

Diabetes: Changing the Fate of Diabetics in the Dialysis Unit

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Key Words

Diabetes mellitus · End-stage renal disease · Diabetic nephropathy · Renal replacement therapy · Maintenance hemodialysis

Abstract

The prevalence of diabetes mellitus (DM) is very high worldwide. According to the World Health Organization in 2000 the worldwide prevalence of DM was 171,000,000. Diabetic nephropathy is a major vascular complication of DM. If DM is not treated early and adequately, many diabetic patients may reach end-stage renal disease (ESRD) secondary to advanced irreversible diabetic nephropathy. In many countries diabetic nephropathy has become the single most frequent cause of prevalent ESRD patients undergoing maintenance hemodialysis (MHD). In the early era of renal replacement therapy (RRT) by means of intermittent hemodialysis the prognosis of diabetic patients undergoing MHD was extremely poor and disappointing. While the prognosis of patients suffering from diabetic ESRD and maintained by chronic intermittent dialysis has greatly improved, the rehabilitation rate and survival of these patients continue to be worse than those of non-diabetic patients. A preexisting severely compromised cardiovascular condition, vascular access problems, diabetic foot disease, interdialytic weight gain, and intradialytic hypotension explain most of the less favorable outcome. Despite improved techniques and more

aggressive medical therapy in recent years, a review of the fate of diabetics in dialysis units since 1972 reveals that these patients have had significant morbidity and mortality. We still have a long way to go in order to achieve more ideal outcomes for our patients. Most of the diabetic ESRD patients are still maintained by MHD, but they can choose other modalities of RRT such as chronic ambulatory peritoneal dialysis (CAPD), kidney and kidney plus pancreas transplantation. The results of different studies and national registries on the mortality and morbidity of ESRD patients being maintained on different modalities of dialysis are conflicting. It can be concluded that the two modalities of dialysis (CAPD and MHD) are almost comparable in terms of survival. The recent suggestions for nocturnal daily hemodialysis, short daily hemodialysis, and an integrative care approach for the management of diabetics with ESRD provides better promise for these patients.

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Introduction

The prevalence of diabetes mellitus (DM) is very high worldwide. According to the World Health Organization (WHO), in 2000 the worldwide prevalence of DM was 171,000,000. In 2005, the WHO estimated that by 2030 the worldwide prevalence of diabetes will reach 366,000,000 [1]. End-stage renal disease (ESRD) second-

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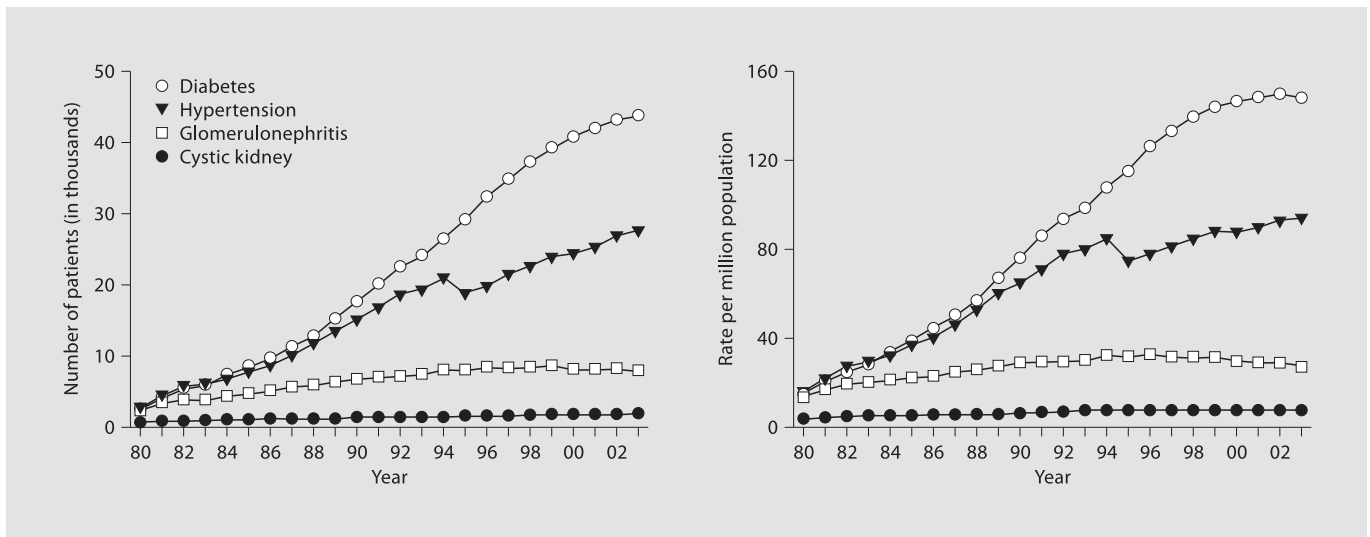


