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Elevated serum xylitol levels and cardiovascular risk: an active component or an innocent bystander?

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This commentary refers to 'Xylitol is prothrombotic and associated with cardiovascular risk', by M. Witkowski *et al.*, https://doi.org/10.1093/eurheartj/ehae244 and the discussion piece 'Erythritol and xylitol and CVD risk: a growing concern', by M. Witkowski and S.L. Hazen, https://doi.org/10.1093/eurheartj/ehae729; 'Xylitol exposure and cardiovascular risk', by B.K. Wölnerhanssen *et al.*, https://doi.org/10.1093/eurheartj/ehae730.

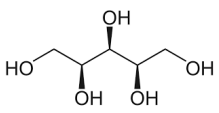
We read the manuscript by Witkowski *et al.*[1] with interest. This retrospective study was performed on patients undergoing elective diagnostic cardiac evaluation. Two separate cohorts were studied, a discovery cohort of 1157 subjects and a non-overlapping validation cohort of 2149 subjects. In the discovery cohort, the investigators observed a higher association of incident (3-year) major adverse cardiovascular events (MACEs) in the patient subgroup with higher fasting plasma xylitol concentrations. This observation was confirmed in the validation cohort in the tertile with the highest elevated xylitol levels. To further support that xylitol exposure is causally related to the incidence of MACEs, additional studies showed that at levels observed in fasting plasma, xylitol enhanced several indices of platelet reactivity and *in vivo* thrombus formation.

In the normal subjects, urinary xylitol excretion was observed to occur soon after oral intake, as the molecule has a half-life of ~13 (±4) min, with a return to rapid xylitol plasma concentrations within hours. This evidence led the authors to conclude, '… the plasma levels observed in our observational (validation) cohort represent variations in endogenous production/levels and not food intake'. The higher incidence of MACEs was found in a subgroup of the study population that is thought to produce higher concentrations of endogenous xylitol.

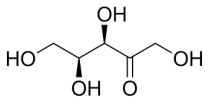
The study does not allow to link xylitol intake with a higher incidence of MACE in the general population. We note that the title of the manuscript provides a misleading concept for the interpretation of the study results, whereas it should focus on specific characteristics of the investigated cohorts. These characteristics raise questions about the reason why high endogenous xylitol levels can be generated. Is it just an occasional observation or a particular metabolic pathway that is activated in the subpopulation involved in the study? Or is it a general population variant?

Witkowski *et al.*[2] also reported that increased circulating erythritol, another sugar alcohol close to the xylitol family, is associated with adverse cardiovascular events in the same xylitol cohort, demonstrating that erythritol enhances platelet activation *in vitro* and *in vivo*. This latter study has been challenged both by the causality between dietary erythritol and cardiometabolic risk[3] and by the lack of evidence from Mendelian randomization analyses that erythritol has adverse cardiometabolic effects.[4]

One more consideration is that in pentosuria, a benign and asymptomatic inborn error of metabolism characterized by the excretion of 1–4 g of pentose L-xylulose in the urine, the plasma concentration of the same reaches 80 μM.[5] As xylulose is the closest analogue of xylitol (see below) and considering that most of Dr Witkowski's studies were conducted at a xylitol concentration almost three-fold lower (30 μM) than the plasma concentration of xylulose in pentosuric subjects, one would expect a similar chemico-physical action to enhance stimulus-induced platelet aggregation responses to multiple agonists (e.g. ADP, thrombin, and collagen) and *in vivo* thrombus formation.



Xylitol



L-Xylulose

However, as mentioned above, pentosuria is harmless and is not associated with any health problems.

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Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

References

1. Witkowski M, Nemet I, Li XS, Wilcox J, Ferrell M, Alamri H, *et al.* Xylitol is prothrombotic and associated with cardiovascular risk. *Eur Heart J* 2024;**45**:2439–52. https://doi.org/10.1093/eurheartj/ehae244
2. Witkowski M, Nemet I, Alamri H, Wilcox J, Gupta N, Nimer N, *et al.* The artificial sweetener erythritol and cardiovascular event risk. *Nat Med* 2023;**29**:710–8. https://doi.org/10.1038/s41591-023-02223-9
3. Mazi TA, Stanhope KL. Elevated erythritol: a marker of metabolic dysregulation or contributor to the pathogenesis of cardiometabolic disease? *Nutrients* 2023;**15**:4011. https://doi.org/10.3390/nu15184011
4. Khafagy R, Paterson AD, Dash S. Erythritol as a potential causal contributor to cardiometabolic disease: a Mendelian randomization study. *Diabetes* 2024;**73**:325–31. https://doi.org/10.2337/db23-0330
5. Pierce SB, Spurrell CH, Mandell JB, Lee MK, Zeligson S, Bereman MS, *et al.* Garrod's fourth inborn error of metabolism solved by the identification of mutations causing pentosuria. *Proc Natl Acad Sci U S A* 2011;**108**:18313–7. https://doi.org/10.1073/pnas.1115888108