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ORIGINAL ARTICLE

Evaluation of glycemic and insulinemic responses of maltitol in Indian healthy volunteers

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Abstract There is a very high prevalence of diabetes in India today which is increasing on a North to South axis. In addition to lifestyle changes, Indian people may be more susceptible to insulin resistance. Observational studies suggest that the consumption of diets with a low glycemic impact is associated with a reduced risk of diabetes. Maltitol is a bulk sweetener belonging to the polyols family and exhibiting a low glycemic response (GR). Genetic background has already been mentioned as an influent factor in modulating the GR of various foods. So, assessing glucose homeostasis including glycemic and insulinemic responses (IR) after maltitol consumption in Indians may be helpful in gaining a better understanding of this result from a physiological standpoint. The objective of this clinical study was to evaluate the GR and IR of maltitol in healthy Indian volunteers. The protocol followed Food and Agriculture Organization (FAO) recommendations. After an overnight fast, GR and IR of maltitol and reference (glucose) were measured on 12 subjects (50 g dissolved in 150 ml of mineral water). Glucose tolerance was assessed both before and after testing, the subjects being randomly allocated either to the maltitol or the glucose groups. Both glucose and insulin plasma concentrations were assessed in venous blood. Mean blood glucose levels were significantly lower after the consumption of maltitol compared with glucose from time points 15 to 90 min. GR of maltitol was found to be 20.4±9.3 % of glucose GR. After maltitol consumption, the mean insulin blood levels were significantly lower from time points 15 to 120 min compared with the reference subjects. IR of maltitol was found to be 17.8±9.9 % of glucose IR. We confirmed that the maltitol GR in healthy Indians is low. Moreover, maltitol displays a very low insulinemic response which may be of interest for diabetics in India.

Keywords Maltitol · Polyol · Glycemic response (GR) · Insulinemic response (IR) · Diabetes

Abbreviations

FAO/WHO	Food and Agriculture Organization/ World Health Organization
GR	Glycemic response
iAUC	Incremental area under the curve
IR	Insulinemic response
NaF	Sodium fluoride
SD	Standard deviation
SEM	Standard error of the mean

Introduction

Diabetes is one of the most common non-communicable chronic diseases worldwide and continues to increase in numbers and significance as changing lifestyles lead to reduced physical activity and increased obesity. Estimated at the beginning of this century in India at 30 million cases, today, the International Diabetes Federation evaluates the total number of diabetic subjects at around 64 million (with more than 90 % of type 2 diabetes) and this is expected to rise further to 100 million by the year 2030 [1]. Furthermore, these estimates do not take into account the increase in associated risk factors such as obesity [2].

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The nationwide prevalence now tops 9 % and is as high as 20 % in the relatively prosperous southern cities [3]. In addition to lifestyle changes, it is reported in the literature that Asian populations including Indians can be more susceptible to insulin resistance and therefore to type 2 diabetes [4]. Although diagnostic tools have been developed that are easy to implement [5], the healthcare costs and depletion of productivity linked with diabetes threaten to undo recent economic development [6]. The Indian diabetes cost is estimated at 120 US dollars per capita representing up to 25 % of a family income [7]. Finding cheaper alternatives therefore for the management and prevention of diabetes is vital, and the reduction in sugar intake or its substitution holds out bright prospects. Indeed, it is hardly surprising that the rising sugar consumption is setting alarm bells ringing with the health professionals. This can be demonstrated by several studies which have shown a strong correlation between sugar consumption, obesity and diabetes incidence [8].

Taking cues from the rising incidence in diabetes, heart disease, obesity and dental caries, major food manufacturers have speeded up the production of healthier products or have repositioned the existing lines of sweetened snack foods towards healthier variants. However, formulating healthier yet appetizing reduced or no added sugar products is often a major challenge faced by food manufacturers and the acceptance continues to be fairly limited as the sugar containing foods still continue to enjoy huge popularity.

