The Role of Water Quality in the Pathogenesis of CKDu with Respect to Fluoride

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Abstract: Despite much research on chronic kidney disease of uncertain etiology (CKDu) in Sri Lanka the etiology and pathogenesis of this disease remains as a debated topic. The fluoride level in the ground water in CKDu prevalent area was considered as one of the suspected etiological factor for the condition. A scoping review was conducted through MEDLINE and Google Scholar databases for peer reviewed publications on ground water analysis related to CKDu areas globally. Groundwater plays as the primary source of drinking water. The occurrence of the disease and the fluoride metabolism in the CKDu patients would give much evidence for the correlation. The factors which decide the water intake of a person, and the fluoride level in the ground water are the critical factors for fluoride intake. There are recommended levels of fluoride for each country. The pathogenesis of Fluoride for the renal damage was well described at cellular level changes. It is associated with oxidative stress leading to organelle damage. Therefore, urinary fluoride can be used as an early indicator of CKDu. Further, Fluoride toxicity is reported with combination of heavy metals such as Mg, Mn and As, Pb etc. Although no clear etiological factor was recognized, Fluoride could be considered as a possible etiological factor for CKDu. As preventive measures, provision of fluoride-free drinking water in the affected areas, early detection of fluoride toxicity can be recommended.

Keywords: Fluoride; Etiology of CKDu; Groundwater; Drinking Water; Heavy Metals.

INTRODUCTION

Chronic kidney disease (CKD) is one of the most prevalent non-communicable diseases in many countries and it is predominantly caused by diabetes, hypertension, and glomerular diseases. Nephrotoxic drugs, herbal medications, toxins, and infection are the causes of CKD in developing countries. It demonstrates that in some tropical/subtropical countries such as Sri Lanka (Jayatilake et al., 2013; O’Callaghan-Gordo et al., 2019) India (Rajapurkar et al. 2012; Reddy and Gunasekar 2013). Egypt (El Minshawy。， 2011) ElSalvador (VanDervort et al. 2014), Nicaragua (Torres et al. 2010) Costa Rica (Cerdas 2005; Wesseling et al. 2013) and some countries in Central America, (Brooks et al., 2012； Ramirez-Rubio et al., 2013) a substantial number of CKD patients in agricultural communities with low socioeconomic living standards, do not have the exact aetiology for the disease. Therefore, still it is unclear whether and how those environmental factors or renal toxins in drinking water matter for Sri Lanka and other countries that are suffering from CKDu-related high morbidity and mortality incidences. Among multiple environmental toxins, fluoride, hardness of water, had been suggested as the possible pathogenic factors leading to CKDu (Kulathunga et al., 2019; McDonough et al., 2020; Wimalawansa, 2016).

METHODOLOGY

In a community based, the drinking water plays an important role for health and well-being. It has long been recognized that the use of water for human consumption depends on its purity. Therefore, the importance of the analysis of waters is well recognized. Drinking water is not a pure chemical compound (H2O) like distilled or osmotic water. The presence of certain amounts of total dissolved solids and some essential elements are needed to ensure an acceptable taste but also to prevent subacute and chronic adverse health effects from the long-term consumption of water (Rosborg and Kozisek, 2020). Groundwater plays as the primary source of drinking water in water supply systems specially managed with a community, and superior quality can be assured in those small scale systems (Abbasnia et al., 2018; Hybel et al., 2015). However, many developing countries encounter problems related to groundwater contamination with hazardous substances, including minerals and fluoride (Ali et al., 2016; Brindha and Elango, 2011). Similarly in the CKDu affected regions studies, the groundwater serves as the primary drinking water source (Balasubramanya etal 2020). These evidence give some positive aspects for the fluoride as an etiological factor for CKDu.

FLUORIDE IN DRINKING WATER

Fluorine is a common very reactive element found in the environment and it naturally occurs in varying amounts in different geographical locations. Chemically, it occurs in free form and found as electronegative anionic form of fluoride (Rashid et al., 2013). Drinking water is the commonest mode of Fluoride ingestion by humans (Nanayakkara et al,2020). Several studies have investigated groundwater fluoride in different regions. Adimalla (2019) examined the groundwater quality for drinking and irrigation purposes in the Medak region of Telangana State, India, and found that 57% of the samples had fluoride concentrations higher than the WHO guideline value. Sahu et al. (2017) investigated the fluoride concentrations in groundwater and urine samples of humans and animals in the Dongargaon Block, Chhattisgarh, India. Reports suggest the presence of high levels of naturally occurring fluoride in groundwater sources in some parts of the dry zone in Sri Lanka, that is over 50% of wells in the dry zone regions of Sri Lanka have fluoride levels higher than 1.0 mg/L while the fluoride content is also higher in deep wells compared to the shallow wells （Chandrajith et al., 2012). They found that at least 20% of humans and domestic animals in these areas were affected by fluorosis diseases. Rao (2017).

