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Endstage Renal Failure in Diabetes Mellitus: Special Problems of Treatment and Monitoring

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INTRODUCTION

There has been a remarkable increase in the number of diabetic patients, mostly of type 2, admitted to renal replacement therapy. Significant differences in frequencies of uraemic diabetic patients between European countries are observed. In some regions of Germany the numbers of newly admitted diabetic patients to renal replacement therapy are as high as those reported for Caucausians in the USA, whereas in Southern Europe (e.g. Italy, France) these figures are markedly less (13,25). It is of great practical importance to distinguish the insulin-dependent type 1 diabetic patient (who could benefit from pancreas or islet transplantation) and the diabetic patient with normal or high circulating insulin levels to which their tissues, are resistant. Because type 2 diabetes is much more prevalent in the general population (85–90%) the high prevalence of type 2 diabetes in patients admitted in endstage renal failure is not surprising. The renal risk, however, is equivalent in both type 1 and type 2 diabetes. The cumulative prevalence of proteinuria and, in proteinuric patients, the prevalence of renal failure, is similar in both type 1 and type 2 diabetes (14).

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EVALUATION OF THE DIABETIC PATIENT WITH PRETERMINAL RENAL FAILURE

The evaluation of the diabetic patient with preterminal renal failure has several assignments to estimate the progression rate of renal failure. The natural history of progression of diabetic nephropathy is described in detail elsewhere in this volume but concomitant renal diseases may influence the history of diabetic nephropathy. Some of this coincident kidney diseases are listed below.

Ischaemic Renal Disease

In addition, a minority of patients suffer from specific renal problems together with the coexisting diabetic nephropathy. Renal ischaemia or atherosclerotic renal atery stenosis is much more common in diabetics than was previously assumed (32). In this case one should be cautious regarding ACE-inhibitors or angiotensin receptor blocking antihypertensives. Frequent control of s-creatinine, s-potassium and bodyweight is mandatory. A two-fold increase in s-creatinine should prompt the physician to stop this type of medication.

Urinary Tract Infection

Urinary tract infection frequently led to renal parychematous infection with purulent papillary necrosis and intrarenal abscess formation. This is now rare due to the frequent use of antibiotics and the better management of urinary tract infection. Urinary tract infection may be frequent in diabetics, especially when residual urine is present.

Glomerulonephritis

Glomerulonephritis, particularly membranous glomerulonephritis, is thought to be more frequent in diabetics, but this has not been not supported by other studies.

Acute Renal Failure

Diabetic patients with nephropathy are exceptionally susceptible for acute renal failure after administration of radiocontrast media (36), the risk being similar with ionic and non-ionic materials. The risk may be reduced by fluid

administration and a temporary stop of diuretics. In patients with severly elevated serum-creatinine a dialysis procedure immediately after the radiographic procedure is warranted, without any delay in time.

Hydroxyethyl starch and ACE inhibitors also cause deterioration of renal function in diabetic patients, especially in those with congestive heart failure (28).

RENAL REPLACEMENT THERAPY IN DIABETIC PATIENTS WITH ENDSTAGE RENAL FAILURE

Haemodialysis: Optimal Start of Dialysis in the Patient with Diabetic Nephropathy

It is generally accepted that renal replacement therapy should be considered at a creatinine-clearance of approximately 9–14 ml/min in non-diabetic uraemic patients (15). It is now accepted that in the patient with diabetic nephropathy, dialysis should be started at a higher residual renal function than in non-diabtetic patients with renal insufficiency (30). In any case, dialysis should be started before the clinical status deteriorates, secondary to fluid overload, malnutrition, hyperkalaemia and infection. This is usually the case when the GFR declines below 20 ml/min. Diabetic patients with progression to endstage renal failure must be seen on a regular basis by a nephrologist. Repeated control of residual renal function by creatinine-clearance (24 h specimen collection) and 24 h urine for urea excretion to determine the magnitude of malnutrition are of great importance. Vascular access surgery (usually arteriovenous fistula) some months before the initiation of the dialysis treatment helps to avoid central venous lines and its concomitant complications. Blood drawing for regular serum chemistry is restricted to the dorsal hand veins only. If these guidelines are accepted, vascular grafts (e.g. PTFE) are inevitable.

