Community-Focused Primary Prevention of Risk Factors of Chronic Kidney Diseases(CKD): An Unmet Need in Reducing the Burden of ESRD in Low and Middle-Income Countries(LIMC) - A Review and Proposition

[1,2]Wokoma Friday, *[1,2]Emem-Chioma Pedro and [1]David-West Manda

[1]Renal unit, Department of Internal Medicine, University of Port Harcourt Teaching Hospital, Alakahia, Port Harcourt, Rivers State, Nigeria;
[2]Department of Medicine, Faculty of Clinical Sciences, College of Health Sciences University of Port Harcourt, Choba, Port Harcourt, Nigeria.

ABSTRACT

Chronic kidney disease is assuming the status of a global pandemic, afflicting over 500 million people worldwide, of all ages, gender and racial groups. ESRD accounts for the 19th commonest cause of death worldwide. The predominant modifiable risk factors being overweight & obesity, hypertension, diabetes mellitus, chronic glomerulopathies, toxic nephropathies and HIV, etc. The latter two especially in Low- and middle-income countries (LIMC).

A tremendous amount of knowledge and developments have taken place in the past 150 years. In spite of these gigantic endeavours, which have indeed ameliorated the sufferings and prolonged survival of patients with CKD and ESRD, especially in the developed countries, CKD and ESRD seem to defile all measures at their containment in the communities globally.

While CKD and ESRD management processes have led to improved longevity and health-related quality of life (HrQoL) in patients in developed countries, the story is different for the majority of patients in LIMC.

To reduce the burden of CKD and ESRD in the present circumstances therefore, the focus should be on measures to reduce the burden of risk factors of CKD and an ERSD in the community.

A public health approach for the Primary prevention of overweight/obesity, hypertension, type 2 diabetes, nephrotoxin exposures and HIV infection becomes inevitable and advocated.

Preventive nephrology as a body of knowledge and practice have not been given a place of prominence in contemporary nephrology practice and is an unmet need in the global management of CKD, especially in LIMC.

The Framingham heart and cardiovascular preventive studies in the United States of America in the 1950s is a classic example and pioneer in the application of primary preventive approach to prevention and control of heart and cardiovascular disease worldwide.

We, therefore, propose a **Preventive nephrology program** for LIMC jurisdiction modelled along the Framingham model for CKD prevention in LIMC jurisdictions. Incorporating the program into the WHO 2013-2018 NCD control program will be cost-saving.

Keywords: *Chronic kidney disease, Risk factors, prevention, unmet need, LIMC*

Corresponding author: Pedro Emem-Chioma, Renal unit, Department of Internal Medicine, University of Port Harcourt Teaching Hospital, Alakahia, Port Harcourt, Rivers State, Nigeria. *Email:* emem.chioma2008@gmail.com

INTRODUCTION

Chronic kidney disease (CKD) and consequent ESRD, is a cause of global morbidity and mortality of public health importance. CKD afflicts about 10 -16% of the world population, with a huge global burden of over **500million** people globally. Over 2.5 million have ESRD of which 1.8million are maintenance dialysis and over half a million persons living with renal allograft. ESRD accounts for 19% of global deaths annually [1,2].

The burden of the disease continues to increase with the ageing population in the western populations and with increasing risk factor exposures in the low- and middle-income jurisdictions [3,4]. The human burden of suffering, financial costs of care and the demand on health services are enormous even in the high-income jurisdiction with optimum facilities for care. For most low- and middle-income countries (LIMC) countries, ESRD is associated with over 80% mortality in the first year of diagnosis [5,6].

In the past 150 years there been has tremendous advancements in the knowledge of the scientific basis of renal disease, the epidemiology of renal disease as well as the development of the Nephrology as a sub-discipline of Medicine [7,8]. This development led to substantial improvement in the quality of life and prolongation of life of patients with kidney disease and kidney failure. In spite of theses monumental achievements, the global prevalence of End-stage renal disease (ESRD) and its associated morbidity and mortality continues to increase. Maintenance dialysis is, however, associated with a number of chronic cardiometabolic complications causing morbidity and mortality. Kidney transplant which approximate to "cure" is fraught with challenges of low access, shortage of available kidneys for transplant, short- and long-term poor graft and patient survival, especially in the low- and middle-income countries (LIMC) as Nigeria [9,10].

It would seem, the tendency is for CKD to ultimately run its natural course from onset to development of ESRD even though, at varying rates. The burden of ESRD globally continues to increase.

It is perhaps, for this reason, the authors of the 2017 Annual data report (ADR)[11] of the United States, Renal Data System (USRDS) stated as follows: ***"Why should we care about the trends and current state of kidney disease in the US? Research has established these as a disease continuum that holds a great cost to both the individual and society. The key to success lies undoubtedly in the realm of prevention and optimal management of CKD in order to slow progression, with the goal of completely avoiding*** *the* ***development of ESRD. This, for the most part, is an unmet challenge of the community-focused management of advanced kidney disease or ESRD"[11].***

The population prevalence of most of the primary risk factors of CKD viz. overweight/obesity, hypertension, diabetes mellitus, hypercholesterolemia, etc, are high in LIMC countries, assuming epidemic proportion in some cases.

Recent data from the ISN Global Kidney Health Atlas show the population prevalence of obesity (10-30%), hypertension (20 -30%), diabetes (8-12%), hypercholesterolaemia (6-9.9%) and smoking (16-29%) respectively LIMC regions [1]. Similarly, cross-sectional studies of the prevalence of these risk factors among CKD and ESRD populations from several studies in the LIMC countries are also relatively high with Obesity (10-29%), Hypertension (12.8-45%), Diabetes (3-16%) hypercholesterolaemia (5-12% respectively).[4-6]

Apart from efforts at pharmacological interventions in the control of these risk factors, which is bedevilled with high costs of ACEI and ARBs with consequent poor drug adherence, there are no concerted structured efforts at the public health levels for the prevention of these risk factors in most LIMC jurisdictions. Intensive population and community health education on lifestyle modifications aimed at kidney health promotion, prevention and amelioration of CKD risk factors is lacking in most LIMC regions. ***An aggressive and sustained population-based program to reduce the incidences and burden of overweight and obesity, hypertension, type2DM, infections associated with kidney disease, as well as nephrotoxin exposures, in the LIMC countries would substantially impact on the magnitude of CKD in the population and progression to ESRD.***

We used the **Input-process-output model** to illustrate some of the difficulties in the process of retarding and arresting the course of progression to ESRD, as well as the difficulties in dealing with the end products of ESRD viz anaemia, CKD-MBD, cardiovascular disorders, etc. These failures or

inadequacies of contemporary efforts crystalizes the imperative for primary prevention of CKD.

The Framingham heart studies (FHS) in the prevention of risk factors of cardiovascular disorders, is a classic example of the success of **Primary risk factor prevention** or reduction in the prevention and amelioration of cardiovascular disease in the Framingham and US populations and subsequently globally [12].

Epidemiology of CKD and the Burden of Human Suffering

Kidney impairment and kidney failure have globally assumed an increasing magnitude of public health concern in recent times. The world health organisation (WHO) have recently enlisted chronic kidney disease (CKD) among the six common causes of non -communicable disease (NCD) deaths worldwide for which long term strategy for their control is being developed for implementation[13].

