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CHOICE OF MODALITY FOR TREATMENT OF DIABETICS WITH END-STAGE RENAL DISEASE. HOW WE TREAT DIABETIC PATIENTS ON MAINTENANCE HEMODIALYSIS – EXPERIENCE FROM THE REPUBLIC OF MACEDONIA

INTRODUCTION

In many countries, diabetic renal disease has become, or will soon become, the single most common cause of end-stage renal disease (ESRD). End stage renal failure (ESRF) in type 2 diabetic patients is increasing worldwide (1,1a).

Diabetic nephropathy (DN) is the most prevalent cause of ESRD in the USA. The proportion of ESRD patients who are diabetic is increasing by more than 1% each year in USA. The rate of admission of uraemic patients with diabetes as a co-morbid condition in the USA was 107 per million population (p. m. p.) per year in 1994 (2) and is currently approximately 120 p. m. p. The corresponding figures in other countries are lower: 66 p. m. p. in Japan and 52 p. m. p. in southwestern Germany (1). The incidence of ESRD in Europe due to diabetes, hypertension and renal vascular disease has nearly doubled over 10 years; in 1998-99, it varied between countries from 10.2 to 39.3 p. m. p. for diabetes, from 5.8 to 21.0 for hypertension, and from 1.0 to 15.5 for renal vascular disease (2a). The figures are lower in Mediterranean countries, as well as in Macedonia, (3) although an increase has recently been reported from Spain (4) and Italy (5). ESRD and ESRF caused by DN was 10%, 5-15% in different haemodialysis Centres for adults in year 2000 in the Republic of Macedonia (3).

The great majority of diabetic patients admitted suffer from type 2 diabetes. The increasing trend may be explained by a number of factors:

(1) the increasing prevalence of type II diabetes in the general population;

(2) improved survival of diabetic patients, particularly diabetic patients with nephropathy, because of better treatment of hypertension and coronary heart disease, so that they live long enough to experience renal failure;

(3) less restriction of admission to renal replacement therapy.

One major problem continues to be late referral.

The poor prognosis of patients with diabetic nephropathy is well known in both in type 1 and type 2 diabetes. The high mortality and morbidity, especially in type 2 diabetic patients with nephropathy, are mainly caused by coronary artery, cerebrovascular and peripheral vascular disease (6).

The survival of type 1 diabetic patients requiring renal replacement therapy has been dramatically improved during the last decade; however, prognosis for type 2 diabetic patients with ESRD continues to be extremely poor (1,1a).

EVALUATION OF THE DIABETIC PATIENT WITH PRETERMINAL RENAL FAILURE

Evaluation of the diabetic patient with preterminal renal failure has the following aims:

(1) to assess the course of renal failure (progression);

(2) to recognize the presence of acute renal failure, or acute or chronic renal failure;

(3) to recognize renal problems other than diabetic nephropathy, for example ischaemic nephropathy, diabetic cystopathy, urinary tract infection;

(4) to monitor the patient for clinical evidence of extrarenal microvascular and macrovascular complications, for example retinopathy or polyneuropathy and coronary heart disease or arterio-occlusive disease.

Some of these coincident kidney diseases are listed below.

Ischaemic renal disease

Renal ischaemia or atherosclerotic renal artery stenosis is much more common in diabetics than previously assumed (7). In this case one

should be cautious regarding ACE-inhibitors or angiotensin receptor blocking antihypertensives. Frequent control of s-creatinin, s-potassium and bodyweight are mandatory. A two-fold increase in s-creatinine should prompt the physician to stop this type of medication.

Urinary tract infection

Urinary tract infection (UTI) has frequently led to renal parenchymatous infection with purulent papillary necrosis and intrarenal abscess formation. UTI may be frequent in diabetics, especially when residual urine is present.

Glomerulonephritis

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

Acute renal failure

Diabetic patients with nephropathy are exceptionally susceptible to acute renal failure (ARF) after the administration of radiocontrast media, the risk being similar with ionic and non-ionic materials. The risk may be reduced by fluid administration and a temporary withdrawal of diuretics. In patients with severely 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.

The points relating to treatment strategies and decision-making in diabetic patients with renal failure present are: evaluation (and treatment) of risk factors for progression, monitoring of progression, evaluation of patient for renal replacement therapy (dialysis, transplantation), informing patient both and care about renal replacement therapy, preparing patients for renal replacement therapy (vascular access, check-up for transplantation) and adjustment of diet and insulin or oral hypoglycaemic agents.

In the table 1 is a check-list for management of diabetic patients with preterminal renal failure.

