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The diabetic patient with renal failure

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There is little doubt that diabetic nephropathy has recently become the single greatest challenge in clinical nephrology. This is due not only to the epidemiology with the ever increasing incidence of diabetic patients with renal failure, but also due to the heavy comorbidity of these patients and the persistingly poor results of renal replacement therapy.

EPIDEMIOLOGY

It has been stated that the Americans live under the illusion that they are one decade ahead of Europe, whilst as a matter of fact they are 6 hours behind. This statement may occasionally be right, it is certainly wrong when it comes to diabetic nephropathy. One decade ago, 29 diabetic patients per million per year (pmp) were admitted for renal replacement therapy in the USA and similar figures were then only encountered in Japan, whilst Europe (including Spain) was still in the state of diabetological innocence (table I). The incidence is today 107 pmp in the US, about 60 pmp in the far East, but also quite sizeable in the diverse European countries. There are notable differences, however. Table II compares Lombardia, the region around Milano, and the lower Necker region around Heidelberg in South-West-Germany. We admit similar numbers of uremic patients per million per year, but there is a striking difference in the incidence of uremic patients with diabetes as a comorbid condition. A similar number of patients with type 2 diabetes is admitted, so that the difference is completely accounted for by a dramatically higher incidence of type 2 diabetes in Germany.

Geneally in Mediterranean countries the prevalence of diabetes and of diabetic nephropathy has been substantially lower. Whilst the figures for Italy and France are currently still relatively low[1], some dramatic changes have recently occurred in Spain[2-4]. The Catalunya registry[2] reported on a continuous increase of the incidence of uremic patients with diabetes type 2 as a comorbid condition in the past decade[2] and similar observations have been made in Badayoz[3] and more recently in Madrid[4]. Pérez García noted an increase of the admission rate of uremic patients with diabetes from 16 to 57 ppm between 1983 and 1998. Diabetic patients represent more than 27% of the total incident dialysis population and 78% of all diabetic patients have type 2 diabetes.

Tabla I. Rising incidence of patients with diabetes and end-stage renal failure

	1984	1994
USA	29.2	107.0
Japan	23.4	66.0
Australia	4.0	14.0
Norway	6.5	15.4 [11.1]
Southwest Germany	–	52.0 [47.0]
Lombardia	6.5 [2.9]	13.0 [7.0]

Data as patients per million population per year; in brackets: patients with type 2 diabetes. After ref. 1.

The observations in Catalunya[2] are given in figure 1.

Why is that the incidence of diabetic patients with renal failure has increased in such a dramatic fashion over the interest world? It may be of interest that Maimonides, a Jewish physician who emigrated from Cordoba to Cairo in the 13th century wrote that he had found a novel disease in Cairo that he had never encountered in Cordoba, i.e. wasting of elderly patients with polydipsia and polyuria – undoubtedly diabetes. This indicates that there was, then at least, less predisposition to diabetes in Spain compared to Egypt, perhaps in part related to genetic factors. Why do we nevertheless see the above increase? One important factor is certainly Westernisation of life style, i.e. physical inactivity and ingestion of a high energy diet with high fat content. This has led to a dramatic increase in the prevalence of type 2 diabetes in all Western countries, including Spain. Another reason is the aging of Wes-

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Tabla II. Admission of diabetic patients for renal replacement therapy - comparison of different regions: Lombardia (Italy), Lower Neckar (Germany), the Netherlands, Denmark, and Nothern Alsace (France)

	Incidence ESRD overal	Incidence ESRD plus diabetes	Type 2 diabetes	Incidence (diabetes) (pmp/year)	
	(pmp/year)	(pmp/year)	% of diabetes	Type 1	Type 2
Lombardia, 1996	123.0	16.2	63	6.1	10.1
Lower Neckar, 1993	125.0	52.0	90	5.0	47.0
The Netherlands, 1996	85.4	13.3	47*	7.1*	6.2*
Denmark, 1997	100.7	20.2	40	12.2	8.0
Nothern Alsace, 1996	143.0	46.0	95	2.4	43.6

*From 1994-1996. pmp: per million population; ESRD: endstage renal disease. After ref. 5.

tern societies – of importance because the risk of diabetes is particularly high at advanced age. Currently approximately 6% of the adult German population and 20% of the German population above age 70, suffer from type 2 diabetes.

