Metabolic Effects of Replacing Sucrose by Isomaltulose in Subjects With Type 2 Diabetes

A randomized double-blind trial

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OBJECTIVE—To test the hypothesis that replacement of sucrose with isomaltulose in sweet foods and beverages improves metabolic control in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS—One hundred ten patients with type 2 diabetes were randomized to receive sweet foods containing either 50 g/day isomaltulose or sucrose for 12 weeks as part of their habitual diet under free-living conditions. HbA_{1c} at 12 weeks was the primary outcome parameter.

RESULTS—In the final analysis comprising 101 patients, isomaltulose did not significantly affect HbA_{1c} at 12 weeks (sucrose: 7.39 ± 0.78%; isomaltulose: 7.24 ± 0.76%; regression coefficient [b]: 0.02 [95% CI: −0.21 to 0.25], $P = 0.844$). Triglycerides at 12 weeks were significantly lower in the isomaltulose versus the sucrose group (b: 34.01 [6.59–61.44], $P = 0.016$). Other secondary parameters did not significantly differ between groups.

CONCLUSIONS—Isomaltulose did not influence glycemic control assessed as HbA_{1c} in type 2 diabetes under free-living conditions but was associated with lower triglyceride levels.

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In patients with type 2 diabetes, a low glycemic diet is recommended to reduce postprandial hyperglycemia and, thereby, improve glycemic control (1). Isomaltulose (Palatinose), a disaccharide composed of α-1,6–linked glucose and fructose, was recently introduced as an alternative sugar with delayed digestion and absorption (2) resulting in a low glycemic index (GI) of 32 (3).

The aim of this study was to examine whether replacing a daily intake of 50 g sucrose by isomaltulose in sweet foods and beverages over a period of 12 weeks would result in improved glycemic control assessed as HbA_{1c} and metabolic parameters in individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS

—The study followed a randomized, controlled, double-blind design with two parallel groups. One hundred ten patients with type 2 diabetes (age > 18 years, BMI 25–40 kg/m^2, HbA_{1c} 6.5–9.0) treated by diet alone or with oral antidiabetic agents were recruited through advertisements between March 2007 and December 2008 in two study centers (Munich and Wuerzburg, Germany) and randomly assigned to either isomaltulose ($n = 57$) or sucrose ($n = 53$) intervention. The study protocol was approved by the ethical committees of the Technical University of Munich and the University of Wuerzburg, Germany.

The participants received sweet foods and beverages (biscuits, toffees, milk drinks, soft drinks) containing either 50 g of isomaltulose or sucrose per day in a double-blinded fashion for a period of 12 weeks and were asked to maintain their habitual diet but to refrain from additional sweetened foods other than the test products.

At study entry, after 6 and 12 weeks, venous blood was taken in the morning after a 12-h overnight fast to determine clinical routine and metabolic parameters.

HbA_{1c}, fasting glucose, serum fructosamine, insulin, C-peptide, proinsulin, nonesterified fatty acids (NEFA), total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, and standard clinical parameters were analyzed by a certified laboratory. Homeostasis model assessment–insulin resistance (HOMA-IR) was calculated as previously described (4).

Commercial ELISA kits were used to analyze oxidized (ox)LDL (Mercodia, Uppsala, Sweden), leptin, and adiponectin (R&D Systems, Abingdon, U.K.).

The primary end point of the study was HbA_{1c} at week 12. With a sample size of 55 patients per group, the study had a power of 80% to show a statistically significant difference of at least 0.3% in HbA_{1c} at week 12 between the groups with a type I error level of 0.05 assuming a common standard deviation of 0.5.

RESULTS

—One hundred patients completed the study (isomaltulose, $n = 52$; sucrose, $n = 48$). Ten patients dropped out for various reasons but not because of side effects (Supplementary Fig. 1). One

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patient who dropped out after the week 6 visit was included in the analysis by use of a last-observation-carried-forward analysis. Baseline patient characteristics were comparable (Supplementary Table 1), with the exception of higher BMI at baseline in the patients receiving sucrose (32.3 ± 4.5 vs. 29.9 ± 4.2 kg/m^2, $P = 0.007$).

