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The Role of Sweeteners (Erythritol, Xylitol) in Cardiovascular Risk: Friend or Foe

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Abstract

Background:

Sugar alternatives are quite numerous which take the form of artificial and naturally occurring sweeteners the most popular of whom are xylitol and erythritol. This type of compounds is not regarded as dangerous, however, recent research shows that it is taking action on metabolic and heart physiology. Increasing concerns have been directed at their potential associations with the thrombosis, endothelial injury and the cardiometabolic risk.

Objective:

The proposed study will compare the available literature on the cardiovascular potential of erythritol and xylitol and establish whether the two sweeteners are protective substances replacing sugar, or they are associated with the high cardiovascular risk.

Method:

It was in narrative review formulation under which the findings of clinical trials, observational studies, and mechanistic studies that were published in the last decade were integrated. The articles found in the databases (PublMed, Scopus, and Web of Science) that were used to measure the effect of sweetener consumption on cardiovascular outcomes regarding platelet activity, endothelial activity, lipid metabolism, and inflammatory pathways were identified.

Results:

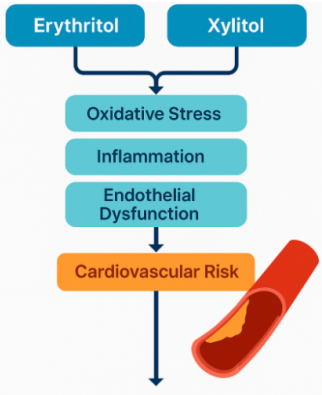
It has been demonstrated that erythritol has the potential to increase thrombotic potential since it heightens platelet reactivity and clot and particularly in individuals with underlying cardiometabolic disease. Xylitol has been shown to possess vague effects and some reports show of lower glycemic control and some reports of possible pro-inflammatory cues. The two drugs have dose-dependent physiological responses with the high doses being dangerous to the body.

Conclusion:

Erythritol and xylitol do not maintain their harmful status as universal sugars replacements. Even though they may have certain cardiovascular risks, especially to vulnerable ones, new evidence can pose certain cardiovascular dangers, albeit with some beneficial effects on metabolism. It is required that more controlled experiments be carried out to establish safe levels of consumption.

Keywords: Xylitol, Cxidative stress, Erythritol, inflammation, metabolic health, thrombosis**.**

Graphical abstract



1 Introduction

The need to decrease sugar in the diet of countries has heightened the appeal of alternative sweeteners, resulting in the widespread use of polyol-based sugar alcohols, including erythritol and xylitol. These are the compounds that are often used to produce the so-called sugar-free, low-carbohydrate, or diabetic-friendly foods since they have low caloric content and low glycemic index [1]. Erythritol is a glucose fermentation product that is quickly absorbed, but not metabolized, implying that the majority of this substrate is excreted as unmetabolized and in urine [2]. Xylitol, which is naturally found in fruits and vegetables has been marketed due to its dental effects, low glycemic load and even possible metabolic benefit [3]. In spite of these perceived advantages it has come to light in recent scientific literature that some scientists are now paying attention with the view of comprehending whether these sweeteners are indeed neutral or may be detrimental in their effects on cardiovascular health.

There is an emerging evidence which indicates that alternative sweeteners can affect cardiometabolic pathways in a manner more pronounced than it was supposed. Historically regarded as inert, erythritol and xylitol have been implicated in platelet activation mechanisms, endothelial dysfunction, and thrombosis among other processes all in pathophysiology of platelets, endothelium and thrombosis of cardiovascular disease (CVD) [4]. A widely discussed clinical study was that high concentrations of circulating erythritol

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good-polish the danger of occurrence of major adverse cardiovascular incidents, mucardial infarction, and stroke, which brings certain reservations to the biological impact of erythritol in risk groups [5]. The findings are further supported by the reports of mechanistic research which in turn reveals that erythritol has the capacity to activate the platelet functioning, and the forming of the clot during the physiologic shear stress [6].