Renal registry data from North America, west European countries, parts of Asia and Australia, indicate that about **10 to 16percent** of their populations have various stages of CKD.[14-16] .With global population increases, the global burden of kidney disease will continue to increase in the absence of deliberate intervention effort. Whereas the annual global population growth rate is 1.1%, the global ESRD growth rate is 6-7% respectively.[9]

As at 2015 the global population of ESRD patients treated with one form of renal replacement therapy(RRT) or the other was about **2.45 million** people, with **1.68million** people on maintenance dialysis and about **568,000**, living with kidney transplant.[2] Data from the US renal registry(USRDS) 2016.[16] showed that population prevalence of CKD is **14.8%,** which translate to about **39million people**, while 0.19%of the populations or **571,414** persons are on renal replacement therapy (RRT) enrolled into the End-stage kidney disease program (ESRD-Medicare).

In Europe, the incidence of ESRD is about 350per million persons per population (pmp) and prevalence of 786pmp. There are approximately 360,000RRT patients in the EU with 66% on maintenance dialysis and the remainder, about 122,000 living with functional graft**.**

In sub-Saharan African countries such accurate statistics are not available as most countries lack functional renal registries. Among SSA countries, only South Africa has a renal registry (the South African renal dialysis and transplant registry), which has 7082 ESRD patients enrolled as at 2015[17].

Data from most SSA countries are mostly hospital-based, admissions prevalence data. These data, however, show a high prevalence of dialysis requiring kidney failures in the region ranging from **3-16** per cent of hospital admissions. [18,19]

In Nigeria, the most populous SSA country with a population of about 170 million people, 3-16 per cent of medical admissions are due to ESRD. These figures tend to corroborate with a recent meta-analysis of publications of chronic kidney disease prevalence in SSA region by Stanifer et-al,[20] who found CKD prevalence of 2-30%with an average prevalence of **13.9%** in the SSA region and **17.6%** prevalence for Nigeria respectively.

Assuming a 0.2% population prevalence of ESRD (which is the trend in most communities), Nigeria with a population of 170million people would have an estimated annual ESRD burden of **340,000**, which translates to 2000pmp. This is higher than 1,738pmp for USA and more than doubles the 695pmp for Europe respectively. Similarly, SSA countries with a combined population of about 800million people at 0.2% ESRD prevalence, would have an estimated **1.6milion** burden of ESRD. This estimated magnitude of ESRD in SSA countries is quite enormous.

The community prevalence of risk factors of CKD based on community surveys from different parts of SSA is relatively high with, Obesity (20-29%), hypertension (25-29%), Diabetes(8-9%), dyslipidemia (10-14%) respectively[18-20].

The relative contributions of HIV-kidney disease and nephrotoxin exposures as risk factors to CKD, in SSA countries have not been properly documented. Globally HIVAN is the 4th common cause of ESRD. HIV-Kidney disease is commonly encountered in medical admissions in SSA jurisdictions. HIVAN is associated with 15-58 percent of medical admissions in many SSA countries.[21,22]. Toxin kidney exposures are quite frequent in SAA and LIMC countries but systematic studies of proven chronic toxic nephropathies (with exception of except acute sub-epidemic exposures) not readily available.

Global differences in the causes of CKD/ESRD
Though the common causes of CKD are universal, there are some epidemiological differences in the distribution of the causes depending on the environmental and socio-economic status of the population in question. Thus, whereas as the non-communicable disease (NCD) and age-related causes are more dominant in the developed countries, communicable disorders, including HIV and toxic exposure-related kidney disorders are playing significantly important roles in the developing countries in recent times.

This is shown in table 1 below. These differences have implications for preventive strategies in different jurisdictions, based on local socioeconomic and environmental ecology.

The need for frequent clinic visits, Dialysis visits, hospitalizations and re-hospitalization put a lot of demand on caregivers and overstretches medical resource of a country. ESRD patients have a more than fourfold higher hospitalization rates compared to matched control populations without CKD. The real economic costs of these are enormous.

The Financial Burden of CKD/ESRD Care
Similarly, the financial costs of CKD and ESRD care in any given population are huge and far outstrips the health budgets of most low and middle-income countries.

The United states renal Registry data system (USRDS) provides perhaps the most reliable and comprehensive up to date source of information on the financial costs of CKD/ESRD care. Whereas

Table 1: Global differences in the distribution of risk factors/causes of CKD/ESRD

Developed Countries	LIMC Countries
❖ Diabetes mellitus (43.3%)	❖ Hypertension (28.1%)
❖ Hypertension (37.3%)	❖ Chronic glomerular disorders (35.2%)
❖ Chronic glomerular disorders (6.3%)	❖ Diabetes mellitus (10.2%)
❖ Polycystic kidney disease (2.23)	❖ Toxic Nephropathies (no data)
❖ Obstructive uropathies (1.4%)	❖ HIV-related kidney disease (10-20%)
	❖ Obstructive uropathies (8.5%)
	❖ Polycystic kidney disease (1-3%)
	❖ Others (3.9)

Refs: ***URSDS-ADR 2017(); Arogundade et al; World Kidney forum 2008; Wokoma et al 2008***

The Burden of Suffering of CKD/ESRD Patients
The chronicity of CKD/ESRD imposes enormous and complex, the burden of human suffering on victims with ESRD comprising intangible and tangible costs to the victim, the family, the health caregivers, the health system and society at large. Some of the physical and psychosocial burdens of the suffering of the patient include the numerous symptoms and manifestations of the disease, poor health, quality of life (HrQoL). The latter is characterized by an inability to engage in gainful employment, near-total dependence on family members, erectile dysfunction, with attendant frustration on patient and spouse, often leading to strain and divorce. Both functional and organic depression, as well as bipolar disorders, have been well documented in CKD/ESRD populations[23,24].

ESRD patients constitute just 9% of Medicare population, they account for 17% of total Medicare costs, indicating the high costs of ESRD costs [9] In 2015, the annual Medicare costs for CKD(1-4) was **$64.6 bn** (N19.7tn), while the Medicare costs for ESRD was **$33.9bn** (N10.3tn) respectively.[25] These amounts constitute far more than Nigeria's Federal annual budgets in the last four years.

In the US and other western countries, the financial costs of care continue to increase annually due to the ageing population and increasing prevalence of CKD/ESRD. Canada with less than 0.1%of the population with ESRD spent over $1.3 billion in 2000 for ESRD care. Even the countries in the developed economies are feeling the economic discomfort of providing for the increasing population of ESRD patients.

In most developing countries like Nigeria, there are no functioning Renal registries, thus there is no accurate data on CKD, ESRD, RRT and costs of care. RRT services are not organized, and not readily accessible and affordable to the majority of patients. There are no Medicare types of the insurance-based payment system. Out of pocket payments at the point of care is the norm [26]. The result is grossly sub-optimal care with an attendant high one-year mortality rate over 80% in most centers[27]. Thus the diagnosis of ESRD is tantamount to a death sentence in most LIMC environments.

