Gastric emptying of preoperative drinks is slower in adults with chronic energy deficiency: A 2 hour cross-over study among Chinese

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Running title: Gastric emptying is slower in underweight adults

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ABSTRACT

Background and Objectives: To investigate the effects of oral preoperative regimens on gastric emptying time in relation to BMI in Chinese adults. **Methods and Study Design:** The enrolled 56 adults were divided into three groups (normal-weight, underweight, and overweight) and completed a regimen of two drinks after a 2-week interval. After drinking a carbohydrate regimen (CD, 50 g carbohydrates) or a carbohydrate glutamine regimen (CGD, 44 g carbohydrates and 6 g glutamine) labelled with 99mTc-DTPA (99mTc-diethylenetriaminepentaacetic acid), gastric emptying times T50 and T90 were measured using a curve derived from scintigraphic images. **Results:** T50 and T90 had no significant difference between the CD and CGD regimens. T50 was significantly delayed in the underweight participants (BMI <18.5 kg/m^2, as Chronic Energy Deficiency, CED) compared with the normal-weight participants after drinking CD (p=0.003) or CGD (p=0.002), as well as T90 after CD (p=0.019). There was no difference in glucose concentrations between the three groups. There are negative correlations between body weight and gastric emptying time T50 (r=-0.461, p=0.016) or T90 (r=-0.553, p=0. 003) after drinking CD, as well as T50 (r=-0.553, p=0.003) after drinking CGD. **Conclusions:** Underweight adults should be careful to take oral preoperative regimens 2 hours before surgery and consider reducing the volume because of a slower gastric emptying rate.

Key Words: gastric emptying time, preoperative drinks, underweight, chronic energy deficiency, gastric emptying rate

INTRODUCTION

Preoperative fasting before anaesthesia was generally considered to start at midnight. However, a 2-hour fast after carbohydrate-containing clear fluids is safer[1] and more conducive to successful recovery.[2,3] Although preoperative fluid intake 2 hours before anaesthesia has not been associated with an increased aspiration risk, prolonged gastric emptying time of solid or liquid meals has been found in obese participants judged by the 13C-breath test compared with normal-weight participants.[4] It's not known whether clear liquid also cause delayed gastric emptying risks for some groups with different body weights, since studies aren't available. It is little known if there is a relationship between gastric emptying and bodyweight. Most investigators have focused on either normal-weight or obese individuals, but the rates of gastric emptying in underweight and overweight participants are little known. Moreover, relevant data in Chinese people are too limited to allow any conclusion to be drawn. Considering the above, well-designed studies are needed to assess the effects of bodyweight on gastric emptying in Chinese adults. This study investigates the gastric emptying time change in participants with different body mass indexes (BMIs) after drinking two types of preoperative carbohydrate fluids and whether it is feasible that regimens could empty completely from the stomach in less than 2 hours.

MATERIALS AND METHODS

Study design

This was a single-blind, two-way crossover study conducted at the Department of Nuclear Medicine in the General Hospital of Guangzhou Military Command from May 2017 to Feb 2018. Each volunteer provided written informed consent before taking part in this study. The study was conducted according to the Declaration of Helsinki for Medical Research involving human participants and was approved by the Research Ethics Committee of the General Hospital of Guangzhou Military Command (K-2016-71). The protocol was registered at www.chictr.org.cn (ChiCTR-OOC- 17011021).

Participants

The volunteers were eligible if they were aged 18 to 60 years. The exclusion criteria were as follows: diseases that affect gastric emptying (e.g., diabetes, neurological, and endocrine diseases), a history of gastrointestinal disorders or abdominal surgery, renal dysfunction (higher-than-normal blood urea nitrogen or creatinine), hepatic dysfunction [higher-than-normal aspartate aminotransferase (AST) or alanine aminotransferase (ALT)], receiving hormones or drugs that affect gastric emptying, and pregnant or lactating women. Designations of underweight, normal weight, and overweight were made based on the nutritional status. BMI = body weight (kg)/height $(m)^2$. Underweight (Chronic Energy Deficiency, CED) was defined as a BMI <18.5 kg/m^2, normal weight as $18.5 \leq$ BMI < 25 kg/m^2, and overweight as $25 \leq$ BMI < 29.9 kg/m^2 according to the standard from the World Health Organization (WHO).

