Comparative Study between the Phramongkutklao's Diabetic Blenderized Diets and Commercial Diabetic Diets on Glycemic Variability in Continuous Tube Fed Patients with Type 2 Diabetes

Teeranun Tiyapanjanit MD*,
Apussanee Boonyavarakul MD*

** Division of Endocrinology and Metabolism, Department of Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand*

Background: *Rapid glucose fluctuations over daily period play an important role on diabetic complications.*
Objective: *To compare glycemic variability, mean plasma glucose, number of capillary blood glucose tests, and cost between the Phramongkutklao's diabetic formula and commercial diabetic formula in continuous tube fed patients with stable condition in type 2 diabetes.*
Material and Method: *A cross-over design study was performed between October 2010 and February 2011 in the medical department in Phramongkutklao Hospital. The researchers enrolled type 2 diabetic patients with stable condition who were on continuous tube fed. Seventy-two-hour continuous subcutaneous glucose monitoring was performed in all patients. Comparison of mean amplitude of glycemic excursions (MAGE), mean plasma glucose, cost, and number of capillary blood glucose tests were analyzed by using non-parametric Wilcoxon signed-rank test. Significance was defined as $p<0.05$.*
Results: *Ten subjects were included in the present study. The Phramongkutklao's Diabetic Formula resulted in significantly lower mean plasma glucose (122±26.25 vs. 144.68±36.91 mg/dL, $p = 0.022$), cost (550.1±33.57 vs. 797.81±42.29 baht, $p = 0.004$), and number of capillary blood glucose tests (5±0.94 vs. 5.3±0.82 times, $p = 0.083$) when compared with commercial diabetic formula, but no significant difference in MAGE level (5.86±2.78 vs. 7.71±4.34 mg/dL, $p = 0.333$).*
Conclusion: *The Phramongkutklao's diabetic formula has significantly lower mean plasma glucose, less number of capillary blood glucose tests, and is less expensive than commercial diabetic formula. The glucose variability (MAGE) of the Phramongkutklao diabetic formula has also less than commercial diabetic formula, but does not reach statistical significance. The level of plasma glucose was lower than 180 mg/dL in both formulas.*

Keywords: *Glycemic variability, Diabetic formula, Type 2 diabetes*

J Med Assoc Thai 2014; 97 (11): 1151-6
Full text. e-Journal: *http://www.jmatonline.com*

In Thailand, the prevalence of people with diabetes was 6.9% by the year 2008[1]. People with diabetes are more likely to be hospitalized and stay longer, increase the risk of death, congestive heart failure, and cardiogenic shock after myocardial infarction[2], and increase in-hospital mortality after ischemic stroke[3] than those without diabetes. Microvascular and macrovascular complications are mainly[4,5] or partly[5,6] depend on dysglycemia, which consists of two components, chronic sustained hyperglycemia and acute glycemic fluctuations from peaks to nadirs, glycemic variation (GV). The first component is integrated by HbA1c[7]. The second component has been proved independent of mean glycemia, and may be due to defects in insulin secretion and suppression of glucagon secretion[8]. Two main mechanisms were postulated, excessive protein glycation and activation of oxidative stress. There is evidence that hyperglycemia and glycemic variation are associated with increased formation and urinary excretion rate of 8-iso-$PGF_{2\alpha}$[9,10]. The systematic review shows that the use of diabetes-specific formulas is associated with improved glycemic control compared with standard formulas. The preliminary study had demonstrated that after ingestion of the Phramongkutklao's diabetic blenderlized diet, postprandial glucose was lower than commercial diabetic diet in patients with type 2 diabetes[11]. The

Correspondence to:
Tiyapanjanit T, Division of Endocrinology and Metabolism, Department of Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, 10400, Thailand.
Phone & Fax: 0-2644-9190
E-mail: teeranun@gmail.com

present study was performed to evaluate the glycemic variability, mean plasma glucose, number of capillary blood glucose (CBG) tests and cost in a variety of different formulated enteral feeding products in patients with type 2 diabetes.

