Review Articles

The diabetic kidney - “A systematic, diabetes renal service, better for patients and clinicians”

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Background

Abstract
The prevalence of diabetes in Sudan and the Eastern Mediterranean and Middle East Region (EMME) in general is increasing and as with many other countries with high diabetes prevalence, the onset of Type-2 diabetes tends to occur at a relatively young age. It is therefore, predicated that the burden of diabetic nephropathy in the region will increase as the incidence of diabetes increases and the age of onset declines in a predominantly young population (37.5% of the population are below 15 years). Diabetic kidney disease is a serious complication of diabetes that can lead to end stage renal disease (ESRD). It is now the most common cause of ESRD in patients accepted onto renal replacement therapy programmes in the developed countries and becoming a significant cause of ESRD in the rest of the world. The risk of developing diabetic ESRD is higher in Type-1 diabetes but in absolute terms more patients with Type-2 diabetes develop ESRD and are treated. In addition, chronic kidney disease amplifies the cardiovascular risk of diabetes and with advancing nephropathy, the mortality rate increases. Patients with nephropathy have a greater probability of dying than of requiring renal replacement therapy. To meet this challenge closer liaison between diabetologists and nephrologists is required to ensure effective surveillance of renal function, to increase early referral and to agree protocols of subsequent care. A systematic, diabetes renal service would add value to patient care.

Key words: Diabetes, Diabetic Kidney Disease, Combined Diabetic Renal Service...
Diabetes Mellitus: Historical background
Ancient Egypt was the first civilization known to have an extensive study of medicine and to have left behind written records of its practices and procedures. The Ebers' Egyptian papyrus written around 1500 B.C., the oldest preserved medical document made reference to diabetes mellitus with an elegant and accurate clinical observation and mentioned remedies for the treatment. It was discovered by Professor George Moritz Ebers in 1872 in Luxor, Upper Egypt.

The papyrus measures about 20.23 meters in length and 30 cm. in height and contained the earliest descriptions of the symptoms of diabetes as the passing of too much urine (polyuria) and contained one of the oldest forms of therapies - diet therapies to eliminate urine which is too plentiful. A measuring glass filled with water from the bird pond, elderberry, fibres of the asit plant, fresh milk, beer-Swill, flower of the cucumber, and green dates was prescribed by the ancient Egyptian physician.

Diabetes Mellitus: The Global pan epidemic
The number of people with diabetes is increasing and the WHO Global Burden of Disease predicted a worldwide increase in the prevalence of diabetes in adults from 2.8% in 2000 to 4.4% by the year 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. The urban population in developing countries is projected to double between 2000 and 2030. The most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people >65 years of age.

In 2007, the EMME had the highest prevalence of Type-2 diabetes. An estimated 24.5 million people, or 7.7% of the adult population, had diabetes with the number of those with diabetes expected to nearly double by 2025. Similarly the number of persons with impaired glucose tolerance (IGT) is expected to also rise markedly by 2025, increasing the likelihood of further increases in the prevalence of diabetes as the century proceeds. Studies performed in six countries – Bahrain, Egypt, Kuwait, Oman, Saudi Arabia and United Arab Emirates have shown their current diabetes prevalence to be among the world’s 10 highest, and a similar situation applies for the prevalence of IGT in some of these countries.

In 2000, the excess global mortality attributable to diabetes was estimated to be 2.9 million deaths, equivalent to 5.2% of all deaths. Excess mortality attributable to diabetes accounted for 2–3% of deaths in poorest countries and over 8% in the U.S., Canada, and the Middle East. In people 35–64 years old, 6–27% of deaths were attributable to diabetes. Diabetes is the fourth largest cause of death in the EMME. The increase in the disease prevalence in the EMME is attributed to the significant social and economic development, progressive urbanization and an increasing life expectancy witnessed over the past 2-3 decades.

Traditional lifestyles and dietary patterns have been replaced by sedentary lifestyle and unhealthy diet particularly in the urban communities. This has led to increasing rates of overweight and obesity. Higher rates of glucose intolerance are consistently observed in urban areas and have been associated with socio-demographic transformation involving changes in nutritional patterns, physical activity, and obesity. Khan et al, reported that the changes in dietary habits that occurred in 20 years in the Kingdom of
Saudi Arabia took 137 years in Japan and 200 years in UK (20) and similar transformation has been reported in Bahrain since the 1970s (21).