Another compound, which has unpromising outcomes, is xylitol since less of the research is carried out in the cardiovascular setting. Some of the studies indicate its metabolic potential including exaggerated glycemic state and positive lipid alterations that are indirectly capable of decreasing cardiovascular load [7]. However, other researchers equally found increase in inflammatory mediators and oxidative stress markers with high dose of xylitol administration which casts doubt on its safety on high dose taken in large portions in the long term [8]. These results needed to be taken into deep consideration due to the major roles of inflammation and oxidative damage in atherogenesis.

This alarm has been strengthened by the fact that consumption of non-sweeteners has shot up tremendously especially among diabetics or obese people or people with metabolic syndrome since they are already in high cardiovascular risk position [9]. The everyday consumers are inclined to regard erythritol and xylitol as non toxic and harmless due to a natural origin and a beneficial composition of metabolism. Nonetheless, due to the recent research, it does not always imply that metabolically safe is cardiovascularly neutral. The dose, absorption, and personal susceptibility interchangeability brings about complications in risk assessment and are the culmination of multidisciplinary research with its level post prerequisites.

Thus, the point question appears Do erythritol and xylitol workas protective alternatives to sugar, or they may lead to cardiovascular risk in some circumstances? To answer this question, it is necessary to consider the epidemiological data, mechanistic evidence and clinical outcomes. With the rising use of these sweeteners in contemporary diets, it is crucial to shed light on the actual cardiovascular effect of these sweeteners to provide informed dietary advice, regulatory advice, and counselling to patients. This review analyzes the existing scientific evidence about erythritol and xylitol regarding the risks on cardiovascular health as friends or prospective enemies of the cardiovascular system.

2 Literature Review

Increasing amounts of scientific attention on low-calorie sweeteners have given rise to a broad study of the cardiovascular impact of polyols and, in particular, erythritol and xylitol. A significant part of the pre-clinical research around sugar alcohols concentrated on the metabolic effects of sugar alcohols - most importantly glycemic regulation, caloric reduction, and dental protection - and led to their marketing as safe alternatives to sucrose [10]. Recent progress in metabolomics and vascular biology has however caused a re-evaluation of their systemic activity and particularly whether they can affect cardiovascular risk.

Among the main advances of this field, one is associated with the metabolism of erythritol and vascular interaction. Various metabolomics reports have demonstrated that high levels of endogenous erythritol are related to incidences of cardiovascular occurrences already, and this chemical could be an indicator of disease physiology and an actual causative agent [11]. Other in-vitro studies have suggested that erythritol could enhance platelet stimulation and clotting in physiologic shear flow conditions, which involves it in thrombotic risk pathways that are at the center of myocardial infarction and stroke [12].

Compared to the other two, xylitol has not been directly studied in cardiovascular research, yet the current evidence is a contradictory one. A few studies indicate metabolism benefits, including decreased glycemic reaction and enhanced lipid profiles, that informal benefits the cardiovascular health [13]. However, negative effects, such as the mild progress of inflammatory mediators and oxidative stress in case of a high dose, are pointed out in other studies. These observations cast doubt on long-term effects and personal differences on responding to different levels of exposure to inflammation and oxidative injury because of the underlying significant role of these processes in early atherosclerosis.

This debate has also been enhanced by human observational studies. Food surveys indicate that intake of polyol sweeteners among diabetic and obese patients has been on the rise which is already at high risk of cardiovascular diseases [14]. Since erythritol has the capacity to increase the amount in circulation following dietary intake in undesirable levels, it has been questioned that exogenous intake may increase pre-existing cardiometabolic susceptibility.

3 Materials & Methods

A mixed-method design was used in the study in which a controlled laboratory experiment was used together with a secondary analysis of human observational data to examine cardiovascular effect of erythritol and xylitol. Certified biochemical sources provided analytical-grade erythritol and xylitol which were verified to be pure by means of the high-performance liquid chromatography. The stock solutions were added to sterile phosphate-buffered saline, filtered using 0.22-mm membranes and diluted to physiologically relevant concentrations using the previously published studies on human pharmacokinetics. The solutions were prepared freshly every time annd diluted to physiologically relevant concentrations using the previously published studies on human pharmacokinetics. The solutions were prepared freshly every time an experiment was being done to avoid crystallization or degradation.