Therefore, it is important to consider the factors which affect the water intake of a person since it directly affects the fluoride intake. Water consumption depends on temperature, humidity, exercise and the state of health of an individual. For example, in people living close to the equator the water consumption is relatively higher than the other parts of the world (Murray and Organization, 1986). Thus, it is important to note that although the fluoride concentration in drinking water is very low, the probability of Fluoride entry into the body over the maximum allowable daily intake in people living in dry zone with hot climates getting exposed to sun for longer hours (Buttler et al., 2018; Laws et al., 2015). In addition to that farmers working in paddy fields also take much water than a person with normal sedentary life, since this is the dry zone and people may take much water as describe above (Murray and Organization, 1986). All evidence that the Fluoride levels in drinking water can be one of the commonest reason for fluoride toxicity. Further, the pathological changes of the animals in these areas have to be investigated. If the animals also show similar changes it will give some evidence to decide the effect of fluoride in the pathogenesis of CKDu.

RECOMMENDED FLUORIDE LEVELS IN DRINKING WATER

At present, the WHO guideline value in general for fluoride concentration in drinking water is 1.5 mg/L (World Health Organization, 2017). However, WHO has suggested that each country set its own guideline value, based on the water consumption of their population. The guideline value of fluoride concentration in drinking water is 1.0 mg/L in China (Ministry of Health of China, 2006). Because people in tropical countries consume more water than those in cold or temperate regions (Hossain et al., 2013), the guideline fluoride concentration in drinking water in Thailand is 0.7 mg/L (Ministry of Public Health (Thailand, 2010). In the USA, the guideline fluoride concentration in drinking water was revised from 0.7–1.2 to 0.7 mg/L in 2015. At low concentrations, fluoride is important for the dental health, protects teeth from decay (Sharma et al., 2017) and from other fluoride-related illness (Carey。, 2014; Aoun et al., 2018). It can be recommended that the groundwater of the study regions with high fluoride is suitable for irrigation purposes but unsuitable for drinking purposes.

PHYSIOLOGICAL FACTORS RELATED TO FLUORIDE STATUS OF AN INDIVIDUAL

Fluoride enters the human body mostly through drinking water and the diet. After fluoride enters the gastrointestinal tract, it is rapidly absorbed into the body by a process of diffusion and distributed to the tissues through the systemic circulation (Rashid et al., 2013). Calcified tissues such as bone and teeth rapidly uptake about 50% of fluoride from the circulation and the rest is primarily excreted in urine. In the kidneys, about 60% of the total daily fluoride absorbed is freely filtered through glomerular capillaries, passes through the tubular system and a variable degree of reabsorption occurs (Whitford, 1994). Kidneys have the ability to concentrate fluoride in urine up to 50-fold as in plasma and maintain a serum fluoride concentration of 10-50 mg/L (Joshi et al., 2011). Renal clearance of fluoride in healthy adults is directly related to the glomerular filtration rate and it is around 30-40 mL/min (Spak et al., 1985; Ludlow et al., 2007). Therefore, the kidneys play a major role in regulating the concentration of fluoride in serum and preventing the accumulation of fluoride to toxic levels. It concludes that kidneys become a key target organ in fluorosis (Jimenez-C ordova et al., 2018).