Maltitol is a sugar alcohol (polyol) used as a sugar substitute in the food industry which has the added benefit of reducing the glycemic index of a product. Maltitol is produced from maltose by catalytic hydrogenation and is also known as 4-O-α-glucopyranosyl-D-sorbitol. Maltitol is principally used as a sugar replacer in food products as it has the major advantage of providing a bulking effect compared with intense sweeteners. Maltitol and other polyols such as sorbitol are also used in oral care products (toothpastes) or in pharmaceuticals [9]. In addition to its technological and nutritional properties, maltitol also has similar organoleptic properties to glucose [10] and offers good digestive tolerance enabling extensive use in adults and in children in various dietary applications [11–13]. Maltitol has even demonstrated some prebiotic-like properties in rats or in humans [14, 15].

The glycemic response (GR) of a polyol is an essential element to be assessed in the context of glycemia management. Data is available in the maltitol literature [16], and ethnicity does not seem to play a role when addressing the GR within groups of United Kingdom inhabitants [17]. However, given the fact that insulin resistance has been described as highly prevalent in Indians and that they may be more susceptible to insulin resistance [4], and since no data is available on maltitol in Indians, it is therefore important to measure both the insulinemic and the glycemic responses in this population simultaneously.

In this study, we have evaluated the insulinemic response (IR) and the GR of maltitol in healthy Indian volunteers in accordance with the Food and Agriculture Organization (FAO) recommendations in order to assess the maltitol impact on glucose homeostasis in further low glycemic index food products.

Materials and methods

The present protocol with all the procedures was validated by the Independent Ethics Committee of Mumbai.

Subjects

Nineteen healthy subjects (16 males and 3 women) were recruited to take part in the present study. Initial screening examinations were held on two successive days. There were repeated screening examinations 1 week later, as some volunteers were rejected on the basis of the assessment of the biochemical parameters (fasting blood glucose, postprandial blood glucose, liver function test, renal function test and complete blood count). Inclusion criteria were as follows: age between 20 and 60 years, body mass index less than 30 kg/m^2, agreement to sign a consent form. Non-inclusion criteria were any chronic illness or any clinical condition, fasting blood glucose greater than 110 mg/dl, any major illness in the past 3 months, any medication consumption in the past week, subjects with systolic blood pressure less than 90 mm or higher than 140 mm of Hg, subjects having an unusual diet, subjects showing abnormal levels of creatinine, lipid profile, pregnant or lactating women. During the study, exclusion criteria were the unexpected occurrence of non-inclusion criteria during the observation period, intolerance due to products in test, non-compliance with the study procedures or restrictions. Subjects were given full details of the study protocol and the opportunity to ask questions before signing a written informed consent.

Study protocol

The protocol used to measure GR and IR was adapted from a previously published study [18] and was in line with the recommendations of the Food and Agriculture Organization (FAO/WHO). Consequently, GR and IR of maltitol were performed on more than 6 subjects offering a higher statistical power and precision. Subjects were asked to restrict their alcohol and vegetable intake on the day before the test. They were instructed not to eat or drink anything (other than water in moderation) 12 h before the test. Maltitol and reference (glucose) were tested (50 g dissolved in 150 ml of mineral

water) during the following four examinations with 7 to 10 days of wash-out between two examinations. On the first examination, all the subjects tested the reference in order to visualize if they were glucose intolerant. If not, they were included in the study. During examinations, 2 and 3 subjects were randomly allocated either to maltitol testing or to glucose testing. Examination 4 corresponded to the third and last glucose challenge. For each examination, after an overnight fast (about 12 h), volunteers were challenged with either reference glucose or maltitol. Venous blood samples were collected from the arm bend at time: −30 min and time: 0 min and then at 15, 30, 45, 60, 90, 120, 150, 180 min in NaF tubes.

