Low-Glycemic-Index Sugar in Type 2 Diabetic Patients: a Randomized Controlled Study

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Abstract

Background and Objectives

There is a need to re assess the value of low-GI food and its specific components. The effect of one of them, namely low-glycemic-index sugar, is unclear, as its impact is usually confounded when reported in the literature. This study attempts to breach this gap, shedding light on its effect in type 2 diabetic patients and evaluate if it could be considered as part of a dietary plan.

Subjects and Methods

The blood sugar level of twenty (20) type 2 diabetics was monitored using a Continuous Glucose Monitoring system during two phases; firstly, an initial period of 5 days, whereby all the included patients were taking their usual dietary meals. Subjects were then randomized into two groups of equal size before embarking on a second phase; 10 subjects were instructed to eat prepared, portioned and delivered meals, the difference for the second group being that low-GI sugar was used for the preparation.

Results

Compared to baseline (day 1), blood sugar dropped by 18% for the group with low-GI sugar and 13% for those who consumed sugar with a normal-GI. The variation in sugar levels was also more contained in the interventional group. A by-product of the study design shows that constant glucose monitoring could raise awareness, and may foster reduction in blood sugar levels. Portioned food was capable of reducing blood sugar levels, with elevated levels of compliance just after start.

Conclusions

Even though the ultimate aim is to reduce sugar consumption by diabetic patients, the intake of a low-GI sugar seems to be less harmful than normal sugar. Compared to using normal sugar for the preparation of portioned foods, the use of a low-GI sugar is encouraged as part of a wider plan for the management of diabetic patients.

Introduction

Glycemic index (GI), usually assigned to different foods, indicates the speed at which the intake of such a preparation can cause an increase in blood sugar levels. Low-GI meals implying slower release of sugar in the blood appears conceptually ideal for consumption by patients suffering from diabetes for known reasons: lower variation in sugar levels following intake, less insulin peaks and therefore less weight gain and less inflammatory mediators released. However, there is a lack of consensus among scholars regarding the advantages related to the use of such nutrients by type 2 diabetics [1], research suggesting the need to re assess the value of GI in meal plans related to diabetics [2]. Low GI promises achievements in terms of several desirable health outcomes; weight loss, improved cholesterol levels, but evidence so

far, with a moderate degree of consistency, suggests modest effects on short and long term blood glucose control [3, 4, 5].

A meta analysis of 14 clinical trials involving diabetic patients revealed a 'small but clinically useful effect on medium-term glycemic control' [1]. When studied in non-insulin-dependent diabetes mellitus patients, glycemic control was significantly improved when subject to a low-GI diet, compared to normal one [4]. This was also true when assessed as part of a starchy diet for diabetics; reductions in HbA1C and fasting blood sugar were noted during the low-GI consumption period as opposed to the high-GI period [7], or when low-GI was compared to high-GI in the form of sweetened beverages consumed by healthy men [8]. Metabolic control was also improved following a 6-week intervention involving a low-GI Mexican diet among type 2 obese diabetics [9]. The potential benefits were also identified among the younger ones suffering from type 2 diabetics [10]. But the use of low-GI sugar *per se* as part of an overall low-GI meal is not documented.

With the advent and introduction of Continuous Glucose Monitoring Systems (CGMs), the management of diabetes has taken a huge leap forward, capable of providing additional insights [11] otherwise not possible. The beneficial effect (in terms of 24-hour glucose profile) of an improved diet involving low-GI among healthy young people was evidenced in a study involving CGM [12]. Another review of seven studies involving the use of such tools revealed the capacity of glycemic index to modify postprandial glycaemia in type 1 diabetic patients [13]. But due to cost constraints and complexity involved in making meaningful inferences from the bulk of data generated, results are minimally documented, more so, when longer periods of observations are desirable.

