SciForschen
Open HUB for Scientific Research

ISSN 2380-5498

International Journal of Nephrology and Kidney Failure

Review Article Volume: 1.3 Open Access

Agrochemicals and Chronic Kidney Disease of Multi-Factorial Origin (CKDmfo): An Environmentally Induced, Occupational Exposure Disease

Sunil J Wimalawansa*

Professor of Medicine, Cardio-Metabolic Institute, Somerset, USA

***Corresponding author:** Sunil J Wimalawansa, Department of Medicine, Professor of Medicine & Endocrinology, Cardio Metabolic Institute, Somerset, USA, **E-mail:** suniljw@hotmail.com

Received date: 07 July 2015; **Accepted date:** 19 August 2015; **Published date:** 23 August 2015.

Citation: Wimalawansa S.J. (2015) Agrochemicals and Chronic Kidney Disease of Multi-Factorial Origin: Environmentally Induced, Occupational Exposure Disease. Int. J. Nephrol Kidney Failure 1(3): doi http://dx.doi.org/10.16966/2380-5498.111

Abstract

The contamination of food and water through waste and agricultural runoff poses serious threats to humans. Pollution with microbes causes noticeable diarrheal diseases, whereas agrochemicals, heavy metals, fluoride, and toxins cause insidious diseases and premature deaths. Chronic kidney disease of unknown origin (CKDuo) was first seen in dry-zonal agricultural regions in equatorial countries in the mid-1960s, and in Sri Lanka, in mid-1990s. A number of agents and toxins have been postulated as the cause of CKD of multifactorial origin (CKDmfo/CKDuo), including heavy metals, agrochemicals, fluoride, fungal and bacterial toxins, climate change; and a number of behavioral factors. Meanwhile, several other potential nephrotoxic causes have not been investigated, including the indiscriminate and excessive use of non-steroidal anti-inflammatory drugs, illegal drugs and illicit alcohol, microbial agents (leptospirosis, Hanta virus etc.), chronic dehydration, and exposure to various combinations of these toxic agents in the presence of unhealthy habits. The incidence of CKDmfo is doubling every 4 to 5 years in Sri Lanka, leading to more than 5,000 deaths annually; excess of 150,000 people are currently affected. Although a number of agents have been postulated, no single offending agent has been identified as the cause of CKDmfo. To alleviate CKDmfo, it is essential to take a broader, holistic approach: carry out a massive awareness campaign, prevent environmental pollution, lessen malnutrition, correct unhealthy behaviors and habits acquired during recent past, and provide clean water completely devoid of nephrotoxins to all inhabitants in the affected communities. A sustained, coordinated, targeted, and effective approach is essential to decrease the disease incidence, prevention of premature deaths, and eradication of CKDmfo. This review explores pros and cons of agrochemicals as a potential cause of this deadly disease.

Keywords: Agribusiness; Agriculture; Behaviour; CKDu; Environment; Fluoride; Heavy metals; Premature death; Renal failure, Water

Abbreviations: CKD: Chronic Kidney Disease; CKDuo: CKD of unknown origin; CKDmfo: CKD of multifactorial origin; DoA: Department of Agriculture; EPA: Environmental Protection Agency; NCP: North Central Province; NWS&DB: National Water Supply & Drainage Board; TSP: Triple Superphosphate Fertilizers; WHO: World Health Organization

Introduction

The demand for fresh water need for domestic, agricultural, and manufacturing use continues to increase worldwide [1]. Because of its inherent chemical structure, water dissolve most substances and thus, is easily polluted [2]. Taken together with the water scarcity, food and freshwater insecurity are increasingly a problem in many communities. Particularly in both, urban and rural sectors in emerging economies. This is aggravated by unpredictable weather patterns and prolonged droughts that are associated with the climate change occurring over the past four decades. Considering these factors, the lack of ready access to affordable and a safe supply of potable water continues to be a serious threat to human health in many countries.

Over the past few decades, freshwater resources have been endangered, not only by over-exploitation, but also by neglect, poor management, ecological degradation, and man-made pollution [3]. Naturally occurring and anthropogenic contaminations exhibit marked geographical variations [4], while unpredictable climate changes exacerbate causes not only economic harm but also ill health [5,6]. Degradation of watersheds and catchment areas in wooded and elevated terrains, deforestation, and the consequent soil erosion lead to harmful ecological changes. These anthropogenic activities increase the need to dredge canals and reservoirs, which further contaminates the water and soil.

Water pollution secondary to expanding agricultural sector and human settlements, poor planning of drainage and safe sanitary facilities, pollution related to the industrial sector, and neglected or sub-optimal watershed management practices [7,8] all contribute to a shortage of clean drinking water [9-11]. In addition, the failure to adopt proper soil and water conservation measures, lack of clean air and clean water policies, irresponsible use of agrochemicals, and lack of enforcement of environmental laws and a nationwide long-term sustainable water plan, further increase the scarcity of clean water [6,12], and escalate the incidences of chronic human ill-health.

Environmental Pollution Related Chronic Kidney Disease

The kidney is one of the body organs receiving the highest blood flow and is highly metabolically active. Although somewhat more resilient than the liver, the kidneys are vulnerable to acute and chronic exposure to ischemia, heavy metals, toxins, and oxidative stress-induced damage. Worldwide, the two most common reasons for the development of chronic kidney disease (CKD) are hypertension and diabetes. In these two chronic diseases, renal glomeruli affected are affected early in the disease. Hence proteinuria or micro-albumin in urine (urine, micro-albumin/creatinine ratio; MCR) is a highly sensitive screening test to identify CKD at an early stage, allowing to intervene effectively.

There are well-known associations between CKD and environmental agents, various disease conditions, immunological entities, and infections [13]. Kidneys also injured by a number of other means, including snake venom, various nephrotoxic agents, and poisons entering the human body through oral, inhalational, or transdermal routes from the environment. In addition, hypersensitivity, and autoimmune diseases, bacterial, viral and fungal infections, other microbes such as leptospirosis and Hanta virus, metabolic abnormalities, heavy metals, fluoride, and circulatory disturbances also causes renal failure.

Toxins, heavy metals, industrial chemicals and agrochemicals, immunogens, infections, and sometimes combinations of these agents causes either acute or chronic renal damage. Instead of the glomerular h damage, most of the aforementioned agents primarily harm renal "tubules", with relative sparing of "glomerular" tissues. Moreover, in certain patients and in conditions, the toxic effects of these agents are modulated by age, sex, genetic susceptibility, nutritional status, exposure amount and the duration, and existing comorbidities [14].

Chronic kidney disease of multifactorial origin (CKDmfo):

CKD of multi-factorial origin (CKDmfo), predominantly affects the North Central Province (NCP) in Sri Lanka. Its associations with various components have been previously discussed [15,16], and thus, will not address here. Recent articles have focused on the excessive use of agrochemicals that contaminates water bodies and reservoirs [17-20], exposure of farmers to chemical fertilizer, organochlorine and organophosphorus pesticides [21], polluted drinking water sources (surface water), including well water [15,24,25] with fluoride, heavy metals, and other toxic components [16,22,23].

With reference to preventive efforts, understanding the contamination of well water is relevant in the NCP because, approximately 75% of NCP inhabitants drink water from shallow wells and 8% from tube wells [18] (Figure 1). In parallel to this, approximately, 90% of those who are affected with the disease, consumed water from such wells. The incidence is less among those who consume water from reservoirs and associated canal system. Figure 1 show the Sources of drinking water supplies in the CKDmfo affected region.

As mentioned above, the vast majority of people in the North Central Province (NCP) drink water from shallow wells and deep tube wells. Although surface water in shallow wells can be contaminated by agricultural runoff and other anthropogenic activities, tube wells are not. The latter is mostly contaminated by natural groundwater fluoride; weathering of underground fluoroapatite structures [18]. All published reports, including those from a group assembled by the ministry of health, Sri Lanka, with the assistance of World Health Organization (WHO), are inconclusive [15,16] with regard to discerning an etiological factors; all studies to-date have failed to clarify the situation [12,16,18, 20-23, 26, 27].

The data and reports from studies, such as the WHO-CKDu [15,16], collaborative Japanese studies and several others [12,18,21,26,27] have failed to support any of the hypotheses regarding potential cause(s) of CKDmfo. The later includes, heavy metals, fluoride, hardness of water, ionicity, and agrochemicals (such as glyphosate, toxaphene, organochlorine and organophosphate pesticides, nitrates, or phosphates) [15,16,28]. Collectively these research data and commentaries published over the last decade, however, have improved the understanding and knowledge of CKDmfo, but there is still much to learn.