Study procedures

Participants were instructed to abstain from medications, alcohol, caffeine-heavy tea, strenuous work, and exercise for 24 hours before the start of the study. All participants and their contacts were blinded throughout the study. A carbohydrate drink (CD) or a carbohydrate glutamine drink (CGD), 50 g dissolved in 400 mL water mixed with 99mTc-

DTPA (HTA Co. Ltd., Beijing, China) as a non-absorbed tracer, was given to the participants (Table 1).

The gastric-emptying test is considered the gold standard to assess gastric motility. And, Tc-99m was used to measure gastric emptying accurately in our study 5. Each volunteer was randomised to drink 400 mL of one of the two drinks within 5 minutes at 8:30 to 8:35 a.m. The end of drinking was defined as time 0 (T=0). Participants lay under a gamma camera (Infinia Hawkeye 4 SPECT system, GE, Wisconsin, USA), and images were taken at 0, 5, 10, 15, and 20 minutes and every 15 minutes thereafter until 120 minutes, while gastric emptying was monitored by scintigraphy. Participants were not allowed to eat and drink but moved freely while being monitored. The monitored time is prolonged if a 90% emptying rate is not reached in 120 minutes. After a 2-week interval, the participants drank another liquid regimen, and we conducted the same test (Figure 1).

Gastric emptying time

A region of interest (ROI) was counted on each image of the stomach to measure radioactivity. A time-activity curve was expressed as a percentage of the total amounts in the stomach versus time, from which the emptying times were derived. T50 and T90 gastric emptying times were calculated from the time at 50% and 90% gastric emptying on the curve.

Blood samples

Venous blood was sampled. Blood glucose concentrations were measured at 0, 40, and 120 minutes using an automatic biochemistry analyser (Cobas C501, Roche, Ibaraki-ken, Japan).

Ethical standard

This study was approved by the Research Ethics Committee of General Hospital of Guangzhou Military Command (K-2016-71). The protocol was registered at www.chictr.org.cn (ChiCTR-OOC- 17011021).

Statistical analysis

All parameters were tested for normality by the Shapiro–Wilk test. Data was expressed as the mean ± standard deviation (SD). Statistical analysis was performed using SPSS 22.0 (SPSS Inc., Chicago, USA). Differences between the two groups were tested for significance using the paired Student t test. Independent t tests were used to compare parametric data with different body weight. Multiple comparisons were analysed using one-way analysis of variance (ANOVA). If equal variances were assumed, the Bonferroni correction was used. If equal variances were not, the Dunnett T3 test was used. Pearson or Spearman correlations were used to determine the relationships between emptying time and BMI. A two-tailed $p<0.05$ was considered significant.

RESULTS

The study enrolled 56 Chinese individuals (24 men and 32 women). The participant characteristics are shown in Table 2. Four participants completed only one of the CD and CGD experiments. One participant had mild nausea after drinking CGD, but there were no other side effects.

Gastric emptying time between CD and CGD regimens

There was no significant difference between the CD and CGD regimens at gastric emptying T50 (36.3±13.5 min vs 38.0±2.5 min, p=0.227) or at T90 (84.7±23.8 min vs. 88.9±22.7 min, p=0.083) (Figure 2).

Gastric emptying at T50

T50 was significantly delayed in the underweight participants compared with the normal-weight participants after drinking CD (47.7±13.3 min vs 32.0±8.5 min, p=0.003) or CGD (47.6±11.2 min vs. 33.9±9.5 min, p=0.002). No significant differences of T50 were observed in the overweight participants compared with the normal-weight participants in after drinking CD (35.2±16.3 min, p=0.850) or CGD (35.7±13.0 min, p=0.957) (Figure 3).

Gastric emptying T90

T90 was significantly delayed in the underweight participants compared with the normal-weight participants after drinking CD (101.1±21.4 min vs 79.6±20.8 min, p=0.019), whereas there was no significant difference at T90 after drinking CGD (96.3±23.6 vs 79.3±19.8 min, p=0.09), although the same trend of longer time was observed.

No significant differences were observed in the overweight participants compared with the normal-weight participants after drinking CD (79.2±25.6 min, p=1.0) or CGD (94.7±22.2 min, p=0.113) (Figure 4).

