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The Effect of A New Mixture of Sugar and Sugar-Alcohol (Lacritose) on Blood Glucose and Lipids and the Possible Adverse Reactions in Patients with Type 2 Diabetes: A Triple-Blind Randomized Clinical Trial

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ABSTRACT

Background: A new sweetener with the commercial name of Lacritose has been recently produced, which is a combination of four simple sugars (lactose, fructose, sucrose, erythritol), with specific ingredients and percentages. This study aimed to assess glycemic response and short term gastrointestinal reactions in type 2 diabetic patients. **Methods:** In this triple-blind randomized clinical trial, 30 diabetic patients referred to Yazd Diabetes Research Center in 2018 were included. After collecting the primary data, they were assigned into three groups, including sucrose consumers as the control group, sucrose-lactose, and lacritose as the groups of consumers group. They were followed for two weeks, and fasting blood glucose (FBG), 2-hour postprandial test (2HPP), fructose amine, SGOT, SGPT, urea, creatinine, and insulin resistance index (HOMA-IR) were assessed. **Results:** In lacritose consumers, significant reductions were seen in FBG and 2HPP ($P < 0.001$ and $P = 0.05$, respectively), although changes among the groups were not significant. In sucrose-lacritose consumers, FBG and cholesterol levels decreased ($P = 0.04$ and $P = 0.03$, respectively). In sucrose consumers, no reduction was seen. HOMA-IR did not significantly decrease, but intergroup changes were obvious. **Conclusion:** The lacritose effects on FBG and 2HPP were significantly evident, but the other metabolic indices did not show any significant change.

Keywords: *Diabetes; Lactose; Sugars; Sweeteners; Blood glucose control*

Introduction

Diabetes mellitus is the most common chronic metabolic disease characterized by blood glucose evaluation; commonly divided into two types of insulin-dependent (type 1 diabetes mellitus, T1DM) and non-insulin-dependent (type 2 diabetes mellitus, T2DM). T2DM is far more prevalent than the others. The overall prevalence of diabetes has dramatically increased over the past two decades, and it was estimated to be increased to more than 552 million by 2030 globally. The prevalence of diabetes is estimated at more than 32.8 million in the Middle East and North Africa

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by 2011, and it will probably reach more than 60 million by 2030 (Whiting *et al.*, 2011). In Iran, the prevalence of diabetes has been reported at 4.6 million in 2011, which is expected to be 8.3 million in 2030 (Hasan *et al.*, 2020, Whiting *et al.*, 2011, Zabetian *et al.*, 2013). Short-term and long-term complications of diabetes include increased risk of myocardial and cerebrovascular diseases, renal failure, retinopathies, and organs amputation (Zheng *et al.*, 2018).

Nowadays, sweeteners are commonly used as food additives. As a natural sweetener, sucrose causes some health problems, such as blood pressure, heart diseases, tooth decay, obesity, increasing blood glucose, and insulin levels (Bruun *et al.*, 2015, Fowler, 2016, Nourmohammadi *et al.*, 2011). In addition to sweetening usage, poly-alcohols low-calorie ketosis like sorbitol, mannitol, and erythritol have blood glucose reduction and anti-oxidative ability. Erythritol reduces blood glucose by reducing glucose intake of the intestine, increasing muscle glucose uptake, and strengthening glucose metabolizing enzymes (Chukwuma *et al.*, 2018, De Cock, 2018, Yokozawa *et al.*, 2002).

A new sweetener with the commercial name of lacritose is a combination of four simple sugars (lactose, fructose, sucrose, and erythritol), prepared with specific ingredients and percentages. This natural sweetener contains fewer calories and also has an appropriate taste for diabetic patients (Mohsenpour *et al.*, 2019).

However, the glycemic response of diabetic patients to this sweetener is not clear yet. Since this is made up of four natural sugars; its glycemic response and probable long-term gastrointestinal complications are discussed. The present study investigated the effect of this sweetener on blood glucose level and possible reactions and difficulties in people with T2DM.

Materials and Methods

Study design and participants: In the current randomized clinical trial, 52 types 2 diabetic patients referred to Yazd Diabetes Research Center were randomly assessed for eligibility. The sample size was calculated by a randomized blocking method. Considering type 1 error 0.05, effect size 0.55, and the power of 80%. The estimated sample size was 10 participants in each group. Also, 15 % was added for the attrition rate. The final sample size was 30 participants in each group.

