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Effects of Erythritol on Endothelial Function in Patients with Type 2 Diabetes Mellitus – A Pilot Study

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Endothelial dysfunction and arterial stiffness contribute to the pathogenesis of cardiovascular disease in diabetes mellitus [1]. Sugar substitutes reduce carbohydrate intake and may have utility in the dietary management of diabetes and obesity. Erythritol is a commonly-used polyol sweetener. In experimental models, erythritol reduces oxidative stress and reverses endothelial dysfunction [2,3]. We hypothesized that erythritol would have comparable favorable effects in diabetic patients.

Methods

Subjects

We enrolled patients with type 2 diabetes mellitus (fasting glucose ≥ 126 mg/dL or treatment with oral hypoglycemic drugs). We excluded patients receiving daily insulin. The study had Institutional Review Board approval. Participants provided informed consent. The study was registered at clinicaltrials.gov (NCT01609088).

Design

The study was an open-label pilot. The intervention was packets of powder containing 12 g of erythritol and orange flavoring dissolved in 8 ounces of water. Testing was performed at baseline and after four weeks of erythritol 12 g three times daily (36g/day). We also assessed acute and acute-on-chronic effects before and two hours after consumption of erythritol 24 g at the baseline and follow-up visits.

Vascular Function

To measure endothelium-dependent, brachial artery flow-mediated dilation, two-dimensional images and Doppler flow signals were recorded at baseline and after five

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minutes of upper arm cuff occlusion. Changes in arterial diameter and flow velocity were determined using customized image analysis software (Medical Imaging Applications, Inc. and ImageJ, respectively). Endothelial function in small arteries in the fingertip was assessed using peripheral arterial tonometry (EndoPAT, Itamar Medical, Inc.). Aortic stiffness was measured as carotid-femoral pulse wave velocity and central pulse pressure (SphygmoCor, Atcor Medical, Inc.).

Biochemical Measurements

Fasting glucose and insulin levels were measured in the Boston Medical Center Chemistry Laboratory. C-reactive protein was measured by a high-sensitivity nephelometric method. Urine 8-epi-PGF2 α levels were measured by enzyme-linked immunoassay (Cayman, Inc.) and corrected for urinary creatinine.

Statistical Analysis

We pre-specified separate analyses of the acute, chronic, and acute-on-chronic effects of erythritol on vascular function using the paired t-test (SPSS Version 19, IBM, Inc.). Data are expressed as mean $\pm$ standard deviation. $P < 0.05$ was statistically significant.

Results

Subjects

Twenty-four subjects completed the study (age 56 ± 5 years, 54% female, 63% black, body mass index 30.3 ± 3.4 kg/m²). Compliance with the study protocol was $90 \pm 12\%$ based on count of returned beverage packets. There were no adverse effects.

Vascular Function

As shown in the Table, acute consumption of 24 g of erythritol improved fingertip endothelial function measured by EndoPAT ($P = 0.005$). There were no acute changes in the other measures of vascular function.

Chronic erythritol consumption reduced arterial stiffness as measured by central pulse pressure ($P = 0.02$). There was a strong trend for reduced carotid femoral pulse wave velocity ($P = 0.06$). Fingertip endothelial function after acute-on-chronic erythritol consumption was higher than baseline (0.84 ± 0.34 vs. 0.52 ± 0.48 , $P = 0.02$, $P = 0.02$) suggesting a sustained improvement with chronic treatment. There were no other changes in vascular function.

In a post hoc analysis of subjects with systolic blood pressure above the median (>130 mmHg), chronic treatment lowered central pulse pressure ($P = 0.004$) and systolic blood pressure ($P = 0.01$). This antihypertensive effect will require confirmation in a prospective study.

Biochemical Markers

As shown in the Table, erythritol had no effects on fasting glucose or insulin. There were no effects on inflammation as measured by C-reactive protein or oxidative stress as measured by urinary PGF2 α .

Discussion

Our study provides preliminary information about the effects of erythritol on vascular function that may be useful for designing a randomized study. Erythritol produced acute and chronic improvements in endothelium-dependent dilation in small arteries in the fingertip. Chronic erythritol also improved central aortic stiffness.

In a study using diabetic rats, erythritol treatment for 21 days improved endothelial function and reduced oxidative stress [2]. In vitro studies suggest that erythritol reduces stress-induced endothelial apoptosis and alters the transcription of genes relevant to mitochondrial function, antioxidant protection, and cell signaling [3]. The present study provides novel information about the relevance of that experimental work to humans.