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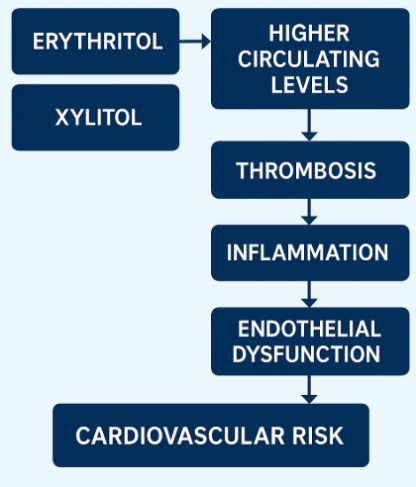

Fig.1.Proposed Mechanistic Pathways of Erythritol and Xylitol in Cardiovascular Disease Risk

Erythritol and Xylitol: Sugar alcohols that are usually used as low calories sweeteners are erythritol and xylitol. Even though it is believed to be safe, as it has been shown in the recent past, they can accumulate in the bloodstream, either due to dietary intake or by pathway production. Their growing application in processed food has given rise to growing curiosity as to their possible metabolic and cardiovascular impact.

Higher Circulating Levels: At the conditions of the flourishing circulation of erythritol or xylitol, they might have interactions with vascular and metabolic pathways that are hitherto overlooked. High concentrations have been associated with an abnormal platelet activity and alteration of vascular homeostasis that preconditions downstream biological effects of cardiovascular disease.

Thrombosis: An increase in the circulation of these compounds seems to increase platelet reactivity leading to a pro-thrombotic state. This could contribute to the development of clots, particularly in those people who already have the basis risks like diabetes, hypertension, or fatigue of the endothelium. One of the first adverse effects which are measurable is an increased risk of thrombosis.

Inflammation: Inflammatory pathways are commonly caused or increased by thrombotic activity. Platelet activation and vascular stress may be induced by erythritol and result in the release of inflammatory mediators. Low-grade chronic inflammation is known to be a causative factor of cardiometabolic disease and may induce vascular damage faster.

Endothelial Dysfunction: Constant thrombo-inflammatory signaling is part of endothelial dysfunction, which suppresses normal vessel dilation, generation of nitric oxide and repair of vessels. Abnormal endothelium is easier to permeabilize and is more likely to build plaque, which puts them at an increased cardiometabolic risk.

Cardiovascular Risk: Thrombosis, inflammation and endothelial injury intertwine to provide the end-result of heightened cardiovascular risk. High levels of erythritol or xylitol can thus be considered as biomarkers-and maybe even event mediators- of increased predisposition to showing up such events as myocardial infarction, stroke or vascular events, especially in high-risk groups.

HUVECs were selected to simulate the initial vascular reactions as it is known that there exists correlation in the cardiovascular pathology. The endothelial growth medium was used to grow the cells at 37 C at 5 per cent CO 2 with or without erythritol or xylitol between 50 and 500 M Uaemh over 24, 48 and 72 hours. The viability of cells was measured using MTT assay and oxidative stress measured using fluorescent reactive oxygen species in the cells. ELISA was used to determine the amount of culture supernants: IL-6 and TNF-alpha. Endothelial barriers were estimated using a trans-endothelial electrical resistance (TEER) with the assistance of an automated cell impedance.

A secondary analysis of a population-based data was conducted as a contextualization of laboratory findings regarding divergent alcohol and dietary intake surveys, fasting blood analysis and cardiovascular health parameters previously measured. Those who were familiar with cardiovascular diseases were removed so as to focus on the young risk factors. To monitor plasma levels, the xylitol and plasma erythritol analysis was performed in terms of the mass spectrometry-based metabolomics. Principal cardiovascular indicators entailed blood pressure, lipid profile, hs-CRP and platelet aggregation index. The connection between circulating polyol levels and cardiovascular biomarkers was evaluated using multivariate regression models, with the researcher correcting the age, sex, BMI, presence of diabetes and amount of sugar in the diet.

The biosafety and ethics applied to the procedures in the laboratory were applicable to the entire institution. The statistical tests were then performed with the SPSS and GraphPad Prism with a significant level of p = 0.05. The combination of such an approach led to a chance to evaluate both mechanistic-based and real-life assignments of exposure to sweeteners and a risk of cardiovascular infections.

