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Impact of Genetic and Environmental Factors on Chronic Kidney Disease in Borno State

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ABSTRACT: Chronic kidney disease (CKD) is a global health issue of concern occasioned with high mortality rate and decreased quality of life, especially in developing countries. The terminal stage of the disease, End-Stage Renal Disease (ESRD), necessitates dialysis or kidney transplantation. However, with better understanding of predisposing factors associated with the disease, highly exposed persons will be properly guided against the development of chronic renal failure. While an estimated population of about 10% of the global population are affected with the disease, 14.3% of Sub-Saharan Africa (SSA) are believed to be affected. In Nigeria for instance, the burden of the disease is more worrisome because it accounts for about 11% of admission in tertiary hospitals. Additionally, an average of 98 patients are being dialysed annually between 1999 to 2018 at the University of Maiduguri Teaching Hospital (UMTH), being one of the centres in the north east. The figure could be higher if only recent statistics are considered. It is clear here that Borno state is one of the high prevalence states in Nigeria with two dialysis centres. Furthermore, while the major aetiology to CKD is Diabetes and Hypertension, infectious diseases, malnutrition etc, there are other CKD of unknown aetiology (CKDu) common in northeast Nigeria with multifactorial causes. Therefore, understanding the genetic and environmental factors responsible for the development of CKD is crucial. This paper examine the impact of genetic and environmental factors on chronic kidney disease in Borno State and recommend solutions towards prevention and care of CKD in Borno State.

I. INTRODUCTION

Chronic kidney disease (CKD) is a major health concern globally, especially in developing country like Nigeria. CKD is a serious threat to public health, but the size of the problem is probably not fully appreciated until now. It is defined as glomerular filtration rate (GFR) <60mL/min/1.73m^2 for more than 3 months, with or without structural kidney damage (Chukwuonye et al., 2018). It is a disease condition which is characterized with high mortality rate, increased healthcare expenditures, and decreased quality of life. The terminal stage of the disease, End-Stage Renal Disease (ESRD), necessitates dialysis or kidney transplantation (Chukwuonye et al., 2018).

An estimated 10 % of the global population is affected with this disease (Palmer et al., 2013) whereas, approximately 14.3 % of the general African population are thought to be affected (Ene-Iordache et al., 2016). There is somewhat dissimilarity of the burden across the world based on region race or gene. Although the disease burden is better reported in the developed countries, developing countries especially the Sub-Saharan Africa (SSA) countries have similar or higher burden but are under-reported. The situation is not different in Nigeria and even more worrisome in Borno and Yobe state in the north-eastern part of the country. Available statistic indicates that there were 1,854 dialysis case recorded between June 1999 and July 2018. This indicates an average of 98 patient dialyzed per year for this period. The data, however, excludes those that cannot afford the cost of dialysis, resist the dialysis or have not even presented themselves in the hospital for management.

The major aetiology to CKD is Diabetes and Hypertension, infectious diseases, malnutrition, acute kidney injury and certain genetic factor are

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all incriminated as cause of the disease (Perico and Remuzzi 2012). It is noteworthy that in most developing countries such as Nigeria, many people are not privy of their health status that could predispose them to the disease either due poor socioeconomic status or ignorance. This is particularly true for people in the north east especially Borno and Yobe.

Interestingly, while the aetiology to CKD has been reported, there are cases of CKD of unknown aetiology (CKDu) with multifactorial causes requiring in-depth investigation. Although, the main cause of CKD disease is said to be multifactorial, environmental factors such as exposure to heavy metals (in water and food products) other source of water contamination, bad hygiene and sanitation practices could contribute to the burden of several diseases that can be linked to CKDu development (Soderland et al., 2010; Jayasumana et al., 2014; Chukwuonye et al. 2018). Additionally, most perishable foods such as fruits and vegetables are normally transported to Maiduguri from different parts of the country to retail markets with a wide product distribution range to meet consumer demand. Under such conditions, it is likely that any associated contamination may be dispersed, and then renders the food quality highly compromised beyond the location of the farmlands (Dima, 2016). Furthermore, some of these fruits and vegetables are eaten raw, thereby increasing the likelihood of exposure to foodborne illnesses. Exposure is also highly possible with heavy metals. Johri et al. (2010) compared the passage of mercury and lead with that of Cadmium (Cd). It was observed that Cd passes more easily from soil to plants than Hg and Pd and could end up in the food chain. Contamination of soil by Cd leads to its accumulation in crops and vegetables. An estimated concentration of 0.025 µg/g of Cd was found in cereals and tubers by dry weight lower than in fruits, meat and fish. Continues consumption of farm produce containing heavy metals like Pd, Arsenic (AS), Cd, Hg etc could trigger severe health challenge such as CKD.