Table 1. Check-list for management of diabetic patients with preterminal renal failure

• Reversible causes of renal failure present? (contrast media, urinary tract infection, angiotensin converting enzyme inhibitors, congestive heart failure)
• Hypovolemia present?
• Coronary heart disease present (percutaneous transluminal angioplasty or coronary bypass surgery required?
• Cardiomyopathy or congestive heart failure present?
• Congestion due to hypervolemia or heart failure?
• Early vascular access?
• Hypoglycemic episodes present? Adequate nutrient intake?
• Eye (exam ined and treated?)
• Foot (neuropathic? ischaemic? foot ulcers? infection?)
• Residual urine present, urinary tract infection?
• Normotension or antihypertensive treatment achieved?
• Orthostatic blood pressure drop?
• Gastroparesis or diarrhoeal episodes?

Option in uremia therapy

Determination of which treatment option is "best" for a particular diabetic ESRD patient, however, is *an individualized judgment* (table 2) depending on the patient's age, education, geographic location, family and social support systems, and the extent of co-morbid conditions, most importantly, of cardiovascular integrity. Major subjects which must be apprised when devising a long-term plan for ESRD management include anticipated patient compliance and potential to participate in self-treatment. Each ESRD treatment option must be explained in understandable terms covering the probable survival rate, the degree of rehabilitation and the expected stabilisation of extrarenal diabetics complications. Ideally, what has been termed a "life plan" should be constructed for every ESRD patient after consultation between the health care team, the patient, and the members of the patient's social support system.

Table 2. Options in uremia therapy for diabetic ESRD patients

1.	**Passive suicide which is the consequence of declining dialysis or kidney transplantation**
2.	**Haemodialysis**
	– Facility haemodialysis
	– Home haemodialysis
3.	**Peritoneal dialysis**
	– Intermittent peritoneal dialysis (IPD)
	– Continuous ambulatory peritoneal dialysis (CAPD)
	– Continuous cyclic peritoneal dialysis (CCPD)
4.	**Renal transplantation**
	– Cadaver donor kidney
	– Living donor kidney
5.	**Pancreas, plus kidney transplantation**
	– IDDM
	– ? NIDDM
	– islet-cell transplantation (type 1)

While the best rehabilitation of diabetic ESRD patients is achieved in recipients of living related donor renal transplants, this superior outcome may reflect a selection bias in which younger, healthier patients are chosen for a transplant leaving a residual pool of more morbid dialysis patients. Morbidity from blindness and neuropathy (but not coronary artery or peripheral vascular disease) is decreased in diabetic kidney transplant recipients (8). Lacking randomized prospective trials of diabetics treated with dialytic therapy versus a kidney transplant, controlled for age, race, gender, and severity of extrarenal complication, caution must be exercised when assessing one ESRD therapy against another. A reasonable policy can be based on the premise that while the best rehabilitation is effected by renal transplantation, there is no distinctly superior treatment for the uraemic diabetic, and therefore, *assessment and treatment of diabetic with ESRD must be highly individualized* (9).

Timing the start of dialytic therapy

As residual creatinine clearance falls to about 20-30 ml/min, available ESRD options should be discussed and a selection made. In practice, bias by the patient's most trusted physician usually is the major factor determining which renal replacement therapy is chosen.

Diabetic complications which persist and/or progress during ESRD and on dialysis are: retinopathy, glaucoma, cataracts; coronary artery disease, cardiomyopathy; cerebrovascular disease; hypertension; peripheral vascular disease: limb amputation; motor neuropathy, sensory neuropathy; autonomic dysfunction: diarrhoea, constipation, hypotension; myopathy; depression; infections; bladder neuropathy; sexual disorders; impotence; eating disorders; gastroparesis with vomiting and food retention; alteration in the metabolic control and dyslipida-emias; ion imbalance and metabolic acidosis.

For the 80% of uraemic diabetic selecting haemodialysis (HD), the construction of a vascular access is of great importance. Once it is clear that uraemia is a near term probability (less than one year), an arteriovenous access should be constructed.

The first choice in HD access in diabetics is an autologous a-v fistula of the Cimino-Brescia type.

When peritoneal dialysis (PD) is selected advance planning should ensure that a suitable peritoneal catheter is *in situ* 2-4 weeks before starting dialysis.

Option for a kidney or a kidney plus pancreas transplant obviously demands referral to and evaluation by a transplant team. In the case of an intended living related donor transplant, interim dialysis' can be avoided by proper planning, performing the transplant at an early stage of uraemic symptoms. A long wait is usual for a cadaver kidney.

Accordingly, patients should be entered on waiting lists when the creatinin clearance is about 10-15 ml/min.

Haemodialysis in diabetics

Haemodialysis has emerged as the most common treatment for all forms of renal failure including diabetic nephropathy. It is generally accepted that renal replacement therapy should be considered as a creatinine clearance of approximately 9-14 ml/min in non-diabetic uraemia patients (10).

In diabetic patients with ESRD, dialysis is started at creatinine clearance as high as 15-20 ml/min, at serum creatinine levels as low as 3-5 mg/dl.

In any case, HD 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.

Vascular access surgery (usually autologous arteriovenous fistula of the Cimino-Brescia type) some month before the initiation of the dialysis treatment helps to avoid central venous lines and their concomitant complications. Blood drawing for regular serum chemistry is restricted to the dorsal hand veins only.

