Transpl Int (1997) 10: 185–191

ORIGINAL ARTICLE

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Pancreas-specific protein (PASP), serum amyloid A (SAA), and neopterin (NEOP) in the diagnosis of rejection after simultaneous pancreas and kidney transplantation

Received: 23 July 1996
Received after revision: 31 December 1996
Accepted: 3 January 1997

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Abstract A reliable, noninvasive indicator of pancreatic allograft rejection is urgently needed. In this study, serum (S), plasma (P), and urine (U) levels of pancreas-specific protein (P-PASP, U-PASP), neopterin (S-NEOP, U-NEOP), amylase (U-AMYL), and amyloid A (SAA) were measured daily in ten type I diabetic patients following simultaneous pancreas and kidney transplantation (SPK). Rejection episodes occurred in three isolated pancreas, nine isolated kidney, and five simultaneous pancreas and kidney transplants. In the case of the eight pancreas rejections, SAA was the rejection marker with the highest diagnostic accuracy (94 %). Using P-PASP and U-PASP, an accuracy of 81 % and 79 %, respectively, was achieved. During viral infections, U-NEOP levels increased to a maximum level of 1904 μmol/mol creatinine, whereas during bacterial infections, SAA levels increased to a maximum value of 43 mg/dl. SAA, measured for the first time in SPK, appears to be a valuable rejection parameter. In combination with U-NEOP and U-AMYL, a differential diagnosis between rejection, bacterial infection, and viral infection was possible. Neither U-PASP nor P-PASP monitoring led to a significant improvement in the results.

Key words Pancreas-specific protein, pancreas transplantation · Neopterin, pancreas transplantation · Serum amyloid A, pancreas transplantation · Pancreas transplantation, rejection parameters · Rejection, pancreas transplantation

Introduction

An early and reliable diagnosis of allograft rejection after simultaneous pancreas and kidney transplantation (SPK) is essential in order to institute effective and successful therapy. A sensitive and specific indicator of pancreatic allograft rejection is urgently needed. In recent years, a number of parameters have been studied with variable success [2, 7, 8, 12, 19, 22]. In 1989, Fernstad et al. described for the first time a novel enzyme called "pancreas-specific protein" (PASP), which appeared to be a marker for pancreatic cellular damage and exocrine pancreas function. An increase in the serum (S) PASP level was seen to provide a sensitive indication of pancreatic graft rejection in SPK with enteric drainage of the pancreas duct [4, 5]. Nyberg et al. measured PASP in patients with SPK and bladder drainage. In contrast to Fernstad, they found that plasma PASP exhibited a low sensitivity as a rejection marker [18]. In 1992, PASP was identified as a human pancreatic procarboxypeptidase B (PCPB) [6, 27].

In the present study, PASP was evaluated in recipients with simultaneous (same donor) pancreas (bladder-drained) and kidney allografts. This was the first time that it was measured daily in plasma (P) and in urine (U) samples. The diagnostic performance of P-PASP and U-PASP was compared with that of neopterin (S-NEOP and U-NEOP) and serum amyloid A (SAA). NEOP is a marker of the cellular immune response, and elevated levels are seen primarily during rejection episodes and viral infections [3, 14, 17, 26]. SAA is a protein associated with the acute phase response; it has been recommended as a rejection marker [9, 15–17]. Thus far, SAA has not been investigated in patients with pancreas transplants.

Patients and methods

Patients

Ten consecutive patients (five female, five male) received simultaneous cadaveric pancreas and kidney grafts at the University Hospital of Marburg between 1991 and 1993. All patients were type I diabetics with end-stage nephropathy. The mean age of the patients was 33.5 years (range 26–43 years).

The surgical technique of pancreaticoduodenocystostomy was used on all patients [20].

Immunosuppressive protocol

The basic postoperative immunosuppressive regimen consisted of quadruple therapy. Prednisolone was given intravenously for the first 8 days at a dosage of 1.5 mg/kg per day. The oral dose started with 1.25 mg/kg per day and was tapered to a maintenance dose of 0.25 mg/kg per day over the next 10 days. Cyclosporin (Sandimmun Sandoz, Nürnberg, Germany) treatment began on the 5th postoperative day, starting at 8 mg/kg per day orally, and was later adjusted to keep whole blood levels between 200 and 250 ng/ml.