Therefore, identification of these factors or pathways responsible for the development of CKD in Borno State, especially, the preventable ones are crucial and to proffer solutions to the problem.

Problem Statement

Chronic kidney disease (CKD) is a major public health concern and with the observed upsurge of cases in recent years and the indication that the state may be a hot-sports. This impact on the quality of life and productivity of both the patients and the family unit. The need to examine the impact of environmental and genetic factors that are implicated in aetiology cannot be overemphasized. This gives a better understanding of the interaction between the factors that influenced kidney function in health and disease. The incidence of CKD is on the rise in Borno state. It is a disease that is characterized with high percentage of mortality, increased healthcare expenditures, and decreased quality of life. Despite having other centers in the north east, the treatment center in UMTH that cater mostly of Borno indigene have 39 % of their patient from Borno, 32 % from Yobe, 17 % from Adamawa and 5 % from Gombe cutting across the age groups. The bulk of the patients are of the productive age which could affect the socioeconomic status of the state and GDP. Therefore, there is urgent need for intervention by authorities concern to reverse the trend. This necessitated the study on the impact of genetic and environmental factors on chronic kidney disease in Brono State.

Study Area

Borno State, North Eastern-Nigeria, with its capital in Maiduguri, was founded in 197. it is located on longitude 11^{o} 30' North and latitude 13^{o} 00' East, with a total land area of 57,799 square kilometre. It is ranked as the second largest State in terms of landmass and 12^{th} in terms of population size in the region. It has a population of 4,171,104 (NPC, 2006) and 4,944,000 (as projected in NP, 2011). The state comprises of 27 Local Government Areas with Eight (8) in Borno Central, Nine (9) in Southern Borno and ten (10) in Northern Borno Senatorial districts respectively. The State is synonymous with the basin of the Lake Chad, the Bama ridge, and a dossier of geomorphologic processes with a history of climate change leading to the drying and receding of the Lake Chad. The drainage system in Borno State is characterized by the morphology of the basin of River Ngadda, having unique stream. A thorough knowledge of human and environment relationship is essential for sustainable development of natural and human resources.

The influence of the physical environment on human land use determines settlement pattern,

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quantity and quality of water supply, agricultural practices and livestock population. Environmental degradation has diverse causes in Borno State and is determined by socio cultural indices aggravated by uncontrolled socio-economic activities. With different geological formation, surface and underground water, soil and Agricultural products all influence the health status of people in Borno State.

II. LITERATURE REVIEW

Genetic factors in kidney diseases

In some cases, the relationship between genetics and renal disease development is evident. Examples such as familial forms of focal and segmental glomerulosclerosis that are caused by mutations in the podocyte molecules podocin, CD2-associated protein a-actinin-4 or the canonical transient receptor potential 6 (Boute et al., 2000; Kaplan et al., 2000) are notable. Screening for mutations in the above-mentioned genes in sporadic cases of nephrotic syndrome has provided new insights and is increasingly being integrated in paediatric nephrology (Papez and Smoyer 2004). Genetic factors frequently have a less direct influence on renal disease development and become manifest only in the presence of 'permissive conditions' such as diabetes mellitus and hypertension. Conversely, not all patients suffering from these conditions develop renal disease or progress to ESRD, and it is likely that genetic factors determine the time of onset and the rate of progression of the kidney disease. Several studies of genetic linkage analyses in diabetic nephropathy have shown a susceptibility locus on chromosome 18q (Bowden et al., 2004; Vardarli et al., 2000). A polymorphism in the DNA sequence of the CNDP1 gene, which encodes the enzyme carnosinase-1, on chromosome 18q in diabetic patients determines susceptibility to develop diabetic nephropathy (Janssen et al., 2005). The substrate of carnosinase-1, L-carnosine, is a potent inhibitor of oxidative stress (Kohen et al., 1988) and the formation of advanced glycation end-products (Hipkiss and Chana 1998), and may thus act as a cytoprotective factor during diabetes. It was postulated that opposing mechanisms, i.e. hyperglycaemia vs the action of protective factors such as L-carnosine, determine the net outcome of diabetic nephropathy (Janssen et al., 2005).