Blood glucose and insulin measurements

Glucose was analysed by the hexokinase method on Dade RxL automated chemistry analyser (Dade Behring, Deerfield, USA), and insulin was analysed by chemiluminescent microparticle immunoassay on the Architect automated chemistry analyser (Abbott Diagnostics, Wavre, Belgium).

Calculation of GR and IR

The incremental area under the curve (iAUC) was calculated geometrically [17] ignoring the area beneath the baseline for each volunteer. The means ± standard deviation (SD) of the iAUCs (for blood glucose and blood insulin) were calculated [17]. For GR and IR of maltitol, the results were expressed as a percentage of the GR and IR, respectively, of the standard meal, *i.e.* glucose.

Statistical analyses

Statistical analyses were performed using SPSS version 10.0 statistical software. Continuous variables were summarized by treatment group using summary statistics (number of observations, mean, standard deviation, or median with range of minimum and maximum). Categorical values were summarized by treatment group using frequencies and percentages. The glucose and insulin responses within the same group of individuals (between the two products or between baseline values and those observed at different times of oral tests) were compared by repeated measures ANOVA followed by Fischer's post hoc least significant difference test. All values were reported based on two-sided significance, and all the statistical tests will be interpreted at 5 % level of significance.

Results

After considering the inclusion and non-inclusion criteria, 19 volunteers were included for the final study. A total of seven dropouts were observed due to the above-mentioned reasons. Twelve volunteers completed the study. The characteristics of the 19 subjects included in the study are given in Table 1. Twelve of them completed the protocol and its series of four examinations. In addition, both test products were well tolerated (data not shown).

Blood glucose and glycemic response calculation

Regarding glycemia at baseline (−30 min and 0 min), all volunteers were similar before challenge with either reference or maltitol (Fig. 1). Mean blood glucose levels measured after the consumption of maltitol were significantly lower than those measured after reference standard glucose consumption from time point 15 to 90 min ($p<0.05$; Fig. 1). At time point 120 min, there was no significant difference in mean blood glucose levels between reference standard glucose and maltitol.

At time points 150 and 180 min, the mean blood glucose levels measured for maltitol were significantly higher than the mean glucose levels measured for reference standard glucose. Two GR outliers appeared clearly and were removed by applying the formula mean±2SD. Two volunteers were outliers and hence not considered for final GR calculations. Glycemic response of maltitol was found to be 20.4±9.3 % of glucose GR (Table 2).

Blood insulin and insulinemic response calculation

Regarding mean blood insulin levels at baseline (−30 and 0 min), there was no significant difference after consumption between the reference standard glucose and maltitol (Fig. 2). There were statistically significant differences at time points 15, 30, 45, 60, 90, and 120 min when the insulin levels for maltitol were lower after consumption than the reference glucose ($p<0.05$; Fig. 2). There were no significant differences at

Table 1 Anthropometric characteristics of subjects who participate in the study

Parameters	No. of cases	19
Age (years)	Mean	25.53
	SD	06.55
Height (cm)	Mean	166.32
	SD	09.53
Weight (kg)	Mean	62.32
	SD	06.73
BMI (kg/m^2)	Mean	22.59
	SD	02.43
Sex (%)	Male	16 (84.2)
	Female	03 (15.8)

