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Effects of consumption of a low glycaemic index formula on glycaemic control in patients with type 2 diabetes managed by medical nutrition therapy

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Abstract

To evaluate the effect of medical nutritional therapy (MNT) combined with low glycaemic index (LGI) formula at breakfast for 4 weeks on the glycaemic control of patients with type 2 diabetes mellitus (T2DM). Ninety-six participants were recruited and randomly equally divided into two groups. The intervention group was offered with 40g LGI formula at breakfast adjusted according to MNT, and the control group with regular MNT. After 4 weeks, fasting blood glucose, glycated albumin (GA), insulin, C-peptide levels and metabolic index were compared between the two groups. Compared to the intervention group, the total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and the change of FBG (–0.64 ± 1.4 vs. 0.3 ± 2.2; $p < 0.05$) and 2h-PBG (–1.8 ± 3.6 vs.0.8 ± 3.2; $p < 0.01$) in the control group were significantly decreased. The LGI formulations, having a significant effect on controlling glucose and lipid metabolism, could be used as a non-pharmacological intervention for T2DM self-management.

Keywords: low glycaemic index; enteral formula; medical nutrition therapy; type 2 diabetes mellitus.

Practical Application: Low glycaemic index formulations could be used as a non-pharmacological intervention for T2DM self-management.

1 Introduction

Strict and appropriate glycaemic control has a positive impact on long-term clinical outcomes in patients with type 2 diabetes mellitus (T2DM) by delaying and slowing the progression of complications related to diabetes (UK Prospective Diabetes Study (UKPDS) Group, 1998; Klaus-Dieter et al., 2011). Specific treatment such as oral hypoglycaemic agents or insulin is given to patients with T2DM according to their condition. Importantly, the adjustment of suboptimal dietary and lifestyle habits has become the primary therapy for T2DM and an important adjunctive treatment in insulin-dependent T2DM (Tuomilehto et al., 2011). However, there are an increasing number of patients who have never received systematic or scientific management and guidance on their daily diet, leading to a poor glycaemic control or malnutrition. Reducing hyperglycaemia to an appropriate range without significant hypoglycaemia is the primary goal; however, over nutrition and malnutrition in diabetic patients can cause serious concern (Franz et al., 2017).

Medical nutrition therapy (MNT) is a therapeutic approach to manage medical conditions and related symptoms, where a specifically tailored diet is devised and monitored by a management team consisting of physicians, registered dieticians and professional nutritionists (Morris & Wylie-Rosett, 2010). Beneficial evidence for diabetes MNT has come from randomized controlled trials (RCTs) showing that nutritional interventions improve metabolic outcomes, such as concentrations of blood glucose, haemoglobin A1c (HbA1C), lipids, blood pressure, body weight and/or quality of life in diabetic patients (Kulkarni, 2006).

Numerous studies on lifestyle interventions suggest that a low glycaemic index (LGI) diet helps control glycaemia in patients with T2DM as well as in healthy people (Yu et al., 2014; Moosheer et al., 2014). During the last decade, diabetes-specific formulae (DSFs), which are designed for special medical purposes for diabetic patients who need nutritional support, have become available for MNT (Hamdy et al., 2014; Ojo & Brooke, 2014). These formulae usually have specific ingredients; they typically contain low levels of carbohydrates and a large amount of monounsaturated fatty acids aimed in improving (postprandial) glucose control. Souza et al. recommended an optimized formula containing 0.70 grams of inulin, 1.56 grams of medium-chain triglycerides (MCT) and 1.73 grams of whey protein isolate (WPI) per 100 grams of the formula. The increased MCT and WPI are beneficial to the product emulsion stability and protein digestibility (Souza et al., 2020). When the final product contains 6% synbiotic fermented milk, the blood sugar, urea and creatinine levels of diabetic rabbits can be reduced by 62.9%, 71.5% and 57.0% respectively (Shafi et al., 2019). A systematic review showed that the usage of DSFs was associated with better glycaemic control when compared with standard formulae

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(Elia et al., 2005). Consumption of dairy products rich in probiotics is also associated with anti-hyperglycemic activity. In vitro and in vivo data show a good correlation. Among them, the type of dairy product matrix rich in probiotics affects anti-hyperglycemic activity. Probiotic Prato cheese can help reduce postprandial blood sugar in healthy individuals (Grom et al., 2020).