Cyclosporin levels were measured with a monoclonal assay (cyclosporin monoclonal whole blood TDX, Abbott Laboratories, USA). Azathioprine (Imurek, Wellcome, Burgwedel, Germany) was given intravenously, with the dosage starting at 2.5 mg/kg per day; it was later adjusted to keep the white blood cell count above 4000 cells/μl. Polyclonal antibodies (20 mg/kg per day ALG, University of Minnesota, Minneapolis, Minn., USA or 2 mg/kg per day Thymoglobulin, Merieux, Lyon, France) were given during the first 2 postoperative weeks. The dosage was monitored by measuring the absolute lymphocyte and T-cell numbers. Acute rejection episodes were treated with either steroid pulse therapy or monoclonal antibodies (OKT3, Orthoclone, Cilag, Sulzbach, Germany).

Parameter measurements

Blood and urine sampling

Morning blood samples were drawn daily into EDTA tubes (Sarstedt, Germany) to which 0.25 ml aprotinin (Trasylol, Bayer, Germany) was added. The samples were immediately cooled and centrifuged at 3000 *g* for 10 min at 4 °C. Supernatants were separated into 300 μl fractions, frozen immediately afterwards, and stored at –70 °C. Urine was collected over a period of 24 h; samples were taken at 6 a.m. and put into sterile containers (Sarstedt, Germany). These samples were separated into 300 μl fractions, frozen immediately, and stored at –70 °C. In cases of pyuria or hematuria, the urine samples were centrifuged beforehand.

PASP

PASP was measured in urine and plasma samples with the same kit (hPASP-RIA, Diagnostic Products, Los Angeles, Calif., USA). U-PASP was measured in ng/ml and mg/day. For these measurements, the urine samples were diluted by up to a factor of 1000.

NEOP

Neopterin was measured daily in urine and serum samples with a RIA (IMMUtest, provided by Henning, Berlin, Germany); U-NEOP was calculated in μmol/mol creatinine.

SAA

A new, rapid immunonephelometric assay was developed to measure SAA levels, as previously described [9]. For this assay, highly specific antibodies were raised against purified SAA. Antigen-antibody complexes were measured with a laser nephelometer (Behringwerke, Marburg, Germany).

Rejection episodes

For the purpose of this study, all rejection episodes were analyzed retrospectively. The criterion for pancreas rejection was taken to be a drop of at least 50 % in the urinary amylase excretion (U-AMYL), whereas renal allograft rejection was presumed when the serum creatinine (S-CREA) level rose by at least 0.3 mg/dl above the level of the previous day.

U-AMYL activity, expressed as U/h, was determined on the basis of measurements done on 8-hourly collections of urine. In accordance with the method described by Squifflet, an individual, postoperative U-AMYL baseline level was calculated [19, 25]. Values used to determine the baselines varied less than 25 % on 3 consecutive days. A drop in activity exceeding 50 % with respect to the baseline value was considered significant in terms of the diagnosis of rejection [19, 20, 25]. In addition, an improvement in graft function after the administration of rejection therapy was mandatory for reaching the diagnosis of rejection. Periods with a deterioration in graft function due to nonimmunological causes (surgical complications, manifest infections, cyclosporin levels above 300 ng/ml) were excluded. The clinical diagnosis of rejection was facultatively supplemented by histological and cytological findings from core biopsies and fine needle aspiration cytologies of the kidney.

The day of rejection was defined as the day rejection therapy began (day 0). The parameter behavior in each rejection episode was analyzed over 6 days, i.e., 3 days before (day –3) and 2 days after (day + 2) the start of therapy (day 0). Due to the multiple factors influencing the parameter behavior during the perioperative period, the first 5 postoperative days were excluded in the evaluation of the rejection markers.

Stable graft function

Every rejection episode was matched against a corresponding period of stable graft function. Stable graft function was defined as a period during which no complications, such as rejection episodes,

Table 1 Diagnostic value of the parameters

	P-PASP (ng/ml)	U-PASP (mg/day)	U-PASP (ng/ml)	SAA (mg/dl)	S-NEOP (nmol/l)	U-NEOP (μmol/mol crea)
Baseline value	96	49	21793	4.3	31	304
SD	52	37	14929	3.3	23	178
Sensitivity (%)	75	71	29	100	57	83
Specificity (%)	87	86	86	87	86	67
Accuracy (%)	81	79	57	94	71	75
Day of first increase/decrease during rejection (mean)[a]	+ 0.1	− 0.3	− 0.3	− 0.3	− 1.4	− 0.3
Mean increase/decrease over previous day during rejection (%)[b]	+ 263	− 54	− 46	+ 333	+ 46	+ 220

