

The Comparison of the Effects of three Meals Feeding a Day and Four Meals Feeding a Day in Type 2 Diabetes Mellitus Hospitalised Patients in Thammasat University Hospital on Blood Sugar Control and Enteral Feeding Complications

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Abstract

Background: As malnutrition negatively impacts hospital outcomes, hospitalised patients should receive proper nutritional management. Enteral nutrition (EN) is the most common route for non-volitional dietary support, usually fed four times/day. It is different from patients with volitional feeding who receive only three meals/day. This practice may affect blood glucose (BG) control in enteral feeding diabetes patients and increase nursing care's working burden. As a result, the study aimed to compare BG control and enteral feeding complications between 3 and 4 times feeding/day in hospitalised diabetes patients who require EN. **Methods:** A non-blind randomised controlled trial study was conducted in 37 types two diabetes hospitalised patients who required EN in Thammasat University hospital (TUH) from April 1 to December 31, 2019. The study patients were randomised and stratified by HbA1C at <8% or ≥8% to treat three meals or four meals/day. BG was controlled based on the insulin injection protocol of TUH. The study data was collected at least five days until the patients were stopped EN or discharged from the hospital. The primary outcome was a percentage of times BG was in controlled at ≤180mg/dl. The secondary outcomes were any feeding complications such as frequency of hypoglycemia, diarrhea and gastric residual volume over 100 ml before the next feeding time. **Results:** 37 patients were included. 83% of the patients were female, and the mean age was 78.44 ± 8.14 and 74.11 ± 10.03 years old in three meals and four meals feeding group, respectively. There were none significant in mean percentage of BG control between three times and four times/day either in HbA1C <8% and HbA1C ≥8% (52.21% and 68.43%, *P* value = 0.192 and 54.29% and 55.10%, *P* value = 0.942, respectively). Percentage of hypoglycemic events were none significant in 3 vs 4 times feeding at 1.70% vs 0.99%, *P* value = 0.552 and 2.53% vs 2.00%, *P* value = 0.727 in HbA1C <8% and HbA1C ≥8%, respectively. However, other complications were not significant between two groups. **Conclusion:** There was no clinically significant outcome on BG control and other complications between three and four times feeding/day in type 2 diabetes hospitalised patients. Therefore, three times feeding can be implied in clinical practice to reduce the burden of nursing care.

Keywords: Blood sugar, diabetes mellitus, enteral feeding, enteral nutrition, feeding intolerance

INTRODUCTION

Type 2 diabetes mellitus is one of the most common non-communicable diseases and has been found in about 95% of diabetes patients. Therapy aims to control an acceptable blood sugar level to prevent complications. The most challenging part of the treatment plan is determining what to eat and following a meal plan. There is not a one-size-fits-all eating pattern for individuals with diabetes, and meal planning should be individualised. Medical nutrition therapy (MNT)

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is associated with A1C decreases of 0.3–2% for people with type 2 diabetes.^[1] The goals of nutrition therapy are to promote healthy eating patterns to improve overall health, including achieving and maintaining body weight, control blood glucose, blood pressure, and serum lipid, and delay or prevent the complications of diabetes. Atherosclerosis complications such as cardiovascular and cerebrovascular diseases can render diabetes patients bedridden, resulting in required caregivers. Enteral nutrition (EN) is the most common route for non-volitional nutritional support, usually used in bedridden patients. Indications of EN are in patients with decreased sensorium level, dysphagia from neurological disease, and loss of appetite from chronic inflammatory diseases such as chronic liver disease and chronic kidney disease. Also, malnourished patients result from surgical or psychological problems and inadequate energy intake for more than five days or underfed less than 50% of calories requirement in 7 to 10 days.^[2,3] However, there was no recommendation about meal frequency in EN feeding. Usually, patients with tube feeding are fed around four times a day as it is compatible with routine nursing care. Therefore, they also are fed four times a day at home. This practice may not be practical for their caregivers as people usually eat only three main meals a day. Moreover, feeding time may affect diabetic patients, for example, the ability to control blood sugar or body weight. There are studies to substantiate lower frequency of meal pattern have positive effect on body weight, insulin resistance, beta cell function and hepatic fat content, as compared to increased frequency of meal patterns.^[4] A previous study found that dietary control with less meal frequency may influence blood glucose, lipid, insulin sensitivity, and metabolism rate. However, in hospitalised diabetes patients with EN feeding, the standard care is to feed four to six meals/day to reduce the risk of aspiration or feeding intolerance. It is different from patients with volitional feeding who receive only three meals/day. This practice may affect blood glucose control in enteral feeding diabetes patients and increases in working burden of nursing care. As a result, this study aimed to compare blood glucose control and enteral feeding complications between three and four times feeding/day in hospitalised diabetes patients who require EN.

