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Prevention in Nephrology: The Issue of Today and the Challenge for the Future

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The number of patients with chronic kidney disease (CKD) is increasing worldwide and end stage renal disease (ESRD) is perceived as a major health problem. According to the United States Renal Data System (USRDS) (1) in 2001 more than 400.000 adults had ESRD and over 300.000 required maintenance dialysis. Over the next decade, the number of patients with ESRD treated by dialysis may double. It is projected to increase to a prevalence of approximately 725.000 by 2010, and there will be more than 2 million patients worldwide on maintenance dialysis, a 400% increase in 20 years (2) This increase is being driven especially by the worldwide increase in number of patients entering ESRD without primary diagnosis of renal disease. The bulk of individuals at risk for renal function loss is composed by patients with hypertension, diabetes type 2, hyperlipidemia and atherosclerosis, accounting presently for more than half of the new ESRD cases.

The number of patients with ESRD is but the tip of the iceberg of the total number of patients with progressive CKD. It has been estimated that CKD population is 20-times larger than the number of new patients reaching ESRD (1). An analysis of data from the NHANES III found a prevalence of renal impairment of approximately 3%, or 5.6 million individuals, defined by serum, creatinine levels (3). A more recent analysis of the NHANES III database (CKD defined as persistent microalbuminuria with a GFR > = to 60 mL/min/1.73 m² or a GFR < 60 mL/ min/1.73m^2), revealed a prevalence rate of approximately 11%, - 19.2 million individuals (4). Furthermore, the increasing number of ESRD is a major public health issue, given the overall poor outcomes and high costs. The societal and financial costs of renal replacement therapy are proving too great for developed nations to cope with, and are an impossible burden for developing nations to meet. Developed countries appear to spend about 10% of their health care budgets on ESRD population and the cost is growing at 10% per year (1)

Given these realities, it is evident that measures need to be taken to help reduce this disease burden. Until recently the medical community has not been effective at implementing appropriate screening and prevention strategies. It is, also difficult to compare Europe and the USA because different criteria are used in data collection. In Europe no large epidemiological studies like the NHANES III have been conducted as yet.

Successful preventive strategies should include identification and treatment of populations at high risk, effective therapy for the known risk factors and should be focused on primary prevention. Prevention needs a clear understanding of the prevalence and outcome of renal disorders, the earlier stages of renal disease, the risk factors, and the appropriate treatment of populations at risk. The core idea of today's preventive strategies is identification of patients at risk for CKD with early risk markers and subsequent intervention aimed at prevention of progressive renal function loss.

The pathophysiological basis of CKD progression is the permanent loss of functioning nephrons, which leads to compensatory changes in the remaining nephrons that, over time, become maladaptative and the latter paradoxically causes further tissue injury, nephron loss and disease progression, independent of the primary cause of the renal disease (5,6). The rate of progression shows considerable inter-individual variability, and is dependent on multiple factors that mediate progression and can be divided into at least 3 groups:

1. Factors that increase vulnerability to develop chronic renal injury and cannot be specifically modified by current therapy ("non-modifiable" or susceptibility factors): genetic factors and racial background (7); gender: males have a two-fold higher rate of decline of CKD (9); age: the natural loss of GFR of 1 mL/min/year from age 25, would suggest that the age at the time of CKD onset influences the amount of remaining viable kidney tissue (8). The prevalence of CKD rises with age; while approximately 2% of individuals ages 40-59 have moderate to severe CKD, 25% of those older than 70 years have stage 3-5 CKD (4); reduced nephron number at birth may have an important role in determining the rate of progression because no new nephrons are formed post-partum (9)
2. The most important initiation factor is the cause of the underlying nephropathy that is an important determinant of rate of progression. Untreated diabetic nephropathy is considered to have the fastest rate of progression - rate of loss of GFR being 10 mL/min/year (10), and the usual rate of progression of chronic glomerulonephopathies is estimated to be 2.5 and 1.5 times faster than chronic tubulointerstitial diseases and hypertensive nephrosclerosis respectively (11)
3. Progression factors are those that accelerate the deterioration in renal function following injury to the kidney (5): sustained elevation in the systemic blood pressure and nephrotic-range proteinuria are the most important progression factors that strongly predict renal function decline, regardless of the underlying cause of CKD (13); the severity of tubular atrophy and interstitial fibrosis (13) and glomerulosclerosis (14) on renal biopsy predict a poor renal outcome. Studies suggest that factors

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such as hyperglycaemia, (15) hyperlipidaemia, (16) and smoking, (17) also predict a more rapid progression.

New insights on the risk factors and pathogenesis of CKD stressed the importance of early screening of high-risk populations and the implementation of evidence-based treatment guidelines as early as possible. Since most of such subjects are asymptomatic, their identification must rely on some sort of laboratory evaluation. Screening programs on the general population or risk groups, and early interception are two possible strategies for identifying CKD patients (18). According to McClellan et al (19) the following conditions are necessary to justify a screening program: the prevalence of the disease should be known and high enough; there should exist a prolonged period for undetected disease; early effective treatments should exist; the screening test should have high sensitivity and excellent receiver operator characteristic curves; access to adequate care should be available. The economics involved need to be understood in order to develop comprehensive, cost-effective strategies. Very few studies have been undertaken on the cost-effective identification of individuals at risk for CKD. In the developed countries CKD screening and prevention programs and studies have been undertaken: NHANES III (4), PREVEND (20), NKF-KEEP (21), AusDiab Study (22), Okinawa Kidney Study (23), but only few in the developing countries: Mexico Zumi Kidney Project, Bolivia Screening Program, Chennai Community Screening Program –India

Next to the blood pressure, albuminuria and renal function assessed by serum creatinine/calculated GFR may be best markers for risk, simple and inexpensive predictors to identify subjects at risk for progressive CKD at all stages from the normal population to the early and late diabetic state.