In our centre, in Nigeria, we estimated the average annual cost of RRT based on prevailing costs in our locality in 2010 as **N706,240.0 ($4,414.0)** per person per year for pre-dialysis treatment, **N2,652,000.0 ($16,575.0)** per person per year for maintenance dialysis and ESA expenses and **8million naira($50,000.0)**per person for kidney transplant and immunosuppressive agents for the first year respectively.

The aggregate total cost of care per patient came to **N11,358,204.0 ($70,988.8)** a year. This is not very different from the $70,216.0 figure for the USA in 2010. Further analysis of our data to determine the financial status and source of funds for treatment of our patients on maintenance haemodialysis showed that in over 50% of the patients, their annual income was less than half the cost of maintenance haemodialysis a year.

Over 65 % of the patients sourced funds from direct family sources (out of pocket). None of the patients had any health insurance nor government-aided social security support.[28]

By our estimates, if, Nigeria with a population of 170million people is to provide Medicare- ESRD for the estimated 340,000 ESRD patients per year, the sum of **N3.88tn ($10.8Bn)** per annum would be required. This amount is about 46.7% of Nigeria Federal Budget for 2018 and 12.9 times (129%) the Federal annual **health budget** of **N300bn** for 2018 respectively.

These data show that neither individual Nigerian patients nor the Nigerian state can cater for their Medicare-like ESRD treatment for Nigerian patients. The situation of Nigeria is similar to other most other LIMC countries are in the same situation.

In addition to the financial burden of care, access to RRT in most LIMC countries is extremely low for a number of reasons, which include limited and skewed distribution of caregivers, grossly inadequate RRT facilities, social and cultural impediments etc.[1]

Their clinical state at first presentation for most patients is often poor. They present in states of acute pulmonary oedema, uraemic encephalopathy or coma. For these reasons the RRT outcomes in most LIMC settings is abysmal. The majority commence RRT as an emergency, while sustenance on maintenance dialysis is often short, with a median period of six months. Most patients receive no more than one dialysis session in a week; others, one session in two or more weeks. The outcome of this scenario is gross dialysis inadequacy, clinical instability, and high mortality rate of over 80percent within the first year of diagnosis.[6,1]

The imperatives for the reduction in the global burden of CKD/ESRD

As highlighted above the global burden of CKD is enormous, with increasing prevalence across all geographic regions. The burden of human suffering and the financial costs of care in spite of significant improvements in the knowledge and skills for management of CKD/ESRD over the last 150 years remain gruesome. This frustration was recently expressed in the executive summary of the 2017 USRDS Annual data report (ADR) report[11] as stated earlier. ***It is thus inferred that the avoidance of ESRD should be the ultimate goal of nephrology practice globally and especially in LIMC jurisdictions.*** This statement is even more sacrosanct for LIMC countries, where the diagnosis of ESRD is almost synonymous with a death sentence.

Even in developed countries with access to all the state-of-the-art intervention facilities for ESRD care, the overall health-related quality of life (HrQoL) of ESRD populations remains poor, morbidity and mortality from cardiovascular disorders far in excess, compared with non-CKD populations in spite of the high socioeconomic investments in the care of ESRD patients [29,30].

Though substantial advances and success have been achieved in the last 150 years in the understanding of renal disease and the development

of standards of care, the currently available treatment modalities do not provide permanent solutions to ESRD. ***Halting the progression of CKD to ESRD has been a herculean challenge and an unmet need and the greatest challenge of Nephrology.***

Maintenance dialysis is technology-intensive, cost-prohibitive even in developed country settings. Long term cardiovascular and metabolic complications are legion which treatments, add to costs of care, with serious impact on HrQoL for the victims. The social and economic costs to society are enormous. Although kidney transplant approximates to cure of ESRD, kidneys for transplant are increasingly becoming scarce, due to patient's reluctance to donate for fear of the surviving kidney developing problems in the future. Fears of illicit organ trades and organ trafficking are real [31-35].

In most LIMC countries, cadaveric kidney transplants are nonexistent, commercial driven live kidney donation is most prevalent, which is unethical. Altruistic live-kidney donations continue to dwindle over time even in developed countries [36]. For patients who have successful transplants, acute or chronic rejections, progressive allograft dysfunction, opportunistic infections and malignancies, etc, threaten allograft and patient survival.

Ten-year allograft and patient survival continue to decrease in spite of improving immunosuppressive therapy. There are few break-throughs in the development of more potent, less toxic immunosuppressive agents. The targeted therapies, biologics and cytokine analogues are more effective as adjuvants for use in combination with the traditional immunosuppressive age. They are also toxic, and quite expensive [37-40]. Alternative sources of kidneys for transplant such as xeno-transplant, cloned kidneys, stem-cell therapies, etc are still at their nascent experimental stages of development with little prospects of replacing human kidneys in the near future [41,42].

Given the above scenario, ***it becomes imperative, therefore, for the Global Renal community, especially the LIMC, to give more attention on preventive measures to reduce the supply side of the CKD to*** **ESRD** conundrum. There is a need for the renal community to develop a **structured and** organized **approach to preventive nephrology practice.** Preventive nephrology could be developed into a sub-speciality in the curriculum of Nephrology training at undergraduate and post-graduate levels especially in LIMC jurisdictions.

Approaches to Preventive Nephrology

In establishing a framework for a Preventive nephrology model, the journey from CKD to ESRD can be likened to the INPUT-**PROCESS-OUTPUT** model of modern management and industrial production [43] as illustrated in fig.1 below.

The inputs being the primary risk factors of CKD. These include genetic/racial factors, overweight/obesity, hypertension, diabetes, glomerular disorders, nephrotoxin exposures, infection-related disorders, etc.

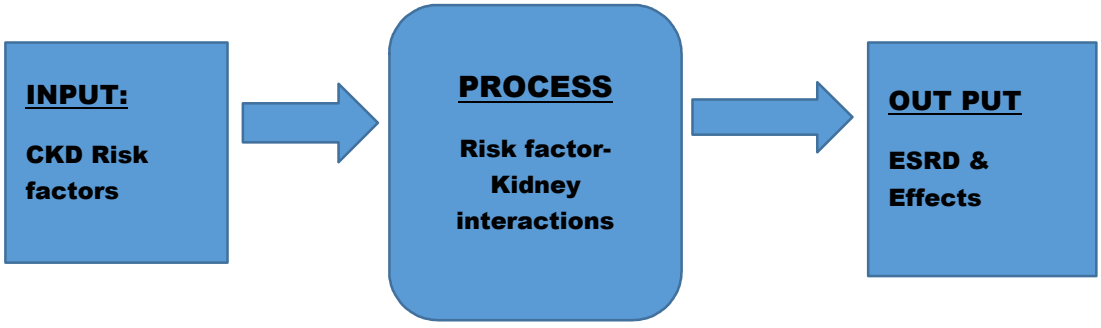

Fig.1: The Input **–Process –Output model** approach to CKD/ESRD prevention and management

The process involves the complex physical, haemodynamic biochemical, and immunological interactions between the pre-morbid healthy kidney

and the risk factors, eventually leading to kidney function impairment and damage.

