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Renal Replacement Therapy in Uremic Diabetic Patients – Experience from The Republic of Macedonia

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1. 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).

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 the 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 (3). The figures are lower in the Mediterranean countries, as well as in Macedonia (4), although an increase has recently been reported from Spain (5) and Italy (6). ESRD and ESRF caused by DN was 10%, 5–15% in different haemodialysis

Centres for adults in 2000 in the Republic of Macedonia (4), as well as 22% in 2006 (4a).

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 (7).

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).

2. Evaluation of the diabetic patient with preterminal renal failure

Evaluation of the diabetic patients 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 arterioocclusive disease.

Some of these coincident kidney diseases are listed below.

2.1 Ischaemic renal disease

Renal ischaemia or atherosclerotic renal artery stenosis is much more common in diabetics than previously assumed (8). 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.

2.2 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.

2.3 Glomerulonephritis

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

2.4 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.

- Reversible causes of renal failure present? (contrast media, urinary tract infection, angiotensin converting enzyme inhibitors, congestive heart failure)
- Hypovolaemia present?
- Coronary heart disease present (percutaneous transluminal angioplasty or coronary bypass surgery required?
- Cardiomyopathy or congestive heart failure present?
- Congestion due to hypervolaemia or heart failure?
- Early vascular access?
- Hypoglycemic episodes present? Adequate nutrient intake?
- Eye (examined 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?

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

3. 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 longterm 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.

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 (9). 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** (10).

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)

Table 2. Options in uremia therapy for diabetic ESRD patients

4. 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 dyslipidaemias; 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.

5. 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 (11).

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.

5.1 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, the 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.

	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
Spain (Catalonia) c	65	30
Germany	–	38/5
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.

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

In table 4 are the causes of death in diabetic patients on HD.

	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.

Table 4. Causes of death in diabetic patients 57 months after start of haemodialysis (12).

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 nondiabetics. Improvement of survival is a matter of reduction of cardiovascular death and infection.

5.2 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 (13). 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 (14). 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

5.3 Special problems of diabetic patients on haemodialysis

5.3.1 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. 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 (14, 15). 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, 16), and ischaemic monomelic neuropathy could be problems related to vascular access.

5.3.2 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 (17).

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 (18,19). "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 (20).

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 HbA1c should be < 8.0% (18, 19, 22).

5.3.3 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 (23). Betablockers 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 haemodialysis 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 haemodialysis-induced hypotension in diabetics (9):

- bicarbonate rather than acetate dialysate,
- acetate free biofiltration,
- high sodium concentration (140–145 mmol/l) 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 near 30% more weight between haemodialysis than non-diabetics.

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

5.3.4 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 HbA1c 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, 28).

In a prospective study (29), 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.

5.3.5 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 (30, 31).

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.

5.4 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.

5.5 Infections in uraemic diabetic patients

Bacterial infections are common complications in uraemic diabetic patients (32), 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 methicillinresistant *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.

6. Microvascular complications

6.1 Diabetic retinopathy

Diabetic retinopathy occurs in 97% of uraemic diabetic patients and 25–30% are blind (33).

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.

6.2 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 (33).

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

7. Macrovascular complication

7.1 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 (34, 35).

There is no reported difference between CAPD and HD (34). 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.

7.2 Hyperparathyroidism

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 D3 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 (36) is associated with reduced survival in end-stage renal disease and vascular stiffness is correlated with the increase in serumphosphate.

8. Peritoneal dialysis (PD)

8.1 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 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.

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

Table 5. Comparison of dialysis options for the diabetic patient (37, 38)

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 6 are given a comparison of dialysis options for the diabetic patient.

8.2 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 (37), a weekly Kt/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 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.

8.3 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 (39). This was confirmed by data from the Lombardy Registry but interpreted as a result of a hidden negative selection of patients (40). In a single-centre evaluation, HD and PD patients had similar survival, whereas the elderly (> 75 years) had a better survival on CAPD (41). Data from a Canadian Registry did not show any difference between the modalities, but a better survival for patients on PD (42). 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.

8.4 Renal and pancreas transplantation

Renal transplantation is a safe and effective treatment modality for diabetic subjects with ESRD. Studies have shown that besides the improvement in quality of life, there is also posttransplantation better survival in uraemic patients (43, 44, 45). Simultaneous pancreas and kidney transplantation can be recommended as it prolongs survival in patients with diabetes and end-stage renal failure (46, 47) 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 (48).

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 (49).

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 (50, 51). 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 (51, 52). 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.

8.5 Pretransplant assessment

Most important is the vascular tree evaluation, the Achilles' heel of every successful transplantation procedure. Careful evaluation of pelvic and lower extremily 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.

9. Post-transplantation in diabetics

9.1 Hypertension

Approximately 80–90% of adult renal transplant recipients develop hypertension post-transplantation (52, 53). 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.

9.2 Hyperlipidemia

Hypercholesterolaemia 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) (53.) 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.

9.3 Infection

Diabetics are at increased risk of infection following transplantation. As well as the effects of immunosuppression, which are similar to those in nondiabetic 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.

9.4 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.