There is now extensive evidence on the optimal management of diabetes, offering the opportunity of improving the immediate and long-term quality of life of those with the condition. Unfortunately, such optimal management is not reaching many, perhaps the majority of the people who could benefit. Accordingly, the International Diabetes Federation (IDF) has developed a global guideline (22).

**Diabetes Mellitus: The Sudan perspective**

Diabetes in Sudan is associated with poor glycaemic control, high prevalence of complications, a low quality of life and increased morbidity. The overall prevalence of long-term complications in patients with a median duration of diabetes of 9 years has been 67% (23). The prevalence of microvascular complications was; retinopathy 43%, nephropathy 22%, neuropathy 37%, for macrovascular complications the prevalence was, cardiovascular disease 28%, peripheral vascular disease 10% and cerebrovascular accidents 5.5% (24).

The incidence of Type-I diabetes in children (7-14 years) living in Khartoum had increased by 71% between 1987 and 1990. The prevalence was approximated to 0.1%. These rates were higher compared to rates from Kuwait, Saudi Arabia, and Poland reported during the same period but were similar to rates reported from Italy and France (25). In 1996 Elbagir et al, estimated the crude prevalence of diabetes in the adult population at 3.4% (men, 3.5%; women, 3.4%) and 2.9% (men, 2.2%; women, 3.3%) for impaired glucose tolerance (IGT). The highest crude prevalence was in Khartoum State (8%) followed by the northern parts of Sudan (5.5%) and the lowest (0.9%) in the western parts of Sudan (26).

The incidence and prevalence of diabetes are increasing in Sudan. The World Health Organisation has estimated an increase from 447,000 in 2000 to 1,277,000 persons in 2030 (6). However, in 2007 the WHO estimated the prevalence of diabetes mellitus and IGT in Sudan among people between the age of 20-79 years to be 3.2% and 2.3% respectively (Table 1). This is expected to rise to 3.8% and 2.5% respectively by 2025 (6).

<table>
<thead>
<tr>
<th>Population (20-79)</th>
<th>DM prevalence (%)</th>
<th>Number of people with DM (000's) in the 20-79 age group</th>
</tr>
</thead>
<tbody>
<tr>
<td>(000's) National</td>
<td>Comparative Rural</td>
<td>Urban Male Female 20-39 40-59 60-79 Total</td>
</tr>
<tr>
<td>19,056</td>
<td>3.2 4.0</td>
<td>255.9 351.6 244.5 363.0 71.6 334.3 201.6 607.5</td>
</tr>
</tbody>
</table>

In 2008 Abu-Aisha et al., investigated the prevalence of hypertension and obesity in police forces households in Khartoum and reported that out of 115 discovered hypertensive subjects, 10 (8.7%) of them were diabetics. Diabetes was more likely present in hypertensive compared to non-hypertensive subjects (27). In another unpublished study, Abu-Aisha et al, estimated the prevalence of diabetes to be 6.99%. In the 275 subjects tested for blood glucose in this study, diabetes prevalence was above the projection of the WHO for Sudan. These results indicate that diabetes is becoming a major public health problem (28). Although there were several other studies addressing different clinical aspects of diabetes (29-50), there is only one study addressing the economic burden of the disease in Sudan (51,52).
Diabetic Kidney Disease

Diabetic nephropathy is a clinical syndrome characterized by persistent albuminuria, arterial blood pressure elevation, a relentless decline in glomerular filtration rate, and a high risk of cardiovascular morbidity and mortality. This major life-threatening complication develops in approximately 35% of type 1 diabetic patients. Table 2 shows the factors that increase the risk of a diabetic patient developing diabetic kidney disease.

Table 2: Factors increase the risk of a diabetic patient developing Diabetic Kidney Disease

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long history of diabetes</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
</tr>
<tr>
<td>Higher than average blood pressure</td>
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<tr>
<td>Higher than average HbA1c</td>
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<tr>
<td>Dyslipidaemia</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Age (older patients)</td>
</tr>
<tr>
<td>Male patients</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>Family history of renal disease</td>
</tr>
<tr>
<td>Family history of vascular disease</td>
</tr>
<tr>
<td>Elevated baseline urinary albumin loss</td>
</tr>
</tbody>
</table>

The epidemiology of diabetic nephropathy has been best studied in patients with Type-1 disease, since the time of clinical onset is usually known. Approximately 20% to 30% will have microalbuminuria after a mean duration of diabetes of 15 years. Less than half of these patients will progress to overt nephropathy; microalbuminuria may regress or remain stable in a substantial proportion, probably related to glycaemic and blood pressure control. Some of the evidence cited in the literature was obtained before the availability of data supporting the efficacy of tight glycaemic control, aggressive blood pressure and lipid control, and the specific benefit of angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs).

