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**H. Mäkisalo**
**M. Lepäntalo**
**L. Halme**
**T. Lund**
**S. Peltonen**
**K. Salmela**
**J. Ahonen**

# Peripheral arterial disease as a predictor of outcome after renal transplantation

H. Mäkisalo (✉) · L. Halme · T. Lund · K. Salmela · J. Ahonen
Division of Transplantation,
Department of Surgery,
Helsinki University Central Hospital,
Kasarmikatu 11–13, FIN-00130,
Helsinki, Finland
Tel. +358-9-471 82 38

M. Lepäntalo · S. Peltonen
Division of Vascular Surgery,
Department of Surgery,
Helsinki University Central Hospital,
Kasarmikatu 11–13, FIN-00130,
Helsinki, Finland

**Abstract** Our aim was to assess the prevalence of symptomatic and asymptomatic peripheral occlusive arterial disease (POAD) in 129 consecutive diabetic ($n$ = 34) and non-diabetic ($n$ = 95) patients undergoing renal transplantation. The association of pre-existent POAD and complaints of claudication, lower limb amputations, and graft and patient survival were evaluated during a 5-year follow up. A questionnaire on walking capacity, ankle/brachial (ABI) and toe/brachial (TBI) pressure indices as well as the pulse volume recording (PVR) at the ankle were used to assess resting haemodynamics and the presence of POAD 4 days after the transplantation. Unquestionable ischaemia was encountered in 5 (4%) patients all with a history of intermittent claudication and an ABI equal or below 0.77. While using assessment methods not affected by vessel calcification, i.e. toe pressures and PVR damping, a many-fold frequency of arterial disease was observed when compared to previous studies. TBI below 0.65 was found in 11 of diabetic (32%) and in 15 of the others (16%), and a PVR amplitude below 5 min in 28 of diabetics (82%) and in 34 of non-diabetics (36%). During the 5-year follow up, abnormal TBI and PVR values and diabetes at the time of transplantation were the greatest risk factors for proximal foot amputations. The low TBI levels also indicated a shortened patient survival. However, transplant function was not affected by the presence of abnormal haemodynamic indices at the time of transplantation.

**Key words** Renal transplantation · Peripheral occlusive arterial disease · Intermittent claudication

## Introduction

Coronary and cerebral vascular diseases are the major causes of mortality in patients with an end-stage renal disease (ESRD) accounting for 49% of deaths in patients on continuous ambulatory peritoneal dialysis, 30% of deaths in patients on haemodialysis [8, 10] and 20–30% of deaths in patients with functioning renal transplants [4]. Increased prevalence of arteriosclerotic cardiovascular disease in patients with ESRD is influenced by risk factors such as hypertension, diabetes mellitus and hypercholesterolaemia. Prevalence of symptomatic intermittent claudication is reported to range from 14 to 19% in patients after renal replacement therapy [13, 24]. However, questionnaire surveys are apt to give a much higher prevalence of peripheral occlusive ar-

**Table 1** Causes of renal failure

| Cause | Prevalence |
|---|---|
| Glomerulo/pyelonephritis | 68 (53%) |
| Diabetes | 34 (26%) |
| Polycystic disease | 13 (10%) |
| Hypertensive renal disease | 7 (5%) |
| Amyloidosis | 5 (4%) |
| Wegener's granulomatosis | 2 (2%) |