Material and Method

Study design

A cross-over design study was done between October 2010 and February 2011 in the medical department Phramongkutklao Hospital, Bangkok, Thailand.

Subjects

The main eligibility criteria for the study were: 1) type 2 diabetes, 2) age more than 18 years, 3) nasogastric feeding tubes, 4) casual capillary blood glucose less than 180 mg/dL without antidiabetic drugs, and 5) stable conditions, afebrile, normotension, without vasopressor drugs and infection controlled at least three days. Exclusion criteria were 1) use of antidiabetic drugs, 2) on intravenous glucose solution, 3) abdominal skin lesion, or 4) refused to participate in the study. Eligibility was assessed by medical history, physical examination, and local measurement of HbA1c. All participants were provided written informed consents before enrolling into the study. The study was approved by the Ethic Committee of the Phramongkutklao Hospital.

Study procedures

After enrollment, subjects were tube fed using a 24-hour continuous feeding schedule for three days (calorie target: 30 kcal/kg/day), the Phramongkutklao's diabetic formula followed by commercial diabetic formula continuously for 36 hours each. The enteral formula nutrient composition was shown in Table 1. The sensor was inserted on Day 1 and removed on Day 3. Continuous measurements, every five minutes, were monitored over a period of three consecutive days by using a CGMS (Guardian REAL-Time CGM System, Medtronic, Northridge, CA) in all patients. The accuracy of continuous glucose monitoring system (Guardian REAL-Time CGM System, Medtronic, Northridge, CA) was 83.27%. Terumo determined that the following items must be included in the analysis of CGMS testing, at least 72 hours of using and averaging four or more calibrations per 24 hours.

The characteristic glucose pattern of each patient was reported via Carelink Personal Software. The mean amplitude of glycemic excursions (MAGE), which has been described by Service et al[12], was used for assessing glucose fluctuations during the day. The measurement of this parameter is of particular interest because when MAGE is greater, glycemic instability is higher.

Statistical analysis

All demographic data, mean average glucose excursion(MAGE), mean plasma glucose, cost, and number of capillary blood glucose (CBG) tests were presented as mean values ± SD. Comorbidity, diabetic complications, glucose measurement below 70 mg/dL, or more than 180 mg/dL were presented as percentile. Comparison of MAGE, mean plasma glucose, cost, and number of capillary blood glucose tests were evaluated using nonparametric Wilcoxon signed-rank test. The level of significance was defined as $p<0.05$.

Results

All ten stable diet-controlled tube fed patients type 2 diabetes were included. Clinical characteristics of participants were reported in Table 2. Between the first and third day of enteral nutrition, the Phramongkutklao's diabetic formula

Table 1. The enteral formula nutrient composition

	Phramongkutklao's diabetic formula	Commercial diabetic formula
Energy (kcal)	1,000	1,000
% Kcal distribution		
Protein	20	15.46
Carbohydrate	50	53.46
Fat	30	31.08
mOsm/kg H_2O (1:1)		300
Source		
Protein (g)	50	38.65
Na caseinate		50.00%
Soy protein		50.00%
Other	Egg, pumpkin	
Carbohydrate (g)	125	133.65
Dextrin		57.35%
Fructose	67%	15.20%
Moltiol		15.20%
Cellulose		1.69%
Oligofructose		10.55%
Fat (g)	33	34.53
MCT	No	No
Soy oil		100.00%
Fiber (g)	4.6	14.73
	Pumpkin, banana	Soy fiber

MCT = medium chain triglycerides

resulted significantly in lower mean plasma glucose (122±26.25 vs. 144.68±36.91 mg/dL, $p = 0.022$), cost (550.1±33.57 vs. 797.81±42.29 baht, $p = 0.004$), number of capillary blood glucose tests (5±0.94 vs. 5.3±0.82 times, $p = 0.083$). There was no significant difference in MAGE level (5.86±2.78 vs. 7.71±4.34 mg/dL, $p = 0.333$) as shown in Table 3 and Fig. 1. Although CBG higher than 180 mg/dL were presented in both formulas, the level was lower than 180 mg/dL after confirmation by plasma glucose. The continuous glucose response was significantly higher in commercial diabetic formula ($p = 0.022$) as shown in Fig. 2.