Fig. 1. The incident counts and adjusted incidence rates by primary diagnosis in ESRD patients according to the USRDS.

ary to advanced diabetic nephropathy (DN) requiring renal replacement therapy (RRT) is one of the most serious complications of DM. According to the 2005 United States Renal Data System (USRDS) estimates, the number of patients suffering from DN and ESRD who are admitted to dialysis units is increasing dramatically. The incidence of reported ESRD was 4.3% with type-1 DM and 40.5% with type-2 DM [2]. Figures 1 and 2 reveal the incidence and prevalence of DM in dialysis according to the USRDS. The incidence of patients with DN requiring dialysis is globally significant. 36 and 22% of incident dialysis patients in Germany and Australia, respectively, have ESRD due to DN [3]. This figure is no less in developing countries, for instance in Iran 25.2% of incident dialysis patients are reported to have ESRD as a result of DN [4]. Figure 3 shows the incidence of RRT according to different registries [5]. Indeed it can be claimed that many developed and developing countries are in the midst of an epidemic of ESRD. Part of this epidemic can be explained by the increase in life expectancy that has occurred worldwide in the past two centuries [6]. Currently the effect of general health improvement is more pronounced in developing countries. For example in Iran, a country which is considered to be a medium human development country, the life expectancy at birth increased to 70.1 years in 2002. As a result, the total population has increased from 33.4 million in 1975 to 68.1 million in 2002. In Pakistan which is considered to be a low human development country, the total population in

1975 was 70.3 million, and in 2002, it increased to 149.9 million. These figures for countries with high human development, e.g. Belgium, have changed less dramatically; the population was 9.8 million in 1975 and 10.3 million in 2002. In the USA the population grew from 220.2 million in 1975 to 291.0 million in 2002 [7]. The remarkable population growth which is being observed in developing countries is a welcome consequence of decreased mortality during infancy and young adulthood, better nutrition and the control of infections, and improved education. An unwanted consequence of these improvements has been the emergence of chronic metabolic diseases including ESRD. It can be concluded from this fact that, in the third millennium, the global epidemic of ESRD will be of importance worldwide and more importantly in developing countries. This fact may not be quite evident as the prevalent worldwide ESRD data are reported from patients who are undergoing maintenance hemodialysis (MHD). In developing countries, the number of patients reaching dialysis is dramatically less than the number of patients who die before reaching dialysis. Another major problem in the developing world is the lack of reliable statistics regarding the incidence and prevalence of diseases, morbidity, and mortality.

Even for the developed countries, providing enough funds for management of RRT has not been easy, and certainly for the developing countries, it is a dream. These facts impact the fate of diabetics in the dialysis unit and elsewhere. Indeed it is very hard to improve the fate of any