This study addresses these two concerns; it aims primarily at assessing the added value of low-GI sugar as part a general low-GI diet using a CGM among type 2 diabetics. As a by product of the study, it also had objective of confirming the capacity of a low-GI meal at enhancing glycemic control. Moreover, the *natural* gains following implantation of a CGM are examined and reported. The study is particularly important among a population with high prevalence of diabetes (approx. 25% among adults). The Island of Mauritius [Indian Ocean 20.2°S 57.5°E] spans over 2000km² with a population size of approximately 1.3 million inhabitants. More than 36% of the surface comprises of cane cultivation, the sugar industry being the third most important source of income for the country. Ethnic-wise, 68% of Mauritians have an Indian background, 27% African, 2% European and 3% Chinese.

Materials, Subjects And Methods

Study design and overview

The study is designed as open, single centre and randomized. All procedures were conducted at the site of the investigating clinic, namely APSA Diabetes Care Centre (ADCC). Included subjects were required to undergo a two-phase intervention and observation period; phase 1 (day 1- day 5) whereby patients were instructed to continue with their usual dietary habits. Before embarking onto the second phase, that is,

from day 6 to day 10, subjects were randomized into two groups; 'low-GI sugar', which comprises of individuals who received and consumed portioned food prepared with low-GI sugar, and 'normal-GI sugar' to indicate those who received portioned food but that included normal-GI sugar. Hence all subjects received the same food during the second phase, the only difference being that the novel low-GI sugar (DinaLife™) was used for the preparation of the various plates.

The design of this study is justified and preferred over a typical cross-over trial for two main reasons: the CGM, once installed raises awareness among patients and intuitively leads to enhanced sugar levels in terms of trend and variation. Thus, while the first phase of the study makes it possible to observe the intrinsic glycemic control of the enrolled subjects, it also serves as an acclimatization period so that any effect due to the sugar being used is not confounded with the rise in consciousness.

Overall, subjects attended three (3) visits at the centre and under continuous study conditions for 10 days (from day 1 and day 10 inclusive). Due to the availability of sensors for the CGM and interruptions related to the COVID-19 pandemic, the dates for the First Subject In (FSI) and Last Subject Out (LSO), initially planned for March 2020 - July 2020 were shifted to July 2020 - Dec 2020.

Subject selection, consent and ethical considerations

In addition to the general eligibility criteria for participation in a study locally (capable to express and give written consent, eligible for free health care services, not serving imprisonment etc.), Mauritian subjects registered on the clinic's database were screened and examined for the following study specific inclusion criteria; subjects had to be above 18 years of age, suffering from type 2 diabetes, ready to embark on a special diet and having a baseline HbA1c of 6.5% or above at screening. Study specific exclusion criteria included subjects with known allergy to food, having a history of bariatric surgery, had experienced microvascular and/or macrovascular complications of diabetes, undergoing hemodialysis or was on insulin treatment, regularly consumes alcohol, is a vegetarian, suffers from chronic psychiatric illness, on antipsychotic prescriptions or is a breastfeeding or pregnant women.

Eligible patients were explained about the study procedures, expected adverse events and reporting strategies put in place. An explanatory leaflet that also included the menu for the second phase of the study was handed over to them during the same visit. Foreseeable advantages for participation to the study were: free CGM for ten (10) consecutive days, including a smartphone for real-time visuals, free portioned food including home delivery, and follow-up by a physician during the study period (including assistance over the phone). Travel costs for the patients were also catered for by the study sponsor. Clearance for ethical considerations was obtained from a local independent committee (CEC, c/o Accrux, Port Louis, 13 March 2020). The study was conducted in the spirit of Good Clinical Practice (GCP).

Meal preparation and logistics

A full description of the menu for the second phase of the study is provided in Table 1. Briefly described, the participants in the control group (normal-GI sugar) were provided with a portioned meal set for breakfast, mid-morning snack, lunch, afternoon snack and dinner that included sugar of $GI\ 103 \pm 3$. The

test group (low-GI sugar) received the same set of meals but prepared with sugar of GI 51, DinaLife™. Irrespective of the group, the GI of the other ingredients used for the preparation of meals was primarily low whenever the choice was present. The total amount of carbohydrate per meal was also the same for both groups. Preparation and organization for home delivery were centralized. The meals were delivered in the evening for the consumption on the following day.

