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Serum levels of alpha-1 microglobulin in recipients of renal allografts

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Abstract. Serum levels of α_1 microglobulin (s-α_1m) in 92 recipients of renal transplants were elevated during pretransplant uremia ($P<0.001$), acute rejection ($P<0.01$), and cyclosporin-induced nephrotoxicity ($P<0.01$). In patients with stable renal function, those treated with cyclosporin had higher s-α_1m than those receiving azathioprine: 81 ± 4 and 64 ± 3 mg/l (mean ± SEM), respectively ($P<0.05$). The serum creatinine levels were 127 ± 5 and 115 ± 7 µmol/l (mean ± SEM), respectively (N.S.). Two of the patients with normal serum creatinine had normal s-α_1m levels. There were positive linear correlations between s-α_1m and serum creatinine levels during stable renal function, rejection, cyclosporin-induced nephrotoxicity, and cytomegalovirus infections ($r=0.7$-0.8, $P<0.01$-0.001) and between s-α_1m and β_2 microglobulin (β_2m) during the same conditions ($r=0.5$-0.8, $P<0.01$-0.001). During infections, serum creatinine and β_2m increased ($P<0.001$), but s-α_1m did not. S-α_1m values did not distinguish between rejection and cyclosporin-induced nephrotoxicity. It is concluded that s-α_1m might be a valuable complement to serum creatinine levels in the evaluation of renal function in renal transplant recipients.

Key words: α_1 Microglobulin - β_2 Microglobulin - Renal transplantation - Cyclosporin nephrotoxicity - Acute rejection - Infections.

Alpha-1 microglobulin (α_1m) is a low molecular weight glycoprotein (mol.wt.33,000) containing 167 amino acid residues which is present in serum and other body fluids [5]. The exact function and site of its production are presently unknown, but the liver has been proposed as being the main site of synthesis [8]. It has been suggested that α_1m is filtered freely by the glomeruli and then reabsorbed and catabolized by the proximal tubular epithelium in the same manner as other low molecular weight proteins, such as β_2 microglobulin (β_2m) [15, 17]. Serum levels of low molecular weight proteins have been proposed as being more reliable indicators of renal function than serum creatinine (s-crea). Several reports have demonstrated a positive linear correlation between serum α_1m (s-α_1m) and s-crea and creatinine clearance [7, 10, 17, 18]. Normal values have ranged from 20 to 42 mg/l using single radial immunodiffusion [18].

Increased s-α_1m levels have been observed during impaired renal function, and disturbances in tubular reabsorption have led to increased α_1m levels in urine [17]. In addition, elevated s-α_1m levels have been reported in connection with plasma cell dyscrasias, leukemias, solid tumors, and hepatitis [16].

The purpose of the present study was to monitor the serum levels of α_1m during different states of renal deterioration in renal transplant recipients. Consideration was also given to whether s-α_1m levels could be used to differentiate between rejection, cyclosporin (Cs)-induced nephrotoxicity, and infections [9].

Patients and methods

Ninety-two recipients of renal allografts (35 females and 57 males) with a median age of 46 years (range 11-73) were studied under conditions of stable renal function, uremia, acute rejection, Cs-induced nephrotoxicity, cytomegalovirus (CMV) infections, and other infections. These patients had received renal grafts from 80 cadaveric and 12 living-related donors. Azathioprine (Aza), in combination with prednisolone, was used for immunosuppressive treatment of 33 patients, while Cs, in combination with prednisolone, was used for 59 patients [14]. Forty-nine patients were studied during stable renal function. These individuals showed no signs of rejection, clinically significant Cs nephrotoxicity, or infection; they had an s-crea <200 µmol/l. In the stable group, 21 patients received Aza in combination with prednisolone, while 28 received Cs in combination with prednisolone. The patients with uremia ($n=25$) were investigated immediately prior to transplantation and were all on dialysis.

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Diagnosis of rejection, Cs nephrotoxicity, and infection

Twenty-seven patients with deteriorated renal function were diagnosed as having an ongoing acute rejection. Twenty-five of these cases were diagnosed by means of biopsy; for the other two this diagnosis was made on the basis of their clinical, Aza-treated condition and the fact that there was improvement in renal function after antirejection therapy with intravenous methylprednisolone. Acute Cs-induced nephrotoxicity ($n=18$) was diagnosed by means of biopsy in eight cases and by improvement in renal function after reduction of the Cs dose ($n=10$). These patients had a mean plasma Cs level of 475 ± 77 ng/ml (± SEM) prior to dose reduction and of 175 ± 32 ng/ml (± SEM) when renal function improved.

