

International Society of Nephrology's Perspective on the Emergence of Chronic Kidney Diseases of Unknown/Undetermined Etiology

Giuseppe Remuzzi MD FRCP and Norberto Perico MD

In 2008 the World Health Assembly endorsed the Global Noncommunicable Disease (NCD) Action Plan, based on growing evidence that NCDs have replaced communicable diseases as the most common cause of premature mortality worldwide.[1] Priority was given to cardiovascular disease, cancer, diabetes and chronic respiratory disease since together they accounted for the major portion of global burden of NCDs and were the leading causes of death. The International Society of Nephrology (ISN), however, welcomed the Declaration of the High Level Meeting on NCDs a few years later in September 2011 stating that "the UN General Assembly recognizes that renal diseases pose a major health threat for many countries and share common risk factors and can benefit from common responses to noncommunicable diseases. [2] ISN saw this important statement as a first step toward proper recognition of chronic kidney disease as a major NCD.[3]

That kidney disease constitutes a public health priority is also underlined by the fact that recent findings from the Global Burden of Disease (GBD) 2010 study have documented an ever-increasing rate of CKD mortality globally.[4] In 2010, CKD ranked 18th among global causes of mortality, in comparison to its ranking of 27th in 1990.[4] Of note, in the last two decades the number of deaths from CKD has risen by 82%, the third largest increase among the top 25 causes of death, behind HIV/AIDS and diabetes.[4] CKD occurs in approximately 10% of the population. However, it must not be assumed that CKD is entirely contained within the cardiovascular risk envelope. Health strategies for prevention, detection, and early treatment of diabetes and cardiovascular disease do not avoid the need to address separately the burden of kidney disease. In the industrialized world up to 40% of those identified with CKD in screening programs have neither diabetes nor cardiovascular disease.[5,6] Such patients are often young, and the health and social costs of the progression of their disease are high and prolonged. Thus, early detection and treatment programs for CKD are also required.

Because the risk factors are not the same worldwide, targeting of populations in all regions only on the basis of previously described risk factors—namely hypertension, diabetes mellitus and obesity—might miss groups at risk of CKD where these factors are not the most common causes. Thus, region-specific high-risk populations should be screened, such as those exposed to harmful herbal preparations or environmental factors.[7] Herbal medicines are widely used by rural populations in Africa and Asia.[8] Toxic herbs can cause kidney injury, tubular dysfunction, electrolyte disturbances, hypertension, renal papillary necrosis, urolithiasis, CKD and urothelial cancer.[9] In countries where traditional medicines are popular and pharmaceutical medicines are frequently substituted or supplemented by products that include herbs containing aristolochic acid, herbal causes should be considered in cases of unexplained kidney disease.[10] Epidemiologic data from Taiwan and China show an association between use of herbs containing aristolochic acid and CKD.[11,12] Similarly, Balkan-endemic nephropathy, which affects people living along the tributaries of the Danube river in Europe, is now considered to be a form of aristolochic acid-related kidney disease.[13]

Clusters of cases of CKD of uncertain etiology (CKDu) have been reported more recently in Sri Lanka and India. An apparently new form of CKD, which cannot be attributed to diabetes, hypertension or other known causes, has emerged in Sri Lanka, with a point prevalence ranging from 2–16% among those aged >18 years. [14–16] Case-control and cross-sectional studies have provided some insights into associations with the condition. Results show chronic exposure of people in the endemic area to low levels of cadmium through the food chain and also to pesticides. They may also be exposed to lead and arsenic through the food chain. Urine concentrations of cadmium and arsenic acid in individuals with CKDu were at levels known to cause kidney damage, and the levels of cadmium positively correlated with CKD stage.[14] This finding led the Sri Lankan Ministry of Health, together with WHO representatives who coordinated the research, to suggest that cadmium contamination could be a risk factor for pathogenesis of this hitherto undetermined CKD in the country. (There could be, however, additional genetic susceptibility predisposing to renal injury where individuals are exposed to the toxin.) Notably, this achievement was the result of combined efforts by several stakeholders and organizations, including ISN, which was invited to be part of the International Advisory Board, based on the fact that ISN is the only nongovernmental organization dealing with renal health care in a formal relationship with WHO.