Prognosis in patients with diabetic nephropathy on haemodialysis and in assessing the adequacy of haemodialysis

In the past, the prognosis for DN was discouraging, with 77% of patients dying within 10 years after the onset of persistent proteinuria. The survival of dialysed diabetics has improved over the past decade. No single factor is credited with reducing the death rate of haemodialysed diabetics, though better control of hypertension, a reduction in intravascular volume overload, better nutrition, and better vascular access surgery have contributed.

Table 3 compares actuarial 5-year survival of non-diabetic and diabetic patients on maintenance haemodialysis in different countries. It is obvious that in countries with a low prevalence of cardiovascular deaths in the general population, e. g. East Asian countries and, to a lesser extent, Mediterranean countries, survival of diabetic patients on RRT is significantly better than that in countries with notoriously high cardiovascular death rates, e. g. USA and Germany.

Table 3. Comparison of actuarial 5 year survival of non-diabetic and diabetic patients on dialysis treatment in different countries (1).

	No diabetes	Diabetes
Australia	60	42/27 [a]
Japan [b]	64/73	50/40
Taiwan	65	37
Hong Kong	70	20
Italy (Lombardy)	61	28
jypain (Catalonia)[c]	65	30
Germany	–	38/5[a]
USA[d]	35	21

Values are expressed as percentage of surviving patients.
[a]   Reported as type 1 / type 2 diabetes.
[b]   Reported as haemodialysis / continuous ambulatory peritoneal dialysis.
[c]   Includes renal transplantation.
[d]   Censored at first transplantation. In table 4 are the causes of death in diabetic patients on HD.

Table 4. Causes of death in diabetic patients 57 months after start of haemodialysis (11).

	Type 1 diabetes (n = 67)	Type 2 diabetes (n = 129)
Myocardial infarction	8	12
Sudden death	7	13
Cardiac other	3	17
Stroke	0	6
Septicaemia	7	11
Interruption of treatment	2	8
Other	2	13
Total	29 (40%)	80 (43%)

Total cardiovascular mortality was 62% in type 1 and 60% in type 2 diabetes.

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 of cardiac death.

Haemodialysis procedures should be with low ultrafiltration rates and prolonged duration of dialysis sessions (12). In practice, ultrafiltration in diabetics should not exceed more than 500-600 ml/h on haemodialysis. This means dialysis sessions of more than 4h and, in larger patients, of more than 5h haemodialysis three times per week.

Guidelines have been created to assure adequate dialysis – "dose of dialysis".

According to DOQI (Dialysis Outcomes Quality Initiative), 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 5h) is adequate (13). Lower

Kt/V, especially below 1, is associated with a higher mortality rate and this is particularly true of the patient with diabetic nephropathy.

Optimal dialysis in diabetic patients:

Need for a dialysis technique which will provide

– absence of acetate
– good cardiovascular stability
– good acid-base correction
– good solute removal
– good biocompatibility

SPECIAL PROBLEMS OF DIABETIC PATIENTS ON HAEMODIALYSIS

Vascular access

In a diabetic patient it is often more difficult to establish vascular access because of a 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. Arteriovenous 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 (14). 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-diabetic.

Radial steal syndrome, venous hypertension, infection/thrombosis (15), and ischaemic monomelic neuropathy could be problems related to vascular access.

Metabolic control

In clinical practice, the need for insulin decreases upon the institution of maintenance HD. The fall in insulin requirements in no way signifies any improvement in the underlying disease. Also, good glucose

control should remain a goal even after initiation of dialysis. It remains important to protect further injury to other organs such as the eyes. Glycaemic control may also be important for preserving residual renal function for as long as possible (16).

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 normogly-caemia if the prescribed insulin dose is too high (17,18). "Tight" metabolic control – a key component in diabetic management – risks potentially fatal hypoglycaemic episodes in haemodialysed patients (14). Oral sulphonylurea must be avoided, in fact is strictly forbidden, because of prolonged hypoglycaemia in endstage renal failure (19).

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 (20).

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 attendant risk of circulatory and pulmonary congestion and hyperkalaemia. Poorly controlled diabetics are also more susceptible to infection.

The HbA_{1c} should be < 8.0% (17, 18, 21).

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, require multidrug therapy more often than non-diabetic uraemic patients. About one-half of haemodialysed diabetics require antihypertensive medications, compared to 27.7% of non-diabetics (22). Beta-blockers should not be used in diabetics as they exacerbate hypertriglyceridemia, worsen glucose control and mask symptoms of severe hypoglycaemia. Improvement is typical in volumen-dependent hypertension after intradialytic fluid extraction.

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.

Hypotension is more prevalent in diabetic than in non-diabetic haemo-dialysis patients. Episodic hypotension is at least 20% greater in incidence while nausea and vomiting are three times more prevalent (23). Episodes of hypotension are highly predictive of cardiac death (24). Severe or sustained hypotension may precipitate *angina pectoris* culminating in acute myocardial infarction.