A perhaps more important reason is that cardiac death and renal death are competing causes of mortality in the diabetic patient. Recently there has been a substantial reduction of cardiovascular mortality in nephropathic diabetic patients[5]. From 1975 to 1985 the 5 year mortality decreased from 65% to 25% for type 2 diabetic patients with proteinuria in the University Hospital of Heidelberg. Consequently, today diabetic patients frequently live sufficiently long, i.e. 15-20 years, with their diabetes to experience the onset of nephropathy and endstage renal failure.

In this perspective diabetic nephropathy is a disease of medical progress, similar to what Joslin noted in the 4th decade of this century, 10 years after Banting and Best had introduced insulin. He noted that then patients no longer died from infection and ketosis, but rather succumbed to a novel complication, i.e. atherosclerosis.

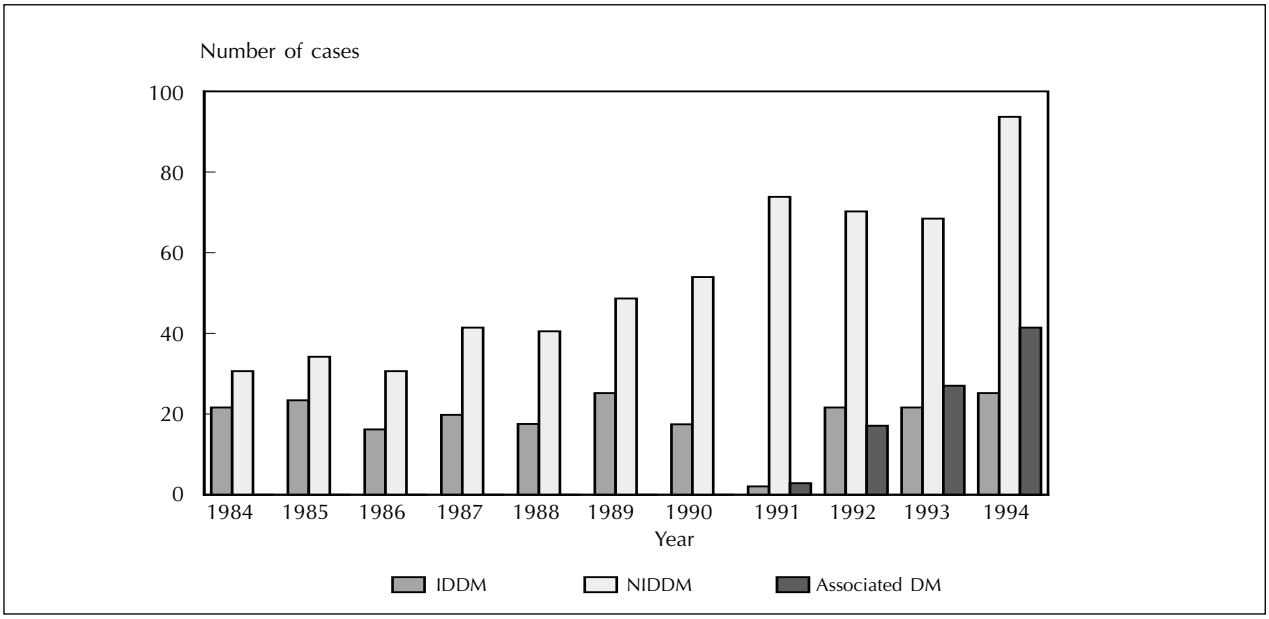

Fig. 1.—Evolution of number of diabetic patients on renal replacement therapy. Period 1984-1994. After ref. 2.