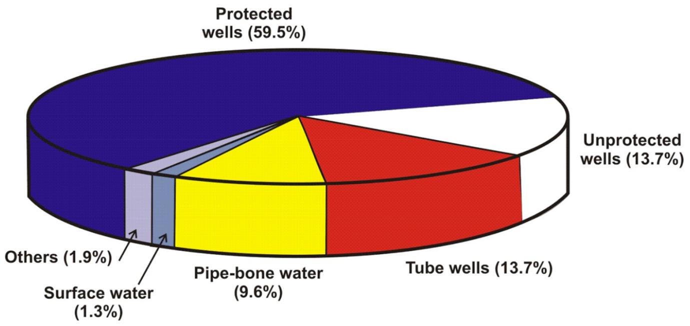

Figure 1: The distribution of drinking water sources in the North Central Province (NCP) in Sri Lanka (after Chandrajith et al. [17]).

Escalating Incidence of Chronic Kidney Diseases

During the past decade, the incidence of CKDmfo in the NCP has increased significantly [16], doubling every 4 to 5 years [21,29]. In addition, the disease continues to spread to adjacent and distant regions in the country [16,18]. However, it is unclear whether this increasing occurrence is attributable to a true increase in the incidence of CKDmfo, or better awareness and thus increased diagnosis and greater reporting of the disease [21]. This is further muddled by the manifestation and reporting of the disease in new regions, in part due to recent trend of migrating families from the NCP to non-affected regions to prevent getting the disease and premature deaths.

In Sri Lanka, CKDmfo causes the deaths of more than 5,000 per year, mostly male farmers (including the occurrence of suicides secondary to sufferings from this disease, approximately one a day); numbers continue to increase [15,21]. The victims are primarily from economically poor agricultural communities in the dry zonal regions. To-date, in the affected regions, only about 7% households have access to a pipe-borne water supply; the rest rely on canals tube-wells, and shallow dug-wells [18], for drinking water, and water for washing, bathing. In spite of having a number of postulated causes, no one specific cause or a combination of elements for the genesis of CKDmfo has been established [15,20,30].

Many investigators have suggested that some substance(s) present in the water is likely to be responsible for the development of CKDmfo [18,31], but a specific factor(s) is yet to be identified [15,21]. Current data suggest a probability of 95% that the disease is originating through consuming contaminated water. However, other sources such as through consumption of food, microbial agents, or inhalation of volatile toxic substances have not been excluded.

Water Pollution and CKDmfo

The industrial development and colonization begin to occur in Sri Lanka, since 1950s. The vast majority of these new settlements occurred in areas that once were forested, particularly in the NCP and in the eastern province. This was further complicated by a major irrigation project, the Accelerated Mahaweli Program that commenced in the mid-1970s. Although unproven to-date, there is a possibility that the combination of these contributing to the genesis of the current epidemic of CKDmfo; also knows as CKD of unknown origin/etiology (CKDuo) [21,32].

Unless such projects are properly designed with long term vision for the human needs and environmental effects and consequences, and due consideration given to human habitats and health, clean water, sanitation and drainage, are fully considered and attended to, these developments can inflict tremendous pressure and harm on the environment, creating adverse impacts on both freshwater systems and humans. One such example is the manifestations and escalating incidence of non-communicable diseases in the region.

A part of the problem is due to the surface water, contamination with plant nutrients (e.g., phosphate, nitrate, and nitrites), pesticides, organic matter, and excessive agrochemicals applied to local farmlands. However, the environmental effects may not necessary manifest in the local area, but areas hundreds of miles downstream; the irrigation water supplied coming through the River Mahaweli [7,8,33,34].

There have been speculations for a while that water coming down from the Hill country brings many agrochemical-based pollutants through this river, to the reservoirs in the dry zone. Almost all reservoirs supplied by Mahaweli water are located in the NCP [24,25,29,32,35,36]. Figure 2 illustrates the sectors and regions that are currently supplied by the water from River Mahaweli and the proposed future expansion areas in the north of the country.

Because the geo-chemical parameters vary markedly from village to village, conclusions based on water quality data from randomly collected samples, analyzed and published can be misleading, and thus cannot be generalized for the region or defining the causes of CKDmfo. In particular analytical quality of water various tremendously depending the season samples were collected (e.g., wet season vs. dry season, and others). Moreover, the samples collected at different times cannot be pooled for drawing conclusions.

Nevertheless, available data suggest that various nephrotoxins derived from environmental contamination and the unique hydro-geochemistry of the directly affected areas playing a key role in the development of CKDmfo [15,17,18,31,37]. In spite of these variabilities, none of the studies conducted to-date [15,18,27] reported contaminant levels of the postulated substances in water, higher than the safe upper limits [maximum allowable limits; (MAL)] stipulated by the WHO and the United States Environmental Protection Agency (EPA).

Epidemiological Data Related to Spreading of CKDmfo in Sri Lanka

The evidence suggests that CKDmfo is disseminating from the NCP to other parts of the country, such as to Girandurukotte, Nagadeepa, Badulla District, Wilgamuwa in the Matale District, Nikawewa in the North Western Province, and recently into distant areas such as Jaffna, Udawalawa, Moneragala, and Hambantota districts (Figure 3). However, data available are insufficient to assess, whether this 'spread' outside the traditional NCP boundaries is attributable to enhanced awareness and thus increased diagnoses (nevertheless, diagnosed too late to recover renal funciotns) because of the recently initiated population-based broader screening by the department of health and a number of volunteer organizations, or migration of families from the affected areas in the NCP to distant regions.

In addition to the "insensitive and non-specific" methods (e.g., MCR) used and solely relied by the department of health for screening and diagnosis [21], the ability to diagnose the disease is no more than 40% out of those affected in the community (i.e., 60% chance being, false negative). On the other extreme, screening methods used also have a high false-positive diagnosis (i.e., diagnosed of having CKDmfo, when it is not - estimated error is over 15%). This is mostly due to secondary to contamination of urine samples with non-urinary proteins due to unstandardized samples collections. Such contamination occur mainly through cross contamination with non-urinary proteins (i.e., poor urine collection methods) and the sample collections containers.

Considering these, only 3 to 4 out of 10 affected persons are rightly diagnosed having CKDmfo by using the currently used methodology. Significantly under diagnosed and in those who have identified, the diagnosed made too late, because in CKDmfo proteinuria is a late sign. It is also plausible that migration of families of the affected individuals with the disease from the NCP into distant areas is a factor indicated in Figure 3B (i.e., new appearance of the disease outside the traditional boundaries of NCP. However, our data confirmed a true increase of the incidence (i.e., previously healthy people, newly contracting the disease,

