Hepatic Nonoxidative Disposal of an Oral Glucose Meal in Patients With Liver Cirrhosis

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Seven patients with liver cirrhosis and five healthy subjects were studied over 4 hours after ingestion of a glucose meal to determine whether alterations of hepatic nonoxidative glucose disposal participate in the pathogenesis of impaired glucose tolerance. Hepatic uridyl-diphosphoglucose (UDPG) turnover was calculated from the isotopic enrichment of urinary acetaminophen glucuronide during continuous infusion of ^{13}C-galactose and used as an index of hepatic glycogen synthesis. Patients with cirrhosis had postprandial hyperglycemia and decreased glucose clearance, but hepatic UDPG turnover was not altered (1.84 ± 0.29 mg/kg fat-free mass · min *v* 1.76 ± 0.15 in controls, nonsignificant). It is concluded that hepatic postprandial glycogen synthesis is unaltered in patients with advanced cirrhosis, demonstrating important hepatic functional reserve.

GLUCOSE INTOLERANCE or overt diabetes mellitus is encountered in approximately three of four patients with liver cirrhosis.[1,2] However, the mechanisms responsible for the development of postprandial hyperglycemia remain incompletely understood. Both extrahepatic (ie, insulin resistance of skeletal muscle and adipose tissue) and hepatic (impaired suppression of glucose production and decreased glucose uptake and glycogen synthesis) mechanisms may be involved.

Several observations indicate that a decrease in glucose utilization contributes to the pathogenesis of postprandial hyperglycemia in patients with cirrhosis. Such patients display a blunted stimulation of whole-body glucose uptake during steady-state hyperinsulinemia, indicating insulin resistance. This impaired insulin effectiveness affects glucose storage (presumably as muscle glycogen) more than glucose oxidation.[3] Elevated concentrations of glucagon[4] and growth hormone[5] are frequently observed and may exert insulin-antagonist actions. In addition, these patients display markedly elevated fasting and postprandial plasma insulin concentrations, which can be attributed to both decreased hepatic clearance of insulin and increased insulin secretion by pancreatic β cells.[4,6] Hyperinsulinemia itself may contribute to the pathogenesis of insulin resistance by inducing a downregulation of insulin receptors.[7]

Given the central role of the liver in the control of blood glucose homeostasis, it can be suspected that alterations of hepatic glucose metabolism contribute to the pathogenesis of glucose intolerance in such patients. In postabsorptive conditions, the liver is responsible for the major portion of endogenous glucose production, while the kidney makes a significant but small contribution. After ingestion of a glucose meal, both suppression of endogenous glucose production and stimulation of hepatic glucose uptake contribute to limit systemic glucose appearance and the increase in glycemia. Endogenous glucose production has been reported to be unchanged or slightly decreased in postabsorptive patients with cirrhosis[8] and to be normally inhibited by increased plasma insulin[9] or glucose[10] concentrations. As a consequence, an impaired suppression of hepatic glucose production is unlikely involved in the postprandial hyperglycemia.

In healthy humans, significant postprandial hepatic glucose uptake has been observed by various methodological approaches.[11-13] Hepatic glycogen synthesis appears to be the major fate of glucose taken up by the liver, and has been recently estimated to represent 15% to 18% of the ingested glucose load using in vivo ^{13}C nuclear magnetic resonance (NMR) spectroscopy.[13,14] It has also been reported that a decrease in postprandial splanchnic glucose uptake may participate in the development of postprandial hyperglycemia in patients with type 2 diabetes.[12] Splanchnic insulin-stimulated glucose uptake has been reported to be normal in cirrhosis.[2] However, it remains unknown whether a decreased glycogen synthesis is present and may contribute to postprandial hyperglycemia.

The aim of this study was to evaluate postprandial nonoxidative glucose disposal in patients with cirrhosis. For this purpose, seven patients with cirrhosis and five healthy subjects were studied over 4 hours following ingestion of a glucose meal. Hepatic glycogen synthesis was indirectly assessed by monitoring the intrahepatic turnover of the uridyl-diphosphoglucose (UDPG) pool noninvasively.[15-17] For this purpose, ^{13}C-labeled galactose, which is exclusively metabolized in liver cells, where it is converted after several metabolic steps to UDPG, was continuously infused in tracer amounts. Acetaminophen was administered as minute repeated doses, and its glucuronidated form was purified from urine collections. Since the glucuronic acid used for detoxification of acetaminophen in the liver is issued from the same pool of UDPG as glycogen, it allowed an assessment of the isotopic enrichment of intrahepatic UDPG noninvasively and a calculation of UDPG turnover. Indirect calorimetry was used to calculate net carbohydrate oxidation and total extrahepatic nonoxidative glucose disposal. The whole-body glucose kinetics was simultaneously assessed with glucose isotope-dilution analysis using 6,6-^{2}H-glucose infusion at a tracer rate.

