

Effects of a Glucose Meal on Energy Metabolism in Patients With Cirrhosis Before and After Liver Transplantation

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Hypothesis: Liver transplantation results in hepatic denervation. This may produce alterations of liver energy and substrate metabolism, which may contribute to weight gain after liver transplantation.

Design: Prospective clinical study.

Setting: Liver transplantation clinics in a university hospital.

Patients: Seven nondiabetic patients with cirrhosis were recruited while on a waiting list for liver transplantation. Seven healthy subjects were recruited as controls.

Intervention: Orthotopic liver transplantation.

Main Outcome Measures: Evaluation of energy and substrate metabolism after ingestion of a glucose load with indirect calorimetry was performed before, 2 to 6 weeks

after, and 5 to 19 months after transplantation. Whole-body glucose oxidation and storage and glucose-induced thermogenesis were calculated.

Results: Patients with cirrhosis had modestly elevated resting energy expenditure and normal glucose-induced thermogenesis and postprandial glucose oxidation and storage. These measures remained unchanged after liver transplantation despite a significant increase in postprandial glycemia. Patients, however, gained an average of 3 kg of body weight after 5 to 19 months compared with their weight before transplantation.

Conclusion: Liver denervation secondary to transplantation does not lead to alterations of energy metabolism after ingestion of a glucose load.

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SEVERAL ALTERATIONS of energy metabolism have been described in patients with liver cirrhosis.¹⁻³ Postabsorptive resting metabolic rate is increased in a subset of patients and is considered a predictor of poor outcome, particularly when it persists after orthotopic liver transplantation.⁴⁻⁶ Resting carbohydrate oxidation is usually decreased at the profit of lipid oxidation, a finding that has been tentatively explained by low hepatic glycogen stores and accelerated starvation secondary to liver failure.⁷ After ingestion of a glucose load, a mild glucose intolerance is observed together with marked hyperinsulinemia secondary to decreased hepatic clearance of insulin.^{8,9} Glucose oxidation rises sharply with proportionate suppression of lipid oxidation. Glucose-induced thermogenesis has been described as normal¹⁰ or decreased.¹¹ A lower hepatic glycogen synthesis was proposed to be responsible for alterations of postprandial energy metabolism.¹²

Orthotopic liver transplantation has become the treatment of choice for terminal liver failure. Provision of a functional hepatic parenchyma has indeed been shown

to restore many major metabolic functions of the liver.¹³⁻¹⁵ The normal liver innervation, however, is irreversibly lost in the process of liver transplantation, which may possibly have unrecognized functional consequences. Liver transplant recipients frequently gain excessive amounts of body weight.^{16,17} Since the sympathetic nervous system is involved in the control of basal metabolism¹⁸ and of glucose-induced thermogenesis,¹⁹ it could be suspected that loss of hepatic innervation would affect basal and/or postprandial energy metabolism. We have been studying a group of patients with cirrhosis since the time they were on a waiting list for liver transplantation up to an average of 38 weeks after liver transplantation.^{15,20} We report herein their energy metabolism and substrate oxidation rates during 4 hours after ingestion of a standardized glucose meal.

RESULTS

Compared with healthy subjects, patients with cirrhosis before liver transplantation had normal plasma glucose concentrations but slightly elevated free fatty

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PATIENTS AND METHODS

Seven nondiabetic patients with liver cirrhosis on a waiting list for a liver transplantation agreed to participate to this study. Primary liver injury was secondary to hepatitis from hepatitis C virus (n=2), hepatitis from hepatitis B virus (n=1), primary biliary cirrhosis (n=1), autoimmune hepatitis (n=1), and alcoholic liver disease (n=2). Patients were studied before transplantation and 2 to 6 weeks after liver transplantation; 6 patients had a third set of metabolic measurements (full investigation in 5, resting metabolic rate in 1) 5 to 19 months after liver transplantation. Alterations in glucose tolerance in these patients have been reported elsewhere.²⁰ Two patients were receiving insulin therapy at the third investigation, and their insulin treatment was discontinued the day before the study. Six healthy volunteers were studied as a control group. Immediately before each metabolic investigation, subjects were weighed and their body composition was assessed from skinfold thickness measurements.²¹ Their physical characteristics and glucocorticoid-immunosuppressive treatments are displayed in **Table 1**.

