Relation between Gastrointestinal Adverse Effects in Gaucher Disease Patients and Intestinal Disaccharidases Activity Evaluated by Methane Hydrogen Breath Test

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Abstract: The aim of this paper is to study the disaccharidase profile in GD (Gaucher disease) patients treated or not with miglustat and compare it with a healthy control group. Miglustat is an iminosugar used as substrate inhibitor in the therapy of some lysosomal disorders, its main side effects resembling carbohydrate maldigestion symptoms and cause more than 50% of medication discontinuation among GD patients. *In-vitro* studies have revealed that miglustat can act as an inhibitor of some digestive enzymes. An exploratory non-interventional study was designed to compare the disaccharidase profile assessed by MHBT (methane hydrogen breath test) and to analyze the correlation with the reported gastrointestinal symptoms in GD patients (40) and healthy subjects (20). MHBT was performed following the ingestion of lactose, sucrose and maltose on different days. Each participant completed two detailed surveys about dietary habits, medications and gastrointestinal symptoms previous and during the test. Twenty-one GD were receiving miglustat, 10 (47.6%) of them reported gastrointestinal side effects, and 7/10 (70%) recorded a positive MHBT (lactose 5, maltose 2, and sucrose 1). In 6/19 (31.6%) patients that never been exposed to miglustat and 7/20 (35%) controls a positive MHBT were detected. The comparison of the malabsorption phenotype between GD patients exposed and not exposed to miglustat ($p = 0.028$) and control group ($p < 0.04$) showed high statistical significance for the group of patients treated with miglustat. These results suggest that miglustat therapy induces persistent changes in digestive enzyme activity in GD patients.

Key words: Methane hydrogen breath test, lactose intolerance, sucrose intolerance, maltose intolerance, gastrointestinal disorders, Gaucher disease, miglustat.

1. Introduction

Several molecules derived from iminosugars, such as miglustat, have demonstrated substrate inhibition function in some lysosomal storage disorders. Miglustat is a potent, reversible inhibitor of the enzyme glucosylceramide synthase; it is an approved therapy for Type 1 GD (Gaucher disease) and NPC (Niemann-Pick C disease). Patients receiving

miglustat therapy frequently experience GISE (gastrointestinal side effects), such as flatulence, diarrhea and borborygmus, which mainly occur in patients with a high carbohydrate diet. In fact, it was found that about 43% of GD patients receiving miglustat therapy discontinue its due to GISE [1]. In Spain, miglustat has been available since 2004, and the 5-year ZAGAL project outcomes revealed a lower incidence of GISE than previously reported; this outcome could be related to the recommendation to maintain a low carbohydrate diet during the first

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weeks of therapy [2]. The mechanism responsible for this high incidence of GISE is not well established, but it is thought that the inhibition of disaccharide enzymes (mainly sucrase and maltase) by miglustat leads to a suboptimal hydrolysis of carbohydrates and subsequent osmotic diarrhea and altered colonic fermentation. This argument is based on various *in-vitro* studies showing that miglustat strongly inhibits the intestinal disaccharidases sucrase and maltase and slightly inhibits lactase [3]. The intraluminal inhibition of these disaccharidases could interfere with the intraluminal digestion of starch and its final hydrolysis and could impair the absorption of oligosaccharides and disaccharides [4].

Lactose is a unique carbohydrate present only in mammalian milk, e.g., at a concentration of 7.2 g/100 mL in mature human milk and at a concentration of 4.7 g/100 mL in cow milk [5]. Lactose malabsorption is defined as inefficient digestion of lactose due to either a lack of lactase or intestinal pathologies, whereas lactose intolerance is defined as malabsorption with gastrointestinal symptoms [6-8]. The primary type of lactose malabsorption, also known as adult-type hypolactasia or non-persistence lactase, is the most common phenotype found in humans. Non-persistence of lactase is an autosomal recessive inherit trait, which, depending on the geographic region, occurs in 3~70% of the Caucasian population in Europe [9, 10]. In Spain, the non-persistence lactase genotype has been identified among 14.8~46.9% of the population [11-15]. Recently, we studied lactase polymorphism in a cohort of Spanish subjects and found that 35.7% of them presented with this genotype [16].