SUBJECTS AND METHODS

Subjects

Seven patients with cirrhosis were selected for the study. The anthropometric characteristics and the etiology and staging of liver disease are shown in Table 1. All patients were on a waiting list for an orthotopic liver transplant. They were all in stable clinical and

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Table 1. Patient Characteristics

Group	Sex/Age (yr)	Weight (kg)	Fat-Free Mass (kg)	Serum Albumin (g/L)	Prothrombin Time (% of control)	Etiology of Liver Disease
Patient No.						
1	F/61	56.3	34.5	55	80	Alcoholic hepatopathy
2	M/22	64	55.6	31	40	Autoimmune hepatitis
3	F/46	77.5	49.7	34	70	Hepatitis B
4	M/34	64.5	54.9	46	70	Primary biliary cirrhosis
5	F/58	64.7	44.6	32	70	Hepatitis C
6	M/54	73	61.6	38	70	Hepatitis C/hepatocarcinoma
7	M/48	80	62.4	36	60	Alcoholic hepatopathy
Mean ± SD	46.1 ± 13.9	68.6 ± 8.5	51.9 ± 9.9	38.9 ± 8.7	65.7 ± 12.7	
Control No.						
1	F/36	58.5	43.6			
2	F/49	61.9	39.7			
3	M/21	76	67.1			
4	M/40	63.3	46.5			
5	M/52	87.2	64.1			
Mean ± SD	39.6 ± 12.3	69.4 ± 11.9	52.2 ± 12.5			

metabolic condition at the time of study (ie, absence of upper-gastrointestinal bleeding, decompensated encephalopathy, acute renal failure, infection, or any acute clinical condition, and no major weight changes for at least 6 weeks). Five healthy individuals were selected as controls (Table 1). The experimental protocol was approved by the ethics committee of Lausanne University School of Medicine, and every participant provided informed written consent.

Protocol 1

Subjects were studied in the morning after an overnight fast. Food records obtained for the 3 days preceding the investigation indicated that the subjects consumed a diet containing greater than 200 g carbohydrates per day.

At their arrival in the metabolic laboratory, the subjects were weighed and measured and the fat mass and fat-free mass were calculated from measurements skinfold thickness[18] (Table 1). The subjects were then transferred to a bed, and one venous cannula was inserted into a wrist vein of the right arm. The right hand was subsequently placed in a thermostabilized box heated at 55°C to achieve partial arterialization of the venous blood. Blood samples were collected from this cannula. A second cannula was inserted into an antecubital vein of the left arm, and primed-continuous infusion of 6,6-^{2}H-glucose (Masstrace, Worcester, MA; prime 4 mg/kg and continuous 40 μg/kg · min) and 1-^{13}C-galactose (Masstrace; prime 15 μg/kg and continuous 3 μg/kg · min) were started at time 0 and continued throughout the 390-minute experiment. Oral acetaminophen (Tylenol pediatric drops; Janssen-Cilag, Baar, Switzerland) was administered as a 150-mg dose at −140, −120, −60, 0, 60, 120, and 180 minutes. After allowing 2 hours for tracer equilibration (time −150 to −30 minutes), two blood samples were taken 30 minutes apart for determination of basal glucose turnover and plasma hormone and substrate concentrations (time −30 and 0 minutes). Thereafter (time 0 minutes), an oral glucose load (1.5 g glucose/kg fat-free mass, dissolved in 300 mL lemon-flavored water) was ingested over 5 minutes. Blood samples were taken every 30 minutes after ingestion of the glucose load until time 240 minutes for determination of tracer dilution and hormone and substrate concentrations. In addition, subjects were requested to void at 150 and 390 minutes. Urine collected between 150 and 390 minutes was used for purification of urinary acetaminophen glucuronide.

Respiratory gas exchange was continuously monitored during the experiments by open-flow indirect calorimetry as previously described.[19] Measurements were briefly interrupted at 150 minutes while the subjects voided and ingested the glucose meal.

Protocol 2

Three healthy subjects (no. 1, 2, and 3) participated in an additional control protocol, which was identical to protocol 1 except that lemon-flavored water was ingested instead of the glucose load. The aim of this protocol was to assess postabsorptive UDPG turnover.