Then 30 patients were qualified to participate in the study (after being aware of the process and completing the consent form). They were divided into three groups were randomly included in two intervention groups and a control group. Participant groups, researchers, and analyzers were not aware of the type of sugar consumption in the groups.

The inclusion criteria were: 1. Having type 2 diabetes, 2. The age group of 30-60, 3. Fasting blood glucose (FBG) of less than 200 mg/dl, 4. 7% ≤ HbA1C ≤ 9% 5. Being under the control of diet or edible medications, 6. The existence of sugar and sweeteners in the diet, 7. Having a medical file at Yazd Diabetes Research Center, and 8. Willingness to participate in the study.

The exclusion criteria were: 1. Being under the treatment of insulin, 2. Unable to follow up (living in another city), 3. The necessity of severe blood glucose control due to the complications of diabetes, 4. Significant changes in their blood glucose and blood pressure level over the past month, 5. Considerable change in their blood lipids profile over the past month, 6. A remarkable change in their caloric volume intake and their activity, 7. History of lactic deficiency, 8. Pregnancy and lactation, 9. Patients with severe infection or endocrine disorders, 10. Patients with hepatic and renal failure, 11. Patients with diabetes complications (nephropathy, neuropathy, retinopathy), 12. Patients with a body mass index (BMI) higher than 35 kg/m^2.

The research center paid all relevant test costs during the two weeks of the study. After blood sampling and measurements, the total number of participants (n=30) were divided into control, group 1, and group 2 based on randomized block design.

The control group was prescribed only sucrose (SG), up to the maximum permissible dose of

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sucrose every day base on an individual's BMI; a man with 70 kg body weight can consume 92 g/day of lacritose. Half of the maximum permissible dose of sucrose plus decreased volume equivalent of lacritose for lacritose group (LG), and lacritose as equivalent to the top dose level of sucrose for lacritose plus sucrose (LSG) after calculating the maximum permissible dose of sucrose were prescribed. The maximum permitted dose was considered for each participant by the estimated energy requirement equation considering the individual's BMI, age, and blood glucose level.

During two weeks, they were followed every three days and were asked about sweetener consuming details and possible complications. Then, after two weeks, when they referred to the center again, they were gone under the blood sampling tests, and the measurements, such as gastrointestinal complications were taken.

Measurements: Factors included baseline characteristics (age, gender, weight, and height), duration of diabetes, BMI, fasting blood glucose (FBG), fructose amine, hemoglobin A1C (HbA1C), 2-hour postprandial test (2HPP), serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), SGOT/SGPT ratio, urea, creatinine, insulin resistance index (HOMA-IR), and gastrointestinal complications.

HbA1C and fructose amine factors reflect the glycemic level in controlling the blood glucose level. 2HPP is a valid diagnostic test that measures the serum glucose level after 2 hours of the breakfast meal (Beck *et al.*, 2011). Also, SGOT, SGPT, and SGOT/SGPT ratio are hepatic diagnostic tests used to assay the hepatic effects (Baygi *et al.*, 2017, Lee and Yang, 2013).

Ethical considerations: This research was presented to the ethics committee of Shahid Sadoughi University of Medical Sciences and approved by the internal medicine department. The ethics committee approved the study with the number IR.SSU.REC.1396.102 on August 15, 2017. The patients were informed about the objective and nature of the study, and each participant provided written consent before the study begins. The trial was registered at the Iranian registry of clinical trials (www.irct.ir) with ID code IRCT2017102418858N7.

Safety of lacritose: The organoleptic and microbial tests of lacritose have been performed by Laboratory of Food and Drug Administration of Yazd province and Pasargad laboratory in Tehran province. Its low-calorie content has already been approved by Pasargad laboratory, Yazd, Iran. Each 100 g of lacritose consisted of 27.4 g of lactose, 12.9 g of fructose, 5.57 g of sucrose, and 54.13 g of erythritol. Its glycemic index was 19.72, and it had about 1.98 kcal/g energy (Mohsenpour *et al.*, 2019)

Data analysis: For numerical variables, descriptive statistics were presented as mean ± standard deviation (Mean ± SD). The data were analyzed by ANOVA test for parametric factors and Kruskal-Wallis test for non-parametric factors. To assess the results normality, Kolmogorov-Smirnov statistical test was used. A P-value of less than 0.05 was considered significant.