Acute kidney injury

CKD is also linked to acute kidney injury (AKI). Thus, both the rate of progression to ESRD and all-cause mortality are increased in patients with CKD after transient increases in serum creatinine when compared with patients without CKD. Moreover, up to 28% of the patients with no pre-existing kidney disease who recover from AKI develop de novo CKD. Non-steroidal anti inflammatory medications, several cardiovascular and diabetes drugs, as well as traditional medicines used in the primary-care setting in developing countries, may lead to the development of transient episodes of AKI. These findings emphasize the relevance of CKD detection and appropriate adjustments in management to optimal outcome in major NCDs (Perico and Remuzzi 2012).

Water and environmental perspective

Water Quality and the Burden of Human Diseases

Nowadays, both surface and groundwater quality can be affected by anthropogenic activities. Improper dumping of industrial, domestic, commercial and agricultural waste into water courses can impact negatively on the water quality. High runoff events may also help in transporting pathogenic organisms, organic and inorganic compounds into the receiving water bodies resulting in deteriorated water quality and increases the burden of diseases.

Access to clean drinking water is a major challenge to over 663 million people living in developing countries (WHO, 2015). While drinking water supplies for human consumption in most developed countries are presumed safe, water related disease outbreak still persist resulting in severe illnesses and even death (Philip and Anne, 2004). At community or household level, waterborne disease outbreaks occur due to poor handling or bad hygiene practices, particularly in urban slums. Conversely, Craun et al., (2002) had shown in a study that majority of waterborne outbreaks in the US occurred as a result of contamination of distribution system, pipe corrosion, poor or non-groundwater treatment and stored water. However, one fundamental method of assessing water quality, is to look at the microbial safety of the drinking water using indicator microorganisms. It has been estimated that over 30% of reported cases of waterborne gastroenteritis have their origin in drinking water that are certified safe and met all legislated quality requirements based on bacterial indicators (Mendez, et al. 2004). For instance, the 1993 Milwaukee cryptosporidium diarrhoea outbreak where more than 403,000 people were affected (Mac Kenzie et al. 1994)

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occurred due to failure of the coagulation unit. Beside the most common indication organisms traditionally used to assess water quality such as pathogenic organisms e.g. E-coli, Shigella, Vibrio cholerae and Salmonella typhimurium which are frequently and usually transmitted to human beings through ingestion of either contaminated water or foods (Momba, et al., 2006), others includes faecal coliforms, and to a lesser extent total coliform. This is because total coliforms group does not constitute a reliable source of information regarding the pollution level of a particular water source, thus, their presence in water is not of great concern to water and environmental engineers. Polluted water with human and animal faeces can serve as agent for the transmission of microorganisms, which can be responsible for many diseases in settlements who totally depend on unimproved drinking water sources (Cabral, 2010). Furthermore, the presence of one or combination of these pathogenic organisms in water could be detrimental to human health. It is noteworthy that some of the diseases if not properly managed or treated can also lead to other forms of ailments.

Arguably, in Maiduguri for instance, prior to the commissioning of the Maiduguri Water Treatment Plant (MWTP) in 1993 and the subsequent introduction for the drilling of boreholes through the upper aquifer between (1995-1997), the number of reported cases of diseases such as CKD and CKDu in Borno State were significantly small compared to recent reports. It is clear that the drilling of borehole with a depth range of between 45 to 70 meters is the order of the day, especially in Maiduguri the Borno State capital. This calls for strict and proactive measures to curb the menace of this disease through environmental assessment. It is suspected that; because the MWTP is supplied with raw water from Alau Dam. After rainfall events, runoff may wash down excessive fertilizers, pesticides, insecticide, herbicides and other agrochemicals used as preservatives on farmlands into the reservoir. After treatment, all these toxins may remain in the clarified water and then distributed to consumers. Although, the goal of water treatment is to make water safe for human consumption devoid of pathogens, such water may still contain heavy metal concentration above the stipulated standard. Similarly, over the years, pollution of groundwater due to anthropogenic activities may have rendered the upper aquifers susceptible to heavy metals and other pollutants. Aquifer recharge from the impounded water from Alau dam and the underlain geological formation could be additional culprits in this regard. However, there is every likelihood of these materials reacting with the bedrocks to produce substances that might cause CKD. This may also require serious and concerted investigations. Other factors may include but not limited to unwholesome consumption of packaged (sachet) water hitherto believed to be safe as an alternative source of drinking water which is very common in Borno State. Even as consumption of sachet water has increased over the years, the question regarding its safety still remain unanswered. This may require thorough investigation about the processing, packaging and the production of the sachet as a whole.