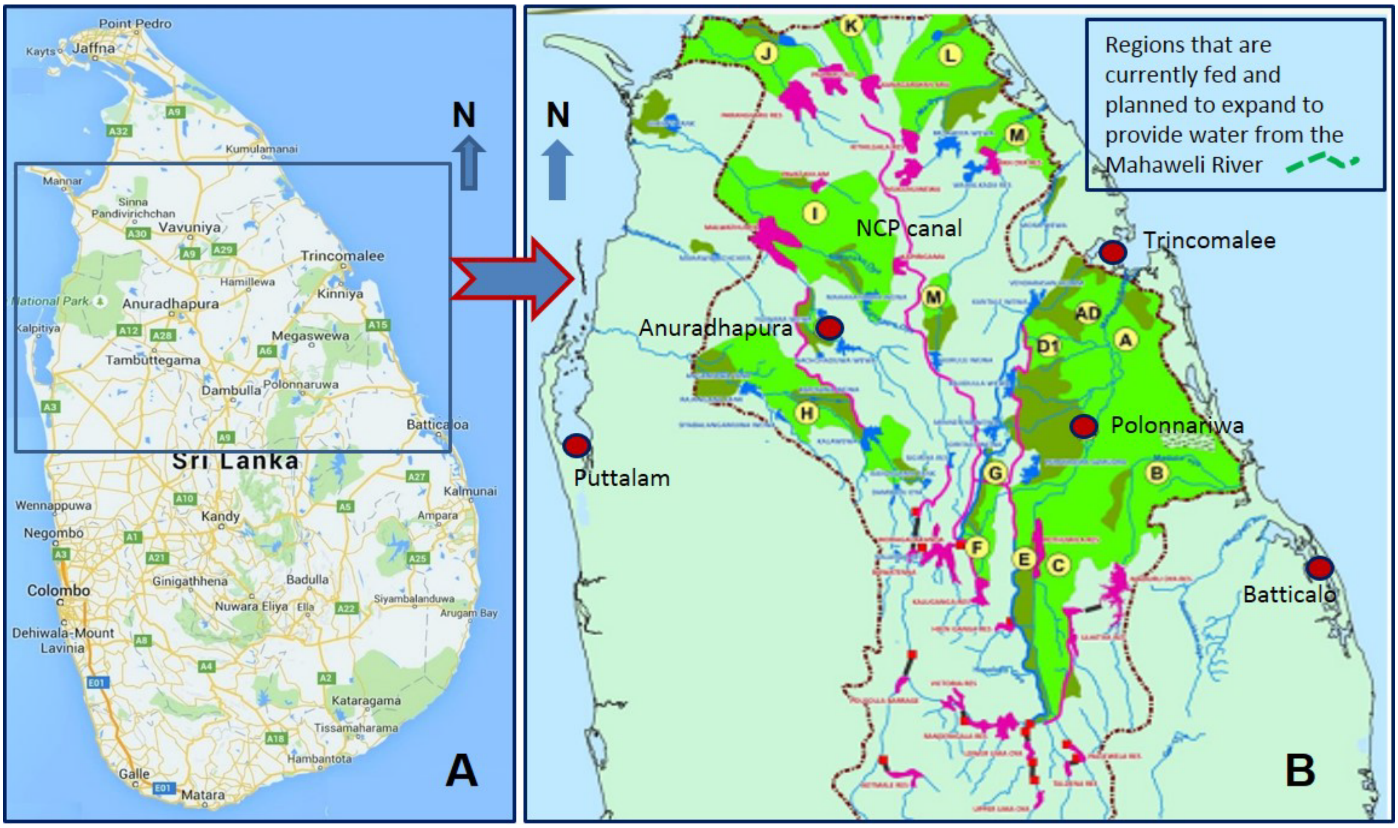

Figure 2: (A) Map of Sri Lanka illustrating major cities, and (B) a magnified geographical area, illustrating the regions fed by the water from the River Mahaweli and the areas that are covered by the Accelerated Mahaweli Developmenet Program in the North Central Province (NCP).

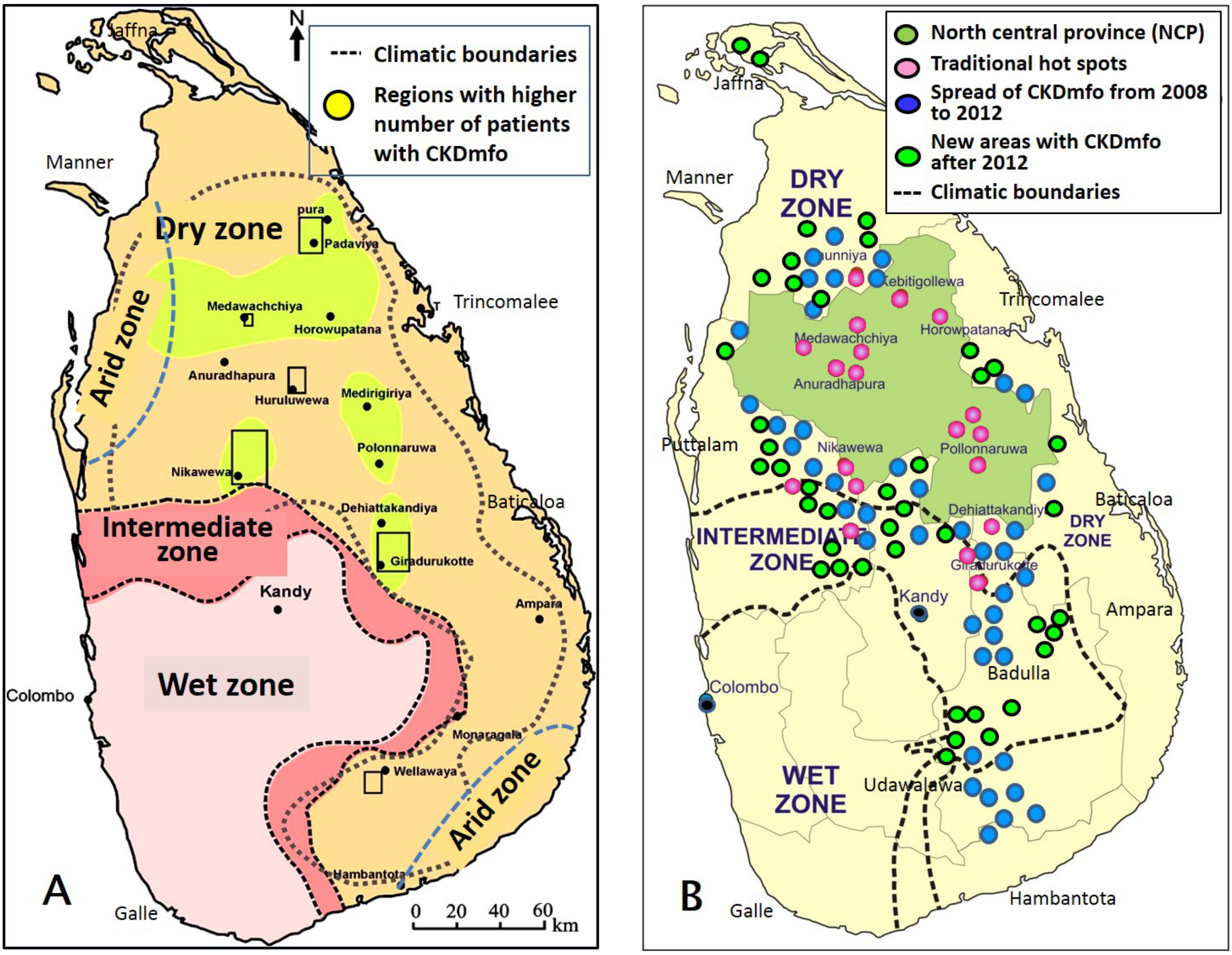

Figure 3: The geographical distribution of patients with CKDmfo in relation to the climatic zones in Sri Lanka. (A) The three climatic zones, wet zone (pink), intermediate zone (red), and dry zone (orange) are illustrated, with the areas originally affected with CKDmfo shown in yellow. (B) A map of Sri Lanka illustrating the pattern of distribution and spread of the disease outside the NCP (NCP region is indicated in light green). Colour coding: The original CKDmfo hot spot areas (pink circles); the spread of the disease from 2008 through 2012 (blue circles), and the spread after 2012 (green circles). The climatic boundaries are super-imposed with broken black lines. Figure A was modified after Smedley and Kinniburgh, 2002 and Figure B was modified from existing data, public domain, and from Wimalawansa et al (2014) with added new data [21].

in new localities) as the primary reason for identifying new patients with CKDmfo in distant regions.

Agrochemicals and CKDmfo

In the late 19th century, agriculture began to change from the traditional, organic model to the use of manufactured agrochemicals in green revolution. This was in part because of the increase in population that could not otherwise, be supported using traditional methods that had been in use for centuries when the population was relatively static. The change started with the "nutrition / the crop revolution," which was followed by the green revolution in 20th century. The latter was characterized by a rapid increase in the use of synthetic agrochemicals on which farmers quickly became dependent for growing crops.

Today, lobbying by various environmental groups, less than 10% of the world's commercial farmlands use organic agricultural methods. 65% of these organic lands are exclusively use for generation of pastures for organic meat production. Other than hybrid cultivation, which uses traditional and modern agricultural methods, no method available today can replace the current conventional agricultural methods that use agrochemicals to generate higher amounts of crops using the same arable land. Nevertheless, the overuse of agrochemicals is hazardous and must be adhere to the levels recommended by the Department of Agriculture (DoA). When agrochemicals used correctly, based on the soil requirements are safe, and unlikely to pollute the environment or generate human health issues.

The presence of very small quantities of herbicide propanil [N(3,4-dichlorophenonyl) propanamide] and the insecticide chlorpyrifos [O,O-diethyl-O-(3,5,6-trichloro-2-pyridinyl) phosphorothioate] has been reported in certain water sources, including in shallow drinking wells in the CKDmfo affected areas [5,16,38,39], but other research has failed to detect the presence of any of these agrochemicals using modern analytical techniques [17,18]. Small quantities of glyphosate [N-(phosphonomethyl) glycine] [40] (the major ingredient in the herbicide, Roundup, that is extensively used, worldwide) have been reported in very small quantity (less than 10 parts per billion) in a minute number of water samples, out of thousands tested to-date [40,41]. Three largest studies conducted to-date, including the WHO-CKDu study, failed to detect meaningful quantities of glyphosate or any other agrochemicals in water sample analyzed [15].

Agrochemicals Are Unlikely To Cause CKDmfo Directly

Long-term exposure to high doses of propanil and chlorpyrifos, whether through the contaminated water, by absorption via the skin, or inhalation during spraying could cause liver and kidney disease [42]. In addition, the mass-scale use of poor-quality, triple superphosphate (TSP) fertilizer and other agrochemicals imported to the country, may have made the situation worse [19,43,44]. Meanwhile, some pesticides that are barred in industrialized countries continue to end up in emerging economies, in part because of commissions given to importers and law makers, the lack of enforcement of import safety regulations and quality controls [45].

