

Oral health benefits and safety of xylitol and potential cardiovascular risk: questioning the validity of the model of Witkowski *et al.*

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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 ‘Xylitol and cardiovascular risks’, M. Witkowski and S. L. Hazen, <https://doi.org/10.1093/eurheartj/ehaf059>.

Decades of well-documented evidence exists for protective effects and safety of low-dose chronic xylitol use against oral disease. Dental caries (tooth decay) and periodontal disease (gum disease) are associated with cardiovascular disease, specifically increased risk of stroke or death.¹ Reducing oral diseases thereby reduces cardiovascular risk. Thus, the validity of the model employed in the research reported by Witkowski *et al.*² merits careful scrutiny.

Witkowski *et al.*² suggest that xylitol is associated with increased cardiovascular risk. We applaud the authors' evaluation of potential long-term health consequences of dietary supplements or food additives. Nevertheless, the population evaluated were disproportionately of higher cardiovascular risk and likely there was bias as a result of the varying degrees of underlying metabolic disease (samples obtained as part of elective diagnostic cardiovascular evaluations). In humans, xylitol is endogenously produced through the pentose phosphate pathway (PPP). The PPP is up-regulated during the reperfusion phase of ischaemic-reperfusion injury,³ such as occurs in cardiovascular disease or shock, thereby increasing the metabolites produced in the PPP including xylitol. Thus, xylitol within these *fasting* samples does not reflect dietary consumption of xylitol but, instead, is likely a benign biomarker of the underlying PPP dysregulation due to underlying disease. These findings raise concerns about the validity of the model and the conclusions drawn from the research. The report would be more complete had the investigators evaluated whether xylose, xylulose, glucuronate, or other metabolites upstream of xylitol are also associated with increased risk of major adverse cardiovascular events, and, therefore demonstrating that the elevations of these metabolites are simply biomarkers of a dysregulated PPP.

Furthermore, Witkowski reported a small ($n = 10$) intervention study where serum xylitol levels were evaluated after healthy adult volunteers ingested xylitol sweetened (30 g) water. Such a large consumption of xylitol as a single dose is associated with significant gastrointestinal side effects and is not recommended.⁴ When xylitol is provided in chewing gum, daily doses of <10 g, divided into 1–2 g doses throughout the day have been shown to significantly reduce dental caries (tooth decay) and clinical metrics of gingivitis (gum disease).⁵ Chewing gum xylitol rarely exceeds 1 g/piece of gum thereby requiring an individual to chew 30 pieces of gum (or more) at one time to achieve this same intake of xylitol, an unrealistic amount. Notably, Bordier *et al.* reported that ingestion of 7 g of xylitol led to no detectable increased plasma levels of xylitol within a double-blinded study demonstrating that modest xylitol dietary consumption has no impact on plasma xylitol levels.⁴ Additionally, xylitol loading studies have revealed no evidence of thrombotic risk and no reported adverse effects other than the known laxative effects with large doses (>30–35 g per intake). Thus, the oral health benefits of xylitol in reducing pathogenic biofilm associated with dental caries and periodontal disease (thereby reducing cardiovascular risk) obtained using a daily dose of 5–6 g in divided doses have neither been shown to have systemic absorption nor toxicity. The conclusions from the present study should be viewed cautiously.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

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