Although, the main cause of CKD disease is said to be multifactorial, environmental factors such as exposure to heavy metals, water contamination, poor hygiene and sanitation practices may contribute to the burden of several disease that could be linked to CKDu development (Soderland et al., 2010; Jayasumana et al., 2014; Chukwuonye et al. 2018). Several identifiable factors or pathways responsible for burden of diseases development should be targets of concern while the preventable ones are crucial to be eliminated.

Heavy metals in drinking water and human health

Metals play some important roles in variety of biological processes of living systems (Jomova and Valko, 2011). They are known to modulate gene expression by interfering with signal transduction pathways that play significant roles in cell growth and development (Valko et al., 2006). However, recently, there has been resurgence of interest on the effects of heavy metals in drinking water supply on human health when consumed over prolong period. Water related diseases can often be attributed to exposure to elevated heavy metal concentration in drinking water. They are occurred naturally in the environment but with increased concentration due to anthropogenic activities (Huang et al. 2014; Cobbina, et al., 2015). There is, however, increased evidence linking toxicants such as Cd, Pd, As, Hg etc to CKD (Bigazzi, 1999; Jayasumana, et al., 2014).

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Food consumption perspective

Linking Food consumption and heavy metal

Food products most often contain small amounts of heavy metals which contribute to dietary intakes and the levels of these metals require regular observations and control. However, contamination of food products by heavy metals is becoming an unavoidable problem and has been important in extensive research in the last decades (Orecchio and Papua, 2009).

Among several natural substances that are concentrated in man's environment, heavy metals are among the most reported (Sodhi, 2006). Generally heavy metals which are not easily degradable or metabolized and are usually persistent and may be biologically accumulated in food items trapped on the outer surface or may be added due to manufacturing or processing of food for consumption (Hamilton, 1979). The concentration of heavy metals in food is of great significance because they are either toxic or essential to human health. Some of these essential metals such as Zn, Fe, Se, Mo and Cu are present in small concentrations which may be bio-toxic to humans if it is sufficiently available (Onianwa et al, 1999; Iwegbue, 2010 and Gopalani et al., 2007).

The essential metals are important components of enzymes in which they attract or subtract molecules and facilitate their conversion to specific end products. For example, Iron is involved in the binding, transporting, and release of oxygen in higher animals. Essential metals also control important biological processes by facilitating the binding of molecules to their receptor sites on cell membrane, by alternating the structures or ionic nature of membrane to prevent or allow specific molecules to enter or leave a cell and in inducing gene expression resulting in the formation of protein involved in life processes (Nielsen, 1990). In addition, some of these essential elements are also important for normal functioning of the body system but when their levels exceed permissible tolerable limit for humans (WHO, 1996), they can lead to deleterious effects resulting into ill health cases, decrease in quality of life and ultimately death. Examples of toxic metals are cadmium, lead, nickel, mercury, Arsenic etc when present even at low levels are deleterious to humans because they are toxic and cannot be tolerated even at low concentrations (Suppin et al., 2005).