The hypothesis presented in the current study is that intervention with LGI formula based on MNT management would improve the glucose and lipid metabolic profiles in patients with T2DM. Thus, we conducted a quasi-randomized clinical trial by recruiting patients with T2DM to assess the effects of LGI formula in combination with breakfast 4 weeks of consumption on metabolic and glycaemic control.

2 Materials and methods

2.1 Participants

From September 17, 2014 to July 3, 2015, 96 patients with T2DM were recruited among the outpatients of the Department of Endocrinology of the Second Affiliated Hospital of the Army Medical University (Third Military Medical University). Patients were included if they met the T2DM diagnostic criteria recommended by the American Diabetes Association (ADA) in 2014 (American Diabetes Association, 2014): 1.FBG concentration >7.0 mmol/L, or 2h-PBG ≥11.1mmol/L, or HbA1C ≥ 6.5%, or patients with classic symptoms of hyperglycaemia or hyperglycaemic crisis, or random plasma glucose ≥11.1mmol/L; 2, aged 30-75 years; 3. with T2DM >6 months. The exclusion criteria included: any malignant tumours, diabetes complications, and severe chronic diseases or liver or kidney dysfunction. Patients were also excluded if they had one of the following conditions: anaphylaxis or serious adverse events, protocol deviation, or requirement to withdraw from the study. Patients that met the inclusion criteria were divided randomly into two groups: control group (n = 48) and intervention group (n = 48) using a computer randomization program chronologically. During the evaluation period, 6 patients in each group were not evaluated because they could not follow up or did not follow the instructions of the dietitian. The general characteristics of the participants were presented in Table 1.

2.2 Ethics

The study was carried out in accordance with the principles of the Declaration of Helsinki. The Medical Ethical Committee approved the study protocol, and informed consent was obtained from all participants before the start of the study. This trial was registered by the Chinese Clinical Trial Registry (ChiCTR-IOR-14005522).

2.3 Enteral formula

The study formula was a DSF which contained a complex carbohydrate blend consisting of fructose, slowly digested carbohydrates, including xylitol, resistant dextrin, polydextrose and fructo-oligosaccharides. The protein source in the LGI formula (Richen, Shanghai, China, Batch Number: 20140607) was whey protein concentrate in addition to decavitamin and multimineral (Table 2).

2.4 Study design

This double-blinded, quasi-randomized controlled intervention was carried out in patients with T2DM. Details of the experimental design are shown in Figure 1. The control group received MNT with their normal breakfast (most were refined cereals, such as bread, noodles, rice porridge, etc.). The energy intake was about 350kcal, based on dietary survey. GI: 59-88. The intervention group received both MNT and an adjusted breakfast (total energy intake of about 350 kcal) including 40g LGI formula (177.6 kcal) and refined cereals in moderation. Each patient received an individualized recommended intake of daily energy according to the ADA guidelines (Daly, 2005). The calorie distribution of their three meals accounted for 20%, 40%, and 40% of the daily intake, respectively. The ratios of calorigenic nutrient intake of protein, fat and carbohydrate provided were 11-15%, 20-30% and 55-65%, respectively.

To study the effect of LGI formula on glycemic control, we dispensed 40g of formula to intervention group at breakfast each day, while the control group recipes served as usual. According to MNT's principles (Chen et al., 2011), each participant received individualized dietary recommendations, including the final

Table 1. General characteristics of participants.

