Renal problems after lung transplantation of cystic fibrosis patients

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**Introduction**

Routine monitoring and early intervention (antibiotics, high caloric intake, pancreatic enzymes and physiotherapy) have increased the life expectancy of cystic fibrosis (CF) patients from 14 years in 1969 to 30 years in 1995 [1]. In 2000, 40% of these patients are adults [2]. Renal function is not affected primarily in CF (except for a reduced capacity to secrete sodium chloride), but the kidney may be involved secondarily in later life. With the increasing numbers of CF patients receiving a lung or a lung/heart transplant, and with the improving results of the transplant procedure, nephrologists are faced with more and more of these patients suffering from renal failure.

Recently, Broekroelofs et al. investigated the long-term renal outcome in 57 patients after lung transplantation [3]. The loss in glomerular filtration rate (GFR) after transplantation was greater for seven CF patients compared with patients with primary pulmonary hypertension or emphysema. In CF patients, GFR decreased to 50% at 1 month post-transplantation compared with pre-transplantation, and GFR continued to deteriorate at a rate of 10 ml/min/year [3]. This rate is comparable to that of untreated diabetic patients. A number of factors may be responsible for renal insufficiency in CF patients, including drug toxicity, hypertension, diabetes and dehydration. Episodes of dehydration are probably caused by the high salt content of CF patients’ sweat and the consequent absence of body fluid hyperosmolarity during a long episode of sweating [4]. In addition, >90% of
CF patients show medullary nephrocalcinosis at autopsy [5], and the incidence of urolithiasis is greatly increased. In this paper we shall discuss the relative contribution of these factors in the genesis of renal failure in CF patients, in particular after transplantation.

**Drug toxicity**

Calcineurin inhibitors and antibiotics are the most important nephrotoxic drugs. Aminoglycosides in combination with β-lactam antibiotics are often prescribed for CF patients with exacerbations of pulmonary infection because of their effectiveness against *Pseudomonas* species, which are the predominant pathogens after the first decade of life [1]. Quinolones are not approved for use in children below the age of 12 years, but have been given to many infants on a compassionate basis without major side-effects [1] and may prove to be an useful alternative. When aminoglycosides cannot be avoided because of the frequent occurrence of resistant strains [6], a once-daily dosing schedule should be adopted since such dosing has been shown to be less nephrotoxic than a twice- or three-times-daily schedule [7]. Routine intravenous prophylaxis with antibiotics is still a matter of debate since it has been associated with the emergence of resistant bacterial strains. In addition, prophylactic use of antibiotics may lead to even greater disturbances of the normal intestinal microflora (see below). Since aminoglycosides penetrate into the bronchial secretions poorly, administration of aerosolized aminoglycosides by inhalation is preferable to the intravenous route. High concentrations of antibiotics can be administered locally by inhalation with less systemic resorption and low oto- and nephrotoxicity, but long-term results are pending [8].

Cyclosporine A (CyA) toxicity is mainly responsible for the 30–50% perioperative decrease of renal function after heart or lung transplantation [3,9,10]. In the first month after transplantation, CyA levels are maintained at much higher concentrations than afterwards, contributing to the early renal function loss. CF patients appear to be at particular risk of CyA nephrotoxicity. Because of malabsorption, two to three times higher doses of CyA (both Neoral® and Sandimmuno®) are needed to achieve target trough levels [11]. Acute changes of absorption may then lead to toxic trough CyA levels, at least temporarily. CF patients have higher CyA levels than patients with other pulmonary diseases after lung transplantation [3]. In addition, many CF patients are treated with three instead of two CyA doses a day [3], possibly resulting in continuous high CyA levels. Since one daily dose of CyA instead of two doses has been demonstrated to result in improved renal function [12], it is reasonable to speculate that continuous high levels aggravate nephrotoxicity. Measuring maximal CyA levels at 2 or 3 h may provide additional information for optimal dosage. The microemulsion formulation of CyA (Neoral) shows improved bioavailability and may be of benefit especially in CF patients [11,13]. Finally, since many CF patients develop liver fibrosis, accumulation of toxic metabolites of CyA may contribute to renal dysfunction, which may be assessed by measuring concentrations of CyA metabolites.

