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The global challenge of chronic kidney disease

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Nephrology Forum

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CASE PRESENTATION

A 48-year-old African woman presented at the Sheffield Kidney Institute complaining of lethargy as well as nausea and vomiting. She had always lived in a sub-Saharan African country devastated over the last quarter-century by war and internal conflict. Over the last 3 years, her health had been deteriorating, with progressive swelling of her legs. She had had nocturia for the last 5 to 6 years. She also mentioned that her two pregnancies had been complicated by severe hypertension and edema and were therefore terminated early. She was not followed up subsequently, and she returned to her village, which has only one general medical practitioner and a witch doctor. She also gave a family history of chronic kidney disease (CKD); her older brother died from end-stage renal disease (ESRD) a few years ago.

When she sought a medical opinion in the capital city of her country one year prior to her arrival in Sheffield, she was told that she had severe hypertension, heavy proteinuria, and progressive renal insufficiency. Some medication was dispensed to her, but she failed to renew her prescription because of its prohibitive cost. When her condition deteriorated, she returned to the capital city's main hospital, where ESRD was diagnosed. She was told that little could be offered to her in view of the lack of dialysis facilities. She was advised to go back to her village to die. This she would not accept and decided to visit her daughter, who had sought asylum in the UK a few months prior to her own arrival.

When the patient presented to the Sheffield Kidney Institute, she was severely anemic; her hemoglobin was 6.7 g/dL with significant microcytosis (MCV, 72 fl) and hypochromia (MCHC, 28 g/dL). The serum urea was 67 mmol/L and serum creatinine level was 1299 μmol/L (14.8 mg/dL). She was hyperkalemic (K, 6.8 mmol/L) and severely acidotic (serum bicarbonate, 12 mmol/L). Her serum protein and albumin were low at 46 g/L and 18 g/L, respectively. Serum calcium was low, 2.1 mmol/L, and phosphorus raised, 2.2 mmol/L, with a high intact PTH level of 576 pg/mL. Clinically, the patient was fluid overloaded with marked peripheral edema, raised jugular venous pressure, and bilateral basal lung crepitations. Her blood pressure was high, 187/94 mm Hg, and cardiac auscultation revealed a gallop rhythm. Urinalysis showed: +1 protein and 1+ blood. The 24-hour urinary protein excretion was 0.9 g. A chest radiograph revealed marked cardiomegaly and congested lung fields. Ultrasound scan of her kidneys showed them to be small, approximately 6 to 7 cm.

It was apparent that the patient was in end-stage renal failure and required the immediate initiation of hemodialysis, which was instituted through a tunneled jugular venous catheter. Over the subsequent 4 weeks, her condition started to improve, her blood pressure was normalized through fluid removal, her anemia improved with intravenous iron supplementation and the institution of erythropoietin treatment, and attention started to be paid to her severe malnutrition.

DISCUSSION

PROF. MEGUID EL NAHAS (*Professor of Nephrology, Sheffield Kidney Institute, Sheffield Teaching Hospitals NHS Trust, Sheffield, UK*): This unfortunate lady is a sad example of an all-too-common problem we encounter in the UK and other Western countries, namely,

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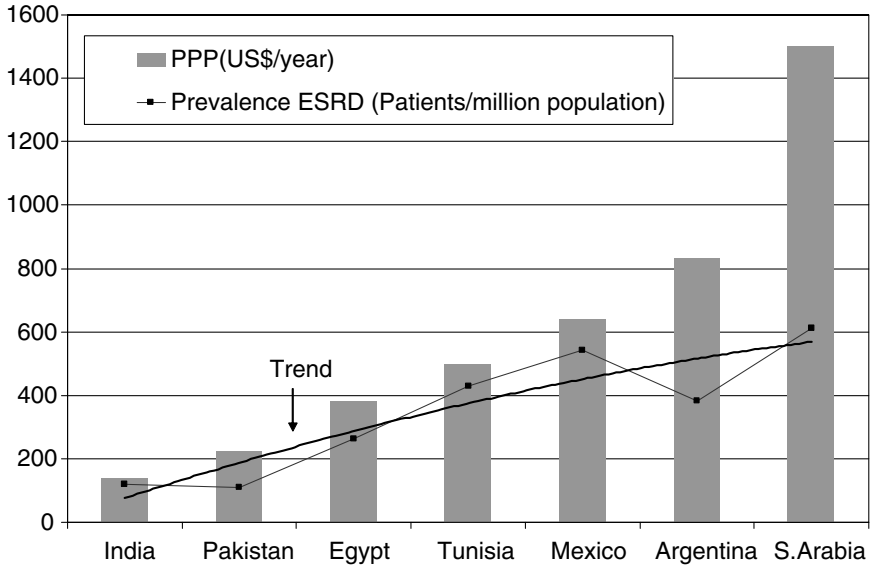

Fig. 1. Purchasing power parity (PPP) and prevalence of ESRD in selected developing countries (modified from [4]).

asylum-seekers and immigrants who come to the West not as much for political or economic motives but for medical treatment. Her case highlights the plight of millions of patients worldwide in developing countries who are denied access to renal replacement therapy (RRT) because of a lack of facilities and resources.