	Groups	
	Control (N=42)	Intervention (N=42)
Age (years)	60.7 ± 8.5	60.5 ± 8.0
Gender (M/F)	16/26	21/21
Height (cm)	159.7 ± 8.2	159.5 ± 8.0
Weight (kg)	62.9 ± 11.1	61.6 ± 9.8
BMI (kg/m^2)	24.6 ± 3.1	24.1 ± 2.3
Diabetes course (years)	7.1 ± 6.4	8.2 ± 6.8
Therapy		
Oral hypoglycaemic agents	12 (28.6%)	20 (47.6%)
Insulin	13 (31.0%)	10 (23.8%)
Hypoglycaemic agents plus insulin	15 (35.7%)	9 (21.4%)
Nomedication	2 (4.8%)	3 (7.1%)

Table 2. Nutrient composition of low-GI formula.

	1 unit 100 g
Total energy (kcal)	444
Protein (g)	21.5
Total lipid (g)	15.5
Carbohydrate (g)	51
Dietary fibre (g)	6.0
Sodium (mg)	200

(Richen Low-GI formula): carbohydrates were derived from a slow-release carbohydrate system, including xylitol oligomeric glucose, physically modified starch. Dietary fibre source: water-soluble dietary fibre (resistant dextrin), oligofructose (GI <45). GI, glycemic index.