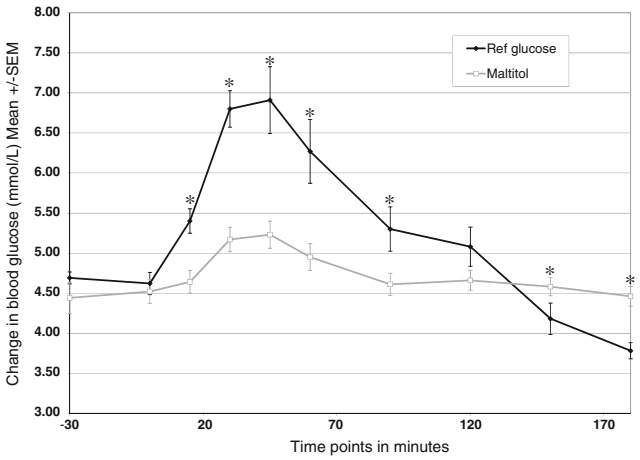

Fig. 1 Mean blood glucose levels from baseline to 180 min after product consumption. Results are mean±SEM, N=12 per group. The *continuous black curve* with *black squares* corresponds to the blood glucose levels of the volunteers after reference glucose consumption; the *continuous grey curve* with white circles corresponds to the blood glucose levels of the volunteers after maltitol consumption. The statistical significance ($p \leq 0.05$) is indicated by an *asterisk* (*) for each time point

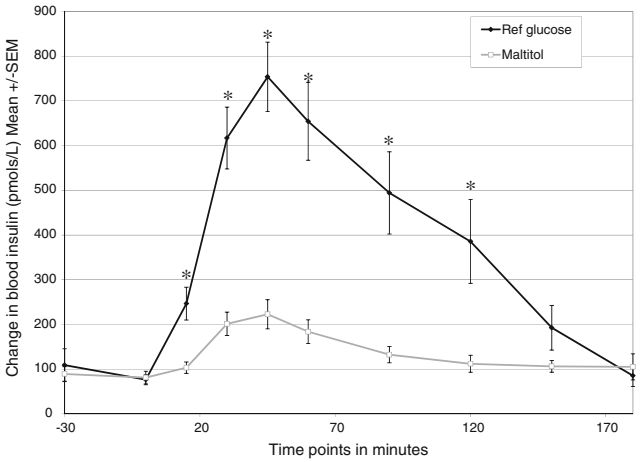

Fig. 2 Mean blood insulin levels from baseline to 180 min after product consumption. Results are mean±SEM, N=12 per group. The *continuous black curve* with *black squares* corresponds to the blood insulin levels of the volunteers after reference glucose consumption; the *continuous grey curve* with *white circles* corresponds to the blood insulin levels of the volunteers after maltitol consumption. The statistical significance ($p \leq 0.05$) is indicated by an *asterisk* (*) for each time point

time points 150 and 180 min (Fig. 2). One outlier was identified as his blood insulin levels were out of the statistical limits when applying the formula mean±2SD (data not shown). Hence, this volunteer was not considered for final insulinemic response calculations. Insulinemic response of maltitol was found to be 17.8±9.9 % of glucose IR (Table 3).

Discussion

To evaluate the glycemic index of a product, the FAO guidelines specify the consumption of 50 g of carbohydrate equivalent. This would reduce volunteer compliance to the study in the event of a tolerance issue. Indeed, it is widely stated in the literature that polyol tolerance depends upon the consumed polyol itself. Although maltitol has previously displayed good digestive tolerance [11–13], we decided to assess GR in the present study in order to minimize this potential compliance issue.

According to recent publications, it seems that Asian Indians may be more susceptible to insulin resistance [4]. Therefore, it appears valuable to assess both the glycemic and insulinemic responses of sugar replacers. Previously, we reported maltitol glycemic response values for South Indians living in the United Kingdom, but insulin levels were not measured in this study [17]. In the present study, the levels of both glucose and insulin were measured in the venous blood. Technically, we used venous blood because it was reported to be the more accurate for insulin measurement [19].

