

Influence of Metabolic Control on Splanchnic Glucose Uptake, Insulin Sensitivity, and the Time Required for Glucose Absorption in Patients With Type 1 Diabetes

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OBJECTIVE — The relationship between splanchnic glucose uptake (SGU) after oral glucose administration and metabolic control in type 1 diabetic patients is controversial. We estimated SGU as well as peripheral glucose uptake and the time required for glucose absorption by a validated method, the oral glucose (OG) clamp, in type 1 diabetic patients with different levels of long-term glycemic control.

RESEARCH DESIGN AND METHODS — An OG clamp (which combines a hyperinsulinemic clamp [$120 \text{ mU} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$] with an OR load [75 g] during steady-state glucose uptake) was performed in eight type 1 diabetic patients with good metabolic control (DG) ($\text{HbA}_{1c} 6.1 \pm 0.2\%$, $\text{BMI } 23.1 \pm 0.7 \text{ kg/m}^2$), eight type 1 diabetic patients with poor metabolic control (DP) ($\text{HbA}_{1c} 8.5 \pm 0.3\%$, $\text{BMI } 25.4 \pm 1.4 \text{ kg/m}^2$), and eight healthy matched control subjects (C) ($\text{HbA}_{1c} 5.1 \pm 0.1\%$, $\text{BMI } 25 \pm 1.3 \text{ kg/m}^2$) to determine SGU, glucose uptake, and glucose absorption.

RESULTS — Glucose uptake calculated from 120 to 180 min during the clamp was $9.13 \pm 0.55 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in C, $8.18 \pm 0.71 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in DG, and $7.42 \pm 0.96 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in DP (NS). Glucose absorption was $140 \pm 6 \text{ min}$ in C, $156 \pm 4 \text{ min}$ in DG, and $143 \pm 7 \text{ min}$ in DP (NS). The respective calculated SGU was $14.5 \pm 5.6\%$ in C, $17.8 \pm 3.1\%$ in DG, and $18.8 \pm 4.2\%$ in DP (NS) and did not correlate with HbA_{1c} values.

CONCLUSIONS — Peripheral glucose uptake, SGU after oral glucose administration, and the glucose absorption time were not different in type 1 diabetic patients independent of glycemic control when compared with healthy subjects.

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Abbreviations: C, control subjects; DG, type 1 diabetic patients with good metabolic control; DP, type 1 diabetic patients with poor metabolic control; GINF, glucose infusion rate; GINF_{OG} , GINF during oral glucose absorption; $\text{GINF}(t)$, GINF during resorption time; OG, oral glucose; OGL, OG load; SGU, splanchnic glucose uptake.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

In the interprandial state, plasma glucose concentrations are determined by hepatic glucose production and peripheral glucose utilization. After glucose ingestion, the liver switches from glucose production to glucose uptake (1). The magnitude of hepatic glucose uptake is regulated by several factors, such as the amount of glucose administered (2), the route of glucose administration (3–5), and hormonal factors such as the portal relation of insulin and glucagon (2,6,7).

It has been shown that hepatic glucose uptake is greater after oral or intraportal glucose administration than after peripheral glucose infusion because of a negative arterial-portal glucose gradient (2–5,8–12). Increased net hepatic glucose uptake has furthermore been observed in the presence of hyperglycemia at basal (3) as well as at elevated insulin levels (2,6,11).

Direct measurement of hepatic glucose uptake is not feasible in humans because the portal vein cannot be cannulated. Therefore, indirect methods measuring splanchnic glucose uptake (SGU), which includes the uptake of glucose by the gut, have been developed. Currently, there are three methods used to estimate SGU in humans. Hepatic vein catheterization allows the measurement of net hepatic glucose output on the systemic side of the liver glucose (1,13). The application of this method, however, is limited by its invasive nature and by radiation exposure. The double-tracer technique uses different tracers to distinguish the ingested glucose from the systemic pool. However, results obtained with this method can be affected by incorporation of glucose tracers into glycogen, which can cause inaccurate calculation of the glucose appearance rate (14). The oral glucose (OG) clamp technique was developed and validated against the hepatic

vein catheterization to noninvasively measure SGU. The method combines a hyperinsulinemic clamp with the administration of oral glucose during steady-state glucose disposal (15). Whereas the hepatic vein catheter technique measures the integrated glucose uptake over the time of glucose absorption, which includes glucose that has already passed through the splanchnic area and has not been taken up by the peripheral tissues, the double-tracer technique and the OG clamp method both determine initial or first-pass glucose uptake. With these methods, it has been shown that first-pass SGU ranges from 9 to 30% in healthy humans (14–17). Although SGU increases in obese insulin-resistant subjects (15), most studies have revealed decreases in SGU in patients with type 2 diabetes (17–20). However, this finding, which could contribute to postprandial hyperglycemia, could be obscured by the 120-min observation period, which is too short to provide sufficient time for intestinal absorption of ingested glucose (21,22).