[a] Day of first true-positive parameter behavior, i.e., increase/decrease > the 50 % cut-off level (0 day clinical rejection was diagnosed, − days before clinical diagnosis, + days after clinical diagnosis)

[b] Mean value of all true-positive increases (+) or decreases (−) in the parameters

viral infections, acute tubular necroses, surgical interventions, and therapies with mono- or polyclonal antibodies, occurred. Again, the first 5 postoperative days were excluded.

Parameter analysis

The clinical course and parameter curves for each patient were displayed graphically. The 6-day periods of rejection and stable graft function were defined as regions of interest, and the parameter behavior was assessed as true-positive (TP), false-negative (FN), true-negative (TN), and false-positive (FP). The cut-off level was defined as either an increase (for P-PASP, SAA, S-NEOP, U-NEOP) or a decrease (for U-PASP) of more than 50 % in the parameter levels from one day to the next. Sensitivity was calculated as TP/(FN + TP), specificity as TN/(FP + TN), and accuracy as (TP + TN)/(TP + FP + TN + FN). The day when the first change exceeded the cut-off level was related to the day when rejection therapy started (day 0) and was defined as that of the first true-positive parameter increase. The baseline value (mean value ± standard deviation) of each parameter was defined by calculating the mean parameter levels during the periods of stable graft function. In order to analyze the level of significance in the difference in the median scores of independent groups, a k-sample median test (Brown-Mood) was performed using the SAS statistical analyzing system.

Results

Patient and parameter characteristics

The total period of observation was 354 days ($\bar{x}$ = 35.4 days per patient); 0.95 measurements per parameter and per patient day on the ward were obtained. After 1 year, the graft survival rate was 60 % for the pancreas and 90 % for the kidney, and the patient survival rate was 100 %. In uncomplicated cases, SAA, P-PASP, U-NEOP, and S-NEOP levels declined steadily after an early postoperative peak. U-PASP levels increased progressively following the operation and reached stable values after 10 days on the average. The baseline values of each marker are shown in Table 1. P-PASP and U-PASP values showed extremely high inter-individual differences. The range for P-PASP lay between 3.6 and 1590 ng/ml; for U-PASP, it was between 258 and 146500 ng/ml and between 0.36 and 336 mg/day, respectively.

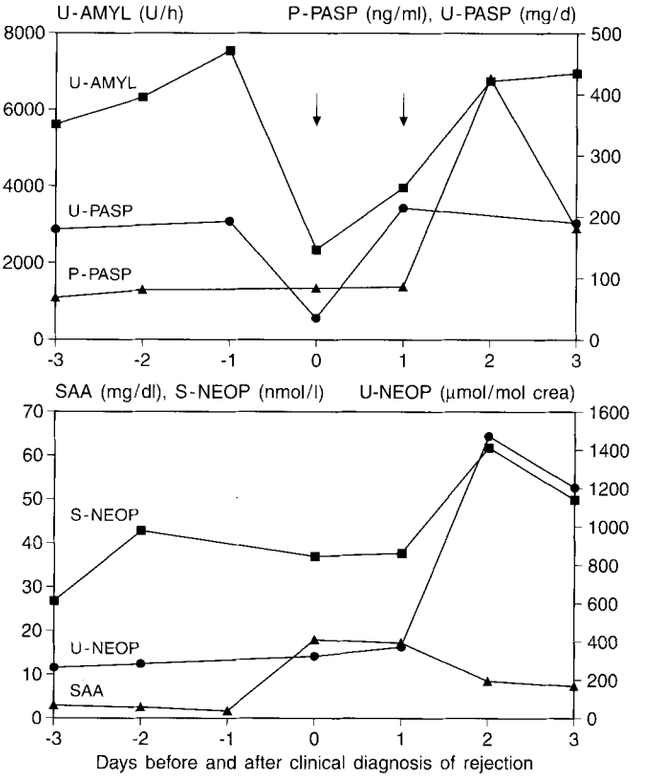

Fig. 1 Example of an acute solitary pancreas rejection episode. *Arrow* indicates i.v. steroid bolus of 500 and 250 mg, respectivly (*0* day clinical rejection was diagnosed)

