Pre-operative carbohydrate loading may be used in type 2 diabetes patients

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Background: Post-operative insulin resistance and hyperglycaemia are associated with an impaired outcome after surgery. Pre-operative oral carbohydrate loading (CHO) reduces post-operative insulin resistance with a reduced risk of hyperglycaemia during post-operative nutrition. Insulin-resistant diabetic patients have not been given CHO because the effects on pre-operative glycaemia and gastric emptying are unknown.

Methods: Twenty-five patients (45–73 years) with type 2 diabetes [glycated haemoglobin (HbA1c) 6.2 ± 0.2%, mean SEM] and 10 healthy control subjects (45–72 years) were studied. A carbohydrate-rich drink (400 ml, 12.5%) was given with paracetamol 1.5 g for determination of gastric emptying.

Results: Peak glucose was higher in diabetic patients than in healthy subjects (13.4 ± 0.5 vs. 7.6 ± 0.5 mM; \( P < 0.01 \)) and occurred later after intake (60 vs. 30 min; \( P < 0.01 \)). Glucose concentrations were back to baseline at 180 vs. 120 min in diabetic patients and healthy subjects, respectively (\( P < 0.01 \)). At 120 min, 10.9 ± 0.7% and 13.3 ± 1.2% of paracetamol remained in the stomach in diabetic patients and healthy, subjects respectively. Gastric half-emptying time (T50) occurred at 49.8 ± 2.2 min in diabetics and at 58.6 ± 3.7 min in healthy subjects (\( P < 0.05 \)). Neither peak glucose, glucose at 180 min, gastric T50, nor retention at 120 min differed between insulin (HbA1c 6.8 ± 0.7%)- and non-insulin-treated (HbA1c 5.6 ± 0.4%) patients.

Conclusions: Type 2 diabetic patients showed no signs of delayed gastric emptying, suggesting that a carbohydrate-rich drink may be safely administered 180 min before anaesthesia without risk of hyperglycaemia or aspiration pre-operatively.

Key words: Carbohydrate drink; diabetes; ERAS; gastric emptying; glucose control; preoperative; surgery.

Metabolic stress and insulin resistance follow major surgery (1). The resulting post-operative hyperglycaemia is associated with increased morbidity as well as mortality (1–3). In non-diabetic patients, avoiding pre-operative fasting substantially reduces post-operative stress and insulin resistance. A pre-operative carbohydrate load improves post-operative glycaemic control, most likely by inducing endogenous insulin release before the onset of surgery. This sets the metabolic state of the patient in a fed rather than a fasted state at the time of surgery (4). Metabolic reactions to surgical stress are thereby markedly reduced (1, 5) not only resulting in a reduced risk for hyperglycaemia during post-operative nutrition but also retained lean body mass, improved muscle strength and nitrogen economy (6–8).

The oral preparation used is a carbohydrate-rich (12.5%) clear beverage (CHO) containing mainly polymers of carbohydrates to minimize the osmotic load and thus reducing the gastric emptying time. The drink, in addition to its metabolic effect, improves patient well-being (thirst, hunger, anxiety) pre-operatively (9).

Patients with diabetes are at particular risk of impaired glycaemic control post-operatively (3). Although a considerable number of patients going through surgery suffer from diabetes, this patient group has been denied the pre-operative carbohydrate drink because of fear of slow gastric emptying and impaired glycaemic control (10, 11).

According to cross-sectional studies, gastric emptying is slower in approximately 30–50% of outpatients with long-standing type 1 or 2 diabetes than in normal individuals (12). However, in many cases the magnitude of the delay seems to be modest. In contrast, it has also been reported that gastric emptying rate is increased in type 2 diabetes...
patients, at least early after onset of the disease. Among type 1 diabetes patients, accelerated gastric emptying has been shown, however, in a minority of cases (12). Thus, there are conflicting data as to gastric emptying in patients with diabetes in general, which makes it difficult to provide firm recommendations regarding the use of pre-operative carbohydrate loading in this patient group.