Table 2 Glycemic response calculation (0–120 min)

	iAUC		Glycemic response
	Maltitol	Reference glucose	
With out layers			
N	12	12	12
Mean	43.13	141.32	50.16
SD	37.05	74.23	87.12
Without out layers			
N	10	10	10
Mean	29.21	153.71	20.45
SD	16.54	73.51	9.29

Glycemic response is expressed as the percentage of glycemic response (iAUC) to the standard meal (glucose)

Table 3 Insulinemic response calculation (0–120 min)

	iAUC		Insulinemic response
	Maltitol	Reference glucose	
With out layers			
N	12	12	12
Mean	45.96	146.80	50.75
SD	38.92	79.72	86.03
Without out layers			
N	11	11	11
Mean	9144.73	53775.01	17.79
SD	6150.99	21693.47	9.89

Insulinemic response is expressed as the percentage of insulinemic response (iAUC) to the standard meal (glucose)

Here, we showed that maltitol exhibited a GR of 20.4 % and an IR of 17.8 % in healthy Indian subjects. In a previous study where the impact of ethnicity on GR was investigated [17], we demonstrated that with the same protocol, maltitol GR was 33.5 % in a Caucasian population, 32.9 % in a Chinese population and 23.1 % in a South Indian population. Even if a decreasing trend was observed in the Indian group compared with the other 2 ethnic groups, the difference was not significant. Consequently, genetic background did not seem to influence maltitol metabolism and GR as it was the only discriminating parameter between the study volunteers. Indeed, the subjects of this earlier study were chosen with various genetic origins but they had to have been living in the United Kingdom for at least 6 months. This last precaution aimed at studying the genetic impact without any environmental influence. In the present study, the GR values obtained in the subjects living in India seemed to be closer to those obtained for the subjects living in the UK with a South Indian genetic background than for the other studied populations. In addition, recent studies have demonstrated that Asian Indians with mild dysglycemia have a reduced β-cell function [20]. Consequently, genetic background seems to be involved in glucose homeostasis and this may even apply to healthy Indian subjects. Other researchers have shown that several ethnic groups (Caucasian, Asian, African, and South American) living in the USA exhibit drastic differences in insulin sensitivity [21] linked to their genetic background, the interesting point being that the β-cell function varies in order to compensate for the different insulin sensitivities [21]. On the basis of these studies, we believe that it could be useful to investigate whether the combination of genetic background and living environment has an influence on the metabolism of maltitol and other polyols and GR. Should a significant difference be confirmed, a gene expression study could be performed to understand the origin of this difference.

In the present study, we observed that maltitol did not induce a late hypoglycemia 150 and 180 min after consumption in contrast to the reference glucose. This fact was previously observed in many GR studies among various ethnic groups [16]. Therefore, this specificity of maltitol may be useful in the context of lifestyle changes and subsequent prediabetes. Indeed, the first step to type 2 diabetes is prediabetes which corresponds to an intermediate hyperglycemia defined by glycemic variables that are higher than normal but lower than the diabetes levels [22]. In addition, the IR of maltitol was 17.8 % which is lower than the value of 25 % demonstrated in previous studies [23]. This could be really promising in India in the context of the increasing occurrence of type 2 diabetes in this country. Given the genetic background and the environment in India, a useful GR and IR study could be performed on types 1 and 2 diabetic Indian volunteers, especially as this data is lacking in the literature.

To conclude, the maltitol GR was significantly lower than the glucose GR up to 90 min after its administration in accordance with the FAO recommendations. The maltitol IR was significantly lower than the glucose IR up to 2 h after its administration in accordance with the FAO recommendations. Maltitol displayed low glycemic and insulinemic responses. In addition, up to a single intake of 50 g, both products were well tolerated by all the volunteers. Several supplemental studies could be conducted in India in order to confirm whether the genetic Indian background and the Indian environment have a significant effect on the maltitol metabolism and whether a specific solution for sugar replacement could be built for Indian diabetic patients.

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AS and PM conducted the experimental study and performed statistical analysis. CT and LGD worked on the protocol. CT interpreted the results and wrote the manuscript. BR, TG, DW, and LGD participated and revised the manuscript.