Example of an acute rejection episode

In Fig. 1, a solitary pancreas allograft rejection episode is shown (day 0 = start of rejection therapy). A deterioration in exocrine pancreas function is indicated by the

Table 2 Parameter performance during eight rejection episodes (*NM* not measured)

		P-PASP (ng/ml)			U-PASP (mg/day)			U-PASP (ng/ml)			SAA (md/dl)			S-NEOP (nmol/l)			U-NEOP µmol/mol crea)		
		Increase			Decrease						Increase								
No.[1]	Rej day[b]	Day[c]	%[d]	Abs[e]	Day	%	Abs	Day	%	Abs	Day	%	Abs	Day	%	Abs	Day	%	Abs
1	P19	0	975	580	–1	55	34	–1	43	9336	–1	54	6	–1	25	60	–2	652	2731
2	P13	0	80	96	0	25	21	0	20	6712	–1	374	15	1	26	7	1	94	217
3	P20	2	392	341	0	82	157	0	77	68585	0	829	16	–2	59	16	2	286	1091
4	P25	–1	170	80	1	54	22	1	40	4643									
	K20										0	71	2	–3	53	9	–2	96	137
5	P27	0	178	106	NM	NM	NM	NM	NM	NM	0	253	12	NM	NM	NM	NM	NM	NM
	K28																		
6	P30	0	41	33	0	36	23	0	47	18663	1	860	30	1	26	50	2	143	1980
	K30																		
7	P33	–2	226	47	0	61	41	0	54	12330									
	K32										1	149	6	–3	75	15	–3	47	157
8	P10	2	44	43	–2	64	16	–2	44	5568									
	K09										–2	76	3	–3	60	60	NM	NM	NM

[a] Rejection episode; 1–3 are solitary pancreas rejections, 4–8 are simultaneous pancreas and kidney rejections [b] Day of first clinical diagnosis of pancreas (P) or kidney (K) rejection; [c] Day of first true-positive parameter increase/decrease with regard to day 0 of clinical diagnosis; – days before clinical diagnosis, + days after clinical diagnosis; [d] First true-positive increase/decrease in the parameter in percentage; [e] First frue-positive increase/decrease in the parameter in absolute units

drop of 66 % in the U-AMYL excretion (fall from the individual baseline level of 6500 to a value of 2200 U/h). The rejection therapy began with steroid pulses. During this rejection episode, all markers showed true-positive behavior (increase/decrease exceeding the cut-off level of 50 %). On day 0, U-PASP excretion decreased from 192 to 35 mg/day (82 %), whereas that of P-PASP increased from 87 to 428 ng/ml (392 %) 2 days later (on day 2). SAA levels increased by 829 %, S-NEOP by 59 %, and U-NEOP by 286 %, respectively.

Diagnostic value of the parameters during eight rejection episodes

In ten consecutive patients, five simultaneous pancreas and kidney, three solitary pancreas, and nine solitary kidney rejection episodes were diagnosed. Three cases of the simultaneous pancreas and kidney rejection cases were biopsy-proven by histology obtained from the renal allograft. During the nine rejections of the kidney graft, neither the exocrine nor the endocrine pancreas function was affected. U-AMYL and PASP values did not show any variations exceeding the 50 % cut-off level.

In Table 2, the parameter performance during the individual eight rejection episodes with pancreatic involvement is shown. The calculated diagnostic value of the parameters is given in Table 1. SAA was the parameter with the highest sensitivity (100 %). U-PASP measurements provided a sensitivity of only 29 % when calculated in ng/ml. An increased sensitivity was obtained by calculating the daily excretion in mg/day (71 %). S-NEOP was the earliest predictor of an impending pancreas rejection, with levels rising on the average 1.4 days before antirejection therapy was initiated. In an analysis of true-negative and false-positive parameter behavior for the 8 corresponding periods of stable graft function, SAA, P-PASP, U-PASP, and S-NEOP showed comparable specificities (87 % and 86 %, respectively). During the eight rejection episodes, SAA showed the highest true-positive peaks, with the mean value rising by 333 % above the previous day's level. The combination of SAA and P-PASP did not show any false-positive increase, i.e., the rise in both parameters was seen exclusively during the eight pancreas rejection episodes.