9.5 Recurrent diabetic nephropathy

Lesions consistent with diabetic nephropathy develop in almost all grafts, with basement membrane thickening and mesangial expansion reported after 2 years and hyalinization of arterioles after 4 years. The development of nodular glomerulosclerosis is, however, rare in the transplant.

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 noncompliant with dietary, metabolic, or antihypertensive	Enthusiastic during periods of good renal allograft function. Exalted when

		component of regimen.	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 favoruably prejudices outcome.
Relative cost	Most expensive over long run	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.

Table 6. Comparison of ESRD options for diabetic patients

10. 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 (54).

11. Diabetics on dialysis in the Republic of Macedonia

Today the nephrologists are challenged both to control the underlying diabetic disease and also to provide an adequate renal replacement therapy. On the other hand, it has to be stressed that treatment of these patients and DM complications is very expensive. For

example, in USA the cost of treatment of these patients per year was estimated to about 100 billion dollars, which is more than the whole health budget of a country like Italy (health budget estimated for 2001). Moreover, in USA around 2 billion dollars are being spent on dialysis treatments [55]. Recently performed, large epidemiological studies have demonstrated that CV morbidity and all cause mortality can be reduced with strict glycaemic and blood pressure control and with the use of anti-angiotensine agents and also lipid lowering agents [56-60]. Certain factors like age, time on dialysis, vascular access complications, co morbidities, type of dialysis membrane, time of dialysis and others have been identified to correlate with the survival of the patients on dialysis [61, 62]. These factors assume even greater importance in diabetics. Biocompatible membranes, ultrapure dialysis fluid and diffuse - convective techniques have also been promoted to reduce cardiovascular instability [63, 64] and to minimize the injuries of the excessive oxidative stress inherent in uremia and the dialysis treatment.

In Republic of Macedonia (RM) in last two decades there was an increase of number of diabetic patients. The number of patients with diabetic nephropathy progressing to the point of need for renal replacement therapy and renal transplantation is also increasing [65-67]. Given the fact of lack of data and valuable epidemiological studies in these patients, we performed a nation wide study with the aim of defining prevalence of these patients in RM, determining the standards of care in diabetics in term of methodological approach, dialysis and drug treatment and analysis of these patients on dialysis. The aim of the study was to make a closer observation in all dialysis centers in 2002 in the country and to compare data with those obtained 2006.

11.1 Patients and methods

Data were collected from medical histories of diabetic patients on dialysis in all dialysis centers in Republic of Macedonia by using a specially developed questionnaire for this purpose. Date of 31 December for 2002 and 2006 year was selected as a "critical day" for data collection. Besides demographic data (name, surname, sex, date of birth and profession), data for cigarette smoking and alcohol consuming were collected as well as type of diabetes (family history for diabetes, therapy, dose and type of the insulin intake, duration of diabetes and kidney disease), hypertension (family history, duration, therapy), other renal diseases including diabetic nephropathy, as well as laboratory findings (residual diuresis, blood glucose level, HbA1C, microalbuminuria, proteinuria, urea, creatinin blood level, creatinin clearance, thryglycerides (TG) blood level, cholesterol, HDL and LDL cholesterol, hepatitis B virus serological markers (HBs Ag, anti HBc-Ig G) , hepatitis C virus serological markers (anti HCV) and human imunodeficiency virus antibodies (anti-HIV); type of dialysis (bicarbonate or acetate); duration and frequency of dialysis sessions, medications used, hypoglycemic events, number of hospitalizations, complications: cardiovascular events (pectoral angina, heart attack, cerebrovascular insult), hypertension, peripherial vascular artheriopathy (diabetic foot), diabetic retinopathy, infection of the urinary system); cause of death – if patient died. The progression of other diabetic complications was obtained by roentgenograms, ECG, echocardiography and examination of eye fundus. Special attention was paid to data on vascular access (type of central venous catheter, A-V fistula, graft, complications on vascular accesses infection/thrombosis, other complications, as well as number of created vascular accesses).

Patients were treated according to the recommendations introduced by University Nephrology Clinic - Skopje, Faculty of Medicine, "Ss. Cyril and Methodius" University in Skopje, as a reference center for dialysis patients in Republic of Macedonia [68]. Duration of dialysis sessions was approximately three times four hours per week divided into three day sessions in same week. Low flux polysulphonic membranes, were used. Water was prepared by a reverse osmosis and blood flow in most of the cases was 250-280ml/min, whereas dialysis flow was usually 500 ml/min. Dialysis machines used were GAMBRO types AK 10, AK 100 and AK 95. There was no reuse of the dialysis filters. A low salt intake diet and malnutrition protective protein intake of 1gr/kg diet were recommended to all patients.