These toxic metals are present in all components of the environment- land, atmosphere and aquatic systems and they have most severely affected the environment. The toxic trace metals have no identified biological function and show toxicological cases even at trace concentrations. The presence of Cadmium in food is poisonous to human health and adsorption of a few milligrams can lead to several serious diseases or neoplasia. Likewise, Lead in food has toxic effects in adults as well as young children. There are reports that indicate Lead in blood to be as low as 10 mg dL^{-1} which is very harmful to growing children (Ogunfowokan et al., 2005). After a number of surveys of heavy metals in food products, Food Safety Authority of Ireland (FSAI, 2009) reported that Pb and Cd were constantly detected in various food stuffs such as meat, fish, vegetables, milk, cereals and fruits. However, the International Agency for Research on Cancer (IARC) categorized Pb and Cd as carcinogenic to humans. In order to safeguard human health, the EU legislation set maximum levels of 0.2 mg/kg Pb and Cd in cereals and cereal based products (flour, wheat, rye) used as a major component for making biscuits (EC,2006).

Food consumption is a constant means of exposure to toxic heavy metals because they are naturally found in food products (Iwegbue, 2012; Asraf, 2006 and Adegbola et al., 2015). Contamination of food products with heavy metals can also occur as a result of their abundance in the environment. Similarly, contamination can also occur due to pick up of metals from equipment, processing or packaging materials. These contaminated food products with heavy metals contribute to human dietary intakes and the levels of these metals need to be regularly observed and controlled. Heavy metals can develop gradually in the body tissue and overtime could exceed tolerable limits which can cause intense toxicity leading to human disease, disorders, defects, illness, malfunctioning and malformation of organs and ultimately death (Ajai et al., 2014). However, heavy metals which are naturally present in most foods, may be added to particular foods as a way of improving diet in regions where dietary intake of certain essential elements may be insufficient. Therefore, in order to ensure appropriate balance of metal content in food items, food standards should be implemented to enforce maximum concentration levels of various metals.

However, majority of trace metals are introduced into food products through

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Volume 6, Issue 5 Sep-Oct 2021, pp: 225-237 www.ijprajournal.com ISSN: 2249-7781

contamination as a result of unhygienic conditions of the processing environments. In addition, inadequate precautionary measures taken could also cause cross-contaminations of food products from other environmental sources. It is therefore essential to estimate dietary intakes of essential metals and evaluate health risk of human exposure to toxic metals, knowing the damage that contamination of food by heavy metals could cause (Soliman and Zikovsky, 1999). In this current stage of economic growth, the concentration of metals in food items at the point of consumption is necessary for the dietary intake of trace metals from food consumption especially in children since they are the most affected age grade. Therefore, continuous research should be taken to determine the levels of some trace elements in food, either for their essential nature or toxicity. It is quite important to do so since some of the essential ones at elevated levels have serious adverse health effects.

There are diverse pathways of exposure of the general public to toxic chemicals like heavy metals. Veritably, food has been known to be the major route of exposure, therefore interest in quality and safety of food consumed has increased in the prospect of reports on contaminated foodstuffs. Currently, there are reports from both developing and developed nations on the increase in the accumulation of heavy metals in the environment ascribing to their presence in the food chain via the ingestion of various foodstuffs. It is in line with these assertions that this study is designed to reveal some heavy metals content of some food products commonly available in Nigerian markets. In order to change the current state of chronic kidney disease knowledge and therapeutics, a fundamental improvement in the understanding of genetic and environmental causes of chronic kidney disease is essential.

This paper provides an overview of the existing knowledge gaps in our understanding of the genetic and environmental causes of chronic kidney disease, as well as their interactions. The second part of the paper formulates goals that should be achieved in order to close these gaps, along with recommendation that are to be involved. A better understanding of genetic and environmental factors and their interactions that influence kidney function in healthy and diseased conditions can provide novel insights into renal physiology and pathophysiology and result in the identification of novel a therapeutic or preventive targets to tackle the global public health care problem of chronic kidney disease,

Background and Gaps in Knowledge

Understanding genetic and environmental factors influencing kidney function in healthy and diseased conditions and the interaction between genetic susceptibility factors and the environment can provide important insights into renal physiology and pathophysiology. It can reveal previously as unknown or unexpected mechanisms, and consequently, research of genetic and environmental factors associated with, chronic kidney disease (CKD) has the potential to identify novel therapeutic or preventive targets.