Parameter behavior during viral and bacterial infections

Seven clinically severe infections (three cytomegalovirus and four bacterial infections), not associated with rejection episodes, occurred. U-PASP and P-PASP did not show parameter peaks exceeding the 50 % cut-off level during these infections. The three acute cytomegalovirus infections were associated with markedly increased S-NEOP and U-NEOP concentrations (maximum values of 287 nmol/l and 1904 µmol/mol creatinine, respectively). The four bacterial infections with septicemia were associated predominantly with strong elevations of the acute phase protein SAA (maximum values of 43.6 mg/dl).

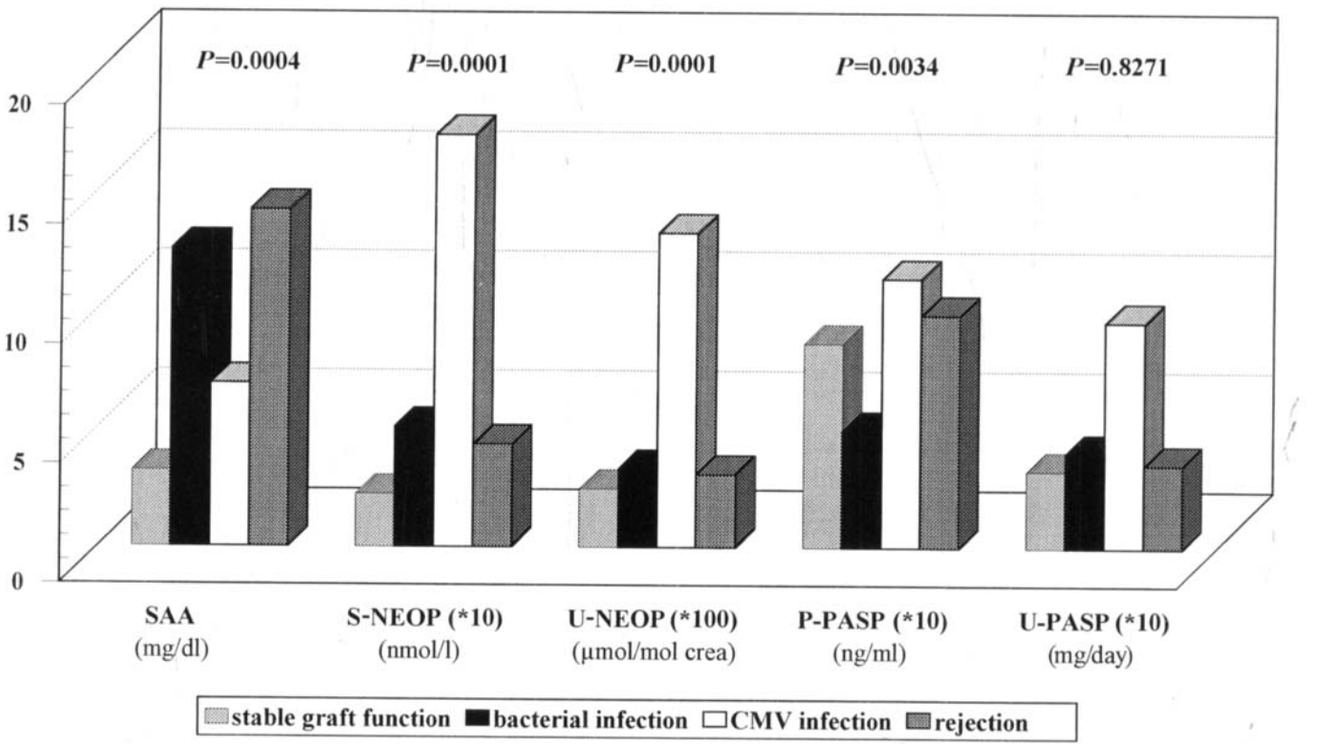

Fig. 2 Median parameter values in four different clinical settings. The values on the x axis have to be multiplied by the scaling factors within the parentheses in order to obtain the correct levels for the individual parameters. *P* values indicate significant differences in the median values obtained in the four clinical settings (Brown-Mood test)

Median parameter values in four different clinical settings

The median values of the five parameters for the periods of bacterial infection, viral infection, allograft rejection, and clinical courses without complications are given in Fig. 2. Median values of U-NEOP and S-NEOP were significantly elevated during the viral infections. They did not discriminate between periods of stable graft function, rejection, and bacterial infection. In contrast, the median levels of SAA were significantly elevated during bacterial infections and acute rejection episodes. The values for U-PASP and P-PASP showed no significant differences with regard to the four clinical settings.

