Pediatr Nephrol (1999) 13:524–529 

ORIGINAL ARTICLE

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# Diabetes mellitus in patients with infantile cystinosis after renal transplantation

Received: 28 July 1998 / Revised: 22 September 1998 / Accepted: 23 September 1998

**Abstract** Diabetes mellitus is a frequent long-term complication of infantile nephropathic cystinosis. We studied 44 cystinotic patients, aged 22.1±5.4 years, transplanted at a mean age of 11.3±2.5 years; 25% were treated with insulin at 20 years of age or 10 years after transplantation, and over half required insulin at latest follow-up. In comparison, diabetes mellitus occurred in only 1% of non-cystinotic transplanted patients. Sequential oral glucose tolerance tests (OGTTs) in these patients showed the progressive deterioration of glucose metabolism. All but 2 patients had an abnormal response at latest follow-up. The high doses of corticosteroid given after transplantation or during rejection episodes were responsible for transient insulin dependency. However, the development of impaired glucose tolerance and diabetes mellitus depended mainly on the cystinotic process, which developed slowly with time. The deterioration of glucose tolerance was correlated with a decreased early phase of insulin secretion, estimated from the plasma insulin level at 30 min of the OGTT, while there was no evidence of insulin resistance. The occurrence of diabetes mellitus correlated with a worsening of the vital prognosis.

**Key words** Infantile cystinosis · Renal transplantation · Diabetes mellitus · Impaired glucose tolerance

## Introduction

Infantile cystinosis is a genetic disorder with autosomal recessive inheritance. The lysosomal transport of cystine is altered [1], leading to an intracellular accumulation of cystine in the cells of a number of tissues. The cystinosis gene, *CTNS*, has recently been mapped to chromosome 17p13 and cloned [2]. *CTNS* encodes a lysosomal membrane protein, which is consistent with a function in lysosomal transport. Although all cells carry the defect, the kidney and the eye are particularly vulnerable, and are the first to express symptoms. A severe renal tubular Fanconi syndrome appears in the first months of life, and later progresses toward renal failure, reaching end stage between the ages of 6 and 14 years [3]. Treatment with oral cysteamine, a drug that favors cystine transport out of the lysosomes, slows this evolution and postpones the need for kidney transplantation [4]. As renal transplantation prolongs survival, cystine may continue to accumulate in other organs, leading to late complications in the 2nd and 3rd decades of life. These include visual impairment [5], diseases of the central nervous system [6, 7], distal myopathy [8], hypothyroidism [9], and endocrine pancreatic insufficiency [6, 7, 10–16].

Histological studies of patients with cystinosis [13, 17] have shown high concentrations of cystine in the β-cells of the islets of Langerhans, which could alter the release of insulin. Indeed, diabetes mellitus is more common in transplanted patients with cystinosis than in those who have been transplanted for other causes [6, 7]. However, there are few published studies, and these have been performed on relatively small numbers of patients, often with a short follow-up after kidney transplantation. Each study has included only one to five cystinotic patients who developed diabetes mellitus [6, 7, 10, 13–16]. Their data indicate that diabetes mellitus often occurs shortly after transplantation, when the patients are on high doses of corticosteroid, and they often need insulin therapy only transiently in these circumstances [6, 10, 13–16]. However, the steroid therapy cannot alone explain the occurrence of diabetes mellitus [13]. Some patients develop diabetes several years after transplantation, when the doses of corticosteroids have been markedly decreased [7, 13]. There are limited data on the oral glucose tolerance test (OGTT) [7, 15], but the rate of ab-

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normal responses in the OGTT varied from 20% in one study [15] to 80% in another [7]. Thus, hyperglycemia is viewed as a long-term complication of cystinosis, but no correlation has been found between the metabolic status and the age of the patient or the time after transplantation [7].

This report describes a retrospective analysis of 44 cystinotic patients who were transplanted in the Pediatric Nephrology Department at Necker-Enfants Malades Hospital and have been followed for more than 10 years. We describe precisely the changes in glucose metabolism and the development of diabetes mellitus in cystinosis.

## Patients and methods

This retrospective study includes 44 patients, 19 female and 25 male, who underwent kidney transplantation between 1974 and 1991. The diagnosis was confirmed in all patients by leukocyte cystine assay. These patients were transplanted at a mean age of 11.3±2.5 years (range 7.4–17.8 years, Fig. 1). They were given various immunosuppressive protocols, depending on the year of grafting. Post-transplantation follow-up varied from 5.4 to 22.4 years (mean 10.8±4.8 years) and the patients were 22.1± 5.4 years old (range 13.7–36.4 years) at latest follow-up. Eighteen patients were treated with cysteamine after transplantation. Treatment was started 11.0±1.2 years (range 1.7–20.6 years) after transplantation, or 2.9 ± 0.6 years before the last follow-up. Transplanted cystinotic patients were compared with 740 patients who underwent 820 kidney transplantations during the same period for causes other than cystinosis.