Other population clusters have recently received attention because of CKDs that await etiologic characterization, especially in poor communities in developing countries. The clinical presentation resembles that of interstitial nephritis. Histology shows interstitial fibrosis, tubular atrophy and interstitial inflammatory cell infiltration. As in Sri Lanka, contamination of water, food or both by heavy metals, fertilizers and pesticides has been suspected. [17] In two studies in India partially funded by the ISN Research and Prevention Committee, no excess of heavy metals was found in the water in the Srikakulam district (MS Ravishankar, Sevenhills Hospital, Mumbai, India, personal communication), while contamination of ground water used for drinking purposes with trace elements such as silica was suspected of causing CKDu described in rural villages in Prakasham and Nellore districts in the state of Andrapradesh (G. Taduri, Nizams Institute of Medical Sciences, Hyderabad, India, personal communication). In the latter case, a program for changing drinking water source was adopted by the communities and strict monitoring of the population for CKD was established.

In the last decade, CKD has been also the subject of many scientific and political debates in Central America, where an epidemic of CKDu has been identified primarily in young male agricultural workers, especially in the sugarcane fields.[18–20] This new kidney disease, named Mesoamerican nephropathy by some researchers, clinically presents with low-grade proteinuria and asymptomatic progressive kidney failure. Kidney biopsies show a chronic tubulointerstitial disease with associated secondary glomerulosclerosis and some signs of glomerular ischemia. This type of CKD is not due to diabetes or hypertension. Although a


variety of causes have been considered, to date there is no conclusive evidence of any specific risk factor being the cause of this epidemic. Nevertheless, recurrent dehydration related to manual labor under very hot conditions in agricultural fields, possibly exacerbated by NSAIDs or other toxins, has been claimed as a likely candidate.[20]

It should be highlighted that if CKD progresses to end-stage renal disease, renal replacement therapy by dialysis or transplantation will be required. However, treatment resources for dialysis are scarce in most middle- to low-income countries, where clusters of CKDu occur more frequently.[5] There is minimal availability of health insurance, and dialysis and transplantation programs are not widely available due to major financial constraints and lack of doctors and clinical staff.

At present, a large number of individuals with CKDu will die of untreated end-stage renal disease. Thus, there is an urgent need to find the cause, and for early prevention and treatment. This is the challenge ISN has pursued since its foundation in 1960, aiming to advance the diagnosis, treatment and prevention of kidney diseases in the developing and developed world through several programs, such as Fellowships, Sister Centers, Continuing Medical Education, and Clinical Research & Prevention, to name a few (see www.theisn.org).[5]

Beside these tools, ISN envisages several important areas to emphasize in developing an approach to CKDu worldwide. Health information systems are urgently required to capture data to better measure incidence and prevalence of renal failure, track patient outcomes, determine the true burden of disease, and support appraisal of nephrology services, detailing unmet patient need.

At the same time, efforts to increase awareness of kidney disease and its complications in communities and among physicians should be pursued, because the generally low awareness of this disorder probably serves as a barrier to appropriate patient care even where available. Moreover, specific national health policies for kidney disease early detection and treatment must be developed, which include strengthening of laboratory infrastructures to improve diagnostic accuracy.

In addition to saving lives, this approach will create major health gains, eventually reducing the current health inequity that arises from unaffordable or unobtainable renal replacement therapies in many parts of the world if end-stage renal disease is not prevented. Furthermore, to better capitalize on the efforts of individual stakeholders to tackle the emergence of CKDu, there is an urgent need to improve international collaboration to establish research consortia among ISN, local national nephrology societies, and regional and global WHO agencies working together with standardized criteria and approaches. 