Discussion

The lack of an early and reliable marker for rejection poses a major dilemma in simultaneous pancreas and kidney transplantation (SPK). Solitary pancreas rejections, in particular, are difficult to detect [1, 8, 11, 12, 22]. A number of nonimmunological causes for the deterioration in pancreatic graft function have to be considered (pancreatitis, infections, graft thrombosis, surgical complications), and invasive diagnostic methods carry a risk. Relative hypoamylasuria is the most commonly used biochemical marker of acute rejection in bladder-drained pancreas transplants [1, 7, 19, 20, 23, 25]. In the present study, the drop in the U-AMYL baseline level, together with the functional improvement following immunosuppressive bolus therapy, was used as the gold standard of pancreas rejection. However, despite its high sensitivity, hypoamylasuria does not necessarily mean rejection [1, 8, 23, 25]. Therefore, the test qualities obtained here for the different markers should be viewed in regard to the inherent unspecificity of U-AMYL levels as a gold standard for rejection.

In the present study, three new parameters, namely, pancreas-specific protein (PASP), serum amyloid A (SAA), and neopterin (NEOP), were investigated. Fernstad et al. were the first to recommend the enzyme PASP as a new, sensitive marker of pancreas cell damage and rejection. They measured PASP in the serum of patients with SPK and with enteric drainage [5]. Their good diagnostic results were not, however, confirmed by Nyberg et al. The latter measured PASP levels for patients with simultaneous segmental pancreas and kidney transplantation and with bladder drainage of the pancreas duct. The sensitivity for S-PASP as a rejection

marker was low [18]. These very different results might have been due to the use of different surgical techniques, long time intervals between the PASP measurements, and/or different criteria for the diagnosis of rejection.

In view of these conflicting results, in this study daily measurements of PASP were taken postoperatively on both plasma and urine samples from ten consecutive recipients of simultaneous (same donor) pancreas (bladder drainage) and kidney allografts. In general, the diagnostic accuracy of U-PASP, even when considering the daily excretion, was not superior to that of P-PASP (79 % compared with 81 %, respectively). In addition, the drop in U-PASP values did not precede the changes in the other parameters.

The procarboxypeptidase PASP is a marker of exocrine pancreas function [27]. The low diagnostic value of U-PASP may be due to the fact that nonimmunological factors, such as alimentation or drug therapy, interfere with the secretion of this enzyme. These changes might superimpose themselves on the effects of the rejection process. As for the kinetics of secretory enzymes, it is possible that even intervals of 24 h may be too long to detect significant peaks in PASP levels [21, 24]. In addition to the rather low diagnostic accuracy of both P-PASP and U-PASP measurements in comparison with that of amylase excretion, PASP determination is more expensive and time-consuming.

SAA is a marker of the acute phase response [13, 14, 16, 17]. It could be shown for the first time that SAA is a sensitive rejection marker not only in liver and kidney but also in simultaneous pancreas and kidney grafting. A marked increase in the SAA levels, on the average 333 % above the previous day's level, occurred during all pancreas rejection episodes. The diagnostic accuracy of SAA was higher than that of P-PASP, U-PASP, S-NEOP, and U-NEOP. The SAA levels seen in rejections of simultaneous pancreas and kidney transplants are higher than those measured in rejections of kidney or liver transplants [16, 17]. This underlines the strong inflammatory response associated with rejection processes occurring in simultaneous kidney and pancreas transplants. This response corresponds to the clinical impression of stronger immunological reactions after the simultaneous grafting of the pancreas and kidney than with the acute rejections of solitary organs [10]. At the same time, systemic bacterial infections induce a strong acute phase response. Consequently, the septicemias seen in these immunosuppressed patients are associated with high SAA levels. Therefore, the sole determination of the parameter SAA does not allow one to discriminate between acute rejection and systemic bacterial infection.

