CASE REPORT

LIVER TRANSPLANTATION ELIMINATES INSULIN NEEDS OF A DIABETIC PATIENT

V. VLAEMINCK-GUILLEM (1), P. GUILLEM (2), P. DEQUIEDT (3), F.R. PRUVOT (2), P. FONTAINE (1)

SUMMARY - Organ transplantation and subsequent therapeutic agents may induce or worsen preexisting diabetes mellitus. We report the case of a diabetic patient whose insulin needs disappeared after liver transplantation. Non insulin-dependent diabetes mellitus was diagnosed when she was 47, and was treated by hypoglycemic drugs and then insulin. Chronic post-hepatitis C cirrhosis was diagnosed at the age of 55 and required liver transplantation 2 years later. During the postoperative course, the insulin doses required to maintain normal glucose levels progressively decreased, and insulin became completely unnecessary by the 29th postoperative day. After insulin was stopped, glucose levels remained within normal ranges for the 5-year-long follow-up, despite the worsening of a preexisting diabetic nephropathy and the occurrence of a diabetic retinopathy. This case highlights the fact that liver transplantation may eliminate insulin needs in a diabetic patient but also shows that degenerative complications may occur despite apparent remission of diabetes.

Key-words: insulin treatment, liver transplantation, nephropathy, retinopathy.

RE´SUMÉ - Disparition des besoins en insuline après transplantation hépatique chez un diabétique.


Mots-clés : insulinothérapie, transplantation hépatique, néphropathie, rétinopathie.

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Because of better survival rates and lower morbidity rates, indications of liver transplantation have been extended to patients with poorer health such as diabetic patients [1]. Although transplantation (whether liver or other organs) and subsequent therapeutic agents tend to induce or worsen preexisting diabetes mellitus [2], some authors have mentioned decreased insulin needs after liver transplantation in diabetic patients [3, 4]. We report the case of a diabetic patient whose insulin needs disappeared after orthotopic liver transplantation for post-hepatitis C cirrhosis.

CASE REPORT

A 55-year-old woman was seen in 1990 for post-hepatitis C cirrhosis. Her medical history primarily included non-insulin-dependent diabetes mellitus and sigmoiditis. Diabetes mellitus was diagnosed in 1982 on the basis of elevated fasting glucose levels (more than 5.5 mmol/l) and was classified as being non-insulin-dependent because of normal insulin (15 µU/ml, normal ranges: 10-20) and increased C-peptide plasmatic levels (2.5 ng/ml, normal < 2). At that time, the patient weighed 54 kg and measured 1.55 m. She was prescribed hypoglycemic drugs (metformine and glicazide) but had to switch to insulin therapy in 1991. By then she weighed 46 kg and received Umulin NPH® (14 U in the morning, 4 U in the evening) and ordinary Umulin® (4 U twice a day).

Complicated sigmoiditis required iterative surgery and blood transfusions in 1983. Chronic hepatitis C and liver cirrhosis were both discovered in 1988 as a result of blood transfusions. Two hepatocellular carcinomas of segment VII (2.5 and 1 cm-wide, respectively) were diagnosed in 1990 on the basis of underlying liver cirrhosis and increased α-fetoprotein blood levels, for which the patient underwent 2 arterial chemoembolization sessions with apparent complete response. Liver transplantation was planned in 1991 and pretransplantation assessment disclosed evidence of stable insulin-dependent diabetes mellitus: normal blood glucose, glycosylated hemoglobin (5.2%, normal ranges < 7.5%) and fructosamin levels (217 pmol/l, normal ranges < 280). Systematic ophthalmologic evaluation failed to detect any changes suggestive of diabetic retinopathy. Moderate renal failure was diagnosed (blood creatinine levels: 105 to 140 µmol/l, creatinine clearance: 60 ml/min; urea: 5.6 to 15 mmol/l). It was thought to be due to a hepatorenal syndrome because of markedly decreased natriuresis (3 mEq/d). No autoantibodies were found: antinuclear, anti-smooth muscle, anti-mitochondria and anti-endoplasmic reticulum autoantibodies were all negative. The Coombs test was positive and polyclonal cryoglobulinemia type III was discovered.

Orthotopic liver transplantation was performed in March 1992, at which time the patient was prescribed a 3-drug immunosuppressive regimen including cyclosporine (225 mg/d), prednisolone (20 mg/d) and azathioprine (25 mg/d). The postoperative course was marked by early acute rejection requiring specific immunosuppressive treatment (corticoid bolus and muriel monoclonal antibodies OKT3). During her hospital stay, the patient was given continuous insulin infusion. However the insulin doses required to maintain normal glucose levels progressively decreased, and insulin became completely unnecessary by the 29th postoperative day. After insulin was stopped, glucose levels remained within normal ranges (Fig. 1). Renal failure worsened transiently but creatinine levels had returned to preoperative levels by the 30th postoperative day (Fig. 1). The patient was discharged on the 48th day.