Intradialytic hypotension is a multi-factorial 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, deterioration of maculopathy and non-thrombotic mesenteric ischaemia.

The following suggestions could be useful for minimizing haemo-dialysis-induced hypotension in diabetics (9):
- bicarbonate rather than acetate dialysate,
- acetate free biofiltration,
- high sodium concentration (140-145 mmol/1) in dialysate,
- slow rate of ultrafiltration,
- schedule sequential ultrafiltration and dialysis in patients who are grossly oedematous,
- prime dialysis circuit with hypertonic albumin solution,
- maintain hematocrit at or above 30 vol% with erythropoietin,
- omit antihypertensive medications on morning of dialysis,
- leg toning exercises to improve venous return, and
- decrease dialysate temperature (particularly near conclusion of treatment).

High interdialytic weight gain. Diabetics gain nearh 30% more weight between haemodialysis than non-diabetics.

Intensified metabolic control facilitated by dietary counselling plus sodium modelling of dialysis, and sequential ultrafiltration curtails weight swings and their deleterious consequences.

Lipid abnormalities in diabetic patients with renal failure

Hypercholesterolaemia and hypertriglyceridaemia are strong predictors of coronary heart disease (25). Major dyslipidaemia is seen only in untreated type-1 diabetic patients. A strong correlation exists between HbA_{lc} and plasma cholesterol, triglyceride and high-density lipoproteins (26). 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 (27).

In a prospective study (28), a relationship between coronary risk and cholesterol concentrations in diabetics admitted for haemodialysis 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 creatinin kinase (rhabdomyolysis) is recommended.

Erythropoietin and iron substitution in uraemic diabetic patients

Len venticular hypertrophy (LVH) is more prevalent in diabetics compared to non-diabetics with end-stage renal disease, and it is possible that the beneficial effects of erythropoietin on LVH could be particularly relevant for diabetic patients (29, 30).

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

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 three times weekly s. c, followed by increments of 2000 at monthly intervals) and careful adjustment of heparinisation during dialysis. If haemoglobin increases by > 1.3 g/dl over two 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. 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 be temporarily 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 a 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 (31), in whom the polymorphnuclear leukocyte function is depressed, particularly when acidosis is present. Leukocyte adherence, chemotaxis and phagocytosis may be affected.

Uraemic diabetics have several particular sites where infections can occur: arteriovenous fistula and central venous catheters, CAPD catheter, the urinary tract, the sinus and diabetic foot ulcer. Infections of the dialysis access, either HD or CAPD, are mostly caused by *Staphylococcus* as a result of increased skin and mucosal colonization with these organisms and need specific therapy. Diabetic patients with prolonged hospital stay should be screened for methicillin-resistant *Staphylococcus*. Diabetics are more prone to urinary tract infections due to diminishing residual diuresis, incomplete bladder emptying because of autonomic neuropathy and following diagnostic or therapeutical instrumentation of the urethra or bladder. Foot ulcer infections often progress to septic gangrene and amputation.

MICROVASCULAR COMPLICATIONS

Diabetic retinopathy

Diabetic retinopathy occurs in 97% of uraemic diabetic patients and 25-30% are blind (32).

Visual loss results from proliferative retinopathy, cataracts, glaucoma, or vitreous haemorrhage.

Diabetic uraemic patients need regular ophthalmologic controls at a frequency of 3-6 months. Laser photocoagulation and other intervention are very frequent in all diabetics either prior to or during treatment for ESRD.

Anticoagulation (heparin) during the haemodialysis procedure and the application of platelet aggregation inhibitors (e. g. aspirin) can cause severe retinal bleeding and blindness.

Diabetic neuropathy

Many patients suffer from the consequences of a peripheral sensorimotor neuropathy, or from gastroparesis or other bowel disturbances caused by autonomic neuropathy.

These are very difficult to treat and respond poorly to conventional treatments. Neuropathy is less likely to progress in a renal transplant recipient. It also tends to be less severe in patients treated with PD, theoretically because of improved clearance of medium-sized molecules (32).

Many patients may also suffer from impotence caused by neuropathy, vascular disease, or medication. These patients may require specialist investigation and treatment.

MACROVASCULAR COMPLICATION

Peripheral vascular disease

Problems related to the diabetic foot are a major cause of hospital admission, and 50-70% of all nontraumatic amputations occur in diabetics. One UK study reported that 6.8% of diabetics receiving renal replacement therapy had a major amputation (33, 34).

There is no reported difference between CAPD and HD (33). The major contributory etiologic factors in diabetic foot problems are peripheral vascular disease, diabetic neuropathy and stress caused by inappropriate footwear.

To prevent diabetic foot complications, patients at risk, should be identified should perform education about foot care, have regular examination of the feet at clinic, provision of appropriate footwear and of podiatry services.

Some studies have reported a symptomatic deterioration in the lower limbs that correlates with falls in blood pressure. Therefore, care should be taken to avoid excessive ultrafiltration in diabetic patients undergoing dialysis. In type 2 diabetics, better glycaemic control is associated with fewer amputations.