1. World Health Organization. Preventing chronic diseases: a vital investment. Geneva: World Health Organization; 2005 Sep. 196 p.
2. The United Nations General Assembly. Political declaration of the high-level meeting of the General Assembly on the prevention and control of non-communicable diseases [Internet]. New York: United Nations; 2012 Jan 24 [cited 2014 Feb 15]. Available from: http://www.who.int/nmh/events/un_ncd_summit2011/political_declaration_en.pdf
3. Feehally J. Chronic kidney disease: Health burden of kidney disease recognized by UN. *Nat Rev Nephrol*. 2011 Dec 6;8(1):12–3.
4. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012 Dec 15;380(9859):2095–128.
5. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major non-communicable diseases. *Kidney Int*. 2011 Dec;80(12):1258–70.
6. Jha V, Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. *Lancet*. 2013 Jul 20–26;382(9888):260–72.
7. Li PK, Chow KM, Matsuo S, Yang CW, Jha V, Becker G, et al. Asian chronic kidney disease best practice recommendations: positional statements for early detection of chronic kidney disease from Asian Forum for Chronic Kidney Disease Initiatives (AFCKDI). *Nephrology (Carlton)*. 2011 Sep;16(7):633–41.
8. Jha V, Rathi M. Natural medicines causing acute kidney injury. *Semin Nephrol*. 2008 Jul;28(4):416–28.
9. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *Natl Health Stat Report*. 2008 Dec 10;(12):1–23.
10. DeBelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. *Kidney Int*. 2008 Jul;74(2):158–69.
11. Guh JY, Chen HC, Tsai JF, Chuang LY. Herbal therapy is associated with the risk of CKD in adults not using analgesics in Taiwan. *Am J Kidney Dis*. 2007 May;49(5):626–33.
12. Yang L, Su T, Li XM, Wang X, Cai SQ, Meng LQ, et al. Aristolochic acid nephropathy: variation in presentation and prognosis. *Nephrol Dial Transplant*. 2012 Jan;27(1):292–8.
13. Stefanovic V, Cukuranovic R, Miljkovic S, Marinkovic D, Toncheva D. Fifty years of Balkan endemic nephropathy: challenges of study using epidemiological method. *Ren Fail*. 2009;31(5):409–18.
14. Jayatilake N, Mendis S, Maheepala P, Mehta FR; CKDu National Research Project Team. Chronic kidney disease of uncertain aetiology: prevalence and causative factors in a developing country. *BMC Nephrol*. 2013 Aug 27;14:180.
15. Gooneratne IK, Ranaweera AK, Liyanarachchi NP, Gunawardane N, Lanerolle RD. Epidemiology of chronic kidney disease in a Sri Lankan population. *Int J Diabetes Dev Ctries*. 2008 Apr;28(2):60–4.
16. Chandrajith R, Nanayakkara S, Itai K, Aturaliya TN, Dissanayake CB, Abeysekera T, et al. Chronic kidney diseases of uncertain etiology (CKDue) in Sri Lanka: geographic distribution and environmental implications. *Environ Geochem Health*. 2011 Jun;33(3):267–78.
17. Wanigasuriya KP, Peiris-John RJ, Wickremasinghe R. Chronic kidney disease of unknown aetiology in Sri Lanka: is cadmium a likely cause? *BMC Nephrol*. 2011 Jul 5;12:32.
18. Wijkström J, Leiva R, Elinder CG, Leiva S, Trujillo Z, Trujillo L, et al. Clinical and pathological characterization of Mesoamerican nephropathy: a new kidney disease in Central America. *Am J Kidney Dis*. 2013 Nov;62(5):908–18.
19. Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman DH, et al. Resolving the enigma of the mesoamerican nephropathy: a research workshop summary. *Am J Kidney Dis*. 2014 Mar;63(3):396–404.
20. Correa R, Wesseling C, Johnson RJ. CKD of unknown origin in Central America: the case for a Mesoamerican nephropathy. *Am J Kidney Dis*. 2014 Mar;63(3):506–20.

Submitted: April 6, 2014

Approved for publication: April 8, 2014

Disclosures: None

Correspondence: gremuzzi@marionegri.it