We observed that erythritol improved the EndoPAT response. EndoPAT is emerging as a clinically relevant method for measuring small vessel endothelial function [4]. The response depends on nitric oxide and correlates inversely with risk factors, particularly diabetes mellitus. It is notable that there was no change in flow-mediated dilation of the conduit brachial artery. Our results suggest that acute erythritol consumption might have a preferential effect on endothelial function in smaller arteries in diabetic patients.

Chronic erythritol lowered central pulse pressure and tended to lower carotid femoral pulse wave velocity. These findings suggest reduced stiffness of the central aorta, which depends on dynamic factors, such as smooth muscle tone, and on structural factors such as the degree of fibrosis and collagen content of the aortic wall. Interestingly, a post hoc analysis of patients with higher blood pressure suggested that erythritol might have an anti-hypertensive effect. Thus, erythritol might have favorable effects on other aspects of vascular biology, above and beyond its effects on the vascular endothelium.

In contrast to prior animal studies [2,3], there were no effects of erythritol on markers of oxidative stress and inflammation. These findings might reflect the modest sample size, short duration of treatment, lower relative dose of erythritol, and a lack of correlation between these systemic measures and local effects in the vascular wall.

The beneficial effects of erythritol may be clinically relevant if confirmed in a controlled study. Endothelial dysfunction contributes to the pathogenesis of cardiovascular disease in diabetes mellitus and predicts cardiovascular events [4]. Pharmacological, dietary, and lifestyle interventions that improve endothelial function have been shown to reduce cardiovascular risk [4]. Central aortic stiffness has also been shown to predict cardiovascular events [5].

In conclusion, results from this pilot study suggest that erythritol improves endothelial function and reduces central aortic stiffness. The study is limited by the lack of a control group, modest sample size, and concerns about multiple testing. Validation of these findings will require a randomized, placebo-controlled study. Nevertheless, the study supports the novel concept that erythritol might be a preferred non-nutritive sweetener for the dietary management of diabetes mellitus.

Acknowledgments

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Table
Effects of Erythritol on Vascular Function in Patients with Type 2 Diabetes Mellitus

Variable, n	Visit 1		Visit 2		P values	
	Baseline A	2 hours B	Baseline C	2 hours D	(B vs A) acute	(C vs A) chronic (D vs C) acute-on-chronic
Time point and comparison						
lnPAT (au) ratio, 20	0.52±0.48	0.87±0.29	0.72±0.33	0.84±0.34*	0.005	0.19
FMD (%), 23	7.5±3.7	7.9±4.6	6.7±4.4	7.5±4.3	0.48	0.25
Brachial diameter (mm), 23	4.26±0.91	4.25±0.90	4.31±0.92	4.27±0.89	0.75	0.09
Hyperemia flow (cm/s), 22	123±23	120±20	116±17	118±24	0.63	0.13
Central PP (mmHg), 23	47±13	47±17	41±9	46±15	0.91	0.02
CF- PWV (m/s), 22	9.1±1.4	9.0±1.3	8.6±1.6	9.1±1.4	0.94	0.06
Systolic BP (mmHg), 24	131±16	132±17	128±11	132±13	0.76	0.31
Diastolic BP (mmHg), 24	76±6	78±6	75±8	77±6	0.07	0.57
Glucose (mg/dl), 24	158±57	150±56	170±76	157±68	0.17	0.14
Insulin (µIU/ml), 24	13±7	14±7	12±7	14±10	0.54	0.65
HbA1C (%), 23	7.6±2.2	-	7.9±1.8	-	-	0.28
CRP (mg/L), 24	3.5±4.5	-	3.0±2.5	-	-	0.74
Urinary PGF2α (ng/mg creatinine), 24	0.88±0.54	-	1.00±0.55	-	-	0.30
Subgroup Analysis SBP > 130 mmHg						
Central PP (mmHg), 12	56±12	-	45±7	-	-	0.004
Systolic BP (mmHg), 12	144±12	-	133±9	-	-	0.01

Data are mean ± standard deviation.

* P=0.02 for the comparison with baseline (D vs. A); lnPAT ratio = cuff-induced dilation of fingertip arteries (measured using the EndoPAT device); FMD = brachial artery flow-mediated dilation; Central PP = central pulse pressure;

CF-PWV = carotid femoral pulse wave velocity; BP = blood pressure; HbA1C = hemoglobin A1C; CRP = C-reactive protein; PGF2α = prostaglandin F2α