Proc EDTA–ERA (1985) Vol 22

SERUM NEOPTERIN AFTER KIDNEY TRANSPLANTATION – A USEFUL TOOL FOR GRAFT MONITORING?

E Pohanka, M Schwarz, G Mayer, *W Woloszczuk, J Kovarik, H K Stummvoll

*Second Department of Internal Medicine, *Ludwig Boltzmann Institute for Clinical Endocrinology, University of Vienna, Vienna, Austria*

Summary

Immunological monitoring by measurement of serum neopterin (sNPT) was performed in 68 kidney transplant patients. sNPT related to the clinical course and was significantly elevated in conditions of immunological activation such as rejection or infection. Adequate treatment of rejection episodes resulted in a marked decrease of sNPT. Though sNPT in dialysis patients was always higher than in patients not requiring dialysis treatment, the differences between conditions of immunological activation compared to those without remained unchanged.

Daily monitoring of sNPT seems to be a useful serological marker, especially for anuric patients and might be useful for the interpretation of phenomena observed on a cellular basis in immunosuppressed transplant patients.

Introduction

Neopterin, an intermediate of pteridin metabolism, is secreted by macrophages on stimulation by activated T-cells. Measurement of urinary neopterin for transplant monitoring has been shown to be a useful method for detecting immunological complications such as graft rejection, graft versus host disease and severe bacterial, viral and protozoal infections [1–3]. In an alternative approach we measured serum neopterin (sNPT) in kidney transplant patients as a diagnostic method independent of urine output which might be advantageous in patients with primary anuria or later oligo-anuric periods.

Patients and methods

sNPT was measured daily for the first five weeks in 68 patients after kidney transplantation. Immunosuppressive therapy consisted of Cyclosporin A and prednisolone according to standard protocols: Cyclosporin A was started before transplantation intravenously (5mg/kg body weight/day) and after three or four

days orally according to blood values (RIA). Prednisolone (200mg) was given during surgery and then rapidly reduced to 20mg/day. Acute rejection episodes, diagnosed by clinical features, laboratory findings and in numerous cases by fine needle aspiration biopsy and/or true-cut biopsy, were treated at first by steroid bolus therapy (500mg methylprednisolone over 3 consecutive days) and in cases of biopsy proven steroid resistant rejections by antithymocyte globulin (ATG, 3mg/kg body weight/day intravenously for 10 days).

Measurement of sNPT was performed by means of a commercially available radio-immunoassay (Henning, Berlin, FRG [4]). This test kit was modified to adapt its sensitivity to a range necessary for investigation of kidney grafts. A normal range of less than 10ng/ml was determined in 25 healthy volunteers ($\bar{X}\pm 3SD$).

In the first part of the study 35 patients (30 first graft, 5 second graft) without any signs of infection were included. The patients were classified into four groups according to their clinical course (group I: patients without any complications who never required steroid bolus therapy; group II: patients with rejection episodes diagnosed clinically, i.e. they received bolus steroids without biopsy; group III: patients with histologically proven rejection; group IV. graft loss due to rejection), and sNPT was compared at day of surgery, 10 days after grafting, and at day of discharge or at the day of graft loss, respectively. Mean values and standard deviations were calculated in each group and significance of differences of groups II, III and IV compared to group I were assessed by Sttudent's 't' test for unpaired data.

In the next step we elucidated the effect of steroid bolus therapy in 74 therapeutic interventions classified into four groups. Group 1 was irreversible rejection leading to graft loss within four days. Group 2 were cases of acute vascular and/or interstitial rejection (biopsy proven). Group 3 had clinical signs of rejection without histological diagnosis. Group 4 were cases when rejection turned out to be not the main reason for graft deterioration, retrospectively (biopsy proven) but was due to Cyclosporin A-toxicity or acute renal failure. For three days before, three days during and three days after treatment an average value of sNPT and serum creatinine was calculated. From these averages the mean values of each group and differences with values before steroid boluses were evaluated by means of Student's 't' test for paired data.