Globally, the number of patients with end-stage renal disease (ESRD) is increasing steadily. Currently, more than 1.6 million individuals worldwide undergo RRT, mostly hemodialysis. Most of these patients (90%) live in the developed world, which accounts for only 20% of the world population [1–3]. In fact, 56% of all patients receiving RRT live in only 5 countries, the United States (US), Japan, Brazil, Italy, and Germany, which represent only 12% of the global population [1]. The stark and alarming reality is that 112 countries representing a population of 600 million remain without RRT [1]. It is therefore not surprising that 1 million patients die every year worldwide from ESRD. Most countries in sub-Saharan Africa, where our patient comes from, have few or no RRT facilities [4]. In Asia, the Indian sub-continent has very limited facilities for a growing population (exceeding 1 billion). In fact, India has a prevalence of patients on RRT of less than 15/million of population (pmp) when at least 200 to 300 pmp is expected [1, 5]. In China, the prevalence varies from around 100 pmp in major urban centers to as little as 3 to 5 pmp in huge and overpopulated rural areas [1, 6]. Similar discrepancies have been described in Russia, where the annual incidence of ESRD is as low as 15 pmp [1, 7]. Comparing this to the annual incidence in the US of over 360 pmp (prevalence: ~1400 pmp) and Europe of around 150 pmp (prevalence: ~700 pmp), it becomes apparent that a huge gap in resources prevents the developing, low-income countries from providing treatment to an ever-increasing number of patients with ESRD [1–3]. In fact, in the developing world, the prevalence of ESRD is proportionate to national income and economy (Fig. 1). As there are no major differences in incidence of ESRD among developing countries, it is most likely that the major, if not sole, determinant of prevalence is the capacity and sustainability of RRT programs; these are all financially determined.

This gloomy situation is likely to worsen over the next decade, as the number of patients with ESRD appears to be rising annually by 5% to 8%, with an expected 2 million patients undergoing RRT by 2010 [2, 8]. Undoubtedly, few of these will be in the developing world, where the cost of such treatment is prohibitive; the expected cost in the US by 2010 to treat more than 600,000 patients will reach around $29 billion [1–3].

The global challenge in nephrology over the next decade is not to provide RRT to the millions who cannot afford it; nor is it to encourage these patients to seek treatment in the West, where resources are already at breaking point. Instead, the nephrology community should try to shift the emphasis away from treatment of ESRD to the early detection and prevention of progressive chronic kidney disease (CKD). Early detection and prevention of CKD should in principle reduce the global burden of this chronic non-communicable disease through management of risk factors and interventions aimed at slowing the development and/or the progression of CKD. To achieve such a goal, it is imperative that we embark on global screening programs for CKD.

In this Forum, I will review the rationale for such programs and the requirements for their implementation. For a screening program to be successful, certain criteria have to be met: The disease screened must be common. Its natural history and stages should be well defined. Screening tests should be reliable and affordable. The prognostic significance of detected abnormalities must be established. Interventions must exist that can successfully

treat those with the disease. Finally, the entire process of screening and treatment must be cost-effective. I will address these issues in relation to CKD, and will examine staffing and financial issues pertinent to the implementation of detection and prevention programs.

Is screening warranted?

In whole population terms, the number of ESRD patients worldwide represents a small percentage (0.1%). Therefore, patients with CKD have long been underserved by many health authorities and governments. In developing countries, this has been compounded by other conflicting health priorities, including those of communicable diseases, especially AIDS. However, emphasis is slowly shifting both in the West and in the developing world as the realization of the scale of non-communicable diseases, including CKD, and their impact on health care is growing.

In the US, data derived from the third National Health and Nutrition Examination Survey (NHANES III) suggest that as many as 11% of the entire adult US population is affected by some degree of CKD [9]. In fact, they estimated that 5.9 million have stage 1 CKD with normal renal function and GFR >90 mL/min, whereas another 5.3 million have stage 2 (GFR 89–60 mL/min) [9]. Studies in other Western countries show that around 6% to 7% of the population has albuminuria, with around 0.6% to 0.7% overt proteinuria [10]. In Australia, the AusDiab study showed that 10% of those screened had impaired renal function; 16% of those had some degree of kidney involvement, impaired renal function, hematuria, and/or proteinuria [11]. Studies in developing countries such as Singapore showed a similar prevalence of CKD [12].

Before we become alarmed by these findings and assume that millions of individuals worldwide are heading toward RRT, we need to be somewhat critical of these analyses and raise some issues. The NHANES III data were cross-sectional in nature, with individuals tested once. The variability of measurements of albuminuria/proteinuria, as well as those based on serum creatinine estimation, is quite high, and rendering definitive conclusions based on such cross-sectional analysis somewhat doubtful. Albuminuria/proteinuria, as we all know, can be affected by a range of factors, including posture, timing of the sample, exercise, infection, and pyrexia. Also, studies have shown that with repeat testing of a random population, only 60% remain positive [9, 13, 14]. Similarly, measurements of serum creatinine require standardized calibration across laboratories, as variation in a given sample estimate can reach 25% [14]. The calculation of glomerular filtration rate (GFR) based on the MDRD formula can add additional bias to the estimation of the number of patients with different stages of CKD, as its accuracy in the estimation of GFR has not been validated for general screening, for testing individuals with normal renal function, or in ethnic minorities [15]. In fact, recent data suggest that Hispanic Americans, particularly those of Cuban descent, have higher serum creatinine levels when compared to whites [16]. Whether this discrepancy reflects a higher prevalence of CKD in this ethnic minority or merely differences in body mass and creatinine handling is unknown, but the finding highlights difficulties with estimation of renal function based on serum creatinine levels. Also, analysis of individuals with reduced GFR does not always take into account age-related changes; it is unlikely that elderly individuals with a mildly reduced GFR would have the same prognosis as patients with chronic glomerulonephritis with hypertension, proteinuria, and declining renal function. A cross-sectional estimation of renal function does not provide insights into the progressive nature of CKD. Debates should be informed by more research and epidemiologic data, including longitudinal studies. This is particularly relevant to developing countries, where resources are scarce and priorities in health care must be carefully justified.