Sucrase-isomaltase enzyme is an intraluminal enzyme located in the small intestinal brush border. This enzyme is built by two distinct polypeptides that have either sucrase or isomaltase activity; its deficiency is a hereditary disorder in which patients retain residual isomaltase activity. The clinical implications primarily include intolerance to sucrose

ingestion, causing abdominal distension and diarrhea. In addition, some patients were shown to develop fermentative diarrhea after starch ingestion but to a much lesser degree than that caused by sucrose ingestion [17, 18].

The symptoms of maltase-glucoamylase deficiency are poorly defined. Glucoamylase deficiency may cause chronic diarrhea in young children [19]. Although the osmolar force of starch is less than that produced by sucrose or lactose due to its higher molecular weight, a starch-free diet has been reported to relieve diarrhea in infants. The prevalence of glucoamylase deficiency is unknown; however, its frequency in children with chronic diarrhea was found to be similar to that in children with sucrase deficiency [19].

The diagnosis of carbohydrate malabsorption is clinically based on response evaluation after the elimination of specific dietary sugars, and it is determined by the quantification of disaccharidase enzyme activities in an intestinal biopsy sample or by the non-invasive MHBT (methane hydrogen breath test) [20]. The current gold standard is diagnosis by intestinal biopsy, with the disadvantage being that this procedure is invasive. The MHBT is a valuable, non-invasive diagnosis strategy widely used in clinical practice. It is useful in the diagnosis of carbohydrate malabsorption and small bowel bacterial overgrowth syndrome and for measuring orocecal transit time [21]. The MHBT exploits the fact that normal colonic flora metabolize these sugars into hydrogen and short chain fatty acids. Then, hydrogen reaches the splanchnic venous circulation by diffusion through the intestinal wall and is transported from there through the portal system to the liver and systemic circulation and is eventually exhaled through the lungs [22]. Some reports show a correlation between symptom intensity and test positivity in patients with lactose intolerance [23].

Using the methane hydrogen breath test, this work studied the disaccharidase profile (lactase, sucrase and

maltase) of patients with GD treated or not with miglustat and compared the profile results with those of a healthy control group. In addition, we analyzed the relationship between the presence (or lack) of gastrointestinal side effects in patients receiving miglustat therapy to understand various side effects experienced by patients with GD to advance personalized therapy for this chronic disease.

2. Material and Methods

2.1 Subjects

Forty adult GD patients included in the Spanish Registry of GD were selected. All of the patients had a confirmed diagnosis of GD by determination of enzymatic activity β -acid glucosidase activity according to protocols based on artificial substrate incubation with 4-methylumbelliferyl-B-D-glucoside-sonicated leukocyte extracts [24] and genetic mutation identification by *GBA* (β -acid glucosidase) gene sequencing [25]. The patients included 17 (42.5%) males and 23 (57.5%) females with a mean age of 42.2 (16~76) years. Twenty-one patients had been receiving miglustat therapy for a mean of 5.3 (0.5~10) years, 3 patients were not receiving any type of therapy (naïve), and 16 patients were receiving ERT (enzymatic replacement therapy).

2.2 Controls

Twenty healthy adults were included in the study. Of these patients, 7 (35%) were males and 13 (65%) were females, with a mean age of 40.5 (23~56 years). Detailed general characteristics of all included subjects can be found in Table 1.

All of the participants completed a detailed survey about their gastrointestinal symptoms, alimentary habits and medications, and each subject had to check off the food ingested every day (breakfast, lunch, snack and dinner) for a week. The age, gender, *GBA* genotype, gastrointestinal symptoms, type of therapy for GD, gastrointestinal symptoms during the MHBT, following variables were also collected: date of

questionnaire completion, number of bowel movements a day and the consistence thereof, presence or absence of flatulence, abdominal pain, and/or slow digestion. Finally, we included a section indicating, if necessary, the name of the food product likely responsible for the discomfort and the type of discomfort. These data were collected to establish an individual profile of eating habits and their effect on intestinal rhythm and symptoms related to miglustat use. In addition, we collected data about concomitant medication intake for all participants before proceeding to the MHBT. Patients were grouped according to whether they presented with gastrointestinal manifestations and the type of treatment they were receiving ERT or SRT (substrate reduction therapy).

