Eur J Med Res (2008) 13: 127-130

Prevalence of Cholecystolithiasis and Its Management among Kidney/Pancreas-transplanted Type 1 (Insulin-dependent) Diabetic Patients

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Abstract

Background: Simultaneous pancreas/kidney transplantation (SPK) should be the procedure of choice for (pre)uremic patients with type 1 diabetes. All standard immunosuppressive protocols for SPK include a calcineurin-inhibitor. Both calcineurin inhibitors, cyclosporine (CyA) and probably tacrolimus (FK506) too, are associated with the occurrence of cholelithiasis due to their metabolic side effects.

Patients and Methods: We evaluated the prevalence of cholelithiasis in 83 kidney/pancreas transplanted type I-diabetic patients (46 males, 37 females, mean age 42.8 ± 7.5 years) by conventional B-mode ultrasound 5 years after transplantation. 56 patients received CyA (group 1) and 27 received tacrolimus (group 2) as first-line-immunosuppressive drug. Additional immunosuppression consisted of steroids, azathioprine or mycophenolate mofetil. Additionally, laboratory analyses of cholestasis parameters (γ-GT and alcalic phosphatasis) were performed.

Results: In total, 23 patients (28%) revealed gallstones and 52 patients (62%) revealed a completely normal gallbladder. In eight patients (10%) a cholecystectomy was performed before or during transplantation because of already known gallstones. No concrements in the biliary ducts (choledocholithiasis) could be detected. In group 2 the number of patients with gallstones was slightly lower (22%) compared with group 1 patients (30%), but without statistical significance.

Cholestasis parameters were not increased and HbA_{1c} values were normal in both groups of patients.

Conclusion: The prevalence of biliary disease in kidney/pancreas transplanted type I-diabetic patients with 28% is increased in comparison to the general population (10-15%). Lithogenicity under tacrolimus seems to be lower as under cyclosporine based immunosuppressive drug treatment. We recommend regular sonographical examinations to detect an acute or chronic cholecystis as early as possible, which may develop occultly in these patients.

Introduction

Cyclosporine A (CyA), a calcineurin phosphatase inhibitor, has revolutionized organ transplantation and is still the most widely used immunosuppressive drug after organ transplantation. It is metabolized in the liver and is excreted predominantly via biliary secretion, which results in an impaired biliary excretion of bile salts and therefore in cholestasis. In heart transplanted patients, for example, a high incidence of cholelithiasis is observed in up to 35% [1].

The immunosuppressive drug tacrolimus (FK506), also a new calcineurin phosphatase inhibitor, has comparable biliary side effects like CyA [2]. The metabolism of FK506 is similar to CyA. Both drugs bind to immunophilins and inhibit the enzyme calcineurin phosphatase [3].

Since a beneficial effect concerning rejection episodes of the pancreas graft has been described, tacrolimus is now widely used after pancreas/kidney transplantation [4]. The incidence of biliary disease has not been investigated after SPK, especially no comparative analysis in cyclosporine versus tacrolimus treated graft recipients.

Kidney/pancreas-transplanted type 1 (insulin-dependent) diabetic patients generally receive either a CyA-based or a FK506-based immunosuppression. Therefore, the risk for development of biliary side effects is probably increased in these patients.

The aim of this study was to evaluate the prevalence of cholelithiasis as well as laboratory hints to cholestasis 5 years after transplantation and to give recommendations for the follow-up investigations and the management of overt cholecystolithiasis in these patients.

Methods

Patients

83 double transplanted type I-diabetic patients (46 males, 37 females, mean age 42.8 ± 7.5 years, 56 receiving CyA, 27 receiving tacrolimus) were included in the study. HbA_{1c} for monitoring of pancreas graft function and γ-GT as well as alcalic phosphatasis for detection of cholestasis were analysed to detect other risk factors of biliary disease (Table 1). Therapeutic serum levels of CyA and FK506 8-10 ng/ml were monitored to adapt the individual dosage of the patients. The levels of the calcineurin inhibitors were dependent on the duration after transplantation and of concomitant immunosuppressive drugs. Patients with recurrent colics localized in the upper right-sided abdominal quadrant were considered as symptomatic.

Table 1. Demographic characteristics and laboratory parameters of 83 kidney/pancreas transplanted type I-diabetic patients receiving either cyclosporin A or tacrolimus as basic immunosuppressive drug. Data are given as mean ± SEM.