Analytical Procedures

Plasma glucose isotopic enrichment was determined on deproteinized samples partially purified over sequential cation-anion exchange resins (AG 1-X8 and AG 50W-X8; Bio-Rad, Richmond, CA). For 6,6-^{2}H-glucose measurements, penta-acetyl glucose was analyzed with a gas chromatograph–mass spectrometer (Hewlett Packard, Palo Alto, CA) in the chemical ionization mode with selective monitoring of *m/z* 331 and 333. For ^{13}C-glucose, samples were purified with high-performance liquid chromatography on an Aminex HPX-87C column (Bio-Rad) as previously described,[20] evaporated to dryness, and analyzed with continuous-flow isotope ratio mass spectrometry (Roboprep CN/Tracermass, Europa Scientific, Crewe, UK).

Urinary acetaminophen-glucuronide was purified and glucuronide was converted to glucose as described by Magnusson et al.[21] To determine the ^{13}C abundance of glucuronide, the glucose obtained with this procedure was purified and its ^{13}C enrichment was measured.

Plasma insulin (kit from Biodata, Guidonia Montecelo, Italy), glucagon (kit from Linco Research, St. Charles, MO), and C-peptide (kit from Biodata) levels were measured by radioimmunoassay. Plasma and urine glucose concentrations were measured with a Beckman glucose analyzer II (Beckman Instruments, Fullerton, CA). Urine nitrogen concentrations were measured with the method of Kjehldahl.[22]

Calculations

The glucose rates of appearance (GRa) and disappearance (GRd) were calculated from plasma 6,6-^{2}H-glucose using Steele's equations for the non–steady state.[23] The metabolic clearance rate of glucose was calculated as GRd divided by the plasma glucose concentration.

Hepatic UDPG turnover was calculated as (^{13}C-galactose infusion rate × 6)/^{13}C enrichment of urinary glucuronide). Systemic release of UDPG-derived glucose was calculated over 30-minute periods as

$$\frac{\mathrm{GRa} \times ({}^{13}\mathrm{CG}_2 + {}^{13}\mathrm{CG}_1)/2 + 0.75 \times 0.2 \times (\mathrm{G}_1 + \mathrm{G}_2)/2 \times ({}^{13}\mathrm{CG}_2 - {}^{13}\mathrm{CG}_1)/(t_2 - t_1)}{{}^{13}\mathrm{C}\ \text{glucuronide enrichment}},$$

where G_1 and G_2 are the glucose concentrations and $^{13}CG_1$ and $^{13}CG_2$ are the ^{13}C glucose enrichments at time t_1 and t_2, respectively, 0.2 is the glucose distribution space, and 0.75 is the pool fraction.[24] The cumulative amount of glucose released from UDPG was subsequently calculated over 4 hours postprandially. Net hepatic glycogen storage was calculated as (hepatic UDPG turnover) − (systemic release of UDPG-derived glucose).

Net carbohydrate and lipid oxidation were calculated from respiratory gas exchange using the equations of Livesey and Elia.[25] Total nonoxidative glucose disposal was calculated as the difference between the ingested glucose load and net carbohydrate oxidation over 4 hours.

Extrahepatic nonoxidative glucose disposal was calculated as total nonoxidative glucose disposal-net hepatic glycogen storage. A splanchnic postprandial glucoregulatory index was calculated as (100-suprabasal GRa)/(ingested glucose load × 100), with suprabasal GRa calculated as postprandial GRa-basal GRa, cumulated over 240 minutes. The rationale for this index is as follows. After ingestion of a glucose-containing meal, both suppression of endogenous glucose production (which mostly occurs in the liver with a contribution from the kidneys[26]) and splanchnic glucose uptake contribute to limit the postprandial increase in plasma glucose.[3] The ratio (ingested glucose load-suprabasal GRa) over ingested glucose represents the fraction of the glucose load retained in the liver and splanchnic tissues. The splanchnic postprandial glucoregulatory index represents 1 minus this ratio, ie, the fraction of ingested glucose that reaches the systemic circulation. This index would be equal to 0 in the theoretical case where no suppression of endogenous glucose production and no stimulation of splanchnic glucose uptake are present.

Hepatic insulin clearance was estimated from the ratio of the incremental areas under the postprandial insulin and C-peptide curves.

Data Analysis

All data were normalized for fat-free mass and are presented as the mean ± SEM. Comparison of mean values was performed by ANOVA and unpaired *t* tests for all parameters except plasma insulin and glucagon. These two hormones showed a large dispersion and a non-normal distribution in patients with cirrhosis, and were thus compared with the Mann-Whitney *U* test.