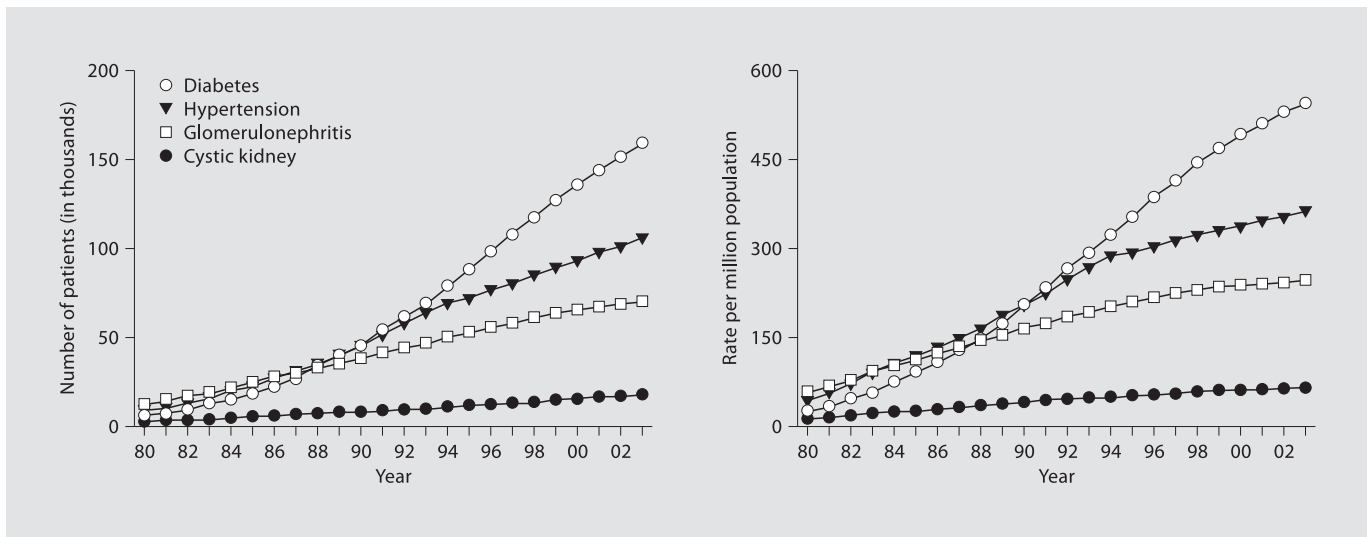


Fig. 2. Prevalent count and adjusted rates by primary disease according to the USRDS 2005 annual data report.

disease in the presence of poverty. Even if newer technology becomes cheaper in the future, the scarcity of funds, wealth and infrastructure in the underdeveloped world will be a barrier to changing the fate of the diabetic patient.

Changing the Fate of Diabetics in the Dialysis Unit

In a symposium on diseases of kidney reported in 1971 Williem J. Kolff was quoted as saying in 1938, 'Gradually the idea grew in me that if we could only remove 20 g of urea and other retention products per day we might relieve this man's nausea and that if we did this from day to day, life might still be possible' [8]. Dunea [8] started his article after this statement and wrote, 'Within three decades dialysis has revolutionized the field of nephrology and opened new vistas in the treatment of uremia. ... Yet, dialysis gradually outgrew its difficult beginnings and became established among the great medical achievements of our age.' In this article there is no mention of the diabetic ESRD patient. A year later in 1972, Ghavamian et al. [9] report on 9 patients with renal failure resulting from DN who were treated by hemodialysis. The average duration of diabetes was 21 years and the average duration of nephropathy was 26 months. One patient survived for more than 3 years. The others survived 9, 20, 19, and 13 months, respectively. Overall mortality was 78% at the end of 1 year. All patients had problems with clotting or

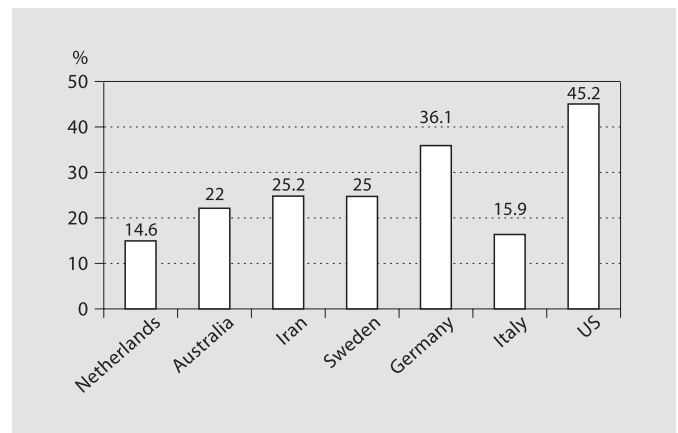


Fig. 3. Year 2000 percentage of incident renal replacement patients with diabetes as the primary diagnosis according to national registries. Modified with kind permission from Prof. Locatelli.

infection of the bloodstream access routes or both. All had further visual deterioration. Neuropathy was not accelerated. Muscle wasting, hypoproteinemia, and fluid overload were common. Dialysis for such patients may be considered as a palliative measure with little likelihood of long-term survival or improvement in quality of life. Four of their patients were male, 3 female, and the age ranged from 26 to 49 years. The duration of proteinuria was 1–5 years.

It is evident that the problems facing diabetic ESRD patients are still the same, maybe with less ophthalmologic problems but more atherosclerotic cardiovascular disease (CVD) and congestive heart failure.