Table 1
Meal plan for second phase, D6-D10 (controlled and portioned food period)

Meals	D6	D7	D8	D9	D10
Breakfast	<i>Caramelized oats:</i> Rolled Oats (55) + Sugar*	<i>Sweet Pancakes and coconut flakes:</i> White Flour (74) + Sugar*	<i>Caramelized oats and seed mix:</i> Rolled Oats (55) + Sugar*	<i>Fairy Brioche:</i> Brioche (75) + Sugar*	<i>French toast:</i> Brown Bread (74) custard + Sugar* + Apple (36)
Mid-Morning snack	<i>Date Balls:</i> Raw Dates (42) + Sugar*	<i>Yoghurt with cooli:</i> Jam (51) + Sugar*	<i>Ice tea:</i> Sugar*	<i>Date balls:</i> Raw Dates (42) + Sugar*	<i>Yoghurt with cooli:</i> Jam (51) + Sugar*
Lunch	<i>Brown panini/sandwich:</i> (74) Brown sandwiches Salad with homemade mayonnaise: Sugar*	<i>Tuna Risotto</i> making use of brown couscous instead of rice: Brown boiled rice (65) Salad: Diced Pawpaw (60)	<i>Satay Lamb served with brown ciabatta bread.</i> Brown Bread (74) Salad: Lettuce and tomato sliced: Tomato (15)	<i>Mac cheese served with tofu.</i> Macaroni (49) Salad: Carrot julienne: Carrot (71)	<i>Salad</i> served on brown bread (74) Salad: <i>Diced tomato and lemon salad</i> (15)
Afternoon snack	Peanut butter slices Sugar* used to make peanut butter	Ginger cookies: Sugar*	<i>Fresh Fruit and peanut butter slices:</i> Sugar* to make peanut butter	<i>Apple muffin:</i> Apple (36) + Sugar*	<i>Ginger cookies:</i> Sugar*
Dinner	<i>Lamb fricassee served with red beans on brown rice:</i> Brown boiled rice (68) Tomato soup: Tomato pureed (15) and sugar*	<i>Soya and vegetables mash up served with brown rice:</i> Brown boiled rice (68) Soup: Vegetable soup	<i>Fish curry served with brown chappati.</i> Brown chappati (62) Salad: Diced Raw Pawpaw (51)	<i>Chicken stir fry/ Brown rice boiled</i> (68) Salad: Boullion brede mourum	<i>Ourite salad served with lentil soup with brown boiled rice</i> (68) Salad: <i>Fricasse calbass.</i>
** For the low-GI group, low-GI sugar (51) was used. For the normal-GI group, granulated white sugar was used (GI = 100).					

Continuous Glucose Monitoring

Each participant wore the CGM (The Guardian™ Connect System, Medtronic) for a total of 10 days; fitted on day 1, worn for 4 days, sensors changed on day 5 and worn for another 5 days. The CGMs were fitted according to the manufacturer's instructions and assisted by the local brand representative in Mauritius. The participants were educated on handling measures and how to calibrate the system 12-hourly using the finger-prick method. Assistance was made available by phone

Oral Glucose Tolerance Tests (OGTT)

Two sets of OGTT were performed on thirteen participants to confirm the low-GI property of the novel sugar on glycemic control. The participants were instructed to consume normal meals or meals that contained approximately 150g of carbohydrates per day for three days preceding the test day. On the day of the test, a fasting blood sample was taken followed by a 1-hour and 2-hour sample after consuming 75 of sugar diluted in water; the participants attended two test sessions for the OGTT, low-GI sugar on OGTT test Day 1 and normal-GI sugar on OGTT test Day 2. The phlebotomy samples were sent to the laboratory for analysis.