The outputs are the components of ESRD such as uraemia, anaemia, renal bone disease, cardiovascular disorders, etc from which the patient dies in the absence of intervention.

Applying the above paradigm to the prevention of CKD, **primary prevention** is feasible if the incidence and burden of the primary risk factors of CKD are reduced in the communities to the barest minimum. Secondary prevention is also feasible by way of early screening detection and early intervention to control the severity of the risk factors as proteinuria, hyperglycaemia, hypertension, dyslipidemia, etc respectively.

The activities in the **Process compartment** generate ESRD. They constitute all the very complex events occurring consequent upon the interaction between the risk factors and the healthy kidney parenchyma that leads to irreversible kidney damage. They include the direct mechanical injury and damage to renal tissues from obstructive nephropathies; the effects of toxic injury to the renal tubules and interstitial tissues by nephrotoxins leading to acute and chronic toxic nephropathies, the immune-based inflammatory reactions, with or without complement mediation, to renal glomerulus, the glomerular basement membrane(GBM) and the podocyte architecture, as well as the glomerular mesangium, as in the glomerulonephritides.

These activities also include the vascular and the haemodynamic effect of the activation of the RAS system, and cytokine pro-inflammatory and pro-fibrotic mediators. The endocrine functions of the kidneys are also impacted by the processes.

The endpoints of these **process activities** are the progressive destruction of the renal parenchyma leading to renal fibrosis and irreparably damaged kidneys or End-stage renal disease (ESRD). The ultimate mechanisms of progression of CKD include **glomerulosclerosis**, **vascular sclerosis** and **tubulointerstitial scarring** culminating finally **into renal fibrosis**.[44-46].

Because of the intricate and complex nature of events at this stage, it has been extremely difficult for medical science to be able to predict the initiation and the time course for these processes. Moreover, these processes occur at the cellular and subcellular levels.

The bulk of the affected patients at this stage are within the community and predominantly asymptomatic. The ice-berg phenomenon of ESRD. Most patients become symptomatic when the pathophysiologic processes are either advanced or completed. ***Thus, detecting these activities in the subjects and intervening early is almost impossible.***

Most of the knowledge of the mechanisms of these pathogenic processes were either acquired from experimentally induced nephropathies in laboratory animals, post-mortem pathologic observations in humans, or from a host of urinary or blood novel biomarkers, generated during the processes and detectable at some points in the process. Some of these novel biomarkers have been found to have diagnostic values in the type of kidney failure (AKI or CKD) and the site of kidney injury whether glomerular (proximal or distal tubules). Some have utility values in the monitoring of disease progression.

Some of the biomarkers associated with CKD include Asymmetric dimethylarginine (ADMA), Neutrophil, gelatinase arginine lipocalin (NGAL), Fibroblast growth factor-23, Osteopontin, Liver type fatty acid-binding protein (L-FABP), Uromodulin, IL-6, IL-18, etc. The bulk of these novel biomarkers are yet to be validated for clinical application[47-49]. Several efforts have been made and are being made to develop targeted therapies against a number of metabolic pathways without much success. These include Early biomarker detection of pathogenic pathways, blockage of inflammatory cytokines, neutralization of soluble substances, etc . These efforts have however not yielded clinically applicable outcomes in the prevention and amelioration of CKD progression.[50,51].

For these reasons interventional measures to prevent, retard or reverse these pathogenic processes are not realizable in the present state of knowledge.

Unfortunately, these complex cellular and sub-cellular pathophysiologic processes of this process stage constitute the engine room of kidney damage.

The limitation of medical science to successfully intervene at this critical and crucial stage of the CKD-ESRD trajectory is one of the greatest challenges to Nephrology practice in contemporary times.

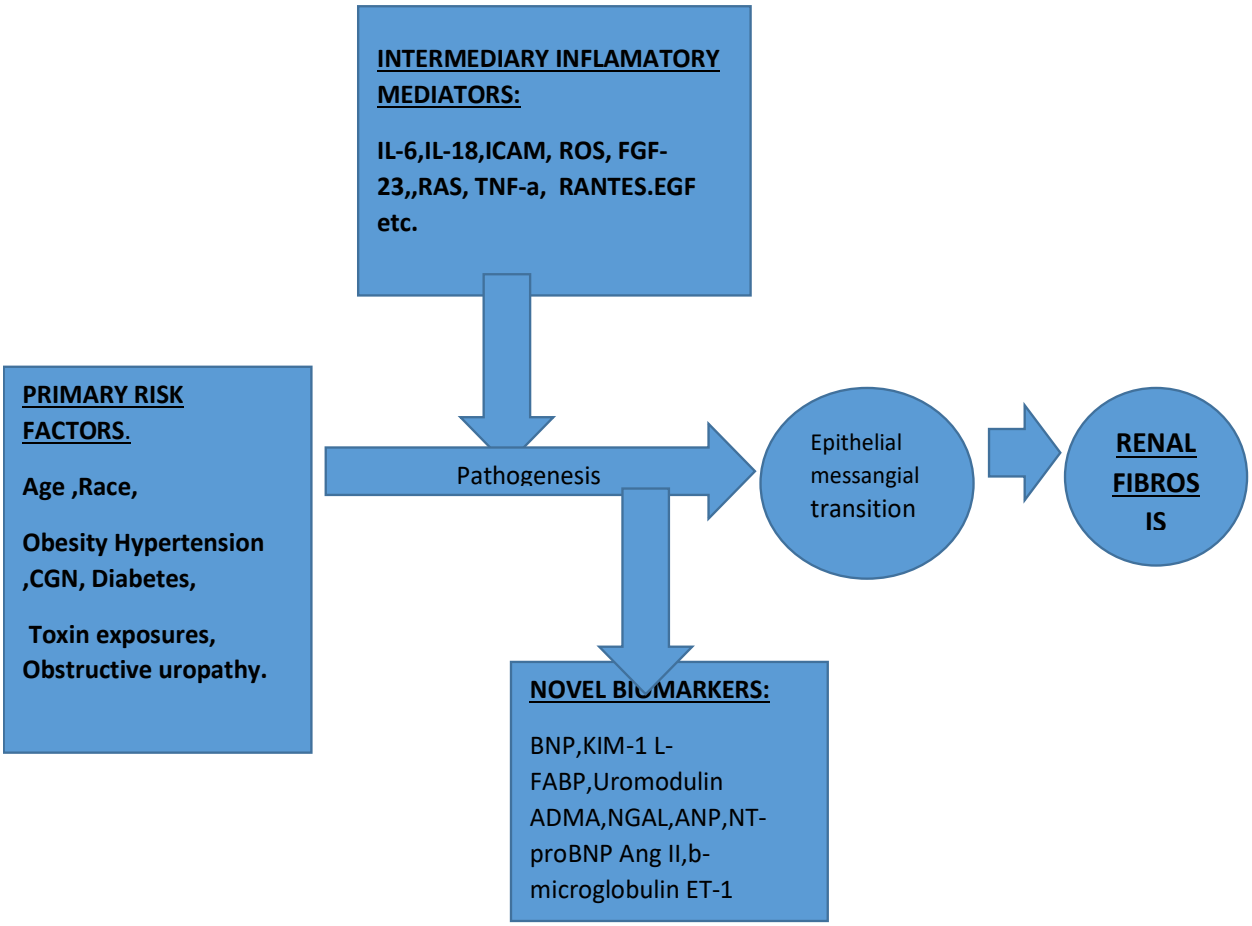

Fig. 2: Schematic representation of pathogenesis of CKD and Renal fibrosis and ESRF