11.2 Results

Total number of dialysis patients in RM was 1114 and 1074 in 2002 and 2006 year, respectively (Figure 1, Table 7). There were 109 (9.78%) diabetic patients on dialysis, 60 (55%) male and 49 (45%) female in 2002. A slight increase of diabetics was determined in 2006, namely there were 115 (10.7%) diabetic patients on dialysis, 74 (64.35 %) male and 41 (35.65%) female in 2006 year, as to compare with 2000 when total number of dialysis patients was 1010 and number of diabetics on dialysis was 103 (10.19%) [65, 66] (Figure 2). There was a difference in distribution of diabetics on dialysis trough different dialysis centers in RM for 2002 and 2006 year (Table 8 and Table 9), respectively. Diabetics on dialysis were from 3% in Veles, to 21 % in Kavadarci for 2002. Similar diversity was obtained in 2006: from 2.43% in Skopje Military Hospital Dialysis Center to 22.07% in University Nephrology Clinic - Skopje. In 2002 most of the diabetics on dialysis (31 patients) were registered in University Nephrology Clinic - Skopje and in the Nephrology Institute - Struga (15 patients) similarly like 2006 when most of diabetics on dialysis (34 patients) were in University Nephrology Clinic - Skopje and in Nephrology Institute - Struga (16 patients). The mean age of all diabetics on dialysis in 2002 was 58±10.29 years (56±10.49 for males and 60±9.56 for females), and in all diabetics on dialysis in 2006 it was 56.5±10.71 years (55.06±8.82 for males and 57.92±12.56 for females) (Table 1). In 2002, 19 (17.43%) patients had DM1, while 90 (82.57%) patients had DM2. 28 (25.68%) patients were treated with oral anti-diabetic drugs and 62 (57.21%) patients were on insulin. In 2006, 15 (13.04%) patients had DM1 while 100 (86.96%) patients had DM2. 31 (26,96 %) of diabetics were treated with oral anti-diabetic drugs and 69 (60%) were on insulin. The mean age of DM1 patients in 2002 was 47±11.6 years, with a diabetic history of 16.2±9.7 years, while the mean age of DM1 patients in 2006 was 45±7.32 years, with a diabetic history of 24.07±11.07 years. The mean age of DM2 patients in 2002 was 60.37±8.33 with a diabetic history of 13.4±8.1 years and the mean age of DM2 patients in 2006 was 61.14±10.23 years with a diabetic history of 14.18±8.42 (Table 1). The mean dose of insulin intake was 9.5±6.63IU and 10.85±9.29IU, for 2002 and 2006 respectively. In 2002, 21% of diabetics on dialysis were smokers, 13% consumed alcohol, while 15% were engaged in sport, as compared to 2006 when 17.39% of diabetics on dialysis were smokers, 5.22% consumed alcohol and 3.48% were doing sport.

The mean duration of dialysis therapy in 2002 for DM type 1 patients was 54.3±44.4 months, whereas in DM type 2 was 34.3±36.3 months. The mean duration of dialysis therapy in 2006 for DM 1 patients was 76.29±74.96 months, whereas in DM 2 was 33.68±43.24. The mean body mass index (BMI) in 2002 was 26.4±3.28 kg/m^2 and 25.5±2.92 kg/m^2 in DM1 and DM2 patients, respectively. In 2006 BMI was 23.49±4.74 kg/m^2 and 24.77±3.70 kg/m^2 in DM1 and

DM2 patients, respectively. There was a need for urgent dialysis treatment and a first dialysis session a trough femoral venous catheter in 90.1% and 94.4% of diabetics on dialysis in 2002 and 2006, respectively. After a period of patient adaptation to dialysis procedure and in order to eliminate possible bacterial infection trough the femoral venous catheter, an arterio venous fistula (AVF) was created as a permanent vascular access for dialysis. Preventive AVF was created in 9.9% and in 5.6% of diabetics on dialysis in 2002 and 2006 respectively. Thrombosis of the newly created AVF was detected in 41% and 24.35% in 2002 and 2006 respectively, whereas AVF infection was detected in 58.6% of the patients in 2002. In 2002 there were 19.26% of patients on acetate dialysis and 80.74% on bicarbonate dialysis while in 2006 there were no patients on acetate dialysis, and all 110 diabetic patients (95.65%) were on bicarbonate dialysis modality (Figure 3).

It has to be stressed that a high rate of HCV infection was noticed in diabetics on dialysis, 57% and 37.39% of these patients were anti HCV positive in 2002 and in 2006, respectively. 81% and 86.09% of the patients were treated with erytropoethin in 2002 and 2006, respectively. In both years hypertension (HTA) was the most frequent co-morbid state: in 2002, 91% diabetics on dialysis had a HTA before dialysis program and following the start of dialysis sessions 40.54% (Table 10). Furthermore, in 2006 HTA was registered in 47.74% of diabetics before dialysis, and in 60% of patients during dialysis. Finally, family history for HTA was noticed in 43% and 29.57% patients, in 2002 and 2006, respectively. The most frequent cardiovascular co-morbidity in these patients for the year 2002 and 2006 are shown in Table 10.