Genetic factors

Important advances in human genetics in the past decade include the sequencing of the human genome, determination of patterns of genetic variation in human populations around the globe, improvements in high throughput genotyping and massively parallel sequencing technologies, and advances in statistical genetics and bioinformatics. These resources together have led to the discovery of many novel risk genes and disease-associated genetic variants. Genome-wide association studies as well as whole-exome and whole-genome sequencing have become standard techniques to identify genetic loci in which variations associate with complex traits and diseases. They have been used successfully in nephrology to identify genetic variants associated with important CKD etiologies as well as with kidney function in healthy and diseased conditions and to detect mutations that cause monogenic kidney diseases. Several hundred genes are currently known to contain mutations that can cause single-gene disorders with a kidney phenotype, as well as dozens of genetic loci in which common genetic variants are associated with kidney function in the normal range and with complex kidney diseases.

Although it is now possible to efficiently discover new disease genes as a basis for the translation of gene discovery into improved CKD prevention and treatment, important gaps in understanding the mechanism of action of the genetic components of CKD remain, hindering translational efforts.

First, there is limited education and awareness of the value and importance of genetic research. This is true not only for the lay public but also for clinicians, researchers, and patients.

Lack of education can pose a particular challenge in clinical genetics, especially with respect to the initiation and type of genetic testing,

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assessment of the pathogenicity of detected genetic variants, and patient counseling. Moreover, realistic expectations and timelines for the clinical translation of genetic findings are often not well communicated.

Second, despite the fact that some indigenous populations of non-European ancestry show especially high rates of kid disease, much of the genetic research so far has been carried out in patients and study populations of European ancestry. Previous studies have supported the existence of region-specific genetic risk factors for CKDY Current evidence is therefore unlikely to be a representative globally, which can have significant implications for research as well as clinical genetics.

Third, genetic research, especially of but not limited to rare diseases, can reach its full potential only through widespread data sharing. This practice is currently limited and often occurs in unstandardized formats. However, comprehensive and current inventories of existing genetic datasets as well as their findability and accessibility are prerequisites to maximize the use of existing genetic evidence.

Fourth, the limited existence of tools for functional genomics research in nephrology is a major roadblock for the identification of causal genes and variants, improved mechanistic insights, and clinical translation.

Environmental Factors

A variety of environmental factors have been associated with the development of CKD. Several of these factors have been implicated as potential causes of CKD in so-called CKD hotspots, which are defined as countries, regions, communities, or ethnicities with higher than an average incidence of CKD. In most CKD hotspots, CKD is not due to traditional causes such as diabetes or hypertension. Despite the suspected causative role of environmental factors, a cause-effect relationship has not been demonstrated in most for regions, and thus, CKD of Unknown etiology (CKD) and infections remain the leading causes of CKD in the majority of CKD hotspots.

In addition to research gaps, advocacy and regulatory issues, which often have a basis in political and financial conflicts of interest, contribute to our incomplete understanding with of the potential role of environmental factors in CKD, and noncompliance with international treaties, laws, and rules and tiled regulations regarding the protection of the labor force's health and control of exposure to toxins that are potentially nephencerotoxic is common. These factors lead to the identification of what has been named Mesoamerican nephropathy in the coastal zones of El Salvador, Nicaragua, and Costa Rica, which has been hypothesized to be caused by multiple factors, including repeated episodes of dehydration and volume depletion, heat stress, and rhabdomyolysis because of the extreme labor among agricultural workers or by exposure to environmental toxins, industrial waste products, agrochemicals, and contaminated drinking water.

Moreover, access to traditional herbal medicines and over-the-counter nonsteroidal anti-inflammatory drugs is poorly regulated in both developing and developed countries, and efforts to eradicate counterfeit drugs appear to be insufficient. Both research and advocacy gaps lead to limitations in clinical practice and education. In combination with the knowledge gaps of specific causes of CKDu, prevention treatment efforts, and appropriate education of health care professionals workers, and the general public are inhibited. Clinical interventions are complicated by the lack of access to health care and renal replacement therapy, insufficient funding, and lack of trained personnel as is often the case in LMICs where most CKD hotspots are located.