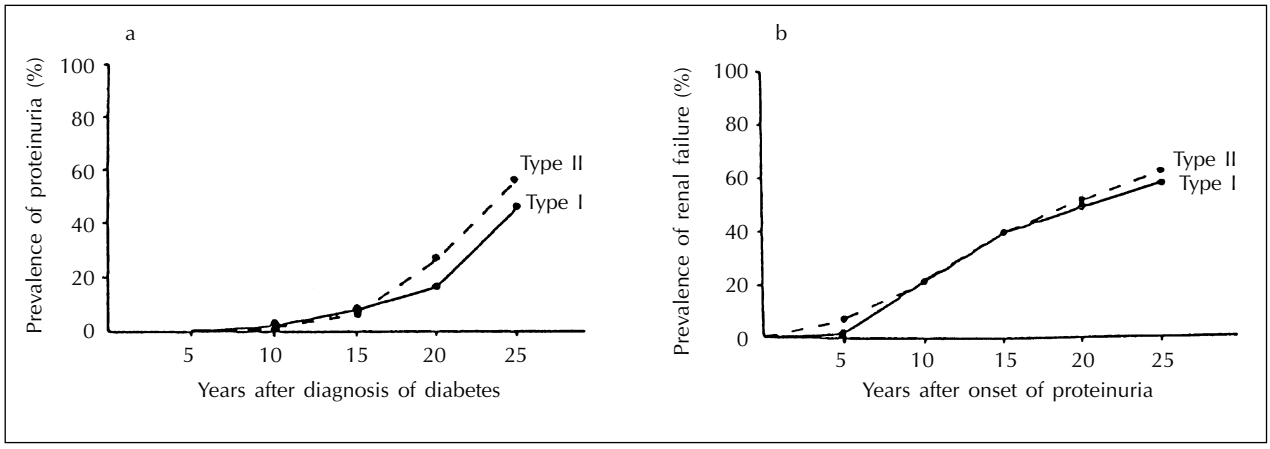

Fig. 2.—Risk of proteinuria and renal failure in patients with type 1 and type 2 diabetes mellitus. After ref. 7.

RENAL RISK IN TYPE 1 AND TYPE 2 DIABETES

Against the background of the rising frequency of nephropathy in type 2 diabetes, it is amusing that 1 1/2 decade ago authors reported in a prestigious journal[6] that the rate of loss of glomerular filtration in type 2 diabetic patients was no more than expected with advancing age. Only 1 out of 510 patients developed renal failure. As shown in figure 2, when we compared the cumulative frequency of patients with type 1 and type 2 diabetes who developed nephropathy, i.e. proteinuria, the risk was absolutely identical[7]. Similarly the risk of renal failure i.e. elevated serum creatinine after onset of proteinuria, was again identical in the two types of diabetes. It is nevertheless true that the medical community is not yet sufficiently aware of the renal dangers of type 2 diabets and it will be an important task to convince physicians, particularly general pracititioners, that prevention of diabetic nephropathy and endstage renal failure is an absolute necessity. Why is it so important to prevent renal failure?

Once the patients are on dialysis, their survival is abysmal. In a prospective study on 400 diabetic patients in Germany we found that 5 year survival was 5% in patients with type 2 diabetes – similar to the life expectancy of the patient with metastatic gastrointestinal carcinoma[8]. Matters are better in Spain. According to Rodríguez[2] diabetics do certainly worse than non-diabetic patients, but 5 years survival is 35%, i.e. higher than in Germany. The high mortality is mainly explained by coronary heart disease. In a prospective study, Koch[9] performed coronary angiography in all consecutive patients and found that significant coronary lesions were present at the time of admission for dialysis in no less than 40% of patients. These lesions have obviously been acquired prior to endstage renal failure. This observation points to the importance of cardiovascular risk factor management in the preterminal phase.

GENETIC PREDISPOSITION

Why is it that despite the fact that all patients are hyperglycemic, only some patients develop nephropathy? Keller et al.[10] evaluated the prevalence of microalbuminuria in patients with recently diagnosed type 2 diabetes. Such early microalbuminuria identifies a high risk population. The single best predictor of microalbuminuria is a history of cardiovascular events in first degree relatives. There was strong interaction between the genetic risk and glycemic control. As shown in table III, if patients had no fa-

Tabla III. Interaction between genetic risk (family history of cardiovascular accidents in first-degree relatives) and glycaemic control and prevalence of microalbuminuria

Group	Prevalence of microalbuminuria
No family history and HbA1C < 8% (n = 12)	0/12 (0%)
Either family history or HbA1C > 8% (n = 52)	1/52 (2%)
Family history and HbA1C > 8% (n = 21)	10/21 (48%)*

Difference between risk groups p < 0,0001. After ref. 10.

Tabla IV. Progression promoters

- Blood pressure.
- Albuminuria.
- Glycaemic control.
- Smoking.
- Dietary intake of protein?
- Hyperlipdaemia.