Care for patients reaching ESRD and requiring RRT is costly. In the US, the current annual cost of $17 billion is expected to climb to $29 billion by 2010 [2, 17]. In Europe, dialysis alone consumes about 2% of the health care budget, with only a small fraction (<0.1%) of the population requiring treatment [3]. The global cost of ESRD treatment has been estimated at $1 trillion. Only high-income economies can afford such high health care costs [1, 2]; developing countries have other health care priorities, including combating communicable diseases such as AIDS, tuberculosis, and malaria.

The cost of CKD is compounded by the high morbidity (hospitalization cost) and mortality (loss of income-generating power) attributable directly to the disease and indirectly to the associated cardiovascular disease (CVD). In fact, albuminuria, proteinuria, and renal insufficiency are important risk markers for the increased morbidity and mortality due to CVD [10, 18–21], especially in patients with diabetes mellitus, hypertension, ischemic heart disease, and congestive heart failure [18]. In addition, the presence of CKD is associated in the general population with an increase in all-cause death as well as cardiovascular mortality [20, 21]. In the developing world, non-communicable diseases including CVD are increasing at an alarming rate because of the urbanization and westernization of lifestyle. Little doubt exists that CKD is a costly disease in financial as well as human terms, and that it warrants screening and prevention.

Natural history and stages of CKD

The risk markers and factors implicated in the development of CKD include non-modifiable as well as

modifiable factors. The former include old age, male gender, race (African and Asian) as well as some genetic variations (polymorphisms) affecting putative genes (reviewed in [22]). Modifiable factors include hypertension, proteinuria, dyslipidemia, obesity, and smoking (reviewed in [22]). Excessive alcohol consumption (>2 units/day) has been linked in one survey to the development of CKD. The role of factors such as chronic consumption of analgesics and nonsteroidal anti-inflammatory drugs remains debatable. Also, herbal remedies have been implicated in the development of chronic interstitial renal disease. Environmental pollution and exposure to heavy metals, including lead, have been associated with a higher prevalence of CKD [7]. Finally, there is little doubt that many of the communicable, infectious diseases affecting the developing world such as malaria, schistosomiasis, hepatitis C, and HIV increase the risk of developing CKD. In established CKD, a faster rate of progression has been associated with systemic hypertension, proteinuria, hyperlipidemia, smoking, and obesity (reviewed in [22]).

Recently, K/DOQI put forward a new classification of CKD, with 5 stages based on the level of renal functional impairment [23]. This classification has been enthusiastically adopted by most. While useful in simplifying the categorization of CKD, this classification has its limitations. Stage 1 CKD, for instance, allows for the inclusion of individuals with minimal renal functional and/or radiologic abnormalities that might prove of little long-term clinical relevance. To categorize those individuals as suffering from CKD might be misguided in more than one respect, not the least psychologically [24]. It would be more appropriate to divide patients into those with some defined abnormalities, such as isolated hematuria or microalbuminuria, and those with impaired renal function. The latter might warrant sub-classifications based on the presence or absence of progression and the associated risk factors such as hypertension and proteinuria [24]. The K/DOQI classification has been of good administrative and educational value in simplifying CKD and generating a standardized global definition. It will undoubtedly undergo revisions with time that will render it more and more accurate and clinically relevant. In fact, it already has been the subject of a recent position statement from Kidney Disease: Improving Global Outcomes (KDIGO) [25].

Having defined the stages of CKD, it is imperative that we appreciate that they are not necessarily biologically linked. A patient in stage 1 is not bound to flow through 2, 3, and 4 and thus end up in stage 5. In fact, little is known about the natural history of stages 1 and 2 CKD. We all are familiar with the assumption that most patients with advanced renal insufficiency (stages 3–5) will eventually require RRT. While this might be true for most, it is not invariable; numerous analyses have shown that a sizable percentage of patients in stages 3 and 4 have stable renal function. In an analysis of the percentage of patients in different stages of CKD followed up at the Sheffield Kidney Institute, we found that as many as 27%, 34%, and 38% of patients in stages 3, 4, and 5, respectively, were non-progressors, based on an estimated GFR calculated from the MDRD 4 variables formula, over a retrospective observation period of approximately 5 years (Al Tahir G, Abdul Wahab H, MMed Sci Dissertations, University of Sheffield 2004, unpublished observations). It is unknown what proportion of patients classified as having stage 1 and 2 or even 3 will progress to ESRD (stage 5). More research is needed to validate modeled projections of future numbers of ESRD patients and relevance as well as cost-effectiveness of screening and intervention. Finally, this calls into question the wisdom of the K/DOQI definition of "stages" of CKD rather than "grades" or "classes"; a stage is by definition a transitory step toward an end (ESRD in this case), while a grade or a class does not have a connotation of progression.

Are screening tests for CKD reliable?

K/DOQI [23] and PARADE [13] have recommended that screening be undertaken by urine dipstick analysis. A positive test should be repeated within 3 months and subsequently confirmed by a quantitative estimation of albuminuria/proteinuria such as a urine albumin/creatinine ratio (ACR) [13]. Of note, different thresholds need to be defined for abnormal ACR in males (>2.5 mg/mmol) and females (>3.5 mg/mmol) [26]. A review of cost-effectiveness of proteinuria dipstick tests concluded that their sensitivity averages 76% with a specificity of around 79% [27]. Such accuracy would be acceptable if, as recommended, positive tests are repeated and subsequently validated. Albuminuria also performs well as a screening test for proteinuria in the general population; the AusDiab study showed that albuminuria was highly sensitive (91.7%) and specific (95.3%) for detecting proteinuria in the general Australian population [28]. From the cost-effectiveness of screening for CKD viewpoint, only routine and cheap dipsticks are a realistic option. The more expensive and more sensitive and specific Albustix might not be a cost-effective option unless we take into consideration the cardiovascular implications of albuminuria detection. Therefore tools are available to us for screening for proteinuria at a relatively affordable cost and with an acceptable degree of accuracy.