All studies were performed in the morning after an overnight fast. Respiratory gas exchange measurements were continuously monitored by means of a ventilated hood, as described elsewhere.²² After basal measurements, an oral glucose load (1.5 g of glucose per kilogram of lean body mass) was ingested over 5 minutes (time 0). Measurements were performed during 60 minutes in the basal state (time -60 to time 0) and during 4 hours after ingestion of 1.5 g of glucose per kilogram of lean body mass (time 0 minutes to time 240 minutes). A timed urine collection was

performed at the end of the test for determination of urinary nitrogen excretion rate.

Plasma glucose concentrations were measured with a glucose analyzer (Beckman Glucose Analyzer II; Beckman Instruments, Brea, Calif). Plasma insulin (kit from Biodata, Guidonia Montecello, Italy) and C-peptide (kit from Biodata) were measured by radioimmunoassay. Plasma free fatty acid concentrations were measured enzymatically by means of a kit (Wako, Freiburg, Germany). Urinary nitrogen was measured with the Kjeldahl method.²³

Energy expenditure and net substrate oxidation rates were calculated from respiratory gas exchanges and urinary nitrogen excretion by means of the equations of Livesey and Elia.²⁴

Cumulated net carbohydrate oxidation was calculated over the 4 hours after ingestion of the glucose load for each metabolic investigation. Nonoxidative carbohydrate disposal was then calculated as the difference between the ingested glucose load and cumulated net carbohydrate oxidation.

Resting energy expenditure was expressed both as kilojoules per minute and as a percentage of values predicted from fat-free mass by means of the equations of Owen et al.²⁵

Glucose-induced thermogenesis was calculated as the cumulated 4-hour incremental energy expenditure above basal values divided by the energy content of the glucose load.²⁶

All results in the text and figures are expressed as mean \pm 1 SEM unless stated otherwise. Data from patients and controls were compared by means of unpaired *t* tests. Patient data before and after liver transplantation were compared by analysis of variance for repeated measurements.

acid concentrations. Their mean plasma insulin and C-peptide concentrations were increased by 315% ($P<.01$) and 51% ($P<.05$) (**Figure 1**). Their resting energy expenditure was similar to that of healthy subjects and amounted to 108% of predicted values according to their fat-free mass (**Figure 2** and **Table 2**). Their resting carbohydrate oxidation tended to be lower and their lipid oxidation higher than in healthy subjects, but the difference did not reach statistical significance.

After ingestion of the glucose load, plasma glucose level increased more markedly in patients than in healthy volunteers and was significantly higher from time 90 to time 120 minutes (**Figure 1**). Plasma insulin and C-peptide concentrations remained higher throughout the measurement period. Free fatty acids were suppressed to similar values in both patients and controls (**Figure 1**). Resting energy expenditure increased similarly in patients and controls (**Figure 2**), resulting in a similar glucose-induced thermogenesis (**Table 2**). Net carbohydrate oxidation increased strongly after glucose ingestion in patients and was higher than in healthy controls from time 150 to time 210 minutes (**Figure 3**). Net lipid oxidation showed minor changes. When cumulated over the 4 hours after glucose ingestion, carbohydrate oxidation was 22% higher and nonoxidative glucose disposal 22% lower in patients with cirrhosis than in controls (not significant in both cases) (**Table 3**).

Two to 6 weeks after liver transplantation, patients had lost an average of 6 kg of body weight (**Table 1**). Their

fasting plasma insulin and C-peptide concentrations were normalized at this time. They had, however, markedly higher glucose concentrations and lower insulin concentrations after oral glucose ingestion (**Figure 1**). Their resting metabolic rate was identical with pretransplantation values and increased similarly after glucose ingestion (**Figure 2**). Their net carbohydrate oxidation and lipid oxidation rates were normalized both in the fasting state and after glucose ingestion (**Figure 3**).