MATERIALS AND METHODS

Study design

We conducted a non-blind randomised controlled trial in hospitalised type 2 diabetes mellitus patients in the medical ward of Thammasat University Hospital (TUH), who required enteral feeding. Study participants received either regular feeding four times at 6AM/12PM/6PM/12AM or experimental feeding three times at 6AM/12PM/6PM. The primary outcome was the percentage of times that blood glucose remained controlled at ≤ 180 mg/dl. Secondary outcomes were any feeding complications such as frequency of hypoglycemia, diarrhea and gastric residual volume (GRV) over 100 ml before the next feeding time. We enrolled hospitalised patients aged

18 years old or more diagnosed with type 2 diabetes mellitus and had a nasogastric tube for gastric feeding. They also had an APACHE II score of less than 30 and were stable on enteral feeding with more than 50% of energy requirement for more than 48 hours. Also, were on enteral feeding for at least five days of duration. Vital signs were stable. Endotracheal tube or tracheostomy tube intubation with ventilator used is acceptable. However, the exclusion criteria were pregnancy, critical illness with unstable vital signs or end-of-life care. Also, patients with a gut obstruction or feeding intolerance with GRV >250ml, diarrhea >3 times/day or >500 ml/day for two days, or who have received continuous dripping of enteral feeding were excluded.

Study protocol

After informed consent, patients will receive commercial diabetic formula with 30–35 kcal/kg/day and protein 0.8–2 gm/kg/day as an enteral feeding protocol of TUH. The study patients were randomised using a block of four and stratified by HbA1C at <8 or $\geq 8\%$ with concealment of allocation by sequentially numbered. Accu-Chek® did blood glucose collection before feeding. Accu-Chek® has an accuracy that can detect blood glucose from 10 to 600 mg/dl in 5 seconds under a temperature of 8 to 44 degrees Celsius. Blood collection used just only 0.6 microliters from fingers, feet, arm or forearm, also possible. The SD values at glucose levels <100 mg/dL are 3.2 mg/dL or less, and coefficient of variance values for glucose levels >100 mg/dL are 3.9% or less compared with venous blood sampling. Thammasat insulin protocol was used to correct blood glucose just only by the investigator. The data was collected for at least five days or until discharge or death.

Statistical analyses

The study was a pilot study; therefore, the total participants at 30 participants could represent the study outcome. Categorical data will be shown as numbers and percentages. The comparison of the two groups will be conducted by Chi-squared test. Continuous data will be shown as mean and standard deviation. The comparison of these two groups will be shown by student T-test or Mann–Whitney U test. The data with $P < 0.05$ is a significant statistic. SPSS version 18 will be used in data analysis. This study was approved by the Human Research Ethics Committee of Faculty of Medicine Thammasat University with project number MTU-EC-IM-1-044/62 and registered to Thai Clinical Trails Registry number TCTR20190723002.