Over the course of the study, there was no significant change in HbA_{1c} within both groups (Table 1). Mean HbA_{1c} at 12 weeks was 7.39 ± 0.78% in the sucrose group and 7.24 ± 0.76% in the isomaltulose group, respectively, with no significant difference between the groups

Table 1—*HbA_{1c} and secondary target parameters over the course of the 12-week intervention period in the sucrose vs. isomaltulose group*

	Baseline	Week 6	Week 12	Adjusted mean difference [95% CI] at week 12*
HbA_{1c} (%)				
Sucrose	7.39 ± 0.66 (49)	7.36 ± 0.70 (49)†	7.39 ± 0.78 (49)	0.02 [−0.21 to 0.25]
Isomaltulose	7.20 ± 0.60 (51)	7.12 ± 0.65 (52)†	7.24 ± 0.76 (52)	
Fasting glucose (mg/dL)				
Sucrose	145 ± 26.2 (49)	144 ± 27.8 (49)	152 ± 29.9 (49)	5.68 [−4.88 to 16.24]
Isomaltulose	142 ± 29.2 (52)	147 ± 25.2 (52)	145 ± 29.6 (52)	
Insulin (mIU/L)				
Sucrose	13.0 [3.90; 79.0] (49)	14.0 [3.40; 98.0] (45)	14.0 [3.60; 71.0] (49)	1.75 [−1.30 to 4.80]
Isomaltulose	9.40 [2.80; 71.0] (51)	11.0 [2.90; 184] (51)	10.3 [2.70; 43.0] (52)	
HOMA-IR				
Sucrose	4.78 [1.11; 21.46] (49)	4.83 [1.41; 19.12] (45)	4.98 [1.39; 29.04] (49)	0.68 [−0.86 to 2.22]
Isomaltulose	3.27 [0.83; 31.91] (51)	4.00 [0.72; 73.60] (51)	3.49 [1.05; 22.82] (52)	
Fructosamine (μmol/L)				
Sucrose‡	275 ± 37.4 (49)	262 ± 39.3 (47)	269 ± 40.8 (49)	−8.44 [−22.54 to 5.66]
Isomaltulose	271 ± 33.1 (51)	268 ± 31.9 (51)	276 ± 41.9 (52)	
Proinsulin (pmol/L)				
Sucrose	7.40 [2.20; 90.0] (49)	7.40 [2.00; 61.0] (47)	6.90 [2.50; 67.0] (49)	0.56 [−1.87 to 3.00]
Isomaltulose‡	5.70 [0.50; 41.0] (51)	5.30 [0.70; 83.0] (51)	6.05 [0.73; 50.0] (52)	
C-peptide (nmol/L)				
Sucrose	1.10 [0.54; 2.80] (49)	1.10 [0.41; 3.30] (45)	1.30 [0.42; 2.60] (49)	0.08 [−0.05 to 0.20]
Isomaltulose‡	0.96 [0.38; 2.70] (51)	0.97 [0.53; 5.90] (51)	1.00 [0.58; 2.80] (52)	
Triglycerides (mg/dL)				
Sucrose‡	151 [79; 459] (49)	171 [53; 385] (49)	179 [76; 728] (49)	**34.01 [6.59–61.44]**
Isomaltulose	159 [44; 458] (52)	145 [57; 446] (52)	144 [63; 456] (52)	
Total cholesterol (mg/dL)				
Sucrose	193 ± 34.8 (49)	191 ± 38.7 (49)	197 ± 37.4 (49)	2.08 [−6.00 to 10.16]
Isomaltulose	197 ± 34.8 (52)	202 ± 36.1 (52)	198 ± 33.2 (52)	
LDL cholesterol (mg/dL)				
Sucrose	119 ± 31.3 (49)	118 ± 31.9 (49)	119 ± 33.3 (49)	−4.13 [−11.42 to 3.15]
Isomaltulose	120 ± 29.2 (52)	123 ± 34.9 (52)	123 ± 30.6 (52)	
HDL cholesterol (mg/dL)				
Sucrose	49.2 ± 9.88 (49)	48.4 ± 8.69 (49)	48.8 ± 9.99 (49)	0.36 [−2.73 to 3.45]
Isomaltulose	50.9 ± 14.0 (52)	52.4 ± 14.8 (52)	49.4 ± 15.1 (52)	
NEFA (mmol/L)				
Sucrose	0.65 [0.10; 1.30] (49)	0.52 [0.16; 1.10] (46)	0.62 [0.14; 1.40] (49)	0.03 [−0.05 to 0.10]
Isomaltulose	0.59 [0.13; 1.20] (51)	0.58 [0.17; 1.00] (51)	0.55 [0.13; 1.00] (52)	
oxLDL (U/L)				
Sucrose	74.8 ± 27.3 (49)	70.7 ± 21.3 (49)	69.7 ± 21.9 (48)	1.04 [−4.13 to 6.20]
Isomaltulose‡	72.1 ± 19.7 (52)	69.2 ± 18.1 (52)	66.7 ± 15.3 (51)	
Leptin (ng/mL)				
Sucrose	11.9 [2.0; 81.1] (48)	10.0 [2.0; 71.0] (49)	10.9 [2.1; 72.7] (48)	−1.44 [−4.75 to 1.88]
Isomaltulose	7.8 [1.1; 56.9] (52)	8.8 [1.2; 58.1] (52)	8.5 [1.2; 61.4] (51)	
Adiponectin (μg/mL)				
Sucrose	3.11 [0.77; 18.10] (47)	3.14 [0.76; 19.6] (48)	3.11 [0.94; 13.40] (47)	0.37 [−0.49 to 1.22]
Isomaltulose	3.58 [0.89; 21.50] (52)	3.62 [0.71; >17.4] (52)	3.15 [0.72; >15.2] (51)	