The aim of the present study was to explore the possibility of providing CHO in patients with diabetes with regard to the potential risk of impaired glycaemic control and pulmonary aspiration during anaesthesia. Therefore, gastric emptying and glucose concentrations after the intake of a carbohydrate-rich drink in patients with type 2 diabetes and healthy volunteers were studied.

Methods

Twenty-five patients with type 2 diabetes were recruited from the outpatient clinic at Ersta hospital, Stockholm, Sweden. Inclusion criteria were glycated haemoglobin (HbA1c) <7% (reference range 3.4–5.0%, MonoS, Swedish standard) and body mass index (BMI) <35 kg/m² while subjects with clinical signs of autonomic neuropathy and/ or peripheral sensory/motor neuropathy were excluded. Eleven patients were treated with insulin [bedtime intermediate duration of action insulin (NPH) (n = 5), biphasic human insulin 30 and bedtime NPH insulin (n = 2), biphasic insulin lispro 25 and bedtime NPH insulin (n = 2), biphasic insulin aspart 30 (n = 2)]. Out of these 11 patients, six were concurrently on oral anti-diabetic drugs (OAD) (metformin). Ten of the patients were on OAD only [metformin (n = 5), glibenklamid (n = 3), repaglinid (n = 1), glimeperid (n = 1)] and four had diet treatment only. None of the patients included showed any symptoms or signs of upper gastrointestinal disease. Ten healthy age- and weight-matched subjects served as controls (Table 1).

Written informed consent was obtained from every participant before the study. The research protocol was approved by the Institutional Ethics Committee at the Karolinska Institutet and was carried out in accordance with the Declaration of Helsinki of the World Medical Association (1989).

Study design

All patients were fasting from 2200 h the night before the investigation. Alcohol, heavy meals, paracetamol intake or strong physical activity were prohibited the day before study. Patients arrived to the clinic at 07:30 hours. The body composition was determined with a Bioimpedance analyzer, Tanita®, Model TBF-300, Tokyo, Japan, followed by bed rest until they took their regular morning medication at 08:00 hours. All patients were then given a 400 ml carbohydrate-rich beverage (12.5 g 100/ml carbohydrates, 12% monosaccharides, 12% disaccharides, 76% polysaccharides, 285 mOsm/kg, Nutricia Preop®, Numico, Zoetermeer, the Netherlands). Paracetamol, 1.5 g (Alvedon Brus®, Astra Zeneca, Mölndal, Sweden) was dissolved in the beverage, for determination of gastric emptying. Patients remained in a reclined position throughout the study period.

Sampling and chemical analysis. After intake of the carbohydrate drink, venous blood samples were obtained from an indwelling catheter in the antecubital vein. Blood glucose concentrations were measured at −5 min, at t = 0 (immediately after

Table 1

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>Diet/OAD-treated subjects (n = 14)</th>
<th>Insulin-treated subjects (n = 11)</th>
<th>Healthy subjects (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range)</td>
<td>58 (45–73)</td>
<td>63 (50–70)</td>
<td>59 (45–71)</td>
</tr>
<tr>
<td>Diabetes duration in years, mean (range)</td>
<td>6.6 (1–14)a</td>
<td>11.6 (6–31)</td>
<td>0</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>(12/2)</td>
<td>(5/6)</td>
<td>(6/4)</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>5.6 ± 0.1ab</td>
<td>6.8 ± 0.2c</td>
<td>4.5 ± 0.1</td>
</tr>
<tr>
<td>BMI</td>
<td>27.5 ± 0.9b</td>
<td>29.6 ± 1.0c</td>
<td>24.6 ± 0.9</td>
</tr>
<tr>
<td>Fat mass (%) (Bio-impedance)</td>
<td>28.2 ± 1.8a</td>
<td>36.0 ± 2.1c</td>
<td>26.5 ± 2.4</td>
</tr>
<tr>
<td>Total insulin dose (U/24h)</td>
<td></td>
<td>54 ± 14</td>
<td></td>
</tr>
</tbody>
</table>