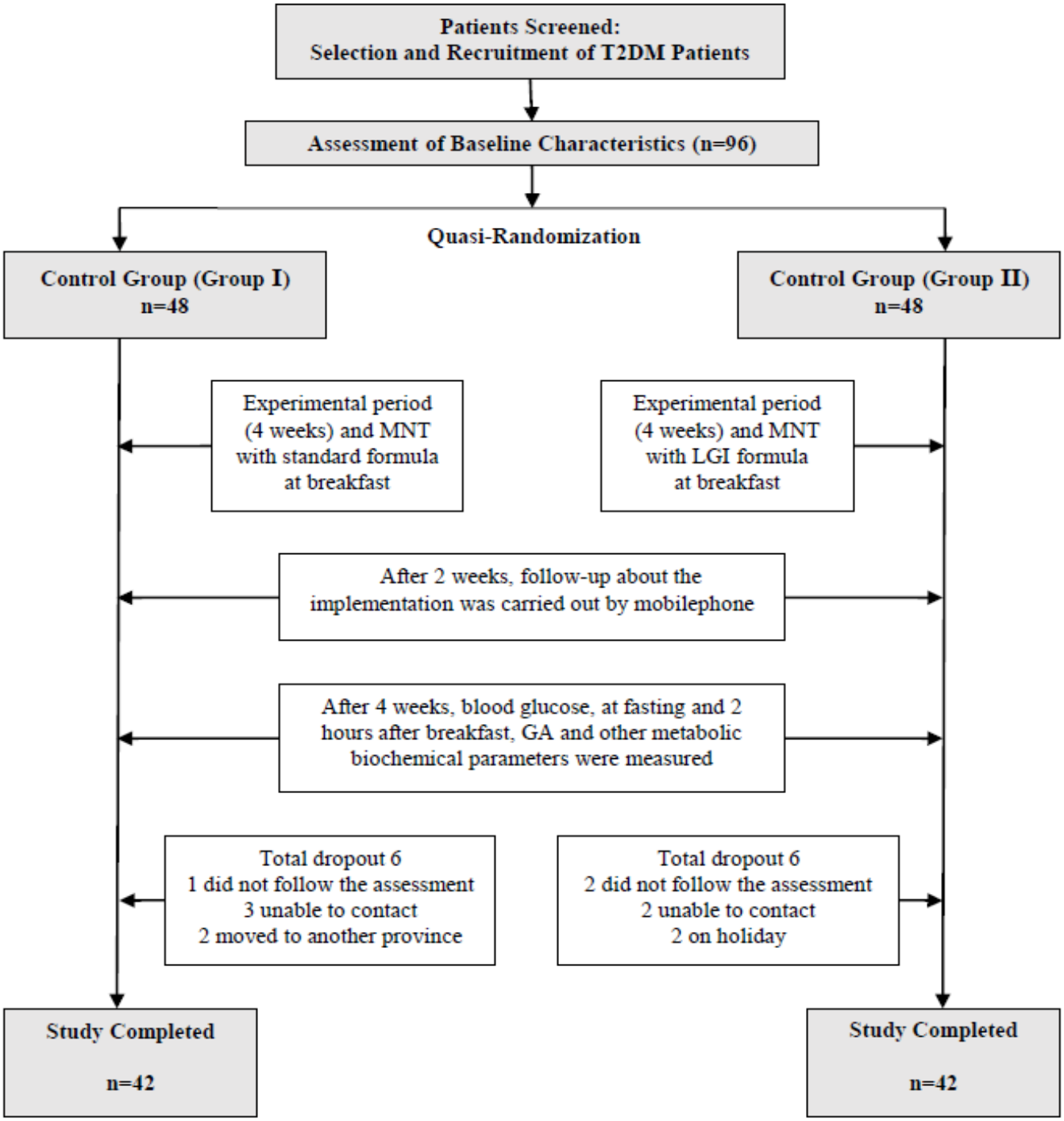

Figure 1. Flow diagram of experimental design.

total calories: 25-30 kcal/kg/day, protein: 0.8-1.2 g/kg/day; fat: 0.6-1 g/kg/ day; carbohydrate: 55-60% of total calories.

Participants were asked to visit the hospital twice before the start of the intervention (baseline) and 4 weeks after the intervention, The participants continued their usual anti-diabetic medication during the study period.

On the morning of the assessment, the participants underwent fasting blood collection without breakfast or anti-diabetic medication, and then ate standard steam bread (100 g) that was equivalent to 75 g glucose within 10 min. After 2 h, a blood sample was drawn for detection of relevant biochemical indexes. The body weight and blood pressure were measured prior to and following treatment by clinical technicians who were blinded to the content and purpose of the study. A 3-day record of their food intake at the baseline and at the end of the trial was completed for estimating nutrient intake by using NCCW 2011 software.

2.5 Laboratory examinations

Body weight was measured using an RGZ120 electronic body scale (calibrated to ±0.2 kg) while the patient was wearing light clothing. Height was also measured by the RGZ120 scale (calibrated to ±0.5 cm) manufactured by the Auxin Scales Factory in Wuxi, China. Blood pressure was measured using an Omron digital sphygmomanometer (model T9P; Omron Healthcare Co. Ltd., IL, USA). The fasting blood samples and 2-h postprandial blood samples were drawn for measurement of blood glucose and serum lipids (AU2700; Olympus, Japan), serum insulin, serum glycated albumin (GA), C-peptide, urea nitrogen and creatinine (measured by radioimmunoassay).

2.6 Data analysis

The data presented as the mean ± SD were analysed by t-test using PASW Statistics for Windows, version 18.0. The Chi Square statistic was used for testing relationships between categorical variables. Two-tailed P values < 0.05 were considered statistically significant.

3 Results

Of the 96 patients enrolled in total, 84 completed the study. There are 42 individuals in each of the control and intervention groups. The two groups of patients were comparable in terms of demographics and baseline characteristics. Gender, mean age and weight did not differ significantly (Table 1).

After intervention for 4 weeks, levels of FPG and 2h-PBG of the intervention groups were decreased prominently (Figure 2, Table 3). GA, which is thought to reflect glycaemic control in diabetic patients sensitively in a short period because of shortened red cell survival, was significantly decreased in intervention groups compared with the control. There were no significant differences in the levels of insulin and C-peptide between the two groups (Table 3). For further comparison of the glycaemic viability of the two groups, we compared the changes in glycaemic control indexes at baseline and 4 weeks later in both groups (Table 3). Changes in glycaemic indexes after intervention further demonstrated a significant reduction of FPG (−0.64 ± 1.4 vs. 0.3 ± 2.2; $p < 0.05$) and 2h-PBG (−1.8 ± 3.6 vs. 0.8 ± 3.2; $p < 0.01$) in intervention groups. In contrast, the FPG and 2h-PBG in the control group was increased. Meanwhile, changes of GA in the intervention and the control groups were −0.3 ± 2.4% and −1.0 ± 2.0%, respectively. The decrease in GA in intervention groups was greater than that in control; however, the difference was not significant.