The treatment of this condition requires a multidisciplinary approach, ideally in a combined clinic with a nephrologist, diabetologist, and a podiatrist. At the first sign of lower limb ischaemia, patients should be assessed by a vascular surgeon.

Hyperparathyro idism

Diabetics undergoing dialysis developed secondary hyperparathyroidism at a slower rate than nondiabetics and this may predispose to adynamic bone disease in which there is a reduced rate of bone turnover without an excess of unmineralized osteoid. The reduced bone formation may lead to enhanced deposition of aluminium at the ossification front. Diabetics appear to accumulate aluminium more readily and are more susceptible to bone pain and fractures related to aluminium bone disease, which may also be unmasked by parathyroidectomy.

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. 10000 U 25-(OH) vitamin D_3 once weekly) is recommended.

Serumphosphate control is important not only to prevent renal bone disease, but to prevent stiffness of the large arterial vessels. Increased stiffness of the aorta (35) is associated with reduced survival in end-stage renal disease and vascular stiffness is correlated with the increase in serumphosphate.

PERITONEAL DIALYSIS (PD)

Continuous ambulatory peritoneal dialysis (CAPD), continuous cycling peritoneal dialysis (CCPD), in diabetic patients

CAPD has both medical and social benefits and most patients with diabetes are eligible for it. This technique enable patients to stay at ho-

me, 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.

Table 5. Comparison of dialysis options for the diabetic patient (37)

Parameters	Peritoneal dialysis		Haemodialysis	
	Advantages	**Disadvantages**	**Advantages**	**Disadvantages**
Technique	Peritoneal access is easy	Low technique survival rate, high hospitalization rate, higher rate of infection	Better technique survival rate, lower hospitalization rate, lower infection rate	Difficulty with vascular access
Blood pressure	Good blood pressure control, slow ultrafiltration and fewer episodes of cardiovascular instability	—	—	Difficult blood pressure control, frequent hypotensive episodes
Biochemical parameters	Steady-state biochemical parameters, preservation of residual renal function for longer	—	Efficient solute and water extraction	—
Social factors	Maintains independence	—	Can be performed at home	—
Nutritional factors	Fewer dietary restrictions	Excessive weight gain, poor nutrition, hyperlipidemia	—	Difficulty with fluid and dietary restrictions

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 administred via the CAPD fluid. This route of application is not without difficulties, because adsorption of insulin into the CAPD bag and possible infection by installation of insulin into the bag are possible.

In table 11 are given a comparison of dialysis options for the diabetic patient.

Assessing the quality of dialysis in CAPD

Adequacy of dialysis is an important issue in CAPD as well as in HD. According to the DOQI guidelines, which are based on numerous studies (36), a weekly Kt/V of 2 or even more (weekly peritoneal creatinine clearance of more than 70 1) 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 1/week) and a considerable residual renal function are combined. This has two implications: a) CAPD in diabetic patients should be started early (as in haemo-dialysis, at a creatinine clearance of approximately 20 ml/min); and b) residual renal function has to be monitored vigorously. If there is substantial fall in residual renal function (below 5 ml/min), in many cases adequate peritoneal dialysis is impossible. Inadequate PD, has a high mortality rate and patients must be taken off PD and either transferred to HD or, if possible, transplanted.

Outcome of patients on PD (CAPD / CCPD)

CAPD / CCPD appears to be associated in different evaluations with different outcomes in diabetics. The data from the United States Renal Data System (USRDS) registry indicate that, within the first 2 years of therapy, outcomes were superior to those for patients on HD. The risk of all-cause death for female diabetics aged >55 years in contrast, was 1.21 (confidence interval 1.17— 1.24) for CAPD / CCPD, and in cause-specific analyses, these patients had a significantly higher risk of infectious death (38). This was confirmed by data from the Lombardy Registry but interpreted as a result of a hidden negative selection of patients (39). In a single-centre evaluation, HD and PD patients had similar survival, whereas the elderly (> 75 years) had a better survival on CAPD (40). Data from a Canadian Registry did not show any difference between the modalities, but a better survival for patients on PD (41). These discrepancies relate most probably to differences in clinical and demographic setting, patient populations, study design, statistical methods, and interactions between the dialytic modality effect and various other covariables.

RENAL AND PANCREAS TRANSPLANTATION

Renal transplantation is a safe and effective treatment modality for diabetic subjects with ESRD. Studies have shown that besides the improve-

ment in quality of life, there is also posttransplantation better survival in uraemic patients (42, 43, 44). Simultaneous pancreas and kidney transplantation can be recommended as it prolongs survival in patients with diabetes and end-stage renal failure (45, 46) compared with kidney transplantation alone. In another series, patient or graft survival in diabetic patients receiving living-related donor kidney transplants or simultaneous pancreas and kidney transplants were not different, whereas unadjusted graft and patient survival rates in diabetic recipients (older and longer on dialysis) of cadaveric renal transplant were significantly lower than in the other group (47).