RESULTS

Plasma Hormone and Substrate Concentrations

Plasma concentrations of glucose, insulin, glucagon, and C-peptide are shown in Fig 1. Patients with cirrhosis had higher postprandial plasma glucose. All met the criteria for impaired glucose tolerance.[27] They also had higher basal and postprandial insulin, glucagon, and C-peptide concentrations. The ratio for the incremental areas under the postprandial insulin and C-peptide curves was higher in patients with cirrhosis (0.22 ± 0.03 mol/mol) versus the healthy controls (0.13 ± 0.02, $P < .05$), indicating decreased insulin clearance in cirrhosis.

UDPG Kinetics

Data for the ^{13}C enrichment of glucuronides purified from postprandial urine samples are shown in Table 2. Postprandial values were about 50% higher than fasting values obtained in healthy subjects in protocol 2. Systemic release of UDPG-derived glucose represented 37% of the total flux in healthy subjects and 42% in patients with cirrhosis after glucose

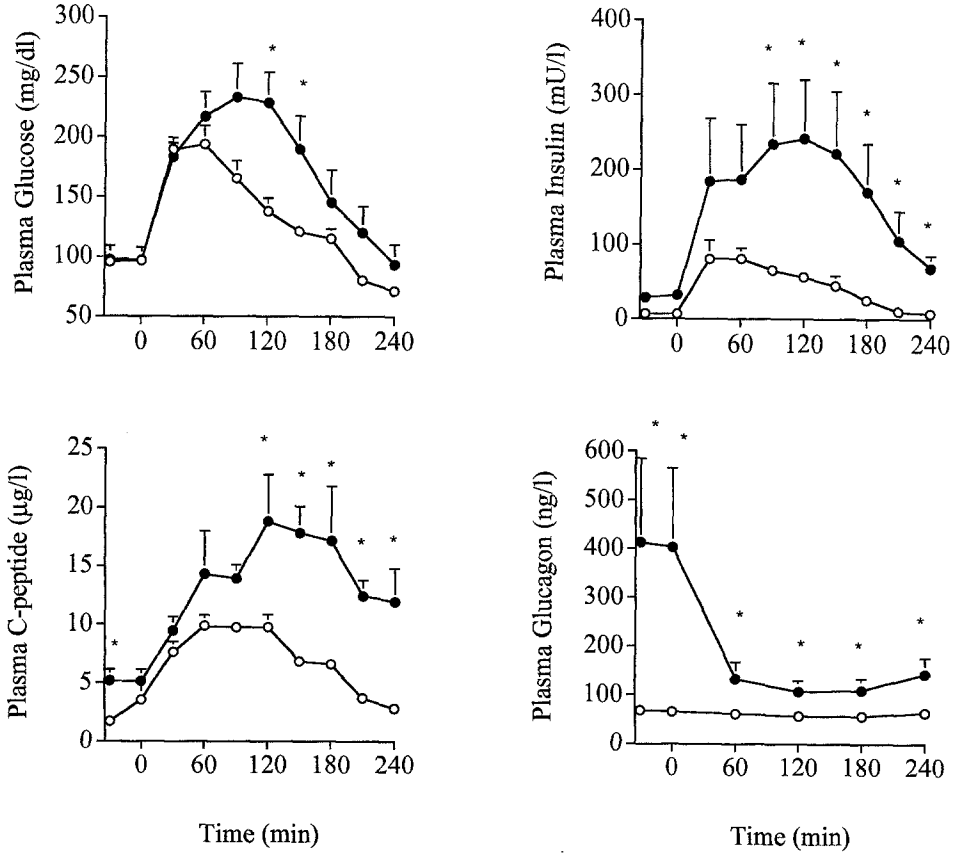

Fig 1. Plasma glucose, insulin, C-peptide, and glucagon following ingestion of a glucose load in patients with cirrhosis (●) and healthy controls (○). *$P < .05$ or less *v* controls.

Table 2. UDPG Kinetics

Parameter	^{13}C-Glucuronide (atom % excess)	^{13}C-Glucose (atom % excess)	UDPG Turnover (mg/kg fat-free mass · min)	Release of UDPG-Derived Glucose (mg/kg fat-free mass · min)	Net UDPG Storage (mg/kg fat-free mass · min)
Postglucose					
Healthy controls	0.039 ± 0.003	0.005 ± 0.001	1.76 ± 0.15	0.65 ± 0.10	1.11 ± 0.14
Patients with cirrhosis	0.044 ± 0.006	0.005 ± 0.001	1.84 ± 0.29	0.77 ± 0.10	1.07 ± 0.22
Postabsorptive					
Healthy controls	0.049 ± 0.006	0.012 ± 0.002	1.17 ± 0.29	0.56 ± 0.17	0.61 ± 0.09

ingestion and 48% in fasted healthy subjects. Postprandial UDPG flux and net UDPG storage were similar in patients with cirrhosis and healthy controls.

