland and colleagues discovered senolytics, compounds that kill senescent cells because these compounds vitiate the cytoprotective pathways that enable the survival of senescent cells (Zhu Y, Tchkonja T, Pirtskhalava T, et al. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell*, 2015;14(4):644-658). Dasatinib possesses powerful senolytic properties, the latter quite weakly exhibited by imatinib. The present findings of Salaami et al thus demonstrate that for a given class of drugs (TKIs), the use of those specific members which are strongly senolytic (dasatinib) are attended by markedly improved glycemic control as compared with those in which such effects are quite weak (imatinib). These



See also pages
3012, 3021, 3130



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findings invite the speculation that it is the senolytic property of dasatinib — the removal of senescent cells in T2DM — that accounts for the improved glycemic control observed with its use. Geroscience, senescence, and senolytics are exciting, rapidly moving areas in biology and medicine, and, indeed, dasatinib and other senolytics are currently undergoing clinical trials, including for diabetes mellitus.

Salaami O, Kuo C-L, Drake MT, Kuchel GA, Kirkland JL, Pignolo R. Antidiabetic effects of the senolytic agent dasatinib. *Mayo Clin Proc.* 2021;96(12):3021-3029.

SPORTS ACTIVITIES: HOW MUCH IS OPTIMAL FOR LONGEVITY, AND HOW MUCH MAY BE HARMFUL?

Longevity and healthspan are generally benefited by physical activity, adequate amounts of refreshed sleep, a Mediterranean diet, freedom from stress, and the avoidance of smoking and immoderate amounts of alcohol. For many of these determinants a salient issue is how much is optimal, and this is particularly true for physical activity. In the present issue of *Mayo Clinic Proceedings*, the study by Schnohr et al evaluated the association between all-cause mortality and the duration of leisure-time sports activity undertaken per week. This analysis utilized data compiled by the Copenhagen City Heart Study, a prospective study of a population of White men and women which began in 1976 and involved periodic examinations in the ensuing years. The present study employed data that were collected between 1991 and 1994 and included 8697 healthy men and women with a median follow-up of 25.6 years. Participants responded to a survey regarding the duration of weekly leisure-time sports activities, the latter specifying 10 types of such activities (tennis, badminton, soccer, handball, cycling, swimming, jogging, calisthenics, health club activities, and weightlifting, as listed by the authors). The data demonstrate a U-shaped relationship with lowest all-cause mortality observed in individuals involved in 2.6 to 4.5 hours of such activities per

week; all-cause mortality increased in those participants involved with either 2.5 or less hours, or 10 hours or more of such activities per week. Moreover, these findings were broadly true for subgroup analysis based on age, sex, smoking, education, and BMI. In discussing their findings, Schnohr et al underscore the following salient points. First, it is unlikely that reverse causality underlies the relationship as these findings were essentially unchanged when the first 5 years of follow up were excluded. Second, not all types of physical activity may confer similar beneficial effects, as leisure-time sports activity may be more salutary as compared with occupation-associated physical activity, in part because of the social interaction that generally occurs in the former. Indeed, their prior study in *Mayo Clinic Proceedings* demonstrates that leisure-time sports activities that were more likely to confer such social interaction were attended by lower mortality (Schnohr et al, *Mayo Clin Proc.* 2018;93(12):775-785). Third, Schnohr et al point out possible explanations for the adverse effects of excessive amounts of sports activities and these involve cardiac arrhythmias, accelerated coronary artery disease, and cardiac fibrosis. Fourth, while they applaud guidelines that underscore the importance of exercise (at least 150 minutes of moderate aerobic activity, or 75 minutes of vigorous aerobic activity per week, or a combination of moderate and vigorous activity), Schnohr et al suggest that such guidelines and recommendations may include a cautionary statement pertaining to the adverse effects of inordinate amounts of weekly exercise.

Schnohr P, O'Keefe JH, Lavie CJ, et al. U-shaped association between duration of sports activities and mortality: Copenhagen City Heart Study. *Mayo Clin Proc.* 2021;96(12):3012-3020.

ESTRADIOL AS A DETERMINANT OF THE BEHAVIOR OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

In recent years, *Mayo Clinic Proceedings* introduced 3 new sections: Women's Health, the Medicine of Sex Differences,

and Understanding Disease. The former two sections are dedicated to issues that have long received insufficient attention, while the latter provides discussion of pathobiology of disease and the biology underlying novel and emerging therapies. The “Understanding Disease” article by Gersh et al in the current issue of *Mayo Clinic Proceedings* is relevant to all 3 sections. The central message of this article is one that is poorly recognized, namely, estradiol influences the behavior of the renin-angiotensin-aldosterone system (RAAS) in health and disease. Gersh et al start from the established premises that ovarian function and estradiol production are vital for the cardiovascular, metabolic, and immune milieu that enable fertility during reproductive years; and that menopause-imposed attrition of ovarian function and estradiol production not only vitiates the relative resistance of women to cardiovascular disease in their reproductive years, but it also predisposes to accelerated cardiovascular disease during menopause. The RAAS is a key signaling system that is influenced either by adequate levels of estradiol, or conversely, by estradiol deficiency. Gersh et al underscore the following considerations. First, the RAAS exists not just systemically but also locally in tissues. Second, the RAAS is composed of two arms, one proinflammatory, and other anti-inflammatory. The long recognized classical proinflammatory arm is part of the “flight or fight” response, as it generates angiotensin II and aldosterone, that, in aggregate, are vasoconstrictive, elevate blood pressure, and promote salt and water retention; its proinflammatory/immune effects are essential in responding to infectious processes. The more recently recognized anti-inflammatory arm of the RAAS largely involves the generation of

angiotensin (1-7) via angiotensin converting enzyme 2; angiotensin (1-7) is antioxidant, vasodepressor, anti-inflammatory, and anti-fibrotic. Third, inordinate and sustained activation of the classical proinflammatory RAAS arm beyond the period during which its acute effects are needed, or the failure for it to be counterbalanced by the anti-inflammatory arm leads to cardiovascular, renal, and other diseases. Fourth, estradiol critically allows the proinflammatory/immune effects of RAAS to be exerted when they are acutely needed, but also enables their balancing by or switching to the anti-inflammatory arm and other offsetting processes such that adverse effects of the RAAS are avoided. Fifth, deficiency of estrogens as occurs during menopause predisposes to unchecked proinflammatory effects of the RAAS and thus the risks of cardiovascular and other diseases. Sixth, agents (for example, ACEIs and ARBs) that block the proinflammatory arm of the RAAS may also, unintentionally, interfere with the anti-inflammatory arm as the two arms are so interconnected. In concluding, Gersh et al emphasize the need for more sex-specific research regarding agents that interrupt the RAAS, especially in postmenopausal women; and they also outline the potential for beneficial effects in postmenopausal women that may be achieved by synergistic approaches founded on hormone replacement therapy and RAAS-modifying agents.

Gersh FL, O’Keefe JH, Lavie CJ, Henry BM. The renin-angiotensin-aldosterone system in postmenopausal women: the promise of hormone therapy. *Mayo Clin Proc.* 2021;96(12):3130-3141.

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