Despite these encouraging data, acturarial patient survival posttransplant 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 (48).

Living related donor graft survival is superior to cadaveric donor grafts in diabetics (80 versus 64%, 5-year survival) as in nondiabetics. The higher mortality rate seen in cadaveric graft recipients is probably a consequence of a higher cumulative burden of immunosuppression and co-morbidities (49, 50). The introduction of improved immunosuppressive agents should further improve patient and graft survival both in the diabetic and nondiabetic population.

Survival of the diabetic patient ranges from 45 to 75% at 5 years. This is significantly lower than in nondiabetic renal transplant recipients and is a consequence of cardiovascular disease: 36% of diabetic transplant recipients die from cardiovascular disease (50, 51). There is also an increased risk of death from infection, cerebrovascular disease, and peripheral vascular disease compared with nondiabetic graft recipients. The pretransplant presence of any vascular disease is reported to have a significant effect on mortality in diabetis transplant recipients, especially preexisting cardiac or peripheral vascular disease. Although patient survival is still suboptimal compared with nondiabetic subjects, it is better than that seen with dialysis. Transplantation is also associated with improved rehabilitation and a better quality of life than dialysis.

Pretransplant assessment

Most important is the vascular tree evaluation, 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. Plain radiography on the pelvis documents the magnitude of media calcification in the uraemic diabetic.

Coronary artery disease is an important issue in diabetic patients on dialysis. Non-invasive testing is often non substantial 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 post-transplant circulatory complications of the lower extremities.

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%, which is roughly comparable to those of non-uraemic cardiac patients.

Chronic infections are common in diabetic patients and several sites of infections in diabetic patients have to be considered. 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.

POST-TRANSPLANTATION IN DIABETICS

Hypertension

Approximately 80-90% of adult renal transplant recipients develop hypertension post-transplantation (51, 52). This incidence is no different in diabetics.

Hypertension is a major risk factor for post-transplant cardiovascular disease and should be very well controlled in the diabetic.

Hyperlipidemia

Hypercholesterolemia and hypertriglyceridaemia following renal transplantation have been reported. Increased total serum cholesterol is usually from increases in low-density lipoprotein (LDL) cholesterol (74% of patients) (52.) Many patients also have elevated levels of triglyceride (29%) and very low-density lipoprotein (VLDL) cholesterol, especially in the presence of proteinuria and graft dysfunction. High density lipoprotein (HDL) cholesterol levels are normal or may be reduced in up to 10% of transplant recipients and the composition of HDL may be abnormal, leading to a reduced cardioprotective effect.

The use of diet and pharmacologic approaches to treat hyperlipidemia is reasonable.

Infection

Diabetics are at increased risk of infection following transplantation. As well as the effects of immunosuppression, which are similar to those in nondia-betic patients, factors specific to diabetics include impaired chemotaxis, increased colonization, and the effects of hyperglycaemia on host defences. Cell-mediated immunity is essentially normal in diabetics. Diabetics are at increased risk of foot infections and fungal infections, especially candidiasis and mucormycosis. Urinary tract infections are more common in diabetic transplant recipients and often associated with glycosuria and urinary stasis as a result of poor bladder emptying. In this situation, antibiotic prophylaxis is often required.

Diabetic control and continuing complication of diabetes

Glycaemic control remains an important post-transplantation factor affecting the development of macrovascular disease and the development of recurrent disease. A number of factors result in altered blood glucose homeostasis. Corticosteroid therapy and cyclosporin (cyclosporin A) alter blood glucose control and insulin requirements. Cyclosporine and, particularly, tacrolimus may lead to *de novo* diabetes. Improved renal clearances may also change post-transplantation insulin requirements.

Recurrent diabetic nephropathy

Lesions consistent with diabetic nephropathy develop in almost all grafts, with basement membrane thickening and mesangial expansion re-

ported after 2 years and hyalinization of arterioles after 4 years. The development of nodular glomerulosclerosis is, however, rare in the transplant.