The study design was approved by the institutional board of FEETEG foundation and by the ethical committee for clinical research in Aragon (CEIC Aragon) and according to the Helsinki declaration. All subjects signed an informed consent form to be included. This prospective study was performed at the translational research unit of Miguel Servet University Hospital between December 2012 and December 2014.

2.3 Methane Hydrogen Breath Test

The test was performed under basal conditions; no colonoscopy procedures or antibiotics intake were allowed during the two weeks before the test. Every test included the administration of only one sugar substrate per day and test completion on three different days (not necessarily consecutive but with at least a 6 h overnight fast for each sugar). A fasting breath sample was analyzed prior to the intake of any sugar solution and designated as baseline breath hydrogen and methane concentration. The test used a substrate containing lactose at 1 g/kg or body weight (maximum 50 g) or sucrose in a dose of 1 g/kg (maximum 50 g) or maltose in a dose of 1 g/kg body weight (maximum 25 g) dissolved into 300 mL of water.

Table 1 General characteristics of GD patients and controls.

Patient No.	Age	Gender	Dx age	<i>GBA</i> genotype	Years ERT	Years SRT	GISE to miglustat	LBT	GI symptoms for LBT	MBT	GI symptoms for MBT	SBT	GI symptoms for SBT
1	59	F	17	N370S/L444P	-	10	No	-	No	-	No	-	No
2	74	F	49	N370S/N370S	-	-	-	-	No	-	No	-	No
3	76	F	53	N370S/c.500insT	-	10	No	-	No	-	No	-	No
4	31	M	5	N370S/RecNciI	-	6	No	+	Yes	-	No	-	No
5	33	M	23	N370S/V398I	4	7	No	-	No	+	Yes	-	No
6	59	F	23	N370S/T134P	22	2	Yes	-	No	+	Yes	-	No
7	53	F	36	N370S/L444P	-	11	No	+	No	-	No	-	No
8	17	M	1.5	R463H/G377S	15.5	10*	No	-	No	-	No	-	No
9	49	M	9	N370S/L336P	20	1*	Yes	+	Yes	-	No	-	No
10	41	M	28	N370S/L444P	3	8	No	-	No	-	No	+	No
11	37	M	26	N370S/L444P	7	-	-	+	Yes	+	No	-	Yes
12	72	M	52	N370S/L444P	-	6	Yes	-	Yes	-	No	-	Yes
13	53	F	45	N370/L444P	-	6	Yes	-	No	+	Yes	+	No
14	52	M	11	N370S/c.1207insA	8	4**	-	-	No	-	No	-	No
15	46	F	24	N370S/L444P	1	8	No	-	No	-	No	-	No
16	48	M	35	N370S/L444P	13	-	-	+	Yes	-	Yes	-	Yes
17	18	F	5.8	N370S/L444P	12	-	-	-	No	-	No	-	No
18	16	F	4	N370S/c.84insG	12	-	-	-	No	-	No	-	No
19	63	F	40	N370S/N370S	9	0.5	Yes	+	No	-	No	-	No
20	15	M	3	N370S/L444P	12	-	-	-	No	-	No	-	No
21	51	F	31	N370S/G202R	11	6	Yes	-	Yes	-	Yes	-	Yes
22	36	M	32	N370S/c.84insG	-	6	Yes	+	Yes	-	No	-	No
23	22	M	6	N370S/R285C	16	-	-	+	Yes	-	No	-	No
24	50	F	16	N370S/L444P	20	-	-	-	Yes	-	No	-	No
25	14	F	2.5	N370S/R47X	10	-	-	-	No	-	No	-	No
26	34	M	33	N370S/L444P	1	-	-	-	No	-	No	-	No
27	28	F	21	N370S/RecNciI	5.5	4	No	+	Yes	-	No	-	No
28	16	F	4	N370S/L444P	12	-	-	-	No	-	No	-	No
29	37	F	18	N370S/N370S	15	2	Yes	-	No	-	No	-	No
30	65	F	31	N370S/P391L	18	3	Yes	+	Yes	-	No	-	Yes
31	33	M	30	S13L/G202R	-	-	-	-	No	-	No	+	No
32	49	F	30	N370S/L444P	19	-	-	-	No	-	No	-	No
33	57	F	37	N370S/L444P	19	-	-	-	No	-	Yes	-	Yes
34	18	F	5	N370S/R463H	9	1	No	+	Yes	+	Yes	+	Yes