Infections ($n=30$) were diagnosed clinically, serologically, from a positive culture, or by isolation of the causative microorganism. The serology was positive in all 18 patients with CMV infections (positive IgM and/or a fivefold rise in IgG titer), and CMV was isolated from blood and/or urine in 15 of these patients. The other infections ($n=12$) consisted of urosepticemia ($n=3$), pyelonephritis ($n=2$), bronchopneumonia ($n=1$), septicemia ($n=1$), *Pneumocystis carinii* pneumonia ($n=1$), osteitis ($n=1$), pancreatitis ($n=1$), acute gastroenteritis ($n=1$), and hepatitis B infection ($n=1$).

Table 1. Serum levels of α_1m and creatinine in patients with stable renal function and uremia. * $P<0.05$; ** $P<0.001$

	n	Serum α_1 microglobulin[a] (mean ± SEM)	Serum creatinine[b] (mean ± SEM)
Stable function	49	74± 3**	121± 4**
Cs-treated	28	81± 4*	127± 5 N.S.
Aza-treated	21	64± 3*	115± 7 N.S.
Uremia	25	268± 16**	868± 40**

[a] mg/l
[b] μmol/l

Analyses of α_1m, β_2m, creatinine, and cyclosporin

Serum samples were frozen at −20 °C and later analyzed. α_1m-Levels were measured by single radial immunodiffusion, using reagents developed at Behringwerke AG (Marburg, FRG). β_2m-Levels were determined by a competitive enzyme-linked immunoassay with a normal range of 1.2-2.5 mg/l (Behringwerke AG, Marburg, FRG). S-crea (normal value < 115 μmol/l) was analyzed using the kinetic Jaffé method [3]. The accuracy of this method has been evaluated using a reference method based on isotope dilution and mass spectrometry. Cs plasma trough levels were analyzed using a polyclonal radioimmunoassay (Sandoz, Basel, Switzerland) with a range of 50-2000 ng/ml.

Statistics

The Mann-Whitney U ranking test was used for statistical comparisons. Values from the day of diagnosis during the different conditions were selected for comparisons. Fischer's exact test and linear correlation analysis were also used when appropriate.

Results

S-α_1m and s-crea were significantly elevated during pretransplant uremia (Table 1). Levels were higher during uremia than during any of the other conditions investigated (stable function, rejection, Cs nephrotoxicity, CMV infections, and other infections; $P<0.001$, Fig. 1). The lowest s-α_1m and s-crea were obtained during stable function. Patients with stable function who were treated with Cs had significantly higher s-α_1m than patients treated with Aza ($P<0.05$), while s-crea was not significantly higher (Table 1). Cs-treated patients with stable renal function had a mean plasma Cs concentration of 160 ± 28 ng/ml (± SEM).