In the PREVEND study (20) it was found that microalbuminuria occurs frequently in the general population, even in subjects without diabetes and hypertension. As in diabetes, already modestly increased levels were associated with an increased GFR in patients with essential hypertension and in non-diabetic non-hypertensive subjects. Microalbuminuria was associated with an enhanced risk for cardiovascular mortality and probably also with an enhanced risk for progressive renal failure not only in diabetic, but also in hypertensive and in non-diabetic, non-hypertensive subjects. The screening of the 41 000 subjects in this study was performed with a budget of ~ 300 000 Euro suggesting the effort was worth the cost.

The conclusion of the AusDiab Study was that while albuminuria may be a suitable test for general population screening for renal and cardiovascular disease, it should not replace testing for proteinuria in those with known or suspected renal disease (22).

In the Okinawa Kidney Study, predictors of ESRD were identified. Besides male gender, they found significant predictors to be proteinuria, hematuria, hypertension and high serum creatinine (23)

Over the past decade there have been a number of relatively large hard-endpoint trials demonstrating the efficacy of several therapeutic strategies for slowing or even preventing the progression of CKD. Strategies which have been proven in randomised controlled trials to slow the progression of diabetic and non-diabetic CKD are summarised in Table 1.

Table 1. Proven Strategies for Retarding Progression of Chronic Kidney Disease

Strategy	Evidence
Tight BP control: target blood pressure 110-130/75-80, if tolerated	Modification of Diet in Renal Disease - MDRD (36)
	Appropriate Blood Pressure Control in Diabetes -ABCD (27)
	African American Study of Kidney Disease and Hypertension - AASK (27)
	ACE Inhibition in Progressive Renal Disease – AIPRD (25)
ACE Inhibitor: target proteinuria <500 mg/d	The Collaborative Study Group, Lewis (37)
	Angiotensin-Converting Enzyme Inhibition in Progressive Renal Insufficiency Study Group - APRI (38)
	Ramipril Efficacy in Nephrology – REIN (39)
	African American Study of Kidney Disease and Hypertension - AASK (27)
ARB: first choice if ACE inhibitor-intolerant	Reduction in Endpoints in NIDDM with Angiotensin II Antagonist Losartan - RENAAL (31)
	Irbesartan Diabetic Nephropathy Trial - IDNT (32)
ACE Inhibitor + ARB for greater antihypertensive and antiproteinuric effect with reduced progression	Candesartan and Lisinopril Microalbuminuria - CALM (34)
	Combination Treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease - COOPERATE (35)
Dietary protein restriction	Modification of Diet in Renal Disease - MDRD (36)
Blood sugar control	Diabetes Control and Complications Trial - DCCT (type 1 DM) (40)
	UK Prospective Diabetes Study -UKPDS (type 2 DM) (41)
Anti-proteinuric therapies	Avoid DHCEB, not antiproteinuric: ABCD (27), AASK (27), IDNT(32)
	beta-blocker: AASK (27)
	Control fluids: MDRD (36)
	Cease smoking: Orth (17)

Although no clinical trial has been performed to test screening strategies of hypertension, by evaluating treatment clinical trials Rembold (24) has shown that if detection is followed by treatment, the screening may

produce the largest clinical benefit. Hypertension and nephrotic-range proteinuria are the most important progression factors that strongly predict renal function decline, regardless of the underlying cause of CKD (12). The single most important means of slowing disease progression is adequate control of hypertension - shown in a recent meta-analysis of 11 trials (25). The need for a low-normal blood pressure applies particularly to proteinuric patients that has been proven in large trials (26,27,28) By far biggest step it has been made by effectively lowering albuminuria and hyperfiltration with the introduction of tools to intervene in the renin-angiotensin aldosterone system, such as ACE inhibitors and Ang II receptor blockers (ARBs). From the trials involving ACE inhibitors the evidence has been gleaned to support the recommendation in the current guidelines for a blood pressure <130/80 (29) and a systolic as low as 110 (25) in proteinuric patients, if tolerated. The protective effect of ACE inhibitors correlates with the initial level of proteinuria, and is seen even in patients with low-grade proteinuria, (28) or advanced renal disease.(30)

ARBs have been shown to slow progression in patients with type 2 diabetes (31,32) The relative risk of ESRD was reduced by 20% to 30% in these studies. In type 2 diabetic patients with microalbuminuria, the ARB irbesartan was shown to reduce the progression to clinical diabetic nephropathy. (33). A combination of an ACE inhibitor and ARB has been shown in several trials to have a greater anti-proteinuric effect than either treatment alone, (34,35).

In order to avoid the devastating health and economic effects of CKD, worldwide action is clearly needed to develop and implement screening strategies and wide scale preventive programs that are of great interest today and will certainly be the challenge for the future. Finally, the primary prevention of CKD, at least in part, by the eradication of type 2 diabetes and obesity (through improvement of lifestyle factors), and adequate treatment of hypertension, have the potential to eliminate up to half of the most common causes of CKD (or ESRD) in developed countries.

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