OAD, Oral anti-diabetic drugs. Glycated haemoglobin (HbA1c) (reference range 3.4–5.0%). MonoS, Swedish standard. Mean ± SEM.
P < 0.05, a = OAD vs. insulin treated. b = OAD vs. healthy. c = insulin treated vs. healthy.
intake) and then every 30 min during 240-min post-administration of the carbohydrate-rich drink and analysed by a whole-blood glucose meter (Hemocue®; Ängelholm, Sweden). Plasma paracetamol concentration was assessed before administration and at 0, 15, 30, 60, 90, 120 and 180 min after intake of fluids.

**Gastric emptying.** The gastric emptying rate was assessed using intestinal paracetamol absorption as a marker. Plasma samples were assayed for paracetamol by fluorescence-immunoassay (IMX, Abbott Laboratories, Chicago, IL). The coefficient of variation was ±5%. Gastric emptying measured with the paracetamol absorption technique shows a correlation to scintigraphic gastric half-emptying time and plasma concentrations of paracetamol at 30 and 60 min ($r = -0.65$) as well as peak plasma concentrations of the compound ($r = -0.77$) (13). Gastric emptying was evaluated as lag-time until 2% of the contents were emptied and as half-emptying time (T50) until 50% of the contents were emptied.

**Statistical analysis**
Results are presented as mean ± standard error of the mean (SEM) or median and range for groups. One-way ANOVA and two-way ANOVA for repeated measurements were used when appropriate. A $P$ value of $<0.05$ was considered to be statistically significant.

**Results**

One insulin-treated patient (female, 70 years of age, BMI 23) experienced mild hypoglycaemia at 150 min (B-glucose 2.7 mmol/L). The experiment was terminated and the patient received oral dextrose, followed by lunch with rapid normalization of glucose and symptoms.

**Gastric emptying**
The appearance of paracetamol reflecting emptying of fluids followed a close to linear pattern in both diabetic patients and healthy subjects (Fig. 1). Gastric half-emptying time (T50) occurred at 49.8 ± 2.2 min in patients with diabetes and at 58.6 ± 3.7 min in healthy subjects ($P < 0.05$). At 120 min, 10.9 ± 0.7% and 13.3 ± 1.2% of the paracetamol given remained in the stomach in diabetic patients and healthy subjects, respectively. Overall, gastric emptying was slightly faster in diabetic patients than in healthy subjects ($P < 0.05$).

At 180 min, 100% of the paracetamol was absorbed in all subjects. T50 and retention after 120 min did not differ between OAD/diet-treated and insulin-treated patients. The amount of paracetamol remaining in the stomach after 120 min equalled approximately 40 ml of the carbohydrate drink given to all groups.

**Blood glucose concentrations**
The fasting glucose concentrations were 6.7 ± 0.2 and 4.7 ± 0.1 mM in diabetic patients and in healthy subjects, respectively ($P < 0.01$) (Fig. 2). In patients with diabetes, peak glucose concentrations (13.4 ± 0.5 mM) occurred 60 min after intake of the carbohydrate drink whereas corresponding values, 7.6 ± 0.5 mM, were achieved at 30 min in healthy subjects ($P < 0.01$). Glucose concentrations returned to baseline after 180 min in patients with diabetes and after 120 min in healthy subjects. Peak blood glucose concentrations...
and glucose at 180 min did not differ between OAD/diet-treated and insulin-treated patients (Fig. 2).

It was not possible to verify any statistically significant association between gastric half-emptying time and HbA1c%, fasting glucose values, peak glucose concentration or gender.

Discussion

This study did not indicate delayed gastric emptying after intake of a 12.5% CHO-rich drink for pre-operative use among patients with well-controlled type 2 diabetes compared with healthy control subjects. If anything, a slightly increased gastric emptying rate was found in the diabetic population. The residual gastric volume 2 h after intake of the drink was similar in healthy subjects compared with diabetic patients. As expected, peak glucose concentrations after carbohydrate intake were higher and occurred later in diabetic patients compared with healthy control subjects but they returned to baseline after 180 min.

