Inversed Diurnal Rhythm of Urinary Prostaglandins E₂ and F_{2α} Excretion in Kidney Graft Recipients

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Dear Sir,

Under physiological conditions certain hormones are rhythmically synthesized or released within a 24-hour period. These rhythms are commonly found to be absent or to have an altered pattern in kidney diseases [1,2]; however, only a few reports have dealt with diurnal rhythms in patients with kidney transplants due to terminal renal failure [3, 4]. Prostaglandins, as local hormones, affect renal blood flow, glomerular filtration rate and water and sodium excretion [5, 6]. An abnormal prostaglandin production has been reported to occur in certain renal diseases [7, 8]. In chronic renal diseases prostaglandins are required for the maintenance of normal renal function, participating actively in the adaptation to progressive nephron loss. However, in more advanced disease prostaglandin excretion is diminished due to a major parenchymal loss [9]. This study was aimed to determine profiles of urinary excretion of prostaglandin E₂ (PGE₂) and prostaglandin F_{2α} (PGF_{2α}) in patients with grafted kidney.

Six patients with a cadaver kidney transplanted 19-38 (41 ± 9) months earlier were included in this study. No patient had clinical evidence of acute rejection. Patients were under immunosuppressive treatment with prednisone (10-15 mg/day) and azathioprine (2 mg/kg/day), given in the morning from 10 to 12 a.m. The control group consisted of 6 age- and sex-matched healthy volunteers. Urine specimens for prostaglandin determination were collected every 3 h for 48 h. PGE₂ and PGF_{2α} were measured by radioimmunoassay using a previously described method [6]. Time-dependent profiles

were constructed as means for each period studied. Means ± SEM are given throughout. The statistical difference between groups was determined by Student's t test.

In this study there were no significant differences between the groups in total 24-hour urinary excretion, either for PGE₂ levels of 2.1 ± 0.5 µg in kidney graft recipients and 2.0 ± 0.5 µg in control individuals, or for PGF_{2α} levels of 5.1 ± 1.6 and 4.2 ± 0.8 µg, respectively. However, profiles of diurnal urinary excretion of both prostaglandins studied in kidney graft recipients were clearly altered (fig. 1). In healthy subjects the highest rate of PGF_{2α} urinary excretion occurred in the morning, followed by a rapid initial fall and the lowest value achieved at midnight. Conversely, in grafted patients the morning levels were low, while the afternoon levels had a permanent tendency to increase with the peak value at midnight. Similar reversal was

noted in urinary excretion of PGE₂. The profile of control subjects shows a surge in the morning, a second lower peak in the afternoon and a decline thereafter. On the other hand, in grafted patients the lowest PGE₂ levels coincided with the highest control values, while a less pronounced and a flattened peak occurred during the late afternoon and early evening hours. In this study, in patients on classical immunosuppressive treatment and apparently normal function of the transplanted kidney, no change in total urinary excretion of PGE₂ and PGF₂ α was found, but an inversed pattern of diurnal rhythmicity was observed. The same type of circadian variations, with minimal plasma levels in the morning and

Fig. 1. Time-dependent profile of urinary prostaglandin excretion in kidney-transplanted patients. O = Control; # = transplanted patients.

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maximal levels in the night, was obtained for cortisol and plasma renin activity. This temporal coincidence, associated with a known interrelationship between prostaglandins, on the one hand, and cortisol and renin, on the other hand, supports some speculations on the nature of an inversed pattern of diurnal urinary excretion of prostaglandins in kidney graft recipients.

Angiotensin II, an indirect product of renin action, was shown to increase prostaglandin synthesis, increasing deacylation of cellular phospholipids, and thus the availability of arachidonic acid, the precursor of prostaglandins [10].

Another factor deserving more consideration is prednisone immunosuppressive treatment. Beside the reversal of the pattern of plasma cortisol rhythmicity due to a feedback effect [11], the alteration in prostaglandins urinary excretion could be attributed to glucocorticoid administration. Urinary ex-

cretion of PGE₂ and PGF₂ α was reported to be elevated in humans receiving glucocorticoids [12]. Chronic dexamethasone treatment in rats was shown previously to increase the release of glomerular PGE₂ and PGF₂ α and the metabolic transformation of arachidonic acid by glomeruli [13]. This assumption is also supported by the observation made in the present study, i.e. urinary excretion of prostaglandins starts to increase very soon after prednisone administration.

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Prostaglandins in Kidney Graft Recipients

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363