Prior to the current period of intensive monitoring and treatment, it was suggested that 25% to 45% of diabetic patients will develop clinically evident disease, the minimal criterion for which is a persistently positive urine dipstick for protein. However, the clinical course of Type-1 diabetes mellitus including its treatment, metabolic outcomes, and long-term clinical complications, has changed dramatically in the past 20 years. Moreover, the Diabetes Control and Complications Trial (DCCT) and its long-term observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study and other clinical trials have demonstrated the powerful effects of more physiologic control of glycaemia on microvascular and macrovascular disease.

The clinical treatment goals of Type-1 diabetes mellitus have changed since the Diabetes Control and Complications Trial (DCCT) demonstrated reduced long-term complications with intensive diabetes therapy. A recent study described the current-day clinical course of Type-1 diabetes and found that after 30 years of diabetes, the cumulative incidences of proliferative retinopathy, nephropathy, and cardiovascular disease were 50%, 25%, and 14%, respectively, in the DCCT conventional treatment group, and 47%, 17%, and 14% respectively, in the EDC cohort. The DCCT intensive therapy group had substantially lower cumulative incidences (21%, 9%, and 9%) and fewer than 1% became blind, required renal replacement therapy, or had an amputation because of diabetes during that time. Treatment innovations, including multiple daily injection regimens, continuous subcutaneous insulin infusion with external pumps, new insulin analogues with more physiologic pharmacokinetic characteristics,
and wide-spread self-monitoring, and improved treatment of comorbidities such as hypertension and dyslipidemia, have all contributed to changes in the management of Type-1 diabetes mellitus. Therefore, the available data suggest that multifactorial intervention targeting blood pressure, albuminuria, glycemic control, and hyperlipidemia will diminish progression of nephropathy and may even induce regression of diabetic nephropathy. Recently, the success of such a combined approach in delaying progression of diabetic microangiopathy has been demonstrated in Type-2 diabetic patients with microalbuminuria\textsuperscript{(68,69)}. It should be mentioned that there appear to be no substantial differences between patients with Type-2 diabetes and those with Type-1 diabetes with respect to initiation, progression, and treatment of diabetic nephropathy\textsuperscript{(70)}.

### Teaching point

**Management of microalbuminuria and proteinuria**

- Inhibition of renin-angiotensin system.
- Tight blood pressure control:
  - <120/70 mm Hg type 1 diabetes.
  - <130/75 mm Hg type 2 diabetes.
- Moderate protein intake:
  - \(\approx 1 \text{ g/kg body weight/day}\).
- Tight blood glucose control.
- Statin therapy.
- Aspirin.

### Diabetic Kidney Disease: Sudan perspective

The accurate prevalence of diabetic nephropathy in Sudan remains undetermined however, few studies has highlighted a high burden of the disease. Osman et al, reported in 1987 that diabetes was the fourth common cause of renal failure in Khartoum after chronic glomerulonephritis, obstructive nephropathy (stone disease) and hypertension\textsuperscript{(71)}. Abboud et al investigated in 1989 the causes of established chronic renal failure presenting to Soba University hospital in Khartoum and reported a 9% prevalence of diabetic nephropathy\textsuperscript{(72)}. In 1991, Elmahdi et al reported a prevalence of diabetic nephropathy in Sudan of 9.2% based on the presence of proteinuria >0.5g/24h or blood urea of >40mg/l\textsuperscript{(40)}. In 1995, Elbagir et al, investigated the pattern of long-term complications in Sudanese insulin-treated diabetic patients and reported a 22% prevalence of diabetic nephropathy\textsuperscript{(24)}. Surprisingly a renal histology study did not identify any diabetic nephropathy among renal biopsies from 86 consecutive patients studied by light and immunofluorescence microscopy\textsuperscript{(73)}. In a most recent pilot study Abu-Aisha et al, identified that 13.3% of patient with CKD were diabetics. However, the authors cautioned when interpreting these results due to the small numbers of patients recruited to the study\textsuperscript{(74)}.

