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EDITORIAL
Thrombosis and antithrombotic treatment

Xylitol: bitter cardiovascular data for a successful sweetener

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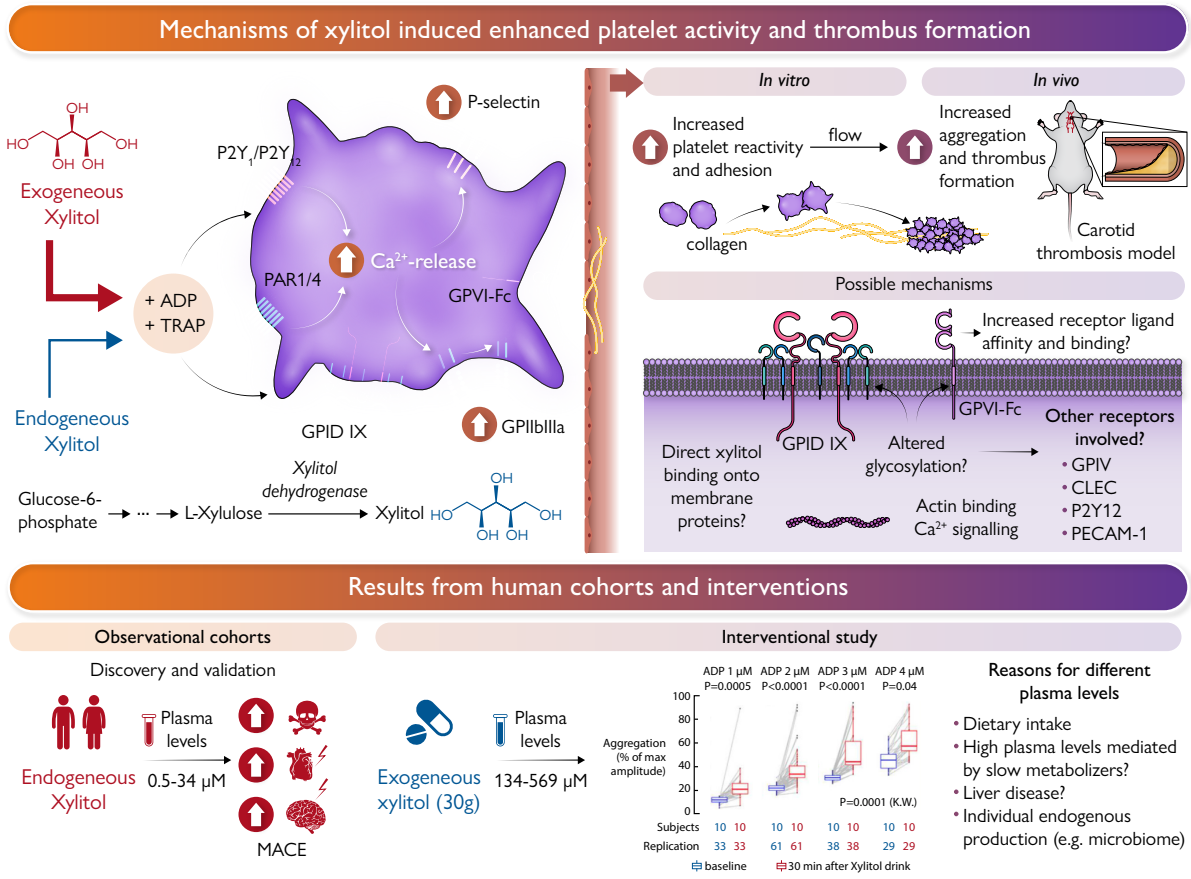
This editorial refers to 'Xylitol is prothrombotic and associated with cardiovascular risk', by M. Witkowski *et al.*, https://doi.org/10.1093/eurheartj/ehae244.