While aforementioned chemicals and toxins are polluting the agricultural soils and water supplies [17], at least some contaminants are likely to end up in the food chain. If this is the case, a portion of the food that is generated from these 'chemically contaminated' farmlands (e.g., in the NCP) as claimed by some (without any scientific evidence), are sent to other parts of Sri Lanka and exported to other countries. Exportation of food to other countries, may even include the ones from which these contaminated fertilizer consignments were sold to Sri Lanka. Nevertheless, no one lives in 'safer regions' in the country in spite of eating food generated in NCP, have contracted CKDmfo by consuming food imported from the NCP region.

In fact, there is no indication that crops generated in the NCP is any different from produce from other regions in the country with reference to contaminants and safety. For example, as per the United States-Food and Drug Administration (US-FDA) annual reports, the rice produced in Sri Lanka (mostly from the NCP region) has less contaminants (e.g., arsenic cadmium, etc.) than that rice produced from most other south east Asian countries). Overall, the proper use and timely management of agrochemicals, agricultural waste, and petroleum spills, etc. [46] is essential to preventing pollution of water bodies and underground water sources [36,44].

Such proactive steps could prevent degradation of water sources [36] and decrease the incidence of CKDmfo in the long run. In addition, it is important to implement a broader pollution prevention educational program for farmers and the merchants who sell agrochemicals regarding the proper use of agrochemicals and water management to minimize water and environmental pollution. Among the large number of agrochemical components use in Sri Lanka, only glyphosate has been suggested to be associated with the CKDmfo by one group [47], but the evidence is scanty, and no reliable and verifiable scientific evidence provided; no other scientific group to-date has been able to verify it [15,18,44,48,49].

There is no evidence that glyphosate causes CKDmfo

It has been hypothesised that glyphosate–heavy metal complexes may facilitate renal failure [47], but no scientific data exist to-date to support this suggestion [20,21,43,50]. Demonstration of the mere presence of some heavy metals and glyphosate in water or soil samples, does not means it causes or even associated with any disease, including CKDmfo. No other scientific group has been able to verify these reports [47,51].

Being a phosphonate, glyphosate has potential of formation of metal complexes (most commonly chelation of Ca and Mg) has been reported using computer modelling [52]. However, none was reported for complexes of arsenic or cadmium with glyphosate; and is it highly unlikely. A number of scientists (including, Professors of chemistry; G. Rajapaksa, C. Dharma-wardena, O. Ileperuma) have pointed out that, based on scientific principles, and chemical and thermodynamic variables, it is impossible for glyphosate molecules to act as a carrier for arsenic or cadmium, especially in the presence of Ca^{++} or Mg^{++}. Presence of Ca and Mg in water is very common, in headwater in the NCP. In the unlikely event, even if such complexes are made, they are insoluble and thus will not be dissolve in water, therefore, not be able to get into human.

The published literature suggests, with the use of even several fold higher quantities of glyphosate than recommended by DoA for farming activities, have no adverse effect on human kidneys [41,53]. To-date, there is no scientific evidence to corroborate glyphosate causing CKDmfo [21,50,54]. As indicated in the Figure 2, hard water is present in a number of regions in Sri Lanka, particularly across the NCP, but with variable distribution of fluoride content. Farmers in these regions are using similar or in some regions, even higher quantities of glyphosate. However, in these areas, the incidence of CKDmfo is not high. There are additional compelling epidemiological, chemical, and other scientific reasons to reject the hypothesis that glyphosate causes CKDmfo.

These reasons include, but not limited to: 1) the disease was prevalent in the NCP several years before this chemical (glyphosate) was introduced to the region, 2) people who drink from shallow wells are more susceptible to develop CKDmfo than those who drink water from tanks and canals (but this chemical has not been found in either of these waters), 3) tube well water has no agrochemical contamination including glyphosate, but those who drink such water also contract CKDmfo, 4) glyphosate binds tightly to the topsoil particles and makes relatively insoluble complexes with the abundant cations in soil, such as calcium and magnesium, making little possibility of leaching into the waterways, and 5) even if ingested, it will bind tightly to surplus of cations available in gut preventing its absorption [43,44,50]. Currently, overall scientific evidence suggest that glyphosate plays no role in causing the CKDmfo epidemic in Sri Lanka [15,20,21].

Adjuvants and Surfactants Can be Harmful to Humans

Adjuvants and surfactants are routinely included in almost all pesticides and herbicides preparations to stabilize, and enhance the intended effects of the active ingredient. Very small quantities of the active ingredient (e.g., glyphosate) present in few tested samples of water (that are not harmful to humans) in certain locations. Nevertheless, accumulating evidence suggests that adjuvants and/or surfactants could be harmful to humans [55-58]. Consequently, it is essential to prevent water resources contaminating with these compounds.

These surfactants include, Cosmo-Flux (in Roundup) and perfluorinated surfactants, and their precursors and adjuvants. If ingested in certain quantities, these can cause human disorders [58,59]. Thus, their presence in drinking waters and food must be eliminated or at least minimized. This is where the right legal regulations are necessary to either limit or ban the importation (and local production) of products containing (and the addition of) dangerous adjuvants, surfactants, and precursors. Banning the active ingredient (e.g., glyphosate), which is relatively harmless, while very important for agriculture is not the right approach.

Role of Low-Quality Chemical Fertilizers

Worldwide, there are several commonalities in the CKDuo/CKDmfo-affected regions in different countries, such as Bangladesh, Sri Lanka, southern China, India, South America, and certain eastern European countries. These similarities includes, poverty, drought-stricken nature, lack of access to modern healthcare, and proximity to the equator. Affected nations all are predominantly has agriculture-based livelihoods and considered as developing or emerging economies.

These communities and nations are economically disadvantaged, many receiving aid from the West [21,60]. Although the European Union and the United States EPA banned the sale of certain manufactured agrochemicals [61], thousands of tons of some of these prohibited chemicals are sold as cheap agrochemical products to the aforementioned developing countries [62].

For example, when the EPA banned the sale of monosodium methyl arsenate (MSMA; sodium hydrogen methyl arsenate, an effective arsenic-based herbicide and fungicide) in the United States, the use of this chemical markedly increased in the developing countries [63]. It is a less toxic form of arsenic that has replaced lead-hydrogen arsenate designed for agriculture, but still retain the capacity converting to toxic inorganic arsenite [64]. Until, replaced by glyphosate, it was one of the most commonly used herbicides on golf courses in developing countries [63].

Phosphate Eutrophication of Reservoir Water does not cause CKDmfo

Fertilizers containing rock-phosphate such as triple superphosphate fertilizers (TSPs) [65] are a source of some cadmium and arsenic pollution in soil [25,32]. Overuse of TSP could pollute farm soil, and its runoff are known to contaminating water bodies with excess phosphate [20,44]. In addition, higher than acceptable levels of cadmium, arsenic, and lead are present in some pesticides and herbicides [66,67] included as active ingredients or as contaminants [68,69].

Therefore, the overuse and chronic exposure to such agents could cause or aggravate chronic health conditions. Because of the high governmental subsidy of fertilizers, many farmers overuse these products and use them carelessly, with the misguided assumption that use of greater quantities than those recommended by the manufacturers and the DoA, continue to increase agricultural output, each year [20,21,44].

Excess fertilizer applied to the soil leaches into surface water, and run off via streams and rivers into reservoirs, as in the case in the NCP, causing ecological changes and harming marine life [2,36]. Excess phosphates and nitrates from the fertilizer facilitate algae blooms and cyanobacterial growth. As the nutrient increases, bacterial growth also increases and rapidly consumes dissolved oxygen in the water. This leads to suffocation of freshwater fish and retards their growth and propagation [36].

In addition, the release of nitrous oxide (from excessively used nitrates fertilizers) contributes to the reduction of ozone present in the stratosphere and thus, adds to global warming and climate change. The ozone layer absorbs much of the harmful ultraviolet (UVA) radiation that radiates from the sun. The erosion of this protective layer is known to be harmful to living beings, including increased cancer risks.

Most governments in developing countries including Sri Lanka, provide a large fertilizer subsidy for farmers. For example, a 23-kg bag of fertilizer is sold for approximately for 350 rupees; at 10% of the real cost. Consequently, the government is spending more than 50 billion rupees a year on the fertilizer subsidy alone. Thus, a 10% reduction of this would save more than 5 billion rupees annually, which is more than adequate to eradicate the CKDmfo from the country. The surplus can be used to enrich the lives of deprived farming communities in the region. These over usage of phosphate-fertilizer is the key reason for phosphate eutrophication of water in all large reservoirs in the NCP region [36]. Almost all of these reservoirs are in fact, fed by water coming from the hill country via the River Mahaweli (Figure 3).