NEOP was measured in urine and serum samples, as recommended by other authors [2, 3, 14, 17]. With regard to rejection episodes, U-NEOP had a higher sensitivity than S-NEOP, whereas S-NEOP had a higher specificity, and its level increased earlier, than that of U-NEOP. In comparison with U-PASP and P-PASP, NEOP values were of the same diagnostic value in the detection of allograft rejection. Extreme increases in the NEOP levels, however, occurred exclusively during cytomegalovirus diseases. The high diagnostic value of NEOP in the detection of viral infections corresponds to the findings of other groups [3, 26].

In summary, SAA was the rejection marker with the highest diagnostic performance in the detection of pancreas rejections in this study. The diagnostic qualities of both P-PASP and U-PASP did not exceed those of other markers. U-PASP, at least when measured only once daily, does not appear to be a diagnostic alternative to the established rejection marker U-AMYL. The drop in U-PASP that is associated with rejection is very short-term, and exogenous factors may influence its performance. The level of P-PASP reflects pancreatic cellular damage. It may be of value in combination with SAA measurements, as the increase in both parameters was always associated with pancreas rejection episodes. Increases in NEOP occurred during rejection episodes, but more significant rises were seen in CMV infections, preceding both the clinical manifestation and the results from serological tests and DNA detection. Nevertheless, given the low number of rejection episodes and the lack of pancreatic graft biopsies, one has to be cautious in evaluating the diagnostic qualities of the parameters. Supported by these preliminary results, a prospective study correlating these noninvasive markers with simultaneously obtained pancreatic histologies in a larger number of patients should be most useful.

In conclusion, in this pilot study, the combination of the parameters SAA, U-NEOP, and U-AMYL had a high diagnostic value for the noninvasive monitoring of recipients of simultaneous pancreas and kidney allografts. Rejections were associated with an increase in SAA and a decrease in U-AMYL levels, viral infections with an increase in U-NEOP levels, and bacterial infections with an increase in SAA and stable U-AMYL values.