Graphical Abstract



Cardiovascular effects of Xylitol: data from observational cohorts, interventions and mechanisms of enhanced platelet activity

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For many years the scientific community and the general population alike were convinced that artificial sweeteners were beneficial because they reduce excessive sugar intake, and hence reduce ingested calories, particularly from soft drinks, thus reducing weight gain and—as implicitly argued—cardiovascular risk. A recent statement of the WHO released in May 2023 recommends against the use of non-sugar sweeteners (NSS) to control body weight or to reduce the risk of noncommunicable diseases.[1] The report suggests that 'there may be potential undesirable effects from long-term use of NSS, such as an increased risk of type 2 diabetes, cardiovascular diseases, and mortality in adults' and is referring to a recent systematic review.[2] However, the recommendation does not apply to low-calorie sugars and sugar alcohols (polyols), which are sugar derivatives containing calories and are therefore not considered NSS.

These polyols, hydrogenated carbohydrates, i.e. sugar alcohols, include sorbitol, xylitol, lactitol, mannitol, erythritol and maltitol and they come with a variety of names (bulk sweeteners, sugar replacers, sometimes also (and incorrectly) named 'sugar-free sweeteners'), and are often termed 'natural' and implicitly harmless resp. beneficial, because they can be extracted from berries, oats, birch, sugar cane bagasse and corn husk. Specifically, the sweetness of xylitol is similar to sucrose but calories per gram are lower (2.4 kcal/g or 9 kJ/g vs. 4 kcal/g or 17 kJ/g for typical sugars) and the FDA recognizes them as safe ('GRAS', meaning 'generally recognized as safe'). Xylitol is also called E967 in the EU and it is approved as a food additive here as well. Xylitol is known to be produced endogenously, but today it is increasingly ingested in a 1000-fold plus quantity compared to the endogenous production with a short plasma half-life, and plasma peak levels occur after 30 min, with rapid clearance/metabolism of 80% by the liver within a few hours.[3]

The xylitol market is rapidly growing and reached $701.3 million in 2023.[4] Annual growth is expected to be >4%, because it is considered 'natural' and because the list of positive effects reported is long: Finland has even proclaimed 'The xylitol week Nr. 6 in 2024' for oral health and recommends an intake of 5–10 g daily.[5] Mechanisms proposed include tooth protection (pH, oral microbiome); fewer respiratory infections such as rhinitis, sinusitis and otitis; positively modified oral and intestinal microbiome content, e.g. with higher (beneficial) butyrate production as a short chain beneficial fatty acid[6]; the glycemic index/insulin production is lower than with sucrose, due to the slower increase in plasma glucose; and an increased satiety may be helpful in losing weight.[7] Interestingly, xylitol may affect non-enzymatic glycosylation.[8] Bone strength increases and skin permeability decreases, skin collagen production is increased and xylitol is, not unexpectedly, used in the cosmetic industry. Up to 20 g are well tolerated; higher doses will lead to more bloating and loose stools, the hitherto the most relevant, but harmless, known dose-limiting side effect. For all these reasons it does not come as a surprise that the use of xylitol is constantly increasing and advocated.[7]

As a word of caution, long-term and high dose use have not been studied. Species differences may be huge, as xylitol in dogs may cause life-threatening hyper-insulinaemic hypoglycaemia[9] and liver disease. Intestinal absorption differs species-specifically and mice absorb almost nothing (a relevant fact for this papers' methodology). Very recent studies in humans show that transaldolase deficiency may cause dramatic accumulation of blood sugar alcohols (in the case of erythrite, several hundred-fold!) and may cause liver cancer.[10]