The following parameters were recorded: yearly height, weight, corticosteroid dosage, and plasma creatinine; periods of insulin therapy; glycated hemoglobin ($HbA_{1c}$); plasma glucose and insulin concentrations during OGTT; HLA-DR types. Retrospectively, it was not possible to determine the precise criteria used to prescribe insulin therapy. However, insulin was given when the clinical or metabolic status of the patient was dramatically altered in all cases, with major increases in plasma glucose or $HbA_{1C}$ levels. Data on $HbA_{1c}$ were not available for a number of patients and could not be used as reliable criteria for analyzing patient follow-up. The OGTT consisted of the ingestion of 1.75 g/kg glucose (maximum 75 g) with measurement of plasma glucose and insulin at 0, 30, 60, and 120 min. Results were interpreted according to the following criteria [18]: normal glucose tolerance, plasma glucose <11 mmol/l at 30 and 60 min, <7.8 mmol/l at 120 min; impaired glucose tolerance, plasma glucose 7.8–11 mmol/l at 120 min; diabetes, plasma glucose >11 mmol/l at 120 min.

The alterations in glucose metabolism and the patient survival rates were estimated using life-table analysis, in conjunction with the age of the patient or the time after transplantation. The log-rank test was used to estimate the equality of the survival distributions. Differences between groups of patients were evaluated using the Mann-Whitney non-parametric test and analysis of variance. Correlations between parameters were estimated by Spearman rank correlation coefficient.

## Results

The actuarial follow-up of transplanted cystinotic patients was performed according to patient age (Fig. 1) and time after transplantation (Fig. 2). Results of 145 OGTTs were recorded, representing a mean of more than 1 test every 3 years for each patient who was not treated with insulin. Fifty-nine percent of the patients had impaired glucose tolerance or a more-severe alteration of glucose metabolism at 15 years of age, and 85% at age 20 years (Fig. 1). The figure was 44% 2 years after transplantation, 69% after 5 years, and only 2 patients (6%) were still normal 10 years after transplantation (Fig. 2). The OGTT reached diabetes criteria in 50% of the patients at age 19 years or 8 years after transplantation, and in 76% at 26 years of age or 14 years post transplantation. The percentage of patients treated with insulin increased with age, reaching 25% at age 18 years and 47% at 26 years of age or 15 years after transplantation (Figs. 1 and 2). Thus, the various alterations of glucose metabolism increased with age or with time after kidney transplantation.

Metabolic abnormalities fluctuated somewhat over the years, as illustrated in Table 1, which shows the detailed follow-up of all 16 patients who were treated with insulin. Insulin therapy was started shortly after kidney transplantation in 6 patients (nos. 2–7), but it was stopped in 5 of them (nos. 3–7) 1 month to 2 years later.

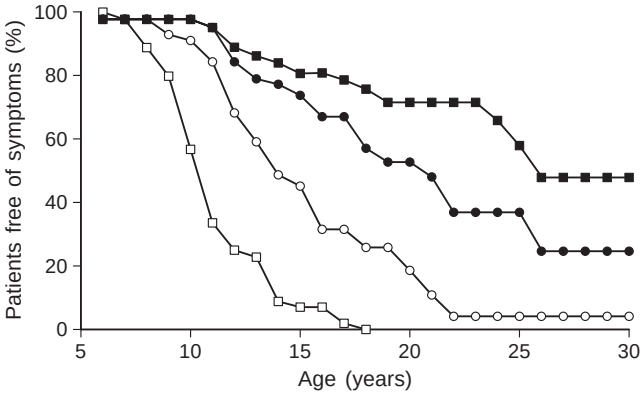


**Fig. 1** Actuarial follow-up of 44 transplanted cystinotic patients: percentages of patients free of criteria of impaired glucose tolerance (○) or diabetes in the oral glucose tolerance test (OGTT) (●) and of insulin treatment (■), as a function of age. The line with (□) symbols represents the times at which these patients were transplanted