Gene-environment Interactions

Our current understanding of the interactions between genetic and environmental CKD risk factors is incomplete. A better understanding of these interactions will provide insights into important patient subgroups and facilitate efforts aimed at the identification of targeted therapies and prevention.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 225-237 www.ijprajournal.com ISSN: 2249-7781

Environmental factors potentially associated with the development of chronic kidney diseases

Factor
Heavy metals (cadmium. Arsenic, mercury, uranium)
Environmental chemicals
Agricultural chemicals
Industrial waste products
Aristolochic acid
Occupational exposures
Nonosterioidal anti-inflammatory drugs
Counterfeit drugs
Traditional herbal medicines
Infections
Illegal alcohol consumption
Sugary beverages
Salty food

CKD, Chronic kidney disease

Environmental and occupational factors that are associated with kidney damage Heavy metals

Lead

- Potential sources include lead paint (pre-1977), water from lead pipes, leaded gasoline, adulterated alcohol (moonshine), food contaminated during processing, and contamination of water, soil, and air in areas close to lead smelters, old mines, or garages.
- Acute toxicity manifests with Fanconi-type syndrome and chronic toxicity with gout, hypertension, and 0(0 due to tubulointerstitial nephritis.
- Body lead burden can be measured by X-ray fluorescence or chelation tests and measurement of urinary lead excretion (normal values are uncertain for the latter test).
- Treatment consists of minimizing exposure and chelation therapy; however, chelation does not remove lead from bone, which may be a continued source of lead.

Cadmium

- Potential sources include tobacco smoke, certain foods (seafood, cereals, and vegetables), nickel-cadmium batteries, fuel combustion, industrial and household waste, sewage, Indian medicinal herbs, and residence in contaminated areas.
- Clinically manifests with Fanconi-type syndrome, nephrolithiasis, and hypercalciuria.
- Itai-itai disease in Japan is due to the Ingestion of rice contaminated with cadmium from the water of the Jinzu River; clinical manifestations include anemia, osteomalacia, severe bone pain ("itai" means "ouch" in Japanese), and progressive CKD. High levels of cadmium in soil and rice and a simultaneous increase in the urinary levels of cadmium have also been reported in inhabitants of the Mae Sot District, Tak Province, Thailand.
- Treatment consists of supportive care and elimination of exposure.

Arsenic

- Potential sources include food contaminated by pesticides, seafood, groundwater, traditional remedies, and wood preservation products.
- Clinically manifests with CKD, and there is a good correlation between serum levels and worsening renal function.
- Treatment consists of supportive care and elimination of exposure.

Mercury

- Potential sources include fish contamination from water, fuel combustion, contaminated water, whitening creams, dental amalgam (controversial), and cereals (treated with ethyl mercury as pesticide).
- A typical example from thel 950s is Minamata disease in Japan, where the local food supply (mainly fish) was contaminated by the water of Minamata Bay due to mercury-containing Waste from a chemical factory.
- Acute toxicity manifests with acute tubular necrosis and potential residual tubulointerstitial nephritis and chronic toxicity because of the damage to the proximal tubule or nephrotic syndrome due to either membranous glomerulonephritis or minimal change disease.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 225-237 www.ijprajournal.com ISSN: 2249-7781

- Treatment consists of elimination of exposure, as mercury-induced nephropathy is often reversible.