Diabetes mellitus is the leading cause of end-stage renal disease (ESRD) in the world. In Sudan, perhaps the historical prevalence rates still prevail with patients with Type-1 diabetes, approximately 20–30% will eventually develop ESRD\textsuperscript{(75)}, whereas about 10–20% of those with Type-2 diabetes will do so\textsuperscript{(76)}. The burden of diabetic nephropathy in Sudan will increase in the future as the incidence of diabetes increases and the age of onset declines, in addition to the poor glycaemic control and the high prevalence of microvascular complications\textsuperscript{(23)}. It is hoped that these effects may be lessened by the use of intensive treatment.

### Teaching point

**Can anything be done to halt the declining renal function and progression to ESRD?**

**Screening of diabetes can halt the decline**

**WHEN**

- Type 1: after 5 years, then annually
- Type 2: at diagnosis, then annually

**HOW**

- Albumin-to-Creatinine ratio in random urine
  - Microalbuminuria = 30-300 mg/g
  - Macroalbuminuria
- Estimate GFR (eGFR) from serum creatinine using formula
- Retinopathy: weak clue

### Implications of diabetic Kidney Disease

Diabetes is estimated to increase the risk of end-stage renal disease (ESRD) approximately 12-fold\textsuperscript{(77)}. In comparison
to the general population, a disproportionately large percentage of patients with ESRD have diabetes. On the other hand, chronic kidney disease amplifies the cardiovascular complications of diabetes and patients with macroalbuminuria and elevated plasma creatinine have a greater probability of dying than of requiring renal replacement therapy in any year. A recent study, showed that with advancing nephropathy, the mortality rate increases. The annual death rates increased with increasing nephropathy (Fig 1). The annual death rate from the no nephropathy stage is 1.4%, from microalbuminuria was 3.0%, and from macroalbuminuria was 4.6%. Patients with elevated plasma creatinine or renal replacement therapy had an annual death rate of 19.2%, including 4.0% (1.4 to 6.6%) per year who died from uraemia. Patients with elevated plasma creatinine, but without renal replacement therapy, had an annual death rate of 18.9% (13.3 to 24.6%). For patients with macroalbuminuria, the annual death rate of 4.6% (3.5 to 5.7%) exceeded the rate of progression to worse nephropathy (2.3%; 1.5 to 3.0%). Relative to patients in the stage of no nephropathy, those with microalbuminuria, macroalbuminuria, or an elevated plasma creatinine or renal replacement therapy had a 2.2-fold, 3.4-fold and 13.9-fold increased risk of death, respectively (78).

Fig 1: Annual transition rates with 95% confidence intervals through the stages of nephropathy and to death from any cause. Adler et al. Kid Intern 2003 (reproduced with permission)

The most common cause of death at all stages of nephropathy was cardiovascular disease with a trend for increasing risk of cardiovascular death with increasing nephropathy. The annual death rate due to cardiovascular disease was 0.7% for subjects in the no nephropathy stage, 2.0% for those with microalbuminuria, and 3.5% for those with macroalbuminuria and 12.1% for those with elevated plasma creatinine or renal replacement therapy. Similarly, the proportion of all deaths due to cardiovascular disease increased with each stage of increasing albuminuria being 51% of deaths in no nephropathy stage, 66% of deaths in those with microalbuminuria, and 75% of deaths in those with macroalbuminuria (78).
It is therefore important to identify patient with diabetic nephropathy early to modify the cardiovascular risk factors and retard the progression of the nephropathy and hence is the call for a systematic diabetic renal service.

A systematic diabetic renal service
Management of diabetic nephropathy patients with multiple co-morbid factors is challenging in a routine outpatient setting, and hence a multidisciplinary approach has been advocated. Recent evidence suggested that a joint diabetic renal clinic reduce the rate of progression to ESRD. Liew et al studied patients referred to a joint clinic in a tertiary referral hospital, and found that the time to ESRD was increased by an average of 2 years(79). Joss et al from the same group studied 170 consecutive patients referred from six different diabetic units, and found that patients who were referred early benefited the most from the clinic and the rate of decline was slowed from 0.52 ml/min/month in the first year to 0.27 ml/min/month in the third year(80). A more recent study suggested that the rate of deterioration of renal function can be reduced by aggressive management of risk factors(81).