Non-steroidal anti-inflammatory drugs such as ibuprofen are sometimes prescribed to reduce the intense airway inflammation in CF patients. However, the combination of ibuprofen and aminoglycosides may cause acute renal failure [14] and should be avoided in the presence of chronic renal failure.

**Diabetes mellitus**

Eighty to 90% of CF patients suffer from exocrine pancreas insufficiency, and 30–50% of transplanted CF patients develop diabetes mellitus. While up to now, the duration of diabetes in CF patients is often too short to result in significant nephropathy, with increasing life expectancy diabetic nephropathy may become an important problem in the future. In addition, early diabetic nephropathy may render the kidney more susceptible to other (toxic, ischaemic or hypertension-related) insults.

**Nephrocalcinosis**

Before reviewing the literature on nephrocalcinosis, we would like to illustrate this serious complication of CF with a personal observation.

**Case report**

A male patient, born in 1968, was diagnosed as having CF in early childhood. In 1979, small bowel resection was performed because of distal intestinal obstruction syndrome. Diabetes mellitus was diagnosed in 1989, and in 1991 he became insulin-dependent. After gradual deterioration of pulmonary function, he received a double lung transplant in December 1992. Serum creatinine was normal pre-transplant but rose to 3 mg% in 1993. He was treated for hypertension and followed a high-calorie diet because of malabsorption due to exocrine pancreas insufficiency. Acute renal failure necessitating haemodialysis developed in 1994 during a period of high serum CyA levels, but serum creatinine stabilized thereafter at 2.6 mg%, corresponding to a creatinine clearance of 27 ml/min in January 1995. Pulmonary function of the graft was normal at all time points. In July 1995, the creatinine rose to 5.6 mg%. At that time, severe joint pain that had been present for months was attributed to an elevation of serum calcium and phosphate. An echocardiography revealed modest left ventricular hypertrophy, and on a microfocus X-ray of the hands, massive arteriosclerosis of the interdigital arteries and
osteoporosis was noted. Serum iPTh level was slightly elevated (150 pg/ml). A renal biopsy was performed that showed striped interstitial fibrosis, arteriosclerosis and deposition of oxalate crystals (Figure 1). Thereafter, the patient received intermittent chronic haemodialysis therapy. He was hospitalized for several episodes of shunt thrombosis due to peripheral artery disease. In 1996, gangrene of both legs developed, and his left thigh and right leg had to be amputated after several attempts of angioplasty. He died in July 1996 after mesenteric infarction and colectomy. On autopsy, severe ischaemic colitis and massive atherosclerosis with calcifications of the arterial media were demonstrated. There were abundant crystals in the renal tubules.

Serum calcium and phosphate levels are difficult to control in CF patients. When pancreatic insufficiency is present, the typical diet contains twice the calories, as well as twice the calcium and phosphate content, and three times the amount of vitamin D contained in normal diet [15]. Thus, when renal failure develops and phosphate is retained, CF patients are at high risk of developing hyperphosphataemia and renal calcification that may accelerate renal failure further.

Deposition of calcium oxalate in kidneys, myocardium and arteries may be an additional and often overlooked factor for the progression of renal failure as well as for peripheral artery disease in CF patients. The colon is the primary site of oxalate absorption. Gastrointestinal diseases such as ileal resection and malabsorption are well known causes of secondary hyperoxalosis since the oxalate delivery to the colon is increased. The exocrine pancreas insufficiency of CF may also lead to an increased oxalate content in the colon, and indeed ~50% of CF patients are hyperoxaluric [16]. In addition, Sidhu et al. reported that 86% of CF patients lacked the Oxalobacter formigenes bacterium in their gut, probably because of the extensive use of antibiotics in these patients for pulmonary reasons. In this report, >50% of CF patients who were not colonized with O. formigenes were hyperoxaluric [17]. Oxalobacter formigenes scavenges dietary oxalate and favours oxalate secretion by the gut. Given the large numbers of O. formigenes in the healthy human colon, the oxalate-degrading capacity of this bacterium is high. Oxalobacter formigenes is therefore an important regulator of oxalate absorption and plasma levels.

