Chronic Peripheral Hyperinsulinemia in Type 1 Diabetic Patients After Successful Combined Pancreas-Kidney Transplantation Does Not Affect Ectopic Lipid Accumulation in Skeletal Muscle and Liver

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OBJECTIVE—So far it is unclear whether chronic peripheral hyperinsulinemia per se might contribute to ectopic lipid accumulation and consequently insulin resistance. We investigated the effects of systemic instead of portal insulin release in type 1 diabetic patients after successful pancreas-kidney transplantation (PKT) with systemic venous drainage on the intracellular lipid content in liver and soleus muscle, endogenous glucose production (EGP), and insulin sensitivity.

RESEARCH DESIGN AND METHODS—In nine PKT patients and nine matching nondiabetic control subjects, intrahepatocellular lipids (IHCLs) and intramyocellular lipids (IMCLs) were measured using ^{1}H nuclear magnetic resonance spectroscopy. Fasting EGP was measured using D-[6,6-$^2H_2$]glucose tracer dilution. A 3-h 75-g oral glucose tolerance test (OGTT) allowed us to assess kinetics of glucose, free fatty acids, insulin, and C-peptide concentrations in plasma and to calculate the clamp-like index (CLIX) for insulin sensitivity and the hepatic insulin resistance (HIR) index.

RESULTS—The PKT patients displayed approximately twofold increased fasting insulin (20 ± 6 vs. 9 ± 3 μU/ml; $P < 0.0002$) compared with that in nondiabetic control subjects and ~10% increased fasting glucose ($P < 0.02$) concentrations, but during the OGTT areas under the concentration curves of C-peptide and insulin were similar. IHCL (PKT, 2.9 ± 2.5%; nondiabetic control subjects, 4.4 ± 6.6%), IMCL (PKT, 1.0 ± 0.4%; nondiabetic control subjects, 1.0 ± 0.5%), CLIX (PKT, 8 ± 2; nondiabetic control subjects, 7 ± 3), HIR (PKT, 25.6 ± 13.2; nondiabetic control subjects, 35.6 ± 20 [mg · min^{-1} · kg^{-1}] × [μU/ml]), and EGP (PKT, 1.6 ± 0.2; nondiabetic control subjects, 1.7 ± 0.2 mg · min^{-1} · kg^{-1}) were comparable between PKT patients and nondiabetic control subjects. IHCL was negatively correlated with CLIX in all participants ($r = -0.55$; $P < 0.04$).

CONCLUSIONS—Despite fasting peripheral hyperinsulinemia because of systemic venous drainage, type 1 diabetic patients after PKT show similar IHCL, IMCL, insulin sensitivity, and fasting EGP in comparison with nondiabetic control subjects. These results suggest that systemic hyperinsulinemia per se does not cause ectopic lipid accumulation in liver and skeletal muscle. ***Diabetes*** **59:215–218, 2010**

Insulin resistance has been linked to lipid accumulation in insulin-responsive tissues such as liver and skeletal muscle (1–3), but it is not yet clear if ectopic fat accumulation induces insulin resistance and consequently hyperinsulinemia or whether increased intracellular lipid content is rather the result of long-term hyperinsulinemia.

Poorly controlled type 1 diabetic patients (4) as well as insulin-resistant type 2 diabetic subjects and the offspring of type 2 diabetic subjects displayed increased intracellular lipid content in skeletal muscle when compared with healthy individuals (1), whereas well-controlled type 1 diabetic patients exhibited an unchanged intramyocellular lipid content (5).

Pancreatic transplantation in diabetic subjects with end-stage renal disease restores insulin secretion and glucose tolerance (6). Combined pancreas-kidney transplantation (PKT) with systemic venous drainage provides a human model that allows to study the long-term effects of systemic instead of portal insulin delivery on glucose metabolism and intracellular lipid content. It is worth noting that insulin replacement in diabetic patients is commonly administered subcutaneously into the systemic circulation and not through the portal vein (4,7). It is unclear whether this peripheral route of insulin delivery has clinically relevant consequences.

We studied whether the systemic route of insulin appearance could affect intracellular lipid content in liver and skeletal muscle, as well as endogenous glucose production (EGP) in type 1 diabetes after successful pancreas transplantation.

RESEARCH DESIGN AND METHODS

Following successful combined PKT, nine type 1 diabetic patients were matched for age and BMI with nine healthy control subjects. The PKT patients had received whole pancreas grafts with systemic venous anastomosis to the iliac vein 5.2 ± 1.6 years prior to the study. At the time of examination, the immunosuppressive regimen in the PKT patients included tacrolimus ($n = 8$) or sirolimus ($n = 1$) combined with either mycophenolate mofetile ($n = 6$) or azathioprine ($n = 2$). None was using insulin or any other antihyperglycemic agent. Five PKT patients received lipid-lowering medication (statins). All subjects had nondiabetic fasting plasma glucose, glycated A1C <6.5%, and

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