RESULTS

The study enrolled a total of 43 patients with type 2 Diabetes Mellitus with EN feeding between April 1 to December 31, 2019. The six participants were excluded due to the length of EN feeding being less than five days. Finally, a total of 37 patients have met the inclusion criteria and underwent randomization. [Figure 1] The baseline characteristic of the participants is shown in Table 1. The study of 37 patients

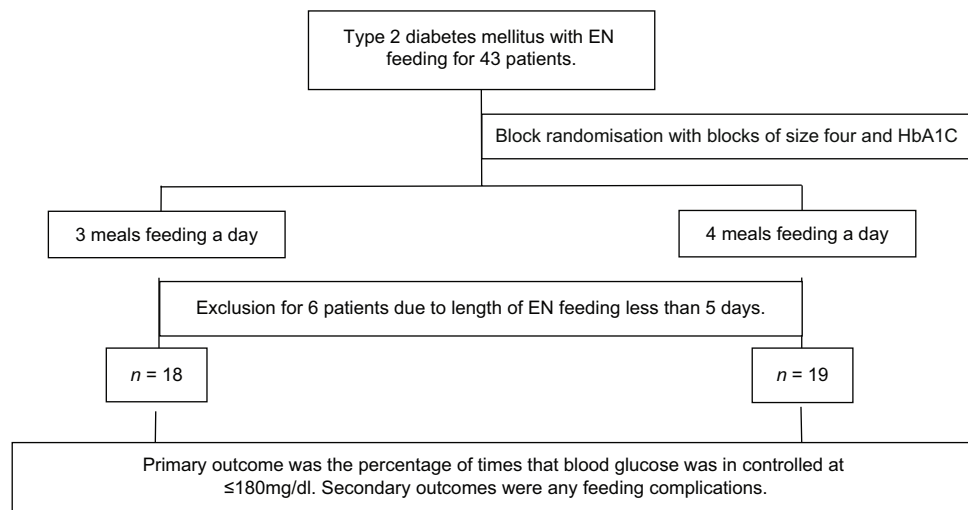


Figure 1: Enrollment of the study participants

Table 1: Baseline characteristic of patients

Baseline characteristic of patients	Treatment A (3 meals/day) (n=18)	Treatment B (4 meals/d) (n=19)	P
Age (years)	78.44±8.14	74.11±10.03	0.159
Sex	Female: 15* (83%) Male: 3 (17%)	Female: 10* (53%) Male: 9 (47%)	0.046
HbA1C (%)	8.31±2.92	8.52±3.47	0.844
Body mass index (kg/m ²)	22.04±4.52	22.07±5.07	0.987
APACHE II score**	15.56±5.74	18.00±6.67	0.241
NAF score***	A=1 (5%) B=7 (39%) C=10 (56%)	A=1 (6%) B=9 (47%) C=9 (47%)	0.871
Pre-study blood glucose (mg/dl)	226.01±59.71	197.95±79.26	0.234
Pre-study anti-diabetic treatment with insulin therapy	16.7%	26.3%	0.476
Pre-study anti-diabetic treatment with oral anti-diabetic drugs	50%	36.8%	0.419
Length of study (day)	17.50±9.87	17.21±14.79	0.945
Calories intake (kcal/kg/day)	31.27±5.06	31.31±3.30	0.975
Protein intake (gm/kg/day)	1.24±0.27	1.27±0.26	0.733
Total enteral feeding volume/day (ml)	1094.12±102.90	1065.00±198.08	0.270
Enteral feeding volume/feed (ml)	368.89±33.46*	268.42±49.89*	<0.001
Serum creatinine (mg/dl)	1.14±0.71	2.52±2.28	0.158
CKD-EPI 2009(ml/min/1.73 m ²)	62.41±29.38	49.50±39.52	0.297

Presented in mean±SD and independent-samples *t* test. Treatment A=3 meals/day, Treatment B=4 meals/day. **P*<0.05. **APACHE II Score (Acute Physiology And Chronic Health Evaluation). ***NAF score A=normal-mild malnutrition, B=moderate malnutrition, C=severe malnutrition

who were randomised to feed three meals/day for 18 patients and four meals/day for 19 patients. There was no significant statistic in baseline characteristic of two groups except there was female for 83% in three meals/day and 53% in four meals/day (p-value = 0.046) and enteral feeding volume was 368.89 ± 33.46 ml/feed in three meals/day and 268.42 ± 49.89 ml/feed in four meals/days (p-value < 0.001). Mean ages were 78.44 ± 8.14, 74.11 ± 10.03 years (p-value 0.159), HbA1C 8.31% ± 2.92, 8.52% ± 3.47 (p-value = 0.844), BMI 22.04 ± 4.52, 22.07 ± 5.07 kg/m² (p-value = 0.987), APACHE II score 15.56 ± 5.74, 18.00 ± 6.67 (p-value = 0.241), NAF score C or severe malnutrition 56%, 47% (p-value = 0.871), Pre-study blood glucose 226.01 ± 59.71,