Results

Thirty patients participated in this study, including 17 (56.6%) male and 13 (43.4%) female with the mean age of 53.6 ± 5.57 (minimum and maximum ages were 38 and 60 years old).

Baseline of factors is presented in **Table 1**. All of the factors did not considerably vary among the groups ($P > 0.05$). Noteworthy, FBG significantly decreased in the two lacritose groups (LG; $P < 0.001$, LSG; $P = 0.04$), while increased in the SG (mean differences: 19.00 ± 55.60 mg/dl). TG and Micro-albuminuria had unimportant reduction in LG ($P = 0.36$ and $P = 0.16$,) and LSG ($P = 0.65$ and $P = 0.22$, respectively), although in SG increased (mean differences: 8.10 ± 58.32 mg/dl, 3.40 ± 8.18 mg/g creatinine; $P = 0.67$ and $P = 0.22$). LSG and SG showed an elevation in SGPT (mean differences: 1.80 ± 22.52 u/l, 3.60 ± 8.46 u/l), SGOT (mean differences: 3.30 ± 20.91 u/l, 1.00 ± 6.00 u/l), and HOMA-IR (mean differences: 0.59 ± 2.95, 1.78 ± 3.01) compared to LG; no significant difference was observed in the results of the groups ($P = 0.05$). Also, intergroup change in HOMA-IR

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was significant (P = 0.01, **Table 1**).

Creatinine decreased in the LSG, but it was not significant (mean differences: -0.04 ± 0.08, P = 0.16) and increased in the LG and SG (mean differences: 0.04 ± 0.13 mg/dl, 0.01 ± 0.13 mg/dl, P = 0.37 and P = 0.82). Total cholesterol significantly reduced in the LSG (mean differences: -36.40 ± 44.95 mg/dl, P = 0.03) compare to the increase in the LG and SG, but it was not significant (mean differences: 3.14 ± 16.26 mg/dl, 6.20 ± 22.61 mg/dl, P = 0.52 and P = 0.40). Level of 2HPP after consuming all sugar mixtures decreased in all groups; although the changes in the LG was significant (P = 0.04), intergroup variety was not significant (P = 0.49). Fructose amine reduction was different in the LSG and SG (mean differences: -0.20 ± 0.34 µmol/l, -0.18 ± 0.86 µmol/l; P = *0.83*, P= 0.52).

Table 1. Mean (±SD) of baseline characteristics of the participants

Variables	Lacritose (LG) (N = 10)	Lacritose and sucrose (LSG) (N = 10)	Sucrose (SG) (N = 10)	P-value
Female (%)	40	60	30	0.95[a]
Age (year)	52.87 ± 7.26	52.30 ± 4.80	55.70 ± 4.08	0.34[b]
Body mass index (kg/m^2)	29.95 ± 3.43	25.49 ± 3.50	27.95 ± 3.41	0.04[b]

[a]*:* Chi square *test;* [b]*:* ANOVA *test.*

Table 2. Comparison of mean (±SD) of varuables within and between the groues.