Statistical considerations and efficacy variables

The analysis was conducted on a modified Intent to Treat population (mITT), comprising of all randomized subjects with available data. One subject's data could not be retrieved from the application's platform for downloading measurements. Thus, the data for 19 patients (10 normal-GI sugar and 9 low-GI-sugar) could be analyzed for efficacy assessment. The analysis method is inspired by Rodbard's 'systematic approach to analysis of CGM data' [14], while also taking into consideration relevant clinical questions and degree of glycemic variation [15].

A graphical illustration of the daily average blood sugar level was provided to identify possible changes from baseline, by treatment group. Since initial analyses revealed a considerable change in behavior between Day 5 (last day of normal food intake) and Day 6 (first day of portioned food intake), this part of the data was further explored to understand hourly variations.

Measurements related to blood sugar collected over 5-minute intervals were averaged daily (or hourly) first at patient level, before aggregating and presented across individuals, by group. Line graphs by time and group represent means. Error bars are not provided since variation is thoroughly analyzed on its own.

Variations in blood sugar levels were analysed using the coefficient of variation [15] and computed in the same order as described for the means.

Results from OGTT are reported in a graphical illustration showing the means, by type of sugar and time.

Results

Patients

All subjects were considered for analysis, but the the CGM for one subject in the control group could not be retrieved due to IT related problems. Hence, the data for 19 subjects (10 low GI sugar and 9 normal GI sugar) were analysed (Fig. 1). Since CGM records blood sugar levels every 5 minutes, except in cases of prolonged disconnection from the attached mobile device, 40678 data points were available over the 10-day period (19096 for low-GI and 21582 for normal-GI). No adverse events were reported by the subjects during the product intake and none observed during the visits by the medical practitioners.

Baseline demographic characteristics are summarized in Table 2, illustrating comparable groups in terms of Hb1Ac and age at study outset.

Table 2
Baseline demographic characteristics by intervention

	Normal food intake followed by portioned food coupled with:	
	Low-GI Sugar	Normal-GI Sugar
Number of subjects, n	10	9
Gender	Male: 9 (90%)	Male: 3 (67%)
	Female: 1 (10%)	Female: 6 (50%)
HbA1c	7.3 ± 0.9	7.3 ± 1.1
Age	63.4 ± 11.3	61.8 ± 9.8

Change in average sugar levels

Irrespective of the intervention (low or high-GI sugar), average blood sugar level was lower during the portioned food control period, computed as 8.5 ± 2.6 from D1 to D5 versus 7.7 ± 2.4 for D6 to D10. Compared to baseline, blood sugar dropped by 18% (9.7 ± 3.2 on D1 to 7.9 ± 2.5 on D10) for the low-GI-sugar group compared to only 13% (8.4 ± 2.7 on D1 to 7.3 ± 2.4 D10) for normal-GI-sugar group (Fig. 2). From D5, a sharper decrease from 8.8 ± 2.6 to 7.9 ± 2.5 was noted in the low-GI sugar group, compared to only from 8.4 ± 2.7 to 7.3 ± 2.4 in the group who consumed normal-GI sugar. Peaks and troughs recorded on D5 reduced considerably on D6 (first day of controlled food intake), but the change was more important for patients with low-GI-sugar intake (Fig. 3).

Change in variations of sugar levels

During the normal food intake period, in particular, from D1 to D4, a general decrease was noted in terms of variations of sugar levels (coefficient of variation dropped from 33.9–28.1%) (Fig. 4) while on D5, which is the last day of normal diet before embarking on portioned diet, coefficient of variation rose back to reach 31.3%. During the controlled food period, a higher degree of fluctuation was recorded for the normal-GI sugar group (oscillating between 26.2% and 33.4%), while the same parameter remained fairly stable for the low-GI sugar participants (minimum and maximum coefficient of variation of 29.2% and 31.5%).