In NHANES III, serum creatinine measurements varied by as much as 25% [14]. Measurement of serum creatinine will have to undergo rigorous calibration and standardization to avoid inaccuracies and variability [14]. Also, estimation of renal function from serum creatinine should take into consideration all the confounding factors such as gender, age, race, muscle mass, timing, and diet.

The calculation of GFR will have to rely on formulas validated for given subgroups of individuals depending on their stage of CKD and ethnicity [15].

Prognostic significance of albuminuria and proteinuria

Little doubt exists that patients with established nephropathies have a worse prognosis in the presence of heavy and sustained proteinuria [29, 30], and evidence is emerging regarding the prognostic significance of proteinuria and albuminuria in the general population [10, 21]. Studies undertaken in Okinawa after 17 years of follow-up indicate that individuals with dipstick-positive proteinuria are at increased risk, proportional to the severity of proteinuria, of developing CKD [31]. Also, data derived from the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study in Groningen revealed that albuminuria is associated with the subsequent development of CKD [32]. Furthermore, individuals with albuminuria in the PREVEND study were at increased risk of all-cause death as well as cardiovascular mortality [10, 21]. Similar observations were made in the EPIC-Norfolk study in the UK [33]. These findings support numerous reports linking albuminuria in the general population, hypertensive as well as diabetic individuals, with the subsequent development of cardiovascular disease (CVD) [33–36]. Albuminuria has been associated with the cardiometabolic syndrome predisposing patients to diabetes, hypertension, and CVD [37, 38]. Albuminuria might be a marker of vascular inflammation as well as endothelial damage and dysfunction with a resulting leakage of albumin from vascular and glomerular beds. Proteinuria is also one of the most predictive markers of CKD [22, 29–31].

The detection of CKD identifies patients at risk of cardiovascular complications; increasing evidence suggests that there is a steady increase in CVD morbidity and mortality with declining renal function [18–20, 39]. In some studies of hypertensive patients with and without left-ventricular hypertrophy, proteinuria and raised serum creatinine were higher risk markers for CVD than were elevation of blood pressure or dyslipidemia [37].

Can interventions prevent or retard CKD?

An increasing number of patients treated by RRT worldwide suffer from diabetic nephropathy and hypertension. In the US and some European countries, diabetic nephropathy is the leading cause of ESRD, accounting for more than 40% of patients [40, 41]. This situation is likely to worsen over the next 20 years as the number of patients suffering from diabetes, mainly type 2, will increase from 154 million to 370 million; this increase will be most noticeable in the developing countries, where the number of diabetics will triple from 99 million to 286 million [42]. Diabetic nephropathy already accounts for more than 30% to 40% of ESRD in countries such as Malaysia, Turkey, Korea, Qatar, and the Philippines [42]. Changing trends in the etiology of ESRD in some European countries also show an increase in type 2 diabetic nephropathy and in the number of patients with hypertension and renovascular disease [43].

As with diabetes mellitus, the global burden of hypertension is due to increase over the next decade [44]. Almost one-third of the population is projected to have hypertension by 2025, an increase of around 60% with a total of 1.56 billion affected [44].

The global rise in the number of overweight and obese individuals is likely to have an impact on type 2 diabetes, hypertension, and CKD. In fact, obesity is the sole risk factor that is currently increasing in parallel with the rise in ESRD [45].

Type 2 diabetes mellitus (DM), obesity, and hypertension are potentially preventable diseases. Research in China [46], the US [47], some parts of Europe, Finland [48], and Sweden [49] has shown that lifestyle modifications, including weight loss and exercise, can reduce the incidence of overt type 2 DM in overweight patients with impaired glucose tolerance by one-half. Similar results were reported with the insulin-sensitizing agent metformin [47]. In addition, recent evidence suggests that angiotensin-converting enzyme (ACE) inhibition also prevents the onset of albuminuria in type 2 DM [50]. Whether this observation is due to a genuine prevention of albuminuria or merely its normalization by treatment is difficult to ascertain, because the patients were not evaluated after ACE inhibitor administration was discontinued. Furthermore, ACE inhibition also might have a salutary effect on the incidence of diabetes.

Hypertension is also preventable by lifestyle modifications including weight loss and a reduction in dietary salt intake [51]. The Dietary Approaches to Stop Hypertension (DASH) diet, which includes a high intake of fruit and vegetables as well as a reduction in saturated fat intake, has proven effective in reducing both systolic and diastolic blood pressure [52, 53]. The DASH-sodium trial showed an additive beneficial effect of combining dietary salt restriction [53].

Lifestyle modifications have the potential to reduce type 2 DM, obesity, and hypertension, but they are difficult to sustain. Also, their adaptability to low-income societies is doubtful as this would require a cultural, societal, as well as economic shift. In low-economy societies, economic forces push individuals to adopt "obesegenic" diets [54]. Healthy diets are expensive; high-sugar, high-fat diets as well as canned foods, which are highly salted, are much cheaper than fresh fruit and vegetables. Low-income individuals might not even have the option of exercise, as they have limited time for leisure and are "time-poor" as well as cash-poor [54].

Social deprivation has been shown in numerous surveys including NHANES III to be a risk factor/marker for CKD [9]. Pharmacologic approaches aimed at weight loss might be more successful, although agents such as sibutramine (a central norepinephrine and serotonin reuptake inhibitor) and orlistat (a gastric pancreatic lipase inhibitor) are not without their side effects, thus reducing compliance and sustainability [55]. Surgical bariatric interventions have been advocated for morbid obesity with good short-term results but decreasing efficacy at 10 years [56].