Uranium

- Contaminated food or groundwater, uranium mining, dermal exposure in children playing in contaminated areas.
- Clinically manifests with Fanconi-type features due to proximal tubule damage, including low molecular weight proteinuria.
- Treatment consists of elimination of the exposure.
- Exposure to AA has been associated with the development of chronic tubulointerstitial nephritis and urothelial cancer. BEN is deemed to be caused by AA consumption through contaminated wheat; several Chinese herbal medications contain AA, and thus, Chinese herb nephropathy is considered to be a form of AAN.
- Replacement of one substance (Stephania) by Aristolochia in Chinese herbal weight loss pills was the cause of the outbreak of kidney failure and urothelial cancer seen in women visiting a clinic in Brussels in the early 1 990s. More cases of AAN due to consumption of Chinese herb remedies have been reported in other countries, particularly in China and Taiwan.
- Exposure to environmental chemicals used for daily consumer activities (dietary intake of food, domestic and commercial food preparation, household maintenance procedures) or medical treatment (routine medical and dental care) may lead to kidney damage; however, further research is needed to claris' the mechanism and long-term effects of these exposures.
- Exposure to certain industrial chemicals has been associated with the development of kidney damage.
- Exposure to occupational chemicals and toxic substances other than metals, such as methylene chloride, carbon tetra chloride, trichioroethylene, toluene, and arsine gas, may lead to acute tubular necrosis, although CKD has rarely been reported; exposure to occupational solvents accelerates the progression of underlying kidney disease even if the primary lesion is unrelated to the exposure.
- MeN mainly affects agricultural workers and is probably related to repeated episodes of AKI secondary to dehydration and volume depletion, heat stress, and rhabdomyolysis associated with extreme labor; hyperuricemia and uric acid crystalluria may contribute to the pathogenesis of heat stress nephropathy; consumption of NSAIDs, illegal alcohol, and fructose containing beverages may also play a role; exposure to pesticides and other agrochemicals, heavy metals, and toxic pollutants are other potential risk factors.
- In Sri Lanka, India (two coastal districts of Andhra Pradesh), and Pakistan, contamination of water and/or food by industrial chemicals, agrochemicals, and heavy metals has been suspected but not confirmed.
- Analgesic abuse has been associated with AKI, reduced GFR, and probably CKD, although the latter is controversial.
- Counterfeit medications may account for 10%-60% of the drugs available in the market of some LMICs and are potential hazards for developing CKD and for patients who already have CKD.
- Herbal remedies are often used in rural populations in Asia and Africa and have become popular in developed countries.
- Unfortunately, they are still available legally in many countries and can be bought via the Internet.
- Herbal remedies have been associated with the development of AKI, CKD, renal papillary necrosis, nephrolithiasis, tubular and electrolyte disturbances, hypertension, and urothelial cancer.
- Infections are still prevalent in many LMIC5 due to insufficient access to safe water, poor sanitary conditions, and high concentrations of disease-transmitting vectors.
- Potential renal Pathogens include Schistosonijasj larjasj5 Ieishmaniasis toxoplasmosis onchocerciasis malaria, leptspirosis, tuberculosis and other mycobacterial diseases (e.g., leprosy ricke5ial diseases (e.g., phus), hemorthagjc fevers, and viral vector borne diseases (e.g., hantavirus dengue fever, and yellow fever).
- Enter and diarrheal diseases (e.g., Escherichia Coli, Shigella dysenteriae and typhoid) may lead to AKI and CKD.
- HlV-associated nephropathy is epidemic in Suhsaharan Africa and highly prevalent in African Americans (potential role of Hepatitis B and C are worldwide causes of 9lomerulopathy and CKD.

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III. RECOMMENDATIONS:

1. Identification of prevalence areas and understanding the environmental characteristics of the area.
2. Improvement in research, increase access to affordable treatment for already affected individual.
3. Increase funding and advocacy for research and clinical care, improved education and awareness among health care professionals, health workers and the general public.
4. Develop a database with interactive maps of kidney disease prevalence and incidence areas, investigating possible risk factors and access to care.
5. Perform studies that consider factors such as scientific-predisposition, prenatal exposures, parents health status, working age and social determinants of health, and epidemiological studies.
6. Promote interracial and multidisciplinary collaboration through research consortium to link efforts around the globe to develop bio-markets for detecting early kidney disease and identifying exposure.
7. Perform interventional studies when risk factors are reasonably well established, perform genetic studies to evaluate genetic susceptibility of specific population to different environment factors implement preventive interventions.
8. Evaluation of local factors and implement preventive interventions based on confirm or presumed risks factors for kidney disease including, children, adolescents and old age people.
9. Enact laws to reduce and control environmental exposure to agrochemical and industrial chemicals.
10. Provides access to safe drinking water, to eliminate or reduce exposure to heavy metals and exposure to organic contaminative.
11. Eradicate infection that are potentially related to kidney disease through good sanitation, vector control and mass treatment programs.
12. Improve working conditions in poor and vulnerable agricultural committees, by developing a legal framework for protecting and enforcement on risk factors to kidney diseases.
13. Offer affordable kidney treatment options to affected individuals, with free screening programs, increase access to quality care and improve access to nephron-protective medicines.
14. Increase funding and advocacy, by supporting research and channeling funds to research related to prevention, develop synergies and strengthen funds raising efforts and collaborate with other develop partners.
15. Improve education and awareness of the health care professionals, regarding the prevention and treatment of kidney disease, build the capacity of the health care workers by training from nephrologists. Educate the general population to increase their awareness about risk of herbal medicines and nethrotoxins.

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