This was the fate of a diabetic ESRD patient in a developed country such as the USA in the early 1970s. There is no doubt that in those days there was no hope even for non-diabetic ESRD patients to have access to dialysis treatment even for one day in many countries. Certainly at present we are equipped with much better technology, medications and understanding of the pathophysiology of the disease, but still we have a long way to go in order to achieve more ideal outcomes for diabetic ESRD patients.

The situation for all ESRD patients was the same until the passage of public law 92-603(HR1) which allowed the federal government to fund the treatment of approximately 85–90% of Americans with ESRD.

Approximately 13,000 patients were being treated by intermittent hemodialysis and 200–300 by peritoneal dialysis when the law became effective in July 1973. Additionally, about 2,400 patients/year received kidney transplants. Publicity related to passage of the bill resulted in a large influx of new patients. The potential impact of the law is put into perspective by envisioning 10,000 to 13,000 new patients entering treatment each year [10]. Nevertheless, 9 months after passage of the law, July 1973, many serious difficulties in implementation remained. In his article discussing the major unwanted effects of hemodialysis treatment in all patients, Ginn [10] concluded that major problems remained regarding: (1) nutrition; (2) hypertension; (3) anemia; (4) bone disease in uremia; (5) pericarditis; (6) blood access; (7) hemodialysis equipment, and (8) water treatment in hemodialysis.

Although there is nothing specific related to diabetic ESRD patients from those days, the general status of dialysis and its problems did exist for all ESRD patients. To realize the different status of the early era of dialysis, Ginn [10] stated, 'Dialysis patients often tolerate very low hematocrit values remarkably well, in part because the myocardium becomes conditioned by chronic anemia, and in part because red cell levels of 2,3-diphosphoglycerate (DPG) increases in anemia, especially during androgen therapy. Contrarily, if serum inorganic phosphate is lowered below normal range by dialysis and/or aluminum gels, then 2,3-DPG levels are reduced. Increased levels of 2,3-DPG improve tissue oxygenation by decreasing the affinity of hemoglobin for oxygen. On the other hand, conventional dialysis usually induces a transient combined respiratory and metabolic alkalosis in patients who

often are initially mildly acidotic. Acidosis increases oxygen dissociation whereas alkalosis reduces oxygen dissociation. Continued frequent hemodialysis generally benefits but does not eliminate the anemia. Because of increased needs, regular iron supplements should be given. Some patients respond to oral iron administration. Others require intravenous iron, e.g., up to 50 ml of Imferon infused over several hours. Meticulous care in returning all blood from the dialyzer and minimizing the number of laboratory tests are obviously important. Androgens in large doses, such as 400 mg of testosterone enanthate per week, have been found to benefit many patients who still have kidneys, but their effect in anephric patients is unpredictable. Androgenic side effects have not been severe, even in female patients, if preparations are used which minimize such effects. If they do occur, however, they are irreversible.'

These statements are contrary to our understanding today. Anemia is not tolerated by the medical community. Regardless of the benefit of 2,3-DPG no one will accept hyperphosphatemia, and the recommendation is to bring serum phosphate down to normal for many different reasons including secondary hyperparathyroidism which can by itself adversely effect anemia. The use of androgen is not recommended, and finally, currently acidosis is considered very harmful and bicarbonate dialysate is the ideal solution for patients on dialysis.

As can be seen, insight into the etiology of anemia in ESRD has come a long way. While the trade-off hypothesis could in part explain the different approach in the early 1970s in the management of patients undergoing MHD [11], at present we are equipped with a more effective armamentarium in our fight against uremia. We do not have to wait for one organ to be sacrificed for the survival of another organ, such as the bone sacrificing part of its structure and quality, in order for the body to tolerate and decrease the adverse effects of renal failure on organs such as the nervous system. Gradually some skepticism grew about this phenomenon. A decade later Fine [12] wrote: 'A number of physiologic adaptations in chronic uremia serve to palliate the functional loss imposed on the kidneys by progression of the toxic aspects of the disease process. Logically, therapeutic strategies should seek to reinforce the adaptive responses while suppressing or retarding the toxic progression. However, such strategies are not without pitfalls and limitations.'

Although the role of the kidney in erythropoiesis was known for a long time, there was clearly no knowledge about clinical use of erythropoietin in those days [13]. It was not until the results of a combined phase I and II

clinical trial were published that erythropoietin therapy became clinically relevant [14]. Up to that time 25% of 150,000 ESRD patients on dialysis required intermittent red cell transfusions [15]. It is easy to assume that those patients would have developed unwanted events such as blood-borne infections, hepatitis, iron overload, further bone marrow suppression and HLA antigen sensitization.