In 1994, renal failure became more severe (creatinine: 202 µmol/l, creatinine clearance: 26 ml/min). A kidney biopsy disclosed focal glomerulosclerosis, predominantly in the vascular part of the glomerulus, and arterial wall thickening. Diabetic glomerulosclerosis was excluded because of normal glucose levels and the lack of retinopathy and proteinuria. The pathological lesions were consistent with cyclosporin-induced injuries and cyclosporine intake was subsequently progressively reduced (150 mg/d).

In 1995, renal failure continued to worsen (creatinine: 220 to 264 µmol/l, creatinine clearance: 20 ml/min), causing nephrotic proteinuria (3.08 g/d). Glu-
cose levels were still normal but diabetic retinopathy was diagnosed in the left eye by angiofluorography, requiring laser photoacoagulation. The former diagnosis of nephropathy was consequently revised in favor of diabetic glomerulosclerosis. Hemodialysis was started in 1996 (creatinine: over 350 mmol/l; creatinine clearance: under 10 ml/min). In 1996, a biopsy of the liver transplant showed evidence that hepatitis C had relapsed. Glucose levels were still within normal range in June 1997 (mean fast levels: 5.47 mmol/l; mean post-meal levels: 7.04 ± 1.47), while glycosylated hemoglobin was at 6.3% (normal ranges < 7.5%). The patient died in October 1997 from deep venous thrombosis and subsequent massive pulmonary embolism.

**DISCUSSION**

Transplantation, whether liver or other organs, is known to induce newly acquired diabetes mellitus and to accentuate pre-existing diabetes mellitus because of physical and psychological perioperative traumatism, infectious complications due to immunosuppressive therapy and the hyperglycemic effects of the immunosuppressive therapy itself [2]. Steroids induce insulin resistance, whereas cyclosporin A and FK506 are known to be diabetogenic through direct toxicity on β cells [2]. The elimination of insulin needs we observed in a diabetic patient after liver transplantation, despite a 3 drug-immunosuppressive regimen, should therefore not go unnoticed. Only a few reports describe similar situations [3, 4], and the mechanisms by which liver transplantation puts an end to the need for insulin therapy remain to be determined.

Several lines of evidence point to an increased risk of diabetes mellitus in cirrhotic patients [5]. Over 80% of cirrhotic patients have carbohydrate intolerance [6, 7], among which about 30% secondarily develop obvious diabetes mellitus. Intolerance to carbohydrates and subsequent diabetes result from [4, 6-8]:
- hyperinsulinism due to decreased insulin catabolism (hepatocellular failure and portosystemic shunts),
- insulin resistance due to decreased amounts and affinity of insulin receptors,
- decreased insulin secretion because of chronic depletion of β-cell secretion.

Among the processes that lead to liver cirrhosis, chronic hepatitis C has been advocated as the one most likely to trigger diabetes mellitus [5, 7]. Direct HCV tropism in the pancreas and auto-antibodies directed against pancreatic islet cells are thought to account for the increased risk of diabetes mellitus in chronic hepatitis and hepatitis C-related liver cirrhosis [9, 10]. Although we failed to detect any significant levels of autoantibodies, we did observe polyclonal cryoglobulinemia type III and a positive Coombs test, which is consistent with the usual HCV infection-related autoimmune status.

In our patient, diabetes appeared about 10 years before hepatitis C and liver cirrhosis and was therefore likely to have resulted from personal diabetes mellitus risk factors rather than from liver cirrhosis itself. However, insulin needs appeared when hepatitis C and liver cirrhosis were diagnosed, suggesting that they contributed to destabilizing diabetes mellitus. The decreasing need for insulin after liver transplantation probably resulted from improved liver function and reduction of portosystemic shunts as well as from reduced viral production and reduced auto-immune reaction against islet β-cells.

Another intriguing feature in our patient’s history was the occurrence of diabetes mellitus complications despite normal glucose levels. Glomerulosclerosis-related renal failure and retinopathy were indeed observed during the post-transplant follow-up. This suggests that degenerative complications of diabetes mellitus may occur despite apparent remission of the disease after liver transplantation. According to other reports, pancreas transplantation has been unable to adequately control diabetes mellitus’ degenerative complications. Fioretto et al. showed that more than 5 years of normoglycemia after pancreatic transplantation are required to reverse the lesions of diabetic nephropathy [11, 12]. Some have suggested that cyclosporine A toxicity may account for the frequent occurrence or worsening of kidney failure after liver transplantation [13]. However it seems unlikely that this would be the sole factor, since smaller doses did not prevent kidney failure from worsening in our patient. Furthermore, direct cyclosporine A effect could not, to our knowledge, explain the onset of diabetic retinopathy we observed in our patient.

This case sheds light on the great challenge that still lies in transplanting diabetic patients. Whether diabetes mellitus confers poor prognosis is still controversial. Degenerative complications may occur despite apparent remission of diabetes. Serum glucose levels and HbA1C levels can therefore not be considered as reliable tools to discriminate patients with progressive diabetes from those whose diabetes is in remission. Diabetic patients with apparent post-transplant remission should therefore be closely followed with respect to kidney and eye functions. The effectiveness of combined pancreas and kidney transplantation is now well established [14]. Whether kidney transplant should be associated with liver transplantation in diabetic patients remains to be determined. Cyclosporin A involvement in the post-transplantation progression of degenerative complications should also be considered.

**REFERENCES**