

# Glycaemic response to three main meals or five smaller meals for patients on rapid-acting insulin

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## KEYWORDS

type 2 diabetes mellitus; insulin aspart; glycaemic control; diet

## ABSTRACT

### Objective

To compare seven-point blood glucose profiles of patients with type 2 diabetes mellitus using rapid-acting insulin, when daily calories were provided as three main meals versus five smaller meals (three main meals + two snacks), while maintaining the same total daily calorie intake and composition of carbohydrates, fats and protein.

### Design

A cross-over study.

### Setting

Xiamen University Zhongshan Hospital, China.

### Subjects

Over a four week period, 22 patients with type 2 diabetes mellitus using fixed doses of rapid-acting insulin were recruited into the study. Two patients failed to complete the study and data from the remaining 20 subjects were analysed.

### Intervention

The subjects using fixed doses of rapid-acting insulin were randomised to five smaller meals versus three main meals treatment periods. Glycaemic response to each meal pattern was measured by seven-point blood glucose profiles.

### Main Outcome Measures

The mean seven-point blood glucose levels and the risk of hypoglycaemia.

### Results

The mean seven-point blood glucose levels with the pattern of eating five smaller meals was lower than that with three main meals (9.1mmol/L vs. 9.5mmol/L), however the difference was not statistically significant ( $F=0.524$ ,  $P=0.474$ ). There were no differences in mean blood glucose levels across the seven-point profile. The risk of hypoglycaemia was also not statistically significant.

### Conclusions

This suggests that it may be unnecessary for patients using rapid-acting insulin to have five smaller meals.

## Acknowledgements

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## INTRODUCTION AND LITERATURE REVIEW

Type 2 diabetes mellitus (T2DM) is a progressive disease, with continued loss of  $\beta$ -cell function after diagnosis. The UK Prospective Diabetes Study (UKPDS) found that nine years after diagnosis, approximately 80% of patients with T2DM were unable to achieve glycaemic targets with diet or monotherapy (Wright et al 2002). Accordingly, many patients with T2DM progress to need insulin therapy. Diabetes health professionals often suggest that patients using insulin switch from eating three main meals throughout the day to three main meals with several snacks, while maintaining the same total daily calorie intake (Lu 2014; Dai et al 2010). This is standard practice in China. The current Chinese Diabetes Education and Care Guidelines recommend that patients should eat fruit between meals as a snack, particularly when insulin therapy is required (Dai et al 2010). However, this dietary regulation is difficult for many patients with diabetes, therefore, this recommendation is often unfeasible in clinical practice.

The advice centres on the assumption that switching from eating three main meals to several snacks throughout the day will minimise postprandial glycaemic excursions and prevent hypoglycaemia. In the past, short-acting insulin formulation, i.e., regular insulin, had been a mainstay of diabetes management. The peak time of short-acting insulin is 2-4 hours so it was postulated that patients on short-acting insulin should eat a snack between meals to prevent hypoglycaemia (Heinemann et al 2011). Owing to the more rapid onset and shorter duration of action of rapid-acting insulin frequently used today (Franzè et al 2015; Home 2012), there is a question as to whether snacks are still necessary. This had not previously been systematically investigated.

Therefore this randomised cross-over study aimed to compare seven-point blood glucose profiles in patients with T2DM treated with fixed doses of rapid-acting insulin when daily calories were provided as three main meals versus five smaller meals (three main meals + two snacks). A further aim was to observe whether there was a difference in relation to hypoglycaemia risk.

## METHOD

### Participants

This study was conducted in the endocrine ward of Xiamen University Zhongshan Hospital in China. Over a four week period 22 patients with T2DM who had been admitted for rapid-acting insulin therapy were recruited into the study. Patients under the age of 18 as well as patients with DKA and unconscious hypoglycaemia, stroke and heart attack were excluded. Pregnant patients, as well as those using medications known to interfere with glucose metabolism were also excluded. A total of 22 patients with T2DM using Continuous Subcutaneous Insulin Infusion (CSII) therapy were recruited for this study. One subject failed to finish the two study periods because of diarrhea. One subject required their dose of insulin to be changed due to significant hyperglycaemia (preprandial blood glucose levels > 16 mmol/L). The results of these two subjects were not included in the analyses leaving data from a total 20 subjects for analysis.