In order to explore other outcomes associated with the intervention, we measured metabolic biochemical indexes (Table 3). Surprisingly, lower TC and LDL-C were found in the intervention group.

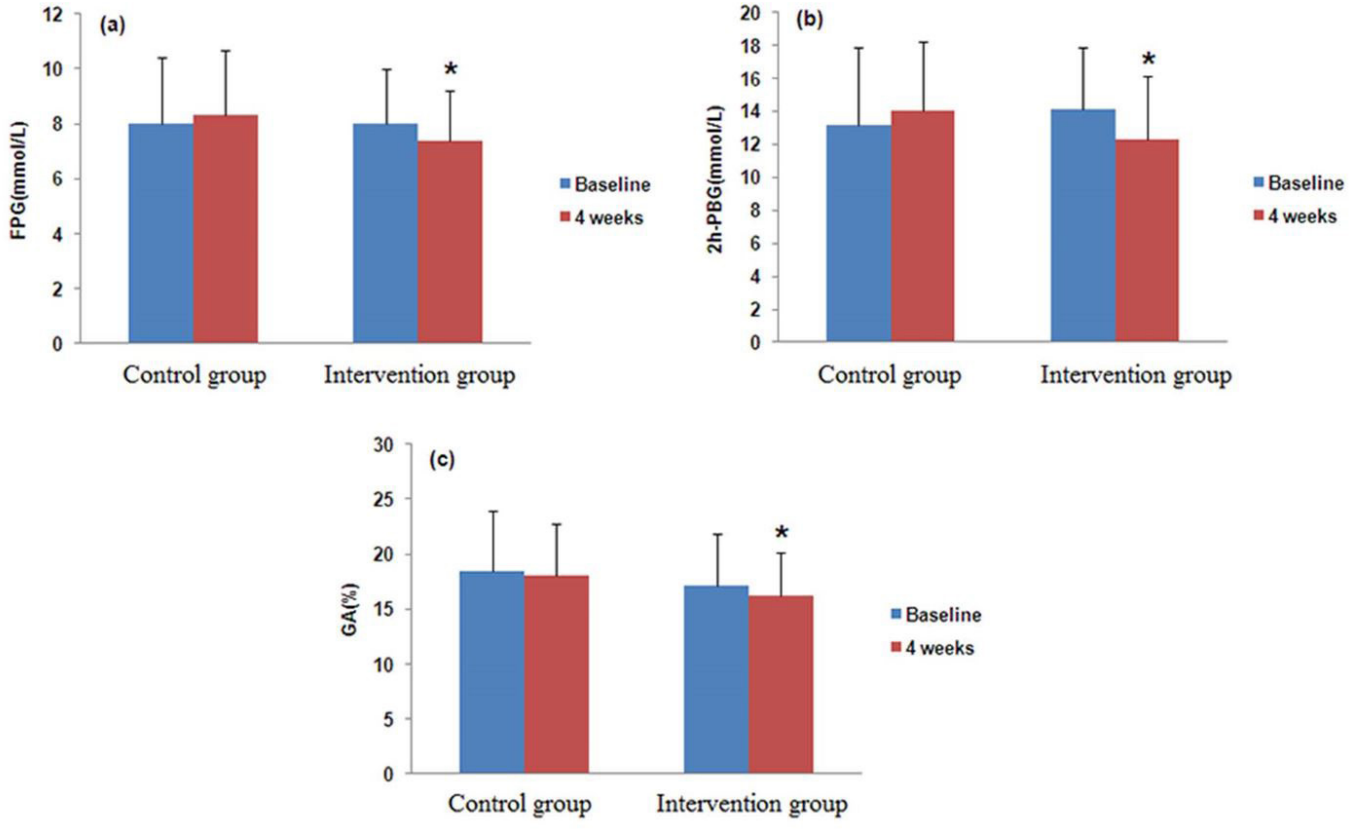

Figure 2. The effect of LGI formula on glycaemic control: (a) FPG; (b) 2h-PBG; (c) GA. Values were means ± SD. *$p < 0.05$ compared to the control group. FPG, fasting plasma glucose; 2h-PBG, 2 h-postprandial blood glucose; GA, glycated albumin.