After ref. 14.

mily history and adequate glycemic control, their risk was zero. If there was either a family history or poor glycemic control, it was still negligible. It was only when patients had both a positive family history and poor glycemic control that the risk was 50%. We do not know which genes are involved in conferring this risk, but genetic predisposition to hypertension apparently plays et al a role, since Strojek y et al.[11] noted higher blood pressures in offspring of parents with type 2 diabetes and nephropathy compared to offspring of patients with type 2 diabetes without nephropathy[11]. Recently, Siffert et al. identified a polymorphism in a G protein, which caused enhanced G protein activation and enhanced intracellular signalling when G protein-associated receptors were stimulated by their agonist[12]. This high activity T-allele was associated with late onset of hypertension (and as we know today also with obesity). Recently we noted that the frequency of the T-allele is significantly higher in patients with type 2 diabetes on dialysis compared to the control population, i.e. 36% *vs* 29%[13]. This polymorphism explains certainly only a moderate proportion of the risk of diabetic nephropathy, but this methodological approach in general is certainly promising.

PREVENTION OF PROGRESSION OF DIABETIC NEPHROPATHY

Table IV summarises factors promoting progression of diabetic nephropathy.

There is some influence of dietary protein intake, glycemic control and smoking, but undoubtedly the major factors are blood pressure and proteinuria per se.

Dietary protein intake: The Eurodiab study showed that individuals who had developed microalbuminuria had a higher dietary protein intake[15], so that an adverse effect of dietary protein is likely. It makes therefore sense to recommend a diet with approximately 0.8 g protein/kg/day in early diabetic nephropathy. This is also the amount recommended for the general population.

We are against rigorous protein restriction, however, in the patient with advanced diabetic nephropathy, primarily because of the high risk of catabolism. Malnutrition is one central problem in the diabetic patient and the rate of progression is very high anyway. An evaluation of benefit and risk argues against dietary restriction.

Glycemic control: Obviously there is no diabetic nephropathy without hyperglycemia, but does correction of hyperglycemia lower the risk of progression of clinically manifest diabetic nephropathy? In the past is has been stated that once patients had overt proteinuria, glycemic control did no longer improve renal prognosis[16]. When insulin pump were made available and near normoglycemia became a reality, it was anticipated that the decrease in GFR could be halted by normoglycemia. There was bitter disappointment that, at least for a period of 18 months, GFR continued to decrease despite normoglycemia, so that investigators assumed that a «point of no return» had been reached beyond which established nephropathy progressed independent of glycemia. This concept led to therapeutic nihilism. Very convincing data (H. H. Parving, personal communication) show that the rate of decrease of GFR is mainly dependent on blood pressure. Nevertheless at any given level of blood pressure patients with HbA1c above 9% had more rapid loss of GFR than those with better glycemic control. A strong rationale for aiming at good glycemic control is also provided by a recent study from Taiwan[17] according to which cumulative survival on maintenance hemodialysis is strongly predicted by the quality of glycemic control at entry into dialysis.

Smoking: Smoking increases the risk to develop type 2 diabetes, increases the risk of the diabetic pa-

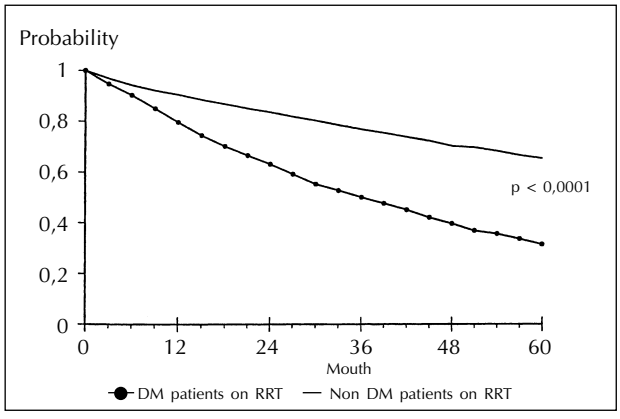

Fig. 3.—Survival of patients on renal replacement therapy (RRT). Cases from 1984-1994. After ref. 2.