Data on the extent of SGU after oral glucose administration in patients with type 1 diabetes are limited. Recently, the double-tracer technique suggested that SGU was not different in patients with moderately controlled type 1 diabetes when compared with healthy control subjects (23,24). This finding applies to all studies observing glucose absorption over a time period of 120 min. Because of the nature of the method, it is not possible to obtain the time required for complete glucose absorption, which might compromise the results for SGU, especially when a delay in gastric emptying, which is not uncommon in type 1 diabetes, is present. Because it was demonstrated by magnetic resonance spectroscopy that hepatic glycogen synthesis after ingestion of a mixed meal is markedly impaired in patients with poorly controlled type 1 diabetes (25), the results of this study can furthermore not be extrapolated to patients with poorly controlled diabetes (26).

Thus, the aim of our study was to determine SGU, peripheral glucose uptake, and the time required for glucose absorption in type 1 diabetic patients in relation to their metabolic control and compare that data with data obtained in healthy subjects using the OG clamp method.

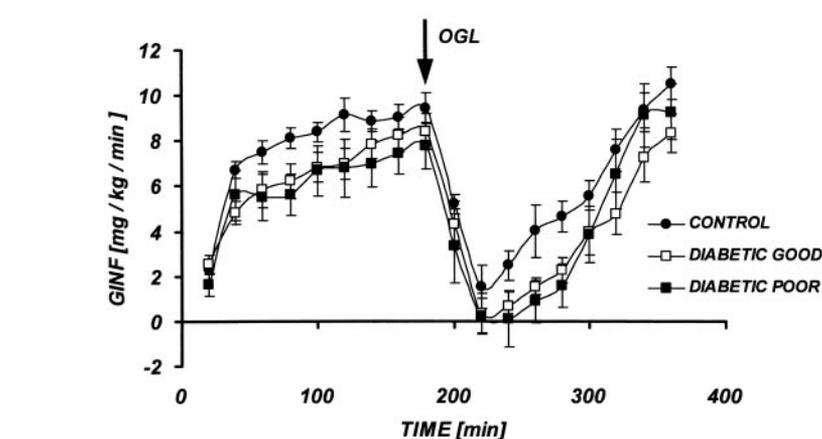


Figure 1—GINF during the an OG clamp in DG, DP, and C. Data are expressed as means \pm SE.

RESEARCH DESIGN AND METHODS

Subjects

A total of 16 male type 1 diabetic patients participated in the study. The patients were divided into two groups (eight patients in each group) according to their metabolic control as defined by HbA_{1c} (type 1 diabetic patients with good metabolic control [DG], age 34.4 ± 2.6 years, BMI 23.1 ± 0.7 kg/m², HbA_{1c} $6.1 \pm 0.2\%$; type 1 diabetic patients with poor metabolic control [DP], age 35 ± 4.7 years, BMI 25.4 ± 1.4 kg/m², HbA_{1c} $8.5 \pm 0.3\%$; NS). All diabetic patients were treated with multiple daily insulin injections. Eight healthy male subjects matched for age and BMI served as control subjects (C) (age 27.8 ± 2.2 years; BMI 25 ± 1.3 kg/m²; HbA_{1c} $5.1 \pm 0.1\%$). In all subjects, an OG clamp was performed after an overnight fast. In diabetic patients, no basal insulin dose was used the evening before the OG clamp. Blood glucose was monitored by patients' self-measurements every 3 h during the night before the OG clamp. Hyperglycemia was avoided using subcutaneous injections of short-acting insulin. The patients injected the last dose of soluble insulin subcutaneously into the abdominal region at 3:00 A.M. None of the subjects were taking any drugs that would affect glucose metabolism, except for insulin in the diabetic subjects. The purpose, nature, and potential risks of the study were explained in detail to all subjects, and written consent was obtained before inclusion into the study.

The study protocol was reviewed and

approved by the Ethics Committee of the Vienna University Hospital.

Experimental protocol

All investigations were performed at 8:00 A.M. after an overnight fast.