	Cyclosporin A n = 56	**Tacrolimus n = 27**
Age	41.8 ± 7.9	43.7 ± 7.1
Male/female (n)	31/25	15/12
HbA_{1c} (%)	5.2 ± 0.1	5.4 ± 0.1
Creatinin (mg/dl)	1.9 ± 0.4	1.4 ± 0.2
AP (< 135 U/l)	113 ± 9	83 ± 5
γ-GT (< 55 U/l)	13 ± 2	20 ± 8

Abdominal Ultrasonography

Ultrasonography was performed using a 3,5 MHZ convex-array scanner (Siemens Sonoline Elegra, Erlangen, Germany) to describe the pancreas (Fig.1) and renal grafts and to detect biliary disease. The gallbladder and the biliary ducts were examined in intercostal and subcostal scans. Gallstones were characterized as hyperechogenic reflexes with posterior acoustical shadow (Fig. 2).

Statistics

For comparison of the patient subgroups a Mann Whitney U and chi-square-test was performed. P-values < 0.05 were considered as statistically significant.

Results

Table 1 shows the baseline demographic and blood chemical characteristics of the 83 kidney/pancreas transplanted type I-diabetic patients.

The total prevalence of gallstones was 28 % (Table 2). In eight patients cholecystectomy had been performed before or during transplantation (10%). 52 patients (62%) revealed a completely normal gallbladder. No concrements in the biliary ducts (choledocholithiasis) could be detected.

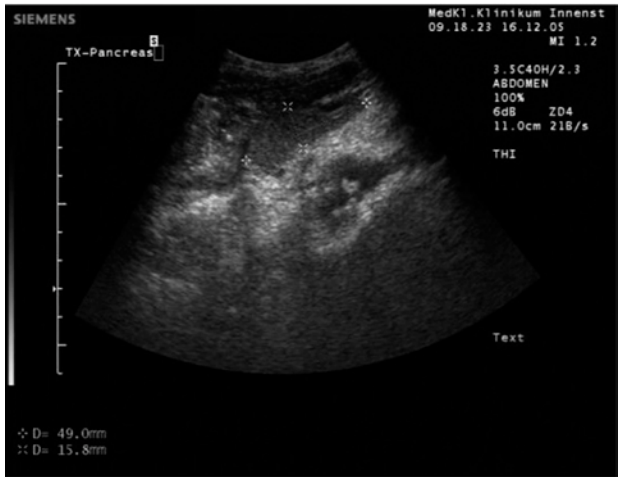

Fig. 1. B-mode scan in the lower right-sided abdominal quadrant showing a pancreas graft of a pancreas/kidney-transplanted type 1 (insulin-dependent) diabetic patient.

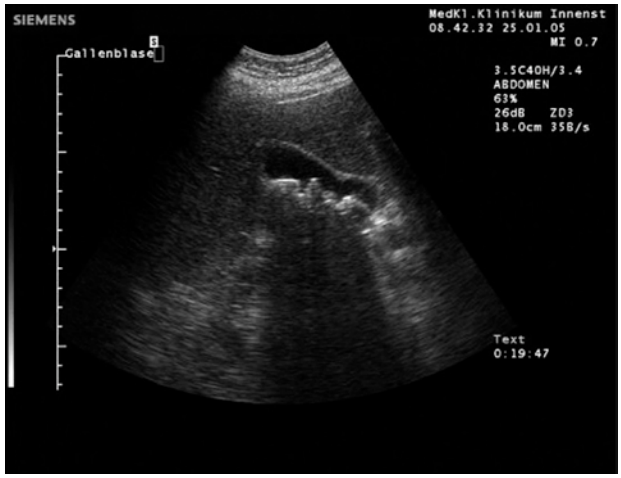

Fig. 2. Cholelithiasis with multiple gallstones of a pancreas/kidney-transplanted type 1 (insulin-dependent) diabetic patient.

Under a tacrolimus-based immunosuppressive drug treatment (group 2) the number of patients with

Table 2. Prevalence of gallstones in 83 kidney/pancreas transplanted type I-diabetic patients receiving either cyclosporin A or tacrolimus as basic immunosuppression.

	Total n = 83	**Cyclosporin A n = 56**	**Tacrolimus n = 27**	**p**
Gallstones	23 (28%)	17 (30 %)	6 (22 %)	0.73
Choledocholithiasis	0	0	0	-
Cholecystectomy (before or during transplant.)	8 (10%)	5 (9%)	3 (11%)	n.s.
Cholecystectomy (after transplant.)	0	0	0	-

*n.s. not significant

cholelithiasis was lower (22%) compared with group 1 patients (30%) under cyclosporine A, but without statistical significance ($p = 0.73$).

