Aging Pathobiology and Therapeutics 2022; 4(3): 84-86 ***84***
DOI: 10.31491/APT.2022.09.091

COMMENTARY

Sex Matters in Aging. The Canagliflozin Story

Jackson Wezeman[a] , Warren Ladiges[a, *]

[a] *Department of Comparative Medicine, School of Medicine, University of Washington, Seattle, WA, USA.*

Abstract

A promising and novel approach for identifying anti-aging therapeutics has been the repurposing of clinically approved and readily available drugs in mice. Canagliflozin, a clinically approved safe, and effective drug for type 2 diabetic patients, was recently shown to robustly retard age-related lesions in male mice but less so in female mice. While this type of sex disparity is often seen in the field of aging, it does represent a dilemma of not knowing the cause or how translationally relevant the sex differences would be in older humans treated with Canagliflozin. Thoughtful and mechanistic investigations are needed to understand why these differences are present and whether they can be eliminated by new drugs or drug combinations. Success in using repurposed drugs for aging intervention studies in humans will depend on preclinical research to uncover pathways that can be targeted for the benefit of both sexes.

Keywords: Aging intervention, canagliflozin, sex disparities, mouse aging, age-related lesions

Aging is complex and multifaceted. It then follows that there would be multiple angles to promote prolonged and resilient healthy aging. One promising and novel approach has been the repurposing of clinically approved and readily available drugs as diet supplements. To formally assess the effects of these compounds on evaluating the potential of extending lifespan, the National Institute on Aging Intervention Testing Program (ITP) has investigated numerous drugs. Type 2 diabetic (T2D) drugs are one such category that has been gaining popularity for their use in delaying aging through managing glucose metabolism and insulin activity. In a recent publication, Canagliflozin, an SGLT-2 inhibitor, was shown to retard age-related lesions in male mice [1]. While impressive, the results represent the tough but not unexpected dilemma that is often seen in the field of aging: sex disparities. How large are these disparities and what does it mean for anti-aging research?

T2D drugs represent a novel therapeutic approach for aging and have already shown promise in their ability to mitigate the effects of dementia and reduce the severity of neurodegenerative diseases [2-5]. Though some drugs like Acarbose have already been studied at length and validated in multiple studies [6-8], many drugs are still being examined. A greater number of validated drugs will be useful for translational therapies and enhance our ability to manipulate mechanisms and more selectively target pathways of aging. In the publication, "Canagliflozin retards age-related lesions in heart, kidney, liver, and adrenal gland in genetically heterogenous male mice", Canagliflozin is shown to have significant differences in healthy aging for male mice as opposed to female mice when looking at age-related lesions [1]. Using a validated geropathology grading platform [6], organs were stained with hematoxylin and eosin, then graded according to lesion presence or severity. Significant decreases were found in males in the incidence of adrenal cortical neoplasm and severity of arteriosclerosis and cardiomyopathy, glomerulonephropathy, hepatic microvesicular lipidosis, and pancreatic atrophy. Females were shown to have significance only in the severity of pancreatic atrophy, while adrenal cortical neoplasm and thyroid adenoma trended toward significance. The breadth of lesions that Canagliflozin was able to increase resilience to in male mice is as noteworthy as it is puzzling to see such a stark difference in its inability to delay aging pathology in female mice.

Snyder *et al.* go on to speculate that the reason for the differences in lesion scores between sexes in mice could be due to either side effects in the female cohort that oppose the benefits, or that there may be differences in aging-related pathways that account for the ineffectiveness of the drug [1]. This is not the first-time differences have been reported for anti-aging drugs. Acarbose, an inhibitor of the breakdown of complex carbohydrates in the upper digestive tract, also shows sex differences favoring males over females, including protein ubiquitination, cardiac hyper-

* Corresponding author: Warren Ladiges
Mailing address: Department of Comparative Medicine, School of Medicine, University of Washington, Seattle, WA 98195, USA.
Email: wladiges@uw.edu

Received: 06 September 2022 / Accepted: 09 September 2022
Published: 30 September 2022

trophy, and hypothalamic inflammation [7-9]. Although both drugs target metabolic pathways, they may indirectly affect other aging pathways such as mTOR signaling [10-11]. Rapamycin, which has been tested at length in mice and is well validated for its lifespan effects, targets the mTOR signaling pathway and has significant anti-aging effects in both male and female mice [12]. It is important to investigate the pathways involved in sex differences, which may not only improve our understanding but may be useful in developing new therapies or drug combination therapies.

To maximize the benefit of the translational research being done, it is important to consider the end user. It is problematic to ignore the sex differences and proceed to develop therapies that only work for a specific subset of the population. With Canagliflozin as a case study, the best course of action is to work on examining the mechanistic differences to determine how to resolve the failure of the drug in female mice to extend lifespan or reduce lesion severity. Due to the significant nature of the differences observed in the paper, it has the potential to be an excellent starting point for answering this scientific query. Ultimately, the resolution of these sex differences comes down to experimentation. Thoughtful and mechanistic studies need to be completed to understand why these differences are present. Multiple lines of mice could be used to verify the sex differences and used as a comparison to narrow down where they originate. RNA sequencing has proven to be valuable in comparing the transcriptome of biological cohorts to examine differences in gene expression, especially in aging rodent populations.