Diabetic nephropathy is the leading cause of end-stage renal failure. Untreated, it causes continuous decline in glomerular function, worsening hypertension and a marked increase in cardiovascular risk(82,83). Only a small proportion of these patients reach ESRD, because of premature cardiovascular disease, especially in Type-2 diabetes. Therefore, these patients are priority candidates for cardiovascular disease-reducing, as well as renoprotective interventions. Well-controlled blood pressure, treatment of dyslipidaemia and hyperglycaemia, angiotensin-converting enzyme (ACE) inhibition(84), smoking cessation(85) and reduced dietary protein intake all reduce the rate of progression to ESRD(86-91).

The diabetic renal service should be operated by a multidisciplinary team consisting of a consultant in diabetes, a consultant in nephrology, a diabetes specialist nurse, a renal specialist nurse, an anaemia nurse, a pre-dialysis renal specialist nurse, a renal dietician, a renal pharmacist and a podiatrist.

Aims of the diabetic renal service
- To identify, investigate and manage renal disease in patients with diabetes at an early stage, in order to slow the progression to renal failure.
- To institute aggressive management of glycaemic control and co-existing cardiovascular risk factors where feasible.
- Patient and family education
- To accumulate data for the purpose of audit and research.

Referral criteria to the diabetic renal service
- Estimated GFR <60ml/min in Type-diabetes
- Estimated GFR <40ml/min in Type-diabetes
- Proteinuria 2+ or greater, regardless of diabetes type, in absence of infection.
Significant deterioration in creatinine or eGFR following use of ACE inhibitor (increase of 20% in creatinine or reduction in eGFR > 15 above baseline value)
- Suspicion of non-diabetic renal disease (especially if haematuria present)

**Management of diabetic renal disease (Fig.2)**
- Improve glycaemic control (Target HbA1c < 7.0%)
- Apply aggressive targets for control of hypertension

**Figure 2 Aims of diabetic kidney disease management**

<table>
<thead>
<tr>
<th>Delay Progression</th>
<th>Modify Co-morbidity</th>
<th>Treat Complications</th>
<th>Prepare for RRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP Control</td>
<td>Statins</td>
<td>Anaemia Bone disease</td>
<td>Education</td>
</tr>
<tr>
<td>Glycaemic Control</td>
<td>Anti-Platelet Life Style</td>
<td>Acidosis Malnutrition</td>
<td>Modality Choice</td>
</tr>
<tr>
<td>Ace Inhibitors</td>
<td></td>
<td></td>
<td>Access Placement</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
<td>Timely initiation</td>
</tr>
</tbody>
</table>

- Type-1 diabetes <120/70 mmHg
- Type-2 diabetes <130/80 mmHg
- Consider introduction of an ACE Inhibitor in patients with microalbuminuria or overt proteinuria, even if blood pressure is within target.
- Encourage smoking cessation
- In all patients, co-existing cardiovascular risk factors should be managed aggressively.
- Consider starting Simvastatin 40 mg daily and Aspirin 75 mg daily

**Teaching point**

**Prognosis**
- Without intervention, 80% of people with type 1 diabetes and 20-40% of people with type 2 diabetes progress from micro- to macroalbuminuria.
- Albuminuria in people with diabetes is associated with increased cardiovascular risk.
- Diabetic nephropathy is the most common cause of end stage renal disease in the western countries.

**Teaching points**

**Use of Angiotensin-Converting Enzyme Inhibitor (ACEI) And Angiotensin II Receptor Blockers (ARBs)**

- If Protein Creatinine Ratio > 100 mg/mmol (1 gm/24hrs) or in diabetics with microalbuminuria.
- Measure creatinine before and 1 week after starting medications or dose change. If creatinine rise > 20% or fall in eGFR of > 15% consider discontinuation and seek nephrology opinion.
- If eGFR fall by 5-15% recheck in 2-3 weeks to ensure decline is not progressive.
- If potassium > 6 mmol/l stop ACEi or ARB. Stop concomitant nephrotoxic drugs (e.g. NSAIDs), reduce or stop potassium-retaining diuretics and reduce loop diuretic dosage if there are no signs of hypervolaemia. Consider arranging low potassium diet and re-instituting ACEi or ARB once potassium normalised.
References


Diabetic kidney Ibrahim H Fahal