(Table 1 continued)

Patient No.	Age	Gender	Dx age	<i>GBA</i> genotype	Years ERT	Years SRT	GISE to miglustat	LBT	GI symptoms for LBT	MBT	GI symptoms for MBT	SBT	GI symptoms for SBT
35	36	F	14	N370S/W(-4)X	-	-	-	-	No	-	No	-	No
36	53	M	47	N370S/G202R	5	-	-	-	No	-	No	-	No
37	58	M	33	N370S/L444P	16	3	No	-	No	-	No	+	No
38	26	F	7	N370S/c.708delC	18	-	-	+	No	-	No	-	No
39	51	M	47	N370S/R163X	-	2	Yes	+	Yes	-	No	-	No
40	44	F	20	N370S/Y412H	18	-	-	+	Yes	-	No	-	Yes
Mean	42.3		23.9		12.1	5.3							
Control													
1	23	M						+	Yes	+	Yes	-	Yes
2	39	F						-	No	-	No	-	No
3	46	M						-	No	-	No	-	No
4	31	F						-	No	-	No	-	No
5	56	F						+	Yes	-	Yes	-	No
6	33	M						-	No	+	No	-	No
7	40	M						-	Yes	-	No	-	No
8	28	F						-	No	-	No	-	Yes
9	41	F						-	No	-	No	-	No
10	55	F						-	No	+	Yes	-	Yes
11	55	F						-	No	-	No	-	No
12	52	M						-	No	-	No	-	No
13	26	M						-	Yes	-	No	-	No
14	43	F						-	No	-	No	-	No
15	56	F						+	No	-	No	-	No
16	51	F						+	Yes	-	No	-	No
17	31	M						-	No	-	No	-	Yes
18	46	F						-	Yes	-	No	-	Yes
19	26	F						+	Yes	-	No	-	Yes
20	32	F						-	Yes	-	Yes	-	No

Dx Age: diagnosis age;

* ERT + SRT simultaneously;

** In this case, the therapy reduction substrate received was Eliglustat;

nd: not done;

LBT: lactose breath test;

MBT: maltose breath test;

SBT: sucrose breath test.

The substrate solution was administered orally, and the amount of exhaled hydrogen and methane was measured at 25, 50, 75, 100, 125, 150 and 175 min after ingestion. During the test, the subjects were warned to avoid eating, smoking and performing physical exercise and were asked to report presence and intensity of gastrointestinal symptoms before, during and after the test, evaluated by a numeric scale (1~10). The final alveolar breath sample was collected using ISOMED® sampling tubes. Gas chromatography was employed to measure the hydrogen and methane breath concentration using QuinTron Model Breath Tracker. The analysis was performed centrally by ISOMED PHARMA (Madrid, Spain). The results were expressed as hydrogen and methane gas in ppm (parts per million). The MHBT results were considered to be positive if the hydrogen peak was > 20 ppm over the baseline value and/or if the methane peak was > 12 ppm over the baseline value in at least two subsequent measurements. Patients were classified as lactose, sucrose and/or maltose malabsorbers if a hydrogen increase > 20 ppm and/or a methane increase > 12 ppm over the baseline value was observed within the colon passage 75~175 min after lactose, sucrose or maltose ingestion, respectively. If lactose, maltose and/or sucrose malabsorption was accompanied by gastrointestinal symptoms, patients were classified as lactose, maltose and/or sucrose intolerant, respectively.