Cholestasis parameters were not increased (alcalic phosphatasis in group 1 and 2: 113 ± 9 U/l and 83 ± 5 U/l; γ-GT: 13 ± 2 U/l and 20 ± 8 U/l). HbA_{1c} values (group 1 and 2: 5.2 ± 0.1 and 5.4 ± 0.1 %) were normal in both groups of patients. Renal graft function was significantly better in the tacrolimus group (1.4 ± 0.2 mg/dl vs. 1.9 ± 0.4 mg/dl; $p < 0.05$) (Table 1).

Discussion

The specific mechanisms for the lithogenicity of CyA treatment have not been definitively elucidated, but various pathophysiological mechanisms have been discussed. Previous studies revealed an inhibition of ATP-dependent export carriers for bile salts, especially taurocholate and cysteinyl leukotriens in the hepatocyte canalicular membrane shown in liver plasma membrane vesicles of rats [5] as well as of humans [6]. Another study has shown a decreased bile salt synthesis and secretion combined with an unchanged cholesterol secretion, which leads to an elevated cholesterol saturation of bile and the consequent occurrence of gallstones [7, 8]. Galan and co-workers described an altering in liver plasma membrane composition, fluidity and function, as well as an induction of oxidative stress and depletion of hepatic glutathione and proteins, which might cause cholestasis [9].

The metabolism of FK506 is similar to CyA. Both drugs bind to immunophilins and inhibit the enzyme calcineurin phosphatase [10]. In this context, the data of Mizuta and co-workers give apparently contradictory results with either reduced or increased bile acid secretion, but in dependence on the dosage of applied FK506 [11, 12]. This has been confirmed by others [13]. Interestingly, Kawamura and co-workers even revealed that CyA decreases, whereas FK506 increases bile flow due to an insulin like growth factor I (IGF-I)-mediated choleretic effect [14], suggesting that both drugs have contradictory side effects.

In spite of numerous animal studies on lithogenic effects of a CyA-based immunosuppressive therapy, only few data exist about the mechanisms in humans. A study in pediatric liver transplant recipients described a lower lithogenity in FK506 treated patients [15]. Another examination of adult liver transplanted patients showed a faster recovered bile secretion after transplantation in tacrolimus treated recipients in comparison to CyA [16]. Deters and coworkers even recommended a combination of sirolimus with tacrolimus as a better alternative than sirolimus with CyA in cholestatic patients [17, 18], suggesting that FK506 is favourable.

In contrast to other groups of graft recipients, our patients may additionally develop concrements due to diabetes mellitus- induced gallbladder dysmotility. There is no data about the influence of pancreas transplantation on this diabetes-related gallbladder dysfunction. Even if glucose and HbA_{1c} levels were normalized in both groups, a persistence of gallbladder dysmotility is possible.

Our study revealed overall a high prevalence of cholelithiasis in type-I diabetic patients (28%) after SPK compared with data of the general population.

Although the prevalence of cholelithiasis was slightly lower under tacrolimus medication, no significant difference was detectable between CyA-based versus FK506-based immunosuppressive treatment.

So far, none of our patients with gallstones became symptomatic so that no surgical intervention was necessary after transplantation.

Several, mostly surgical authors described a high complication rate in cases of acute cholecystitis in transplanted patients [19]. Urgent biliary surgery has supposed to carry significant morbidity and mortality in immunosuppressed patients and appeared to increase the risk of graft failure as well [20]. Therefore it has been recommended to perform prophylactic laparoscopic cholecystectomy prior to or post transplantation in patients with gallstones [20-22]. The suitability of even laparoscopic cholecystectomy in kidney/pancreas transplant recipients has already been shown in the literature [23, 24]. The policy of our centre is to perform a cholecystectomy before transplantation only in symptomatic patients. A regular follow up with ultrasound is necessary, especially in those patients with known gallstones, however.

Steck and co-workers, who described only a minority of symptomatic heart transplanted patients with cholelithiasis confirm our experiences and recommended a conservative procedure during follow up investigations as necessary [25].

In consideration of the small number of symptomatic patients and our even well tolerated surgical interventions in clinical relevant biliary disease, we suggest that an elective surgery in asymptomatic patients is not indicated. Nevertheless, regular abdominal ultrasonography to assess morphology of the gallbladder to detect cholecystitis as early as possible should be performed. Maybe the posttransplantational application of ursodeoxycholic acid as prophylactic treatment can reduce the incidence of cholelithiasis in organ transplantated patients.

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Received: November 11, 2007 / Accepted: January 30, 2008

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