Specific times of the day

Figure 5 confirms the baseline HbA1c of participants; for both groups, the mean glucose level was close to 7 units between in the morning before the normal time for breakfast. Over the 10-day period of observation, a general decreasing trend was noted when assessing the average glucometer readings from 5.00 to 6.00 in the morning, which is used as a proxy for fasting blood sugar. Once more, significant changes in behavior were noted between D5 and D6, i.e. the last day of normal food intake and first day of controlled food.

Focusing on 12:00 to 13:00, it is interesting to note the drop in average glucose levels from D5 to D8 for the low GI group, while the same readings did not show much improvements between the same time points for the normal-GI sugar group.

Looking closely at the readings between 23:00 to midnight, a general decrease was recorded between D1 to D5, and blood sugar levels was systematically lower throughout the second phase for the low-GI sugar group, despite starting at relatively the same position at baseline.

Variations occurring between 5 and 6 am improved consistently from D5 to D10 for the group of interest (Fig. 6), while no such progress was seen for the participants who were subject to high-GI sugar. The measurements obtained from 23 to midnight also showed convincing results from D5 to D10, low-GI capable of keeping the variations lower levels systematically.

OGTT

The results from the OGTT confirms the characteristic of the low sugar, namely DinaLife™. The increase in blood glucose level was slightly lower after one hour of intake, compared to the normal-GI sugar (Fig. 7).

Discussions

Dietary changes are always recommended but never really studied, especially in Mauritius where the concept of GI is still new and exposure to low-GI foods in traditional diets is very limited. As the GI of a food represents the degree that a particular food can raise the blood glucose after consuming it, it is important to study its effect in people and thus confirm the laboratory attributed GI which is based on structure. This study is a short-term randomized controlled study to assess the effect of incorporating a novel low-GI sugar into portion-controlled diet on the glycemic control in type 2 diabetes patients in Mauritius. As a by product of the study design, it confirms the rise in consciousness following implantation of the CGM and change in eating behavior, leading to more controlled sugar levels. This, in terms of average blood sugar over a medium term assessment (first 4 days of study) and in terms of levels of variation, examined over the first phase of the study itself. Surprisingly, participants apprehended the upcoming controlled portion period, and relaxed on their self-motivational gains.

Between the last day of the normal diet and first day of controlled diet, blood sugar levels increased, and higher variations were noted across subjects.

While most studies from the existing literature focused on the impact of low-GI diets, this study examined the effect of low-GI sugar *per se*, as part of an overall low-GI dietary. The low-GI-sugar group showed a more pronounced reduction in average sugar levels when compared to the normal-GI-sugar group. This reflects the lower HbA1c noted during consumption of low-GI diet, a frequently analyzed end-point [1]. It is worth noting that a reduction as little as 1% in mean HbA1c reduces the risks of diabetes-related complications significantly [16]. The results are more interesting just after embarking on the second phase of the study, that is, just after starting to consume controlled portions. This is suggestive of enhanced compliance at earlier timepoints of the study, a phenomenon that is not uncommon or unknown in clinical trials [17, 18].

Fasting blood sugar (CGM from 5:00 to 6:00 in the morning) exhibited the same patterns as noted overall; improved glycemic control was detected as early as just after implantation of CGM, despite participants instructed to eat *ad libitum* during the first phase. Along the controlled portion period, improvements were maintained in terms of average blood sugar, without any obvious distinction between the two treatment groups. However, variations occurring at that time of the day showed promising results for the low-GI group, with a consistent reduction from D5 to D10.

Postprandial glycemic control was enhanced during the second phase, i.e. when subjects were consuming low-GI diets. Lower variations were noted between noon to 13:00, typical post lunch-time period, irrespective of the group they were assigned to. Lower variations were observed on D7 for the low-GI group. Post-lunch glucose levels have been observed to account for a relatively larger portion of HbA1c [19]. Our observation of lower postprandial, more specifically, post-lunch excursions, is clinically significant and is likely to lead to improved glycemic control defined as a reduction in HbA1c and ultimately lower incidence of diabetes-related complications.