Prognosis of Patients with Diabetic Nephropathy on Haemodialysis and Assessing the Adequacy of Haemodialysis

In the past, the prognosis for diabetic nephropathy was discouraging, with 77% of patients dying within 10 years after the onset of persistent proteinuria. Despite some improvement, diabetics do fare worse on renal replacement therapy than non-diabetics, athough patient survival has continously increased in recent years. In a matched control study, actuarial 5 year survival in diabetics is worse than in matched non-diabetic dialysis patients

and this difference has not diminished in recent years (31). According to the EDTA report of 1991, the actuarial 5 year survival between 1985 and 1990 was 38% in 45–54 year old type 1 diabetics vs. 70% in age-matched non-diabetic patients. Similar figures were noted for type 2 diabetics in the age group 55–64 years with an actuarial 5 year survival of 31% vs. 58% in age matched non-diabetic dialysis patients (29).

This is in agreement with the data of the Collaborative Transplant Study (courtesy of Professor Opelz), where overall patient and graft survival is worse in diabetic renal transplant recipients than in non-diabetics. This, however, contrasts the experience of some major centres with particular experience in diabetic patients who currently find no difference (23).

Cardiovascular disease and serious infections are the major causes of death in haemodialysed and transplanted diabetics. Despite recent improvement, rehabilitation of haemodialysed diabetics continues to be inferior to that of non-diabetics. Improvement of survival is a matter of reduction of cardiovascular death and infection.

Cardiovascular Death and Adequacy of Dialysis

Cardiac death is strongly predicted by a history of vascular disease (peripheral vascular and/or carotid), myocardial infarction and angina pectoris. Proliferative retinopathy and polyneuropathy were associated with an increased cardiac risk, in the latter possibly due to an imbalance of autonomic cardiac innervation. Hypotensive cardiac episodes during dialysis are also predictive for cardiac death.

This has major implications for hemodialysis procedures with low ultrafiltration rates and prolonged duration of dialysis sessions (24). In practice, ultrafiltration in diabetics should not exceed more than 500–600 ml/h on haemodialysis. This means dialysis session of more than 4 h and in larger patients of more than 5 h hemodialysis three times per week.

The intensity of dialysis is an issue which is currently under discussion. Guidelines have been created to assure adequate dialysis. Although the measurement of the ''dose of dialysis'' is difficult, the DOQI (8) (Dialysis Outcomes Quality Initiative) for adequate dialysis are summarized. According to DOQI, a Kt/V (indicator for adequacy of dialysis, where K is the dialyser clearance rate, t the net duration of dialysis and V the corrected body volume) of above 1.2 (e.g. a 70 kg patient dialysed for 5 h) is adequate. Lower Kt/V, especially below 1, is associated with a higher mortality rate and this is particularly true for the patient with diabetic nephropathy. Besides adequate dialysis the following factors must be considered to improve the survival of diabetics on dialysis.

Special Problems of Diabetic Patients on Haemodialysis

Vascular Access

It is often more difficult to establish vascular access in a diabetic patient because of poor arterial inflow (atherosclerosis, media calcification of the artery) and venous run-off (hypoplasia or thrombosed veins) in chronically ill patients, with numerous stays in hospital. Arterio-venous anastomosis should be placed in the upper forearm to maintain adequate shunt blood flow. It is therefore advisable to establish vascular access early, when creatinine clearance is above 20–25 ml/min. In malnourished, older individuals, this level of GFR impairment can be reached even at a serum-creatinine of 2 mg/dl.

One should patiently wait for maturing of the fistula: early puncture tends to be associated with haematoma formation, scarring, stenosis and thrombosis and should be avoided, even if dialysis has to be performed by a central venous catheter. Some authors have reported poor functioning of the vascular access in diabetics, with only 64% of fistula functioning after 1 year compared to 83% in non-diabetics (1).

Metabolic Control on Renal Replacement Therapy

In clinical practice, the need for insulin decreases upon the institution of maintenance haemodialysis. The insulin supplementation remains complex because of the prolongation of the insulin half-life in uraemic patients and the confounding effects of reduced food intake (anorexia of renal failure) and of refeeding (during the haemodialysis session). Most nephrologists prefer to dialyse against glucose (200 mg/dl) to achieve better stabilization of plasma glucose concentrations. One must consider, however, that glucose-containing dialysate does not guarantee normoglycaemia if the prescribed insulin dose is too high. Oral sulphonylurea must be avoided, in fact is strictly forbidden, because of prolonged hypoglycaemia in endstage renal failure (22). If glucose-free dialysate is used, glucose loss (amounting to 80–100 g per dialysis session) may occur. It has been argued that the glucose loss into the dialysate contributes to catabolism but no convincing evidence for this was produced in a control trial (9).