A large body of evidence suggests that reduction of blood pressure and proteinuria can lower the rate of progression of CKD in patients with diabetic and non-diabetic nephropathy by as much as 50% [30, 57]. In most of these studies, ACE inhibition or the use of angiotensin-receptor blockers (ARBs) has proven protective through combined antihypertensive and antiproteinuric effects [57]. The protective effect of these agents might be proportional to their proteinuria-lowering effects [30]. Reduction of albuminuria and proteinuria is key to the prevention of the progression of diabetic nephropathy. Remuzzi's group has argued that aggressive and multifactorial risk reduction interventions can either normalize the annual rate of loss of renal function or even reverse the trend [30]. In high-risk ethnic minorities such as the Northern Territories' Aborigines, treatment with an ACE inhibitor not only decreased the incidence of ESRD but also reduced mortality rates [58]. It is of interest that when such treatment programs had to be discontinued because of administrative difficulties, there was a surge in both morbidity and mortality within a short period of time [57].

Is screening for CKD cost-effective?

A model simulation based on the Markov model has consistently shown that screening diabetic patients for albuminuria is cost-effective [27]. In the RENAAL study, treatment with the ARB losartan reduced albuminuria and slowed the progression of type 2 diabetic nephropathy [59]. In this study, a reduction by 28.6% of the risk of ESRD was estimated to lead to a net savings per patient in ESRD-related cost at 3.5 years by $3522; net cost savings per patient at 3.5 years (between $11,000 and $12,000) was the highest in those with the highest baseline albuminuria (>4000 mg/g creatinine) [59]. In another study, treatment with another ARB, irbesartan, in patients with type 2 diabetic nephropathy led to an average cost savings of as much as $11,922 per patient after 25 years [60]. In non-diabetic nephropathies, similar simulation modeling demonstrated that a reduction of 10%, 20%, and 30% of the rate of progression of CKD in patients with GFR <30 mL/min led over 10 years to a cost saving of $9 billion, $19 billion, and $33 billion, respectively [17]. Such cost savings were projected to be twice as high if treatment was applied earlier to patients with GFRs of <60 mL/min [17]. Little doubt exists, then, that slowing the progression of established diabetic and non-diabetic nephropathies leading to delay or prevention of ESRD is cost-effective.

It is not as clear, however, whether general population screening for proteinuria by dipstick testing is cost-effective. One study concluded that, in patients under the age of 60 years, the cost of screening for proteinuria would be $282,818 per quality-adjusted life-year compared to $53,3272/QALY in those over 60 years [27]. Thus the cost of screening and treating patients with CKD under the age of 60 was not deemed cost-effective. However, this analysis did not take into consideration the cost- and life-saving potential of proteinuria detection on CVD. Screening individuals identified at risk of CKD, such as diabetic and hypertensive individuals, the elderly, as well as relatives of patients with CKD, is likely to be more cost-effective as long as these individuals would represent a substantial proportion of future patients with ESRD. Screening patients with diabetes, hypertension, at-risk ethnic minorities, or relatives of patients with CKD is likely to be the way forward. The US National Kidney Foundation Kidney Early Evaluation Program (KEEP) has detected functional or structural abnormalities in 47% of high-risk individuals screened [61]. Such a high prevalence of CKD would justify screening and prove cost-effective.

Recommendations

Screening high-risk individuals should be the priority. Those would include diabetics, hypertensives, at-risk ethnic minorities, the elderly, and relatives of patients with CKD [13, 61]. Other at-risk individuals include patients with autoimmune diseases known to affect the kidney. Whole-population screening might be too costly and not as cost-effective [27]. Screening should consist of dipstick testing for proteinuria with confirmatory re-testing within 3 months. Persistent abnormalities would then be validated by an estimation of spot urine ACR [13, 23]. A raised ACR would justify further functional, radiologic, and/or histologic investigations.

Having established the need for screening at-risk individuals for proteinuria, it remains to be determined how such screening would be implemented. In Western countries, this is most likely to take place in the primary care setting. In developing countries, screening individuals within rural areas where the majority of patients with CKD reside would require considerable staffing. Most developing countries are in shortage of doctors and nurses [62, 63]. There is a massive "brain drain" of skilled medical workers away from Africa and the Far East. It has been estimated that in Africa around 20,000 skilled workers,

Table 1. Nephrologists and their training in some sub-Saharan African countries

	Somalia	Ethiopia	Tanzania	Kenya	Sudan	Congo Republic	Chad	Nigeria
Population, *millions*	8.4	67	36.3	30	30	3.5	9.2	130
Nephrologists	0	7	0	16	15	3	0	50
Nephrology training, *months*	0	2	0	4	4	3	0	24

Table modified from [64].

including doctors, leave the continent every year. They are lured by a better standard of living in the West and disillusioned by the lack of opportunities at home [63]. In Africa, the majority of sub-Saharan countries have a handful of nephrologists located primarily in urban centers [64] (Table 1). It is unlikely that one nephrologist for 10 million people would be able to implement detection and prevention of CKD programs. It is more likely that such an initiative will depend heavily on health care workers who live in rural areas and can be trained within days to perform the necessary screening tests [65]. Such screening initiatives have been successful in Australian Aborigines [66], in the Chennai community of southern India [65], and in Soweto in South Africa [67]. The success of these programs depended heavily on the dedication and commitment of health care workers to screen, educate, and treat CKD patients. They would report to a local doctor and act under the guidance of the nephrology program leader.

Having established the need for screening for CKD to initiate primary and secondary preventive measures, the question remains that of funding and infrastructural support for such programs. Logically, government agencies should take the lead. However, reluctance due to limited funds and conflicting health care priorities militates against their involvement. They might require concrete evidence of cost-effectiveness before committing scarce resources and shifting health care priorities [68]. Consequently, it might be necessary to recruit the support of non-governmental organizations (NGOs), charities, and the pharmaceutical industry to offer financial assistance. The pharmaceutical industry might see an advantage in supporting screening initiatives, as they would provide an untapped pool of potential customers [69]. Data collected through pilot studies subsequently might encourage reluctant governments to become involved.