More notably, T90 in two underweight participants was more than 120 minutes after drinking CD (135.6 min and 128.5 min) and CGD (141.1 min and 138.1 min), respectively. At 120 minutes, their gastric emptying rates were 82% and 85% after drinking CD, and 76%

and 81% after drinking CGD. Accordingly, their gastric residual volumes were approximately 60 to 96 mL.

Glucose concentrations

There was no difference in glucose concentrations at 0 minutes, 40 minutes, and120 minutes after drinking CD or CGD (p=0.588, p=0.473, p=0.052, respectively) in all participants.

The differences between the three groups (normal-weight, underweight, and overweight) were also not statistically significant following drinking the CD (Figure 5A) and CGD regimens (Figure 5B).

The relationship between BMI and gastric emptying times

BMI was not associated with gastric emptying times T50 (r=0.163, p=0.238) or T90 (r=0.047, p=0. 736) after drinking CD.

There was no relationship between BMI and gastric emptying time T50 after drinking CGD (r=0.134, p=0.333). Only a weak positive association existed between BMI and gastric emptying time T90 after drinking CGD (r=0.315, p=0.02).

There were negative correlations between body weight and gastric emptying time T50 (r=-0.461, p=0.016) or T90 (r=-0.553, p=0. 003) after drinking CD, as well as T50 (r=-0.553, p=0.003) after drinking CGD, but not T90 (r=-0.254, p=0.201) after drinking CGD.

DISCUSSION

In our study, compared with the normal-weight participants, the underweight participants had significantly delayed gastric emptying rate at T50 for both regimens and T90 for CD, as well as longer gastric emptying time at T90 for CGD. Moreover, T90 of two participants was more than 120 minutes with much gastric residual volumes. Similarly, there are significant inverse correlations between body weight and gastric emptying time, although their coefficients are lower.

There is little evidence about the effect of being underweight with chronic energy deficiency on gastric emptying. CED is a critical condition characterized by low energy stores.[6] Our results are in agreement with the results reported by Sena et al, which showed that gastric emptying time was prolonged in underweight patients with anorexia compared to normal-weight and obese participants.[7] This can lead to lower bodyweight because slower gastric emptying rate was associated with less calorie intake and there was a significant negative correlation between gastric emptying rate and the calorie intake.[8] Similar results were also found in the animal study, that underweight mice with limited food had a delayed gastric emptying rate compared with controls.[9] These results indicated that the safety factors of taking preoperative fluid 2 hours before surgery in underweight individuals should be carefully considered to avoid increasing the risk of aspiration during anaesthesia, since delayed gastric emptying is significantly associated with nausea and vomiting.[10]

As for the relationship between gastric emptying and body weight, there are many research studies with contradictory findings in recent years, with gastric emptying rate being reported to be equivalent,[11,12] faster,[13] or slower[14] in overweight and obese individuals compared with normal-weight individuals.[15]

Our results indicated there is a negative correlation between gastric emptying time and body weight. This is consistent with a study that a more rapid emptying rate was observed in the overweight male participants compared with normal-weight.[16] Seimon RV et al also showed overweight and obese males had faster gastric emptying rate than normal-weight individuals, though there was no difference in overall gastric emptying time.[11] Similarly, Verdich et al found no differences in emptying rate between obese participants and their lean counterparts, whereas percentage of gastric emptying during the initial 30 min was higher in the obese participants.[17] Meyer-Gerspach et al suggested that the obese participants had relatively delayed gastric emptying rates compared with normal-weight controls, but there were only 9 obese participants in their study.[4] These contradictory results are probably caused by differences in test meal (solid, liquid or clear), methodologies for measuring gastric emptying (13C-breath test, scintigraphy and so on) or other factors that may affect gastric emptying rates.

Although underweight adults have delayed gastric emptying, there is limited evidence that indicates low body weight as an independent risk factor for delayed gastric emptying. In our study, all correlation coefficients between gastric emptying time and body weight were either small or insignificant, although underweight participants had longer gastric emptying time. One of the reasons is that the normal-weight and overweight group had similar gastric emptying times.