Diabetic control is occasionally rendered difficult by diabetic gastroparesis and the tendency of gastric motility to deteriorate acutely during dialysis sessions.

Adequate control of glycaemia is important: hyperglycaemia causes intense thirst and subsequent increased fluid intake, as well as osmotic water shift and shift of potassium from the intracellular to the extracellular space, with the attending risk of circulatory and pulmonary congestion and

hyperkalaemia. Poorly controlled diabetics are also more susceptible to infection.

Intradialytic and Interdialytic Blood Pressure

Blood pressure in the diabetic is primarily volume-dependent. Consequently, hypertension tends to be more common in dialysed diabetics, who have higher predialytic blood pressures, are more frequently on antihypertensive drugs and more often require multidrug therapy than non-diabetic uraemic patients. The problem is compounded by the fact that intradialytic hypotension is more frequent in diabetics; as a consequence it is often difficult to reach the target dry weight. On the other hand, interdialytic weight by excessive fluid intake is associated with survival on dialysis (20).

Intradialytic hypotension is a multifactorial problem; inadequate circulatory adjustment to volume subtraction (as a consequence of autonomous polyneuropathy) and left ventricular diastolic malfunction (necessitating higher left ventricular filling pressures) have both been implicated in its genesis. Hypotensive episodes have been associated with an increased risk of sudden cardiac death, acute myocardial ischaemia, deterioraton of maculopathy and non-thrombotic mesenteric ischaemia.

Treatment of Lipid Abnormalities in Diabetic Patients with Renal Failure

In diabetic patients, prospective studies have shown that hypercholesterolaemia and hypertriglyceridaemia are strong predictors of coronary heart disease (12). Major dyslipidaemia is seen only in untreated type 1 diabetic patients. A strong correlation exists between HbA_{1c} and plasma cholesterol, triglyceride and high density lipoproteins (34). In type 2 diabetes, dyslipidaemia persists even when glycosaemia is well controlled, presumably due to an underlying genetic defect which predisposes to both diabetes and disturbed lipid metabolism (21).

In a prospective study (37), a relationship between coronary risk and cholesterol concentrations in diabetics admitted for hemodialysis has been established. Non-accumulating fibrates or HMG-Co-reductase inhibitors are indicated for the treatment of dyslipidaemia which does not respond to dietary manipulation. Regular control of creatinine kinase (rhabdomyolysis) is recommended.

Erythropoietin and Iron Substitution in Uraemic Diabetic Patients

Left ventricular hypertrophy (LVH) is more prevalent in diabetics compared to non-diabetics with endstage renal disease, and it is possible that

the beneficial effects of erythropoietin on LVH could be particularly relevant for diabetic patients (18).

To date, the effects of erythropoietin on peripheral vascular disease and microangiopathic complications associated with diabetes have not been systematically assessed. The possible benefits of an improved oxygen supply to target areas require further study. Several case reports indicate that anaemia may develop in diabetic patients prior to preterminal renal failure.

Currently, there is no reason to recommend a different target haemaglobin for diabetic and non-diabetic patients; a haemoglobin of 11–12 g/dl is therefore also appropriate for diabetic patients.

Attention must be paid to the rate at which the haemoglobin is increased in diabetic patients. These patients are particularly at risk of adverse effects related to rapid expansion of the red cell mass and the impact of such expansion on blood volume and viscosity. Furthermore, glycosylation of erythropoietin can modify the erythropoietin clearance rate.

Increases in blood pressure, vascular access clotting and even seizures have been observed more frequently in diabetic dialysis patients when haemoglobin was increased too rapidly. A suggested mode of correction of anaemia in diabetic patients is as follows: a cautious dosage of erythropoietin (initial dose of 2000 IU three times weekly, followed by increments of 2000 IU at monthly intervals) and careful adjustment of heparinization during dialysis. If haemoglobin increases by > 1.3 g/dl over 2 weeks, the erythropoietin dose should be reduced. Once the target haemoglobin has been reached, the weekly dosage should be reduced and haemoglobin monitored at regular intervals.