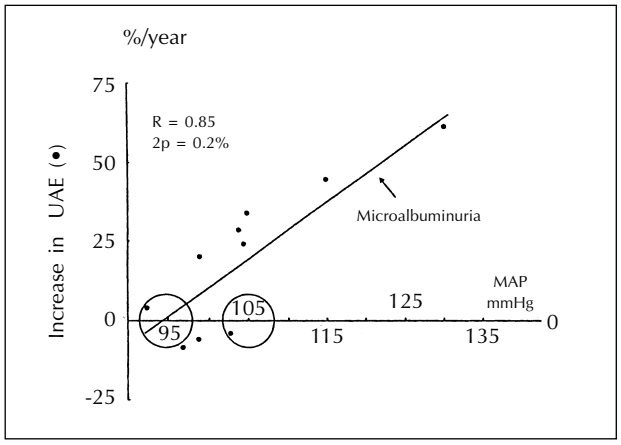

Fig. 4.—Relation between mean arterial pressure (MAP) and annual percentage increase of urinary albumin excretion (UAE) in patients with type 1 diabetes. After ref. 28.

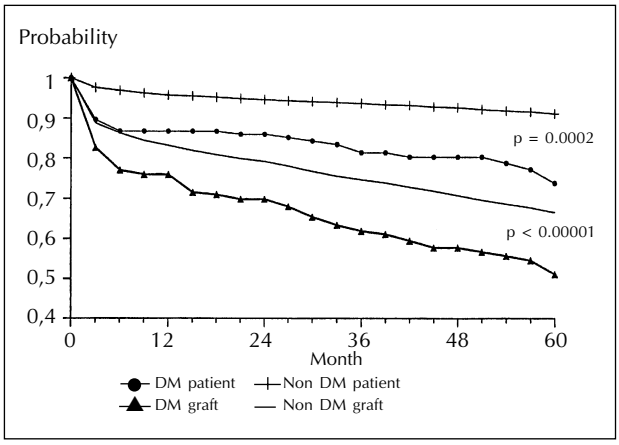

Fig. 5.—Patient and graft survival of patients on renal replacement therapy. Transplants 1984-1994. After ref. 2.

tient to develop microalbuminuria, accelerates transition from microalbuminuria and finally doubles the rate of loss of GFR in diabetic patients with advanced diabetic nephropathy[18]. Conversely, cessation of smoking reduced the rate of loss of GFR in patients with type 1 diabetes. In a recent study, the rate of progression to endstage renal failure was significantly increased in patients with non-diabetic renal disease who smoked, but interestingly an increased risk could no longer be demonstrated if renal patients who smoked were on ACE inhibitors[19].

Proteinuria: In the study of Yokohama[20], the rate of protein excretion was the most potent predictor of loss of GFR in diabetic patients with advanced nephropathy. This is not surprising in view of the recent concept that proteins are nephrotoxic[21]. Proteins in tubular urine activate tubular epithelial cells by inducing NF-kappa-B-dependent signalling pathways this causing expression of endothelin, cytokines and other molecules which ultimately promote fibrosis. This may explain why antihypertensive agents with superior effects on proteinuria such as ACE inhibitors, have particular therapeutic potential in diabetic nephropathy[22,23].

Blood pressure: An abnormal circadian blood pressure profile is found in almost 80% of patients at the time type 2 diabetes is diagnosed[10]. As a result, practically all type 2 diabetic patients require antihypertensive treatment from the very beginning, if one adheres to current recommendations about target blood pressures[24,25]. One particular problem is high risk conferred by abnormal nocturnal blood pressure[26,27]. The recommendation of a target blood pressure of 125/75 mmHg[25], as advocated by the National Kidney Foundation, appears rigorous, but is well founded in view of the observation of Mogensen[28] which is depicted in figure 4. When annual percent increase in urinary albumin excretion rate (on the ordinate) is evaluated as a function of blood pressure in the diabetes outpatient clinic (abscissa) UAE increases by 25% at a MAP of 107 mmHg, i.e. 140/90 mmHg. If one extrapolates this relationship to the point where an increase in albuminuria is no longer demonstrable, a value of 90-95 mmHg MAP is found. This is in good agreement with the results of the Modification of Diet in Renal Disease (MDRD) Study, where it was found that considerable further lowe-

Tabla V. Diabetic patients admitted to German nephrological centers – data at the time of admission

Parameter	Median and range or number of patients
Age (years)	67 (31-95)
Sex	90 men, 83 women
Type of diabetes	16 type 1, 157 type 2
Duration of diabetes (years)	type 1: 19 (10-26) type 2: 11 (0-44)
HbA1C (%)	7.9 (4.9-15.7)
Cholesterol /mg/dl)	
Total-cholesterol	244 (88-521)
HDL-cholesterol	34 (13-111)
LDL-cholesterol	170 (67-307)
Triglycerides (mg/dl)	228 (49-400)
Lipid lowering therapy	12/159

After ref. 37.