OG clamp

This method combines an euglycemic-hyperinsulinemic clamp and an OG load (OGL). The glucose clamp was performed to maintain plasma glucose and serum insulin concentrations at required values and to measure the peripheral glucose uptake quantitatively (23,27,28). To this end, an antecubital vein was cannulated in a retrograde manner to administer glucose and insulin infusions. On the contralateral arm, a dorsal hand vein was cannulated in a retrograde fashion and kept in a warming device to arterialize the venous blood samples. A loading dose of human insulin (Actrapid HM U 40; Novo Nordisk, Gentofte, Denmark) was administered in a logarithmically decreasing manner over a 10-min time period followed by a constant infusion rate ($120 \text{ mU} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$ for 360 min).

Plasma glucose was maintained at 5.5 mmol/l by monitoring plasma glucose every 5 min with a glucose analyzer (Glucose Analyzer II; Beckman Instruments, Fullerton, CA) and adjusting the infusion rate of a 20% dextrose solution. After 3 h of insulin infusion, steady-state glucose disposal was reached and an OGL (75 g) was administered. Because the glucose disposal rate remained unchanged during and after the OGL, as shown previously (15), any absorbed glucose, which bypasses the liver to enter the systemic cir-

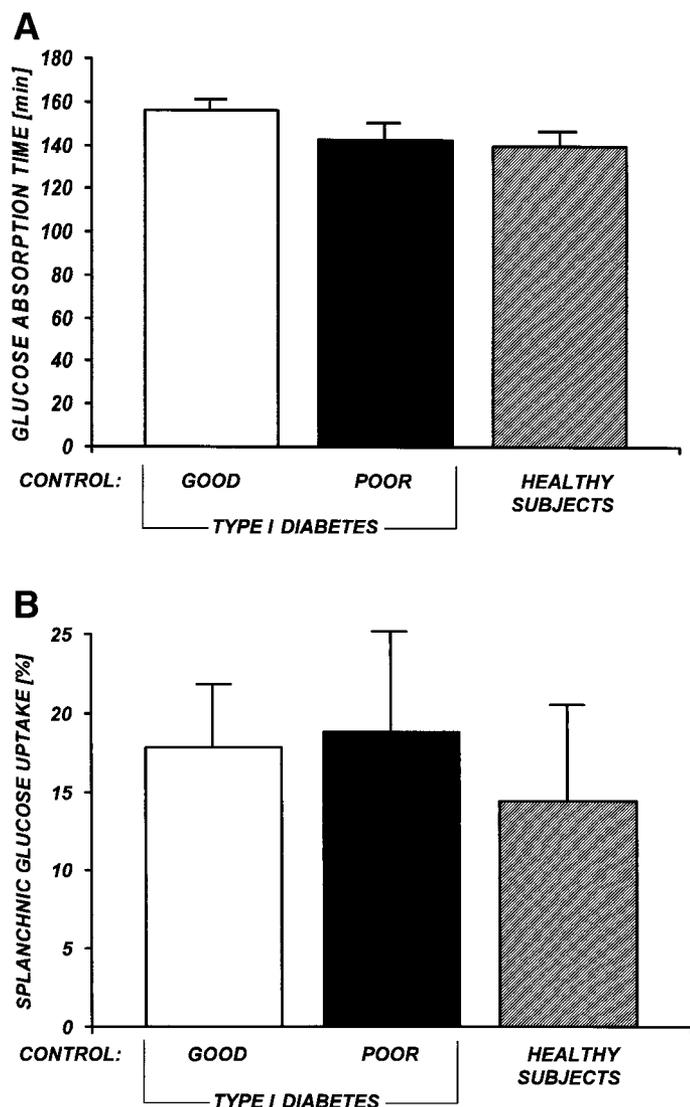


Figure 2—Glucose absorption time (A) and SGU (B) during an OG clamp in DG, DP, and C. Data are expressed as means \pm SE.

culuation, will raise the glucose plasma level unless the glucose infusion rate (GINF) is decreased to keep the blood glucose level at 5.5 mmol/l. GINF was decreased after 10–20 min, indicating the beginning of glucose absorption.

Plasma glucose was maintained at steady state by adjusting the GINF to compensate for the gastrointestinal glucose absorption. Completion of glucose absorption was indicated when glucose infusion reached the values again during steady state before oral glucose administration. The rate of SGU was then calculated by subtracting the integrated decline in GINF from the amount of orally ingested glucose.