In summary, the patient we discussed today highlights the desperate plight of millions of patients with CKD who are denied renal replacement therapy because of a lack of dialysis facilities in the majority of developing countries. These patients are left with the sole option of death or asylum in a country that can provide them with the lifesaving treatment that they so desperately need. The future would seem darker and gloomier if it weren't for an upsurge of global initiatives aimed at the detection of CKD and its prevention. These should be targeted to populations at risk to maximize their cost-effectiveness. The programs should involve nephrologists but also primary care physicians and should rely heavily on dedicated health care workers. These initiatives should call upon the support of governments but also of NGOs and the pharmaceutical industry. A global task force is needed to coordinate these programs; the International Society of Nephrology Commission for the Global Advancement of Nephrology (ISM COMGAN) has taken a lead through its research committee by setting regional networks to foster detection and prevention of CKD initiatives.

QUESTIONS AND ANSWERS

PROF. RASHAD BARSOUM (*Cairo University, Cairo, Egypt*): The pragmatic issue is whether we should screen for diabetes and hypertension or whether we should screen diabetics and hypertensives for microalbuminuria and evidence of CKD. We know that if someone is diabetic, it might be worthwhile to treat him with ACE inhibitors or ARBs as well as statins without having to screen for microalbuminuria. The same might apply to hypertensive patients. Would you care to expand on that?

PROF. EL NAHAS: There is no question that we need to identify diabetics and hypertensives in the general population, as untreated diabetes and poorly controlled hypertension bear considerable cardiovascular risks. We also know that a 5 mm Hg reduction in average diastolic blood pressure reduces the risk of stroke by as much as 40%. The DCCT study showed that for every 10% reduction in glycosylated hemoglobin, we can expect a 40% reduction in cardiovascular complications. Mani and co-workers in India showed that both hypertension and diabetes are underdiagnosed in a large percentage of rural communities, that detection programs are feasible at low cost if health care workers are used, and that effective treatment can be achieved on a limited budget [65].

Regarding screening diabetics and hypertensives for microalbuminuria and CKD, most guidelines recommend such screening, although debates are ongoing about the value of screening patients with type 2 diabetes. Identifying those at increased risk offers the advantage of a concentrated effort at reducing their cardiovascular and renal risks. Unfortunately, most surveys have shown that the percentage of those screened remains unacceptably low.

DR. GARABED EKNOYAN (*Baylor College of Medicine, Houston, Texas*): I would like to make a few points. The

first relates to the NHANES III data that you mentioned. In fact, serum creatinine measurement was standardized before GFR calculations were made using the MDRD formula. Also, although proteinuria was not repeatedly measured in all the participants of the survey, the data were calculated based on those with persistent proteinuria as highlighted in the survey report; I guess these details have not filtered through and this has led to misconception of the data.

The second point I would like to make relates to the word "screening." I think we should avoid the word screening and talk of detection. Most screening programs in medicine did not live up to their initial promise. Regarding CKD detection, we should be careful and set progressive goals, starting by looking at our own practices before we go global. Data from many centers have consistently shown that we fail in a significant number of patients to achieve targets and objectives such as BP control, use of ACE inhibitors/ARBs, and calcium and phosphate control, in CKD. We therefore need to carefully develop models for detecting CKD and models for implementing treatment based on realistic feasibility and expectations, not on idealized models.

PROF. EL NAHAS: Regarding the NHANES III-derived data suggesting that over 10% of the US adult population has some element of CKD, it is imperative that such data be verified prospectively and those at risk defined so we can avoid being alarmist and unrealistic. Studies underway in the US and supported by the NIH [Chronic Renal Insufficiency Cohort (CRIC)] and some planned in the UK, including Sheffield, will allow us to have more definitive data either confirming or refuting such an alarming prospect. The question of achieving targets for detection (such as microalbuminuria in diabetics) or treatment in CKD is a real issue that might reflect the fact that guidelines and targets are slow to filter down through the various tiers of the medical profession. In the UK, the government is encouraging primary care physicians to meet treatment targets through quality initiatives with financial incentives; this might be one way forward.

DR. EKNOYAN: My question takes us back to the case of the unfortunate young sub-Saharan woman you presented. Are you advertising the fact that if patients in countries where RRT is not available travel to the West, dialysis will be offered with no restrictions? I face a similar dilemma in Houston with patients traveling from neighboring Mexico.

PROF. EL NAHAS: This is the question I was hoping would not be asked. It is a politically loaded issue in our day and age when debates rage in Europe on immigration and asylum seeking. There is a trend to encourage the immigration of those who are fit and capable of serving Western societies by providing much needed manpower and to discourage as well as limit that of others. The case of the patient I reported here illustrates the fact that beside politically or economically motivated immigration, there are those who come to the West seeking "medical asylum." These patients are at as much, if not higher, risk of death compared to political refugees. When confronted with such patients, we as doctors should do our utmost to provide them with treatment options regardless of political or administrative considerations.

DR. JOHN T. HARRINGTON (*Dean Emeritus, Tufts University School of Medicine, Boston, Massachusetts*): There are recent arguments in the US that one of the determinants of a person's health status is not the ability to get to a physician, but rather social class and economic status. Many of the socially deprived suffer poor health because of a lack of awareness and education. Should we therefore divert some of our health care resources to general education? There is little doubt that educating individuals in developing countries, particularly women, thereby increasing family assets, would lead to greater health for that family and its descendents.