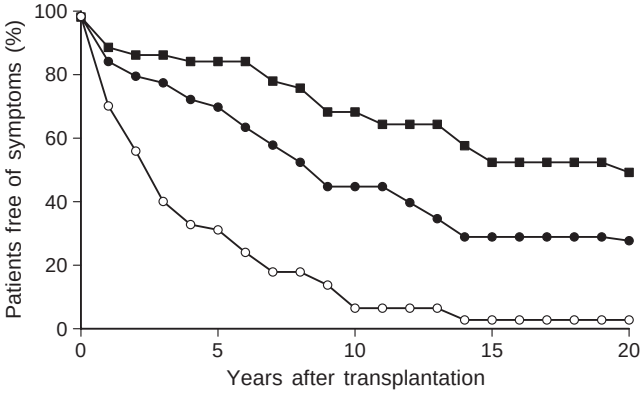


**Fig. 2** Actuarial follow-up of 44 transplanted cystinotic patients: percentages of patients free of criteria of impaired glucose tolerance (○) or diabetes in the OGTT (●) and of insulin treatment (■), as a function of years after transplantation

**Table 1** Follow-up of 16 insulin-treated cystinotic patients for 15 years after renal transplantation[a]

| Patient no. | Years | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| 1 | Ins | Ins | Ins | Ins | Ins | Ins | Ins | * | * | * | * | * | * | * | * | * |
| 2 | | Ins | Ins | Ins | Ins | Ins | Ins | Ins | Ins | Ins | dcd | | | | | |
| 3 | | Ins | | Ins | | | Db | | | | | Ins | * | * | * | * |
| 4 | | Ins | | | | IGT | Db | Db | | | Ins | Ins | Ins | Ins | Ins | Ins |
| 5 | | Ins | | Ins | Ins | | | | | Db | * | * | * | * | * | * |
| 6 | | Ins | Ins | | | | | | | | * | * | * | * | * | * |
| 7 | | | Ins | | | dcd | | | | | | | | | | |
| 8 | | | | | Ins | Ins | dcd | | | | | | | | | |
| 9 | | IGT | IGT | | Nl | IGT | Db | Ins | Ins | Ins | Ins | Ins | dcd | | | |
| 10 | | IGT | IGT | | Db | | | Ins | Ins | Ins | Ins | Ins | * | * | * | * |
| 11 | | | | Nl | IGT | | | | | Ins | * | * | * | * | * | * |
| 12 | | | | IGT | | | | | | Ins | dcd | | | | | |
| 13 | | | | | | | | Db | | | | Ins | dcd | | | |
| 14 | | | Nl | | | | Nl | | | Nl | IGT | IGT | Db | Db | Ins | dcd |
| 15 | | Db | | | | Db | | IGT | IGT | Nl | | Db | | | | Ins |
| 16 | | IGT | IGT | IGT | | | | Db | Ins | | | | Nl | | IGT | Db |

Nl, Normal oral glucose tolerance test (OGTT); IGT, impaired glucose tolerance; Db, diabetic criteria in the OGTT; Ins, treatment with insulin; dcd, deceased
* End of follow-up

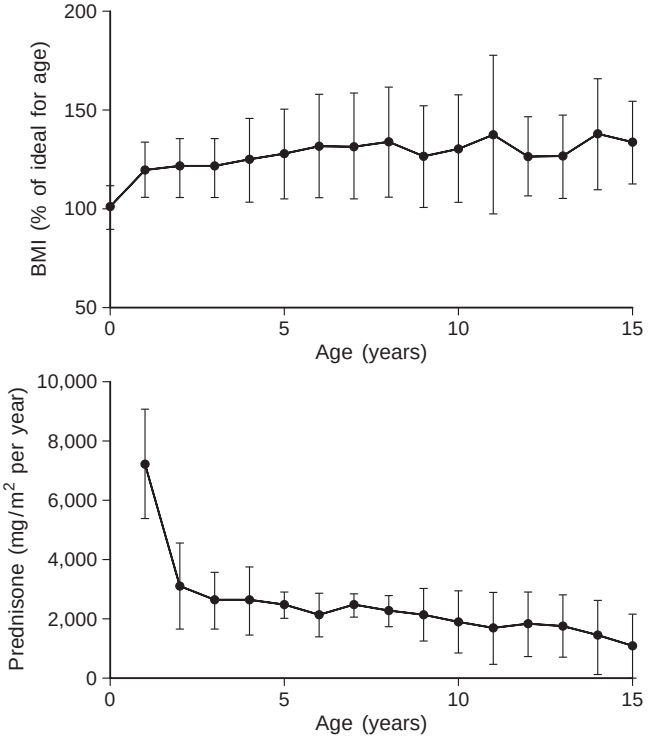


**Fig. 3** Body mass index (*BMI*) and dose of prednisone during the 15 years after renal transplantation in 44 cystinotic patients