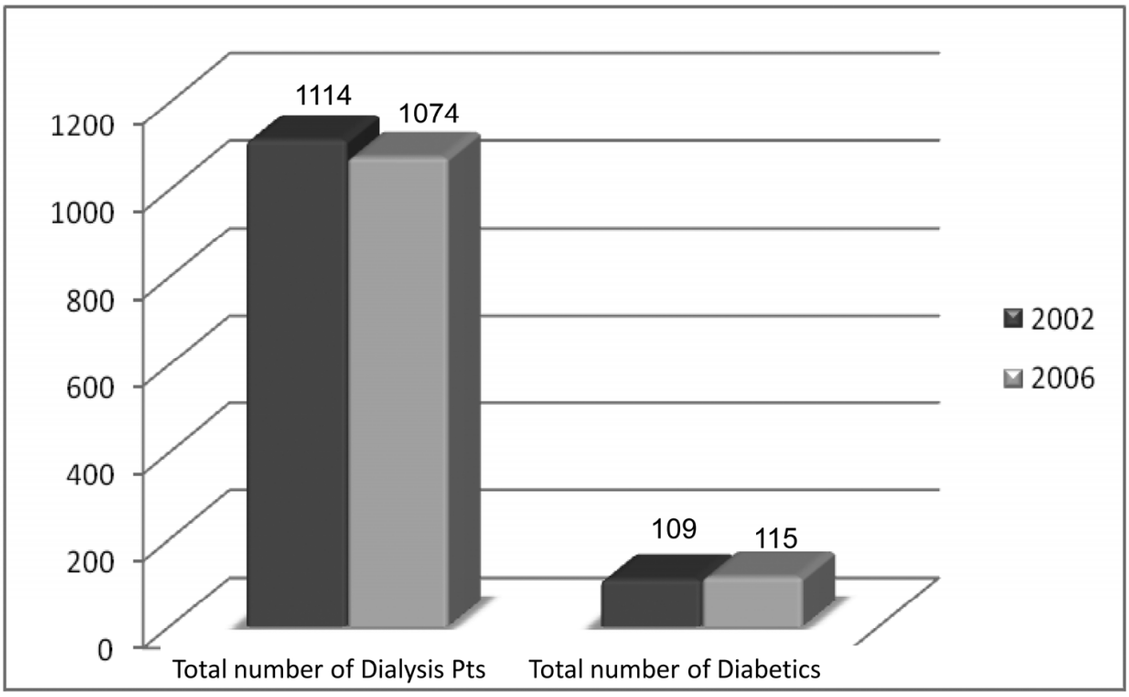

Fig. 1. Total number of patients on dialysis and diabetics on dialysis.

	2002 year	**2006 year**
N° dialysis patients	1114	1074
N° of diabetics	109 (9.78%)	115 (10.7%)
Male Pts	60 (55%)	74 (64.35%)
Female Pts	49 (45%)	41 (35.65%)
Mean age	58±10.29	56.5±10.71
Mean age male	56±10.49	55.06±8.82
Mean age female	60±9.56	57.92±12.56
Patients with DM1	19 (17.43%)	15 (13.04%)
Mean age DM1	47±11.6	45±7.32
DM history DM1 (years)	16.2±9.7	24.07±11.7
DM1 dialysis history (months)	54.3±44.4	76.29±74.96
Patients with DM2	90 (82.57%)	100 (86.96%)
Mean age DM2	60.4±8.33	61.14±10.23
DM history DM2 (years)	13.4±8.1	14.18±8.42
DM2 dialysis history (months)	34.3±36.3	33.68±43.24
On OADD	28 (25.68%)	31 (26.96%)
On insulin	62 (57.21%)	69 (60%)
Dose of insulin (IU)	9.5±6.63	10.85±9.29
BMI in DM1 kg/m^2	26.4	25.5
BMI in DM2 kg/m^2	23.49±4.74	24.77±3.70
First dialysis on FVC (%)	90.1	94.4
Preventive AVF (%)	9.9	5.6
Thrombosis of first AVF (%)	41	24.35
Anti HCV positive (%)	57	37.39

DM1 - Diabetes mellitus type 1, DM2 - Diabetes mellitus type 2 ; OADD – Oral antidiabetic drugs ; BMI – Body mass index; FVC – femoral vascular cathether ; AVF – Arterio venouse fistula