Table 3. The effect of low-GI formula on plasma insulin level, C-peptide and metabolic biochemical indexes

Parameters	Control group		Intervention group	
	Baseline	At 4 weeks	Baseline	At 4 weeks
FPG (mmol/L)	8.0 ± 2.4	8.3 ± 2.4	8.0 ± 2.0	7.4 ± 1.8*#
2h-PBG (mmol/L)	13.2 ± 4.7	14.0 ± 4.2	14.1 ± 3.8	12.3 ± 3.8*#
GA (%)	18.4 ± 5.5	18.1 ± 4.7	17.2 ± 4.7	16.2 ± 4.0*#
Fins (μU/mL)	22.7 ± 45.0	22.7 ± 42.8	19.0 ± 25.9	24.6 ± 46.4
P2hIns (μU/mL)	41.6 ± 56.6	43.7 ± 56.9	50.3 ± 55.0	48.8 ± 54.2
fastingC-P (ng/mL)	1.74 ± 0.8	1.8 ± 0.7	1.62 ± 0.7	1.6 ± 0.8
2h C-P (ng/mL)	4.1 ± 1.4	4.2 ± 1.8	4.9 ± 2.3	4.5 ± 2.6
TC (mmol/L)	4.8 ± 1.2	4.8 ± 1.0	5.1 ± 0.9	4.6 ± 1.0#
TG (mmol/L)	2.4 ± 3.1	2.0 ± 1.5	2.1 ± 1.1	1.9 ± 1.2
HDL (mmol/L)	1.2 ± 0.3	1.2 ± 0.2	1.2 ± 0.3	1.2 ± 0.3
LDL (mmol/L)	3.0 ± 0.8	3.0 ± 0.8	3.3 ± 0.7	2.9 ± 0.7#
Ur (mmol/L)	5.7 ± 1.5	5.9 ± 1.6	6.1 ± 1.6	6.1 ± 1.8
Cr (μmol/L)	70.0 ± 16.2	71.0 ± 17.0	72.9 ± 18.1	72.8 ± 8.0
UA (μmol/L)	349.5 ± 80.1	345.3 ± 75.3	341.5 ± 80.1	336.5 ± 84.3

*$p < 0.05$, compared with the control; #$p < 0.01$, compared with the baseline; FPG, fasting plasma glucose; 2h-PBG, 2 h-postprandial blood glucose; GA, glycated albumin; Fins, fasting insulin; P2hIns, 2 h-postprandial insulin; C-P, C peptide; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; Ur, urea; Cr, serum creatinine; UA, uric acid.

4 Discussion

As the incidence of T2DM rises globally, we urgently need a treatment that can address dietary risk factors (Zhang et al., 2017; Micha et al., 2017; Xu et al., 2013). In this study, patients with T2DM underwent MNT, including personalized nutritional education, were informed of appropriate food choices. Each MNT scheme provided the required daily intakes and compositional ratios of energy, protein, fat, carbohydrate and other nutrients. To ensure that patients consume a variety of foods, the food and beverages allowed and prohibited were explained in detail to the patient. Although many studies have already revealed that the preferential consumption of LGI diets could attenuate glucose, lipid metabolic responses and inflammatory reactions associated with complications of T2DM (Gomes et al., 2017; Bolsinger et al., 2017), little is known about the effect of LGI formula on glycaemic control as a nutritional supplement. Few reports have described the effects of LGI formula, when used as a nutritional supplement in T2DM, on the changes in glucose concentrations. Therefore, this study addressed this question and found that consuming the LGI formula at breakfast improved glycaemic control in intervention group when compared with the control, patients in the intervention group showed a significant decrease of FPG and 2h-PBG.