Considering the above-mentioned facts, one can imagine how much the fate of diabetic patients has been under constant change in the dialysis unit since 1970.

Today diabetes is the most common global cause of chronic kidney disease (CKD), present in one fourth to two thirds of all patients with renal impairment [4, 16]. Anemia is more severe in diabetic ESRD patients and 2–3 times more prevalent in diabetics with CKD and ESRD than in non-diabetics with the same degree of renal impairment [17]. It has recently been recognized that in diabetic patients anemia is seen not only in pre-terminal renal failure, but frequently also in patients with only minor derangement of renal function [18]. A major cause of anemia is an inappropriate response of erythropoietin to anemia. Additional factors are iron deficiency and iatrogenic factors, e.g. ACE inhibitor treatment. Because most of the late complications of diabetes involve ischemic tissue damage, it would intuitively be plausible that treatment with human recombinant erythropoietin should be beneficial to ESRD patients. With regard to the question of the management of anemic patients with DN, there is not sufficient evidence from controlled clinical trials to come up with a satisfactory answer. The question remains whether correction of anemia with erythropoietin treatment is beneficial with respect to diabetic end-organ damage in patients with diabetic ESRD. The new KDOQI anemia guidelines published in May 2006 define anemia as a Hb of <13.5 g/dl for males and <12.0 g/dl for females and a target Hb of ≥ 11 g/dl with caution when intentionally maintaining Hb at >13 g/dl. For target iron stores, the recommendation is a TSAT of at least 20%, and a lower ferritin limit of 200 ng/ml in HD-CKD and 100 ng/ml in non-HD-CKD [19]. A ferritin level of >500 ng/ml is not recommended. Adjuvant therapy such as L-carnitine and ascorbate are not routinely recommended because of low quality evidence, lack of efficacy, and also safety concerns regarding ascorbate. Androgen use is not recommended as current guidelines reflect serious safety concerns. Evidence for efficacy is low quality.

A hyporesponse to an erythropoiesis-stimulating agent (ESA) and iron therapy can occur. The patient with

anemia and CKD should undergo evaluation for specific causes of hyporesponse if the Hb level is persistently <11 g/dl, and if the ESA dose is equivalent to epoetin of >500 IU/kg/week. Factors most commonly associated with persistent failure to achieve target Hb levels for at least 6 months despite ESA therapy include persistent iron deficiency, frequent hospitalization, hospitalization for infection, temporary catheter insertion, permanent catheter insertion, hypoalbuminemia, and elevated C-reactive protein (CRP) levels. Other contributing factors include pancytopenia/aplastic anemia, hemolytic anemia, chronic blood loss, cancer, chemotherapy, or radiotherapy, inflammatory diseases, acquired immune deficiency syndrome, and infection.

Nowadays susceptibility to infection is more common in countries where the dialysis dose is less than the recommended dose of the HEMO study [20]. Financial restrictions and a shortage of manpower and equipment especially in diabetic ESRD patients play a role in the susceptibility to infections. In dialysis units in developed countries, tuberculosis has been reported in immigrants from endemic areas; this is especially more common in DN [21]. Except in patients suffering from HIV and ESRD, more efficient dialysis and as a result better nutrition has decreased the incidence of TB in diabetics in the dialysis unit.

Despite significant improvements in technology and the knowledge of RRT, the morbidity and mortality of ESRD patients remains high. Poor nutrition and protein and calorie intake are major contributing factors for protein-energy malnutrition (PEM). The recommendations for better and healthier nutrition have not changed since the early 1970s. The recommendation was: '... to prevent (or to correct) body protein deficiency, to provide adequate calories ... usually 1–1.5 g of high biologic value protein per kg/day' [10]. Although the importance of adequate nutrition and calories has been recognized since the 1970s, for various reasons inadequate nutrition has continued to be a problem. There are many causes of protein-calorie malnutrition in maintenance dialysis patients. The three major causes are probably a low nutrient intake, intercurrent or underlying illnesses, and the dialysis procedure itself [22]. In underdeveloped countries, a shortage of equipment and manpower plus the expense result in inadequate dialysis. Sometimes uneducated patients decide to eat less so as to have less waste byproduct of protein. This poor nutrition decreases the blood urea measured, so the patients think their need for dialysis will be less, while it is known that low serum nitrogen levels as a result of PEM are associated with an increased