In a final approach we evaluated sNPT at the time of graft biopsy (n=64) in 42 patients and of bacterial infection episodes (n=18) in 16 patients. In addition, patients receiving haemodialysis (HD) and others with good graft function (n-HD) were compared in each group. In the biopsy series three groups were established according to different histological diagnosis. The group with vascular rejection included 18 biopsies (8 HD, 10 n-HD), the group with interstitial rejection 31 biopsies (12 HD, 19 n-HD) and in 16 cases (5 HD, 11 n-HD) no rejection was found (Cyclosporin A toxicity or acute renal failure). The group with infection episodes comprised five cases on haemodialysis and 13 with good graft function. 'Infection' was defined as positive bacterial blood or urine culture and clinical signs, without evidence of rejection. Mean values and standard deviations of each group were calculated, the significance of differences was estimated by Student's 't' test.

Results

sNPT decreased rapidly in patients without any complications to values comparable to those of healthy controls within 10 days of transplantation. In groups II and III decrease of sNPT was significantly delayed, but finally, at day of discharge nearly normal values were reached. This delay was expressed more in patients with a histologically proven diagnosis of rejection (group III). In contrast, the highest sNPT values were in the cases of group IV, i.e. in patients who lost their graft due to irreversible rejection (Figures 1–3).

sNPT increased after steroid bolus therapy in only three cases with steroid resistant rejection leading to graft loss within four days of the last steroid bolus. In reversible rejection episodes, however, sNPT decreased from the onset of therapeutic intervention whereas mean values of serum creatinine reached a peak during therapy. Decrease of sNPT was only low in group 4, when rejection was not the main cause of deterioration of graft function (Figure 4).

Comparing sNPT at times of infection episodes and different histological diagnoses of rejection, no significant differences could be found. In contrast, sNPT was significantly lower in cases without rejection compared to all other groups. Marked differences between patients with and those without haemodialysis were observed in all groups (Figure 5).

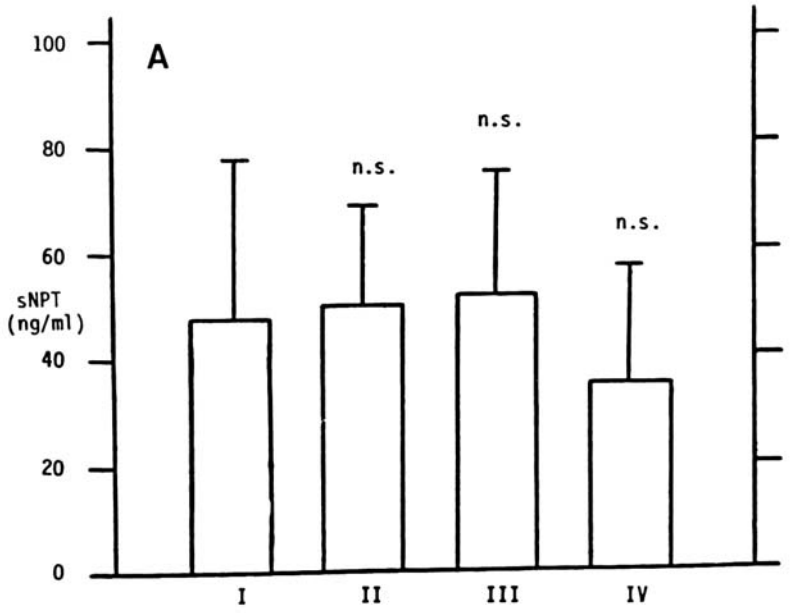

Figure 1. sNPT before transplantation ($\bar{X} \pm SD$). Group I: patients without any complications (n=8); Group II: patients with rejection episodes, diagnosis based on clinical symptoms, received steroid bolus therapy (n=12); Group III: patients with rejection episodes, at least one episode proven by biopsy, received steroid bolus therapy (n=10); Group IV: patients with severe rejection leading to graft loss, received steroid bolus therapy (n=5)