Over the 10-day observation period, a steady decreasing trend was recorded when the CGM data was averaged between 23:00 to midnight. Moreover, lower peaks were noted for the low-GI sugar group during the second phase, and the level of variation was consistently lower across evaluation days, indicating enhanced glycemic control during sleep compared to normal-GI sugar. The results support the rather widely accepted notion that low-GI foods lead to a sustained rise in blood glucose levels, i.e., a sustained decrease in postprandial glucose level with less glycemic peaks [20]. A decrease in the latter is shown to be associated with improvements in insulin sensitivity [20], decreased insulin resistance and loss of weight (spike in insulin bring about weight gain) [21].

The findings of this study, that involved the use of a novel sugar with a remarkable difference in GI of 49 units, are contrary to those from similar previous studies among non-diabetic and obese/overweight patients, whereby even moderate to large differences in GI did not affect 24-hr glucose concentrations [22, 23]. But on another occasion, a GI difference of as little as 8 units resulted in improved 24-hour glucose concentration [24]. Glycemic variability, which is a clinically important characteristic of low-GI

foods, was not assessed in any of the above studies. Moreover, all these studies had been performed in non-diabetics.

One limitation of this study is that the majority of the participants included were retired individuals who spend most of their days being sedentary, the effect was thus not studied on individuals who are more physically active. Moreover, with more time on their hands, the participants were able to consume the 5-meals per day provided to them. Five meals were provided in an attempt to reduce the number of drop-outs due to perceived insufficient amount of food. We could expect the study to produce better results with a 3-meal plan; a decrease in the total number of GI consumed over a period of 24-hours. The effect on weight was not investigated (too short period to notice a change in weight). Food intolerances were not investigated, more specifically the effect of gluten in the meals was not investigated.

Unlike the DASH (Dietary Approach to Stop Hypertension) diet [25] for hypertension, there is no universal approach to a diabetic diet and there exists, till date, some controversies about the usefulness of low-GI diets.

Conclusions

The study thus contributes to reinforce recommendations regarding the added value of low-GI sugar as part of controlled dietary portioned food in patients with type 2 diabetes. Although the changes appear small, it appears to be an interesting tool in the management of dietary meals; the results comparable to pharmacological effects, thus clinically meaningful. While the use of sugar cannot be promoted for diabetic patients, they find it very challenging to cut all rapid sugars, and the use of a low-GI alternative appears to be a good option. It would be interesting to study this effect in type 1 diabetic patients and evaluate the decrease in insulin requirement over 24 hours.

Declarations

Ethical Approval and Consent to Participate

All study participants provided written consent. The ethical considerations for the study were examined by CEC, c/o Accrux, Port Louis, and approval was obtained on 13 March 2020.

Consent for publication

Not applicable. Only aggregated data are presented in this report.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors, including the Principal Investigator, have received consultancy fees for the design & conduct of the study, including write up of the report from the sponsor, namely Omnicane group. The latter is also the developer and manufacturer of DinaLife™ novel Low-GI-sugar.

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Authors' contributions

DS is the principal investigator and contributed to the study design and provided clinical inputs. SMHA was the study coordinator, and was in charge of seeing the patients at every visit, device installation, reporting of adverse events, input of data, and providing insights for the analysis part. MH is the study statistician and was in charge of conducting statistical analyses and reporting. AG is the dietician, she primarily proposed the meal plan.

All authors provided inputs for the writing up, and eventually, read and approved the final manuscript.

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Figures

Figure 1

Patient disposition

Figure 2

Average blood sugar by intervention and day

Figure 3

Hourly average by intervention from day 5 to day 6

Figure 4

Daily variation (coefficient of variation) by intervention

Figure 5

Hourly average of blood sugar, by day and intervention, at specific times of the day

Figure 6

Hourly variation of blood sugar, by day and intervention, at specific times of the day

Figure 7

Blood glucose level, by type of sugar (OGTT)