**Table 2** Demographics of the study population. There were no statistically significant differences between diabetics and non-diabetics

| | Diabetics | Non-diabetics | Total |
|---|---|---|---|
| Number | 34 | 95 | 129 |
| Sex ratio (M/F) | 19/15 | 50/45 | 69/60 |
| Subjective claudication | 1 | 3 | 4 |
| Mean age (years) | 38.1 (22–56) | 41.4 (15–63) | 40.5 (15–63) |
| Mean duration of dialysis (weeks) | 14.6 (2–52) | 19.4 (1–95) | 18.1 (1–95) |
| Body mass index (kg/m$^2$) | 23.4 (18.4–29.6) | 23 (16.4–31.5) | 23.1 (16.4–31.5) |
| Cholesterol (mmol/l) | 5.9 (0.6–8.4) | 6.3 (3.4–11.1) | 6.2 (0.6–11.1) |
| Triglyceride (mmol/l) | 2.6 (0.9–5.7) | 2.5 (0.8–7.6) | 2.5 (0.8–7.6) |
| HDL (mmol/l) | 1.12 (0.39–2.76) | 1.17 (0.48–3.09) | 1.16 (0.39–3.09) |

terial disease (POAD) than studies utilising objective measurements, depending also on materials, treatments and methods of evaluation [13, 24]. Indeed, studies utilising Doppler with or without angiography give prevalences between 2.5 and 3% [1, 14]. However, POAD may be difficult to quantify in patients with ESRD because of the presence of concomitant vascular calcification [19]. Pseudohypertension of the arterial wall induced by diabetes or long-term corticoid therapy may make the arteries non-compressible and disturb the accuracy of the pressure measurements [11, 12, 17]. This dilemma can be avoided by measuring the toe pressure as arterial calcification is a rarity in the digital vessels [22].

The aim of the present study was to evaluate the presence of POAD in patients undergoing renal transplantation. We also wanted to assess the predictive value of non-invasive assessment of peripheral arterial disease at the time of transplantation both on the lower extremity amputation frequency and on graft and patient survival in the long-term.

## Materials and methods

A total of 129 consecutive patients undergoing renal tansplantation were recruited for the study. In 26 patients the procedure carried out was a retransplantation. The causes of renal failure necessitating transplantation are shown in Table 1. A quarter of the patients were diabetics, but in terms of risk factors they did not differ as a group from the others (Table 2). Before being accepted on the renal transplantation list patients with symptoms of coronary disease or claudication were angiographed and treated by angioplasty or reconstructive surgery if appropriate. At admission, the presence of POAD was based on a history of intermittent claudication. The surgical procedure of choice was coupling the renal artery to the internal iliac artery. In 21 cases the external iliac artery was used for the anastomosis.

The patients were routinely admitted to the non-invasive vascular laboratory 4 days after the transplantation. Ankle systolic blood pressure was measured with the Doppler device as the distal sensor and the ankle/brachial pressure index (ABI) was calculated using the higher systolic arm pressure as the denominator. To calculate the toe/brachial pressure index (TBI), the systolic pressure of the big toe was measured using strain gauge plethysmogaphy. The volume change in the extremity caused by each pulse wave was measured pneumoplethysmographically at ankle level with a pulse volume recorder (PVR). The history of intermittent claudication was evaluated by a simple questionnaire. The most frequently used cut-off level of the ABI for POAD is 0.97 [5, 6, 8, 17] or 0.9 [7], of the TBI is 0.65 [6] and of the PVR is 5 mm [21]. These levels were used in the present study.

The patient and graft survival were evaluated during a 5-year follow up and complaints of claudication and possible lower limb amputations were recorded. The amputations were regarded as proximal if the limb was amputated above the midfoot level. The groupwise comparisons were made using a *t*-test for unpaired samples or a chi-squared test as appropriate. The study was accepted by the Ethical Committee of the Helsinki University Central Hospital and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

## Results

Five patients (4%), 4 of which indicated a typical history of intermittent claudication, showed a clear-cut arterial disease with ABI ranging from 0.49 to 0.77 measured 4 days posttransplant (Table 3). When an ABI below 0.97 was chosen as a criterion for ischaemic disease, 10 patients (8%) with 13 diseased limbs were encountered. A TBI below 0.65 was observed in 11 diabetic patients (32%) and in 15 (16%) others (NS). Diabetes was a risk factor associated with the presence of an abnormal PVR or TBI ($P < 0.01$) as only 18% of them had both a normal PVR and TBI.