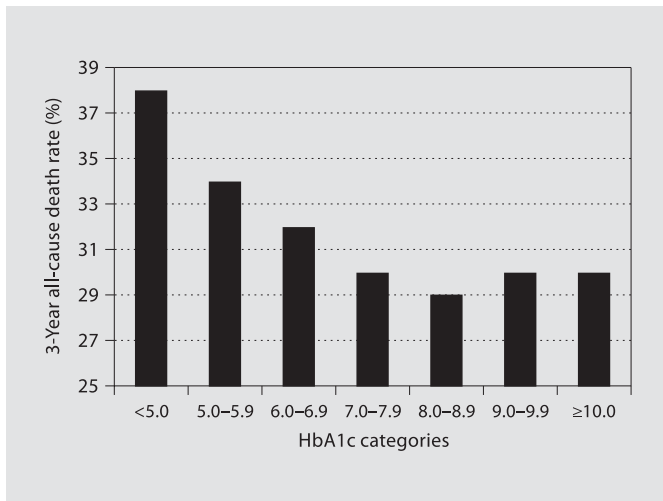


Fig. 4. Raw unadjusted mortality rate.

mortality in ESRD patients undergoing MHD. Even in developed countries the prescribed dose of dialysis is usually not adequate. The result of inadequate dialysis is loss of appetite and anorexia leading to decreased protein and calorie intake. Diabetic patients appear to be more sensitive than non-diabetics to inadequate dialysis [23]. PEM is a common phenomenon in maintenance dialysis patients and a risk factor for poor quality of life and increased morbidity and mortality, including cardiovascular death in these individuals [24]. To explore the effects of CRP and the normalized protein catabolic rate on serum albumin and creatinine, the laboratory data from 364 hemodialysis patients were analyzed for 6 consecutive months using a multivariate mixed model with conservative biases. The conclusion was that inflammation and dietary protein intake exert statistically significant and clinically meaningful competing effects on serum albumin and creatinine over time. Therapeutically, the model would predict that by increasing the normalized protein catabolic rate from 0.8 to 1.2 g/kg/day, one might expect an increase in albumin of approximately 0.5 g/dl and an increase in creatinine of approximately 4.4 mg/dl over a 6-month period, all else being equal [25]. Atherosclerotic CVD, PEM and the wasting syndrome are common in patients with ESRD and contribute to the increased morbidity and mortality of these patients. Serum albumin, CRP, and interleukin-6 predict malnutrition [26]. In a random sample of 4,025 patients the prevalence of coronary heart disease was 38%. The incidence was significantly more common in diabetic patients (46.4%)

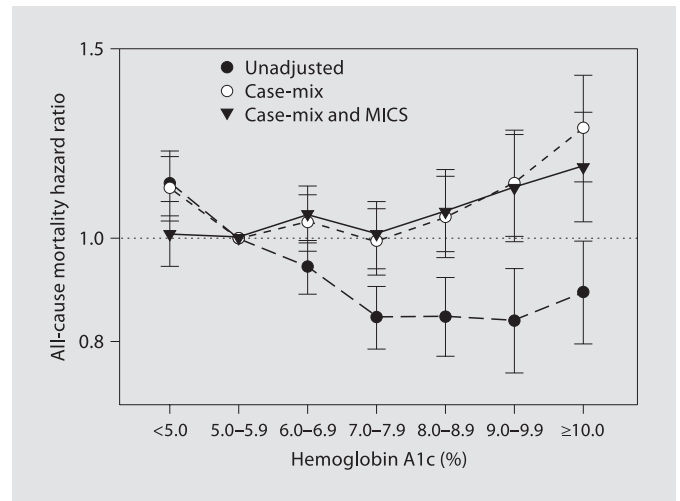


Fig. 5. Mortality rate adjusted for case mix and malnutrition-inflammation complex syndrome (MICS).

than in non-diabetic patients (32.2%). Much of the cardiac pathology is acquired even prior to establishment of end-stage renal failure [27]. In another study about causes of death among patients with ESRD, 84 diabetic and 74 non-diabetics were evaluated by coronary angiography. Triple vessel coronary artery disease was significantly more common among the diabetic subjects (27 vs. 12%, $p = 0.005$) [28].