Carbohydrate loading reduces insulin resistance and may be effective in the prevention of delayed gastric emptying.[18] Since blood glucose is not different between the two drinks in the present data, other mechanisms of different gastric emptying rate must be involved. Compared with normal-weight participants, gastric emptying rates of overweight participants were increased with higher ghrelin,[16] also the obese with decreased GLP-1 (glucagon-likepeptide-1) and PYY (Peptide YY).[4] A growing body of evidence suggests that ghrelin accelerates gastric emptying.[19] Taking ghrelin by underweight outpatients with anorexia nervosa could speed gastric emptying significantly, and aid them in gaining weight.[20,21] On the contrary, GLP-1and PYY have an inhibiting effect on gastric emptying.[22]

The use of additional glutamine in preoperative drinks may be beneficial for patients who are potentially undergoing surgery.[23,24] Our results show that there were no significant differences in the gastric emptying times between the two clear drinks with or without glutamine, both of which are standard recipes and generally used in ERAS studies. This is similar to a previous study, in which a small amount of 15 g glutamine alternative to carbohydrate (carbohydrate 36 g and glutamine 15 g in 460 mOsm/kg) did not lead to delayed gastric emptying.[25] However, another study in the literature has demonstrated that an additional 15 g of glutamine based on carbohydrate (carbohydrate 50 g add glutamine 15 g in 508 mOsm/kg) significantly reduced the gastric emptying time compared with carbohydrate alone.[26] A possible explanation is that the additional glutamine increased osmolality and subsequently delayed gastric emptying times. In our study, 6 g glutamine substitute of carbohydrate in 100 g did not change osmolality and gastric emptying very much (294 mOsm/kg vs 425 mOsm/kg). Furthermore, preoperative drinks enriched with glutamine modified postoperative insulin resistance and increased glucose disposal in patients undergoing cholecystectomy.[27] Our results show no differences in blood glucose between the two drink regimens, which indicates that a small amount of glutamine substitute did not change the gastric emptying times and glucose concentrations. The gastric emptying rates were significantly slower for the two drinks with or without glutamine in the underweight group.

There are several limitations in our study. One potential limitation originated from the small sample population. The relation between gastric emptying time and body weight is not entirely linear and should be analysed according to weight standard (BMI) to divide into four groups (underweight, normal, overweight, and obese). Unfortunately, we could not analyse findings for each group because the numbers were too small for statistical analysis, and we had no obese participants in this study. It is not clear whether the correlation exists between gastric emptying time and body weight in the obese group.

In summary, for normal-weight and overweight adults, a carbohydrate drink or a carbohydrate drink with a small amount of glutamine substitute has no differences in effect on gastric emptying for preoperative purposes. Our results suggest that individuals who are underweight with chronic energy deficiency should be careful to take oral preoperative regimens 2 hours before surgery and consider reducing the volume because of a slower gastric emptying rate. But, there was a small number of participants and no obese participants in this study. Therefore, further study is necessary to determine the suitable volume of preoperative drink regimens in the underweight population and evaluate their safety.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

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Table 1. Contents of 100 mL (approximately 25 g) of CD and CGD drinks

	CD	CGD
Carbohydrate, g	12.5	11
maltodextrin, g	10	9
fructose, g	2.5	2
Glutamine, g	0	1.5
sodium, mg	50	281
chloride, mg	6	57
potassium, mg	120	580
Osmolarity, mOsm/kg	294	425
Energy, kcal	50	50

CD, carbohydrate drink; CGD, carbohydrate glutamine drink

Table 2. Participant characteristics (Mean values and standard deviations)

Characteristics	Underweight (n=14)	Normal-weight (n=26)	Overweight (n=16)	*p*1	*p*2	*p*3
Age (years)	34.3±8.9	37.6±8.7	38.1±10.6	0.209	1	0.242
Weight (kg)	49.0±5.6	59.3±6.8	69.9±4.5	0.007	0.002	0.000
Height (cm)	164.0±7.4	163.5±7.0	161.9±8.7	1	1	1
BMI (kg/m^2)	18.2±0.3	22.1±1.2	26.8±1.9	0.000	0.006	0.000

*p*1: underweight vs normal weight, *p*2: overweight vs normal weight, *p*3: overweight vs underweight.