Whole-Body Glucose Kinetics

Plasma 6,6-^{2}H- and ^{13}C-labeled glucose values are shown in Fig 2, and the GRa, GRd, and glucose metabolic clearance rate are shown in Fig 3. GRa and GRd increased similarly after glucose ingestion in healthy controls and patients with cirrhosis,

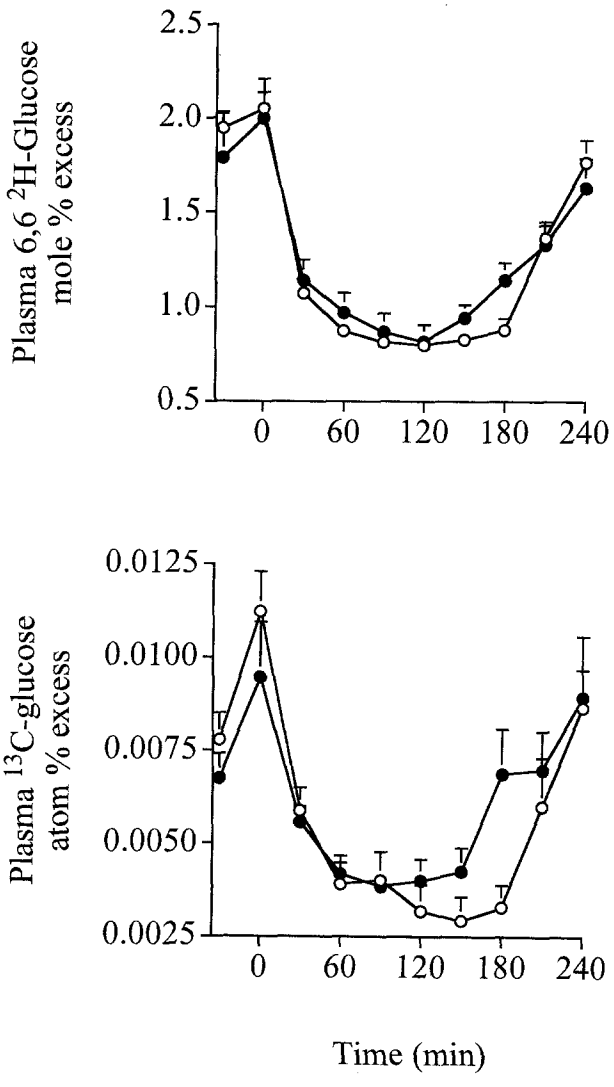

Fig 2. Plasma 6,6 ^{2}H-glucose and ^{13}C-glucose enrichment after ingestion of a glucose load in patients with cirrhosis (●) and healthy controls (○). *$P < .05$ or less *v* controls.

but the metabolic clearance rate of glucose was significantly lower in patients between 150 and 180 minutes. Suprabasal GRa cumulated over 4 hours was 816 ± 24 mg/kg fat-free mass · min in healthy controls and 744 ± 36 in patients. The splanchnic postprandial glucoregulatory index was 0.47% ± 0.02% and 0.52% ± 0.03% in healthy controls and patients with cirrhosis, respectively (nonsignificant).

Substrate Oxidation and Nonoxidative Glucose Disposal

Net carbohydrate oxidation was nonsignificantly higher in patients with cirrhosis compared with healthy subjects (0.74 ± 0.04 g/kg fat-free mass · 4 h *v* 0.90 ± 0.08). Total and extrahepatic nonoxidative glucose disposal were lower in patients with cirrhosis (0.76 ± 0.04 g/kg fat-free mass · 4 h *v* 0.60 ± 0.08 and 0.49 ± 0.03 g/kg fat-free mass · 4 h *v* 0.36 ± 0.07, respectively). However, the differences did not reach statistical significance (Fig 4).

DISCUSSION

In this study, we compared postprandial nonoxidative glucose metabolism in glucose-intolerant patients with advanced cirrhosis and healthy controls. For this purpose, both noninvasive assessment of hepatic UDPG turnover and standard glucose kinetics were used.