PROF. EL NAHAS: There is little doubt that social and economic deprivation is a risk factor for the development of CKD as shown by NHANES III. We have just completed a small survey in Sheffield that showed that a significantly higher number of patients presented with CKD from low socio-economic classes. In my talk, I stressed the importance of education and awareness. Evidence suggests that people in general have little awareness of renal disease. Also, primary care physicians are not always fully aware of the scope and implications of CKD; their education is of paramount importance if we hope to implement more effective detection and management of CKD programs. Efforts are already underway with that emphasis, including the Disease Education Program launched by the US National Kidney Foundation (NKF) in 2004. Overall, diverting some resources from health care to education might be a cost-effective way of improving primary prevention of chronic diseases including CKD.

DR. AHMED ADAM (*University of Alexandria, Alexandria, Egypt*): Do you think that more needs to be done by governments within the developing countries to improve public education in relation to lifestyle changes to prevent CKD?

PROF. EL NAHAS: This is an important and topical issue not only in the West but also in developing countries, where western lifestyles are adopted. The world population over the last 50 years has adopted increasingly sedentary lifestyles with limited exercise and overeating. Obesity is becoming a global threat and pandemic with links to hypertension, diabetes, and CKD. Interestingly, Western societies and their socio-economic infrastructure often mitigate against a healthy lifestyle; recently, a very informative editorial in the *Lancet* by McCarthy highlighted the social forces and difficulties facing obese individuals who would like to change their lifestyle [54].

In the UK, the government recently started a campaign to improve lifestyle and discourage high salt and calorie intake, promote exercise, and encourage smoking cessation. Such initiatives can start early in life with educational programs at school, and it could be decades before we reap the benefits of such initiatives in terms of disease risk reduction. In the US, the National Kidney Foundation launched its Disease Education Program in 2004.

DR. MOHAMED HAFEZ (*Cairo University*): In the PREVEND study, the response rate was almost 50%, while in the KDIGO survey [70], the response from the Middle East was a mere 5%. Do you think this poor response reflects physicians' frustration with the lack of the public's interest in being screened or changing their lifestyle? Maybe an incentive for screening would be to offer access to inexpensive, if not free, medical care.

PROF. EL NAHAS: You are right; for people to participate in detection programs, they have to be motivated by the knowledge of the impact disease can have on their health and the assurance that detection will mean prevention and/or treatment. This takes us back once more to the issue of population education and awareness of CKD and related complications. The PREVEND example of high response and population participation also might reflect the social behavior of the people of Groningen. I doubt that a similar response rate would have been obtained, for instance, in Amsterdam; I recall in the 1980s how compliant the CKD patients of Groningen were to a low-protein diet, unlike their Amsterdam counterparts. Regarding provision of treatment for those with hypertension, diabetes, albuminuria, or CKD, we need not be discouraged in the developing countries by the inaccessible cost of medications such as ACE inhibitors and ARBs; good and comparable results have been achieved with cheaper and older drugs such as thiazide diuretics, hydralazine, and reserpine [65]. We also need to remind the pharmaceutical industry of its duty toward provision of accessible care in developing countries.

DR. METWALLY EL SHAHAWY (*Benha University, Benha, Egypt*): Would you please expand on your reference to the DASH study, which suggested that combining the DASH diet with a low salt intake was additive in its antihypertensive effect?

PROF. EL NAHAS: In general, the DASH diet leads to lower systolic and diastolic blood pressures when compared to ordinary diets. Also, the DASH-sodium studies showed that a low dietary salt intake (~60 mmol/day) combined with a DASH diet further reduces blood pressure. In general, we don't pay enough attention to dietary salt restriction in the management of patients with CKD; I would like to refer you to an excellent review article published in the *American Journal of Kidney Disease* that discusses the role of dietary salt restriction in CKD [71]. The difficulty with sustained salt restriction is compliance; for that, we advise our patients to reduce consumption of processed food, which is rich in salt, and to avoid adding salt to food at the table.

DR. EL SHAHAWY: Would screening for albuminuria be of value in detecting industrial and environmental nephrotoxicity?

PROF. EL NAHAS: Numerous studies have examined toxic industrial exposure and renal function; some of the UK studies in the 1990s were performed in Liverpool in automobile workers [72]; in 1995, Stevenson et al detected tubular injury and dysfunction based on the presence of high levels of proximal tubule enzymuria [72]. It is unlikely that measurement of microalbuminuria would be of value in such patients although decreased reabsorption of filtered albumin due to proximal tubule damage could be manifested by increased urinary excretion. They also noted circulating markers of glomerular basement membrane damage induced by hydrocarbon exposure, including auto-antibodies to basement membrane components. As far as environmental nephrotoxicity in Egypt is concerned, this has been a subject of concern over many years. Exposure to lead, mercury, and cadmium all have been mentioned. In the US, chronic lead exposure has been linked to increased serum creatinine levels [73]. But little hard evidence implicates environmental pollution as a major factor in the rising incidence of CKD and ESRD in Egypt.

DR. MOHAMED ZAATER (*Cairo University*): Would you please comment on the role of uric acid on progression of CKD? Do you think clinical trials on the use of allopurinol on CKD progression are warranted?

PROF. EL NAHAS: This is an interesting and timely question, as there is mounting experimental data linking uric acid to hypertension and possibly CKD. Dr. Rick Johnson in Florida and Dr. Agnes Fogo in Nashville have put forward a hypothesis stipulating the nephrotoxicity of hyperuricemia [74]. Work by Johnson's group confirmed an association in experimental models between uric acid and hypertension as well as kidney scarring [75]. A growing body of evidence links hyperuricemia to increased cardiovascular risk [76]. However, more evidence is needed before we prescribe allopurinol to asymptomatic CKD patients with hyperuricemia. Regarding clinical trials in CKD, it is imperative that they be adequately powered; too many clinical trials undertaken in nephrology have been underpowered in the past and therefore inconclusive. Trials in CKD require a large number of patients followed for long periods. In the UK and the EU, trials have to comply with Good Clinical Practice (GCP) regulations on the conduct of clinical investigation.