Calculations

The GINF ($\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was calculated every 20 min using a glucose clamp algorithm and corrected for changes in pool fraction. We have shown previously that peripheral glucose disposal is not affected by oral glucose administration per se (15) but shows a tendency to increase during the clamp. To know the amount of glucose retained by the splanchnic bed during the OGL period, it was necessary to calculate an estimate of the ideal glucose infusion (GINF_{OGL}) that would be used to maintain euglycemia if no OGL was given. By analyzing a group of preliminary infusion patterns, the function that

better describes the whole GINF behavior was found to be the following exponential equation:

$$\text{GINF}(t) = A [1 - B_{\text{exp}}(-\lambda_1 t) - C_{\text{exp}}(-\lambda_2 t)]$$

where A is the maximum GINF level, hypothetically reached at infinity, and parameters B , C , λ_1 , and λ_2 describe the time course of GINF in every individual. When the GINF during resorption time [GINF(t)] pattern is transformed in a semi-log space, it can be easily divided into two straight lines. The first line takes into account the transient period before reaching the steady state during which the OGTT is performed; the second line is the steady-state part of the experiment and is where the virtual GINF_{OGL} must be estimated. A simple analysis of the bi-exponential function shows, for instance, that on average the second linear part begins around 140 min. Therefore, it is assumed that the $\log(\text{GINF})$ can be described by a line from 140 to 360 min. During this period, the values at 140, 160, 180, and 360 min are known, and a linear regression provides the angular coefficient of the line and the constant parameters for every single experiment. By using these estimated constants, characteristic of every single subject, it is possible to estimate the value of $\log(\text{GINF})$, and thus of GINF_{OGL}, for any time point inside the interval of 180–360 min, which is that of the OGL.

The absolute reduction of glucose infusion (in grams) was then assessed by calculating the area under the curve (AUC_{GINF}) of the function obtained by subtracting the actual GINF from the estimated GINF_{OGL}, after normalization with the body weight of the single subject. SGU, i.e., the amount of glucose retained by the splanchnic bed, was calculated (in percentage) as:

$$\text{SGU} = 100 (\text{OGL dose} - \text{AUC}_{\text{GINF}}) / \text{OGL dose}$$

where OGL dose is the administered oral glucose dose (75 g).

Measurements

Glucose was measured enzymatically by a glucose analyzer (Glucose Analyzer II). Insulin was assayed by a double-body antibody radioimmunoassay (Insulin RIA 100; Pharmacia & Upjohn, Uppsala, Sweden). HbA_{1c} was assayed in each subject

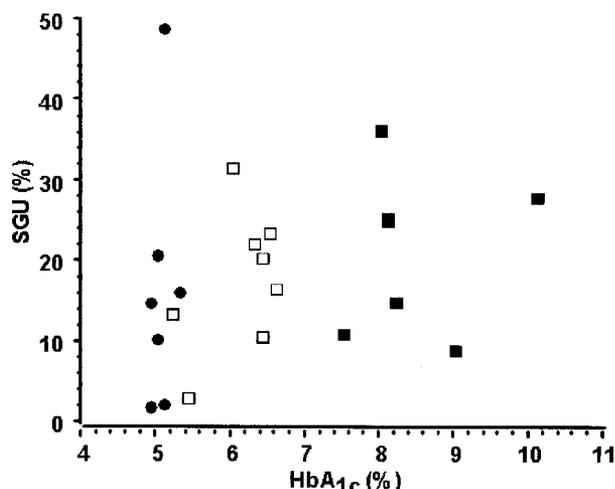


Figure 3—Correlation between SGU and HbA_{1c} in DG (□; $r = 0.44$, $P = 0.28$), DP (■; $r = 0.01$, $P = 0.98$), and C (●; $r = 0.07$, $P = 0.87$).

using the liquid chromatography method (VARIANT-HPLC; Bio-Rad Laboratories, Munich, Germany). Normal range of HbA_{1c} in our laboratory was 4.0–6.0%.

Statistical analysis

All data were presented as mean values \pm SE. All statistical comparisons between the three groups were performed by the unpaired *t* test analysis. The correlations were done using StatView Regression Model.

RESULTS— During the insulin infusion, GINF gradually rose, reaching $9.45 \pm 0.69 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in C, $8.42 \pm 0.79 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in DG, and $7.81 \pm 1.02 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in DP at 180 min (Fig. 1, NS). The peripheral glucose uptake, which equals the GINF at the highest dose of insulin administered ($120 \text{ mU} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$), which would almost completely suppress hepatic glucose production, was 9.13 ± 0.55 in C, 8.18 ± 0.71 in DG, and 7.42 ± 0.96 in DP (NS) calculated from 120 to 180 min.

The completion of glucose absorption was indicated by the return of the GINF to at least the values before glucose ingestion. The time required for glucose absorption fluctuated to some extent, but was not different among C (140 ± 6 min), DG (156 ± 4 min), and DP (143 ± 7 min, NS) (Fig. 2).