The principle of the method used to estimate hepatic UDPG turnover is shown in Fig 5. ^{13}C-labeled galactose was continuously infused in tracer amounts throughout the experiments. Galactose is essentially taken up by liver cells, where it is converted successively into galactose-1-phosphate, uridyldiphosphogalactose, and UDPG. Both glycogen and glucuronic acid involved in the conjugation of xenobiotics are issued from the same pool of hepatic UDPG, which can be sampled noninvasively by administration of acetaminophen and purification of urinary acetaminophen-glucuronide. The measurement of the isotopic enrichment of isolated glucuronides allows the calculation of UDPG turnover by isotopic dilution, assuming that the entire amount of infused ^{13}C-galactose has been converted to UDPG. Glycogen synthesis proceeds with the conversion of glucose-6-phosphate to glucose-1-phosphate and UDPG, followed by deposition of glycosyl units on the glycogen molecules. The conversion of glucose-1-phosphate to UDPG and pyrophosphate is essentially irreversible due to the pyrophosphorylase reaction. Although UDPG also contributes to the synthesis of glucuronic acid, this pathway is quantitatively small, and UDPG turnover can be reasonably equated to intrahepatic glycogen synthesis.[17]

The use of acetaminophen as a probe to assess UDPG kinetics and particularly the absence of a significant delay in the hepatic glucuronidation of acetaminophen and the rapid kinetics

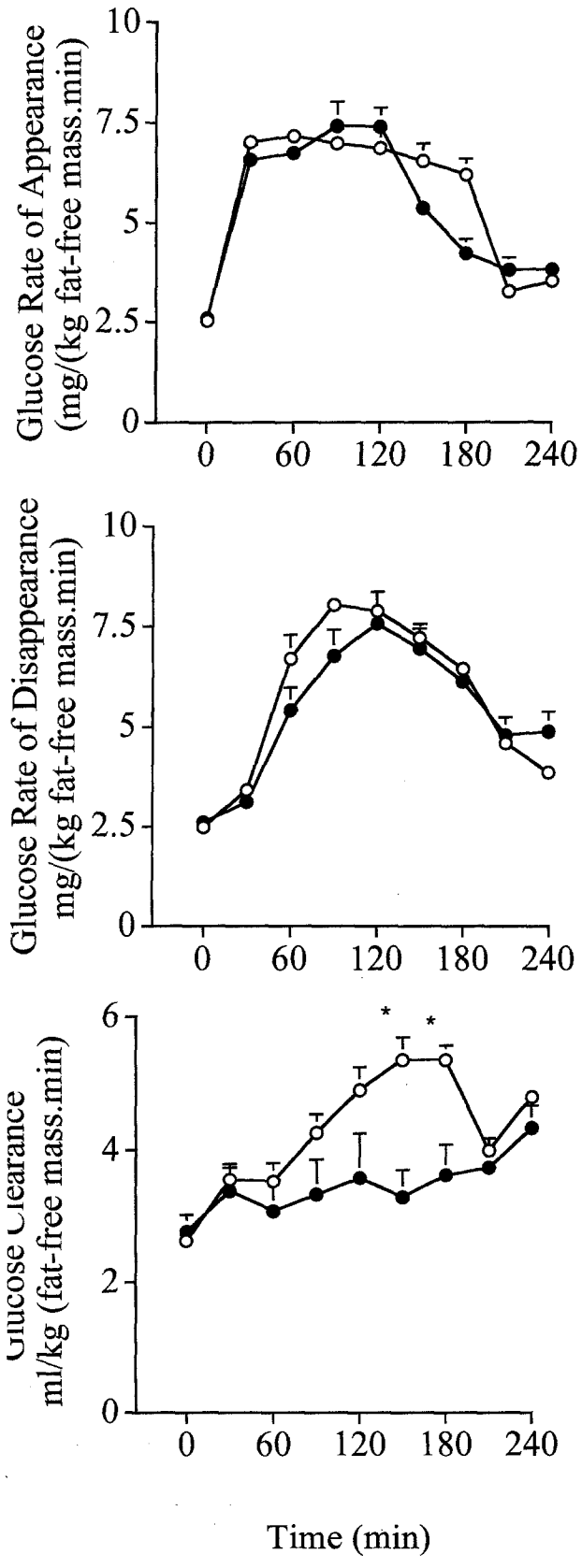

Fig 3. Glucose kinetics after ingestion of a glucose load in patients with cirrhosis (●) and healthy controls (○). *$P < .05$ or less *v* controls.

of acetaminophen glucuronide have been extensively discussed by Hellerstein et al.[16,17] In our hands, this method yielded estimates of UDPG turnover in healthy postabsorptive subjects that were comparable to those reported by Hellerstein et al. Ingestion of a glucose meal increased the mean UDPG turnover rate by 50%, a stimulation slightly lower than that observed by Hellerstein et al after 8 hours of continuous intravenous or oral administration in healthy subjects. The net UDPG storage over 4 hours postprandially corresponded to 17.7% and 17.1% of the ingested glucose load in healthy subjects and patients with cirrhosis, respectively. This is in agreement with the values reported in healthy subjects using NMR spectroscopy.[13,14] We are therefore confident that our results reflect hepatic UDPG turnover and glycogen synthesis.