Table 7. Characteristics of diabetics on dialysis in Republic of Macedonia

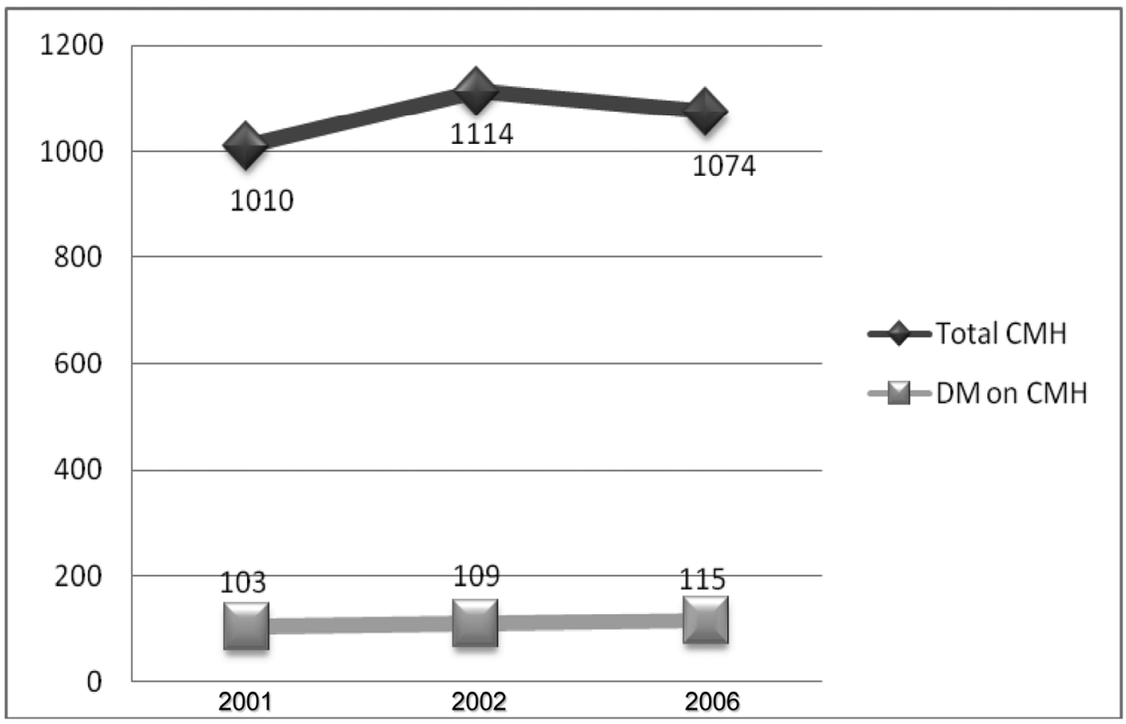

Fig. 2. Oscillations in the total number of dialysis patients and diabetics on dialysis period 2001 – 2006 in RM

Dialysis center	N° of Dialysis pts	N° of Diabetics	% DM
University Clinic of Nephrology, Skopje	201	31	15.42
Institute of Nephrology, Struga	204	15	7.35
Tetovo	63	9	14.28
Gevgelija	28	1	3.57
Debar	15	2	13.30
Gostivar	53	4	7.54
Kočani	24	3	12.50
Kumanovo	60	6	10.00
Delčevo	31	4	12.90
Strumica	46	4	8.69
Prilep	60	6	10.00

Bitola	38	4	10.52
Štip	49	3	12.50
Železara	125	5	4.00
Military hospital, Skopje	40	3	7.5
Veles	39	1	2.56
Kavadarci	38	8	21.50
Total	**1114**	**109**	**9.78**

Table 8. Distribution of dialysis patients by dialysis centers in RM, year 2002

Dialysis center	**N° of Dialysis pts**	**N° of Diabetics**	**% DM**
University Nephrology Clinic, Skopje	171	32	19.88
Nephrology Institute, Struga	171	16	9,36
Tetovo	69	11	15,94
Gevgelija	30	2	6,67
Kriva Palanka	26	3	11,54
Gostivar	46	4	8,70
Kočani	31	1	3,23
Kumanovo	49	7	14,29
Delčevo	32	7	21,88
Strumica	47	3	6,38
Prilep	56	6	10,71
Bitola	43	2	4,65
Štip	60	4	6,67
Železara	162	12	7,41
Military hospital	40	2	5
Veles	41	1	2,44
Total	**1074**	**115**	**10,71**