Calculated SGU was $14.5 \pm 5.6\%$ in C, $17.8 \pm 3.1\%$ in DG, and $18.8 \pm 4.2\%$ in DP (NS; Fig. 2) and did not correlate with pooled HbA_{1c} values ($r = 0.16$, $P = 0.45$; Fig. 3) or with HbA_{1c} of the single

groups (C: $r = 0.07$, $P = 0.87$; DG: $r = 0.44$, $P = 0.28$; DP: $r = 0.01$, $P = 0.98$).

CONCLUSIONS— The liver is considered an important factor in glucose homeostasis because abnormalities of hepatic glucose metabolism contribute to hyperglycemia in type 2 diabetes (14,17,19,29). Although increased basal hepatic glucose production is assumed to be a major cause of fasting hyperglycemia (1,17,19,29,30), reduced hepatic glucose uptake or SGU might contribute to postprandial hyperglycemia. In that regard, SGU has been shown to be increased in nondiabetic obese insulin-resistant subjects (15), thereby potentially decreasing postprandial hyperglycemia. Most investigators, however, found a decrease in SGU in patients with type 2 diabetes (17–20). Because this decrease is also seen with methods matching glucose and insulin levels of patients and control subjects throughout the experiment such as the OG clamp method (18), the reduction of SGU seems to be an intrinsic hepatic defect. The decrease of SGU seen in patients with type 2 diabetes is quite significant and leads to a 25–30% increase in the amount of glucose delivered to the systemic circulation (31–35).

Patients with type 1 diabetes experience an excessive increase of plasma glucose concentration after carbohydrate consumption, primarily because of an inappropriate response of plasma insulin concentration. The data on SGU with regard to the contribution to postprandial hyperglycemia in patients with type 1 di-

abetes are very limited and somewhat controversial. In the present study, we demonstrate that SGU is not different in healthy subjects and patients with type 1 diabetes, regardless of metabolic control. This conclusion from our data is further supported by the large SEs for SGU in the respective groups (Fig. 2B). Investigators using nuclear magnetic resonance spectroscopy revealed impaired hepatic glycogen synthesis after a mixed meal in patients with poorly controlled type 1 diabetes (25). When glucose and insulin levels were matched with that of control subjects by the hyperglycemic-hyperinsulinemic clamp technique, hepatic glycogen synthesis was not different in type 1 diabetic patients (36). In the latter experiment, however, glucose was brought by an intravenous infusion, and the results can thus not be extended to oral glucose administration, which provides the portal-arterial glucose gradient as an additional signal for hepatic glucose uptake. Taken together, these findings suggest that decreased SGU in patients with poorly controlled type 1 diabetes is caused by insulin deficiency rather than by an intrinsic hepatic defect. Recently, these considerations were confirmed by a study investigating SGU in type 1 diabetic subjects with moderately good metabolic control (mean HbA_{1c} $7.5 \pm 0.5\%$) by double-tracer technology (23). In these experiments, glucose, insulin, and glucagon levels were matched between the diabetic and control subjects. Neither initial SGU, which was in the range reported in our study, nor hepatic glycogen synthesis was changed in diabetic subjects. Although these findings are in line with those reported by other investigators, there are some limitations that prevent an extrapolation of the results to poorly controlled diabetic patients. The double-tracer technology cannot determine the completion of glucose absorption, which is a prerequisite in patients with diabetes who might suffer from delayed gastric emptying. In this regard, the OG clamp method allows an estimation of the time required for glucose absorption. In our study, we could demonstrate that there is no difference for the time of glucose absorption between the diabetic patients investigated and control subjects and thus exclude delayed gastric emptying as a consequence of gastroparesis or chronic hyperglycemia.

Since insulin doses sufficient to sup-

press hepatic glucose are administered during the OG clamp, the steady-state GINF is equal to the glucose disposal rate and thus provides an estimate of insulin sensitivity. In this study, we did not detect any differences with regard to insulin sensitivity between healthy subjects and diabetic patients with good and poor metabolic control, respectively. Although insulin resistance is a well-known feature of type 2 diabetes, it has been shown that patients with reasonably controlled type 1 diabetes are insulin sensitive (23). Insulin resistance due to glucotoxicity, however, develops in animals (37) as well as in patients with poor metabolic control (38). Although we could observe a trend toward decreased glucose disposal in our patients with poor control, we could not detect any significant difference compared with control subjects. Obviously, worse diabetes control than that shown in our study ($8.5 \pm 0.3\%$) is required to induce hepatic insulin resistance, because this was the case in the study mentioned above ($HbA_{1c} = 11.7 \pm 0.6\%$) (38).

In conclusion, we could demonstrate that SGU, the time required for absorption of orally administered glucose, and peripheral glucose disposal are not altered in patients with type 1 diabetes, even in individuals with poor glycemic control.

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