Table 6. Comparison of ESRD options for diabetic patients

Factor	Peritoneal Dialysis	Haemodialysis	Kidney Transplant
Extensive Extrarenal disease	No limitation	No limitation except for hypertension	Excluded in cardiovascular Insufficiency
Geriatric patients	No limitation	No limitation	Arbitrary exclusion as determined by programme
Complete Rehabilitation	Rare, if ever	Very few individuals	Common so long as graft functions
Death rate	Much higher than for nondiabetics	Much higher than for nondiabetics	About the same as nondiabetics
First year survival	About 75%	About 75%	> 90%
Survival to second decade	Almost never	Fewer than 5%	About 1 in 5
Progression of complications	Usual and unremitting. Hyperglycaemia and hyperlipidemia accentuated	Usual and unremitting. May benefit from metabolic control.	Interdicted by functioning pancreas + kidney. Partially ameliorated by correction of azotemia.
Special advantage	Can be self-performed. Avoids swings in solute and intravascular volume level.	Can be self-performed. Efficient extraction of solute ' and water in hours.	Cures uraemia. Freedom to travel.
Disadvantage	Peritonitis. Hyperinsulenemia. Long hours of treatment. More days hospitalized than either hemodialysis or transplant.	Blood access a hazard for clotting, haemorrhage and infection. Cyclical hypotension, weakness. Aluminium toxicity, amyloidosis.	Cosmetic disfigurement, hypertension, personal expense for cytotoxic malignacy. HIV transmission.
Patient acceptance	Variable, usual compliance with passive tolerance for regimen.	Variable, often non-compliant with dietary, metabolic, or antihypertensive component of regimen.	Enthusiastic during periods of good renal allograft function. Exalted when pancreas proffers euglycaemia.
Bias in comparison	Delivered as first choice by enthusiasts though emerging evidence indicates substantially higher mortality than for haemodialysis	Treatment by default Often complicated by in attention to progressive cardiac and peripheral vascular disease.	All kidney transplant programme preselect those patients with fewest complications. Exclusion of those older than 45 for pancreas + kidney simultaneous grafting obviously favourably prejudices outcome.
Relative cost	Most expensive over long ran	Less expensive than kidney transplant in first year, subsequent years more expensive.	Pancreas + kidney engraftment most expensive uraemia therapy for diabetic. After first year, kidney transplant C alone C lowest cost option.

The future

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 a graft is 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.

Comparison of ESRD options for diabetics patients are given in table 6 (53).

HOW WE TREAT DIABETIC PATIENTS ON MAINTENANCE HEMODIALYSIS – EXPERIENCE FROM THE REPUBLIC OF MACEDONIA

AIM:

The aim of the present study is to evaluate a cohort of patients with DM, type 1 and type 2, on maintenance HD in all 17 centers for dialysis in the Republic of Macedonia and to get an overview for future acting.

The day 31. 12. 2002 was taken as a critical day for data evaluation of patients on HD with DM. Data were collected by specially prepared questionnaire.

MATERIALS AND METHODS:
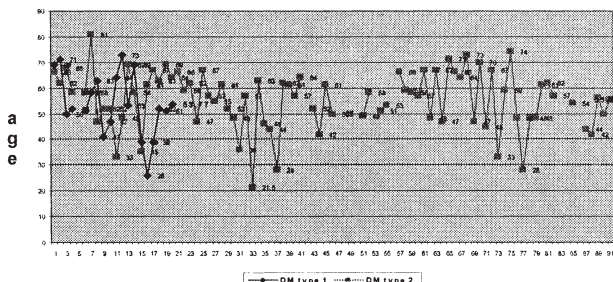*Patients on HD and patients with DM*
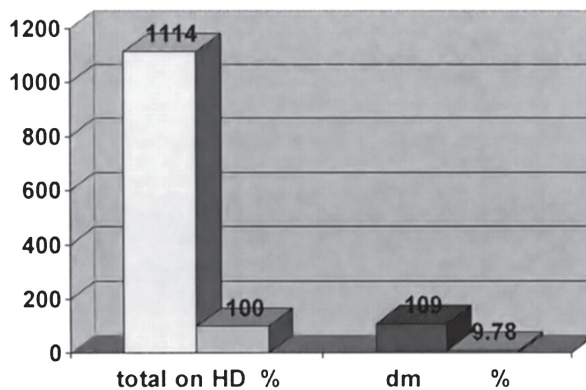
Patients Gender
Male   60 (55 %)
Female   49 (45%)

Patients distribution in HD centers in Macedonia

Centers	total on HD	DM	%

Patients Age and duration of DM, when DM is found

DM Type 1
Age   30.4 years
Duration of DM   16.6 years

DM Type 2
Age   46.2 years
Duration of DM 13.4 years

Patients Age when HD is started
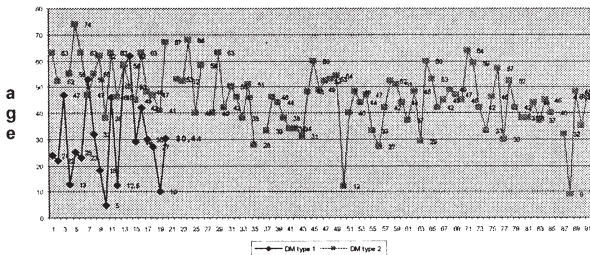
DM Type 1
Age   53.8 years