Postprandial blood glucose plays an important role in overall glycaemic control in patients with diabetes. The contribution of the postprandial glucose level to overall glycaemic control ranged from 70% in patients in the lowest HbA1c quintile (<7.3%) to 30% in patients in the highest quintile (>10.2%) (Monnier et al., 2003). Poor FPG variability also serves as a risk factor for inadequate glycaemic control (Ketema & Kibret, 2015). Consistent with our findings, reduced postprandial blood glucose was observed following the administration of glycaemia-targeted specialised nutrition without reducing the quantity of carbohydrate consumed (Devitt et al., 2013).

Glycaemic variability, defined as the average extent of upward and downward fluctuations in blood glucose over time (Monnier & Colette, 2008), has gained significant attention as a parameter because of its relationship to hypoglycaemia risk and oxidative stress in patients with diabetes.

In this study, changes in FPG, 2h-PBG and GA were measured to provide information about glycaemic control after initiation of treatment. We found that the LGI formula significantly decreased FPG level in comparison with the standard formula ($p < 0.05$), and prominently decreased 2h-PBG level ($p<0.01$). GA was also decreased in both groups: the reduction in the intervention group was greater than that in the control group, but the difference was not significant. This suggests that not only nutritional interventions, but also MNT including nutrition education contributes to glycemic control to some extent.GA has been reported to reflect glycaemic control within a shorter period of time (2-3 weeks), when representing as a ratio to serum albumin, it may be more useful and accurate than HbA1c in monitoring short-term glycaemic control (Dolhofer & Wieland, 1980; Lee et al., 2013). That was reason for us to evaluate GA as an indicator of glycaemic control in a 4-week intervention study. Won et al. (2012) found that a short-term and periodic change in glycated albumin was significantly correlated with long-term percentage change in HbA1c. Therefore, we speculate that GA changes occurring within 4 weeks after intervention can predict the upcoming HbA1c changes in the next 3 months, but this requires further experimental verification.

There was a better glycaemic control in the intervention as compared with the control group. The LGI formula applied in this study contained sustained-release carbohydrates and dietary fibre, which can resist the decomposition of digestive enzymes, and effectively reduce the digestion and absorption of glucose in the human body, with a lower insulin response, therefore maintaining a stable blood glucose, and controlling hunger. This also reduces the risk of hypoglycaemia. At the same time, fructose in the diet produced a smaller glycemic response than glucose or sucrose with the same calorie load (Lee et al., 2016). As reported by Ojo & Brooke, (2014), DSF, which usually has a low glycemic index, appears to show a trend toward glucose and other indicators such as HbA1c. Similarly, reduction of postprandial glycaemia, mean glucose concentration, glycaemic variability, and short-acting insulin requirements has been demonstrated by Alish et al. (2010) in hospitalized patients.

Our previous study has shown that consumption of a macro-nutrient preload in patients with gestational diabetes mellitus resulted in lower postprandial blood glucose and more

stable fasting blood glucose (Li et al., 2016). Nevertheless, the current findings focused on the glycaemic control of patients with T2DM who consumed LGI formula at breakfast, which was more similar to their regular eating pattern.

The LGI formula had a potential effect on glycaemic improvement, but the effects generated on the other metabolic biochemical indexes were not understood. Our study showed that levels of TC and LDL-C declined in the intervention group, this may be related to dietary fiber in this formula, which reduces the absorption of fat in the gut and promotes the formation of short-chain fatty acid-dietary fiber metabolites. This, in turn, may reduce the blood lipid level, therefore improving the patient's lipid metabolism (Bazzano, 2008; Fechner et al., 2014).

This study was limited by its quasi-randomized design and short-term intervention. However, these findings may highlight the early positive effect of LGI formula on glycaemic control when it was used as a nutritional supplement. Further prospective, randomized studies with a large sample are needed to confirm its potential therapeutic consequences and longer-term outcomes.

5 Conclusion

The LGI formula should be useful to achieve glycaemic control. MNT has a potentially positive effect on glycaemic control for the diabetic patients. The LGI formula improved glucose and lipid metabolism in patients with T2DM, help control glycaemia and GA, and regulated blood lipid level. These results revealed the necessary for MNT in patients with diabetes and demonstrated the potential clinical usefulness of LGI formulations as a non-pharmacological intervention for improving glycaemic control.

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