The ranges of phosphate levels reported in these waterbodies in the NCP are between 0.07 and 0.15 mg/L, with an average of 0.12 mg/L [36]. This increase in water phosphate levels in reservoir suggests that over use of fertilizer in the upper terrains (in the hill country in Sri Lanka) as the most likely cause for phosphate eutrophication of the River Mahaweli and consequently, reservoirs in the NCP [32]; the region that is also most affected by CKDmfo.

These levels of phosphate (phosphorus) in water causes significant negative ecological effects on freshwater fauna and flora and cause algae blooms as described above. However, there is no evidence that the reported low levels of phosphate in water are harmful to humans. Even if water from these reservoirs is consumed by people, there is no evidence that it can harm kidneys or causing CKDmfo.

Overuse of Pesticides and Lack of Precautions during Agrochemical use

In developing countries, including Sri Lanka, most famers do not take precautions when handling agrochemicals [70,44] and in some houses, these are stored together with food. Nevertheless, these dangerous habits are not different from that in the CKDmfo-endemic and non-endemic areas in the country, so this factor alone is unlikely to play a major role in the development of CKDmfo.

In this regards, it would be very useful to gather comprehensive and comparative information about social habits, dietetic patterns, storage of food and agrochemicals, the ways these chemical are used, advice on pest and plant-disease control measures, handling of pre-harvests and post-harvests, socioeconomic and cultural basis in farming families. In addition, Geographical Information System (GIS)-linked CKDmfo case distribution, and the presence of clean and contaminated water sources are needed.

These data should be compared between the CKDmfo affected and non-affected communities within the region, and distantly located non-affected communities in the country. Such a comparison is likely to be very productive not only to identify the causes of this lethal disease but also to implement preventative strategies.

Since the abolition of agricultural-extension advisory services in Sri Lanka in mid-1980s, there is no established, reliable structure in communities for farmers to obtain proper information and advice on agricultural matters. In recent years, instead of the DoA, farmers have begun to rely on the vendors of agrochemicals for such information, adding to the complexity of mismanagement.

Quantities of fertilizer use by farmers need to be regulated:

The amount of fertilizer imported to Sri Lanka is approximately 8,000 metric tons per year (1 metric ton=1,000 kg). This can be approximately quantitated into addition of 2 ppm arsenic (~2 mg/kg of fertilizer) and 6 ppm cadmium (~6 mg/kg of fertilizer) each year to farm soil in the country. However, these small amounts unlikely to saturate soil or its binding capacity. When excess fertilizer is applied to farm fields, what is not absorbed by soil and plants leaches out and finds its way into waterways. Therefore, the use of right quantity and the proper use of agrochemicals are important measures not only to protect the environment but also to prevent CKDmfo.

The Lack of Agricultural Extension Services to Farmers

Sri Lanka had an effective and well-organized agricultural extension and advisory system that was dismantled three decades ago by the government, following advice from the International Monetary Fund (IMF) and the World Bank, as condition for their loan packages. Not only they were trained and appointed by the DoA, but also these extension workers had a close relationship with farmers. They provided an efficient and useful advisory services with reference to farming practices, including fertilizer use.

This valuable scheme was replaced with the Provincial Council Administration System. It created a new title, Grama Niladhari (government-appointed (paid by the government) "village headmen"], whom agricultural training is not a prerequisite. This change led to a virtually complete breakdown of the nation's valuable agricultural extension system, adding to the current problem. It is highly advisable to re-establish the agricultural extension worker system.

In spite of lack training in agriculture, Grama Niladhari's were expected to provide the same advisory services that previously provided by trained agricultural extension officers. This created a major vacuum of delivery of expertise and services across the country. The lack of extension workers was quickly filled by agrochemical agents and merchants; self-created advisory service (but with conflicts of interest).

Desperate for money, a desire to increase crop output, lack of a proper agricultural advice and supervision, and the availability of highly subsidized fertilizer, created a "perfect storm"; farmers began to overuse agrochemicals, which led to the current situation. It is essential that the Ministry of Agriculture re-establishing this valuable institution, similar to the cultivation committees handling paddy cultivation, and the use of fertilizer can be effectively attended to by this entity.

Importance of Preventing CKDmfo

Chronic, non-communicable diseases have affected many areas in the NCP, and the incidences are continuing to rise. One of the main goals of the chronic disease prevention program in the region should be to minimize the incidence of CKDmfo. This can be achieved by providing clean water devoid of nephrotoxins, and limiting the environmental and water pollution at the source level, so that watersheds and the environment are preserved. In addition, the cascade of irrigation tanks need to be restored for agriculture, bathing, and for other uses. In parallel, economical ways to collect rainwater should be encouraged (and perhaps provide one-time material subsidy to establish these units) to provide fresh water for domestic use.

Recent statistics indicate a doubling of the incidence of CKDmfo during the past 4 to 5 years [23]. Although there is no causality established, agrochemicals are one of the suspects in causing this fatal disease. Therefore, it is of paramount importance to educate farmers and merchants to reduce the overuse of fertilizers and inappropriate use of pesticides, and to assure strict quality control on all locally manufactured and imported fertilizer consignments [30]. This does not mean imposing a ban on agrochemicals. Instead, existing regulations should enforced and programs should be established to educate farmers of appropriate and responsible use of fertilizer based on soil testing data. Adhering to these in a responsible manner would at least maintain or even increase the agro-output, while decreasing costs and protecting the environment.

This necessitates increasing the number of trained, quality assurance inspectors, empowering and allocating appropriate resources for pesticide regulation authorities, re-establishing large-scal e agriculture extension services, and allowing unrestricted access for inspectors to all imported and locally produced fertilizers and agrochemicals consignments, to examine and assure the quality. To safeguard human health, enhancement of inspections and certification programs also would be useful with reference to all agricultural and fisheries products (i.e., on the spot food inspection) before coming to the market.

Diversification of the economy to manufacturing and assembly, and other creative opportunities using locally available resources in the NCP region needs boosting. Such should minimize future economic catastrophes caused by relying purely on agriculture. These value-added industries would also alleviate poverty, improve the socioeconomic standard of residents in the region, traditionally known to be poor.

Programs to be implemented to Prevent CKDmfo

It is essential that environmental and customs officials impose strict quality control measures for all imported fertilizer and pesticide shipments at the ports of entry. However, this must be done without political interference. It is ironic that industrialized or economically advantaged countries do not allow local distribution or importation of contaminated material such as fertilizer to their counties, yet knowingly allow dumping of such toxic "waste" in developing countries, many times using intermediaries.

In addition, it is of paramount importance that a long-term plan for watershed management of the entire country be developed (i.e., a global plan for the country) to stop the process of continuing water pollution [2]. Preventing watershed degradation and associated soil erosion would improve agricultural output and decrease the burdens seen with CKDmfo and other chronic ill health problems [2,28,36].

To prevent any potential decrease of agricultural production, the gradual reduction of fertilizer subsidies should be tied to enhancing organic farming, and the use of hybrid methods, countrywide use of subsidized soil chemistry/fertility analysis, and implementation of strict legislations to prevent overuse of fertilizer and pesticide. This should automatically decrease the quantities of fertilizer released to farmers based on their "actual" need, as determined by the soil analysis data. The reduced fertilizer consumption would save the government billions of rupees, prevent soil and environmental pollution, saving money for farmers while maintaining good quality agricultural output.

On the user end, the unwarranted practice of applying pesticides just before and after harvest must be banned. Meanwhile, the Department of Health, EPA, and the Consumer Affairs Authority should be empowered and funded to analyze vegetables, fruits, rice, meat, fish, and other food items regularly, and educate farmers on the appropriate and responsible use of pesticides and fertilizer. However, this requires collaboration and participation of several ministries and government departments that can be coordinated by an independent CKD-Eradication Authority. An example of multi-pronged approach to curbing CKDmfo is illustrated in (Figure 4).

