Original Article

Oral carbohydrate loading with 18% carbohydrate beverage alleviates insulin resistance

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Preoperative 12.6% oral carbohydrate loading is an element of the Enhanced Recovery After Surgery (ERAS) protocol aimed at alleviating postoperative insulin resistance; however, in Japan, beverages with 18% carbohydrate content are generally used for preoperative carbohydrate loading. We investigated the effect of 18% carbohydrate loading on alleviating insulin resistance. Six healthy volunteers participated in this crossover-randomized study and were segregated into 2 groups: volunteers in the carbohydrate-loading group (group A) who fasted from after 9 pm and ingested 375 mL of a beverage containing 18% carbohydrate (ArginaidWater^{TM}; Nestle, Tokyo, Japan) between 9 pm and 12 pm, and 250 mL of the same liquid at 6:30 am. Volunteers in control group (group B) drank only water. At 8:30 am, a hyperinsulinemic normoglycemic clamp was initiated. Glucose infusion rate (GIR) and levels of ketone bodies and cytokines (IL-1β, IL-6, and TNF-α) before clamping were evaluated. $P<0.05$ was considered statistically significant. Levels of blood glucose, insulin, and cytokines at the start of the clamp were similar in both the groups. The GIR in group A was significantly higher than that in group B (11.5±2.4 vs 6.2±2.2 mg/kg/min, $p=0.005$), while blood ketone body levels were significantly lower in group A (22±4 vs 124±119 μmol/L, $p=0.04$). Preoperative 18% carbohydrate loading could prevent the decrease in insulin sensitivity and suppress catabolism in healthy volunteers. Thus, carbohydrate loading with a beverage with 18% carbohydrate content might contribute to improvements in perioperative management.

Key Words: carbohydrate loading, insulin resistance, enhanced recovery after surgery, hyperinsulinemic normoglycemic clamp, perioperative management

INTRODUCTION

The Enhanced Recovery after Surgery (ERAS) protocol has recently garnered attention as an evidence-based method for perioperative care used in hospitals worldwide to improve patient prognosis. This protocol recommends carbohydrate loading via oral administration before surgery,[1] which reduces thirst, hunger, anxiety, and nausea, while preventing muscle wasting and loss of nitrogen and protein.[2-4] Furthermore, the ERAS protocol has been shown to prevent the aggravation of insulin resistance that occurs as a result of surgery.[2] Insulin resistance can cause hyperglycemia, which causes immunosuppression and an increase in inflammatory cytokines.[5] Hyperglycemia is also an important risk factor for surgical site infections in postoperative patients.[6] Since optimal glycemic control can reduce the frequency of infections, improvement in insulin resistance is an important component of perioperative patient management.[7]

The ERAS protocol recommends orally administered 12.6% carbohydrate loading before an operation.[1] A previous study reported that the intake of this concentration leads to an improvement in insulin resistance.[8] The use of such a preoperative carbohydrate drink has been highly associated with improved clinical outcomes.[9] Unfortunately, in Japan, drinks containing 12.6% carbohydrates are not available; therefore, a readily available 18% carbohydrate drink is typically used for preoperative carbohydrate loading. One package includes 125 mL of this carbohydrate drink, and this small size is suited for the Japanese population. However, no studies have thus far examined whether such an 18% carbohydrate solution can improve insulin resistance to the same extent as a 12.6% solution. We hypothesized that an 18% carbohydrate drink could prevent the aggravation of insulin resistance; therefore, we investigated the effect of 18% carbohydrate loading on preventing the decrease in insulin sensitivity in healthy volunteers.