References

1. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. Indian J Med Res. 2007;125(3):217–30.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87(1):4–14.
3. Shetty P. Public health: India's diabetes time bomb. Nature. 2012;485(7398):S14–6.
4. Weber MB, Oza-Frank R, Staimez LR, Ali MK, Narayan KM. Type 2 diabetes in Asians: prevalence, risk factors, and effectiveness of behavioral intervention at individual and population levels. Annu Rev Nutr. 2012;32:417–39.
5. Mohan V, Deepa R, Deepa M, Somannavar S, Datta M. A simplified Indian Diabetes Risk Score for screening for undiagnosed diabetic subjects. J Assoc Physicians India. 2005;53:759–63.
6. Scully T. Diabetes in numbers. Nature. 2012;485(7398):S2–3.
7. Ramachandran A, Snehalatha C. Current scenario of diabetes in India. J Diabetes. 2009;1(1):18–28.
8. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA. 2004;292(8):927–34.
9. Imfeld TN. Clinical caries studies with polyalcohols. A literature review. Schweiz Monatsschr Zahnmed. 1994;104(8):941–5.
10. Portmann MO, Kilcast D. Psycho-physical characterization of new sweeteners of commercial importance for the EC food industry. Food Chem. 1996;56(3):291–302.
11. Lee A, Wils D, Zumbe A, Storey DM. The comparative gastrointestinal responses of children and adults following consumption of sweets formulated with sucrose, isomalt and lycasin HBC. Eur J Clin Nutr. 2002;56(8):755–64.
12. Ruskone-Fourmestraux A, Attar A, Chassard D, Coffin B, Bornet F, Bouhnik Y. A digestive tolerance study of maltitol after occasional and regular consumption in healthy humans. Eur J Clin Nutr. 2003;57(1):26–30.

13. Thabuis C, Cazaubiel M, Pichelin M, Wils D, Guerin-Deremaux L. Short-term digestive tolerance of chocolate formulated with maltitol in children. Int J Food Sci Nutr. 2010;61(7):728–38.
14. Beards E, Tuohy K, Gibson G. A human volunteer study to assess the impact of confectionery sweeteners on the gut microbiota composition. Br J Nutr. 2010;104(5):701–8.
15. Thabuis C, Herbomez AC, Desailly F, Ringard F, Wils D, Guerin-Deremaux L. Prebiotic-like effects of SweetPearl® Maltitol through changes in caecal and fecal parameters. Food Nutr Sci. 2012;3:1375–81.
16. Livesey G. Health potential of polyols as sugar replacers, with emphasis on low glycemic properties. Nutr Res Rev. 2003;16(2):163–91.
17. Pratt M, Lightowler H, Henry CJ, Thabuis C, Wils D, Guerin-Deremaux L. No observable differences in glycemic response to maltitol in human subjects from 3 ethnically diverse groups. Nutr Res. 2011;31(3):223–8.
18. Rizkalla SW, Luo J, Wils D, Bruzzo F, Slama G. Glycemic and insulinemic responses to a new hydrogenated starch hydrolysate in healthy and type 2 diabetic subjects. Diabetes Metab. 2002;28(5):385–90.
19. Brouns F, Bjorck I, Frayn KN, Gibbs AL, Lang V, Slama G, et al. Glycemic index methodology. Nutr Res Rev. 2005;18(1):145–71.
20. Staimez LR, Weber MB, Ranjani H, Ali MK, Echouffo-Tcheugui JB, Phillips LS, et al. Evidence of reduced beta-cell function in Asian Indians with mild dysglycemia. Diabetes Care. 2013;36(9):2772–8.
21. Chiu KC, Cohan P, Lee NP, Chuang LM. Insulin sensitivity differs among ethnic groups with a compensatory response in beta-cell function. Diabetes Care. 2000;23(9):1353–8.
22. Tabak AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M. Prediabetes: a high-risk state for diabetes development. Lancet. 2012;379(9833):2279–90.
23. Livesey G. Tolerance of low-digestible carbohydrates: a general view. Br J Nutr. 2001;85 Suppl 1:S7–16.