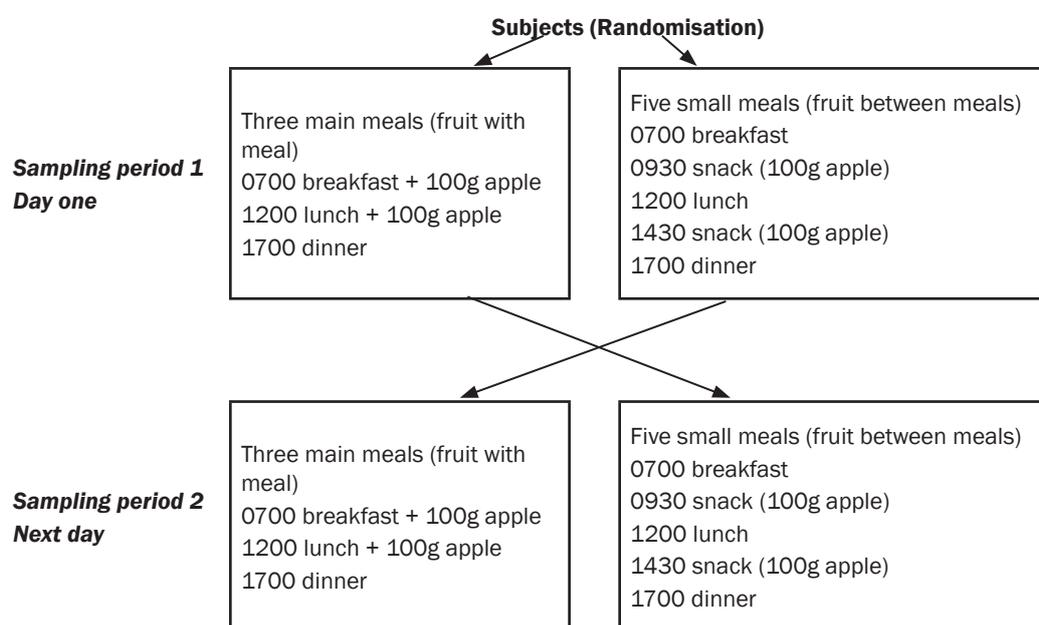
### Procedures

In this study, all subjects received rapid-acting therapy using CSII (Medtronic MiniMed 712, USA). The insulin pump infusion set was sited in the subcutaneous tissue on the abdomen and the insulin pump was filled with rapid-acting insulin aspart. Insulin doses, including bolus insulin and basal insulin rates, were determined for each subject on an individual basis by their treating physician and were kept constant throughout the study. Subjects requiring the dose of insulin to be changed due to significant hyperglycaemia (preprandial

blood glucose levels > 16 mmol/L) or hypoglycaemia (blood glucose level < 3.5mmol/L) were excluded from this study.

Subjects were randomized using a random digit table to one of two possible sequences as shown in figure 1. Trial procedures were performed over two consecutive days. The total daily caloric content of hospital diets for each subject were set up according to the criteria of 25–30 kcal/kg (standard weight) by a dietitian. The total daily calories and composition of carbohydrates, fats and protein were kept identical between the two study periods. The only difference between the two periods was whether the calories were given as three main meals or five smaller meals. Subjects were fed a standardised evening meal the night preceding study period. This was followed by an overnight fast of 10h to limit the impact of the meal on the fasting glucose level.

**Figure 1: The meal distribution in the two study periods**



As shown in figure 1, when randomised to three main meals, the subjects were fed a standardised breakfast and 100g apple at 0700hrs. This was followed by a standardised lunch and 100g apple at 1200hrs and a standardised dinner at 1700hrs. When randomised to five smaller meals, the subjects received the same standardised breakfast, however the 100g apple was held over and consumed as the first snack at 0930 hrs. At 1200hrs the subjects were fed the standardised lunch with the 100g apple given as the second snack at 1430hrs. At 1700hrs the subjects received the same standardised dinner. All the foods were weighed using digital scales (CUBIII, METTLER-TOLEDO INTERN, 3kg max/ 1g resolution). No additional food or drink (except water) was consumed during the study periods unless required to treat hypoglycaemia, which for the purpose of this study, was classified as a blood glucose level <3.5mmol/L.

A standard dose of bolus rapid-acting insulin was administered using CSII immediately prior to each main meal by a ward nurse not involved in the study. No bolus of insulin was administered with the snack. The subjects kept the same activity and were asked to abstain from extra exercise during the two study periods. Seven-point blood glucose levels were monitored using an Optium Xceed blood glucose monitor (Abbott Laboratories, Maidenhead, UK) for all the subjects. Preprandial blood glucose level measurements were collected immediately before boluses of insulin were administered and postprandial blood glucose level measurements were collected at two hours post-meal (2h post-meal). Bedtime blood glucose level was measured at 2200hrs each night.

### Statistical analysis

This sample size was calculated by the software of statistical considerations for a cross-over study developed by Harvard University (David 2015). A sample size of 20 patients provided 80% power to demonstrate a 0.7mmol/L difference in mean seven-point blood glucose concentration, assuming a standard deviation for this measure of 1.0mmol/L at the 5% significance level.