It is important to establish adequate iron substitution in erythropoietin-treated dialysed diabetic patients. Gastrointestinal blood loss must be excluded, particularly in diabetic patients who receive anticoagulants for vascular complications. Anorexia and malnutrition are further factors for low plasma iron levels. In clinical practice intravenous iron substitution, at the end of the dialysis procedure, is safe and effective. A target ferritin level of above 250 mg/dl is advisable. During infection episodes, however, iron substitution should temporarily be stopped.

Malnutrition in Dialysis-dependent Diabetics

It is important that diabetic patients on dialysis maintain adequate energy (35–40 kcal/kg/day). In addition, protein intake should not be below 1.3 g/kg day because of the known higher protein requirements of dialysis patients. Anorexia and prolonged habituation to dietary restrictions are important reasons for malnutrition of the diabetic patient on dialysis. Malnutrition is a common concern in dialysed diabetic patients.

Infections in Uraemic Diabetic Patients

Bacterial infections are common complications in uraemic diabetic patients (19), in whom polymorphnuclear leukocyte function is depressed, particularly when acidosis is present. Leukocyte adherence, chemotaxis and phagocytosis may be affected. Antioxidant systems involved in bactericidal activity may also be impaired. Cutaneous responses to antigen challenges and measures of T cell function may be depressed. There is evidence that improving glycaemic control in diabetic patients improves immune function, e.g. the efficiency of intracellular killing of microorganisms may improve with better glycaemic control. Blood glucose levels should be closely controlled in diabetic patients with infections.

Uraemic diabetics have several particular sites where infections can occur: arteriovenous fistula and central venous catheters, CAPD catheter, urinary tract, sinus and diabetic foot ulcer. Infections of the dialysis access, either haemodialysis or CAPD, are mostly caused by *Staphylococcus* and need specific therapy. Diabetic patients with prolonged hospital stay should be screened for methicillin-resistant *Staphylococcus*, an emerging problem.

Urinary tract infections are common in diabetic dialysis patients due to diminishing residual diuresis, imcomplete bladder emptying from autonomic neuropathy and following diagnostic or therapeutical instrumentation of the urethra or bladder.

Chronic sinus infections may be detected by X-ray and should be treated by antibiotics and if necessary drainage. Diabetic foot infection is detected by routine foot inspection and should be avoided by appropriate prophylaxis.

Diabetic Retinopathy in Uraemic Diabetic Patients

Diabetic retinopathy is the leading cause of blindness in patients 25–74 years of age, and current estimates suggest it is responsible for 12 000–24 000 new cases of blindness in the USA each year (7). It is subdivided into nonproliferative retinopathy and proliferative retinopathy. Proliferative retinopathy is associated with haemorrhagic activity of retinal neovascularization. The presence of and severity of neovascularization are the factors with the strongest association with visual loss. Anticoagulation (heparin) during the haemodialysis procedure and the application of platelet aggregation inhibitors (e.g. aspirin) can cause severe retinal bleeding and blindness.

Diabetic uraemic patients need regular ophthalmologic controls at a frequency of 3–6 months.

In the past, visual prognosis in the dialysed diabetic was extremely poor. Diabetic patients beginning dialysis between 1966 and 1971 had a 29% risk

of becoming blind and vision was lost in 41% of eyes at risk. These figures have improved in parallel with improvement of dialysis procedures and better control of blood pressure: patients admitted between 1976 and 1979 had only a 1% risk of amaurosis. This documents the overriding roles of blood pressure control and prophylactic laser treatment.

Bone Disease and the Importance of Serum-phosphate Control

Bone formation and turnover are generally diminished and osteopenia is common in patients with type 1 diabetes without nephropathy, but not in the type 2 diabetic patients (38). In the uraemic diabetic, serum parathyroid hormone levels tend to be low. Relative hyposecretion of parathyroid hormone may therefore account for the common observation of low trabecular volume and low cellular activity on the bone trabecules. This low bone turnover may explain the fact that diabetics are more likely to accumulate aluminium in their bones (2).

The diabetic uraemic should be treated with calcium-containing phosphate binders, which are ingested with every meal (500–1000 mg according to the amount of food). Aluminium-containing phosphate binders should be avoided because of possible aluminium intoxication. Vitamin D supplementation (e.g. 10 000 U 25-(OH) vitamin D_3 once weekly) is recommended.