Table 9. Distribution of dialysis patients by dialysis centers in RM, year 2006

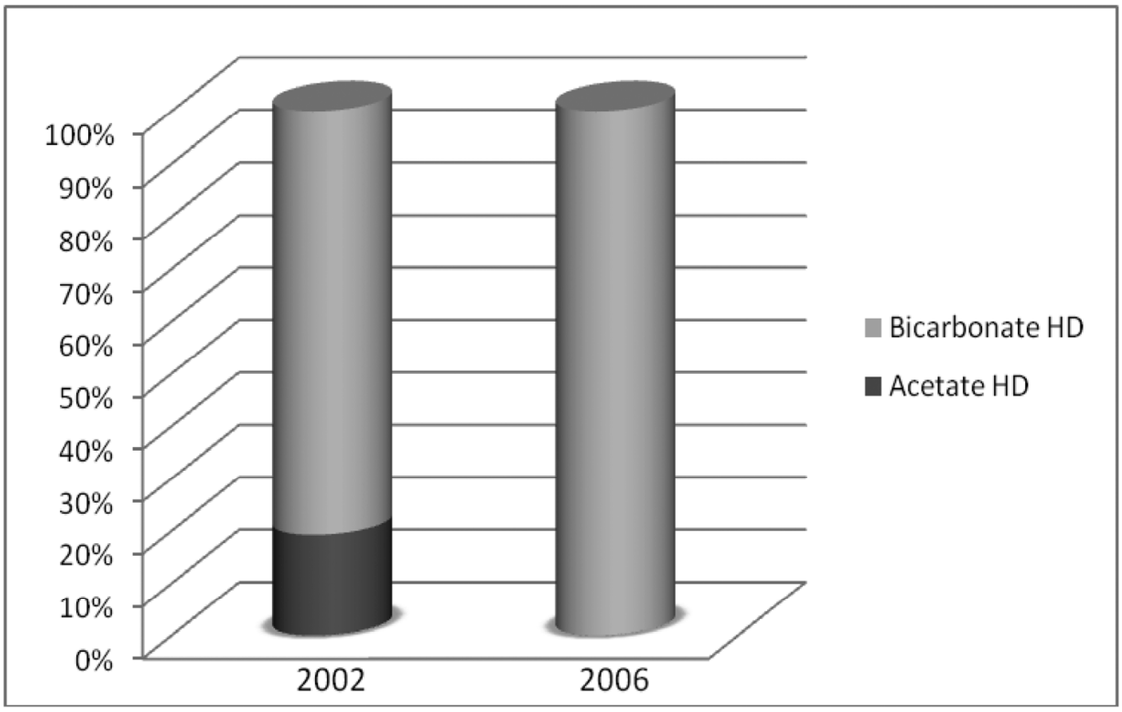

Fig. 3. Use of acetate and bicarbonate haemodialysis (HD) in 2002 and 2006

Condition	Before Dialysis (2002)	During Dialysis (2002)	Before Dialysis (2006)	During Dialysis (2006)
Pectoral angina	7.2%	19%	1.12%	3.4%
Heart attack	5.4%	5.4%	1.12%	4.43%
Intermitent claudication	10%	10%	2.25%	11.3%
Cerebrovascular attack	7%	8%	8.7%	9.57%
Hypertension (HTA)	91%	40.54%	47.74%	60%

Table 10. Distribution of the most frequent cardiovascular co-morbidity in diabetics on dialysis in 2002 and 2006.

11.3 Discussion

In the present analysis we have demonstrated an increase in the prevalence on diabetic dialysis patients in certain dialysis centers of RM. It has been reported before that the annual incidence of patients who initiate dialysis is constantly increasing in all industrialized

countries and a significant part of this increase is explained by the influx of diabetic patients on dialysis [68, 69]. This study shows the importance of the need to increase the number of specialists nephrologists in RM who will take an important role in healthcare of these patients in collaboration with endocrinologists and other specialists practitioners.

We have previously shown that the number of diabetics on dialysis in RM enlarges slowly but progresively [65-68]. In current analysis, beside the fact that mean total prevalence of DM was just slightly increased as compared to our previous studies [66], we show that there is an important difference in prevalence of diabetics on dialysis between different dialysis centres. In certain dialysis in RM the prevalence of diabetics reached a level similar with that of Northern European countries [69] while in others it was lower than expected. This diversity in the number of diabetics on dialysis could be explained by the fact that RM is a developing country, geographically European with predominance of Mediterranean diet, and this difference could be due to a numerous economical, sociological, genetic, environmental and nutritional factors in different parts of the country.

We included in the study all diabetic patients on dialysis in RM, without differentiating diabetics who started dialysis because of diabetic nephropathy from those who started dialysis with other renal pathology. We show that diabetics with CKD in most of the cases were diagnosed at the University Nephrology Clinic - Skopje, and diagnosis most often was in developed phase of CKD. It has been shown that these patients present an extraordinary acceleration of all clinical complications and it is a well known fact that accelerated development of terminal uraemia constitutes a devastating clinical event [1, 55, 69, 70, 71]. Phase of the disease when diabetes is installed is accompanied usually with a certain variety of cardiovascular complications, predominatelly as a result of a long-term hypertension, nephrotic syndrome and infections. Metabolic and blood vessels modifications induce constant overweight and problems with vascular access leading to quality of life decrease in these patents. Consequently, as it has been showen by the others and us, the survival rate of diabetics on dialysis is significantly reduced, Figure 4 [72, 73]. When compared with other dialisys patients it has been shown that the best survival rate was observed in those with balkan endemic nephropathy and adult polycystic kidney disease. This observation goes in line with other studies confirming that in diabetics on dialysis the quality of life is impaired and survival is significantly curtailed [1, 74, 26]. It has been shown also that the clinical results depend on both the severity of complications present at the initiation of dialysis and on capacity to slow its evolution during dialysis [74]. In current analysis we did not evaluate the effect of patient therapies on the incidence of complications and on patient mortality.

Besides the fact that most of the nephrologists and internal medicine specialists in RM are aware of the importance of the timely initiation of dialysis for diabetic patients, this analysis underlines the fact that dialysis initiation often starts in emergency conditions and most of the patients start dialysis program at University Nephrology Clinic – Skopje trough urgently and temporary placed femoral venous catheter. We found that almost 90% of first dialysis sessions in 2002 as well as in 2006 were started in emergency conditions, confirming that diabetics are reffered to the nephrologists late in the course of CKD. Analysing why this happens, we think that a part of responsibility for the delay of dialysis initiation could be explained by patient mentality but it is also important to stress the important role of medical

personnel in preparing the patient for dialysis. We have to underline insufficient coordination between physicians such as general practitioners, internists, endocrinologists and nephrologists, and lack of their influence on patient dialysis reality acceptance. It is also important to notice that in two dialysis centres where the prevalence in diabetics on dialysis is much higher, dialysis patients are followed by educated and well trained nephrologists. In these centres accessibility of other specialties practitioners is higher as compared to dialysis centres where patients are followed by internal medicine specialists and other specialized doctors are also accessible. This might explain the high difference in number of diabetic's among different dialysis centers and it also underlines the need for more trained nephrologists in the country and their more important implication in follow up of diabetics on dialysis.