Six patients were restudied again 5 to 19 months after liver transplantation. They had regained an average weight of 9 kg compared with immediately after transplantation (**Table 1**). This corresponded to a 3-kg increase in body fat mass compared with their body composition before transplantation. Their plasma hormone and substrate concentrations in the basal state and after glucose ingestion were unchanged compared with values observed 2 to 6 weeks after transplantation. Their resting metabolic rate and glucose-induced thermogenesis remained also unchanged (**Table 3**). There was no significant correlation between the number of kilograms of body weight gained and resting energy expenditure or glucose-induced thermogenesis.

COMMENT

Patients before liver transplantation had markedly elevated fasting and postprandial plasma insulin concentra-

Table 1. Characteristics of Patients*

	Sex, No. M/F	Age, y	Body Weight, kg	Fat-Free Mass, kg	Height, cm	Mean Cyclosporine Dose, mg/d†	Mean Tacrolimus Dose, mg/d†	Mean Prednisone Dose, mg/d†
Liver cirrhosis, before transplantation	4/3	46 ± 14	68 ± 5	52 ± 10	171 ± 8	NA	NA	NA
Early posttransplantation (2-6 wk)	4/3	46 ± 14	62 ± 7	48 ± 9	171 ± 8	358 ± 168 (6)	12 (1)	21 ± 2 (7)
Late posttransplantation (5-19 mo)	4/2	47 ± 14	71 ± 10	51 ± 9	173 ± 7	250 ± 92 (5)	10 (1)	12 ± 7 (6)
Healthy control subjects	4/2	39 ± 11	72 ± 13	55 ± 13	173 ± 11	NA	NA	NA

*All data are expressed as mean ± 1 SD.

†Figures in parentheses indicate the number of patients treated. NA indicates not applicable.