METHODS

The study was conducted after obtaining the approval of the Kochi University Hospital ethics committee and informed consent from the participants. The participants

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Manuscript received 25 June 2012. Initial review completed 28 August 2012. Revision accepted 10 November 2012.
doi: 10.6133/apjcn.2013.22.1.20

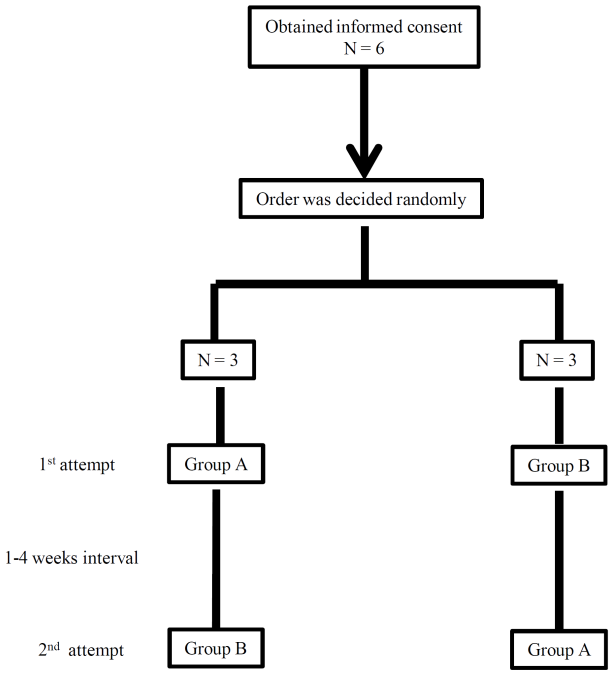

Figure 1. Study design. After obtaining informed consent, the order in which the participants joined the 2 experiments was decided randomly.

were healthy volunteers aged 20 years or older. The study was conducted according to a crossover design. The participants joined the study 2 times, with a gap of 1-4 weeks between each experiment (Figure 1). In the carbohydrate-load group (group A), the volunteers fasted after 9 pm on the day before the experiment, ingested 375 mL (300 kcal) of Arginaid Water (Nestle Health Science, Tokyo, Japan) – a beverage that contains 2% arginine and 18% carbohydrates (sucrose and dextrin) – between 9 pm and 12 am on the same day, and then ingested 275 mL (200 kcal) of the beverage at 6:30 am on the morning of the experiment. In the control group, namely the fasting group (group B), the volunteers fasted on the day before the experiment after 9 pm and only ingested water. The order in which the participants joined the 2 experiments was decided randomly. On the day of the experiment, blood was collected at 8:30 am from both the groups. Hyperinsulinemic normoglucose clamping using the STG-22 artificial pancreas (Nikkiso, Tokyo, Japan) was then performed for 2 hours, according to the protocol described by DeFronzo *et al.*[10] The protocol used in the present study is shown in Figure 2. Clamping using STG-22 is a common technique in Japan, and many studies evaluating insulin resistance have been conducted using this method.[11,12] The STG-22 collects blood continuously from the peripheral veins at a rate of 2 mL/h, and measures blood glucose levels in real-time via the glucose oxidase method. To set a target blood glucose level, the optimal glucose and insulin doses are calculated using an algorithm, and insulin and glucose are administered automatically from a pump. This method enables automatic blood glucose monitoring. During hyperinsulinemic normoglucose clamping, insulin priming-infusion was performed manually for the first 10 min. Thereafter, a fixed quantity of insulin was injected at a rate of 1.25 mIU/kg/min. After the insulin priming-infusion was completed, glucose was injected automatically for 2 hours, with a target blood glucose level of 95 mg/dL. The items evaluated were as follows: the glucose infusion rate (GIR) where insulin resistance finally stabilized; catabolic state, evaluated by measuring blood ketone body levels before clamping; the levels of the cytokines IL-1β, IL-6, and TNF-α, measured before clamping; as baseline evaluation, fasting blood glucose and insulin levels were measured before clamping. Serum ketone body, blood glucose, serum insulin, and serum cytokine levels were determined by a clinical laboratory testing company (SRL Inc, Tokyo, Japan). The data were recorded as mean±SD. A paired *t*-test was conducted using JMP 9.00 (SAS Institute Japan, Tokyo), with statistical significance set to $p < 0.05$.