197.95 ± 79.26 mg/dl (p-value = 0.234), Pre-study antidiabetic treatment with insulin therapy was 16.7%, 26.3% (p-value 0.476), Pre-study antidiabetic treatment with oral anti-diabetic drugs was 50%, 36.8% (p-value = 0.419), Length of study 17.50 ± 9.87, 17.21 ± 14.79 days (p-value = 0.945), Calories intake 31.27 ± 5.06, 31.31 ± 3.30 kcal/kg/day (p-value = 0.975), Protein intake 1.24 ± 0.27, 1.27 ± 0.26 gm/kg/day (p-value = 0.733), Total enteral feeding volume 1094.12 ± 102.90, 1065.00 ± 198.08 ml/day (p-value = 0.270), Baseline Serum Creatinine 1.14 ± 0.71, 2.52 ± 2.28 mg/dl (p-value = 0.158) and CKD-EPI (2009) 62.41 ± 29.38, 49.50 ± 39.52 (ml/min/1.73 m²) (p-value = 0.297) in three meals and four meals feeding, respectively.

There were none significant in mean percentage of BG control in ≤ 180 mg/dl between three times feeding and four times feeding a day, 53.14% and 62.12% (p-value = 0.275), respectively. Percentage of hypoglycemia were none significant in both groups, 2.19% and 1.93% (p-value = 0.849), three meals and four meals, respectively [Table 2].

There were none significant in percentage of blood glucose control ≤ 180 mg/dl in three meals/day and four meals/day in HbA1C $< 8\%$ or $\geq 8\%$ (52.21% and 68.43%, P value = 0.192 and 54.29% and 55.10%, P value = 0.942, respectively). Hypoglycemic events happened in 52 times in 2521 times of blood collection, 2.06%. Hypoglycemic events were 27 times in 1231 times of blood collection, 2.19% in three meals/day and 25 times in 1290 times of blood collection, 1.93% in four meals/day (p-value = 0.849). Both HbA1C $< 8\%$ and HbA1C $\geq 8\%$ has non-significant hypoglycemic events in three meals/day or four meals/day, 1.70% and 0.99% (p-value = 0.552) and 2.53% and 2.00% (p-value = 0.727), respectively as in Table 3. All patients with hypoglycemic events had no hypoglycemic symptoms. We corrected hypoglycemia by early feeding and repeat BG at 15 min after fed. Hypoglycemic events were in morning for 15 times in 27 times, 55.56% in three meals/day. In four meals/day, hypoglycemic events were in morning for 9 times and lunch for 8 times from total hypoglycemic events 25 times, 36% and 32%, respectively.

There were none significant in complication of EN feeding.

DISCUSSION

There was no study on meals frequency in EN before. Based on our knowledge, our study was the first study to identify the effects of feeding time to the impacts on blood sugar control and feeding complications in diabetic patients who required

EN. We decided to do the study on hospitalised patients because if there were any complications from EN, we can correct the problem immediately.

As in recommendation of American Diabetes Association 2022,^[5] the treatment goal of diabetes mellitus elderly patients with multiple coexisting chronic illnesses or impairments of activities of daily living or long-term care, fasting or preprandial glucose is 90-150 mg/dl and HbA1C which $< 8\%$ is acceptable. In this studied, we designed to subgroup in HbA1C $< 8\%$ and HbA1C $\geq 8\%$ group to analyze the effect of HbA1C to blood glucose control because most of study populations were elderly and had co-morbidity with macrovascular complications. So, the cut point of HbA1C of this studied can be implied to use with safe.