Key:
IL-6(Interleukin6.) IL-18(Interleukin-18, ICAM(Intercellular adhesion molecule), ROS(Reactive oxygen species) FGF-23(Fibroblast growth factor23), RAS(Renin-angiotensin-spironolactone)TNF-á(Tumour necrosis alpha), BNP(B- Natriuretic peptide), KIM-1(Kidney injury molecule1) L-FAPB(Liver type fatty acid-binding protein.), ADMA(Asymmetric dimethylarginine.), NT-proBNP (N-Terminal probrain natriuretic peptide) ANP(Atrial Natriuretic peptide) Betamicrooglobulin, ET-1(Endothelin transmembrane 1)

ESRD is the **undesirable output** and endpoints of the pathophysiologic damages inflicted on the kidney by the risk factors during the Process stage.

The components of ESRD are **uraemia** and its metabolic consequences, **anaemia** of kidney failure**, CKD-MBD,** cardiac **and athero-thrombotic** vascular abnormalities occasioned by excessive RAS activation and sympathetic overactivity respectively. ***These outcomes cannot be prevented but can be ameliorated through some interventions, such as RRT, Management of CKD-MBD which constitute tertiary prevention***

Maintenance Dialysis therapies for ESRD, which ameliorates the outcomes of the process stage has no preventive potentials. Maintenance dialysis has tremendously provided relief for most of these conditions such as correction of azotemia, acid-base disequilibrium, control of fluid overload and hypertension.[52,53]. The advent of recombinant human erythropoietin (rhEPO) and iron replacement therapies have dealt reasonably with the problem of

anaemia and most of its consequences in ESRD patients in spite of their untoward effects [54,55]. CKD-MBD has been reasonably controlled with phosphate binders, correction of vitamin-D3 deficiency with calcitriol, oral calcium and calcimimetics[56,57].

Secondary hyperparathyroidism is being managed with calcimimetics and surgical ablation of the parathyroid glands. These measures have helped to reduce the incidence of falls, bone fractures and bone deformities in ESRD patients.[58,59].

Less success has however been achieved in the area of cardiovascular morbidity. Supplementary vitD3 have not been able to satisfactorily address the problem of widespread tissue(calciphylaxis), vascular- intimal and medial, cardiac valvular and aortic vascular calcifications that induce and aggravate cardiovascular morbidities

Although maintenance dialysis coupled with some of the interventions highlighted above led to significant improvement in the overall wellbeing of the ESRD population. Symptoms of uraemia abate, energy level and appetite improve, patients become less dependent on immediate caregivers able to work. The HrQoL status and survival while waiting for kidney transplant also improved reasonably.[60,61]
However, the downside of maintenance dialysis is that maintenance dialysis is cost-intensive, highly technologically driven and dislocates patient's life schedules, having to visit the dialysis centre an average of three times weekly and lifelong in the absence of renal transplant.

After years on maintenance dialysis, the initial metabolic and haemodynamic gains begin to wane. Progressive weakness, muscle wasting, malnutrition, frailty, the progression of CKD-MBD complex with a high frequency of bone deformities and spontaneous pathological fractures, multiple cardiovascular pathologies, etc, ensue with attendant morbidity and mortality.

From the foregoing, the contemporary nephrology practice focuses attention mainly on the secondary and tertiary prevention with minimal attention to primary prevention of the risk factors CKD and ESRD.

Contemporary CKD preventive modalities and their inadequacies

At the present, most of the CKD/ESRD preventive efforts are geared towards early detection, control and modification of established risk factors. These include:

1. The therapeutic interventions in the control of microalbuminuria and macroalbuminuria with ACEI or ARBs, the control of hypertension with ACEIs, CCBs, BBs, etc, singly or in combinations, close metabolic control of diabetes mellitus with insulin and safe oral hypoglycemic, control of dyslipidemia with diet and statins. all in accordance with international and local therapeutic guidelines. [62-65]

This practice has become the gold standard. The recent studies showing renoprotective and cardiovascular benefits effect of the Serum glucose transport2 (SGLT2) inhibitors (empagliflozin, canagliflozin,etc,) in diabetic kidney disease are promising but their long term benefits are yet to be proven.

The major drawback for most LIMC jurisdictions is the relatively high costs of ACEIs and ARBs, Gliptins, SGLT2 inhibitors which are not readily affordable to the majority of CKD or ESRD patients.

2. The annual World Kidney Day (WKD), exercise introduced by the international society of nephrology (ISN) in 2006[66] to create global awareness of kidney disease and kidney failure. During such one-day exercises, volunteer subjects in communities, schools, market places, etc are given kidney health education and screened for risk factors of kidney disease. Subjects found to have risk factors or have any stage of CKD are referred to nearby hospitals for further evaluation. and follow up. A laudable global kidney disease awareness program which has been widely embraced by most LMIC countries.

The shortcoming of the WKD preventive model is that it is ad hoc in nature with no structured long term follow up of at-risk subjects. The major plank of the WKD exercise is in creating global awareness of the problem of kidney disease and kidney failure globally.

3. The United States, Kidney Early detection and Evaluation Program (KEEP) and similar programs in other countries[67-69]**.** are long term CKD risk factor modification and early detection of CKD, intervention, monitoring and evaluation for time trends and outcomes. They are limited to selected or voluntary self-reporting enrollees.

The shortcomings of the US KEEP and similar programs is that they are mostly secondary preventive in nature. Secondly, the KEEP-like programs are most suited for developed country settings, in urban and literate population, with effective telephone and IT communication systems. They are not suitable in predominantly illiterate and semi-illiterate' populations in LIMC rural communities with poor IT facilities. The Indian SEEK and the Guatemala Fundainer programs were donor-driven, the reason for their relative success. For the above reasons, KEEP-like CKD control programs are hardly operational in most LIMC countries.

Imperatives for the prevention of risk factors of CKD

From the foregoing, therefore, there is the imperative for the unmet need for globally directed effort in the primary prevention of risk factors of CKD as a veritable means of reducing the **supply-side** to the CKD-ESRD conundrum. At the present, there little if any global efforts geared toward the primary prevention of risk factors of CKD globally. This relative inertia is perhaps understandable because such primary preventive efforts are entirely community-based, cost-intensive and may be of short-term benefit.

The gestation period of measurable outcomes may belong. Finally, being preventive in nature, the industry may have little investment interests in the process. ***For any success to be achieved, programs for primary prevention of CKD risk factors must necessarily be government-driven, as public social responsibility.***

In spite of these potential shortcomings however, any significant reduction in the population incidence of hypertension, diabetes, obesity/ overweight, and nephrotoxic exposures, will have a significant impact on the reduction in the burden of CKD and ESRD.