Oxalate levels rise with chronic renal failure due to diminished oxalate excretion. High plasma oxalate concentrations predispose the patient to systemic crystal deposition. In patients with end-stage renal disease not due to primary hyperoxaluria (PH), reten-

![Fig. 1. Renal biopsy. Proximal tubule with intraluminal radial oxalate crystals and destruction of tubular epithelium. Interstitial fibrosis and tubular atrophy (PAS staining).](image-url)
PH children, but only in 25 of 33 non-PH children [18]. Post-dialysis, the calcium oxalate product was still oversaturated in all PH children, but only in two of the non-PH children. Similarly, Marangella et al. found oversaturation of calcium oxalate pre-dialysis only in dialysis patients with primary or enteric hyperoxaluria, but not in patients without altered oxalate generation [19]. Whether oxalate crystals are formed in the urine that is always almost supersaturated with respect to oxalate salts depends on the presence of oxalate-binding proteins, produced by the kidneys, that prevent crystal formation [20]. Damage of proximal tubules and urothelium (e.g. by aminolycosides) induce nucleation of oxalate crystals [20]. Thus, several factors predispose CF patients to systemic oxalosis. CF patients may be hyperoxaluric: (i) because of malabsorption due to exocrine pancreatic insufficiency or due to small bowel surgery after meconium ileus; (ii) because of high oxalate ingestion with high-calorie diets; and (iii) because of the lack of colonization with oxalate-degrading bacteria. When renal function declines (e.g. with the use of calcineurin inhibitors after transplantation), oxalate levels increase exponentially, while at the same time calcium-containing phosphate binders are given to control hyperphosphataemia, leading to an increase in serum calcium and possibly calcium oxalate oversaturation.

**Perspectives**

Understanding the mechanisms of the progression of renal failure, in particular after lung or heart-lung transplantation, should increase the awareness of health care professionals in charge of CF patients. The detection of diabetes mellitus and early control of hyperglycaemia by intensive insulin treatment may prevent or at least retard diabetic nephropathy [21]. The availability of more recent immunomodulatory drugs such as mycophenolate mofetil (MMF), anti-IL2R antibodies or sirolimus may enable the transplant physician, in co-operation with the nephrologist, to use immunosuppressive protocols that are less nephrotoxic. In fact, the addition of MMF with concomitant reduction of CyA after heart transplantation [22], or even omission of CyA after liver transplantation [23], has been shown to improve renal function without a major increase in rejection episodes. The fact that the lung is considered a highly antigenic organ at high risk of acute and chronic rejection may prevent the use of calcineurin inhibitor-free immunosuppressive regimens, but calcineurin inhibitors may at least be reduced with the addition of other less nephrotoxic drugs. When a high-calorie diet is prescribed, it is crucial to consider the phosphorous and oxalate content of the diet, and calcium-free phosphate binders such as Renagel® are of theoretical advantage in preventing oversaturation of calcium phosphate and calcium oxalate [24]. With chronic renal insufficiency, a high fluid intake and urinary volumes of 2–3 l/day prevent the depositions of calcium-based crystals in the renal medulla. CF patients must be monitored closely for serum levels of calcium, phosphate and oxalate, and elevations must be treated vigorously to prevent rapid progression of renal disease due to nephrocalcinosis as well as of peripheral artery disease. When chronic dialysis therapy becomes necessary, special attention should be given to optimal blood access and highly efficient dialysis treatment.

**References**