RESULTS

Six healthy volunteers participated in the study: 5 men and 1 woman. Three participants were initially allocated to group A, and subsequently to group B after 1-4 weeks. The other three participants were allocated to group B first, and subsequently to group A after 1-4 weeks. All participants consumed the stipulated amount of Arginaid Water when included in group A. The average age was 29±3 years, height was 166±6 cm, weight was 62±13 kg, and BMI was 22±4 kg/m^2. No significant difference was

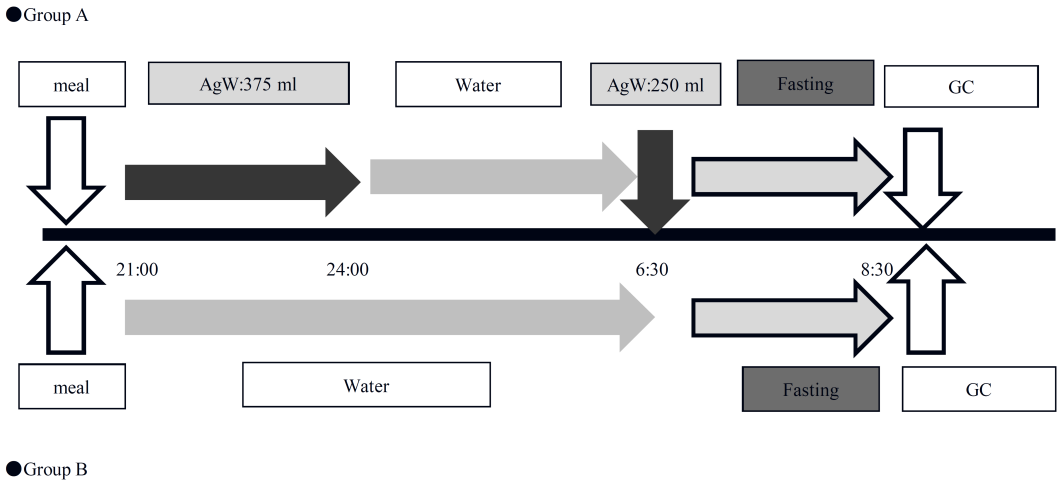

Figure 2. Study protocol. The volunteers in group A fasted from after 9 p.m. and ingested 375 mL of a beverage containing 18% carbohydrate (ArginaidWater™; AgW) between 9 pm and 12 pm and 250 mL of the same liquid at 6:30 am, while volunteers in group B were allowed to drink only water. At 8:30 am, a hyperinsulinemic normoglycemic clamp (GC) was initiated.

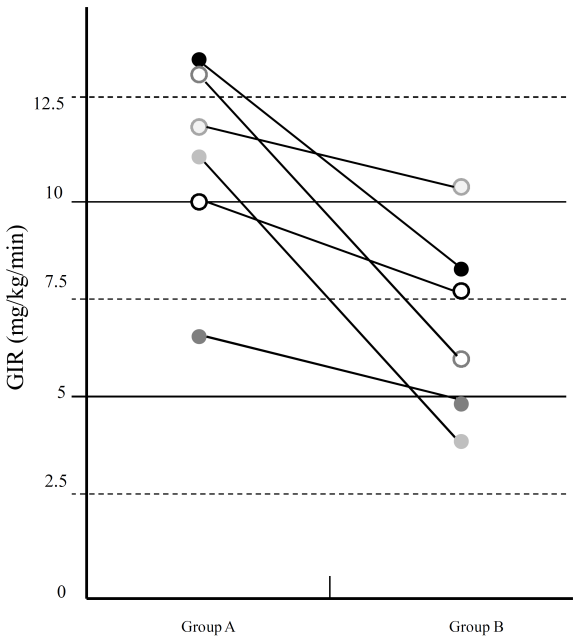

Figure 3. Result of glucose clamping. Glucose infusion rate (GIR) for each volunteer was plotted. The GIR was significantly higher in group A, indicating lower insulin resistance (11.5 ± 2.4 vs. 6.2 ± 2.2 mg/kg/min, $p = 0.005$).

found between groups A and B in fasting blood glucose or pre-examination insulin levels (90±15 vs 93±10 mg/dL, and 22±20 vs 23±44 μIU/mL, respectively). Pre-examination blood ketone body levels were significantly lower in group A (22±4 vs 124±119 μmol/L, p=0.04). The GIR was significantly higher in group A, indicating lower insulin resistance (11.5±2.4 vs 6.2±2.2 mg/kg/min, p=0.005) (Figure 3). There were no significant differences in IL-1, IL-6, and TNF-α levels prior to examination (10±0 vs 11±1 ng/L, 1.3±0.6 vs 1.4±0.5 ng/L, and 1.0±0.3 vs 1.0±0.2 ng/L, respectively).