Data are presented as mean ± SD (*n*) for normally distributed variables or as median [min; max] (*n*) if the distribution was skewed. Individuals who dropped out from the study before the week 6 visit were excluded from the analysis ($n = 9$). Patients who dropped out thereafter ($n = 1$) were included by using a last-observation-carried-forward analysis. Significant differences at week 12 are in boldface. *Data are presented as the regression coefficient [b] along with the 95% CI from multiple linear regression analyses controlling for BMI and baseline levels. †Mean of HbA_{1c} measured at weeks 4 and 8. ‡Significant change over time, $P < 0.05$ (repeated-measures ANOVA for normally distributed variables; Friedman test for skewed variables).

(regression coefficient [b]: 0.02 [95% CI −0.21 to 0.25], $P = 0.844$) in the final analysis controlling for BMI and baseline levels. There were no significant differences between the groups for insulin, fasting glucose, fructosamine, proinsulin, C-peptide, and HOMA-IR (Table 1). Within the sucrose group, a significant linear increase in triglycerides was observed over the course of the study ($P = 0.023$), whereas in the isomaltulose group, there was a tendency toward reduced levels, resulting in a significant difference between the groups at week 12 (b: 34.01 [6.59–61.44], $P = 0.016$).

In addition, there were significant changes over time within the sucrose group for fructosamine ($P = 0.019$) and within the isomaltulose group for proinsulin ($P = 0.039$), C-peptide ($P = 0.038$), and oxLDL ($P = 0.013$). All other parameters remained unchanged.

CONCLUSIONS—Short-term studies have consistently shown a reduced glycemic and insulin response after isomaltulose compared with sucrose/glucose ingestion in healthy patients as well as in individuals with type 2 diabetes (5–8). Our study is the first to investigate the effects of a 12-week dietary intervention with 50 g/day isomaltulose compared with sucrose in sweet foods and beverages in patients with type 2 diabetes under free-living conditions. Both dietary interventions were well-tolerated by the participants, independent of the antidiabetic medication. HbA_{1c}, the primary outcome parameter, remained virtually unchanged in both groups after 12 weeks of intervention. Likewise, no profound effects on most other secondary metabolic parameters and cardiovascular risk factors were observed. However, triglyceride levels were significantly lower in the isomaltulose group, which is in accordance with findings from an animal study (9) and might indicate a potential metabolic benefit if sustained over the longer term.

Thus, the results of our study suggest that replacement of 50 g/day sucrose with isomaltulose is not enough to induce a pronounced and clinically relevant effect on HbA_{1c} in individuals with type 2 diabetes in addition to their standard antidiabetic treatment and under free-living conditions. This may be explained by the fact that isomaltulose and sucrose, respectively, constituted only approximately 10% of total caloric intake resulting in an approximate reduction of the overall GI by ~6 units according to a simple calculation (3), and it is obvious that this proportion within a mixed diet is too small to evoke distinct effects on metabolic control. This finding is in line with a recent 1-year trial in type 2 diabetic patients that shows that an only modest reduction of the dietary GI does not affect HbA_{1c} as a long-term marker for glycemic control (10), although meta-analyses have provided evidence for low GI diets as a useful strategy in the management of diabetes (11–13).

In conclusion, substitution of 50 g/day sucrose by isomaltulose in sweet food and beverages over 12 weeks did not significantly affect HbA_{1c} and most other metabolic and cardiovascular risk parameters, despite significantly lower triglyceride levels in the isomaltulose versus the sucrose group.

Although the principle of isomaltulose action is unquestionable, a more marked modification of the dietary GI may be required to achieve a clinically significant improvement in glycemic control in type 2 diabetic patients.

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S.B. and I.H. interpreted data and wrote the manuscript. I.H., S.T., A.G., U.A.-G., W.S., and H.H. conceived and designed the study. I.H. and U.A.-G. implemented the study. R.M., W.S., and H.H. supervised the study. P.W. performed statistical analysis. S.T., W.S., and H.H. were responsible for critical revision of the manuscript and its important intellectual content. H.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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