The Framingham Heart studies (FHS)[12] is a classic example of such community based primary disease preventive endeavour, with unprecedented success both in the prevention of cardiovascular disease and death from cardiovascular in the US and subsequently globally.

The huge data generated from the FHS, with over 1000 publications in highly rated journals has led to a better understanding of the role of traditional and non-conventional risk factors in the aetiopathogenesis of most cardiovascular diseases. The term **risk factor** was first used in the Framingham studies.

The roles of social habits as alcohol, cigarette smoking, sedentariness, overweight/obesity as well as hypertension, diabetes dyslipidaemia, etc, in the development of cardiovascular were established beyond reasonable doubts [70-72].

The tremendous amount of knowledge of the epidemiology of the risk factors, pathogenesis and characteristic of cardiovascular disorders, necessitated the need for intensive nation-wide cardiovascular health education in the United States, driven by the Center for disease control (CDC). The outcomes of Framingham studies led to the promotion of US-Nation-wide intensive public health campaigns towards the encouragement of exercise programs, discouragement of cigarette smoking, reduction in consumption of refined carbohydrates, and saturated fats a promotion of consumption of polyunsaturated (PUFA) oils among adults in the US.

CDC in collaboration with Dieticians and Nutrition specialists developed HHF dietary prescriptions to promote healthy living [73-75].

The US food and drugs administration (FDA) made it compulsory for the food industry to display details of the ingredients (**Nutrition facts**) in manufactured food packages.

This cardiovascular prevention and reduction of health educations permeated the entire fabric of US society, leading to widespread lifestyle modifications among the US populations. Short- and long-term data from several Framingham studies and other studies over the years have unequivocally demonstrated the reduction in incidence and burden of modifiable traditional risk factors of cardiovascular disorders. The time trend in the incidence of obesity, hypertension, diabetes, and hypercholesterolemia showed a consistent downward trend not only in the Framingham populations but in the wider US populations. Similarly, there has been a significant reduction in the incidence of coronary heart disease and other cardiovascular disorders except for strokes. Similarly, the mortality of coronary heart disease and other cardiovascular mortalities have reduced among Framingham and wider US populations.

Form the above it is incontrovertible that **primary risk factor prevention advocacy and practice** contributed immensely to the prevention of

cardiovascular disease in the US population reinforced by secondary risk factor intervention.

Similar studies have been done in other places outside the United States with similar outcomes.[76-78]. The lessons and benefits of the US campaigns against CVD have been globally accepted as standard practices. A recent CDC reported a 54% decline in the incidence of ESRD among American Indians and Alaskan natives have been attributed to the public health measures in the control and management of Diabetes [79].

Drawing lessons from the Framingham program and its outcomes.

Although the Framingham study and outcomes did not focus on risk factors for CKD/ ESRD, the latter have shared risk factors with Framingham cardiovascular disorders. This is because the clinical entity CKD, as presently known was not yet well defined and the major risk factors of CKD were not well delineated during the period of Framingham studies in the 1950s. Similarly the impact of Framingham interventions of renal indices may not have been studied.

The Primary CKD risk factor prevention program can thus be modelled along with the Framingham heart study approach with some modifications. Whereas as FHS started off by trying to identify the notable risk factors for cardiovascular disease, the risk factors for CKD and their implication for kidney and public health are already well known and established [25].

So, the primary objective of the proposed primary prevention of risk factors of CKD is the application of public health education and lifestyle modification to reduce the incidence of overweight /Obesity hypertension, diabetes, exposures to nephrotoxins.

This will be a dominant **population advocacy and intervention program** aimed at promoting Kidney health and lifestyle practices in the populations, as was done in the US populations and later in some developed countries based on lessons from the Framingham heart studies. The strategies for the attainment of these objectives are discussed below.

The justification for the Primary prevention of CKD risk factors in LIMC populations

Attainment of the primary prevention of CKD risk factors is contingent upon intensive, aggressive permeating and sustainable Public health campaigns aimed at the lowering of the population incidence of hypertension, type2 diabetes, dyslipidemia, exposures to nephrotoxins, infections related to glomerulonephritis, HIV-infection, in LIMC communities.

Sustainable efforts in creating the awareness for lifestyle modifications, and prevention of risk exposures, as was the case in the USA following the findings in the Framingham studies.

Presently the level of awareness of kidney disease and kidney failure is very low among LIMC countries. [25,80.] With increasing urbanization, most people in LIMC jurisdictions, in spite of relative social deprivation, live lifestyles that predispose to CKD risk factors. Sedentary lifestyles are domineering over labour intensive agrarian lifestyle, there is increased consumption of refined carbohydrates, soft drinks and beverages in the home, social gatherings and in schools among adults and children.

Childhood over-overweight /obesity has become quite common with a consequent rising incidence of childhood diabetes and hypertension [81-83].

Similarly, the incidence and prevalence of the known risk factors of CKD viz, overweight/obesity, hypertension, diabetes have shown a steady rise in LIMC countries in recent times. Population burden of type2 diabetes and hypertension in SSA countries are huge [84-86].

Community-based studies in some LIMC countries have shown that cigarette smoking is rife and, on the increase, resulting from aggressive direct and indirect marketing of tobacco products by tobacco companies. Due to economic potentials of the cigarette industry, most LIMC governments are incapable of either banning or restricting the production, marketing and sale by tobacco companies in the LIMC countries [87,88].

Though nephrotoxin exposures in the LIMC jurisdictions are rife, with over 80 per cent usage in most LIMC countries [89,90]. the contributions of nephrotoxin exposure to CKD/ESRD is largely unknown. This is due to the difficulties of ascertaining cause and effect relationship in the clinics, except in

acute mass nephrotoxin poisoning often of epidemic proportion.

Due to the long interval between nephrotoxic exposure and onset of CKD, patients would hardly ascribe their illness to nephrotoxin exposure.

In the LIMC countries, therefore, nephrotoxic damage to the kidneys are likely to be quite common. In a low kidney biopsy environment [91] as in most LIMC countries, the definitive diagnosis of the cause of CKD is largely conjectural. Some of the diagnosis ascribed to hypertension may be secondary renal parenchymal hypertension developing after the onset of kidney damage, rather than essential hypertension.

It is traditional, in the listing of causes of CKD in literature, to ascribe a significant 20 to 30 per cent of causes to **"unknown"** causes. In LIMC jurisdictions, nephrotoxic exposures may account for the bulk of the unknown causes of CKD.

So in most LIMC countries, toxic nephropathies may be contributing more to CKD than documented. ***The need therefore for prevention of nephrotoxic exposures in the LIMC communities cannot be overemphasized.***

Herbal medications and orthodox drugs (restricted and OTC) are openly advertised, marketed and sold in open markets, commuter buses, using government media outlets.

The use of **skin lightening and bleaching** soaps and lotions is very popular among adolescents and young adults and those in the entertainment industry. [92,93] Similarly so-called **Nutritional supplements** some of which contain nephrotoxins are frequently used by the relatively affluent members of the society with claims of multiple cures and longevity [94]. They are highly patronized by the members of the society. They are often combined with prescribed orthodox medications. Patients on orthodox medications often abandon their prescribed medications for Nutritional supplements and herbal formulations.