Twenty patients had normal s-crea levels

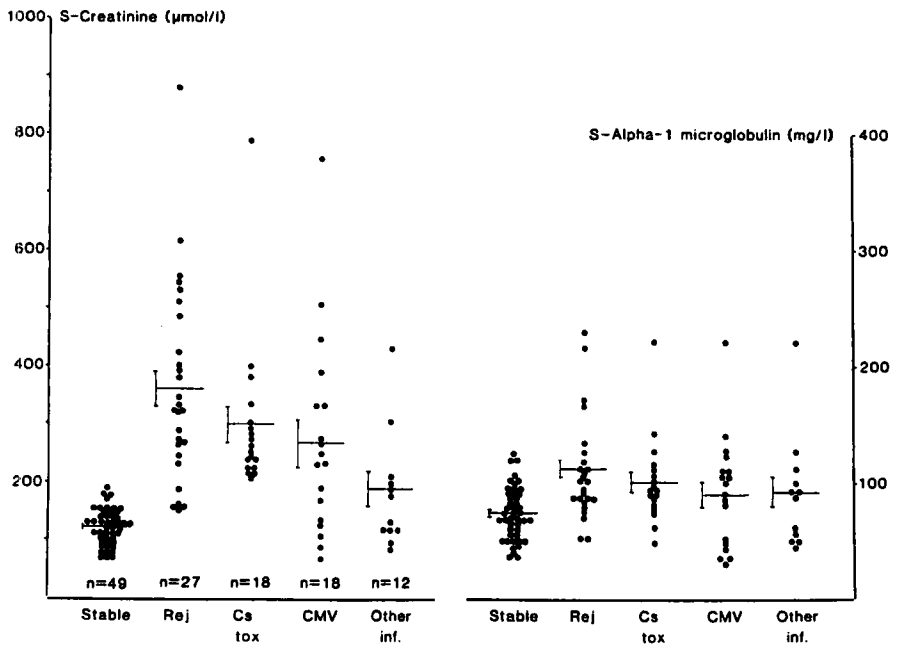

Fig. 1. Individual serum levels of α_1m and creatinine during stable renal function, rejection (Rej), cyclosporin-induced nephrotoxicity (Cs tox), cytomegalovirus infection (CMV) and other infections. *Horizontal lines* indicate means, *vertical bars* indicate SEM

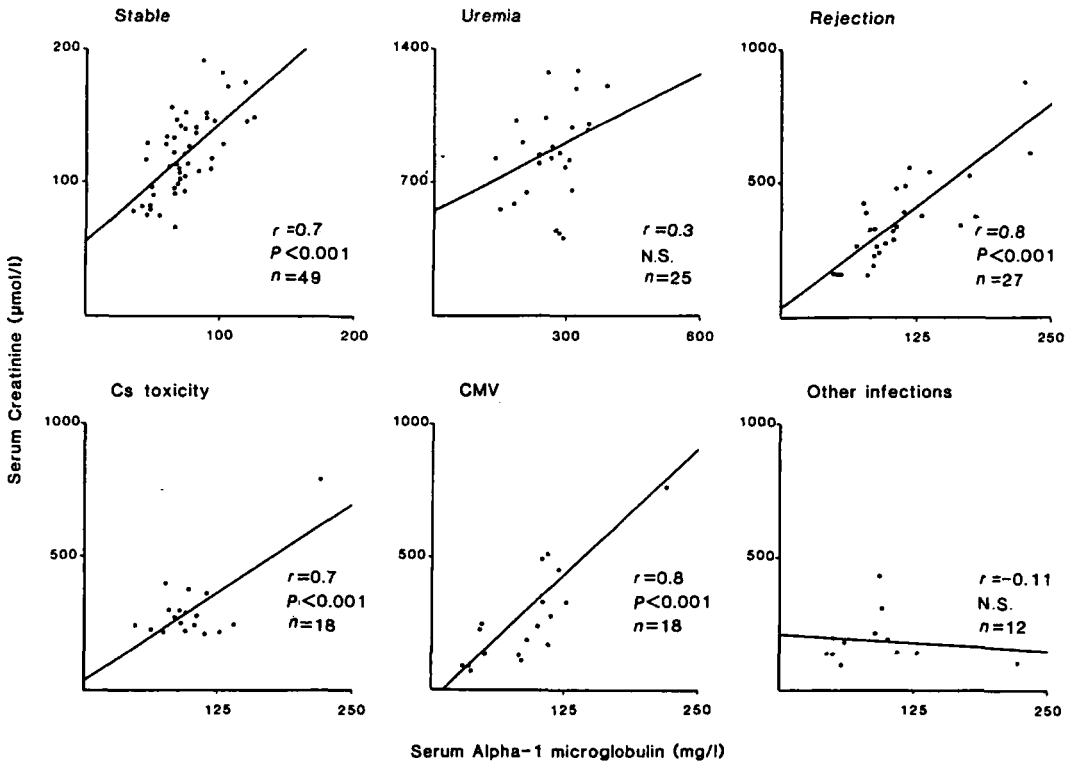

Fig. 2. Linear correlations between serum levels of α_1m and creatinine during stable renal function, uremia, rejection, cyclosporin-induced nephrotoxicity, CMV, and other infections

Table 2. Linear correlation between serum levels of α_1m and β_2m in patients with stable renal function, uremia, acute rejection, cyclosporin nephrotoxicity, CMV, and other infections. * $P<0.01$; ** $P<0.001$

	n	Serum α_1 microglobulin[a] (mean ± SEM)	Serum β_2 microglobulin[a] (mean ± SEM)	*R*-value
Stable function	49	74± 3	3.7±0.2	0.6**
Uremia	25	268±16	40.2±4.4	0.5*
Acute rejection	27	107± 9	15.0±2.5	0.8**
Cyclosporin nephrotoxicity	18	101± 9	10.2±1.3	0.8**
CMV infections	18	90±11	12.2±2.7	0.7*
Other infections	12	91±14	6.2±0.9	0.1 N.S.