Variables	Period	Lacritose (LG) (N = 10)	Lacritose and sucrose (LSG) (N = 10)	Sucrose (SG) (N = 10)	P-value
Fasting blood glucose (mg/dl)	Before	158.90 ± 21.54	177.30 ± 46.83	156.50 ± 23.67	0.43[a]
	After	125.40 ± 30.04	149.50 ± 21.75	175.50 ± 48.64	0.06[b]
	P-value[c]	< 0.001	0.04	0.30	
	Changes	-33.50 ± 35.9	-27.80 ± 34.18	19.00 ± 55.60	0.01[a]
Triglycerides (mg/dl)	Before	173.60 ± 35.68	223.00 ± 99.8	167.90 ± 51.63	0.94[b]
	After	153.20 ± 74.53	155.20 ± 99.81	176.00 ± 65.56	0.23[b]
	P-value	0.36	0.65	0.67	
	Changes	-20.40 ± 68.09	-67.80 ± 122.95	8.10 ± 58.32	0.55[b]
Cholesterol (mg/dl)	Before	150.60 ± 32.78	187.20 ± 36.84	163.30 ± 32.03	0.20[a]
	After	154.00 ± 44.66	150.80 ± 39.65	169.50 ± 28.24	0.03[b]
	P-value	0.52	0.03	0.40	
	Changes	3.14 ± 16.26	-36.40 ± 44.95	6.20 ± 22.61	0.54[b]
Creatinine (mg/dl)	Before	0.78 ± 0.13	0.82 ± 0.15	0.83 ± 0.17	0.73[b]
	After	0.82 ± 0.13	0.78 ± 0.16	0.84 ± 0.10	0.11[b]
	P-value	0.37	0.16	0.82	
	Changes	0.04 ± 0.13	-0.04 ± 0.08	0.01 ± 0.13	0.37[b]
Micro-albuminuria (mg/g creatinine)	Before	24.20 ± 5.14	18.30 ± 6.99	16.50 ± 3.80	0.76[b]
	After	15.00 ± 0.01	15.90 ± 1.91	19.90 ± 11.25	0.23[b]
	P-value	0.16	0.35	0.22	
	Changes	-9.20 ± 19.14	-2.40 ± 7.69	3.40 ± 8.18	0.32[b]
Urea (mg/dl)	Before	26.90 ± 5.62	27.20 ± 8.20	31.30 ± 8.23	0.35[a]
	After	25.70 ± 6.48	26.10 ± 7.35	27.80 ± 4.68	0.47[a]
	P-value	0.38	0.11	0.15	
	Changes	-01.20 ± 4.15	-1.10 ± 1.69	-3.50 ± 7.12	0.73[a]
HOMA-IR	Before	5.47 ± 4.10	3.95 ± 1.75	3.76 ± 1.31	0.80[b]
	After	3.48 ± 2.52	4.54 ± 2.33	5.55 ± 2.83	0.01[b]
	P-value	0.80	0.95	0.79	
	Changes	-1.99 ± 3.80	0.59 ± 2.95	1.78 ± 3.01	0.06[b]

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2HPP (mg/dl)	Before	230.90 ± 47.97	235.20 ± 64.31	272.70 ± 61.02	0.41[a]
	After	181.00 ± 50.19	215.30 ± 69.80	264.80 ± 110.05	0.49[a]
	P-value	0.05	0.43	0.78	
	Changes	-49.90 ± 72.53	-20.10 ± 77.34	-7.90 ± 88.92	0.08[a]
Uric acid (mg/dl)	Before	5.02 ± 1.30	4.41 ± 1.86	4.17 ± 0.83	0.38[a]
	After	4.84 ± 1.26	4.48 ±1.44	4.17 ± 1.18	0.77[a]
	P-value	0.30	0.97	0.76	
	Changes	-0.18 ± 0.52	0.07 ± 1.14	-0.00 ± 0.56	0.52[a]
Fructose amine (µmol/l)	Before	6.60 ± 5.65	4.02 ± 2.29	2.62 ± 1.02	0.58[b]
	After	7.02 ± 6.53	3.81 ± 4.40	2.44 ± 1.26	0.02[b]
	P-value	0.12	0.83	0.52	
	Changes	0.43 ± 0.81	-0.20 ± 0.34	-0.18 ± 0.86	0.11[b]
SGOT (u/l)	Before	24.50 ± 5.21	18.20 ± 6.64	18.20 ± 6.22	0.19[b]
	After	24.10 ± 13.67	21.50 ± 21.88	19.1 ± 5.54	0.50[b]
	P-value	0.89	0.63	0.61	
	Changes	-0.40 ± 8.98	3.30 ± 20.91	1.00 ± 6.00	0.50[b]
SGPT (u/l)	Before	33.20 ± 15.33	25.20 ± 9.39	26.20 ± 13.04	0.28[b]
	After	30.10 ± 24.22	27.00 ± 20.65	29.80 ± 12.26	0.07[b]
	P-value	0.45	0.80	0.21	
	Changes	-3.10 ± 12.66	1.80 ± 22.52	3.60 ± 8.46	0.54[b]
SGOT/SGPT	Before	0.78 ± 0.25	0.73 ± 0.24	0.73 ± 0.14	0.81[a]
	After	0.92 ± 0.23	0.76 ± 0.28	0.69 ± 0.25	0.19[a]
	P-value	0.13	0.93	0.38	
	Changes	0.14 ± 0.27	-0.76 ± 0.28	-0.03 ± 0.18	0.14[a]

2HPP: 2-hour postprandial *test*; SGOT: serum glutamate oxaloacetate transaminase; SGPT: serum glutamate pyruvate transaminase; [a]: ANOVA *test*; [b]: Kruskal-Wallis *test*; [c:] Paired *t-test*.