Occupational exposures to **heavy metals** (gold, mercury, etc) are very common among artisanal miners and petroleum-related industries workers. Blood levels of such heavy metals in these occupational groups are often several folds in unexposed control [95, 96].

Infection-related kidney failure is also relatively common in LMIC populations. Chronic hepatitis B, C and HIV-related renal disease are more prevalent. HIV-related kidney failure is increasingly becoming a common cause of renal hospitalization with high case fatality rates in recent times. The hospital admission rates range from 20 to 30 percent in most series [97,98].

Though public awareness of HIV is common, awareness of HIV-renal disease is very low even among HIV infected subjects. Access to and compliance with HAART is poor [99, 100].

Differences in approach to Primary risk factor prevention between the developed and LIMC countries

In most developed countries, because of high educational level, enlightenment effective communication, awareness as well as early entry and easy access into the health system, community awareness of CKD and most risk factors of CKD is relatively high. Subjects have motivations to take actions for their health. Also, there are effective communication systems which literally connect everyone within a given community and with the health system. So, community and population public health education and interventions are not very herculean and are often integrated into the national health systems.

The scenario in most LIMC countries is completely different. Community public health education is neither structured nor organized and not integrated into the health system. There are a high illiteracy rate and poor communication system. Most health caregivers are themselves ignorant of CKD and risk factors.

Existing departments of Public health are often more engaged in donor-driven international disease control programs like HIV/AIDS, Leprosy-Malaria-Tuberculosis programs, etc.

Awareness of CKD and CKD risk factors is very low even among the staffers of LIMC public health departments[11]. So, there is neither plan nor the architectural framework for the public health awareness and education on risk factors of CKD, and NCDs.

The imperative therefore to develop and install durable CKD-AWARENESS and control of CKD- risk factors into the health system of LIMC countries cannot be overemphasized.

The illustrations (figs 2,3, and table 2) are the theoretical framework of approach to the primary and secondary prevention of CKD risk factors and consequent prevention of ESRD especially in the LIMC countries.

In most LIMC jurisdictions, the facilities for maintenance dialysis, and renal transplantation for dealing with ESRD are scarce, sparse and not within the reach of the broad majority of patients. Consequently, the mortality rate within the first year of diagnosis is over 80 percent. Given the persistently poor socioeconomic status of the LIMC countries, there is little likelihood that the situation will improve in the foreseeable future.

Secondary prevention of CKD by way of strict control and amelioration of severity of risk factors through the process of proteinuria control, glycaemic control, hypertension control etc, are currently in practice in LIMC jurisdictions, however, the drugs for this purposes ACEI, ARB, CCBS, Gliptins and recently the SGLTI are quite expensive, import-dependent and not readily affordable and accessible to the broad majority of CKD/ESRD patients in these regions. So, their use is generally limited.

This leaves primary risk factor prevention, the KEEP-like and world kidney day models as the preventive options for LIMC countries.

Given below are the proposed strategies for the actualization of this CKD prevention in the LIMC jurisdictions adopting the Framingham and the WHO 2008-2013 approach.

Strategies for primary and secondary prevention and control of risk factors of CKD

Operational strategies for the implementation of the Primary prevention of risk-factors of CKD and interventional program in LIMC countries

These are summarized below as follows:

1.The Political will and Program ownership

Creating the enabling **political will** by LIMC Governments for the ownership of the program. Working in collaboration with the global international nephrology society (ISN), the National Renal societies, like the Nigeria Association of Nephrology (NAN), and the WHO, respectively.

2.National CKD Database

The development of National data-base for CKD through the development of National renal registries.

3.Appropriate Legislations

The introduction of stringent enforceable **legislation** to outlaw open advertisements, marketing and sale of herbal medications, nutritional supplements, unproven substances etc. The prohibitions of manufacturing, marketing and sale of skin lightening and bleaching soaps and creams in the LIMC countries. The prohibition of the use of public and private media for promotion of any form of unapproved medicinal.

4.Multi-stake holder advocacy

Developing strategies for multi-stakeholder advocacy system for the promotion of renal health and the primary prevention of obesity, hypertension, diabetes, exposure to nephrotoxins, at the community levels in all LIMC countries**.**

The advocacy team will in conjunction with the Central and Regional departments of Public health, develop the templates and formats for field deployment for the effective delivery of the advocacy. At each LIMC country level, the message content of the advocacy will be uniform to avoid conflicts in the message content and delivery. The medium and language of advocacy delivery may, however, differ from target community to target community. Delivery of advocacy in the indigenous language or dialect of the target community is ideal.

The multi-stakeholder advocacy group shall be driven by the LIMC country ministry of health (Government), with other members drawn from: comprise representatives from:

- Directorate of Public health of the Central and regional governments
- The primary health care (PHC) directorates of Central and regional governments
- The representatives of the National and Regional Legislative Assemblies
- The WHO country representatives
- The National and regional chapters of the International Society of Nephrology (ISN), International Diabetic Federation (IDF), International hypertension Society (HIS), etc.
- National Trado-medical associations

Levels of prevention

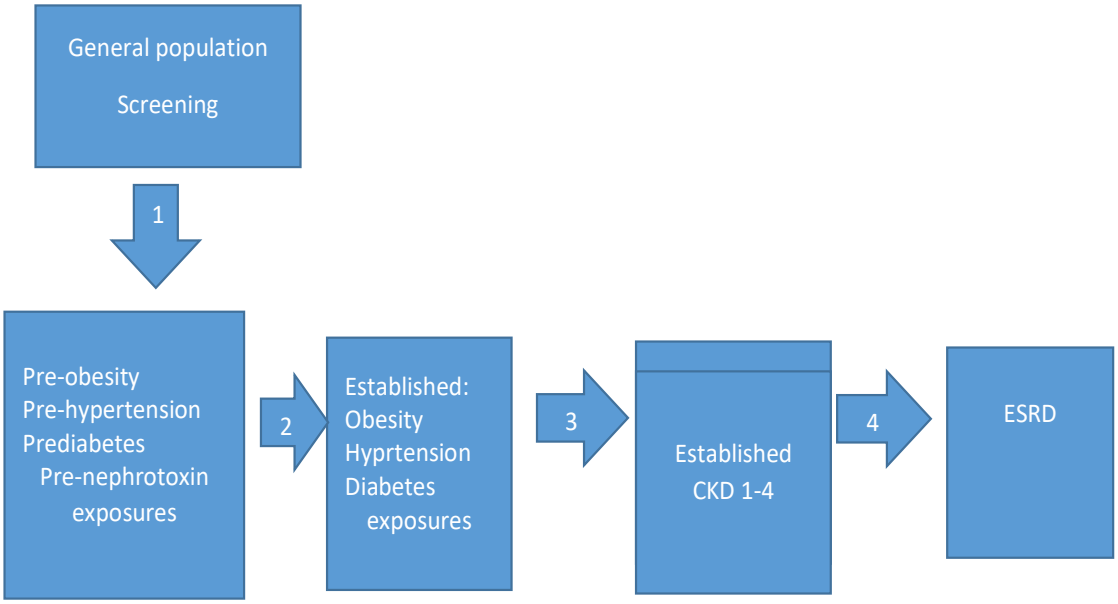

Fig.2: CKD /ESRD road map and steps in prevention

Level 1 Prevention: Community wide sustained health education on Lifestyle modification for the primary prevention of risk factors of CKD.
Level 2 Prevention: Health education, dietary and pharmacological interventions to prevent the translation of early stages of CKD risk factors (e.g. Pre diabetes to diabetes) to established risk factors.
Level 3 Prevention: The amelioration and modification of established risk factors to retard progression of CKD.
Level 4 Prevention: Intensive efforts using pharmacologic interventions such as ACEI, ARB Statins, etc. to retard the progression of CKD to ESRD.