Also, calories and protein intake in this study is appropriate as in recommendation of nutrition support for adults EN,^[6] as the participants in both three meals/day and four meals/day have received DM formula commercial EN with calories intake $31.27 \pm 5.06, 31.31 \pm 3.30$ kcal/kg/day (p-value=0.975) and protein intake $1.24 \pm 0.27, 1.27 \pm 0.26$ gm/kg/day (p-value = 0.733), respectively, which there was non-statistic significant between the groups. DM formula EN was used in this studied, so blood glucose may not have an effect by feeding formula.

Patients in three meals feeding have serum creatinine 1.14 ± 0.71 mg/dl with CKD-EPI 2009 62.41 ± 29.38 ml/min/1.73 m², chronic kidney disease stage II. While patient in four meals feeding have serum creatinine 2.52 ± 2.28 mg/dl with CKD-EPI 2009 49.50 ± 39.52 ml/min/1.73 m², chronic kidney disease stage IIIA. But there were none significant in statistical analysis of both groups (p-value = 0.158 for serum creatinine and P value = 0.297 for CKD-EPI 2009).

Glycemic target is < 180 mg/dl as in recommendation of glycemic targets in hospitalised patients.^[7,8] Insulin being infused if blood glucose exceeds 180 mg/dl by Thammasat insulin injection protocol. As in this protocol, the blood glucose correction makes sure that blood glucose variation does not depend on investigators.

The result has shown that there were none significant in mean percentage of BG control in ≤ 180 mg/dl between three times feeding and four times feeding a day, 53.14% and 62.12% (p-value = 0.275), respectively. Percentage of

Table 2: Percentage of time of blood sugar in three meals feeding and four meals feeding

Percentage of time in blood glucose level	Treatment A (3 meals/day, n=18)	Treatment B (4 meals/day, n=19)	P
≤ 180 mg/dl	713 in 1231 times 53.14%	831 in 1290 times 62.12%	0.275
< 70 mg/dl	27 in 1231 times 2.19%	25 in 1290 times 1.93%	0.849

Table 3: Percentage of time of blood sugar in HbA1C $< 8\%$ and HbA1C $\geq 8\%$

Percentage of time in blood glucose level	HbA1C $< 8\%$		HbA1C $\geq 8\%$	
	Treatment A (3 meals/day, n=10)	Treatment B (4 meals/day, n=10)	Treatment A (3 meals/day, n=8)	Treatment B (4 meals/day, n=9)
≤ 180 mg/dl	354 in 606 times 52.21%	501 in 762 times 68.43%	359 in 625 times 54.29%	330 in 528 times 55.10%
		$P=0.192$		$P=0.942$
< 70 mg/dl	9 in 606 times 1.70%	13 in 762 times 0.99%	18 in 625 times 2.53%	12 in 528 times 2.00%
		$P=0.552$		$P=0.727$

hypoglycemia were none significant in both group, 2.19% and 1.93% (p -value = 0.849), three meals and four meals, respectively.

In subgroup analysis of HbA1C <8% or \geq 8%, percentage of time in which blood glucose were in controlled was non-significant in three meals/day and four meals/day, 52.21% and 68.43%, P value = 0.192 and 54.29% and 55.10%, P value = 0.942, respectively.

Hypoglycemic events in HbA1C <8% or \geq 8% was no statistically significant in both three meals/day and four meals/d groups, 1.70% and 0.99% (p -value = 0.552) and 2.53% and 2.00% (p -value = 0.727), respectively. There was a study in 2009 found that hypoglycemic in hospitalised patients were 10.1% in critical illness ward and 3.5% in general medical ward. Our study had hypoglycemic events lower than the past studied.^[9] The hypoglycemic events of our study were occurred in morning for 55% in three meals/day but in four meals/day, hypoglycemics not correlated to each meal. This maybe because three meals/day had longer fasting time. However, in our study the participants did not have any hypoglycemic symptoms. We also corrected by early feeding and checked blood glucose 15 min after that. Therefore, we suggest that in three meals feeding practice, delaying the third time feeding for 1-2 hours of regular dinner time at 6PM may help decrease the risk of morning hypoglycemia.