Discussion

Ten long-term facility-dwelling subjects with nasogastric feeding tubes type 2 diabetes were sequentially administered the Phramongkutklao's diabetic formula followed by commercial diabetic formula continuously for 36 hours each in a non-randomized, unblinded fashion. Caloric consumption was equivalent between the two phases (calorie target: 30 kcal/kg/day). In the present study, the Phramongkutklao's diabetic formula resulted in lower mean plasma glucose, cost, and test of capillary blood glucose than commercial diabetic formula significantly.

The mean average glucose excursion was not significantly lower in the Phramongkutklao's diabetic formula. The Phramongkutklao's diabetic formula has a fructose of 67% (83.8g per 1,000 kcal), while the commercial diabetic formula has a fructose of 15%. This made the lower mean plasma glucose as the fructose is absorbed from the gut to the portal vein. It is nearly completely metabolized in the liver through metabolic pathways, distinct from those of glucose. Furthermore, the initial steps of its metabolism are insulin-independent, and hence, fructose is largely metabolized without increasing plasma glucose. This is because 1) part of the fructose appears to be directly metabolized in enterocytes, where it is converted into lactate and glucose, and 2) the bulk of absorbed fructose is taken up by liver cells, where it is rapidly converted into fructose 1-phosphate and triose-phosphates through the sequential actions of fructokinase and aldolase B and triokinase[12]. Some nutritionists regard fructose as a relatively safe form of sugar, at least in the short term. In addition, when compared with sucrose, short-term fructose consumption appears less likely to cause symptoms of reactive hypoglycemia, or to trigger hypoglycemia-related overrating. For these reasons, fructose is often recommended for people with diabetes and is included in many weight-loss products and energy bars[13]. In short-term studies in human, fructose ingestion did not have deleterious effect on glucose metabolism, except when it was fed in very large amounts. On the contrary, it generally improved glycemic control, presumably because only a small proportion of ingested fructose is converted to glucose. In one study, Carpo et al,

Table 2. Baseline characteristics of the 10 patients

Characteristic	Mean ± SD or %
Age (year)	79.80±11.03
Female (%)	60
Male (%)	40
Duration of diabetes (year)	11.50±11.24
HbA1c (%)	5.61±0.74
Comorbidity	
Hypertension (%)	90
Dyslipidemia (%)	80
Cerebrovascular disease (%)	60
Coronary artery disease (%)	50
Diabetic complication	
Diabetic retinopathy (%)	40
Diabetic nephropathy (%)	50

Table 3. Effect of Pharmongkutklao's diabetic formula and commercial diabetic formula on MAGE, mean plasma glucose, cost, number of times fingertips, CBG >180 mg/dL and CBG <70 mg/dL

Parameters	Phramongkutklao's diabetic formula	Commercial diabetic formula	*p*-value
MAGE (mg/dL)	5.86±2.78	7.71±4.34	0.333
Mean plasma glucose (mg/dL)	122.00±26.25	144.68±36.91	0.022
Cost (bath)	550.10±33.57	797.81±42.29	0.004
Number of capillary blood glucose	5.00±0.94	5.30±0.82	0.083
CBG >180 mg/dL (%)	20%	30%	
CBG <70 mg/dL (%)	0%	0%	