2.4 Statistical Analysis

A database was created, and statistical analysis was performed using SPSS 18.0 software. Descriptive statistics, nonparametric tests and correlation analysis were performed. Differences were considered to be statistically significant if $p < 0.05$.

3. Results

Regarding the lactose MHBT, 14/40 (35%) GD patients and 5/20 (25%) control subjects had a

positive result; for the maltose MHBT, 5 (12.5%) GD patients and 3 (15%) control subjects had a positive result; regarding the sucrose MHBT, only 5 (12.5%) GD patients had a positive result. One patient had a positive result for all three tests, and one control subject had a positive result for the lactose and maltose tests.

During the different MHBT, some participants developed gastrointestinal symptoms; these data are reflected in Fig. 1. During the lactose test, 11/14 (78.6%) GD patients with a positive test result experienced an intolerance phenotype and 3/26 (11.5%) patients with a negative result reported some symptoms. The correlation between malabsorption phenotypes (positive tests) and intolerance (symptoms during the breath test) was statistically significant ($p = 0.0001$).

With regard to maltose, 4/5 (80.0%) GD patients with positive maltose methane hydrogen breath test results showed intolerance phenotypes (symptoms) during the test and 3/35 (8.6%) with negative maltose methane hydrogen breath test results also reported symptoms. The correlation between positive test results and gastrointestinal symptoms was statistically significant ($p = 0.002$). With regard to sucrose, 1/5 (20.0%) GD patients with positive sucrose methane hydrogen breath test results reported symptoms and 7/35 (20.0%) GD patients with negative sucrose methane hydrogen breath test results also reported symptoms. No statistically significant correlation was found between the positive test results and intolerance symptoms ($p = 1.000$).

There were no significant differences between GD patients (11/20, 55%) and control group subjects (18/40, 45%) who reported gastrointestinal symptoms during the methane hydrogen breath test ($p = 0.586$).

With regard to exposure to miglustat, 10 of the 21 (47.6%) GD patients receiving miglustat therapy reported GISE-like flatulence, diarrhea and borborygmus; of these patients, 5 (50%) had positive

Fig. 1 Gastrointestinal symptoms during hydrogen and methane breath test and correlation between malabsorption phenotype and intolerance phenotype in GD.

breath test results for lactose, two (20%) had positive breath test results for maltose, and one (10%) had a positive sucrose methane hydrogen breath test result. This latter patient was positive for both sucrose and maltose. In the control group, 5/20 (25%) subjects showed a lactose malabsorption phenotype, as shown in Table 1.

Regarding the development of a malabsorption phenotype, the differences in exposure or not to miglustat were not significant ($p = 0.326$). Specifically, 9/21 (42.9%) patients exposed to miglustat showed symptoms during the test compared with only 4/19 (21.1%) from the not-exposed group. When the prevalence of malabsorption phenotype is calculated by summarizing all three studied sugars, in the group of those exposed to miglustat ($n = 21$), the percentage increased to 66.7% and the difference compared to the never-exposed to miglustat ($n = 19$) group was statistically significant, with a higher incidence among the exposed patients ($p = 0.028$); similarly, when comparing the exposed group with the control group (35%), the difference was significant ($p = 0.04$), and no differences were observed between patients without miglustat therapy and the control group (Fig. 2).

The dietary habits, medications, and gastrointestinal symptoms survey completed by all of the participants

provided important information. In fact, ten out of 40 (25%) GD patients reported avoiding milk consumption due to poor tolerance and in 6 (60%) of these patients, a positive breath test to lactose was registered. The patients with a positive MHBt for lactose who reported gastrointestinal symptoms and intake of dairy products with lactose were advised to associate commercial lactase, and the subsequent result was satisfactory with a reversal of gastrointestinal symptoms (appendix).