Other complications were not different in two groups. Only one event of gastric residual volume (GRV) >100 ml occurred in each group. As in Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient,^[10] GRVs not be used as part of routine care to monitor ICU patients receiving EN to prevent automatic cessation of EN. Also in another guideline, GRV should not be used routinely as a monitor in hospitalised patients on EN.^[11] In our study, GRV measurement was done to raise concern of feeding intolerance, prevented complication and prompt of intervention to ensure a nutrition goal. However, the volume per feed of three meals at about 368.89 ± 33.46 ml/feed was higher than four meals, 268.42 ± 49.89 ml/feed, this amount of volume in three meals feeding did not contribute to feeding intolerance complication.

There was no previous study on diabetes EN and blood glucose. Munsters *et al.*^[12] studied in 2012, healthy male subjects with BMI 21.6 ± 0.6 kg/m² who were randomised to receive low meal frequency (3 meals/day) and high meal frequency (14 meals/day) with same calories intake consisting of Carbohydrate: Protein: Fat in ratio of 55:15:30. This study showed that low meal frequency (3 meals/day) had better glycemic control, improve ment in resting metabolic rate, increased satiety and reduced hunger as compared to higher meal frequency (14 meals/day). Three meals/day can be relevant for blood sugar and body weight control on the long term.

Another study in 2014 by Kahleova *et al.*,^[4] a comparison the effect of six meals vs two meals a day, on body weight, hepatic

fat content (HFC), insulin resistance and beta cell function. A randomised studied in 54 patients with type 2 diabetes treated with oral hypoglycemic agents, both men and women, age 30-70 years, BMI 27-50 kg/m² and HbA1C 6-11.8% to follow two regimens of diet, six and two meals, each for 12 weeks. The result found that body weight reduction, hepatic fat content, insulin resistance, fasting plasma glucose and C-peptide also glucagon was also improved in two meals a day.

Another study evaluated the effects of meal frequency on indices of carbohydrate and lipid metabolism parameters in healthy obese women.^[13] During phase 1 (14 days) of this randomised cross-over trial, subjects were asked to eat or drink from normal diet on six occasions/day (regular meal pattern) or to follow three to nine meals/day in a chaotic manner (irregular meal pattern). In phase 2 (14 days), subjects were asked to crossover to alternate meal pattern from phase 1. Blood sugar, lipid, insulin concentrations were collected before and 3 hours after meals. The result found that regular meal pattern associated with lower energy intake, greater postprandial thermogenesis and lower fasting total and LDL cholesterol. However, fasting blood glucose and insulin values were not affected by meal pattern, only the peak insulin concentration was lower in regular meal pattern.

Another study investigated three meal patterns for three 12 hours study days between consuming a low-frequency meal regimen (three meals (3M); consumed every 4 hours), a high-frequency meal regimen (six meals (6M); consumed every 2 hours) and a high-frequency, high-protein meals ((6MHP); consumed every 2 hours) in 13 obese patients who has fasting blood glucose <100 mg/dL. Blood samples were drawn at baseline and every 10 min for 12 hours for glucose, insulin, C-peptide and glucose-dependent insulinotropic peptide (GIP). The study found that there were no significant differences in fasting glucose, insulin, C-peptide or GIP concentrations between the study days. Post-prandial changes in peak glucose concentrations were greater in the 3M condition due to larger energy and carbohydrate load/meal but overall glucose concentrations were lower for longer periods of time during the day while on the 3M regimen.^[14]

The result of this study has been correlated with the previous research that fewer meals influence blood sugar control.

Our trial has some limitation that is a pilot study with a small size of the population. Larger study with more population size may show an effect.

CONCLUSION

There was no clinically significant outcome on blood glucose control and other complications between three and four times feeding/day in type 2 diabetes hospitalised patients. Therefore, three times feeding can be implied in clinical practice to reduce burden of nursing care.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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