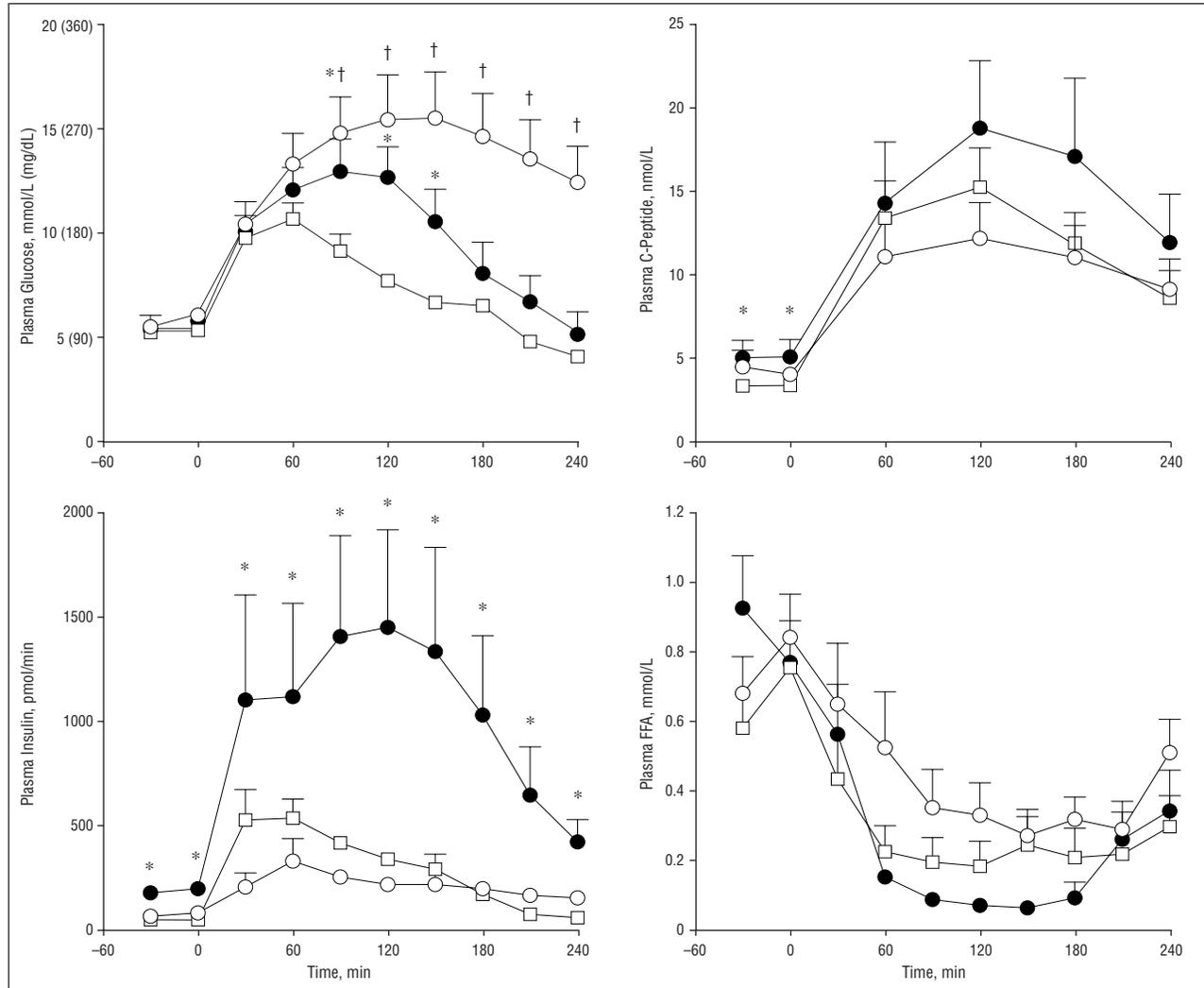


Figure 1. Plasma glucose, insulin, C-peptide, and free fatty acid (FFA) concentrations after ingestion of a glucose load at time 0 minutes in patients with liver cirrhosis before (solid circles) and 2 to 6 weeks after (open circles) liver transplantation and in healthy controls (squares). Asterisk indicates $P < .05$, patients with cirrhosis before liver transplantation vs control patients; dagger, $P < .05$, patients with cirrhosis 2 to 6 weeks after liver transplantation vs control patients.

tions, which could essentially be attributed to decreased hepatic insulin clearance in such patients.^{1,8,9} They also had mildly impaired glucose tolerance and increased basal plasma free fatty acid concentrations, which were completely suppressed after glucose ingestion. Their glucose oxidation was low in the basal state but increased after ingestion of a glucose load, whereas the nonoxidative disposal of the ingested glucose was decreased. These alterations of glucose metabolism have been widely documented in patients with cirrhosis. They bear many similarities to

the metabolic changes induced by fasting,²⁷ and it has been proposed that the cirrhotic liver is unable to sustain its function of glucose production during the interprandial periods, leading to accelerated starvation.⁷ These metabolic alterations of liver cirrhosis reverted early after liver transplantation. This indicates that denervation of the liver does not grossly impair its metabolic functions. It is consistent with previous reports indicating that metabolic control was adequately restored after liver transplantation in patients with liver cirrhosis^{13,14} or with inherited hepatic enzyme

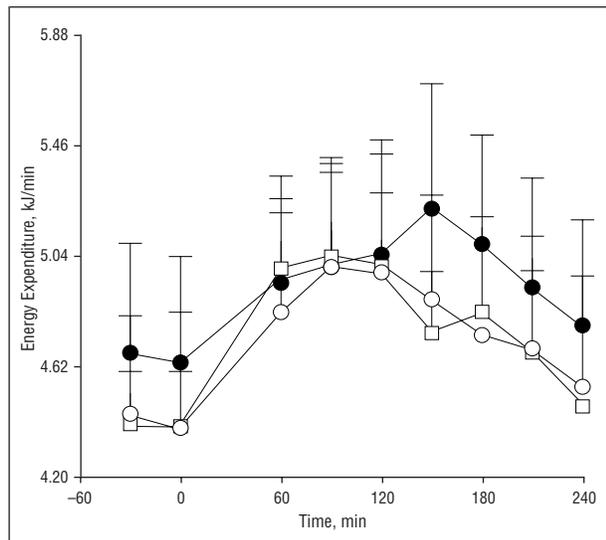


Figure 2. Energy expenditure after ingestion of a glucose load at time 0 minutes; symbols are the same as in Figure 1.