Focusing on the cohort of patients receiving miglustat therapy ($n = 21$), 10 (47.6%) patients reported gastrointestinal disorders; in 6 of these patients, these symptoms caused them to abandon therapy. Two of these patients reported severe episodes of diarrhea following the intake of certain foods (chocolate, cookies rich in milk ingredients and breaded fried foods). Nevertheless, all of the reported, occasional episodes of diarrhea were mild to moderate, and none of the patients required an antidiarrheal drug prescription.

4. Discussion

Diarrhea, flatulence and abdominal discomfort have been widely reported as the main gastrointestinal side effects associated with miglustat administration, both in clinical trials and in real life studies. These adverse

Relation between Gastrointestinal Adverse Effects in Gaucher Disease Patients and Intestinal Disaccharidases Activity Evaluated by Methane Hydrogen Breath Test

Fig. 2 Positive hydrogen and methane breath test and prevalence of malabsorption phenotype according different sugars and miglustat therapy.

Control vs. GD miglustat: $p = 0.04$; GD no miglustat vs. GD miglustat: $p = 0.028$.

events are primarily characterized by a mild or moderate intensity and occurrence during the initial weeks of therapy. The mechanism underlying these gastrointestinal disturbances could be the result of inhibition of the digestive enzymes, mainly sucrase and maltase, by miglustat, leading to a suboptimal hydrolysis of carbohydrates and subsequent osmotic diarrhea and altered colonic fermentation. Transient decreases in body weight, which are often observed at the beginning of miglustat therapy, are considered to be secondary to carbohydrate malabsorption with a negative caloric balance.

In-vitro studies have shown that miglustat inhibits intestinal disaccharidase activity, such as sucrase, maltase and lactase [3]. Although this inhibition is not parallel with the cellular content of disaccharidases, miglustat could affect the regulation of enzymatic intestinal metabolism and could consequently induce maldigestion of carbohydrates and osmotic diarrhea long term due to its interference with the intracellular mechanisms of enzyme production [26].

To the best of our knowledge, this is the first study to focus on gastrointestinal disturbances in GD

patients receiving miglustat therapy and the first study to use a methane hydrogen breath test to assess and diagnose carbohydrate malabsorption. It was found that 1 of every 5 GD patients overall showed a carbohydrate malabsorption profile compared with only 1 of every 10 control group subjects. When we only have considered GD patients receiving miglustat therapy, the rate of carbohydrate malabsorption profiles has increased substantially to 3 of every 5 GD patients receiving miglustat therapy, leading us to question the presence of a strong relationship between both conditions.

Despite the limitations involved in studying a rare disease, such as GD, the difference observed in the presence of malabsorption phenotypes between patients receiving miglustat therapy or not could be related to a functional inhibition of the digestive enzymes in the miglustat-exposed patients. Although this hypothesis cannot be confirmed at this time due to the lack of information before the initiation of miglustat therapy, it is in line with results obtained from previous *in-vitro* studies [3].

Another point to keep in mind is the lack of

information about the prevalence of the malabsorption phenotype in GD patients, as well as that among the general population. Although some studies have been performed among the general population, especially children with abnormalities, such as intolerance and functional gastrointestinal disorders that present with similar complaints, such as abdominal pain, diarrhea and bloating, these studies are biased and can not be extrapolated to other populations [27].

Recently, our group studied the prevalence of the lactose persistence genotype, which has also been presented elsewhere [16]. Regarding the GD patients with gastrointestinal adverse effects secondary to miglustat therapy included in this study, 60% present with a non-persistence lactase genotype (SNP-13910 CC), which translates to no persistence of lactase activity, a higher tendency than reported in other studies [15].

With respect to maltose, the frequency of glucoamylase deficiency is unknown; however, in children with chronic diarrhea, the incidence is similar to that in children with sucrase deficiency [19]. Based on the finding that older children with lactase or sucrase deficiency present mainly dyspeptic symptoms, Karnsakul hypothesized that glucoamylase deficiency might also cause dyspepsia [28]. There is only one study on sucrase-isomaltase deficiency; that study focused on 9 patients (8 children and 1 adult) and concluded that some sucrose-isomaltase deficient patients also have a maltase-glucoamylase deficiency [29]. In our study, approximately 10% of patients with gastrointestinal symptoms had positive methane hydrogen breath test results for sucrose and maltose.