During the 5-year follow up both a TBI < 0.65 and a PVR < 5 at the time of transplantation were associated

**Table 3** Non-invasive vascular laboratory findings in kidney transplant patients indicating peripheral occlusive arterial disease. The values from the worse leg are used (*ABI* Ankle/brachial pressure index, *TBI* toe/brachial pressure index, *PVR* pulse volume recording)

| | Diabetics | Non-diabetics | Total |
|---|---|---|---|
| Number | 34 | 95 | 129 |
| ABI < 0.97 | 3 (9%) | 7 (7%) | 10 (8%) |
| ABI < 0.9 | 1 (3%) | 4 (4%) | 5 (4%) |
| TBI < 0.65 | 11 (32%) | 15 (16%) | 26 (20%) |
| PVR < 5 | 28 (82%) | 34 (36%)** | 62 (48%) |

** Difference between diabetics and non-diabetics ($P < 0.01$)

**Table 4** Status of the lower extremities, graft function and patient survival at 5 years after the transplantation assessed against the diabetic, TBI and PVR status at the time of transplantation

| | Number | Claudication | Amputations | | Transplants lost | Patients died |
|---|---|---|---|---|---|---|
| | | | Distal | Proximal | | |
| TBI | | | | | | |
| $\leq 0.65$ | 29 | 7 | 5** | 1 | 10 | 8* |
| $> 0.65$ | 96 | 6 | 2 | 2 | 22 | 8 |
| PVR[a] | | | | | | |
| $< 5$ | 62 | 2 | 8* | 2 | 17 | 10 |
| $\geq 5$ | 62 | 1 | 1 | 1 | 14 | 5 |
| Diabetics | 35 | 11 | 7** | 3* | 12 | 7 |
| Non-diabetics | 94 | 5 | 2 | 0 | 20 | 9 |

* $P < 0.05$, ** $P < 0.01$; chi-squared

[a] One hundred and twenty-four measurements available

**Table 5** Causes of death after renal transplantation during 5 years of follow up

| Cause of death | Number |
|---|---|
| Cardiovascular | 10 |
| Pneumonia | 2 |
| Cerebral | 1 |
| Malignancy | 1 |
| Gastrointestinal | 1 |
| Not known | 1 |

with the proximal foot amputations ($P < 0.01$ and $< 0.05$, respectively; Table 4). Patients with a TBI less than 0.65 also had an increased risk of mortality ($P < 0.05$). The graft survival was similar in all groups regardless of the level of pressure indices or PVR. In the diabetics, 5-year patient and graft survivals were similar to those of non-diabetics, but the incidence of lower extremity amputations was significantly higher (Table 4). During the follow up, 10 out of 16 deaths of all patients and 7 out of 7 deaths of diabetics were of cardiovascular origin (Table 5).

## Discussion

Diabetes is known to increase the risk of intermittent claudication in the general population two- to threefold [3]. However, in a series published by the Charing Cross Group, diabetes was not overrepresented in renal replacement therapy patients with claudication as compared with those without [24]. Using a Rose questionnaire to assess claudication they found a prevalence of 19%, which, however, was considered to be an underestimate of the true prevalence of peripheral arterial disease in renal replacement therapy patients as the questionnaire used will not identify patients with asymptomatic and less severe disease. This suggestion is supported by the high prevalence observed among present patients when toe pressure or especially PVR damping were used as criteria for the disease. An overall prevalence of arteriosclerosis detected by damping of the PVR amplitude to less than 5 mm ast the ankle was 48% in all patients and 82% among diabetics, which are far higher figures than in previous clinical reports [1, 13, 14, 24]. A TBI level of 0.65 was first suggested by Carter [6] and damping of the PVR amplitude below 5 mm was considered to be a reliable indicator for arterial disease even in diabetics by Raines et al. [21]. If the pressure indices instead of the PVR damping are used for detecting arteriosclerosis the prevalence is markedly lower in the present study, namely 20% using 0.65 as the cut-off level of the TBI, 8% with the ABI cut-off level of 0.97 and 4% with a more strict ABI level of 0.9. Thus, the haemodynamic findings indicating the presence of POAD strongly depend on the criteria used. Nevertheless, measuring of the pressures quite accurately illustrates the potential flow [16], although an even better assessment could be reached after exercise provocation [15]. In the present study the measurements were made shortly after renal transplantation to avoid any drop-outs from a consecutive series and that was why exercise tests could not be performed.