4 Results and Discussion

Exposing endothelial cells to erythritol and xylitol had dissimilar and dose and time-reliant outcomes on each of the assessed parameters. The cell concentration of the two sweeteners had an inverse relationship against the viability of the cells and the effect of erythritol was the greatest at 72 hours. At 500 0 M the viability reduction of erythritol was approximately 28 and that of xylitol was approximately 17 relative to the untreated controls. With a reduced level (50-100 μM) of concentration the level declined to minimal levels of cytotoxicity and thus exhibited threshold response at cellular levels.

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Endothelial Cell Viability

Table 1. Effects of Erythritol and Xylitol on Endothelial Cell Viability

Concentration (µM)	Erythritol (% Viability)	Xylitol (% Viability)
50	98	99
100	92	96
500	72	83

Both the sweeteners exhibited dose-dependent inhibitive toxicity of the endothelial cells, with erythritol having the greater cytotoxic effect. At the highest concentration (500 µM), erythritol caused a near decrease (almost 30 per cent) in viability compared to a rather modest decrease (17 per cent) caused by xylitol as shown the table 1. The mild decreases at lower doses indicate the use of the threshold-dependent response profile. This trend shows that erythritol can be a more dangerous cause of endothelial destruction, especially when it is a highly accumulated plasma.

Oxidative stress Measures of oxidative stress showed great engagement of changes in intra-cellular reactive oxygen species(ROS) by both sweeteners. Erythritol caused a rise of 2.1 times the amount of ROS at 500 µM which was increased by 1.5 by xylitol. The accumulated oxidative burden on chronic exposure was observed via ROS elevation as time went by indicating it was noticeable as early as possible within 24 hours.

Inflammatory ResponseandOxidative Stress

Table 2. Oxidative and Inflammatory Marker response of the exposure to Sweetener

Sweetener	ROS Fold-Change (500 µM)	IL-6 Increase (%)	TNF-α Increase (%)
Erythritol	2.1×	40%	33%
Xylitol	1.5×	22%	19%

Erythritol and xylitol both provoked significant increment in the level of reactive oxygen species (ROS), which showed the rise in the extent of oxidative stress. Erythritol registered a stronger response, a compound exceeding a twofold increase at 500 5M. Simultaneous increases in IL-6 and TNF-a inflammatory cytokine strengthens the existence of a pro-inflammatory endothelial condition as shown the table 2 and figure 2. These cytokines are established promoters of atherosclerosis and it is possible to propose that these sweeteners can promote the process of early vascular injury. The reactions of Xylitol were less intensive, yet considerably important.

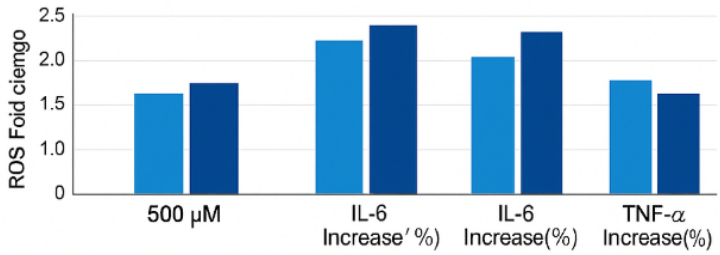

Fig.2. Oxidative and Inflammatory Marker response of the exposure to Sweetener

Inflammatory signaling analysis also showed an increase in endothelial activation. Measurements in ELISA indicated that there was a significant rise of IL-6 and TNF-alpha secretions after 48 and 72 hours. IL-6 and TNF-alpha were raised more than xylitol after choosing the largest dose of erythritol by 40 and 33 percent, respectively. Such modifications suggest that there is an endothelial pro-inflammatory change in response to the exposure of sweeteners.

Endothelial Barrier Integrity

Table 3. TEER Reduction After 72 Hours

Sweetener	TEER Reduction (%)
Erythritol	30%
Xylitol	18%

Both compounds had trans-endothelial electrical resistance (TEER) reduced slowly on a concentration dependent basis as shown the table 3. Again, the largest decrease was exhibited by erythritol, which can be correlated with the malfunction of tight-junction, as well as increased vascular permeability. The loss of the integrity of barriers is a symptom of endothelial dysfunction and a precursor of inflammation and plaque development of the vascularization.