Another consideration to unlocking the benefits of T2D drugs showing sex differences in mice is a multi-targeted approach. For the increasing number of studies that have provided evidence of sex differences, there is now interest in combinations of drugs that target different pathways, are designed to work better, and have lower hazard ratios than the individual drugs, even with sex accounted for [3]. This raises the question of whether the complexity of aging and the sex differences observed can be mitigated with combination therapy using drug cocktails. In a recent study, a combination of rapamycin, phenylbutyrate, and acarbose was able to increase resilience to aging and reduce the severity of age-related lesions [13]. Though there were some sex differences in the endpoint assays, the cocktail was overall better in comparison to any individual drug. It is possible this method could be used to alleviate the sex inequalities in the case of Canagliflozin and even enhance the effect seen in males.

In conclusion, Canagliflozin is an excellent case study of the sex differences challenging T2D drugs for aging intervention approaches. Investigations to help determine the mechanisms for these differences will help move studies from mice to humans. Future success using repurposed T2D drugs will depend on basic research to uncover pathways that can be targeted for the benefit of both sexes.

Declarations

Authors' contributions: Both authors contributed to the writing of this manuscript.

Availability of data and materials: Not applicable.

Financial support and sponsorship: Supported in part by NIH grant R01 AG057381 (Ladiges, PI).

Conflicts of interest: Warren Ladiges is a member of the Editorial Board of *Aging Pathobiology and Therapeutics*. The author declares that there are no conflicts.

Ethical approval and informed consent: Not applicable.

Consent for publication: Not applicable.

References

1. Snyder JM, Casey KM, Galecki A, Harrison DE, Jayarathne H, Kumar N, *et al.* Canagliflozin retards age-related lesions in heart, kidney, liver, and adrenal gland in genetically heterogenous male mice. *Geroscience*, 2022. [Crossref]
2. Alsharif AA, Wei L, Ma T, Man KKC, Lau WCY, Brauer R, *et al.* Prevalence and Incidence of Dementia in People with Diabetes Mellitus. *J Alzheimers Dis*, 2020, 75(2): 607-615. [Crossref]
3. Kim JY, Ku YS, Kim HJ, Trinh NT, Kim W, Jeong B, *et al.* Oral diabetes medication and risk of dementia in elderly patients with type 2 diabetes. *Diabetes Res Clin Pract*, 2019, 154: 116-123. [Crossref]
4. Heneka MT, Fink A, & Doblhammer G. Effect of pioglitazone medication on the incidence of dementia. *Ann Neurol*, 2015, 78(2): 284-294. [Crossref]
5. Katsel P, Roussos P, Beeri MS, Gama-Sosa MA, Gandy S, Khan S, *et al.* Parahippocampal gyrus expression of endothelial and insulin receptor signaling pathway genes is modulated by Alzheimer's disease and normalized by treatment with anti-diabetic agents. *PLoS One*, 2018, 13(11): e0206547. [Crossref]
6. Snyder JM, Snider TA, Ciol MA, Wilkinson JE, Imai DM, Casey KM, *et al.* Validation of a geropathology grading system for aging mouse studies. *Geroscience*, 2019, 41(4): 455-465. [Crossref]
7. Harrison DE, Strong R, Allison DB, Ames BN, Astle CM, Atamna H, *et al.* Acarbose, 17-α-estradiol, and nordihydroguaiaretic acid extend mouse lifespan preferentially in males. *Aging Cell*, 2014, 13(2): 273-282. [Crossref]
8. Harrison DE, Strong R, Alavez S, Astle CM, DiGiovanni J, Fernandez E, *et al.* Acarbose improves health and lifespan in aging HET3 mice. *Aging Cell*, 2019, 18(2): e12898. [Crossref]
9. Dodds SG, Parihar M, Javors M, Nie J, Musi N, Dave Sharp Z, *et al.* Acarbose improved survival for Apc(+/Min) mice. *Aging Cell*, 2020, 19(2): e13088. [Crossref]
10. Sun P, Wang Y, Ding Y, Luo J, Zhong J, Xu N, *et al.* Canagliflozin attenuates lipotoxicity in cardiomyocytes and protects diabetic mouse hearts by inhibiting the mTOR/HIF-1α *pathway. iScience*, 2021, 24(6): 102521. [Crossref]
11. Garratt M, Bower B, Garcia GG, & Miller RA. Sex differ-

ences in lifespan extension with acarbose and 17-α estradiol: gonadal hormones underlie male-specific improvements in glucose tolerance and mTORC2 signaling. *Aging Cell*, 2017, 16(6): 1256-1266. [Crossref]

12. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, *et al*. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature*, 2009, 460(7253): 392-395. [Crossref]
13. Jiang Z, Wang J, Imai D, Snider T, Klug J, Mangalindan R, *et al*. Short term treatment with a cocktail of rapamycin, acarbose and phenylbutyrate delays aging phenotypes in mice. *Sci Rep*, 2022, 12(1): 7300. [Crossref]

Cite this article as: Wezeman J, & Ladiges W. Sex Matters in Aging. The Canagliflozin Story. *Aging Pathobiol Ther*, 2022, 4(3): 84-86. doi: 10.31491/APT.2022.09.091