Glycemic control appears to impact the survival of diabetic ESRD patients. In a study investigating 150 diabetic ESRD patients, it was found that good glycemic control (HgbA1c <7.5%) predicted better survival [29]. In order to determine the optimal target for glycemic control in diabetic dialysis population, the DaVita national dialysis database was analyzed. Of 82,933 patients undergoing MHD in DaVita outpatient clinics over 3 years, 26,187 MHD patients had HbA1c measurements at least once. Raw mortality data revealed that lower HbA1c values were associated with higher all-cause mortality rates (fig. 4); accordingly, unadjusted survival analyses indicated lower death risks in MHD patients with higher HbA1c values. Similar findings were noted with cardiovascular death. However, after adjusting for potential confounders including case-mix, age, gender, race, dialysis vintage and dose, comorbidity, and surrogates of the malnutrition-inflammation complex syndrome (MICS), HgbA1c values of >8% were incrementally associated with higher all-cause and cardiovascular death risk. The authors concluded that the greatest survival was observed with HbA1c of <8% (fig. 5) [30].

Diabetic ESRD patients on dialysis respond to insulin differently. The risk for hypoglycemia increases during hemodialysis sessions. The compensatory homeostatic response to hypoglycemia may increase the risk of abnormal blood pressure regulation. Similarly, if glucose-free dialysates are used, then diabetic patients may become hypoglycemic, as insulin is not removed during dialysis and there may be an inappropriate neuroendocrine response [31].

In a randomized, placebo-controlled, unblinded, cross-over study of 44 hemodialysis patients, 34 patients without diabetes and 10 patients with diabetes were allocated to treatment with and without glucose in the dialysate during two 10-week periods. Blood pressure and blood glucose levels were determined 5–8 times in each dialysis session during both periods. Systolic and diastolic blood pressures decreased with glucose in the dialysate in patients with ESRD, presumably because of insulin-induced vasodilatation in patients without diabetes. Blood glucose level regulation improved in the diabetic subgroup, and blood glucose levels were not greater in patients with diabetes with glucose in the dialysate [32].

The presence of autonomic dysfunction can also impair patients' ability to maintain blood pressure following a large degree of fluid removal by ultrafiltration. The incidence of intradialytic hypotension has been reported to be from 5 to 40% of all the patients on MHD [31]. As dysfunction of the autonomic nervous system is more common in diabetic ESRD patients, intradialytic hypotension is more common in this subgroup of dialysis patients [33]. Activation of the Bezold-Jarisch reflex, which involves decreased sympathetic and increased parasympathetic nervous system activity, may also occur with ultrafiltration, causing sudden intradialytic hypotension [34]. A less common and much more obscure derangement of blood pressure control during hemodialysis in ESRD patients is increases in blood pressure, that is, intradialytic hypertension. This syndrome is multifactorial and the pathogenesis is not clearly understood [35]. Most patients with ESRD on MHD have chronic hypertension. There is no disagreement on the role of hypertension as a risk factor for increased cardiovascular or cerebrovascular events in the general population [36]. Despite the accepted danger of high blood pressure in the general population, there is evidence that in ESRD patients there is a link between low blood pressure and poor survival [37]. This phenomenon has been referred to as reverse epidemiology, and besides hypertension, other known risk factors behave in opposite ways in patients with ESRD as a result

Table 1. Components of reverse epidemiology in dialysis patients

Obesity
Hypercholesterolemia
Hypertension
Homocysteine
Creatinine
Calcium
Potassium
Iron
Advanced glycation end products
Others: leptin, bicarbonate

of MICS. Components of reversible epidemiology are shown in table 1.

There are many different intradialytic and interdialytic complications that diabetic ESRD and ESRD patients have, albeit occasionally they are more pronounced in diabetic ESRD patients. Adverse cardiovascular effects of hyperphosphatemia may be more extensive and severe in diabetic ESRD patients because of the unwanted effects of nephropathy on the cardiovascular system prior to the establishment of ESRD.

The well-being of diabetic patients is greatly influenced by diabetic foot disease. In one report, diabetic foot disease resulted in amputation of lower limbs in 14% of ESRD patients [38]. The association of diabetic foot lesions with advanced DN may be explained by the long duration of diabetes, macroangiopathic and neuropathic complications or a combination of both [39].

Another major determinant of the fate of diabetic ESRD patients includes hemodialysis equipment. In the early 1970s approximately 50–55% of patients were being treated by coil dialyzers, some 25–30% by parallel plate units, and about 20% by hollow fiber capillary dialyzers [10]. At present, dialyzers are more biocompatible and efficient with lower capacity facilitating more efficient dialysis in comparison with the past [40].