Adhering to the protocol provided to the government authorities by the Preventive Health, Environmental Protection & Research Organization

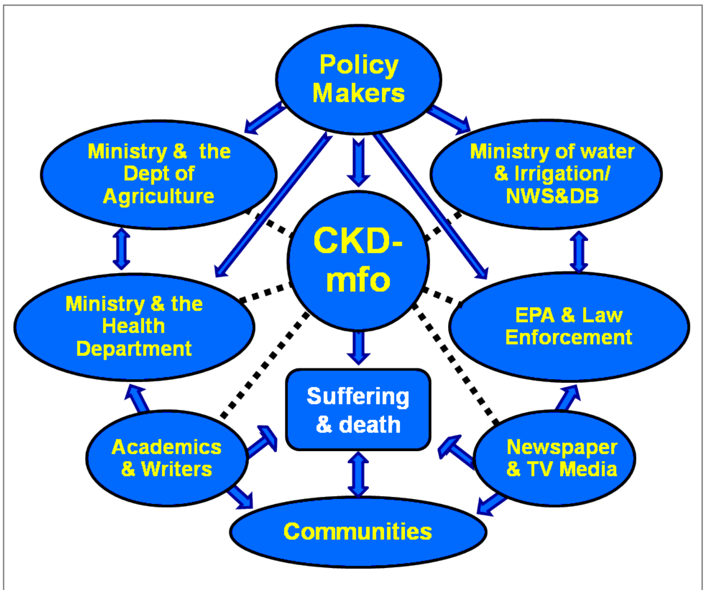

Figure 4: Shown are the multi-pronged approach and the broader network of interconnected strategies needed to prevent and eradicate the occurrence of chronic kidney disease of multi-factorial origin (CKDmfo) from an affected country.

[PHEPRO foundation] and the Wimalawansa Foundation, it would not only provide safe clean water to all inhabitants in the NCP regions between 18 and 24 months and prevent this deadly disease but also be able to eradicate it from the country within 12 to 15 years [https://wimalawansa.org/phepro].

The need for a Mass-Media–Based Educational Campaign

Nationwide, government-sponsored, mass-media–based educational campaign needs to be initiated on prevention of environmental pollution and protecting the watersheds, and the steps needed to take to minimize the risk of developing CKDmfo. Meanwhile, ineffective approaches such as the distribution of domestic water filtration systems should be stopped. The later has failed for a number of reasons, including (A) fewer than 10% of people who were provided the filters (even though given free of charge) have actually using them; (B) virtually none of the users replaces filtering material; (C) the inefficiency of the removal of pollutants by water filtration systems (i.e., unreliability–inefficiency and poor capacities); and (D) with the average purchase cost of approximately, Rs. 4,000, these filtration systems are not cost-effective. Therefore, the use of such systems should not be promoted. Moreover, while boiling would not remove most of the nephrotoxic agents, it is a highly energy consuming task that most villagers cannot afford to.

The need for interim clean water supply, and Focused, Locally-Applicable Research

While waiting for the National Water Supply and Drainage Board (NWS&DB) to provide a centrally purified, pipe-borne water supply for all municipalities and villages, interim methods, such as reverse osmosis [71] or ozonization of water [30], or at least larger-capacity, activated carbon filters that would adsorb organics and agrochemicals (but it does not remove heavy metals, fluoride, ions, etc.) with ion-exchange columns must be implemented to give potable water to each household in the region.

To overcome CKDmfo, the country needs a broad, multidisciplinary approach to research and development, and implementation of programs with a focus on finding the root cause(s) and its prevention, and problem solving. The availability of clean and safe drinking water will have a profound impact on curbing the spread of waterborne pathogens and chemical and toxin-induced diseases.

Such approaches should reduce the healthcare costs, and morbidity and mortality associated with not only CKDmfo but also many other preventable diseases. All villagers have the right to access to clean water that is free from chemicals and toxins, just as has been provided to those who live in cities and urban areas. In addition, there should be regular testing of water, particularly in the affected areas.

Proactive Actions are Needed

The provision of safe and clean water and sanitation saves more lives than all other medical advances and technologies put together. In fact, this is the number one reason for increased life-expectancy in most countries. In addition, prevention costs only are a fraction of the cost of the provision of acute medical care.

In fact, it is ironic that most countries do not allocate adequate resources for preventive health. The average healthcare budgets that spent for preventive healthcare in Southeast Asian countries is approximately 14% of the total health budget. This is far from adequate for disease prevention efforts, keeping the nations healthy and productive.

Unhealthy behaviour, anthropogenic pollution, and climatic changes, all contribute to human ill health, and increase personal, public, and governmental costs. All citizens must take the responsible for minimizing pollution and taking proper personal actions to ensure a better future for generations to come. Behavioral studies have taught us that current choices and incentives, rule processes and the outcomes. Therefore, proper and fact-based education of farmers and consumers, and appropriate and right incentives (not fertilizer subsidies) are likely to decrease future unwanted issues and disasters.

The Importance of Protecting the Environment

In addition to education and environmental protection, it is also necessary to provide basic safe amenities (such as access to potable water, safe sanitary facilities and shelter, affordable nutritious food, and access to basic modern healthcare and disease prevention efforts), and then let the public decide which path to take. The government's role should be to act as a referee, not as a controller or a player.

Fertilizer overuse because of a massive governmental subsidy program, expanding environmentally unfriendly technologies, unfair distribution of services and inequalities, and interfering politics are all externalities that negatively change the course of the health and well-being of the population. These also disrupt the peace and prosperity of a country. These not only introduce adverse health outcomes but also drive up expenses for individuals and the government.

However, some externalities require governmental intervention, such as negotiations for putting together the correct policies, regulatory oversights, distribution of clean water and energy, standardized education across the country, and enforcement of law and order, etc. When implement properly with healthy long-term goals and good intentions, such interventions tremendously benefit the society.

In addition to the common elements of poverty, malnutrition, environmental pollution, etc., collective evidence suggests that some substances present in the local water sources likely is the reason for the genesis of CKDmfo. Therefore, the provision of safe, clean water (i.e., devoid of all nephrotoxins) must be given a high priority. Identification of the cause and mechanisms of renal failure in CKDmfo and providing appropriate and cost-effective treatment for those who are affected with the disease should also peruse in parallel.

Sri Lankan farmers' uses excess amounts of chemical fertilizers and pesticides [29]. In fact, per hectare of arable land, Sri Lanka is the highest user of chemical fertilizer and pesticides in Southeast Asia [72]; approximately 284 kg of synthetic fertilizer per hectare of arable land. This usage has increased by three- to four-fold during the past three decades, but the usage has plateaued over the past five years [72]. More is not always better [28]; thus, attempts must be directed to reducing the excessive use of fertilizer and inappropriate use of pesticides [29,44].

Discussion

Although may be associated with the disease, all of the potential single-cause hypotheses tested were found not to be causative for CKDmfo in Sri Lanka. However, multiple nephrotoxins (especially when they have different mode of harmful actions in renal tubules), even at levels lower than those at which individual components (less than the maximum allowable limits; MAL) can cause renal damage. In addition, these agents can harm kidneys via additive or synergistic effects.

This is particularly important when toxins have different mechanisms of actions enhancing oxidative stress on renal tubular cells causing tubular damage [14,73-75]. However, such multifactorial effects have not yet been studied. With reference to the identification of causative factors, moving directly from the "hypothesis" to the "conclusions," as has been done recently not only in Sri Lanka but also in other CKDuo-affected countries, including El Salvador and Nicaragua, hinders scientific progress and preclude implementing effective preventative programs.

Fallacies related to competing to 'prove' one's favorite hypothesis (instead of collaborating and "testing" a hypothesis), and equating causality by mere demonstrating the presence of an agent in water samples would further derail the progress of finding the real cause(s), divert research funding, and identifying the most effective preventative strategies [76]. In addition to preventing scientific progress of identification of real cause(s) the compartmentalized research and lack of collaboration between local scientific groups further hinder the finding of practical solutions. These inferior approaches, including bypassing theory and experiments, and biased interpretation of data, not only misleading everyone but also prevent making firm and practical conclusions and solutions.

In spite of the longer exposure period needed to contract CKDmfo, the relatively short period living from the time of diagnosis, makes most people who acquire the disease not living beyond the age 65. However, residents in the NCP who are older than 65 years have a higher incidence of CKD because of glomerular diseases; hypertension and diabetes, but have a lower incidence of renal failure due to tubular disease, CKDmfo [29,31]. This age disparity most likely is attributable to the high death rate associated with CKDmfo; deaths occur when patients are at relatively younger ages.

Moreover, due to the relatively high incidence of false positive diagnosis (i.e., diagnoses is made having CKDmfo, when kidney functions are normal), some people claim that they are curing people 'diagnosed as CKDmfo' using magic or native treatments. This have led to some of those actually having the disease, opting to go to people who claim that they can cure CKDmfo with charm and traditional treatment, instead of going to hospital for their needs. Overall, our data suggest that more than 10 to 15 years of regular exposure to causative agent(s) is necessary to develop CKDmfo. Thus, such exposures should have commenced between 30 and 35 years ago [29].