MAGE = mean amplitude of glycemic excursions; CBG = capillary blood glucose

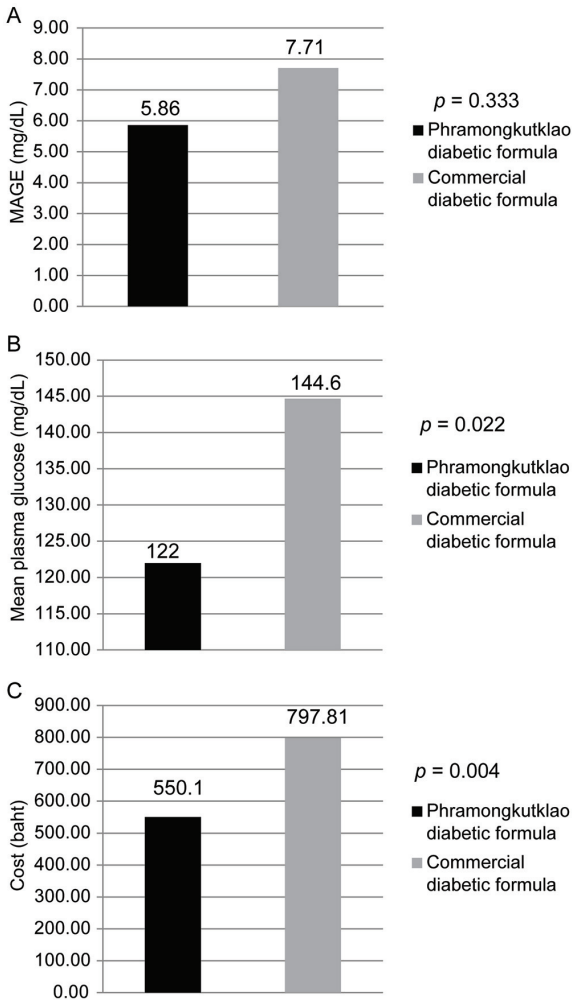

Fig. 1 Effect of Pharmongkutklao's diabetic formula and commercial diabetic formula on A) mean average glucose excursion (MAGE) (mg/dL), B) mean plasma glucose (mg/dL), C) cost (baht).

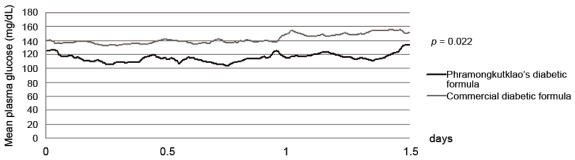

Fig. 2 Continuous glucose response graph between Pharmongkutklao's diabetic formula and commercial diabetic formula.

nine healthy individuals, 10 with impaired glucose tolerance, and 17 with type 2 diabetes were given a 50-g load of glucose, sucrose, or fructose. In all three groups, ingestion of fructose, compared with glucose or sucrose, when given either alone or with a meal, resulted in significantly lower insulin responses, serum glucose levels, and glycosuria[14]. In diabetic patients on insulin, consumption of a test meal containing 30 g of fructose resulted in less fluctuation in insulin requirements over the ensuing 24 hours than a meal containing 30 g of sucrose[15]. In a series of patients with diet controlled type 2 diabetes, substitution of sucrose by fructose (13% of calories) for three months had no significant effect on fasting plasma glucose levels or postprandial plasma glucose and insulin responses[16].

However, while fructose consumption has not adversely affected glycemic control in most studies, fructose has deleterious effects on other aspects of metabolism. High fructose intake is associated with increased plasma triglyceride concentrations, hepatic steatosis, increase visceral fat, and ectopic fat in muscle leading to impaired glucose tolerance, insulin resistance, high blood pressure, and hyperuricemia[17,18]. A recent meta-analysis concluded that fructose intake >50 g/d was already associated with altered plasma triglyceride concentrations[19]. The advantage of the Phramongkutklao's diabetic formula is less glycemic variability, lower mean plasma glucose, less hyperglycemia, and low cost. However, the commercial diabetic formula taste better, is more convenient, release slowly, has an advanced carbohydrate system, has high MUFA formulation, and is a complete and balanced nutrition. Eventually, the level of plasma glucose is lower than 180 mg/dL in both formulas as the ADA recommendation.

Strengths of the present study were performed in inpatient department of Phramongkutklao Hospital, processing and monitoring by one physician, and using continuous glucose monitoring system (CGMS). The present study was limited by the small sample sizes. There was only small number of patients eligible for our inclusion criteria, so it could only be a preliminary report.

Finally, the researchers would like to propose to modify the carbohydrate component in the Phramongkutklao's diabetic formula to avoid the deleterious effect of high fructose component in long-term use.