[a] mg/ml

(<115 µmol/l). Of these, only two had s-α_1m levels ≤42 mg/l. Both of these patients were treated with Aza. None of the 28 patients with stable function who were receiving Cs had s-α_1m ≤42 mg/l.

Rejection and nephrotoxicity

Both s-α_1m and s-crea were elevated during rejection in comparison to stable function ($P<0.01$ and $P<0.001$, respectively, Fig. 1). Elevated levels of s-α_1m and s-crea were also found during Cs nephrotoxicity ($P<0.01$ and $P<0.001$, respectively). There were no differences in s-α_1m or s-crea levels during rejection and Cs nephrotoxicity.

Infections

S-crea was elevated during CMV and other infections in comparison to stable function ($P<0.01$ for both groups); s-α_1m was not, however. In 3 of the 30 patients with CMV and other infections, s-α_1m increased beyond the range of values for patients with stable function. For s-crea this was true in 17 of the 30 cases ($P<0.001$, Fischer's exact test).

Correlations between α_1m, creatinine, and β_2m levels

The linear correlation (*r*) between s-α_1m and s-crea was 0.7 ($P<0.001$) during stable renal function, 0.3 (N.S.) during uremia, 0.8 ($P<0.001$) during rejection, 0.7 ($P<0.001$) during Cs nephrotoxicity, 0.8 ($P<0.001$) during CMV infections, and −0.1 (N.S.) during the other infections (Fig. 2). The linear correlations between s-α_1m and s-β_2m during the different conditions investigated are given in Table 2. The correlations were positive and significant during all conditions except the other infections.

Discussion

The highest s-α_1m levels were found during deterioration in renal function, i.e., uremia, rejection, and Cs nephrotoxicity. There were linear correlations between s-α_1m, s-crea, and s-β_2m. The lowest values were observed in patients with stable renal function.

Slightly higher s-α_1m was seen during infections, although this did not reach significance. Only 2 of the 20 patients with a normal s-crea also had normal s-α_1m levels. Cs patients with stable function had higher s-α_1m levels than Aza patients, whereas their s-crea did not differ (Table 1). Patients treated with Cs generally have a poorer renal function with a reduced glomerular filtration rate than patients treated with Aza [1, 4, 6].

These data suggest that s-α_1m is a more sensitive indicator of renal function than s-crea. This is in line with previous reports of an increase in s-α_1m preceding increases in s-crea and s-β_2m during a mild degree of renal dysfunction [7, 17]. The poor correlation between s-α_1m and s-crea during uremia may have been influenced by the dialysis treatment, which eliminated α_1m and crea by different forms of kinetics. However, the correlation between s-α_1m and s-β_2m, which is well established as being eliminated by glomerular filtration, was positive and significant during uremia (Table 2).

S-α_1m did not differentiate between rejection and Cs nephrotoxicity, since the elevations paralleled the rises in s-crea that were observed in the two groups.

S-α_1m levels were not affected by infections, as is the case for s-β_2m and neopterins, both of which are considerably elevated during CMV infections [1, 2, 11, 12]. Similar observations have been made in connection with hepatobiliary disorders and malignancies, in which s-α_1m levels have not been substantially elevated, but s-β_2m levels have [17].

During infections s-crea was significantly elevated, while s-α_1m remained unchanged. A simultaneous increase in s-α_1m during an infection may indicate rejection or Cs nephrotoxicity and should motivate other diagnostic approaches (e.g., biopsy), while an isolated s-crea elevation usually suggests an infection. During CMV infections a significant linear correlation between s-crea and s-α_1m levels was found, but this was not the case during the other infections. This finding indicates that the rise in s-crea during CMV infections is due to a deterioration in renal function; however, in the case of other infections, another explanation for this increase must be sought.

It is well known that s-crea is not an ideal indicator of renal function and glomerular filtration and that the s-crea level may be normal even when glomerular filtration is reduced [13]. The s-α_1m level might, therefore, be a better indicator of renal function and glomerular filtration than s-crea. It might also serve as a complement to s-crea in evaluating actual renal function in patients with slight renal deterioration.

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