Table 2. Resting Energy Expenditure and Glucose-Induced Thermogenesis*

	Resting Energy Expenditure, % of Predicted Values	Glucose-Induced Thermogenesis, %
Before transplantation	111.4 ± 4.5	7.2 ± 1.1
Early posttransplantation (2-6 wk)	108.3 ± 5.6	8.2 ± 1.7
Late posttransplantation (5-19 mo)	107.2 ± 4.3†	8.2 ± 0.8‡
Healthy control subjects	101.6 ± 3.4	7.7 ± 1.0

*All data are expressed as mean ± 1 SD.

†n = 6.

‡n = 5.

deficiencies (glycogenosis).²⁸ This suggests the presence of redundant mechanisms in the control of metabolic liver functions.

Little information is available regarding the effects of immunosuppressive drugs on basal and postprandial substrate oxidation. Basal glucose oxidation was shown to be increased during the second month after kidney transplantation but returned to normal values gradually thereafter.²⁹ In healthy volunteers, a short-term administration of glucocorticoids produced either a slight decrease or no changes in basal and postprandial glucose oxidation.^{30,31} It is therefore unlikely that the changes observed after liver transplantation were secondary to immunosuppressive glucocorticoid treatment, although we cannot exclude that they exerted minor effects.

Patients with cirrhosis had a slight elevation of resting metabolic rate (on average, 111% of predicted values according to their fat-free mass). This is consistent with several reports showing higher-than-predicted resting metabolism in cirrhosis.⁴⁻⁶ There is, however, considerable interindividual variability among patients,³² and the deviations from predicted values were modest in the patients included in the present study. There is no definite explanation for this apparent increase in resting metabolic rate in cirrhosis. Changes in body composition, with a predominant loss of muscle mass that has a relatively mi-

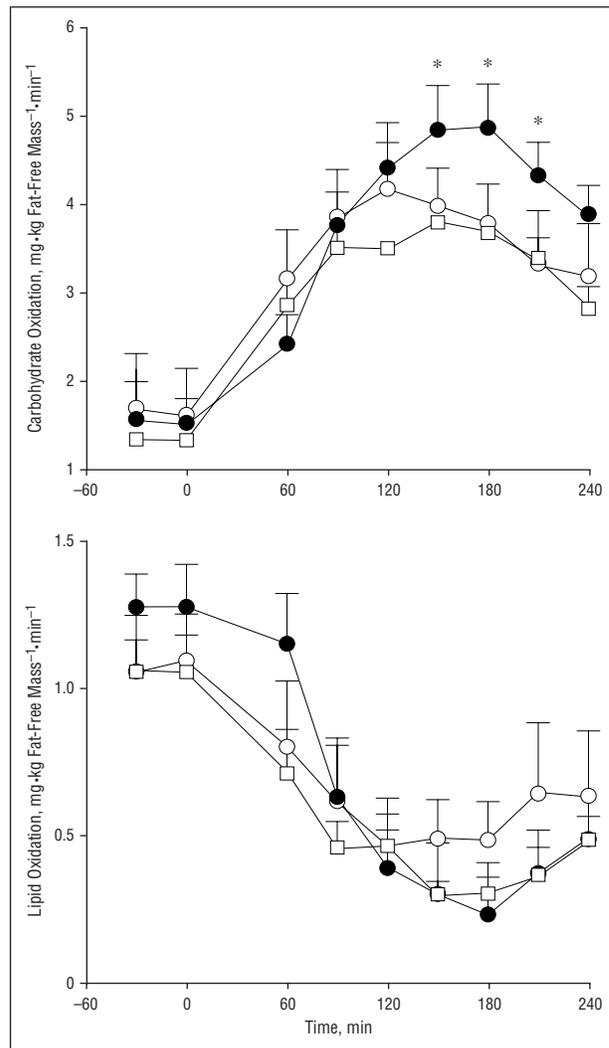


Figure 3. Net substrate oxidation rates after ingestion of a glucose load at time 0 minutes; symbols are the same as in Figure 1.