Patient survival in diabetics on maintenance dialysis is lower than that seen in non-diabetics. As noted in the 2005 USRDS report, approximately 25% of diabetic ESRD patients survived 5 years after the initiation of dialysis [2]. Survival also varies inversely with age, being best in young normotensive patients without any clinical CVD [5]. The USRDS excludes patients who died within the first 90 days of the initiation of dialysis, so the result is of limited value [2]. The situation is comparable in other countries. In Iran, the dialysis outcome was reported for

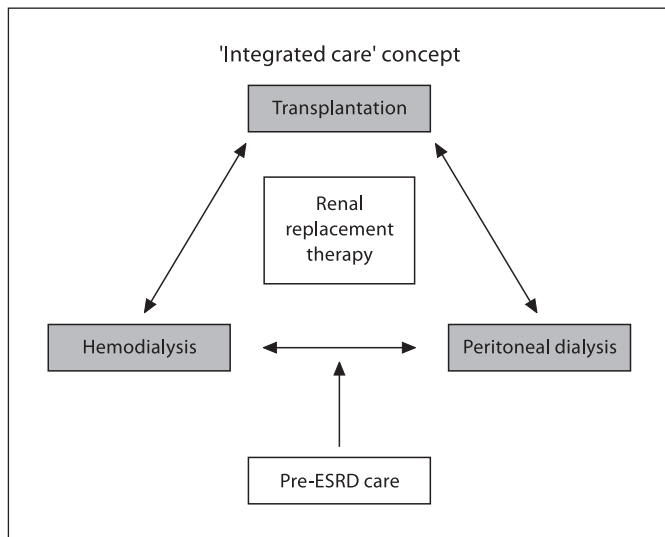


Fig. 6. Different modalities of renal replacement therapy.

68 patients with DN and 66 non-diabetics. The mortality was 52.9% in diabetic patients. Survival seems somewhat better because of the selection criteria [41]. The adequacy of dialysis and the decrease in nutritional status may also be contributors to the worse outcome in diabetics. Diabetic patients appear to be more sensitive than non-diabetics to inadequate dialysis prescriptions.

The morbidity associated with insufficient dialysis in diabetics may be mediated through anorexia, leading to decreased caloric and protein intake. Death by withdrawal from dialysis is also more likely to occur in diabetics.

MHD is the most common dialysis modality used worldwide [2]. For many reasons, different modalities may be more ideal for different patients. In a national cohort study of 1,041 patients starting dialysis (274 patients receiving peritoneal dialysis and 767 patients receiving hemodialysis at baseline) it was concluded that the risk of death in patients with ESRD undergoing dialysis depended on dialysis type [42]. It has been suggested that short daily hemodialysis will improve the quality of life, rate of hospitalization and mortality [43]. It has been suggested that home daily nocturnal hemodialysis may have the highest survival for diabetic patients on MHD [44]. Nocturnal hemodialysis offers a high dose of dialysis, improves biochemical parameters and quality of life. Despite the significant losses, in a study of 24 patients under daily nocturnal hemodialysis, protein malnutrition was not seen. Most of the patients were anabolic [45]. Further studies are needed to see how short daily hemodialysis or

Table 2. The integrated care concept

- Patient survival and quality of life are two very important factors in the selection of a dialysis modality
- The majority of studies have compared the two modalities as 'competitors' rather than as 'complementary' techniques
- Since every RRT has a technical 'drop-out', it is very likely that a patient will need several modalities during his lifetime and transfer from one technique to another will often be needed
- Survival studies of patients on RRT should evaluate 'the best therapeutic strategy', i.e. the succession of modalities that:
 - Allows an optimal total survival
 - Utilizes the specific advantages of each modality at any given moment of the patient's life in an optimal way
 - Avoids the drawbacks of each modality as much as possible
- Appropriate statistical statistics should be applied for correct analysis

daily nocturnal hemodialysis affect diabetic ESRD patients.

Finally, it has been suggested that the different modalities of RRT should be complementary and not competitive. For this reason an integrative care approach is necessary for ESRD patients whereby, when appropriate, patients are started on peritoneal dialysis, followed by kidney transplantation whenever possible and transferred timely to hemodialysis when peritoneal dialysis-related problems arise. This approach would perhaps enable us to make use of the entire RRT arsenal (table 2; fig. 6) [46].

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