Data were analysed using Statistical Package for the Social Sciences (SPSS) 16.0 software. Continuous data were checked for normality and presented as mean  $\pm$  standard deviation (SD). Categorical data were presented as proportions. A two-way ANOVA model for cross over design, including patients, treatment and period effects, was used to compare all variables. Statistical significance was based on 2-sided t-test and accepted at the  $p < 0.05$  level of significance.

### Ethics Approval

This study was approved by the local ethics committee of Medical College Xiamen University Medical Research Ethics Committee and written informed consent was obtained from all participants.

## RESULTS

Descriptive data are presented as the mean  $\pm$  1 standard deviation. The twenty subjects included in the study had a mean age of  $59.4 \pm 15.6$  years; body mass index  $25.3 \pm 3.0$  kg/m<sup>2</sup>; duration of diabetes  $8.6 \pm 6.0$  years, and 60% were male. The majority of patients had sub-optimal glycaemic control as indicated by glycosylated haemoglobin (HbA1c) of  $8.7 \pm 1.4\%$  ( $95.0 \pm 15.0$  mmol/mol). The fasting blood levels of C-peptide was  $0.45 \pm 0.24$  pmol/ml (normal range:  $0.3 \sim 0.6$  pmol/ml) and the levels of C-peptide after-75g glucagon stimulationin at 120min was  $1.44 \pm 0.76$  pmol/ml. The bolus insulin dose was  $22.5 \pm 9.0$  units per day and the basal insulin dose was  $14.1 \pm 6.2$  units per day.

### Seven-point blood glucose profile

When the subjects were randomized to eat five smaller meals each day, the mean seven-point blood glucose levels was lower than when they ate three main meals ( $9.1$ mmol/L vs  $9.5$  mmol/L). However, the ANOVA for cross over design indicated that the difference was not statistically significant ( $F=0.524$ ,  $P=0.474$ ). The differences on mean preprandial blood glucose levels, postprandial blood glucose levels and preprandial to postprandial glucose excursions at all meals were also not statistically significant (table1).

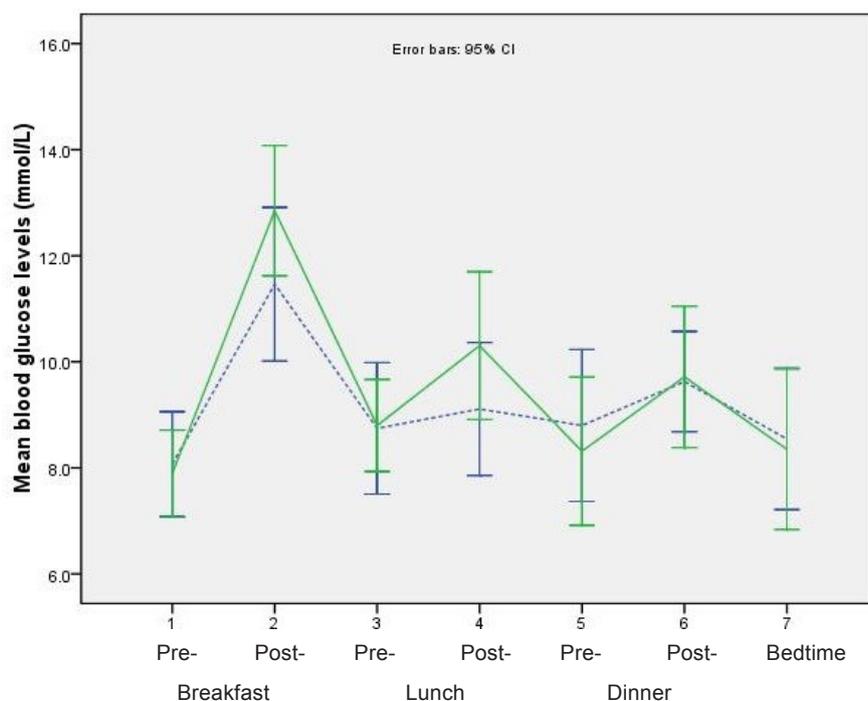
**Table 1: Mean blood glucose levels [ $\pm$  sd(mmol/L)] in 20 patients randomised to five smaller meals versus three main meals**

	Five meals	Three main meals	F	P
Seven-point blood glucose levels	$9.1 \pm 1.7$	$9.5 \pm 1.8$	0.524	0.474
Preprandial blood glucose levels	$8.5 \pm 2.1$	$8.3 \pm 1.8$	0.105	0.748
Postprandial blood glucose levels	$10.0 \pm 1.7$	$10.9 \pm 2.2$	1.926	0.174
Preprandial to postprandial glucose excursions	$3.0 \pm 1.1$	$3.5 \pm 1.0$	2.036	0.162