Significant amounts of ^{13}C-labeled glucose were detected in plasma over 4 hours following ingestion of the glucose load. Since labeling of glucose by galactose occurs at the UDPG level and UDPG is not directly converted to glucose-1-phosphate, the appearance of ^{13}C-glucose in the systemic circulation is explained by the degradation of newly formed glycogen. This observation is in agreement with the concept that the most recently synthesized glycogen is the first to be hydrolyzed. However, only a fraction of infused label was recovered as plasma glucose even in the postabsorptive condition, when net hepatic glycogen breakdown occurs. This indicates that labeled glycosyl units were deposited at the same time that unlabeled glycosyl units were released. The existence of such an active glycogen turnover process has been recently documented in fed humans using in vivo ^{13}C NMR spectroscopy.[28]

The patients in our study had severe liver disease at the time they were investigated. All subsequently underwent an orthotopic liver transplant, and postoperative histology of the liver confirmed the presence of cirrhosis in all cases. Despite this severe reduction in functional liver cell mass, the total UDPG turnover, systemic release of UDPG-derived ^{13}C-labeled glucose, and net hepatic UDPG storage were all similar to the levels observed in healthy subjects, suggesting that postprandial stimulation of glycogen synthesis and glycogen turnover were comparable in both groups of subjects. These results are consistent with the observation that hepatic glucose uptake assessed during splanchnic catheterization studies was essentially unchanged in patients with cirrhosis.[2] These observations indicate a large functional reserve regarding glucose metabolism.

Standard isotope-dilution methods also provide substantial information on postprandial splanchnic glucose metabolism. Following ingestion of a glucose meal, both splanchnic glucose uptake and suppression of endogenous glucose production occur.[11] These two metabolic processes contribute to limit the postprandial increase in plasma glucose, and can be globally assessed as the difference between the amount of glucose reaching the systemic circulation in excess of basal glucose production during the 4-hour postprandial period and the ingested glucose load. This difference, expressed as a percentage of the ingested glucose load (and referred to as the splanchnic postprandial glucoregulatory index), was used to compare the global impact of hepatic glucose uptake and suppression of endogenous glucose production in patients with

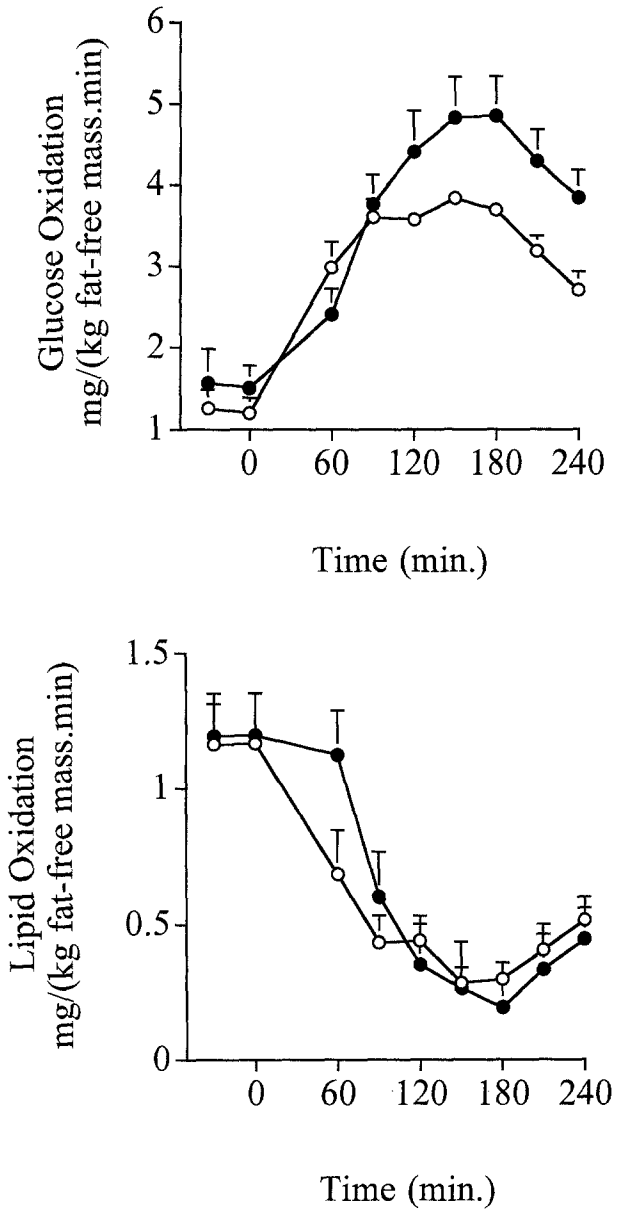

Fig 4. Net carbohydrate and lipid oxidation after ingestion of a glucose load in patients with cirrhosis (●) and healthy controls (○).

cirrhosis and healthy controls. This index was similar in both groups of subjects, suggesting that suppression of hepatic and/or renal glucose output and stimulation of splanchnic glucose uptake were globally similarly effective in regulating glucose homeostasis.