In this study, 47.6% of patients treated with miglustat presented gastrointestinal adverse effects and 60% showed a malabsorption phenotype to at least one of the three disaccharides as a result of the methane hydrogen breath test. When the results of patients who had never been exposed to miglustat are analyzed and compared with those of patients who had been exposed, the presence of a malabsorption

phenotype to any of the disaccharides studied using the MHBT was significantly higher ($p = 0.028$) in the miglustat-treated patients; the same phenomenon occurs when these patients were compared with the control group ($p = 0.04$). From these observations, it can be inferred that patients treated with miglustat have a persistent inhibitory effect on the activity of the digestive enzymes, as described by Amiri and Naim [26] in 2014 *in-vitro* experiments.

These results suggest that the subjects with less functional activity of lactase, sucrose, or maltase enzymes have a higher risk of developing gastrointestinal adverse events during miglustat therapy than those without this functional deficiency. Accordingly, it will be recommended that before initiating miglustat therapy, patients be assessed using the methane hydrogen breath test to identify those who are most suitable and also to obtain information to adequately prepare for possible secondary side effects during therapy.

According to the results from the dietary survey, the frequency of adverse effects to miglustat is also primarily related to dietary habits. Modification on this aspect with a reduction in the carbohydrates (sucrose, maltose and lactose) daily consumption have result in an improvement on symptoms and the gastrointestinal tolerability of miglustat.

5. Conclusions

The results of this study demonstrated that, overall, there were few differences between the control group and the GD patients regarding the malabsorption profiles determined by the MHBT. Nevertheless, the patients exposed to miglustat therapy more commonly present with a malabsorption phenotype profile, which could be induced by the miglustat therapy.

The knowledge of the individual profile of the activity of intestinal disaccharidases in patients with Gaucher disease susceptible to treatment with the substrate inhibitor miglustat allows us to advise dietetically, as well as recommend the oral addition of

enzymatic substitutes to avoid or minimize gastrointestinal disorders and consequently improve the quality of life of the patients.

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Appendix Supplementary table: survey results in GD patients.