DISCUSSION

This study showed that the decrease in insulin sensitivity could be significantly prevented with preoperative 18% carbohydrate loading, similar to the improvement achieved with the 12.6% carbohydrate loading recommended by the ERAS protocol.

Aggravation of insulin resistance usually occurs during the perioperative period and is related to undesirable complications.[13] Therefore, preventing the decrease in insulin sensitivity can play an important role in improving the prognosis of patients undergoing surgery. Even healthy, non-diabetic patients who fast before elective surgery have a 50% chance of developing insulin resistance aggravation from the preoperative fasting period,[14] and this deterioration in insulin resistance begins during preoperative fasting. Although this study used healthy volunteers, insulin resistance has also been observed during short fasting periods in healthy volunteers.[14] Similar to the present study, administration of a 12.6% carbohydrate solution could prevent the decrease in insulin sensitivity.[8] Our data showed that fasting-induced insulin resistance in healthy participants could be reversed by preoperatively administering an 18% carbohydrate solution. The treatment also led to a reduction in blood ketone body levels, indicating a lower degree of the catabolic state.

The present study revealed that the oral administration of a higher concentration but lower amount of carbohydrate led to almost identical effects in preventing the decline in insulin sensitivity. In a previous study, volunteers consumed a total 151 g of carbohydrate (101 g in the evening and 50.4 g in the morning), while in our study, they received a total of 113 g of carbohydrate (67.5 g in the evening and 45 g in the morning).[8] These amounts are similar with respect to the dose per kg of body weight (2.0 vs 1.8 mg/kg) (the average European body weight of 75.6 kg was used to calculate this dose based on a recent study, since the average body weight was not cited in the concerned previous study.[8,15]). Therefore, we consider that the total amount of carbohydrate consumed, rather than the concentration, may be important in preventing decrease in insulin sensitivity. Although the use of a 12.6% carbohydrate drink is recommended by the ERAS protocol, such a beverage is not available in Japan. Preoperative carbohydrate loading plays an important role in improving patient outcome.[9] Therefore, these results are an important step toward the implementation of a modified ERAS protocol in Japanese hospitals.

One possible mechanism by which carbohydrate ingestion itself improves insulin resistance is the fact that fasting markedly increases the expression of pyruvate dehydrogenase kinase 4 (PDK4), which has been linked to deterioration in insulin resistance.[16] Preoperative carbohydrate loading can suppress the expression of PDK4, resulting in a decreased incidence of insulin resistance.[17] Another possible mechanism is the phosphatidylinositol 3-kinase/protein kinase B (PI3K/PKB) signaling pathway − the intracellular signal that has the greatest influence on insulin activity.[18] PI3K/PKB signaling increases upon carbohydrate loading prior to surgery, thereby improving insulin resistance.[18] The third mechanism is the downregulation of excessive β-oxidation in mitochondria. In our study, a significant number of group B participants

Table 1. Glucose infusion rate and laboratory data for this study

	Group A (n=6)	Group B (n=6)	p-value
Glucose level at start of clamp,mg/dL	90 ± 15	93 ± 10	0.67
Insulin level at start of clamp, mIU/L	22 ± 20	23 ± 44	0.54
Ketone bodies level at start of clamp, μmol/L	22 ± 4*	124 ± 118	0.04
Glucose infusion rate, mg/kg/min	11.5 ±2.4*	6.2 ± 2.2	0.005
IL-1, ng/L	10.0 ± 0.0	10.5 ± 1.2	0.81
IL-6, ng/L	1.3 ± 0.6	1.4 ± 0.5	0.79
TNF-α, (ng/L	1.0 ± 0.3	1.0 ± 0.2	0.56

Data shown as mean ± SD. * indicates $p < 0.05$ between groups.