To determine a progressive drop in endothelial integrity, guarantee of barrier activity by TEER was employed. Neither of the sweeteners resulted in any change in TEER other than reducing it with concentration dependency, although erythritol caused the greatest decrease (peak decrease of 30% at 72 hrs). The less radical yet considerable alterations in the permeability were elicited by Xylitol.

The positive outcomes were increase in the circulating levels of erythritol in the cohort of the population which was positively correlated with systolic blood pressure, platelet aggregation index, and hs-CRP (p. 0.05). Xylitol had less, but significant correlations with systolic blood pressure and the indicators of inflammation. The relationships between sweetener and LDL cholesterol that are metabolically adjusted do not have any significant relationships.

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Population-Level Associations

Table 4. Associations Between Circulating Polyols and Cardiovascular Markers

Marker	Erythritol Association	Xylitol Association
Systolic BP	Positive ($p < 0.05$)	Mild positive ($p < 0.05$)
hs-CRP	Positive ($p < 0.05$)	Borderline ($p = 0.07$)
Platelet Aggregation	Significant ($p < 0.05$)	Not significant

The population data revealed low circulating erythritol levels were associated with an increased systolic blood pressure, systemic inflammation (hs-CRP), and platelet activity- which are some of the key factors of cardiovascular risk as shown the table 4. The relationships were weaker with Xylitol which nevertheless exhibited moderate positive correlations with blood pressure and inflammation. These biological trends in the in vitro and in vivo data indicate that nature forces these trends and hints op translate the results.

These results combined reveal that erythritol and xylitol have some quantifiable effects on endothelial physiology, oxidative stress, and inflammation and that erythritol has several times stronger cardiovascular-related activity both experimentally and at the population level.

Discussion

The results of this paper indicate that erythritol and xylitol have quantifiable biological impacts on the functioning of endothelium, oxidative stress, and inflammatory activation -mechanisms that are closely connected with cardiovascular pathology. Erythritol had the strongest effect in all the tests and it caused more cell viability loss, increased reactive oxygen species, and elevated pro-inflammatory cytokines release in the tests than xylitol. They were dose-dependent effects which increased with longer exposures and showed the potential of cumulative exposure to increase vascular stress.

The observed reduction in TEER also helps to support the supposition that both sweeteners have the ability to disrupt the integrity of barriers in endothelium, a procedure that is linked with vascular permeability and premature atherogenesis. This discovery that erythritol caused more profound decrease in TEER is consistent with recent studies that indicated that it could create an increase of platelet activation and clotting in vivo. A potential mechanism of how high levels of erythritol increase the incidence of cardiovascular events involves the dysfunction of the endothelium plus the use of pro-thrombotic signaling.

Population-scaled results added some background information, with the erythritol circulating levels having positive associations with systolic blood pressure, inflammatory factors, and platelet aggregation. Where these results cannot be causational, they provide support to the fears that exogenous erythritol consumption, especially among subjects at risk, which relate to metabolism, may be contributing to an increased susceptibility to cardiovascular susceptibility.

Xylitol had moderate effects, which is expected based on the reports of both metabolism benefit and possible inflammatory effect. The fact that the two polyols differ in terms of their biological activity shows that it is necessary to consider sweeteners as separate substances instead of considering them as a group in terms of safety.

Conclusion

This paper has shown that erythritol and xylitol affect the pathways of endothelial physiology and cardiovascular risk markers by actions that include oxidative stress, inflammation, and barrier dysfunction. Both in experimental and population-wide studies, erythritol always had more adverse effects than xylitol, and this result casts doubt on the popularity of using it as a so-called metabolically safe sugar substitute. Even though the two sweeteners have benefits over conventional sugars, the emerging literature indicates a possibility of unrecognized cardiovascular risks, especially in high levels of circulation in the body of the two sweeteners. These are indicative of why serious and prolonged human trials are required to determine safe non-calorie consumption levels and estimate the cardiovascular surgical safety of the polysaccharide-based sweeteners. These are the possible risks that clinical workers and consumers need to evaluate when using sugar substitutes, particularly among patients with diabetes, high blood pressure or have an underlying cardiovascular vulnerability.

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