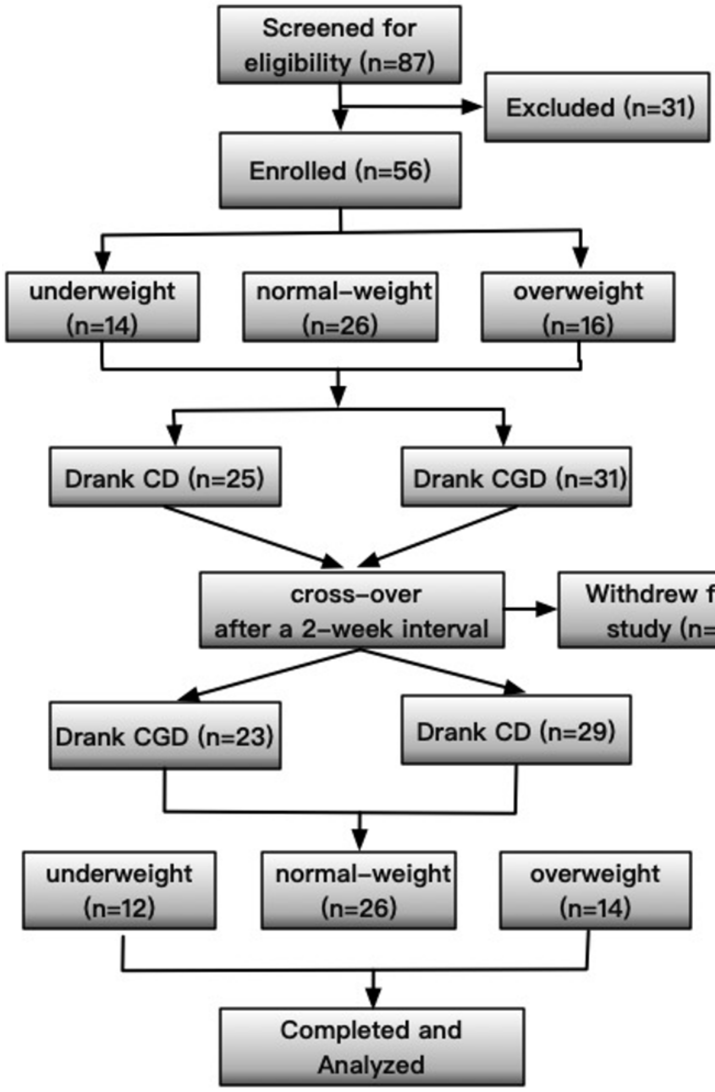

Figure 1. Flowchart of recruitment and withdrawal from the cross-over study.

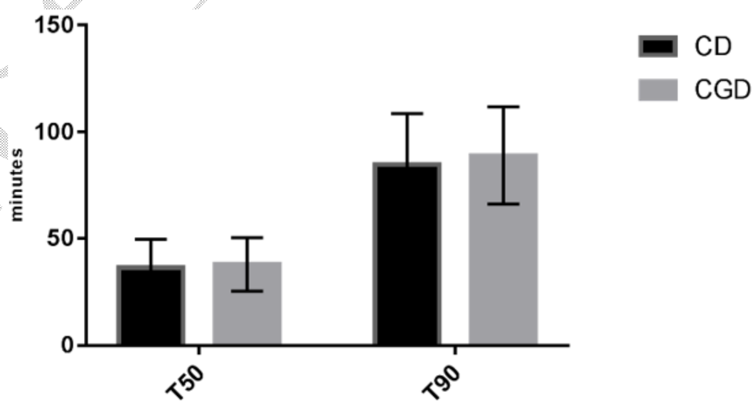

Figure 2. T50 and T90 gastric emptying times. For all participants, the differences between CD and CGD were not significant. $p>0.05$. CD - carbohydrate drink: CGD -carbohydrate glutamine drink.