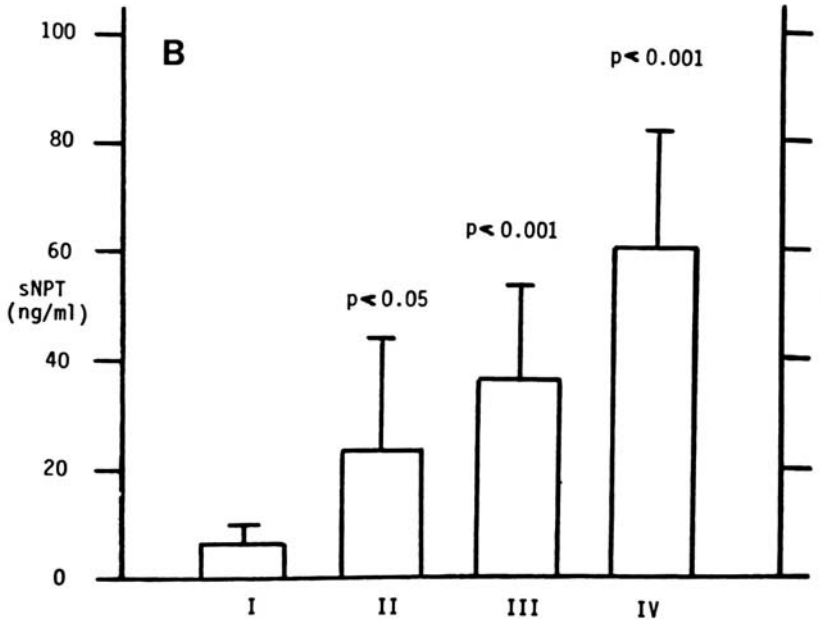

Figure 2. sNPT 10 days after transplantation ($\bar{X}\pm SD$). For definition of groups see Figure 1

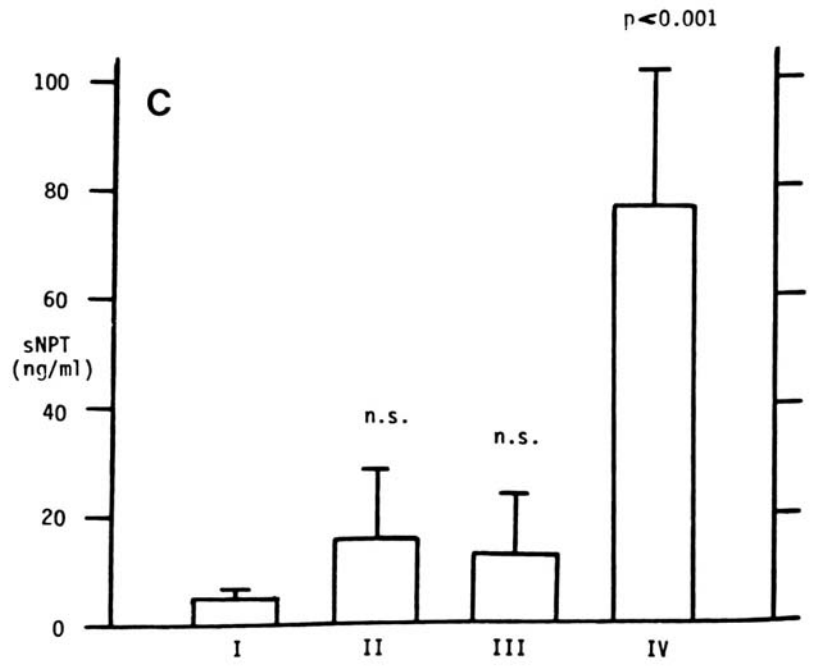

Figure 3. sNPT at day of discharge (groups I, II, III) or graft loss (group IV), respectively ($\bar{X}\pm SD$). For definition of groups see Figure 1