It was reinstituted and stopped a second time in 2 patients (nos. 3 and 5) during rejection episodes treated with high doses of corticosteroids. Subsequent OGTTs in 3 of these 5 patients (nos. 3, 4, and 5) showed diabetic levels and 2 patients (nos. 3 and 4) were finally treated with insulin 10 and 11 years after transplantation. Thus, the need for insulin therapy immediately after renal transplantation or during rejection episodes was often transient, and parallelled the use of high doses of corticosteroids.

However, the metabolic abnormalities gradually worsened over the years, while the mean doses of corticosteroids decreased (Fig. 3) to one-quarter the initial dosage 10 years after transplantation. Insulin therapy could not be interrupted when started some time after transplantation. This was the case in 8 patients (nos. 8–15) who were treated with insulin 4–15 years after transplantation, aged 14–26 years (Table 1). Insulin could be interrupted in only 1 patient (no. 16) of this group. This patient was first given insulin 8 years after transplantation and it was stopped a few months later, when the corticosteroid treatment was stopped. Glucose tolerance was normal 4 years later, but subsequent OGTTs showed a progressive deterioration (Table 1).

Patient no. 1 had insulin-dependent diabetes mellitus diagnosed when he was 1 year old and he was HLA-DR3/4. Except for this patient, who required about 1 unit/kg per day in two injections and had elevated $HbA_{1c}$ levels (8%–9%), all patients were well controlled ($HbA_{1c}$: 5.4%–6.3%, normal 4.2%–5.6%) with low insulin doses (19±3 units/day) in one or two daily injections. HLA-DR types were DR3 or DR4 in 46% of these patients, which is similar to the general population.

The mean body mass index (BMI) of the patients was 100% of ideal for age [19] at the time of kidney transplantation, but increased to 120% during the 1st year after transplantation, and stabilized at 136%±13% of ideal for age after 5 years (Fig. 3). No correlation was found between impaired glucose tolerance and the patients' weight or creatinine levels.

Statistical analyses of plasma insulin levels were performed on two groups of data, each including only one OGTT per patient. One group ($n$=32) included the

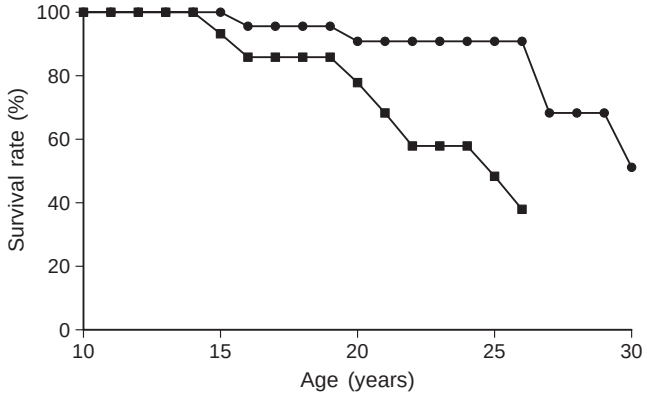


**Fig. 4** Actuarial survival rates in 44 cystinotic patients who were ($n$=16, ■) or were not ($n$=28, ●) treated with insulin for 20 years after renal transplantation

OGTTs performed 2–6 years after transplantation, corresponding to patient ages of 12–16 years. The other group ($n$=23) included the OGTTs performed 6–12 years after transplantation, at age 18–24 years. Plasma insulin levels were 14±2 and 13±2 mU/l (mean±SEM) in the basal state, 64±6 and 61±5 mU/l at 60 min, and 53±6 and 54±4 mU/l at 120 min of the OGTT, in the younger and the older group, respectively. There was no difference between the two groups of patients or between the normal, impaired, and diabetic OGTTs. Conversely, plasma insulin levels at 30 min of the OGTT were inversely correlated with the plasma glucose levels at 60 and 120 min of the OGTTs; this was significant in the younger age group ($P$<0.01 and $P$<0.02, respectively).

Of the 44 transplanted cystinotic patients, 12 died between 15.4 and 36.4 years of age (mean age 22.3±6.3 years). The actuarial survival rates are 76% at 25 years and 43% at 30 years for the overall population. However, 7 of the 16 patients who were treated with insulin died, compared with 5 of the 28 remaining patients. The actuarial survival rates of insulin-treated patients differed significantly from non-insulin-treated cystinotic patients ($P$<0.05, Fig. 4). There were no differences in the causes of death between the insulin-treated and untreated groups.