DM Type 2
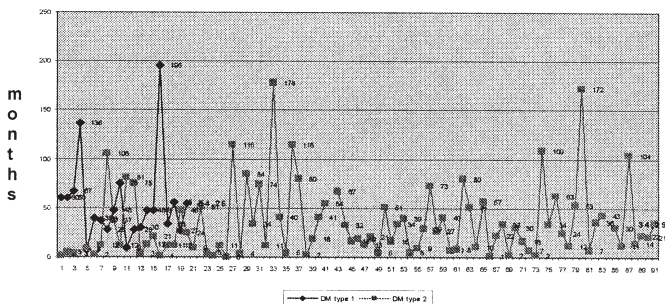Age   55.3 years

Months on HD in patients with DM
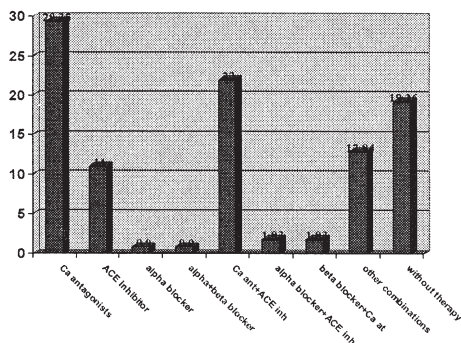
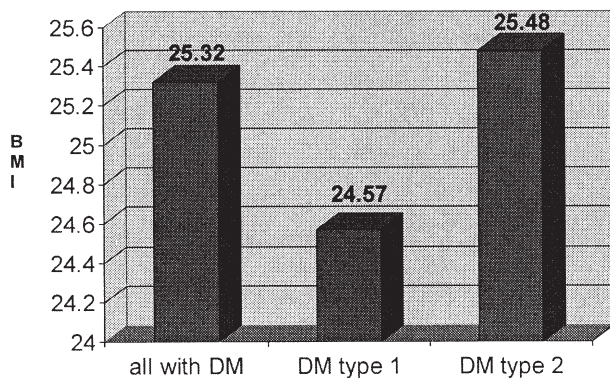| DM Type 1 months | 54.3±44.4 | DM Type 2 months | 34.3+36.3 |

Cardiovascular diseases at start of HD

Complication	(%)
Hypertension	91%
Angina pectoris	7.2%
Myocardial infarction	5.4%
Peripheral vascular Disease	10%
CVI	7.2%

Distribution of antihypertensive drugs

Years of hypertension in patients with DM on HD: 12.3 years

BMI in patients on HD with DM

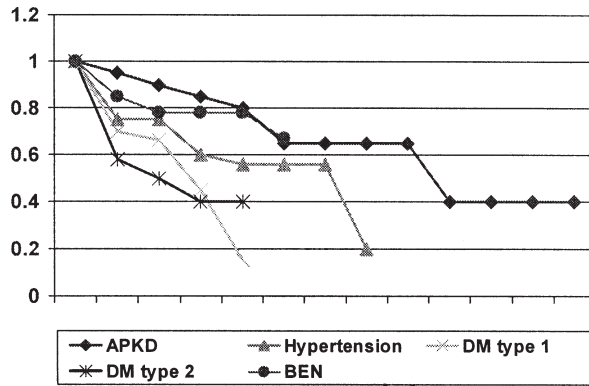|	
Смокерс	21%
Alcohol consumers	12.9%
Physical Active	14.7%

First vascular access in patients with DM on HD
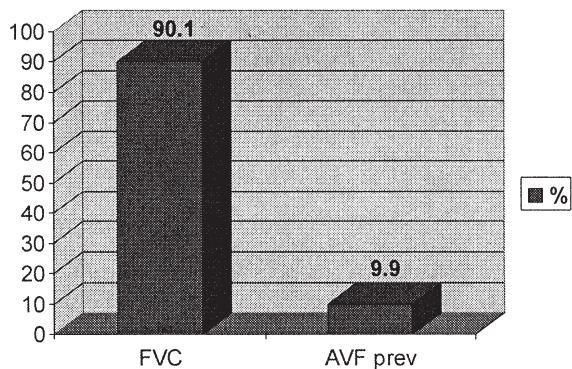
Complications of vascular access in patients with DM on HD

Thrombosis of AVF	41.4%
Infection of AVF	58.6%

Survival of patients with DM on HD at Dep't of Nephrology

Letal outcome of patients with DM on HD at Dep't of Nephrology
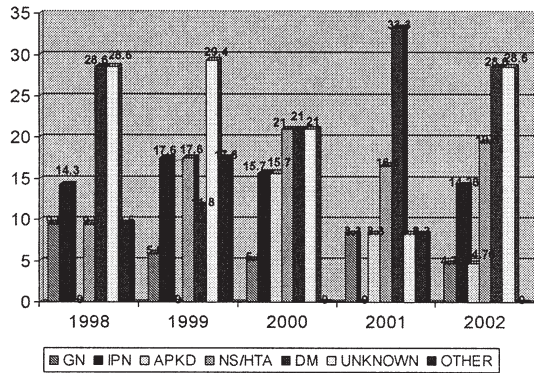
CONCLUSION

There is no early detection of diabetic nephropathy and the patients have been hospitalized with end stage of renal failure and cardiovascular complications.

There is obvious need for team treatment of these patients by GP, specialists of internal medicine and by diabetologists, nephrologists, cardiologists, ophthalmologists and neurologists.

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