There were no differences in blood glucose levels across the seven point profile as shown in figure 2. Pre-breakfast blood glucose level did not differ between treatment groups (five smaller meals vs three main meals [ $8.07 \pm 2.12$  vs  $7.89 \pm 1.76$ ,  $P=0.742$ ]). Post-breakfast blood glucose level (five smaller meals vs three main meals [ $11.47 \pm 3.09$  vs  $12.85 \pm 2.62$ ,  $P=0.129$ ]), pre-lunch blood glucose level (five smaller meals vs three main meals [ $8.75 \pm 2.65$  vs  $8.80 \pm 1.85$ ,  $P=0.925$ ]), post-lunch blood glucose level (five smaller meals vs. three main meals [ $9.11 \pm 2.68$  vs  $10.31 \pm 2.97$ ,  $P=0.179$ ]), pre-dinner blood glucose level (five smaller meals vs. three main meals [ $8.80 \pm 3.06$  vs  $8.32 \pm 2.99$ ,  $P=0.635$ ]), post-dinner blood glucose level (five smaller meals vs three main meals [ $9.63 \pm 1.96$  vs  $9.72 \pm 2.77$ ,  $P=0.909$ ]) and bedtime blood glucose level (five smaller

meals vs three main meals [ $8.55 \pm 2.85$  vs  $8.35 \pm 3.04$ ,  $P=0.856$ ]) were also not statistically significant between treatment groups (figure 2).

**Figure 2: Seven-point blood glucose profiles [mean $\pm$ sd(mmol/L)] among the 20 patients when randomized to eat five smaller meals (dash line) or three main meals only (solid line)**



### Hypoglycaemia

There were no episodes of hypoglycaemia (blood glucose level  $<3.5$  mmol/L) during the two study periods. One subject felt hungry at bedtime in both study periods but the blood glucose levels remained within the normal range on both occasions, 3.9 mmol/L and 4.4 mmol/L respectively.

### DISCUSSION

In this study, the differences in seven-point blood glucose profiles were not statistically significant for subjects using rapid-acting insulin regardless of whether their total daily caloric intake was divided between three meals or three meals and two snacks. Postprandial blood glucose levels at the three main meals group was slightly higher than the result at the five smaller meals group, which is probably attributed to the three main meals having a higher intake of carbohydrate with the main meal, but the difference was not significant ( $P=0.174$ ). The main reason for this result may be due to the more rapid onset of action of rapid-acting insulin and more effective prandial insulin coverage is available (Takeshita et al 2015; Tanaka and Hiura 2015).

Theoretically, with rapid-acting insulins' shorter duration of action (Morrow et al 2013; Nosek et al 2013), snacks eaten between meals, when rapid-acting insulin action has decreased, the peak time of rapid-acting insulin is about 1 hour (Home 2012), and may result in slightly elevated blood glucose prior to the next meal. In our study preprandial blood glucose levels for those receiving five smaller meals was slightly higher than the result of the three main meals group, (five smaller meals vs. three main meals 8.5 mmol/L vs. 8.3 mmol/L), but the difference was not significant ( $P=0.748$ ).

Previous studies have shown the importance of controlling blood glucose variability in relationship to attenuating

the risk for cardiovascular complications. In this study, the difference on the glycaemic variability, based on preprandial to postprandial glucose excursions at all meals was also not statistically significant.

This study also showed no difference in risk of hypoglycaemia. Of note, one subject had a relative low blood glucose level when measured before bed during both of the study periods, 3.9mmol/L and 4.4mmol/L respectively. These levels were recorded 4.5 hours after dinner, by which time most of the meal time bolus of rapid-acting insulin would have been absorbed (Nosek et al 2013). These low blood glucose levels are more likely to be related to basal insulin and could be addressed by changes to CSII basal insulin rates.

## LIMITATIONS

A continuous glucose monitoring system was not used in this study. Further research is required to better understand the 72 hour glucose profiles for patients using rapid-acting insulin to eat three main meals versus five smaller meals.

## CONCLUSION

Due to changes in insulin preparations seen within recent decades, this advice to switch three main meals to five smaller meals may no longer be evidence based. This study has shown that there is minimal impact on day to day glycaemic control if the daily caloric intake is consumed as three main meals or five smaller meals. There were no differences in mean blood glucose levels across the seven-point profile and the risk of hypoglycaemia was also not statistically significant for patients on rapid-acting insulin. To switch from eating three main meals throughout the day to five smaller meals may not be necessary, thereby allowing people with diabetes to follow a more flexible diet.

## RECOMMENDATIONS

The important finding is people do not need to switch from eating three main meals throughout the day to five smaller meals, as this advice is often misinterpreted. We mean 'spread your calories/carbs across the day' whereas many patients interpret this as 'eat extra'.

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