Table 3. Cumulated Glucose Oxidation and Nonoxidative Glucose Disposal During the 4 Hours After Ingestion of a Glucose Load*

	Glucose Oxidation	Nonoxidative Glucose Disposal
Before transplantation	0.90 ± 0.08	0.60 ± 0.08
Early posttransplantation (2-6 wk)	0.81 ± 0.12	0.69 ± 0.12
Late posttransplantation (5-19 mo)†	0.63 ± 0.07	0.87 ± 0.07
Healthy control subjects	0.74 ± 0.03	0.76 ± 0.03

*Data are expressed as grams per kilogram of fat-free mass per 4 hours (mean ± SD).

†n = 5.

nor contribution to energy expenditure compared with more metabolically active tissues such as brain and kidney,³³ may be responsible. The relatively small loss of fat-free mass in the patients included in this study may therefore explain this relatively modest increase in resting metabolic rate above predicted values. Additional factors, such as increased sympathetic nervous system activity, may also be involved in producing hypermetabolism in patients with cirrhosis.

Liver transplantation produced significant changes in body composition over time. Early after liver transplantation, total body weight and fat-free mass decreased. This is likely the result of both reversal of ascites and loss of muscle and fat mass secondary to major surgery and to the consecutive metabolic stress. Five to 19 months after transplantation, the lost body weight was regained, and an additional 3 kg of body weight was deposited essentially as fat mass. Throughout these changes in body composition, resting metabolic rate remained constant at 107% to 108% of values predicted from fat-free mass. This observation indicates that liver transplantation does not decrease resting energy expenditure, as might have been expected if basal sympathetic activity targeted to the liver had stimulated hepatic energy expenditure. In addition, it suggests that alterations in resting metabolic rate were not involved in the body weight changes that occurred over time in these patients.

Glucose-induced thermogenesis was not affected by liver transplantation. Glucose-induced thermogenesis can be partitioned into 2 major components: an obligatory portion, corresponding to the energy cost of glucose phosphorylation to fructose 1,6-diphosphate and of glycogen synthesis; and a facultative portion secondary to sympathetic activation elicited by carbohydrate feeding.¹⁹ The latter portion can be evaluated from the reduction in glucose-induced thermogenesis observed during administration of β -adrenergic antagonists. It is, however, inconstantly observed after oral glucose administration, as in the present protocol. Part of this sympathetically mediated thermogenesis is thought to take place in skeletal muscle.³⁴ It remains unknown whether the splanchnic organs, which account for about half of overall glucose-induced thermogenesis,^{35,36} contribute to this facultative thermogenesis. The present observation of an unaltered glucose-induced thermogenesis in patients with denervated liver grafts suggests that sympathetic activation of the liver is not a major factor in the thermic effect of an oral glucose meal.

Excessive weight gain has been reported in a substantial number of liver transplant recipients.³⁷ Since changes in body weight and, hence, body energy content obey the laws of thermodynamics, weight gain in these patients results from an imbalance between energy intake and expenditure. The latter can be partitioned into 3 major components: basal energy expenditure, thermic effect of food, and the energy expended in physical activity.³⁸ Our present observation indicates that the former 2 components of energy expenditure are not decreased by the sole hepatic denervation secondary to liver grafting, nor by immunosuppressive and glucocorticoid treatments. It is therefore likely that decreased physical activity and/or increased energy intake is responsible for excess fat deposition in weight-gaining patients.

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