Serum-phosphate control is important not only to prevent renal bone disease, but to prevent stiffness of the large arterial vessels. Increased stiffness of the aorta (4) is associated with reduced survival in endstage renal disease and vascular stiffness is correlated with the increase in serum-phosphate.

Continuous Ambulatory Peritoneal Dialysis (CAPD) in Diabetic Patients

CAPD has both medical and social benefits and most patients with diabetes are eligible for it. This technique enables patients to stay at home, where they can rapidly be taught the home dialysis regime and allows flexibility in treatment. The medical benefits of CAPD include slow and sustained ultrafiltration and a relative absence of rapid fluid and electrolyte changes and preservation of residual renal function. The choice of the dialysis therapy depends on such factors as nephrologist's bias, existence of extrarenal disease (visual capacity which enables the patient to perform the bag exchanges properly), treatment availability and other medical and social factors.

In CAPD the major osmotic agent for water removal is glucose. It is therefore of note to consider an extra amount of glucose (approximately

600–800 kcal) per treatment-day in the uraemic diabetic. Insulin dosage has to be adjusted. Some authors propose that insulin be administered via the CAPD fluid. This route of application is not without difficulties, because adsorption of insulin into the CAPD bag and possible infection by instillation of insulin into the bag are possible.

Assessing the Quality of Dialysis in CAPD

Adequacy of dialysis is an important issue in CAPD as well as in haemodialysis. In the past years several studies were undertaken to correlate the dose of dialysis (e.g. adequacy of dialysis) and survival in the CAPD patient population. According to the DOQI guidelines, which are based on numerous studies (6), a weekly $k\ t/V$ of 2 or even more (weekly peritoneal creatinine clearance of more than 70 l) is nowadays considered an adequate dose of dialysis. In most patients this is only achievable when a certain amount of peritoneal fluid (more than 50 l/week) and a considerable residual renal function are combined. This has two implications: (a) CAPD in diabetic patients should be started early (as in haemodialysis, at a creatinine clearance of approximately 20 ml/min); and (b) residual renal function has to be monitored vigorously. If there is a substantial fall in residual renal function (below 5 ml/min), in many cases adequate peritoneal dialysis is impossible. Inadequate peritoneal dialysis has a high mortality rate (6) and patients must be taken off peritoneal dialysis and either transfered to haemodialysis or, if possible, transplanted.

RENAL AND PANCREAS TRANSPLANTATION

In the meantime, studies have shown that besides the improvement in quality of life, there is also better survival in uraemic patients post-transplantation (5,26,33). Despite these encouraging data, acturarial patient survival post-transplant is less favourable in diabetes compared to other primary renal diseases. It is indispensable to examine a diabetic uraemic thoroughly for vascular complications and infectious foci before the patient qualifies for the transplant waiting list.

Pretransplant Evalulation of the Uraemic Diabetic Patient

In the pretransplant evaluation of a diabetic patient, several aspects should be considered. Most important is the vascular tree, the Achilles' heel of every successful transplantation procedure.

Careful evaluation of pelvic and lower extremity arteries must be performed. Non-invasive methods (e.g. Doppler and Duplex techniques) as well as invasive procedures (e.g. angiography) may be applied. If the patient has a considerable residual renal function, CO_2 angiography or magnetic resonance angiography are the procedures of choice. Plain radiography of the pelvis documents the magnitude of media calcification in the uraemic diabetic (4).

Coronary artery disease is an important issue in diabetic patients on dialysis. Non-invasive testing is often not substantial (16) and coronary angiography is still the most helpful procedure to rule out severe coronary stenosis in this patient population. Additional information on cardiac valves are no less important, since aortic stenosis is a common problem in dialysis patients.

Before transplantation, peripheral vascular surgery is mandatory, particularly on the ipsilateral side of the graft, to avoid circulatory complications of the lower extremities post-transplant.

Cardiac surgery (bypass or valve replacement) is nowadays a common procedure in non-diabetic and diabetic patients with an in-hospital mortality rate of 5.4% (17), which is roughly comparable to those of non-uraemic cardiac patients.

Chronic infections are common in diabetic patients and several sites of infection in diabetic patients have to be considered (see above). Infection of the native kidneys may be due to renal calculi or papillary necrosis and secondary obstruction, and infection of the bladder is often due to multiresistant bacteria.