For all these reasons, in this issue of the *EHJ*, the findings of Marco Witkowsky *et al*. from Stanley Hazen's group is an important, timely and serious warning signal, because it elegantly shows relevant, alarming cardiovascular complications associated with endogenous and exogenous xylitol, namely major adverse cardiovascular events (MACE); first demonstrated in two carefully studied, large, independent patient cohorts (discovery and derivation cohort) with the use of metabolomics and stable-isotope-dilution LC-MS/MS method. The 3-year endpoints MACE and stroke were statistically significant and clinically relevant, positively associated with higher fasting levels of xylitol. Then, the authors went on to show that xylitol increased platelet reactivity *in vitro* and *ex vivo* to classical low-dose aggregation with adenosine diphosphate (ADP), Thrombin Receptor Activation Peptide (TRAP) and collagen. Further, an increased adhesion under flow, an augmented activation of GPIIb/IIIa and expression of *p*-selectin was observed using flow cytometry after addition of xylitol. Alongside this, increased calcium mobilization, increased platelet–leucocyte aggregates and shortened occlusion times in the mouse carotid thrombosis model were demonstrated. Finally, 10 human volunteers showed upon an oral challenge of 30 g of xylitol (as usually ingested by a portion of soft drink with the artificial sweetener) a clearly increased platelet reactivity as early as 30 min thereafter, strongly suggesting causality.

Collectively, the data send a warning sign that xylitol may have platelet-activation–mediated prothrombotic effects and may precipitate (pre-existing?) clinical cardiovascular disease as shown by this 3-year observation time; a possibly similar effect is also induced by other sugar alcohols such as erythritol, as was convincingly shown by the same group earlier.[11] Unfortunately, these sugars are indeed frequently used in the patient group at risk with obesity and diabetes.

The study raises many mechanistic questions for further interesting analyses. Is the observed effect receptor-mediated? The fact that multiple agonists show a similar enhanced pattern with xylitol makes this somewhat less likely. Can aspirin or specific receptor blockades of P2Y12, GPIIb/IIIa, GPIb/IX, GPVI, PAR-1, Clec, etc., alone or in combination, reduce/inhibit the effects? The glycosylation profile could provide interesting answers: Ppatelet receptors—particularly GPIbalpha—are heavily glycosylated. Xylitol and sugar alcohols are known to affect enzymatic and non-enzymatic glycosylation, as has been shown with collagen,[8] and it appears likely to happen with platelet glycoprotein receptors as well and with their ligands (von Willebrand factor, fibrinogen, collagen, etc.), with relevant functional consequences. Typical glycosylation and deglycosylation patterns were shown earlier, e.g. with (isolated) GPIb with important structure/function consequences of collapsed GPIbalpha and altered platelet function.[12] Modified glycosylation may affect platelet clearance and increase production, resulting in a younger and hyper-responsive platelet population. Typically altered glycosylation of von Willebrand factor is well known to alter receptor–ligand affinity and function.[13]

As the observed effects may appear rapidly after exogenous challenges, could there be a direct membrane and charge effect that is operative, i.e. by molecular on-docking, and could it then lead directly to receptor affinity and functional changes? Interestingly, this seems to be the case; indeed, xylitol has been shown to spontaneously bind to proteins, to induce conformational changes and to alter function, as nicely demonstrated in the case of carboxypeptidase A with altered enzyme activity (raised V_{max}) induced by spontaneous xylitol binding.[14] Typical binding occurred at tryptophane residues.

No inflammatory responses or sex differences were observed by the authors. However, what about other potential subgroups at risk, e.g. patients with low transaldolase activity who are then exposed to very high levels of sugar alcohols due to individually slower metabolism/clearance? Are they more prone to a particular cardiac risk as has been shown for patients with liver disease? Xylitol is mainly

metabolized/oxidized in the liver and there are multiple active metabolites including the phosphorylated form D-xylulose-5-phosphate, which may influence the nuclear transport and activates protein phosphatase 2A.[15]

The data and a myriad of questions collectively call for a closer look by the authorities and researchers alike at sugar alcohol sweeteners as a cardiovascular hazard. Confirmatory studies, longer exposure analyses and elucidations of mechanisms will have to confirm these not-so-clear skies for the widespread use of sugar alcohols.

Declarations

Disclosure of Interest

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