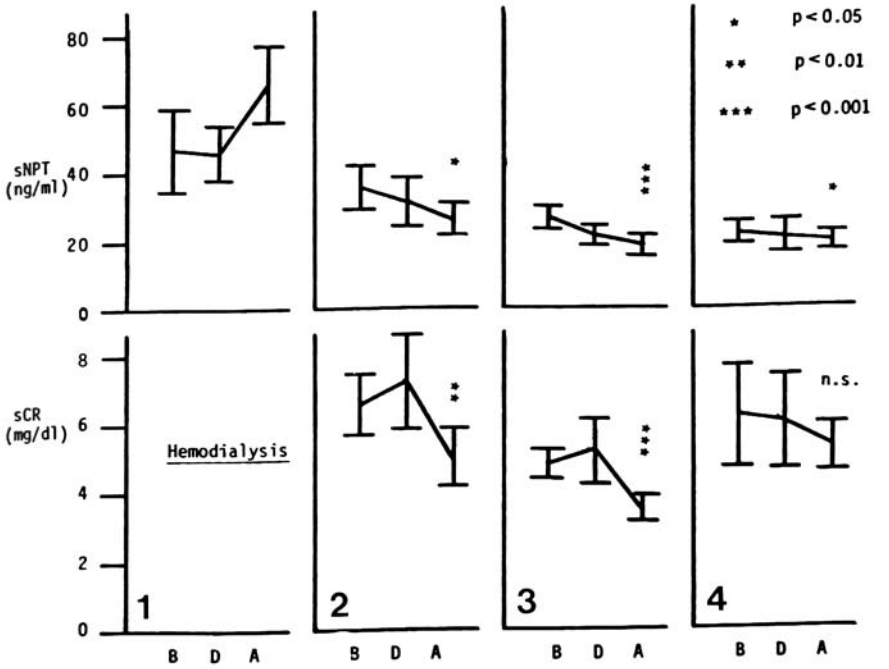

Figure 4. Time course of sNPT and serum creatinine before (B), during (D) and after (A) steroid bolus therapy. 1. Irreversible graft rejection within four days after steroid bolus therapy (n=3); 2. Histologically proven rejection episodes (n=10); 3. Rejection episodes, diagnosis based on clinical signs (n=54); 4. Rejection not main reason of graft failure or deterioration of function (n=7)

Discussion

In our experience low values of sNPT made immunological activation such as acute rejection and severe bacterial infection unlikely. Clinical course and serum NPT demonstrated good correlations. sNPT was elevated before transplantation, decreased quickly in graft recipients with uncomplicated course to values comparable to healthy controls. In contrast, very high sNPT values were observed in severe rejection. Whereas in cases of irreversible rejection sNPT continued to rise to extremely high values despite steroid bolus therapy, reversible rejection episodes were characterised by a decrease of sNPT and accompanied by reduction of serum creatinine. Therefore we suggest that a decrease of sNPT is indicative of reduction in immunological activation, thereby leading to an improvement of organ function resulting in a fall of serum creatinine.

Efficiency of anti-rejection therapy was demonstrated best in the group with a histologically proven diagnosis. The degree of sNPT reduction was less in cases not biopsy proven or in those in whose rejection was not the main reason for graft deterioration. An explanation for this observation might be relatively milder immunological activation, i.e. Cyclosporin A toxicity and/or acute renal