The geographical distribution of CKDmfo; having the disease in the absence of diabetes and hypertension; the prevalence of the disease among farming communities; and histopathologic findings of tubular pathology collectively suggest the involvement of hydro- geo-chemistry and environmental exposure to one or more nephrotoxins in the genesis of CKDmfo. Moreover, "multi-factorial" as a description of this environmentally acquired disease refers not only to multiple unknown chemicals, but also to potential combinations of multiple known and unknown physical phenomena, behaviors, and biological pathways.

CKDmfo has not been linked to a particular incident, event, habit, organism, or component yet. However, a combination of some of these factors could precipitate the disease; CKDmfo is an environmentally acquired, chronic, occupational disease leading to premature death. Evidence are flimsy and the collective data fall short of confirming any agrochemical component as the causative factor for CKDmfo in Sri Lanka. Because origination of this disease likely is attributable to multiple causes, any single-cause, narrowly defined research is unlikely to generate meaningful data for implementing a program that would achieve an effective, intended outcome. Prevention of CKDmfo is the only cure and the only way forward.

Acknowledgements

The author is grateful for constructive suggestions made in early versions of this manuscript by Chamandika Warusavitharana, Geethanjalie Selvendran, and Dr. Douglas Olcott. For the past 17 years, the author has been studying issues related to water contamination, escalating chronic diseases including CKDmfo, educating he public, and provision of clean water to prevent the propagation of CKD in Sri Lanka.

Conflicts of Interest

The author has no conflicts of interest. No funding received for this writing.

References:

1. Writing Groups (1992). Environmental problems and developing countries. Finance Dev 29:22-23.
2. Wimalawansa SA, Wimalawansa SJ (2015) Clean water, healthy environment, and watershed preservation: Correct, enforceable policies are essential. Hydrology 1: 3-15
3. Burkart MR (2007)Diffuse pollution from intensive agriculture: sustainability, challenges, and opportunities. Water SciTechnol 55:17-23
4. Anonymus (1979) Environmental geochemistry and health. Philos Trans R SocLond B BiolSci 288:1-216
5. Baumgarten A, Steinnes E, Friesl-Hanl W (2009)This special issue of "Environmental Geochemistry and Health," compiles the output of the Symposium "Soils and their implication on Health." Preface. Environ Geochem Health 31:521-522.
6. MertensTE, Fernando MA, Marshall TF, Kirkwood BR, Cairncross S, et al. (1990) Determinants of water quality, availability and use in Kurunegala, Sri Lanka. Trop Med Parasitol 41:89-97.
7. Sarkar A, Patil S, HugarLB, vanLoon G (2011) Sustainability of current agriculture practices, community perception, and implications for ecosystem health: an Indian study. EcoHealth 8:418-431.
8. Krauss J, Gallenberger I, Steffan-Dewenter I (2011) Decreased functional diversity and biological pest control in conventional compared to organic crop fields. PLoS One 6:e19502.
9. Holt MS (2000) Sources of chemical contaminants and routes into the freshwater environment. Food ChemToxicol 38:S21-S27.
10. Jianguo J, Jun W, Xin X, Wei W, Zhou D, et al. (2004) Heavy metal stabilization in municipal solid waste incineration flyash using heavy metal chelating agents. J Hazard Mater 113:141-146.
11. Susset B, Grathwohl P (2011) Leaching standards for mineral recycling materials--a harmonized regulatory concept for the upcoming German Recycling Decree. Waste Manag 31:201-214.
12. Rathnamalala NK, Nagodavithana KC, Mihirini AT, Lanerolle RD (2011) Patient perceptions of risk factors for chronic kidney disease and methods of delaying progression of the disease in a tertiary care setting in Sri Lanka. Int J ClinPract 65:1108.
13. Kalantar-Zadeh K, Stenvinkel P, Pillon L, Kopple JD (2003) Inflammation and nutrition in renal insufficiency. Adv Ren Replace Ther10:155-169.
14. Soderland P, Lovekar S, Weiner DE, Brooks DR, Kaufman JS(2010) Chronic kidney disease associated with environmental toxins and exposures. Adv Chronic Kidney Dis 17:254-264.
15. Wimalawansa SJ (2014) Environmental pollution-associated chronic kidney disease of multi-factorial origin in Sri Lanka (CKDmfo). Proceedings of the 5th Int. Conference on Sustainable Built Environment-2014, Kandy, Sri Lanka. Climate Change, Community-Environment and Ecosystem, and Environmental Pollution, and Chronic Kidney Disease [ICSBE/14/244]; 244-250.
16. WHO-Group, JayathilakaNMP, Mendis S, Mehta FR, Dissanayake LJ, et al.(2013) Investigation and evaluaiton of chronic kidney disease of uncertain aetiology in Sri Lanka: Final Report. http://dh-web.org/place.names/posts/index.html#ckdu.
17. ChandrajithR, Dissanayake CB, TobschallHJ (2005) The abundances of rarer trace elements in paddy (rice) soils of Sri Lanka. Chemosphere 58:1415-1420.

18. Chandrajith R, Nanayakkara S, Itai K, Aturaliya TN, Dissanayake CB, et al. (2011) Chronic kidney diseases of uncertain etiology (CKDue) in Sri Lanka: geographic distribution and environmental implications. Environ Geochem Health 33:267-278.

19. Chen W, Krage N, Wu L, Pan G, Khosrivafard M, et al (2008) Arsenic, cadmium, and lead in California cropland soils: role of phosphate and micronutrient fertilizers. J Environ Qual 37:689-695.

20. Dharma-Wardana MW, Amarasiri SL, Dharmawardene N, Panabokke CR (2014) Chronic kidney disease of unknown aetiology and ground-water ionicity: study based on Sri Lanka. Environ Geochem Health 37: 221-231.

21. Wimalawansa SJ (2015) Escalating Chronic Kidney Diseases in Sri Lanka: Causes, Solutions and recommendations. Environ health and prev med 19:375-394.

22. Warusavitharana CJ, Wimalawansa SJ (2015) Analysis of cost-effective approaches to prevent chronic kidney disease of multifactorial origin (CKDmfo). Submitted to Scand J Work, Environ & Health.

23. Athuraliya NT, Abeysekera TD, Amerasinghe PH, Kumarasiri R, Bandara P, et al. (2011). Uncertain etiologies of proteinuric-chronic kidney disease in rural Sri Lanka. Kidney Int 80:1212-1221.

24. Bandara JM, Senevirathna DM, Dasanayake DM, Herath V, Bandara JM, et al. (2008) Chronic renal failure among farm families in cascade irrigation systems in Sri Lanka associated with elevated dietary cadmium levels in rice and freshwater fish (Tilapia). Environ Geochem Health 30:465-478.

25. WanigasuriyaKP, Peiris-John RJ, Wickremasinghe R (2011) Chronic kidney disease of unknown aetiology in Sri Lanka: is cadmium a likely cause? BMC Nephrol 12:32.

26. Nanayakkara S, Komiya T, Ratnatunga N, Senevirathna ST, Harada KH, et al. (2012) Tubulointerstitial damage as the major pathological lesion in endemic chronic kidney disease among farmers in North Central Province of Sri Lanka. Environ Health Prev Med 17:213-221.

27. Nanayakkara S, Senevirathna ST, Abeysekera T, Chandrajith R, Ratnatunga N, et al. (2014) An integrative study of the genetic, social and environmental determinants of chronic kidney disease characterized by tubulointerstitial damages in the North Central Region of Sri Lanka. J Occup Health 56:28-38.

28. Nagarajah S, EmersonBN, AbeykoonV, YogalingamS (1988) Water quality of some wells in Jaffna and Kilinochchi with special reference to nitrate pollution. Tropical Agriculturist 144: 61-78.

29. Wimalawansa SA, Wimalawansa SJ (2014) Impact of changing agricultural practices on human health: Chronic kidney disease of multi-factorial origin in Sri Lanka. Wudpecker Journal of Agricultural Research 3:110-124.

30. Wimalawansa SJ (2013) Water pollution-associated ill health: Special emphasis on chronic kidney disease in Sri Lanka. Olcott Oration.

31. Senevirathna L, Abeysekera T, Nanayakkara S, Chandrajith R, Ratnatunga N, et al. (2012) Risk factors associated with disease progression and mortality in chronic kidney disease of uncertain etiology: a cohort study in Medawachchiya, Sri Lanka. Environ health Prev Med 17:191-198.

32. Bandara JM, WijewardenaHV, BandaraYM, JayasooriyaRG, Rajapaksha H (2011) Pollution of River Mahaweli and farmlands under irrigation by cadmium from agricultural inputs leading to a chronic renal failure epidemic among farmers in NCP, Sri Lanka. Environ Geochem Health 33:439-453.

33. Paez-Osuna F (2001) The environmental impact of shrimp aquaculture: causes, effects, and mitigating alternatives. Environ Manage 28:131-140.