Conclusion

The Phramongkutklao's diabetic formula is significantly lower the mean plasma glucose, less number of capillary blood glucose tests and less expensive than commercial diabetic formula. The glucose variability (MAGE) of the Phramongkutklao's

diabetic formula is also less than commercial diabetic formula, but not statistical significant.

What is already known on this topic?

There is increasing evidence that glycemic disorders such as rapid glucose fluctuations, or glycemic variation (GV) over a daily period might play an important role on diabetic complications. Nowadays, there are many commercial diabetic formulas, facilitate glycemic management by delaying gastric emptying (fat and fiber), delaying the intestinal absorption of carbohydrate (fiber), and producing smaller glycemic responses (fructose). The preliminary study had been demonstrated that after ingestion of the Phramongkutklao's diabetic blenderized diet, postprandial glucose response was lower than after ingestion of commercial diabetic diet in patients with type 2 patients.

What this study adds?

The Phramongkutklao's diabetic formula is less glycemic variability, lower mean plasma glucose, less hyperglycemia, and low cost. In addition, the commercial diabetic formula taste better, has convenient preparation, is slow-released, and has advanced carbohydrate system, high MUFA formulation, and a complete and balanced nutrition. However, the level of plasma glucose was lower than 180 mg/dL in both formula as the ADA recommendation.

Potential conflicts of interest

None.

References

1. Aekplakorn W, Porapakkham Y, Taneepanichskul S. Diabetes mellitus. In: The Fourth Thai public health surveys by physical examination. Nonthaburi: National Health Examination Survey Office, Health System Research Institute; 2008-9: 135-9.
2. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000; 355: 773-8.
3. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke 2001; 32: 2426-32.
4. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 1995; 44: 968-83.
5. Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. Diabetes Care 1995; 18: 258-68.
6. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405-12.
7. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care 2003; 26: 881-5.
8. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. Diabetes Care 2002; 25: 275-8.
9. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006; 368: 1696-705.
10. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes 1970; 19: 644-55.
11. Hirsch IB. Glycemic variability: it's not just about A1C anymore! Diabetes Technol Ther 2005; 7: 780-3.
12. Elia M, Ceriello A, Laube H, Sinclair AJ, Engfer M, Stratton RJ. Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes: a systematic review and meta-analysis. Diabetes Care 2005; 28: 2267-79.
13. Intarasupht N, Boonyavarakul A, Ngow S, Siripiroj C. Comparative Study between the Phramongkutklao's diabetic blenderized diets and standard commercial diets on plasma glucose level in type 2 diabetic patients: preliminary study. RTA Med J 2006; 59: 199-208.
14. Crapo PA, Kolterman OG, Olefsky JM. Effects of oral fructose in normal, diabetic, and impaired glucose tolerance subjects. Diabetes Care 1980; 3: 575-82.
15. Hassinger W, Gaberle E, Schultz G, Krause U, Cordes U, Beyer J, et al. Blood glucose levels and

insulin requirement after fructose as sweetener in diabetic diet [abstract]. Diabetologia 1980; 19: 281.
16. Thorburn AW, Crapo PA, Griver K, Wallace P, Henry RR. Long-term effects of dietary fructose on carbohydrate metabolism in non-insulin-dependent diabetes mellitus. Metabolism 1990; 39: 58-63.
17. Seematter G, Tappy L. Effect of nutritional support on glucose control. Curr Opin Clin Nutr Metab Care 2007; 10: 210-4.
18. Dirlewanger M, Schneiter P, Jequier E, Tappy L. Effects of fructose on hepatic glucose metabolism in humans. Am J Physiol Endocrinol Metab 2000; 279: E907-11.
19. Livesey G, Taylor R. Fructose consumption and consequences for glycation, plasma triacylglycerol, and body weight: meta-analyses and meta-regression models of intervention studies. Am J Clin Nutr 2008; 88: 1419-37.