No.	Age	BMI	Intake			BM	Food	GID	SNP-13910	Breath test results			GI symptoms breath test		
			Lactose	Maltose	Sucrose					Lactose	Maltose	Sucrose	Lactose	Maltose	Sucrose
1	59	23.6	Yes	Yes	Yes	4/7 (0.6)	/	/	CC	-	-	-	No	No	No
2	74	30.1	Yes	Yes	Yes	7/7 (1)	/	/	TT	-	-	-	No	No	No
3	76	21.6	Yes	Yes	Yes	2/7 (0.3)	/	/	TT	-	-	-	No	No	No
4	31	20.9	*	Yes	Yes	10/7 (1.4)	/	/	CC	+	-	-	Yes	No	No
5	33	21.1	Yes	Yes	Yes	14/7 (2)	/	/	CT	-	+	-	No	Yes	No
6	59	22.5	Yes	Yes	Yes	7/7 (1)	/	/	CT	-	+	-	No	Yes	No
7	53	23.7	****	Yes	Yes	8/7 (1.1)	Cookies	Diarrhea	CC	+	-	-	No	No	No
8	17	19.1	Yes	Yes	Yes	8/7 (1.1)	/	/	CT	-	-	-	No	No	No
9	49	24.2	Yes	Yes	Yes	7/7 (1)	/	/	CC	+	-	-	Yes	No	No
10	41	25.4	Yes	Yes	Yes	6/7 (0.9)	/	/	CT	-	-	+	No	No	No
11	37	27.8	Yes	Yes	Yes	7/7 (1)	/	/	CC	+	+	-	Yes	No	Yes
12	72	24.1	Yes	Yes	Yes	8/7 (1.31)	/	/	TT	-	-	-	Yes	No	Yes
13	53	21.3	***	Yes	Yes	6/7 (0.9)	Fried, 3	Diarrhea	CC	-	+	+	No	Yes	No
14	52	22.8	Yes	Yes	Yes	4/7 (0.6)	/	/	CT	-	-	-	No	No	No
15	46	22.7	Yes	Yes	Yes	4/7 (0.6)	/	/	TT	-	-	-	No	No	No
16	48	25.5	Yes	Yes	Yes	7/7 (1)	/	/	CC	+	-	-	Yes	Yes	Yes
17	18	19.2	Yes	Yes	Yes	7/7 (1)	/	/	CT	-	-	-	No	No	No
18	16	22.2	Yes	Yes	Yes	5/7 (0.7)	/	1, 2	CC	-	-	-	No	No	No
19	63	29.4	Yes	Yes	Yes	7/7 (1)	/	/	CC	+	-	-	No	No	No
20	15	22.8	Yes	Yes	Yes	7/7 (1)	/	/	CC	-	-	-	No	No	No
21	51	16.7	****	Yes	Yes	19/7 (2.7)	/	Flatulence	CT	-	-	-	Yes	Yes	Yes
22	36	23.9	Yes	Yes	Yes	6/7 (0.9)	/	/	CC	+	-	-	Yes	No	No
23	22	21.6	****	Yes	Yes	12/7 (1.7)	/	/	CC	+	-	-	Yes	No	No
24	50	23.2	Yes	Yes	Yes	4/7 (0.6)	/	/	CC	-	-	-	Yes	No	No
25	14	21.9	Yes	Yes	Yes	10/7 (1.4)	/	/	CT	-	-	-	No	No	No
26	34	24.3	Yes	Yes	Yes	13/7 (1.9)	/	/	CT	-	-	-	No	No	No
27	28	22.1	Yes	Yes	Yes	7/7 (1)	/	/	CC	+	-	-	Yes	No	No
28	16	24.4	Yes	Yes	Yes	7/7 (1)	/	/	CT	-	-	-	No	No	No
29	37	24.2	****	Yes	Yes	9/7 (1.3)	Milk, 5	Diarrhea, 4	TT	-	-	-	No	No	No

(Appendix continued)

No.	Age	BMI	Intake			BM	Food	GID	SNP-13910	Breath test results			GI symptoms breath test		
			Lactose	Maltose	Sucrose					Lactose	Maltose	Sucrose	Lactose	Maltose	Sucrose
30	65	25.5	Yes	Yes	Yes	6/7 (0.9)	Fried	Flatulence	CC	+	-	-	Yes	No	Yes
31	33	30.9	Yes	Yes	Yes	4/7 (0.6)	/	/	TT	-	-	+	No	No	No
32	49	28.2	Yes	Yes	Yes	3/7 (0.4)	/	/	CT	-	-	-	No	No	No
33	57	29.7	Yes	Yes	Yes	5/7 (0.7)	/	/	TT	-	-	-	No	Yes	Yes
34	18	24.6	**	Yes	Yes	5/7 (0.7)	/	Flatulence	CT	+	+	+	Yes	Yes	Yes
35	36	18.3	****	Yes	Yes	7/7 (1)	/	/	CT	-	-	-	No	No	No
36	53	25.6	Yes	Yes	Yes	7/7 (1)	/	/	CT	-	-	-	No	No	No
37	58	22.9	Yes	Yes	Yes	6/7 (0.9)	/	/	CT	-	-	+	No	No	No
38	26	19.4	Yes	Yes	Yes	6/7 (0.9)	Fried, 6	Flatulence	CT	+	-	-	No	No	No
39	51	23.4	****	Yes	Yes	4/7 (0.6)	/	/	CC	+	-	-	Yes	No	No
40	44	33.7	****	Yes	Yes	6/7 (0.9)	/	/	CC	+	-	-	Yes	No	Yes

BM: bowel movements;

** : lactose free milk intake;

****: no drink milk;

1: abdominal pain;

2: slow digestion;

3: chocolate;

4: nausea;

5: fried egg dinner;

6: industrial bakery;

GID: gastrointestinal disturbances.