ROLE OF KIDNEY IN FLUORIDE METABOLISM AND THE PATHOGENESIS OF CKDU

High concentrations of fluoride in drinking water adversely affect the human health (Dey and Giri, 2016; Roy and Dass, 2013). Long term consumption of fluoride rich groundwater has become a widely discussed risk factor for (CKDu) (Chandrajith et al., 2011a; Dissanayake and Chandrajith., 2017). The kidneys are the target organ of exposure to excessive amounts of fluoride from drinking water and diet. This can lead to structural, functional and metabolomics changes in the kidney (Yang et al., 2011). It is well established that fluoride exposure is associated with chronic renal failure in humans and animals in a dose dependent manner (Bharti et al., 2014) and are discussed in several recent reviews (Barbier et al., 2010; Wimalawansa., 2020). The evidence for this assumption is based on the high Fluoride levels in serum and urine samples of CKDu subjects. Therefore, Urinary fluoride is widely used as an early indicator of fluoride ingestion in inhabitants of high-fluoride areas (Kanduti et al., 2016). The CKDu subjects in the study regions showed the mean serum fluoride level of 1.39 ± 1.1 mg/L, while it was 1.53 ± 0.8 mg/L for urine (Fernando et al., 2020). These values are much higher than the levels reported in other studies in the world. The serum fluoride concentrations of CKDu patients were higher than that of end-stage renal disease (ESRD) patients of Saudi Arabia where serum fluoride of male and female subjects was 1.43 and 1.26 mg/L, respectively (Schiffl and Binswanger, 1980). High fluoride concentrations can also damage the nervous system (Zhang et al., 2008), liver and kidneys (Nanayakkara et al., 2012; Xiong et al., 2007). The available evidence, mostly based on animal studies reports that the detrimental effects of fluorosis to the skeletal system and teeth, organs such as the brain, liver (Dote et al., 2000; Shashi and Thapar, 2001; Xiong et al., 2007; Yang et al., 2011). Environ Geochem Health Animal experiments also showed that prolonged exposure to excessive fluoride through drinking water could damage kidneys with increased fluoride concentrations in urine (Liu et al., 2005; Xiong et al., 2007).

These affected patients showed elevated serum and urinary fluoride. Higher fluoride exposure would be the reason for higher fluoride levels in serum, while urinary excretion would be due to deterioration of the kidney, suggesting the possible nephrotoxic role of fluoride exposure. It is evident that once the renal function is impaired, it can cause an accumulation of fluoride in the human body causing further damage to the renal tissue and accelerating the disease progression (Liu et al., 2005; Torra et al., 1998; Xiong et al., 2007). This suggests that CKDu patients are more sensitive to fluoride toxicity and have a lower margin of safety for fluoride induced adverse effects than a healthy person with normal renal function.

EFFECTS OF FLUORIDE AND HARDNESS TOGETHER IN THE PATHOGENESIS OF CKDU

There are few studies in which Fluoride toxicity is reported with some heavy metals. For instance, the higher hardness and fluoride levels in drinking water were considered the important parameters to induce kidney diseases in the north-central province (NCP) and dry regions of Sri Lanka and India (Chandrajith et al., 2011a; Dharma-wardana, 2018; Fernando et al., 2020). Significance of Mg-hardness and fluoride in drinking water was carried out in Sri Lanka where the CKDu is highly prevalent using both dipstick proteinuria test and Albumin-Creatinine Ratio (ACR). Nearly 87 % of the wells used by CKDu cases showed higher fluoride levels that exceed the threshold level (1.0 mg L−1). It is conspicuous that the elevated fluoride levels together with water hardness is associated with higher Mg2+ levels have a possible relation with CKDu and may influence the disease progression (Chandrajith et al., 2011b). Fluoride and arsenic in groundwater are two of the most discussed elements in the emerging science "Medical Geology" Studies conducted during the last 30 years in Sri Lanka. These studies have clearly indicated that several regions of the dry zone of Sri Lanka are affected by excessive quantities of fluoride and as in the groundwater. In another study in India focused on the monitoring and assessment of groundwater quality the lead concentration in the groundwater samples were found to be above the Bureau of Indian Standards (BIS) permissible limit (0.01 mg/l). But the Fluoride (F−) concentration in groundwater was found well below the BIS permissible limit (1.5 mg/l) in 95% of villages of study area with mean concentration (0.54 mg/l, SD = 0.40). Therefore, Synergic effects on kidney function of lead, fluoride, silica and water hardness in acidic water need to be explored. In a study examining exposure to sodium fluoride administrated rats showed increased levels of serum urea, creatinine, uric acid, sodium ions, and chloride ions and serious histopathological changes in the kidney tissues as evidence of fluoride induced nephrotoxicity (Perera et al., 2018). When considering kidney injury associated with fluoride, effects on proximal tubular injury is more pronounced than glomerular injury according to experimental animal models (Usuda et al., 1997). The major effects include inhibition of tubular reabsorption, inhibition of kidney enzymes affecting the functioning of enzyme pathways, disruption of collagen biosynthesis and changes in urinary ion excretion (Dharmaratne, 2019). Some research suggests that there is a possibility for systemic fluorosis in patients with diminished renal function due to impaired excretion of fluoride Thus, these patients have relatively lower margin of safety than a healthy person when it comes to the adverse effects of fluoride.