The data obtained with these two approaches indicate that alterations of postprandial splanchnic glucose metabolism, hepatic glucose uptake, or hepatic glycogen synthesis are not responsible for the postprandial hyperglycemia in patients with cirrhosis. However, the presence of modest alterations of hepatic glucose metabolism in patients with cirrhosis cannot be excluded. At the level of the liver cells, plasma glucose itself regulates hepatic glucose uptake and glucose production. Since postprandial plasma glucose concentrations were increased in these patients, it can be speculated that postprandial hepatic glycogen synthesis would have been decreased in patients with cirrhosis if the plasma glucose concentrations were identical to those of healthy controls. According to this scheme, portal hyperglycemia may have restored the splanchnic glucose metabolism toward normal and thus may have masked alterations secondary to cirrhosis. It is also possible that the pathways for glycogen synthesis (ie, from glucose or three-carbon compounds) differed between cirrhotic patients and healthy subjects. Further studies will be needed to clarify these points. However, the present data show that liver alterations are not primarily responsible for the development of postprandial hyperglycemia in cirrhotic patients.

We also evaluated the possibility that methodological limitations of our study design may have precluded our detection of alterations in glucose metabolism induced by cirrhosis. A decreased hepatic uptake of galactose secondary to a reduction of functional liver cell mass appears unlikely at this low rate of galactose administration. A decreased glucuronidation of acetaminophen may be present in such patients but will not interfere with the determination of UDPG flux, since ^{13}C enrichment, not the amount of urinary acetaminophen-glucuronide, is used in this calculation. Finally, we studied a group of patients awaiting orthotopic liver transplantation for liver disease of various etiologies. It may therefore be argued that the heterogeneity of this population prevented the detection of significant differences in hepatic glucose metabolism. Although this possibility cannot be completely discounted, it appears unlikely because the values for both glucose and UDPG kinetics showed no marked variability. Furthermore, it has been reported previously that the mechanisms responsible for alterations of glucose homeostasis appear similar among the various etiologies of liver diseases.[1] The postprandial metabolic clearance rate of glucose was decreased in patients with cirrhosis, probably secondary to the insulin resistance observed in such patients.[2] Postprandial glucose oxidation was also somewhat higher, while total nonoxidative glucose disposal was lower, versus healthy con-

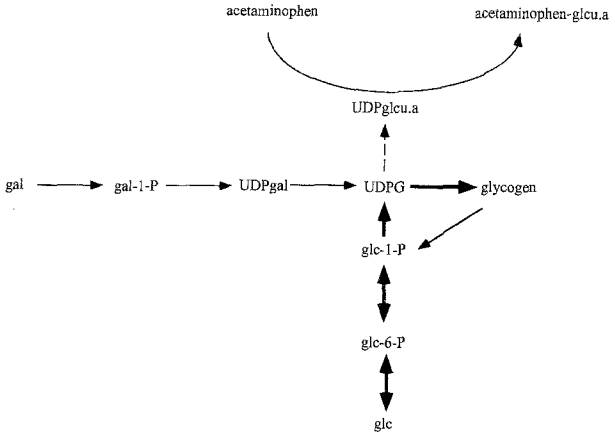

Fig 5. Pathways of glycogen synthesis and galactose metabolism. gal, galactose; gal-1-P, galactose-1-phosphate; UDP gal, uridyl-diphosphogalactose; glc, glucose; glc-6-P, glucose-6-phosphate; glc-1-P, glucose-1-phosphate; UDP glcu.a, uridyl-diphosphoglucuronic acid.

trols. However, these differences did not reach statistical significance, most likely due to the small number of subjects tested.

In conclusion, the measurements performed in this study indicate that the contribution of splanchnic organs to postprandial glucose homeostasis is not altered in a group of patients with cirrhosis. Given the severity of liver disease in these patients, this indicates an important functional reserve of the liver regarding glucose metabolism. This observation of normal splanchnic glucose metabolism strongly suggests that peripheral insulin resistance is primarily responsible for the development of glucose intolerance and/or diabetes mellitus in patients with cirrhosis.

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