Tabla VI. Common problems in patients with type 2 diabetes and advanced diabetic nephropathy

Microvascular complications
Retinopathia (non-proliferative, proliferative).
Polyneuropathy (including autonomic polyneuropathy).
Cystopathy (detrusor paresis).
Gastroparesis.
Diarrhea/constipation.
Impotence.
Diabetic foot (neuropathic).
Loss of frequency-dispersion (heart).
Macrovascular complications
Coronary heart disease.
Ischemic cerebrovascular disease.
Arterio-occlusive disease (lower extremities, distal arteries).
Ischemic nephropathy (renal artery stenosis, cholesterol embolism).

ring of progression was noted when blood pressure was further decreased by antihypertensive medication in the upper range of blood pressure values within the range of normotension according to WHO criteria[29]. A remarkable illustration of the value of blood pressure lowering was recently provided by the UK Prospective Diabetes Study[30] where standard *vs* intensified blood pressure control was compared. The small difference of 10 mmHg systolic, 154 versus 144 mmHg and the difference of 5 mmHg diastolic pressure, 87 *vs* 82 mmHg, led to a reduction of microvascular endpoints by 37% and strokes by 44%. In an accompanying editorial it was stated that «antihypertensive treatment is more effective than tight glucose control and the beneficial effect comes sooner». According to our experience, blood pressure control is very difficult in such patients and the recommended target of 125/75 mmHg is actually reached only in a minority of our patients, although on average we use 4 different classes of antihypertensive agents when treating diabetic patients[31].

There has been much controversy in the past concerning the superiority of ACE inhibitors in diabetic patients. After the seminal study of Ed Lewis[32] a comparable study in mostly non-diabetic patients[33] showed also a remarkably positive effect of ACE inhibition in an admittedly small subgroup of type 2 diabetic patients. Consequently there can no longer be any doubt about the beneficial renal effect of pharmacological blockade in diabetes patients with renal disease. This consideration justifies the recommendation[24] to use ACE inhibitors in all diabetic patients, irrespective of type, once they have develop microalbuminuria. Whether angiotensin receptor blockers will be similarly beneficial is currently unknown, but two large international trials assessing the effect of Irbesartan and Losartan respectively in type 2 diabetic patients with nephropathy will provide a definitive answer in one or two years time.

THE DIABETIC PATIENT WITH ENDSTAGE RENAL FAILURE

In view of the unsatisfactory outcomes of patients with diabetes, particularly type 2, on renal replacement therapy[8,35], it is deplorable, that when most patients with diabetic nephropathy are seen by the nephrologist they are usually in advanced renal failure. Part of the explanation for late referral is that serum creatinine in these wasted patients with reduced muscle mass grossly underestimates the loss of glomerular filtration. As shown in table V, blood pressure control, use of ACE inhibitors, glycemic control, lipid control as well as ophthalmological and cardiological care, is strikingly deficient as recently documented by our unit[36,37]. This illustrates how important it is to educate our non-nephrological colleagues and the diabetec patients about the renal risks of type 2 diabetes. We have the instruments at hand to improve renal outcomes and to reduce cardiovascular risk.

Once the patient has reached endstage renal failure, there are a number of specific medical problems. Generally nephrologists see diabetic patients in a much more desperate state with more advanced late complications than do diabetologists, because these patients are at an excessive risk of microvascular and macrovascular complications (table VI). In particular, they have a high rate of coronary heart disease, 40% at the time when they are admitted to renal replacement therapy[9]. When they are on dialysis they acquire coronary heart disease at a more rapid rate than non-diabetic patients[38]. Also arterio-occlusive disease is frequent and is usually located more distally than in non-diabetic patients with peripheral arterial disease. Gastroparesis may cause vomiting and it is occasionally impossible to know whether the patient is vomiting because of uremia or because of gastroparesis. We found that several patients who undoubtedly vomited because of gastroparesis stopped vomiting when they were taken on dialysis.