DR. SALAH NAGA (*Alexandria University*): I would like to raise the important issue of drug-induced nephrotoxicity in developing countries, where many drugs including nonsteroidal anti-inflammatory drugs (NSAIDs) are available over the counter.

PROF. EL NAHAS: That is a very important issue. There is little doubt that in many countries where NSAIDs are readily available over the counter they can affect long-term kidney function. Of interest, the odds ratio for ESRD is high with NSAIDs (up to 8.8 in one large study of 716 patients) but interestingly not with aspirin [77]. This difference might be due to the stimulation by aspirin of the release of lipoxygenase interaction products (lipoxins; aspiring-triggered lipoxins) that have anti-inflammatory and anti-fibrotic effects. Another important issue in sub-Saharan Africa, where the patient we discussed came from, is herbal remedies and their potential nephrotoxicity and impact on CKD and its progression (reviewed in [78]). It is important that we be aware of the potential nephrotoxicity of such remedies in the developing world.

DR. GAMAL SAADI (*Cairo University*): You showed some cost-effectiveness of screening older individuals rather than the young population. However, it would make good sense to screen and educate the youngest; it would, for instance, be advisable to start screening at school level to detect albuminuria, glucosuria, and urinary tract infections. Would you recommend such an approach, and what would the age cut-off be?

PROF. EL NAHAS: This takes us back to the timing and target of general population screening. The study I referred to by Boulware et al [27] was based on computer modeling, and simulation showed that it was more cost-effective for screening those over 50 years of age. Regarding screening children, this has been undertaken by the National Kidney Foundation of Singapore (NKFS), where they found up to 6% hematuria in school children [12]. However, before we embark on an across-the-board screening project, we need to ascertain the implications and cost. I suspect that in view of the low prevalence of ESRD in children, screening might not be cost-effective. The NKFS model with community-based "prevention centers" might be an experiment worthwhile following [79].

DR. AHMED ADEL HASSAN (*Zagazig University, Zagazig, Egypt*): As you are aware, hepatitis C is endemic in Egypt. Should we therefore screen patients who are carriers for hepatitis C for microalbuminuria?

PROF. EL NAHAS: I would have thought that in view of the high prevalence of hepatitis C infection in Egypt (up to 25% in some age groups) and the association between hepatitis C infection and CKD, it would be worthwhile identifying those who have microalbuminuria, as it could highlight a subgroup at increased risk of CKD and CVD. In fact, recently published data derived from the US NHANES III showed a higher prevalence (around 12%) of microalbuminuria among patients positive for hepatitis C [80]. This should prompt further investigation of this important epidemiologic area so pertinent to Egypt.

PROF. AHMED ELBELBESSI (*Alexandria University*): I would like to know how you obtained data on provision of renal care in sub-Saharan countries.

PROF. EL NAHAS: You touch upon an important issue here. Renal data collection from Africa and most of the developing world is poor. Most countries don't have a renal registry, and the ones that do are vulnerable to incomplete data collection. Most of the data I presented came from Prof. Sarala Naicker, Chair of COMGAN's Africa committee. She undertook a postal survey to ascertain the levels of nephrologic services in African countries. There is a sharp contrast between nephrology health care in northern African countries like Egypt, Tunisia, and Morocco, as well as South Africa, where nephrologists and dialysis provision are satisfactory, and sub-Saharan African countries, where huge deficiencies exist in service provision.

DR. EL EISH (*Alexandria, Egypt*): While hypertension and diabetes are common causes of CKD in adults, they constitute a small percentage of children with CKD. Should we treat children with CKD who are normotensive and have no proteinuria with ACE inhibitors or ARBs?

PROF. EL NAHAS: Dysplastic kidneys and reflux nephropathy are common causes of CKD in children. Whether we should treat those who are normotensive and with no proteinuria is an interesting question. I think that they should be screened for microalbuminuria. Also, all too often we assume that patients with CKD have normal blood pressure when in reality their blood pressure levels are high for their age and gender. Further, we don't measure 24-hour ambulatory blood pressure often enough in "normotensive" CKD patients who might have lost the nocturnal blood pressure dip. I think that those defined as pre-hypertensive (JNC VII) and those with progressive microalbuminuria should be treated. ACE inhibition is protective in reflux nephropathy [81]. On the other hand, if renal function is stable, and in the absence of albuminuria, I would recommend observing and monitoring CKD rather than prescribing ACE inhibitors or ARBs when they are not indicated.

DR. HARRINGTON: You said little about sources of funding for detection and prevention programs. To approach governments as well as NGOs, we need to have careful and specific plans. How should we collectively put together grant proposals that have chances of being funded to address the huge demands and issues addressed in your lecture?

PROF. EL NAHAS: Many national organizations and kidney foundations including those in the US are putting together carefully thought through strategic plans. Many initiatives are underway, as recently reviewed by Eknoyan and colleagues [82]. I referred previously to the efforts of the NKF of Singapore. In the UK, discussions are underway for a national detection

and prevention of CKD strategy. Globally, the ISN and COMGAN under the leadership of John Dirks (Chair) and Giuseppe Remuzzi (Chair for Research) have made huge efforts through setting up regional meetings to increase awareness of CKD. A meeting was organized, with the support of the Rockefeller Foundation, and attended by representatives from the World Health Organization, in the spring of 2004 in Bellagio, Italy, involving a number of interested nephrologists from developing and developed countries to put together a global strategic approach [83]. Since then, numerous regional initiatives have been fostered by ISN COMGAN to facilitate detection and prevention of CKD in developing countries. We also need to engage the pharmaceutical industry to provide much-needed research funds as well as supply developing countries with necessary renoprotective and cardioprotective drugs. Once data from pilot studies are available, it will become much easier to convince governments to act.

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