34. Nair PK (2011) Agroforestry systems and environmental quality: introduction. J Environ Qual 40:784-790.

35. Wanigasuriya K (2012) Aetiological factors of chronic kidney disease in the north central province of Sri Lanka: a review of evidence to-date. J College Community Physicians Sri Lanka 17: 15-20.

36. Wimalawansa SA, Wimalawansa SJ (2014) Protection of watersheds to prevent phosphate eutrophication and consequent environmental health hazards in Sri Lanka. Int J Res Environ Sci 1: 2s, 1-18.

37. Dissanayake CB, Chandrajith R (2007) Medical geology in tropical countries with special reference to Sri Lanka. Environ Geochem Health 29:155-162.

38. van der Hoek W, Konradsen F (2005) Risk factors for acute pesticide poisoning in Sri Lanka. Trop Med Int Health 10:589-596.

39. Eddleston M, Rajapakshe M, Roberts D, Reginald K, Rezvi Sheriff MH, et al. (2002) Severe propanil [N-(3,4-dichlorophenyl) propanamide] pesticide self-poisoning. J ToxicolClinToxicol 40:847-854.

40. Franz JE, MaoMK, SikorskiJA (1997) Glyphosate: A unique global herbicide, American Chemical Society.

41. Mink PJ MJ, Lundin JI, Sceurman BK (2011) Epidemiologic studies of glyphosate and non-cancer health outcomes: a review. RegulToxicolPharmacol 61:172–184.

42. Orantes CM, Herrera R, Almaguer M, BrizuelaEG, Nunez L, et al. (2014) Epidemiology of chronic kidney disease in adults of Salvadoran agricultural communities. MEDICC Rev 16:23-30.

43. Wimalawansa SJ (2015) The role of ions, heavy metals, fluoride, and agrochemicals;critical evaluation of potential aetiological factors of chronic kidney disease of multifactorial origin (CKDmfo/CKDuo) and recommendations for its eradication. Environ Geochem Health, 10.1007/s10653-015-9739-3 (published online).

44. Wimalawansa SA, Wimalawansa SJ (2014) Agrochemical-Related Environmental Pollution: Effects on Human Health. Global Journal of Biology, Agriculture and Health Sciences 3:72-83.

45. Pellow DN (2007) Transnational movements for environmental justice. Cambridge, MA: MIT Press

46. Orisakwe OE, Njan AA, AfonneOJ, Akumka DD, OrishVN, et al (2004) Investigation into the nephrotoxicity of Nigerian bonny light crude oil in albino rats. Int J Environ Res Public Health 1:106-110.

47. Jayasumana C, Gunatilake S, Senanayake P (2014) Glyphosate, hard water and nephrotoxic metals: are they the culprits behind the epidemic of chronic kidney disease of unknown etiology in srilanka? Int J Environ Res Public Health 11:2125-2147.

48. Wimalawansa SJ (2015) Escalating chronic kidney diseases of multi-factorial origin (CKD-mfo) in Sri Lanka: causes, solutions, and recommendations-update and responses. Environ health PrevMed 20:152-157.

49. Jayatilake N, Mendis S, Maheepala P, Mehta FR (2013) Chronic kidney disease of uncertain aetiology: prevalence and causative factors in a developing country. BMC Nephrol 14:180.

50. Multiple-Authors (2014) Glyphosate does not cause CKDu.

51. Jayasumana M, Paranagama P, Amarasinghe M, Wijewardane K, Dahanayake K, et al. (2013) Possible link of chronic arsenic toxicity with chronic kidney disease of unknown etiology in Sri Lanka. J Nat Sci Res 3: 64-73.

52. Caetano M, Ramalho T, Botrel D, da Cunha E, de Mello W (2012) Understanding the inactivation process of organophosphorus herbicides: A DFT study of glyphosate metallic complexes with Zn2+, Ca2+, Mg2+, Cu2+, Co3+, Fe3+, Cr3+, and Al3+.Int J Quantum Chem 112: 2752-2762.

53. Wunnapuk K, Gobe G, Endre Z, Peake P, Grice JE, et al. (2014) Use of a glyphosate-based herbicide-induced nephrotoxicity model to investigate a panel of kidney injury biomarkers. Toxicol Lett 225:192-200.

54. The National Academies Collection: Reports funded by National Institutes of Health (1997) Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.

55. Sachdev DP, Cameotra SS (2013)Biosurfactants in agriculture. ApplMicrobiolBiotechnol 97:1005-1016.

56. Coroi IG, De Wilde T, Cara MS, Jitareanu G, Steurbaut W (2011) Influence of surfactants on the sorption of two chloroacetanilide in an Romanian chernozem soil. CommunAgricApplBiolSci 76:939-947.

57. Brain RA, Solomon KR (2009) Comparison of the hazards posed to amphibians by the glyphosate spray control program versus the chemical and physical activities of coca production in Colombia. J Toxicol Environ Health A 72:937-948.

58. Garry VF, Burroughs B, Tarone R, KesnerJS(1999) Herbicides and adjuvants: an evolving view. ToxicolInd Health 15:159-167.

59. Skutlarek D, Exner M, Farber H (2006) Perfluorinated surfactants in surface and drinking waters. Environ SciPollut Res Int 13:299-307.

60. Hossain MP, Goyder EC, Rigby JE, El Nahas M (2009) CKD and poverty: a growing global challenge. Am J Kidney Dis 53:166-74

61. USA-EPA (2008) USEPA Office of Ground Water and Drinking WaterContaminant Candidate List 3 (CCL3). USEPA Office of Ground Water and Drinking Water.

62. Bezirtzoglou C, Dekas K, Charvalos E (2011) Climate changes, environment and infection: facts, scenarios and growing awareness from the public health community within Europe. Anaerobe 17:337-340.

63. Schlenk D, Wolford L, Chelius M, Steevens J, Chan KM (1997) Effect of arsenite, arsenate, and the herbicide monosodium methyl arsonate (MSMA) on hepatic metallothionein expression and lipid peroxidation in channel catfish. Comp BiochemPhysiol C PharmacolToxicolEndocrinol 118:177-183.

64. Shimizu M, HochadelJF, Fulmer BA, Waalkes MP (1998) Effect of glutathione depletion and metallothionein gene expression on arsenic-induced cytotoxicity and c-myc expression in vitro. ToxicolSci 45:204-211.

65. Topcu S, Incecik S, Unal YS (2003) The influence of meteorological conditions and stringent emission control on high TSP episodes in Istanbul. Environ SciPollut Res Int 10:24-32.

66. Zejda JE, McDuffie HH, Dosman JA (1993) Epidemiology of health and safety risks in agriculture and related industries. Practical applications for rural physicians. West J Med 158:56-63.

67. Damalas CA, Eleftherohorinos IG (2011) Pesticide exposure, safety issues, and risk assessment indicators. Int J Environ Res Public Health 8:1402-1419.

68. Company R, Serafim A, Lopes B, Cravo A, Shepherd TJ, et al. (2008) Using biochemical and isotope geochemistry to understand the environmental and public health implications of lead pollution in the lower Guadiana River, Iberia: a freshwater bivalve study. Sci Total Environ 405:109-119.

69. Divasta AD, Feldman HA, Brown JN, GiancaterinoC, Gordon CM, Holick MF (2011) Bioavailability of vitamin D in malnourished adolescents with anorexia nervosa. J ClinEndocrinolMetab 96:2575-2580.

70. Mejía R, Edgar Quinteros, E, López, A, Ribó, A, Cedillos, H, et al. (2014) Pesticide-handling practices in agriculture in El Salvador: An example from 42 patient farmers with chronic kidney disease in the BajoLempa region. Occupational Diseases and Environmental Medicine 2: 56-70.

71. Wimalawansa SJ (2013) Purification of contaminated water with reverse osmosis: Effective solution of providing clean water for human needs in developing countries. Journal of Emerging Technology and Advanced Engineering 3:75-89.

72. WorldBank (2013) Fertilizer consumption (kilograms per hectare of arable land).[http://data.worldbank.org/indicator/AG.CON.FERT.ZS

73. Sabolic I (2006) Common mechanisms in nephropathy induced by toxic metals. Nephron Physiol 104:107-114.

74. Sabath E, Robles-Osorio ML (2012) Renal health and the environment: heavy metal nephrotoxicity. Nefrologia 32:279-286.

75. de Burbure C, Buchet JP, Leroyer A, Nisse C, Haguenoer JM, et al. (2006) Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: evidence of early effects and multiple interactions at environmental exposure levels. Environ Health Perspect 114:584-590.

76. Jayasumana C, Gunatilake S, Siribaddana S (2015) Simultaneous exposure to multiple heavy metals and glyphosate may contribute to Sri Lankan agricultural nephropathy. BMC Nephrol 16:103.