Discussion

Lacritose as a sweetener is a combination of lactose, fructose, sucrose, and erythritol; erythritol is known as a chemical sweetener. This study assessed the effects of this new mixture sweetener compared to the same amount of sucrose. Serum glucose level significantly decreased in lacritose consumers; while no significant decrease was seen in sucrose consumers. Triglyceride level decreased in LG and LSG and increased in the SG, although none of them was significant. Also, 2HPP showed a significant reduction in LG, which was not seen in LSG and SG. In the other assessment indices, no significant change was considerable.

Ishikawa, M *et al.*, in 1996, investigated the effect of erythritol oral administration on diabetic patients in a trial study. The study suggested that erythritol consumption had no significant adverse effect on glycemic indices, such as serum glucose and HbA1C levels. The renal function indices, such as blood urea nitrogen, creatinine, and beta 2-microglobulin did not change significantly (Ishikawa *et al.*, 1996). In 2002, Yokozawa et al. documented the benefits of erythritol consumption to induced diabetic rats. They suggested that erythritol attenuates the lipid peroxidation and decreases glucose levels of serum, liver, and kidney. Also, the serum level of creatinine as a renal function test decreased (Yokozawa *et al.*, 2002).

Recent studies especially review types, revealed the benefits of erythritol consumption to either diabetic or healthy state. They suggested that erythritol consumption as a sweetener has not only adverse effects on glycemic indices, but also has beneficial effects and helps diabetic patients to control their serum glucose level. Its mechanism was related to gastric hormone secretion and intestinal glucose absorption (Ruiz-Ojeda *et al.*, 2019, Shin *et al.*, 2016, Wen *et al.*, 2018, Wölnerhanssen *et al.*, 2016, Wölnerhanssen *et al.*, 2020). A study done by Chukwuma et al. on rats suggested that other mechanisms probably increase muscle glucose uptake and metabolic enzyme activity of glucose. They noted that erythritol has benefits due to control hyperglycemia, particularly

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for diabetic type 2 (Chukwuma *et al.*, 2018).

Due to the unexpected liver test results, the effect of lacritose effect on liver tests is not exactly possible. Inconsistently the serum creatinine level in lacritose consumers increased; however, it was not significant. Osei *et al.*, in a 12-week study on 9 diabetes patients, reported that average amounts of fructose did not appear to be detrimental to the blood glucose control and the metabolism of lipids and lipoproteins of T2DM with obesity. However, a slight improvement in blood glucose control and alterations in Apo-protein composition may decrease the risk of coronary artery disease (Osei *et al.*, 1987, Wölnerhanssen *et al.*, 2020). In a recent study by Mohsenpour *et al*. lacritose in diabetic and non-diabetic patients led to a modest reduction in serum glucose level. In accordance with the present study, there was a significant decrease in cholesterol levels in the lacritose-sugar consumers. The effect of lactose on FBG, 2HPP, and insulin resistance index was also significantly evident, but other metabolic index did not show any significant change. In present study individual calculation lacritose amount in daily consumption was used, while calculation of Mohsenpour was generally 50 g dose daily (Mohsenpour *et al.*, 2019).

The limitations of the study included selecting the limited number of participants and the study duration time was 2 weeks, so it was not possible to assess the long term effects. The participants were selected from patients with prediabetes to reduce the effect of drugs and insulin type, and chronic diseases may be more informative.

Conclusion

Lacritose as a newly produced sweetener showed proper effects on serum glucose level, control, and hyperglycemic management states in type 2 diabetes. It showed no significant adverse effects on blood lipids and liver or kidney function tests were. Further studies are required to be conducted on more participants, with longer period, and factors of study to assess longtime effects, and on gastrointestinal macrobiotic behavior.

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Authors' contributions

Rahmanian M and Mozafari Z participated to study concept and design. Shukohifar M and Jam-Ashkezari S participated to analysis and interpretation of data. Chaleshi D participated to drafting of the manuscript. Rahmanian M and Chaleshi D participated to critical revision of the manuscript for important intellectual content. Shukohifar M participated to statistical analysis.

Conflict of interest

The authors declare that there is no conflict of interest. There were no financial or relationship between authors and people or organization that could affect the results.

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