A brief comment on retinopathy. In the late 70ies, 80% of patients were blind one year after start of dialysis. In a prospective study in Germany on 200 patients we found only one case of de novo amaurosis developing on dialysis[39]. In our opinion today blood pressure control in so much better that the risk of retinal hemorrhage is dramatically reduced.

The diabetic foot is a serious problem. Many patients develop a diabetic foot while on dialysis. It is indispensable to distinguish the neuropathic and the ischemic foot. The neuropathic foot is warm and pulses are palpable, there are trophic lesions of the skin and the characteristic ulcers develop preferentially over the metatarsal area. In contrast, the ischemic foot is cold, often (but not always) painful, pulses are absent, the patients are usually smokers and necroses develop in acral location (tip of toe or heel). It is important to make the distinction because otherwise many unnecessary amputations are performed.

Another particular problem is glycemic control. Prior to renal replacement therapy, diabetic patients are prone to hypoglycemia for several reasons. The half life of exogenous or endogenous insulin is prolonged. Sulfonylurea compounds cumulate (with the exception of gliquidone and glimepirid). Furthermore, patients are anorectic. On the other hand, however, circulating inhibitors of the insulin action cumulate in renal failure. These cause insulin resistance and a tendency to hyperglycemia. These inhibitors are removed by dialysis. Because of the above opposing influences, it is very difficult to predict for a given patient the net outcome on glycemic control, so that intensive blood glucose monitoring is necessary.

The diabetic patients who goes on renal replacement therapy has the following therapeutic options: hemodialysis, CAPD or transplantation. In the past CAPD was thought to have unique advantages for the diabetic patient because of more stable continuous volume and blood pressure control and less retinal bleeding because heparin is not required. The latter is no longer an argument given the fact that today the haemodialysis diabetic retinal bleeding has become exceptional with laser treatment and blood pressure control. The argument of better blood pressure control on CAPD is in part correct. Volume correction is indeed better as long as patients have residual diuresis and there are some indications that early on mortality is lower on CAPD.

Nevertheless, once patients loose residual diuresis, they tend to be hypervolemic and more hypertensive[40]. On balance, most studies show that survival of the diabetic patient is similar on CAPD than on hemodialysis. Consequently the decision of which treatment modality to adopt should be made on the basis of individual assessment including consideration of the patient's preference.

Vascular access continues to be a nagging problem of the diabetic patient on maintenance hemodialysis. It has often been stated that fistula survival is poorer in the diabetic compared to the non-diabetic patient. This is not true in our experience and we think that there is a very simple explanation. The main problem in the diabetic patient is not venous run-off but low arterial inflow because of lesions of the distal radial artery. In patients with poor arterial inflow, fistulae in the elbow region using different techniques including the Gracz technique, i.e. using perforating vein for anastomosis, gave similar if not superior, primary fistula survival in diabetic compared to non-diabetic patients[41].

Of course, the ultimate aim is transplantation. Although islet cell transplantation currently gives encouraging results, it is still in the experimental stage. Consequently today the option is kidney *vs* kidney plus pancreas transplantation. It is certain that after transplantation survival in diabetic patients is lower than in non-diabetic patients (fig. 5). This must not be taken as an argument, however, to not transplant the diabetic patient. Port compared uremic patients maintained on hemodialysis while being on the waiting list with patients who had been transplanted. The relative risk to die was higher in the first half year after transplantation, but later on survival was much better with a graft[42]. This was true for renal patients in general, but the relative benefit was greatest for diabetic patients. In other words, although less diabetic than non-diabetic patients survive after transplantation, if they receive a cadaver graft they have better chances to survive than if they are kept on dialysis. There are recent indications that survival is better in type 1 diabetic patients who received a combined pancreas and kidney graft compared to an isolated kidney graft. Impressive results have also been reported in this respect by the Catalunya registry[2]. Should one restrict transplantation to the type 1 diabetic patient or should one offer it also to the type 2 diabetic patient as well?

Survival is very poor in the transplanted type 2 diabetic patient, but this is only half the truth. Hirschl y cols.[44] noted that if vascular disease was excluded in uremic patients with type 2 diabetes, the outcome after transplantation was almost indistinguishable from that of non-diabetic recipients. Unfortunately because of graft shortage these patients are not frequently considered for transplantation, particularly in Germany.

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