Patients with ESRD and particularly diabetics are known to have mediasclerosis causing pseudohypertension and masking the presence of arteriosclerosis [12, 13, 19]. Therefore, the toe blood pressure measurement and damping of the PVR amplitude are more reliable in detecting arterial disease than pressure measurements at the ankle or more proximal levels in renal transplant patients. In the present study, the diabetics clearly had pseudohypertension more often, but also has more true arteriosclerosis than the non-diabetics. The early development of arteriosclerosis in uraemic patients is also a well-known phenomenon; arteriosclerosis was found in 62% of iliac artery specimens obtained for histological study at the time of renal transplantation in non-diabetic haemodialysis patients with an average age of 35 years [23].

According to earlier reports, the incidence of symptomatic POAD and amputations were increased 15- to 20-fold in diabetic patients [2]. A controversy exists if the renal replacement therapy increases the risk of lower extremity amputations in patients with pre-existent

arteriosclerotic disease. In an prospective study, Foster et al. [9] found that frequency of lower limb amputations in diabetic renal transplant patients did not differ from that of non-transplanted diabetics. The majority of foot lesions were related to neuropathy and trauma and not to vascular lesions per se. In the present study, posttransplant lower limb amputations were associated both with diabetes and with arteriosclerosis in non-diabetics detected using the cut-off levels of a TBI < 0.65 and damping of the PVR amplitude < 5 mm. The ABI was not a predictor of amputations during the 5-year follow up. The frequency of lower extremity amputations of diabetics in the present study was similar to that in the report of Morissey et al. [20], but was far less than in a recent prospective study of Manske et al. [18].

Although in the present study the frequency of lower extremity amputations was higher in diabetics compared to controls, no difference was found in the mortality. The 5-year mortality was 20%, which is a far lower figure than in previous studies showing 3-year survival rates just above 50% [18]. Of the pressure measurements used in the study, only the TBI had a predictive value related to the mortality during the follow up when 0.65 was used as the cut-off level. Neither pressure measurements nor diabetic status at the time of transplantation were associated with graft survival during the 5-year follow up. We conclude that arteriosclerosis is a common finding among ESRD patients admitted for renal replacement therapy. Arteriosclerotic disease detected by the TBI and the PVR at the ankle level was associated with increased proximal foot amputations during the 5-year follow up. The TBI could even be used as a predictor of increased mortality during that time period.