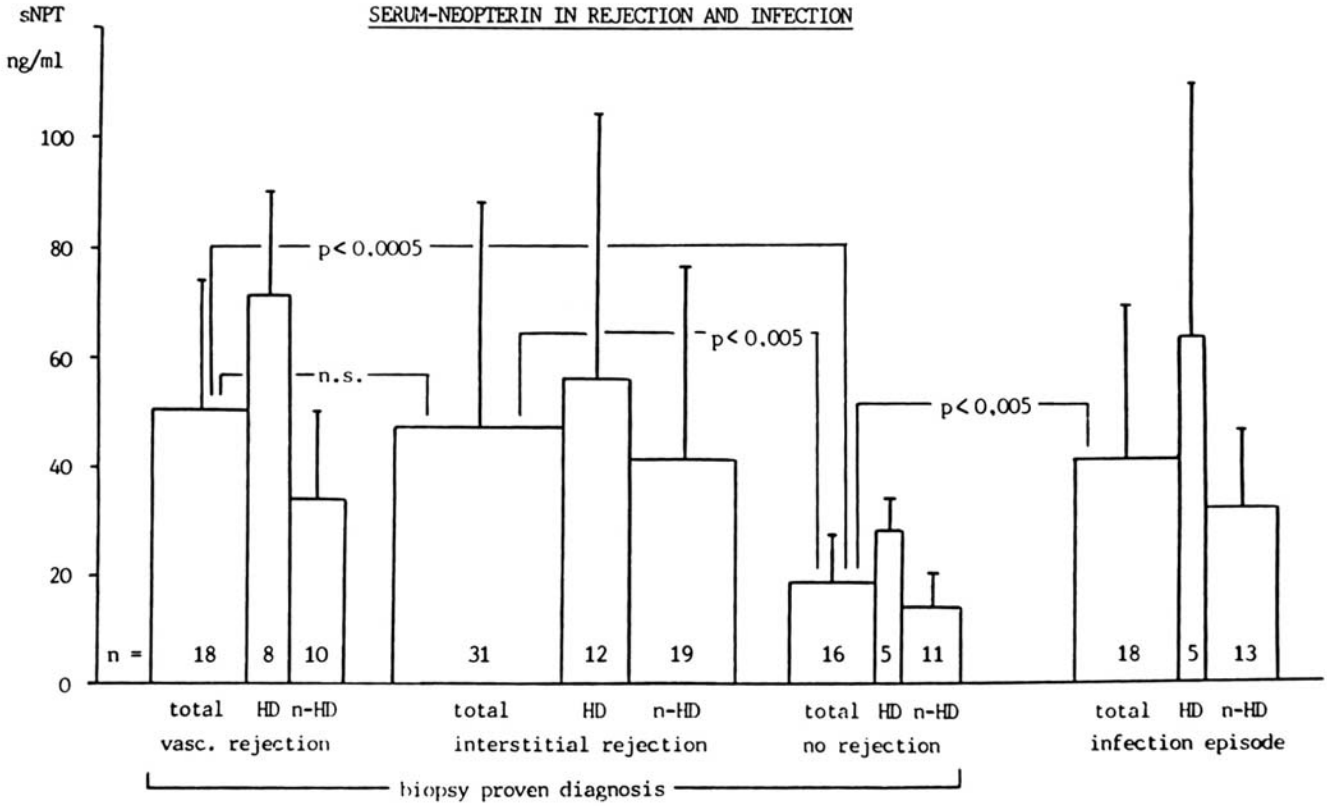

Figure 5. Comparison of sNPT at days of histological examination or infection episodes. 'total': all episodes of each group. 'HD': episodes in patients on haemodialysis. 'n-HD': episodes in patients not on haemodialysis. Each column $\bar{X} \pm SD$, width of column representing number of episodes

failure as the predominant factors in some cases (group 4), and the fact that steroid bolus therapy was based only on clinical features in others (group 3). However, the extent of sNPT elevation did not allow differentiation between infection episodes, acute vascular and interstitial rejections, whereas in cases when rejection was excluded histologically and infection was unlikely by clinical and laboratory findings sNPT was significantly lower indicating a lack of immunological activation.

These data indicate that daily measurement of sNPT by RIA is useful in monitoring kidney transplanted patients. sNPT levels do not only reflect the development of immunological activation, but also enables monitoring of the effect of therapeutic interventions on the immune system.

References

1 Margreiter R, Fuchs D, Hausen A et al. *Transplantation 1983; 36:* 650
2 Huber C, Fuchs D, Hausen A et al. *J Immunol 1983; 130:* 1047
3 Huber C, Batchelor JR, Fuchs D et al. *J Exp Med 1984; 160:* 310
4 Rokos K, Rokos H, Frisius H. In Wachter H, Curtis H Ch, Pfleidevir W, Leiderer PF, eds. *Biochemical and Clinical Aspects of Ptendines.* Berlin: Walter de Gryter. 1952: 117