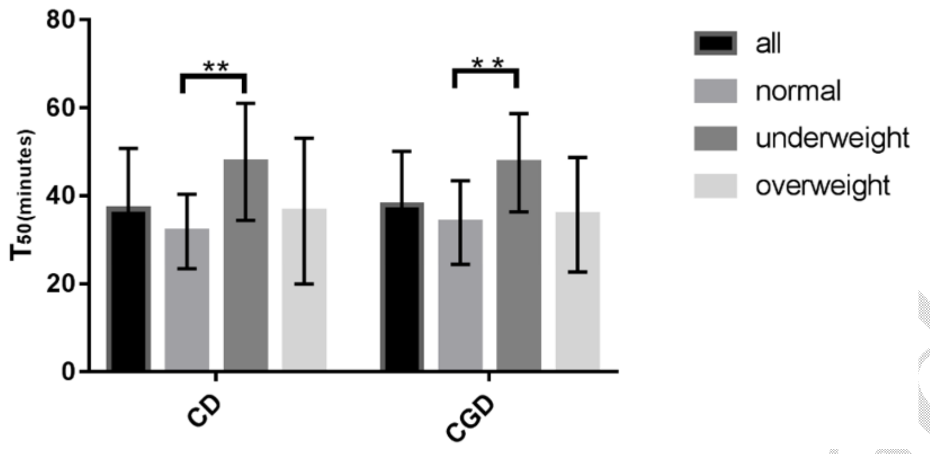

Figure 3. T50 gastric emptying time following CD or CGD regimens of 400 mL in all, normal, underweight, and overweight participants. ** p<0.01 underweight vs. normal. CD - carbohydrate drink: CGD -carbohydrate glutamine drink.

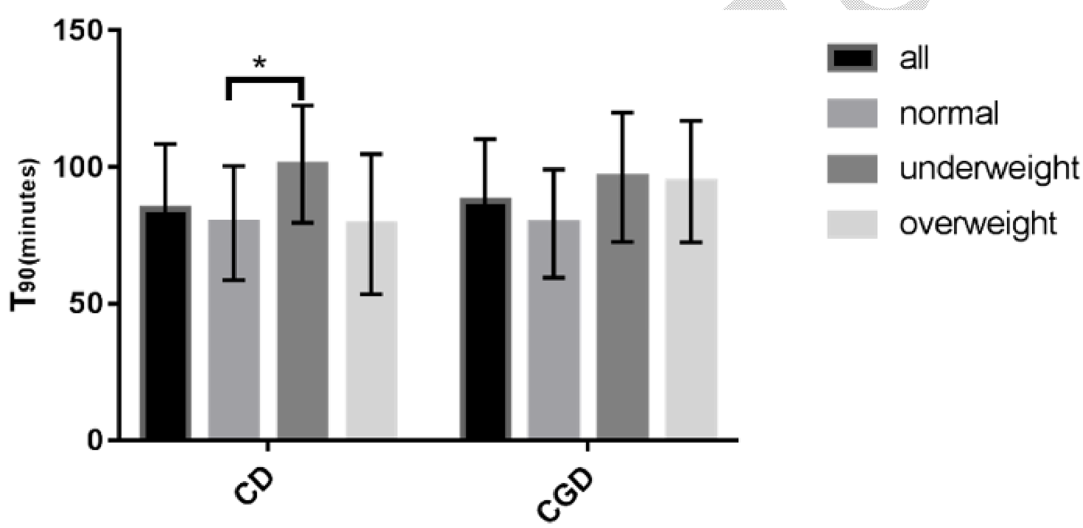

Figure 4. T90 gastric emptying time following CD or CGD regimens of 400 ml in all, normal, underweight and overweight participants. ** p<0.05 underweight VS normal. CD - carbohydrate drink, CGD - carbohydrate glutamine drink.

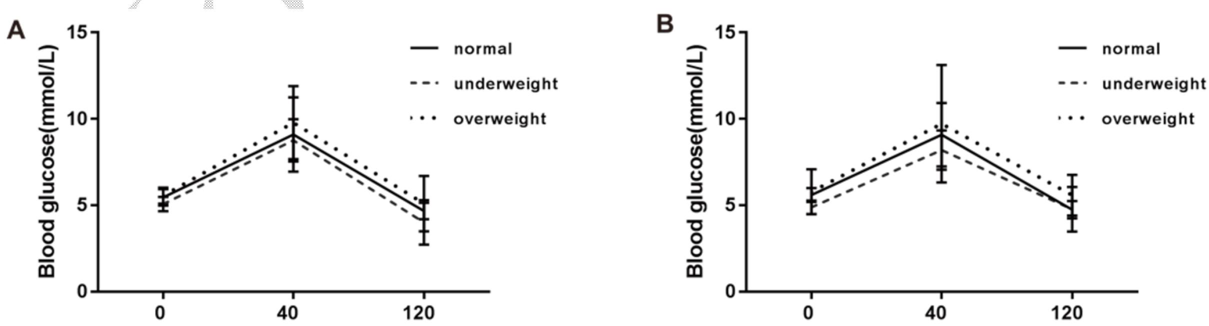

Figure 5. Plasma glucose concentrations following ingestion of the drinks CD (A) and glutamine CGD (B) in normal-weight, underweight and overweight participants. CD - carbohydrate drink, CGD -carbohydrate glutamine drink.