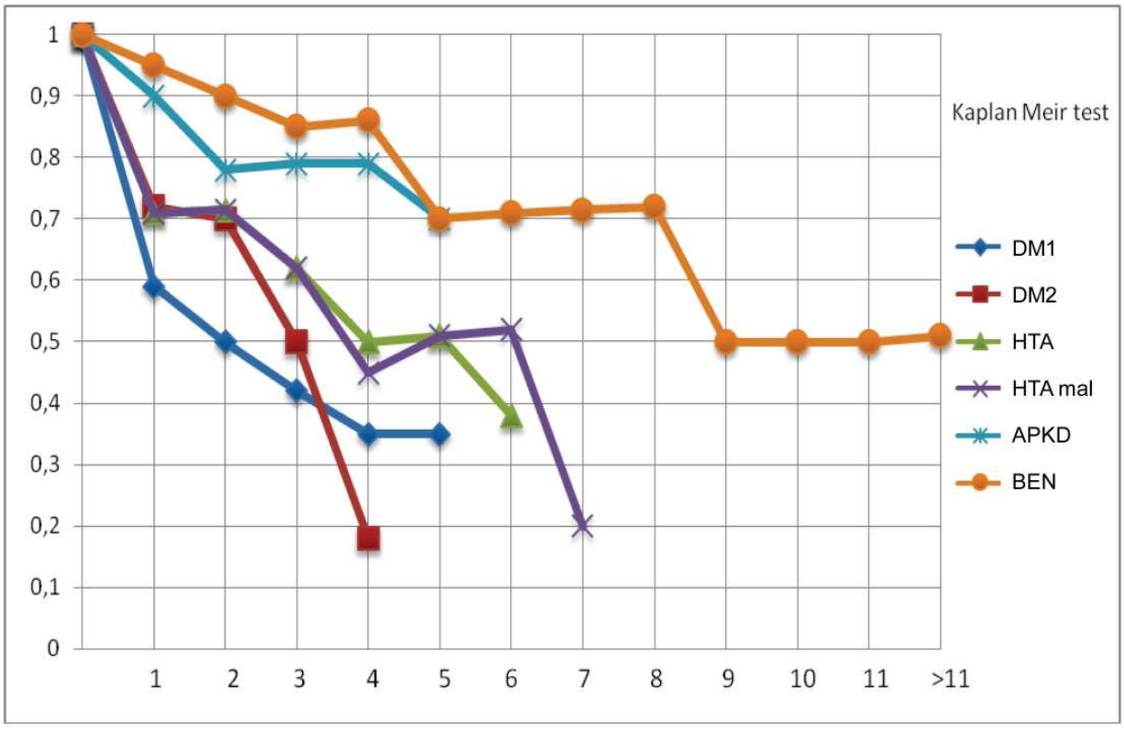

Fig. 4. Distribution of survival (Kaplan Meier test) of dialysis patients, distribution by basic renal disease (University Clinic of Nephrology - Skopje); abbrevations: Diabetes Mellitus Insulin Independent – DM1, Diabetes Mellitus Insulin Dependent DM2, Arterial Hypertension – HTA, Malignant HTA – HTA mal., Adult Polycystic Renal Diseases-APKD, Balkan Endemic Nephropathy – BEN).

It has been shown previously that a very large difference exists in the ratio of DM2 to DM1 on dialyisis in different European countries and among different regions in a same country [1]. A recent study of Italian population showed that most diabetics on dialysis were DM2 patients, probably because of high prevalence of this disease among the general population [75]. In our study we found that the ratio of DM2 to DM1 patients was approximately 4,3 : 1. As expected, patients with DM2 were older, with higher body weight and body mass index.

Epidemiological studies has also shown that cardiovascular morbidity and mortality can be reduced with pharmacological therapy that normalizes blood pressure values and controls hyperglicemia, hyperlipidemia, platelet agreggation and hypercoagulability [56-58]. Proportion of diabetics od dialysis treated with ACE inhibitors and / or angiotensin receptor blockers (ARB), beta blockers and antiplatelat drugs was still quite low as compared to propositions of the guidelines. There was a negligible number of patients treated with lipid lowering agents.

In conclusion, the present study underline the importance of an interdisciplinary approach in early diagnosis and treatment of diabetes, diabetic nephropathy and treatment of diabetics on dialysis, as well as importance of introducting preventive measures for progression of CKD in these patients. In most dialysis centres in the Republic of Macedonia prevalence of diabetics on dialysis did not increase in the period from 2002 to 2006 where these patients were followed mostly by internal medicine specialists. Frequency of complications was increased in DM2 compared to DM1 dialysis patients. Blood glucose level control is important as well as a strict control of the blood preasure. Bicarbonate dialysis is a dialysis of choice with an optimal duration of minimun 12 hours per week. More nephrologists need to be involved in the dialysis centres and together with an improvement of colaboration between general practitioners, internternal medicine doctors, endocrinologists, nephrologists, cardiologists, ophtalmologists, neurologists in order to improve health care for these patients. This kind of studies should be carried out on a regular basis in Republic of Macedonia.