Retrospective analysis of the 740 non-cystinotic patients given a kidney transplant for causes other than cystinosis during the same period showed that only 8 patients developed diabetes; 7 of them were treated with insulin, 4 transiently and 3 long-term [20].

## Discussion

Forty-four cystinotic patients were followed for a mean period of 11 years after kidney transplantation. The evaluation was based on the need for insulin therapy and sequential OGTTs. Diabetes mellitus or impaired glucose tolerance was clearly linked to the age of the patient or the number of years after transplantation, and the metabolic disturbances became very common when the follow-up was long. All but 2 patients suffered from impaired glucose tolerance and over half the patients had diabetic criteria in the OGTT, at 20 years of age or 10 years after transplantation. A quarter were given insulin at this age, but 50% required insulin at the end of follow-up, a few years later. Thus, diabetes mellitus was much more frequent in cystinotic patients than in other transplanted patients, less than 2% according to previous estimates [7, 12] and slightly more than 1% in 740 patients transplanted in our hospital during the same period as the cystinotic patients. These results also differ from those of a previous study of 80 cystinotic transplanted patients, only 5 of which were treated with insulin [6]. However, only 20% of patients in that study were over 20 years old, while more than half our patients were over 20 years. Impaired glucose tolerance also appears to be frequent in cystinotic transplanted patients, but we had no good control group of non-cystinotic transplanted patients.

The long-term follow-up of a number of patients confirms that corticosteroid therapy can be a contributory factor [7, 10, 13–15], causing insulin dependency when used at high doses immediately after transplantation or during rejection episodes. However, the results presented in Table 1 suggest that the later occurrence of permanent insulin dependency, previously described [13], is not linked to the early post-transplantation insulin requirement. The delay before relapse of insulin dependency was generally long, 8–11 years, and 2 of our patients did not require insulin at the end of follow-up, 9 years after transplantation. The patients who did not require insulin immediately after transplantation became insulin dependent 4–15 years later, between 14 and 26 years of age. Thus, the cystinotic process alters the glucose metabolic status very slowly, while doses of corticosteroids decrease regularly. Of particular interest is patient no. 16 (Table 1), who became insulin dependent 8 years after transplantation, needed no insulin when the corticosteroids were stopped, had a normal OGTT 4 years later, but had diabetic criteria after 3 more years, still without corticosteroids. Cysteamine treatment might reduce the possible impact of corticosteroid treatment on the progression toward diabetes mellitus, by delaying the age of renal transplantation [4], but it could also have a direct effect on cystine accumulation in β-cells. We did not show data of patients who were treated early and permanently with cysteamine, because they have not yet been transplanted or were transplanted later than those in this study, and are still too young to suffer from diabetes mellitus or even impaired glucose tolerance. The prospective follow-up of these patients is in progress.

Cystine accumulation in the pancreas [13] is responsible for a marked endocrine hyperplasia, particularly of the β-cells, while the exocrine pancreas remains normal [17]. The high concentration of cystine could interfere with insulin secretion and cause the slow deterioration of glucose metabolism. The OGTT is not the best test for measuring insulin secretion, because plasma insulin levels depend on plasma glucose, which differs between pa-

tients. However, plasma insulin levels at 30 min have been correlated with the acute phase of insulin secretion produced by the intravenous glucose tolerance test [21], a reliable index of insulin secretion in insulin-dependent [22] as well as non-insulin-dependent diabetes mellitus [23]. The negative correlation between plasma insulin at 30 min and plasma glucose at later times of the OGTT in our patients strongly suggests that hyperglycemia results from a deficient early insulin response to glucose. Thus, the lack of insulin release appears to be the main defect leading to the development of diabetes mellitus in cystinotic patients. In contrast, our results show no evidence of insulin resistance. The plasma insulin was within the normal range [24] in all categories of patients, while higher plasma insulin levels would have been expected in the case of insulin resistance, particularly in the hyperglycemic patients. This suggests that the increase in BMI following transplantation [25] or the possible deterioration in kidney function [26] was not so marked as to cause a major insulin resistance, which could have worsened the glucose metabolic status of the patients. High doses of corticosteroids certainly create a major insulin resistance [27] and a transient need for insulin, but no OGTT was performed during these phases of treatment. This question can only be answered by measuring insulin resistance using techniques such as the hyperinsulinemic euglycemic clamp.