References

1. Benedetti E, Najarian JS, Gruessner AC, Nakhleh RE, Troppmann C, Hakim NS, Pirenne J, Sutherland DER, Gruessner RWG (1995) Correlation between cystoscopic biopsy results and hypoamylasuria in bladder-drained pancreas transplants. Surgery 118: 864–872
2. Brattström C, Tydén G, Reinholt FP, Bohman SO, Borgström A, Bäckman L, Bolinder J, Groth CG (1989) Markers for pancreas graft rejection in humans. Diabetes 38 [Suppl 1]: 57–62
3. Denz H, Fuchs D, Hausen A, Huber H, Nachbaur D, Reibnegger G, Thaler J, Werner ER, Wachter H (1990) Value of urinary neopterin in the differential diagnosis of bacterial and viral infections. Klin Wochenschr 68: 218–222
4. Fernstad R, Sköldefors H, Pousette Å, Groth CG, Tydén G, Öst L, Lindholm A, Carlström K (1989) A novel assay for pancreatic cellular damage. III. Use of a pancreas-specific protein as a marker of pancreatic graft dysfunction in humans. Pancreas 4: 44–52
5. Fernstad R, Tydén G, Brattström C, Sköldefors H, Carlström K, Groth C, Pousette Å (1989) Pancreas-specific protein: new serum marker for graft rejection in pancreas transplant recipients. Diabetes 38 [Suppl 1]: 55–56
6. Fernstad R, Kylander C, Tsai L, Tydén G, Pousette Å (1993) Isoforms of procarboxypeptidase B, (pancreas-specific protein, PASP) in human serum, pancreatic tissue and juice. Scand Clin Lab Invest 53 [Suppl 213]: 9–17
7. Grewal HP, Kotb M, Salem A, El Din ABM, Novak K, Martin J, Gaber LW, Gaber AO (1993) Elevated tumor necrosis factor levels are predictive for pancreas allograft transplant rejection. Transplant Proc 25: 132–135
8. Gruessner RWG, Sutherland DER (1996) Clinical diagnosis in pancreatic allograft rejection. In: Solez K, Racusen LC, Billingham ME (eds) Solid organ transplant rejection. Marcel Dekker, New York Basel Hong Kong, pp 455–499
9. Hocke G, Ebel H, Bittner K, Müller T, Kaffarnik H, Steinmetz A (1989) A rapid laser immunonephelometric assay for serum amyloid A (SAA) and its application to the diagnosis of kidney allograft rejection. Klin Wochenschr 67: 447–451
10. Hopt UT, Büsing M, Scharek W, Pfeffer F, Irkin I, Becker HD (1992) Is HLA matching worthwhile in pancreas transplantation? Transplant Proc 24: 909–910
11. Klassen DK, Weir MR, Schweitzer EJ, Bartlett ST (1995) Isolated pancreas rejection in combined kidney-pancreas transplantation: results of percutaneous pancreas biopsy. Transplant Proc 27: 1333–1334
12. Kubota K, Reinholt FP, Tydén G (1992) Pancreatic juice cytology for monitoring pancreatic grafts in the early postoperative period. Transpl Int 5: 133–138
13. Malle E, Münscher G, Müller T, Vermeer H, Ibovnik A (1995) Quantification and mapping of antigenic determinants of serum amyloid A (SAA) protein utilizing sequence-specific immunoglobulins and Eu^{3+} as a specific probe for time-resolved fluorometric immunoassay. J Immunol Methods 182: 131–144
14. Margreiter R, Fuchs D, Hausen A, Huber C, Reibnegger G, Spielberger M, Wachter H (1983) Neopterin as a new biochemical marker for diagnosis of allograft rejection. Experience based upon evaluation of 100 consecutive cases. Transplantation 36: 650–653
15. Maury CPJ, Teppo AM (1984) Comparative study of serum amyloid-related protein SAA, C-reactive protein and β2-microglobulin as markers of renal allograft rejection. Clin Nephrol 22: 284–292
16. Maury CPJ, Höckersted K, Lautenschlager I, Scheinin TM (1987) Monitoring of high-density lipoprotein-associated amyloid A protein after liver transplantation. Transplant Proc 19: 3825–3826
17. Müller T, Schindler S, Sprenger H, Steinmetz A, Hocke G, Ebel H, Gemsa D, Lange H (1992) Prospective analysis of 10 different parameters of acute renal allograft rejection. Transplant Proc 24: 2731–2734
18. Nyberg G, Olausson M, Nordén G, Mjörnstedt L, Blohmé I, Hedman L (1991) Pancreas specific protein (PASP) monitoring in pancreas transplantation. Transplant Proc 23: 1604–1605
19. Pietro M, Sutherland DER, Fernandez-Cruz L, Heil J, Najarian JS (1987) Experimental and clinical experience with urine amylase monitoring for early diagnosis of rejection in pancreas transplantation. Transplantation 43: 73–79
20. Pietro M, Sutherland DER, Rosenberg ME, Goetz FC, Najarian JS (1987) Pancreas transplant results according to technique of duct management: bladder versus enteric drainage. Surgery 102: 680–691
21. Pitchumoni CS, Scheele G, Lee PC, Lebenthal E (1986) Effects of nutrition on the exocrine pancreas. In: Go VLW, Brooks FP, Di Magno EP, Gardner JD, Lebenthal E, Scheele GA (eds) The exocrine pancreas: biology, pathobiology, and diseases. Raven Press, New York, pp 387–406
22. Ploeg RJ, D'Alessandro AM, Groshek M, Gange SJ, Knechtle SJ, Stegall MD, Eckhoff DE, Pirsch JD, Sollinger HW, Belzer FO (1994) Clinical experience with human anodal trypsinogen (HAT) for detection of pancreatic allograft rejection. Transpl Int 7 [Suppl 1]: S426–S431
23. Powell CS, Lindsey NJ, Nolan MS, Wiley KN, Boyle PF, Herold A (1987) The value of urinary amylase as a marker of early pancreatic allograft rejection. Transplantation 43: 921–923
24. Rinderknecht H (1986) Pancreatic secretory enzymes. In: Go VLW, Brooks FP, Di Magno EP, Gardner JD, Lebenthal E, Scheele GA (eds) The exocrine pancreas: biology, pathobiology, and diseases. Raven Press, New York, pp 163–183
25. Squifflet JP (1990) Pancreas transplantation: experimental and clinical studies. Karger, Basel München Paris, pp 1–188
26. Tilg H, Königsrainer A, Krausler R, Aulitzky WE, Margreiter R, Reibnegger G, Wachter H, Huber C (1992) Urinary and pancreatic juice neopterin excretion after combined pancreas-kidney transplantation. Transplantation 53: 804–808
27. Yamamoto KK, Pousette Å, Chow P, Wilson H, Shami ES, French CK (1992) Isolation of a cDNA encoding a human serum marker for acute pancreatitis. J Biol Chem 267: 2575–2581