Cholecystolithiasis is common in diabetics and recurrent cholecystitis should be an indication for cholecystectomy. Uraemic patients often suffer from chronic constipation and colonic diverticula are common. In female diabetic patients, gynaecological infections or tumours must be excluded by bacteriological work-up and cytology.

RESULTS

Since the introduction of cyclosporin, graft survival has improved continously for diabetic and non-diabetic transplant recipients. Thorough pretransplant work-up of the diabetic patient, as mentioned above, has led to an almost identical 1 year patient survival post-transplant in specialized centres (23).

The effect of glucose control is important for patient and transplant long-term function. Mesangial expansion has been shown in transplanted kidneys in type 1 diabetics but several studies have documented beneficial effects of combined pancreas transplantation on the renal allograft (3). The

transplantation of a pancreas with normalization of glucose metabolism makes lesions of diabetic nephropathy in native kidneys reversible (10,11). Glucose control for the prevention of extrarenal diabetic lesions (vascular, neuropathic) by successful pancreas transplantation is documented by several studies (27, 35).

In the future, new techniques such as insulin gene manipulation in autologous cells (e.g. myoblasts, hepatocytes or fibroblasts) or islet cell transplantation will be the procedure of choice. Such grafts are currently technically feasible in patients who are recipients of other, usually renal, grafts. Another possibility is to graft encapsulated xeno-islets, protected against immune attack by encapsulation in a biocompatible membrane.

REFERENCES

1. Martin LC, Lewin NW, Smith DW. Hemodialysis access site morbidity. *Proc Clin Dialysis Transpl Forum* **10**: 277–82.
2. Andres DL, Kopp JB, Maloney NA, Coburn JW, Sherrard DJ. Early deposition of aluminium in bone in diabetic patients on hemodialysis. *New Engl J Med* 1987; **316**: 292–6.
3. Bilous RW, Mauer SM, Sutherland DER et al. The effects of pancreas transplantation on the glomerular structure of renal allografts in patients with insulin-dependent diabetes. *N Engl J Med* 1989; **321**: 80–85.
4. Blacher J, Guerin AP, Pannier B et al. Impact of aortic stiffness on survival in endstage renal disease. *Circulation* 1999; **99**: 2434–9.
5. Bonal J, Cleries M, Vela E. Transplantation versus hemodialysis in elderly patients. Renal Registry Committee. *Nephrol Dialysis Transpl* 1997; **12**: 261.
6. Churchill DN. Implications of the Canada–USA (CANUSA) study of the adequacy of dialysis on peritoneal dialysis schedule. *Nephrol Dialysis Transpl* 1998; **13** (6): 158–63.
7. D'Amico DJ. Diseases of the retina. *N Engl J Med* **331**: 95–110.
8. *DOQI: Clinical Practice Guidelines: Executive Summaries*. National Kidney Foundation; 17.
9. Farrel PC, Hone PW. Dialysis induced catabolism. *Am J Clinic Nutr* 1980; **33**: 1417–22.
10. Fioretto P, Mauer SM, Bilous RW et al. Effects of pancreas transplantation on glomerular structure in insulin-dependent diabetic patients with their own kidneys. *Lancet* 1993; **342**: 1193–6.
11. Fioretto P, Steffes MW, Sutherland DE, Goetz FC, Mauer SM. Reversal of lesions of diabetic nephropathy after pancreas transplantation. *N Engl J Med* 1998; **339**: 69–75.
12. Fontbonne A. Hypertriglyceridaemia as a risk factor of coronary artery disease mortality in subjects with impaired glucose tolerance. *Diabetologia* 1989; **32**: 300–304.
13. Geberth S, Lippert J, Ritz E. The apparent epidemic increase in the incidence of renal failure from diabetic nephropathy. *Nephron* 1993; **65**: 160.
14. Hasslacher C, Borholte G, Ritz E, Wahl P. Impact of hypertension on prognosis in IDDM. *Diabet Metab* 1989; **15**: 338–42.