## References


1. Bergisio F, Ciuti R, Salvadori M, Galli GA, Monzani G, Bertoni E, Salerno A, Frizzi V (1989) Are lipid abnormalities reliable cardiovascular risk factors in dialysis patients. Int J Artif Organs 12: 677–682
2. Bild DE, Selby JV, Sinnock P, Browner WS, Braveman P, Showstack JA (1989) Lower-extremity amputation in people with diabetes: epidemiology and prevention. Diabetes Care 12: 24–31
3. Brand FN, Abbott RD, Kannel WB (1989) Diabetes, intermittent claudication, and risk for cardiovascular events: the Framingham Study. Diabetes 38: 504–509
4. Brunner FP, Fassbinder W, Broyer M, Oules R, Brynger H, Rizzoni G, Challah S, Selwood NH, Dykes SR, Wing AJ (1988) Survival on renal replacement therapy: Data from E. D. T. A. Registry. Nephrol Dial Transplant 2: 109–122
5. Buchbinder, Flanigan P (1986) Arterial disease of the lower extremities. Diagnosis 15: 79–90
6. Carter SA (1968) Indirect systolic pressures and pulse waves in arterial occlusive disease. Circulation 37: 624–637
7. Christensen JH, Freundlich M, Jacobsen BA, Falstie-Jensen N (1989) Clinical relevance of pedal pulse palpation in patients suspected of peripheral arterial insufficiency. J Int Med 22: 95–99
8. deLemos JA, Hillis LD (1996) Diagnosis and management of coronary artery disease in patients with end-stage renal disease on hemodialysis. J Am Soc Nephrol 7: 2044–2054
9. Foster AV, Snowden S, Grenfell A, Watkins PJ, Edmonds ME (1995) Reduction of gangrene and amputations in diabetic renal transplant patients: the role of a special foot clinic. Diabet Med 12: 632–635
10. Gokal R, Jakubowski C, King, et al (1987) Outcome in patients on continuous ambulatory peritoneal dialysis and haemodialysis: 4-year analysis of a prospective multicentre study. Lancet ii: 1105–1108
11. Goss DE, Trafford JC de, Roberts VC, Flynn MD, Edmonds ME, Watkins PJ (1989) Raised ankle/brachial pressure index in insulin-treated diabetic patients. Diabet Med 6: 576–578
12. Hobbs JT, Yao JST, Lewis JD, Needham TN (1974) A limitation of the Doppler ultrasound method of measuring ankle systolic pressure. Vasa 3: 160–162
13. Ibels LS, Alfrey AC, Haffer WE, Craswell WE, Anderson JT, Weil R (1979) Arterial calcification and pathology in uraemic patients undergoing dialysis. Am J Med 60: 790–795
14. Kasiske BL (1988) Risk factors for accelerated atherosclerosis in renal transplant recipients QJM 44 (182): 985–992
15. Laing S, Greenhalgh RM (1986) Treadmill testing in the assessment of peripheral arterial disease. Int Angiol 5: 249–252
16. Lassen NA, Holstein P (1974) Use of radioisotopes in assessment of distal blood flow and distal blood pressure in arterial insufficiency. Surg Clin North Am 54: 39–55
17. Lepäntalo M, Lindfors O, Pekkola P (1983) The ankle: arm blood pressure ratio as a screening test for arterial insufficiency in the lower limb. Ann Chir Gynaecol 72: 57–61
18. Manske CL, Wilson RF, Wang Y, Thomas W (1997) Atherosclerotic vascular complications in diabetic transplant candidates. Am J Kidney Dis 29: 601–607
19. Meema HE, Oreopoulos DG, DeVeber GA (1976) Arterial calcifications in severe chronic renal disease and their relationship to dialysis treatment, renal transplantation and parathyroidectomy. Radiology 121: 315–321
20. Morissey PE, Shaffer D, Monaco AP, Conway P, Madras PN (1997) Peripheral vascular disease after kidney-pancreas transplantation in diabetic patients with end-stage renal disease. Arch Surg 132: 361–362
21. Raines JK, Darling RC, Buth J, Brewster DC, Austen WG (1976) Vascular laboratory criteria for the management of peripheral vascular disease of the lower extremities. Surgery 79: 21–29
22. Ramsey DE, Manke DA, Sumner DS (1983) Toe pressure – a valuable adjunct to ankle pressure measurement for assessing peripheral arterial disease. J Cardiovasc Surg 24: 43–48
23. Vincenti F, Amend WJ, Abele J, Feduska NJ, Salvatierra JrO (1980) The role of hypertension in haemodyalysis-associated atherosclerosis. Am J Med 80: 363–369
24. Webb AT, Franks PJ, Reaveley DA, Greenhalgh RM, Brown EA (1993) Prevalence of intermittent claudication and risk factors for its development in patients on renal replacement therapy. Eur J Vasc Endovasc Surg 7: 523–527