Our results also suggest that the vital prognosis was poorer for insulin-dependent patients, as they died approximately 5 years earlier than the other patients. The retrospective analysis of these data provide no objective explanation for this. The cystinotic process may cause other tissues of vital importance to deteriorate more rapidly in patients with severe alterations of glucose metabolism. Latent preclinical hyperglycemia might also be responsible for the alteration in the clinical status of the patients, which suggests that they should be monitored more closely in order to start insulin therapy as early as possible. This latter hypothesis seems more unlikely than the former, because the patients who were put on insulin had no clinical symptoms of diabetes, no change in nutritional status, and only moderate elevations of $HbA_{1c}$. Blood glucose control was always very good with low insulin doses.

A similar case to patient no. 1 has been published previously [28]. He was insulin-dependent at 1 year of age and HLA DR3/4, so that he differed from all the other cystinotic patients and appeared more like a case of early autoimmune type 1 diabetes mellitus associated with cystinosis. Unfortunately, we could not check to see if he had islet cell antibodies in order to confirm this rather exceptional coincidence.

In conclusion, diabetes mellitus is a frequent long-term complication in transplanted patients with nephropathic cystinosis. High doses of corticosteroids given after transplantation or during rejection episodes aggravate the glucose metabolic status and are responsible for insulin dependency that is often transitory. However, the development of impaired glucose tolerance and diabetes mellitus depends mainly on the cystinotic process, which gradually alters β-cell function over the years, so that more than half the patients become insulin dependent by the age of 25 years.

**Acknowledgement** We thank Dr. P. Landais for performing the actuarial statistical analyses.

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## LITERATURE ABSTRACTS

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### Cutaneous necrosis from calcific uremic arteriolopathy

Am J Kidney Dis (1998) 32:384–391

Calcific uremic arteriolopathy (calciphylaxis) is an uncommon complication of chronic renal failure that is associated with high morbidity and mortality. We report 16 patients (13 female) who presented between 1985 and 1996. All patients developed painful livido reticularis that progressed to cutaneous necrosis and ulceration (11 cases on the proximal extremities and five cases on the distal extremities). Two patients with predominately distal leg disease survived; the cause of death in the other 14 patients was sepsis (six patients), withdrawal from dialysis (three), cardiac arrest (three), and gastrointestinal hemorrhage (two). Mesenteric ischemia from intestinal vascular calcification occurred in two cases. Clinical factors identified included the use of warfarin therapy in seven cases and significant weight loss (>10% body weight) in seven cases in the 6 months preceding the development of calcific uremic arteriolopathy. Skin pathology was studied in 12 cases, with all showing calcific panniculitis and small vessel calcification. Electron microscopic spectral analysis of the mineral content of the calcific lesions in the subcutaneous tissue showed only calcium and phosphorous. In two cases, substitution of low molecular weight heparin for warfarin therapy resulted in clinical improvement. Current theories of pathogenesis and treatment are reviewed. This study confirms the high morbidity and mortality of calcific uremic arteriolopathy producing ischemic tissue necrosis while drawing attention to significant weight loss and warfarin therapy as risk factors for the development of ischemic tissue necrosis. Hyperbaric oxygen therapy warrants further study.

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### Outcome in cadaveric renal transplant recipients treated with cyclosporine A and mycophenolate mofetil versus cyclosporine A and azathioprine

J Surg Res (1998) 76:131–136

**Background** Recent multicenter reports have demonstrated improved outcome in recipients of cadaveric renal transplants treated with mycophenolate mofetil (MMF) versus azathioprine (AZA) in combination with cyclosporine A (CSA) and prednisone. We compared the outcome at our center in patients treated with MMF versus AZA, CSA, and prednisone.
**Methods** We retrospectively reviewed 242 adult cadaveric renal transplant recipients treated between 11/91 and 5/97. We compared 25 donor variables and 27 recipient variables and outcome parameters between patients treated with MMF versus AZA. There were 117 patients treated with CSA+AZA, 84 with CSA+MMF, and 42 who received other immunosuppressive strategies.
**Results** There were no significant differences in any clinically important donor variables. Patients treated with MMF versus AZA and CSA had significantly fewer rejections and readmissions. There was no significant difference in 1- or 2-year patient survival. Recipients treated with MMF had a 5% higher graft survival at 2 years, although the difference did not reach statistical significance.
**Conclusions** Outcome is improved in adult recipients of cadaveric renal transplants treated with MMF versus AZA in combination with CSA and prednisone.