15. Hakim RM, Lazarus JM. Initiation of dialysis. *J Am Soc Nephrol* 1995; **6**: 1319–28.
16. Herzog CA, Marwick TH, Pheley AM et al. Dobutamine stress echocardiography for the detection of significant coronary artery disease in renal transplant candidates. *Am J Kidney Dis* 1999; **33**: 1080–90.
17. Herzog CA, Ma JZ, Collins AJ. Long-term outcome of dialysis patients in the United States with coronary revascularization procedures. *Kidney Int* 1999; **56**: 324–32.
18. Isamail N. Use of erythropoietin, active vitamin D3 metabolites and alkali agents in predialysis patients. *Semin Nephrol* 1997; **17**: 270–84.
19. Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. *Engl J Med* 1999; **341**: 1906–11.
20. Kimmel PL, Varela MP, Peterson RA et al. Interdialytic weight gain and survival in hemodialysis patients: effects of duration of ESRD and diabetes mellitus. *Kidney Int* 2000; **57**: 1141–51.
21. Kostner GM, Karadi I. Lipoprotein alterations in diabetes mellitus. *Diabetologia* 1988; **36**: 1113–17.
22. Krepinsky J, Ingram AJ, Clase CM. Prolonged sulfonylurea-induced hypoglycaemia in diabetic patients with endstage renal disease. *Am J Kidney Dis* (2000); **35**: 500–505.
23. Larrson O, Attman PO, Blohme I, Nyberg G, Brynger H. Morbidity and mortality in diabetic and non-diabetic patients of living related kidney donors. *Nephrol Dialysis Transpl* 1987; **2**: 109–16.
24. Laurent G, Calemard E, Charra B. Haemodialysis for French diabetic patients. *Nephrol Dialysis Transpl* 1999; **14**: 2044–5.
25. Lippert J, Ritz E, Schwarzbeck A, Schneider P. The rising tide of endstage renal failure from diabetic nephropathy type II—an epidemiological analysis. *Nephrol Dialysis Transpl* 1995; **10**: 462–5.
26. Lufft V, Kliem V, Tusch G, Dannenberg B, Brunkhorst R. Renal transplantation in older patients: is graft survival affected by age? A case control study. *Transplantation* 2000; **15**: 790–94.
27. Navarro X, Kennedy WR, Loewenson RB, Sutherland DER. Influence of pancreas transplantation on cardiorespiratory reflexes, nerve conduction and mortality in diabetes mellitus. *Diabetes* 1990; **39**: 802–6.
28. Packer M, Lee WH, Medina N, Yushak M, Kessler PD. Functional renal insufficiency during long-term therapy with captopril and enalapril in severe chronic heart failure. *Ann Intern Med* 1987; **106**: 346–54.
29. Raine AE. Epidemiology, development and treatment of endstage renal failure in type 2 (non-insulin-dependent) diabetic patients in Europe. *Diabetologia* 1993; **36**: 1099–104.
30. Ritz E, Koch M, Fliser D, Schwenger V. How can we improve prognosis in diabetic patients with end-stage renal disease? *Diabetes Care* **22** (Suppl 2) B80–B83.
31. Ritz E, Strumpf C, Katz F, Wing AJ, Quellhorst E. Hypertension and cardiovascular risk factors in hemodialysed diabetic patients. *Hypertension* 1985; **7**: 118–25.
32. Sawicki PT, Kaiser S, Heinemann L, Frenzel H, Berger M. Prevalence of renal artery stenosis in diabetes mellitus-an autopsy study. *J Intern Med* 1991; **229**: 489–92.
33. Schnuelle P, Lorenz D, Trede M, van der Woude FJ. Impact of renal cadaveric transplantation on survival in endstage renal failure: evidence for reduced

mortality risk compared with hemodialysis during long-term follow-up. *J Am Soc Nephrol* 1998; **9**: 2135–41.
34. Semenkovic CF, Ostlund RE, Schechtman KB. Plasma lipids in patients with type I diabetes mellitus: influence of race, gender and plasma glucose control. *Arch Intern Med* 1989; **149**: 51–6.
35. Smets YF, Westendorp RG, van der Pijl JW et al. Effect of simultaneous pancreas-kidney transplantation on mortality of patients with type-1 diabetes and end-stage renal failure. *Lancet* 1999; **353**: 1915–19.
36. Spinosa DJ, Angle JF, Hagspiel KD, et al. Lower extremity arteriography with use of iodinated contrast material or gadodiamide to supplement CO_2 angiography in patients with renal insufficiency. *J Vasc Interv Radiol* 2000; **11**: 35–43.
37. Tschöpe W, Koch M, Thomas B, Ritz E. Serum lipids predict cardiac death in diabetic patients on maintenance hemodialysis. *Nephron* 1993; **64**: 354–8.
38. Van Daele PLA, Stolk RP, Burger H. Bone density in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1995; **122**: 409–14.