Even though scintigraphic methods may be considered to be the gold standard when assessing gastric emptying, the technique is expensive and involves radiation exposure. The paracetamol absorption technique is well established and correlates well with scintigraphy of liquid phase gastric emptying (13, 14). This method was therefore chosen for the present study.

Insulin resistance leading to poor glucose control is a key factor in the development of post-operative complications (2). Strict perioperative glucose control leads to improved survival with a concomitant decrease in the incidence of infections, neuropathies and renal failure (2, 15).

In non-diabetes patients, avoiding pre-operative fasting reduces post-operative insulin resistance by approximately 50% (5, 16, 17) and attenuates post-operative impairment in nitrogen losses, lean body mass and muscle function (6–8).

Patients with diabetes mellitus are at risk for post-operative impaired glycaemic control and have so far been known to run greater risk of complications when subjected to surgery (3, 18). Patients with diabetes might be at risk of delayed gastric emptying. For this reason, they have not yet been given pre-operative carbohydrates.

The highest prevalence of slow gastric emptying is reported from studies where emptying of both solids and liquids has been measured. However, diabetes seems to affect gastric emptying of solids decidedly more than for clear fluids and nutrient liquids (19, 20). Furthermore, compared with water or low-nutrient liquids, high-nutrient liquids show a delayed and a more linear than exponential emptying pattern (19–21). The carbohydrate-rich beverage used in the present study has a relatively high nutrient content, which may explain why we generally found long gastric emptying times in controls as well as in patients compared with some previous studies (22).

In order to implement adequate fasting guidelines including pre-operative carbohydrate loading as a routine also for diabetic patients, it would be advantageous if patients with a reduced gastric emptying rate could be identified. However, physical examination and other indirect tests are of little value because the correlation between gastric emptying rate and autonomic neuropathy or upper gastrointestinal symptoms is weak (23–25).

The duration of disease is suggested to influence the risk of delayed gastric emptying in diabetic patients (12). In the present study, the patients had a mean diabetes duration of 6.6 years in the OAD/diet group vs. 11.6 years in the insulin-treated group ($P < 0.05$). Despite the difference in duration and possible severity of disease, the gastric emptying rate was similar between the two groups of diabetic patients and, also, not different from healthy subjects.

Pre- and post-operative glycaemic control may be important in diabetic patients in order to avoid slow gastric emptying. It is known that acute elevations in blood glucose concentrations delay gastric emptying (26–28) in both healthy subjects and inpatients with diabetes. However, despite the association between glucose levels and gastric emptying rates, blood glucose levels per se have not been shown to be a reliable predictor of gastric emptying. Moreover, we found no evidence of an association between the peak glucose concentration and gastric emptying rates. Thus, measurements such as gastric emptying of paracetamol or residual gastric volumes are the only reliable options for predicting potential risk patients with regard to anaesthesia.

One patient experienced a mild hypoglycaemia during the experiment. This patient was comparatively lean and old and was treated with a low dose of biphasic insulin aspart, displaying a more insulin-sensitive phenotype compared with the other patients investigated. It remains warranted to control glucose levels liberally in lean types 2 or
1 patients during the pre-operative period when adopting the regimen presented here.

Owing to the small sample size, it may be difficult to apply these data safely as a recommendation for all diabetic patients about to undergo surgery. Nonetheless, the present study indicates that it is safe, within the current fasting guidelines (11), to administer a pre-operative carbohydrate drink to patients with uncomplicated type 2 diabetes pre-operatively. Larger randomized studies are warranted in order to establish a standard with a reliable safety level with regard to the risk of aspiration. Moreover, future studies are needed to determine whether intake of a pre-operative carbohydrate drink has similar effects on metabolism and surgical outcomes among diabetes patients as demonstrated previously among non-diabetic patients.

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