who experienced hunger and aggravated insulin resistance after 12 hours of fasting had increased ketone body levels as compared to group A participants, indicating a catabolic state. Lipolysis and non-esterified fatty acids are expected to be higher after overnight fasting in the absence of carbohydrate loading, which could lead to higher ketone body formation regardless of b-oxidation activity and improvement in insulin resistance. Since we did not assess PDK4 activity, the exact mechanism for insulin resistance could not be clarified in this study; however, on the basis of the mechanisms proposed above, we infer that administration of an 18% carbohydrate drink prevented the decrease in insulin sensitivity. In a previous review article, the presence of cytokines, such as IL-1, IL-6, and TNF-α, have been implicated in altered insulin sensitivity via the modulation of glucose transporter (GLUT)-4.[19] However, cytokine activity did not differ significantly between the two groups in the present study. Therefore, cytokines might not play an important role in the deterioration of insulin resistance caused by fasting.

This study has a few limitations. Firstly, we demonstrated the improvement in insulin resistance in healthy volunteers who did not undergo an operation. Therefore, whether similar improvement can be achieved postoperatively in actual patients with 18% carbohydrate loading needs to be studied. A prospective randomized clinical study will be required to clarify this point. Secondly, study participants received the carbohydrate load 2 hours prior to assessment by the glucose clamp technique, which may have affected insulin resistance measurements. Since we did not observe a significant difference between the 2 groups with respect to blood glucose or insulin concentration immediately before glucose clamping, we posit that the method did not affect the measurement. Moreover, we were able to show improvement in insulin resistance using a clinically relevant time frame of 2 hours, suggesting that this protocol will also be effective in a clinical setting. Thirdly, we did not stipulate the contents of the evening meal consumed on the day before the experiment, similar to the protocol in the previous study.[8] Therefore, we cannot deny that differences in the meal may affect our data. Finally, a beverage used in this study contained 2% arginine. A previous study reported that arginine could affect insulin-mediated glucose disposal.[20] Therefore, not only carbohydrate but also arginine might contribute to preventing the decrease in insulin sensitivity.

In conclusion, our study showed that ingestion of an 18% carbohydrate drink could prevent decrease in insulin sensitivity and suppress catabolism in healthy volunteers. Although further clinical studies on postoperative patients are required to determine whether preoperative 18% carbohydrate loading contributed to improvements in patient outcome, the results provide vital information for implementing a modified ERAS protocol in countries where the recommended 12.6% carbohydrate solution cannot be obtained.

AUTHOR DISCLOSURES

No author has a conflict of interest. This work was supported by MEXT/JSPS KAKENHI Grant Number 23791708 (http://kaken.nii.ac.jp/en/p/23791708).

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Original Article

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以含 18%醣類的飲料做為口服醣類負載可減輕胰島素阻抗

手術前給予 12.6%口服醣類負載(能量儲備)是加速術後康復(ERAS)的療程之一，目的為減輕手術後胰島素阻抗；然而在日本，含 18%醣類的飲料普遍被用於術前醣類負載。本研究試驗 18%醣類負載對減輕胰島素阻抗的影響。6 名健康自願者參與這個隨機交叉研究，並被分為兩組。醣類負載的自願者(A 組)從下午 9 點後禁食，並在下午 9 點至 12 點間攝取 375 mL 含有 18%醣類的飲料，早上 6 點半攝取 250 mL 相同液體。控制組的自願者(B 組)只攝取水。早上 8 點半，開始高胰島素-正常血糖箝制試驗。在箝制前評估葡萄糖流速(GIR)、酮體量及細胞激素(IL-1β、IL-6 和 TNF-α)。以 $P<0.05$ 認定達統計顯著性。血糖、胰島素及細胞激素量在箝制前兩組是相似的。A 組的 GIR 顯著的高於 B 組(11.5±2.4 比上 6.2±2.2 mg/kg/min，$p=0.005$)；同時 A 組的血液酮體量顯著較低(22±4 比上 124±119 μmol/L，$p=0.04$)。在健康的自願者，手術前 18%醣類負載可以預防胰島素敏感性的降低及抑制分解。因此，以含 18%醣類飲料的醣類負載可能對手術期治理的改善具有貢獻。

關鍵字：醣類負載、胰島素阻抗、加速術後康復、高胰島素-正常血糖箝制試驗、手術期治理