การศึกษาเปรียบเทียบการผันแปรระดับน้ำตาลในเลือดจากการให้สูตรอาหารเบาหวานสองชนิดผ่านทางสายให้อาหารแบบต่อเนื่อง ในผู้ป่วยเบาหวานชนิดที่ 2 ในหอผู้ป่วยในโรงพยาบาลพระมงกุฎเกล้า

ธีรานันท์ ติยะปัญจนิตย์, อภัสนี บุญญาวรกุล

ภูมิหลัง: *ภาวะการผันแปรระดับน้ำตาลในเลือดระหว่างวันมีบทบาทสำคัญต่อการเกิดภาวะแทรกซ้อนของเบาหวาน*
วัตถุประสงค์: *เปรียบเทียบการผันแปรระดับน้ำตาลในเลือด ระดับน้ำตาลเฉลี่ย จำนวนครั้งจากการวัดระดับน้ำตาลปลายนิ้ว ค่าใช้จ่ายจากการให้อาหารเบาหวานสูตรโรงพยาบาลพระมงกุฎเกล้าเปรียบเทียบกับอาหารเบาหวานสูตรที่มีจำหน่ายปัจจุบัน ในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีสภาวะคงที่และได้รับอาหารผ่านทางสายให้อาหารแบบต่อเนื่องเท่านั้น*
วัสดุและวิธีการ: *การศึกษาแบบ cross-over ระหว่างเดือนตุลาคม พ.ศ. 2553 ถึง กุมภาพันธ์ พ.ศ. 2554 ในหอผู้ป่วยอายุรกรรม โรงพยาบาลพระมงกุฎเกล้า ผู้เข้าร่วมการศึกษาเป็นผู้ป่วยเบาหวานชนิดที่ 2 ที่มีสภาวะคงที่ และได้อาหารผ่านทางสายให้อาหารเท่านั้น ผู้เข้าร่วมทุกรายได้รับการติดเครื่อง continuous glucose monitoring system (CGMS) ทางหน้าท้องระหว่างการศึกษาเป็นระยะเวลา 72 ชั่วโมง เปรียบเทียบการผันแปรระดับน้ำตาลในเลือด ระดับน้ำตาลเฉลี่ย ค่าใช้จ่าย และจำนวนครั้งจากการวัดระดับน้ำตาลปลายนิ้วระหว่างการให้อาหารเบาหวานสูตรโรงพยาบาลพระมงกุฎเกล้ากับอาหารเบาหวานสูตรที่มีจำหน่ายปัจจุบัน*
ผลการศึกษา: *ผู้ป่วย 10 รายที่เข้าร่วม พบว่า อาหารเบาหวานสูตรโรงพยาบาลพระมงกุฎเกล้า ทำให้ระดับน้ำตาลเฉลี่ยน้อยกว่า (122±26.25 vs. 144.68±36.91 มิลลิกรัมต่อเดซิลิตร, p = 0.022), ราคาถูกกว่า (550.1±33.57 vs. 797.81±42.29 บาท, p = 0.004), และจำนวนครั้งของการเจาะน้ำตาลปลายนิ้วน้อยกว่า (5±0.94 vs. 5.3±0.82 ครั้ง, p = 0.083), อาหารเบาหวานสูตรที่มีจำหน่ายปัจจุบันอย่างมีนัยสำคัญและการผันแปรระดับน้ำตาลในเลือดน้อยกว่า (5.86±2.78 vs. 7.71±4.34 มิลลิกรัมต่อเดซิลิตร, p = 0.333) แต่ไม่มีนัยสำคัญทางสถิติ*
สรุป: *อาหารเบาหวานสูตรโรงพยาบาลพระมงกุฎเกล้า ทำให้ระดับน้ำตาลเฉลี่ยน้อยกว่า ราคาถูกกว่าและจำนวนครั้งของการวัดระดับน้ำตาลปลายนิ้วน้อยกว่าอาหารเบาหวานสูตรที่มีจำหน่ายปัจจุบันอย่างมีนัยสำคัญและการผันแปรระดับน้ำตาลในเลือดน้อยกว่า แต่ไม่มีนัยสำคัญทางสถิติ อาหารเบาหวานทั้งสองสูตรไม่ทำให้ระดับน้ำตาลเกิน 180 มิลลิกรัมต่อเดซิลิตร*