12. Could we prevent or postpone diabetic kidney disease and development of chronic renal failure?

The World Kidney Day, 11 March 2010 was devoted to diabetic kidney disease, under the auspices of the International Society of Nephrology (ISN) and the International Federation of Kidney Foundations (IFKF), together with the International Diabetic Federation (IDF).

R.C. Atkins and P. Zimmet in their paper: *Diabetic kidney disease: act now or pay later* [76] point out the importance of a better understanding of the global pandemic of type 2 diabetes and diabetic kidney disease. They suggest that it is necessary to alert governments, health organizations, providers, doctors and patients to the increasing health and socioeconomic problems due to diabetic kidney disease and its sequels: end-stage kidney disease requiring dialysis, and cardiovascular death. It should be emphasized that its management involves prevention, recognition and treatment of its complications.

The most important measure is primary prevention of type 2 diabetes. It will require massive lifestyle changes in the developing world, supported by strong governmental commitment to promote lifestyle and societal change.

In the Republic of Macedonia there are about 100,000 patients with diabetes mellitus type 1 and 2; 85–95% have diabetes mellitus type 2. Around 28,000–30,000 patients are on therapy with insulin.

Some of them are candidates for development of diabetic kidney disease.

We should develop a strategy to detect early diabetic kidney disease by screening for albuminuria as well as reduced glomerular filtration rate. It is very important to introduce

public education about the relationship between diabetes and kidney disease. There is a remarkable lack of awareness among patients about their condition.

In our papers: *Chronic Kidney Disease: a Hidden Epidemic* [77] and *Public Health Aspects of Renal Disease in the Republic of Macedonia* 1983–2007 [78] we have shown a continuous increase in end-stage renal disease and renal replacement therapy (RRT) in the Republic of Macedonia. In 2002, we had 1,056 patients on RRT compared to 1,216 in 2005. In some dialysis centres 20% of the patients on haemodialysis are diabetics. Our message was that there is an urgent need for a screening programme for the detection of Chronic Kidney Disease (CKD) in the Republic of Macedonia. Health authorities, nephrologists and general physicians should collaborate on the detection of CKD.

"There is evidence that early therapeutic intervention in patients with chronic kidney disease or diabetes can delay the onset of complications and improve outcomes. For example, the UKPDS [79, 80], STENO-2 [81] and ADVANCE studies [82, 83, 84] all demonstrated that tight control of blood glucose level and blood pressure (and lipids in STENO-2) significantly reduced the incidence and progression of diabetic kidney disease. In people with type 2 diabetes, inhibition of the renin-angiotensin-aldosterone system using an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) decreased the progression from normoalbuminuria to microalbuminuria [85] and slowed the development of ESRD [86]. Thus the use of an ACE inhibitor or ARB is now standard therapy for patients with diabetic nephropathy, as well as glucose, lipid and blood pressure control." [76]

12.1 How should we act now?

We are going to repeat our message from 2008 [77]: "there is an urgent need for a screening programme for the detection of CKD" and we will add as well as of diabetic kidney disease in the Republic of Macedonia.

We can follow the steps suggested by Atkins and Zimmet (76):

"i. prevention of type 2 diabetes;
ii. screening for early diabetic kidney disease;
iii. increasing patient awareness of kidney disease;
iv. using medications of proven strategy"

"The ultimate challenge is to get action from primary health care to all higher levels, from the individual patient, to those at risk, in various health jurisdictions, in all countries despite varying economic circumstances and priorities. The problem is a global one and yet requires action at a local level; prevention screening and treatment strategies; education, including increasing awareness both in diabetic patients and those at risk of developing diabetes; and health priorities and governments. Basic research and clinical trials searching for a new understanding and therapies must be supported." [76]

In our country we should work harder on the prevention of diabetic kidney diseases, to stop or postpone the development of CKD and chronic renal failure with modern therapy and the need for RRT.

13. References

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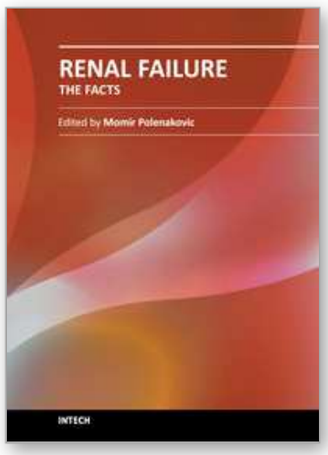

Renal Failure - The Facts

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The book "Renal Failure - The Facts" consists of some facts about diagnosis, etiopathogenis and treatment of acute and chronic renal failure. Acute, as well as chronic renal failure is great medical problems and their treatment is a burden for the budget of each government. The purpose of the chapters is to present some important issues of diagnosis and causes of AKI, as well as caused by snakes and arthropods, after cardiac surgery, as well as some therapeutic achievements in AKI. Well presented are the psychological condition in patients on haemodialysis, as well as the treatment of diabetic uremics. The book is aimed at clinicians with a special interest in nephrology, but it should also prove to be a valuable resource for any generalists who encounter a nephrological problems in their day-to-day practice.

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