- National and regional food and drug regulatory body
- Reputable Non-Governmental organizations (NGO) and Community based advocacy organizations (CBO) in health
- Faith-based advocacy groups, etc.

5. Target populations for advocacy and content of advocacy.

In order to provide advocacy for all members of the community-focused and target groups are identified and targeted for advocacy. Such target populations from segments of the communities would include:

- General Adult populations
- Antenatal women
- School children and adolescents
- Artisanal groups
- The Chemical and drug industry
- Herbal and traditional medicine practitioners
- Promoters and distributors of Nutritional supplements
- Faith-based organizations, etc.

6. Program measurable outcomes and evaluation

The time trend of the incidence and prevalence of the individual risk factors of CKD/ ESRD as well as the burden of the risk factors can be periodically determined. At any given point comparisons can be made between baseline data and current data to determine the effectiveness or otherwise of the Advocacy intervention program.

Table 3: Community-based CKD Preventive activities

Stages of CKD risk factors.	Preventive activities
General Prevention	❖ Sustained community-wide advocacy and health education against CKD risk factors ❖ Periodic screening detection of CKD risk factors
Pre-obesity	❖ Regular exercise ❖ Dietary program for reversal of pre-obesity and prevention of obesity
Obesity	❖ Exercise and dietary program for the reduction of obesity. ❖ Medical (Drug and non-drug interventions ± to ameliorate obesity ❖ Surgical procedure for obesity care
Pre-diabetes	❖ Exercise and dietary measures to reverse pre-diabetes ❖ Medical (Metformin) intervention to reverse prediabetes
Diabetes	❖ Strict dietary restriction ❖ Medical interventions to prevent DN ❖ Strict diabetic control to goal (FBS <7mmol/L; /HbA1c <6.5%)
Pre-hypertension	1. Dietary salt restriction 2. Maintain optima BMI 3. Keep Blood pressure levels below Prehypertension levels
Hypertension	❖ Strict salt restriction ❖ Maintain optimal BMI. ❖ Pharmacologic intervention to ensure optimal blood pressure control.
Dyslipidaemias	❖ Dietary measures to ensure normal lipid leve ❖ Use of Statins to keep serum level of total cholesterol level <5,2mol/l (NCEP Panel)
Prevention of nephrotoxic substance exposures	❖ Advocacy for the avoidance of the use of nephrotoxic bleaching soaps and creams. ❖ Prevention of exposures to nephrotoxic drugs and chemical substances ❖ Public health measures to control drug sales and access.

Thus, the measurable outcomes of the primary risk factor prevention advocacy program to demonstrate positive change in:

- v Population awareness of risk factors of CKD and ESRD.
- v Knowledge, attitude and practice (KAP) of lifestyle modification for prevention of risk factors of CKD
- v Time trends in the incidence of Overweight and obesity, prehypertension and hypertension, pre-diabetes and diabetes
- v Time trends in knowledge and exposure to nephrotoxins
- v Time trends of the population incidence of CKD and ESRD

7. Program continuity and sustainability

The program should be designed to be durable by integrating it into the health system of the country. Sustainability and continuity should be assured irrespective of the governance or administrative regime in place.

8. National pilot study

In view of the relatively large populations of the LIMC countries, it will be necessary to conduct pilot studies in select cohort populations for a period of time to determine the feasibility, cost-benefit and cost-effectiveness of the program as well as opportunities for operational and logistic lessons before embarking on Nation-wide advocacy interventions.

The period of the pilot studies in chosen populations may be between two and three years.

9. Integrating the program into the WHO 2008-2013 Action plan

Integrating the Primary prevention of CKD risk factors program into the WHO 2008-2013 Action plan for global prevention and control of Non-communicable diseases (NCD) program as a vehicle for program delivery. The six broad objectives of the WHO 2008-2013 Action plan for the global prevention and control of risk factors for non-communicable diseases are in consonance with the strategies enunciated for the primary prevention of risk factors of CKD as enunciated above.

Given the shared risk factors between NCDs and CKD, the plans as enunciated in the NCD prevention and control plan are applicable to proposed CKD prevention and control program. It therefore makes operational and economic sense to integrate the two preventive programs. This will be tantamount to using one stone to kill two birds. Such integrations would significantly reduce operational, logistics and financial costs.

No doubt the proposed program is an ambitious and in the short run, with a long gestation period. With better structuring and integration into the health system of LIMC countries, the initial high cost will come down. By reducing the supply of risk factor of CKD, the burden of CKD and subsequently that of ESRD will reduce over time.

CONCLUSIONS

In spite of the significant advances in the understanding of kidney disease the development of Nephrology as a distinct medical discipline, and the development of technologies for the care of kidney disease patients, spanning over 150 years, the burden of ESRD globally and especially in the developing countries, continues to increase over time.

The huge burden of individual human suffering and societal burden of care of persons with ESRD put an enormous financial strain on society. Even the developed countries with all the state-of-the-art facilities for care are being financially overstretched.

It is increasingly becoming evident that the **CKD- ESRD - DIALYSIS/TRANSPLANT** paradigm of care, seem not to be providing lasting solutions to the increasing burden of **ESRD** globally. It is envisaged that a successful primary risk factor preventive program has the potential of reducing the **supply side** of the CKD to ESRD journey.

Therefore, the primary risk factor preventive program, running together with intensive secondary preventive activities would go a long way in significantly reducing the risk factor burden of CKD and significantly reduce the rate of progression to ESRD in the society, especially in the LIMC communities which are worst afflicted and grossly deficient in ESRD care system

Preventive nephrology as a **sub-discipline of nephrology,** with emphasis on kidney health

promotion, primary and secondary prevention of the major risk factors of kidney disease have not been properly articulated and given the attention and identity it deserves. This is more so in the LIMC jurisdictions, that bear the greatest burden and have the least access to RRT. For most persons in the LIMC jurisdictions, ESRD the diagnosis of ESRD is tantamount to death sentence within one year.

Given the success of the Framingham heart studies in creating the necessary population awareness and leading to interventions in cardiovascular risk factor modulation in the United States, the burden of cardiovascular diseases and related deaths reduced to a reasonable extent.

We propose, that the Global Nephrology community, as led by ISN, encourage the development of Preventive nephrology as a sub-discipline of nephrology, to be integrated into the currently prevailing CKD-ESRD-RRT model of care.

We envisage that by substantially reducing the **supply side** of risk factors of CKD, the quantum of CKD transforming into ESRD would be substantially reduced.

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