THE FLUORIDE TOXICITY AT CELLULAR LEVEL

The mechanisms of fluoride toxicity can be attributed to inhibition of proteins, organelle disruption, altered pH and electrolyte imbalance. Even though prokaryotes show some mechanisms for the survival at high Fluoride levels, it has not been reported whether mammals, including humans, have any detoxification mechanisms (Breaker, 2012).

Previous studies, mostly on animals have suggested different pathophysiological mechanisms for fluoride induced organelle damage such as oxidative stress, cell cycle arrest, altering gene expressions and cell apoptosis (Barbier et al., 2010; Ozbek and Akman, 2012; K. Rashid et al., 2013). The oxidative stress mediated mechanism of renal tissue injury in excess fluoride exposure is well documented based on in-vitro studies and animal studies (Anuradha et al., 2001; Barbier et al., 2010; Jiménez-Córdova et al., 2018; Johnston and Strobel, 2020). Some studies have also indicated that fluoride can alter gene expression and induce cell apoptosis leading to organ damage (Barbier et al., 2010; Zhang et al., 2008). It is noteworthy that these adverse effects of fluoride on human organs are closely related to the dose and concentration of exposure. Sodium fluoride has the ability to induce oxidative stress in renal tissues and liver tissues altering function (Azab et al., 2018). Fluoride induces oxidative stress, by increased production of ROS and free radicals, leading to excessive lipid peroxidation, and reducing antioxidant enzyme activities (Quadri et al., 2016; Varol and Varol, 2013). One experiment with sodium fluoride on rats showed 45.9% suppression of SOD activity and a loss of catalase activity by 41.5% compared to control (Nabavi et al., 2012). In another experiment by (Thangapandiyan and Miltonprabu, 2014) they observed that the levels of lipid peroxidation products such as TBARS, LOOH and PCC were significantly increased in fluoride-treated rats when compared to control (Thangapandiyan and Miltonprabu, 2014). In the same experiment, significant decrease in the activities of renal antioxidant enzymes, namely SOD, CAT, GPx, glutathione-S-transferase (GST), glutathione reductase (GR) and glucose-6-phosphate dehydrogenase (G6PD) were observed. Reduced levels of some antioxidants such as GSH, Vitamin C and vitamin E levels were also observed with fluoride exposure (Thangapandiyan and Miltonprabu, 2014). In an experiment using TCMK-1 cell line, authors observed a high level of oxidative stress with sodium fluoride exposure. In addition to oxidative stress, mitochondrial dysfunction and apoptosis are the most significant toxicological functions activated by fluoride toxicity (Sayanthooran et al., 2018). In addition to apoptosis, necrosis also reported in mice tubular cells subjected to chronic fluoride exposure (Kour and Singh, 1980). Fluoride toxicity also activates pathways such as G-protein activation, Cdc42 signalling, Rac signalling and RhoA signalling prominently (Mott et al., 1999; Sayanthooran et al., 2018). The proteins Cdc and RAc are members of the Rho family of small GTPases (G proteins) and they are involved in controlling signal-transduction pathways leading to rearrangements of the cell cytoskeleton, cell differentiation and cell proliferation (Mott et al., 1999).

PREVENTION OF FLUORIDE TOXICITY AND RECOMMENDATION

There is evidence that once renal function is impaired, fluoride retention can exert a potential risk of further damage to the renal tissue. Controlling the disease progression and reducing the rate of CKDu patients progressing to a stage requiring costly and resource intensive management will help to reduce the overall burden on the healthcare system and also CKDu related deaths which is one of the most common causes of hospital mortality in CKDu affected regions in Sri Lanka. In Sri Lanka, parallel with the efforts to identify the aetiology for CKDu, there is an urgent need to identify the potential risk factors involved in the rapid progression of CKDu to end stage renal disease (ESRD). Other than providing fluoride-free drinking water on a priority basis in affected areas, early detection of fluoride toxicity should also be ensured for implementing preventive measures. Since high fluoride is a major problem in the dry zone regions with severe health concerns, suitable defluoridation methods need to be introduced at the household level. Further investigations should be conducted to evaluate the correlation between serum fluoride concentration and the gender。 Recommendation of non-fluoridated water to patients with CKD was a much-debated topic from the time the artificial fluoridation came into action. However, the United Sates National Kidney Foundation (NKF) or Kidney Health Australia (KHA) have not issued specific recommendations regarding fluoride intake and kidney disease due to the limited available research. It is advisable to monitor and control the serum fluoride concentration in CKDu patients with respect to patient management. Further research is required to identify the threshold of tolerance for fluoride exposure to establish a safe drinking water fluoride concentration for CKD patient. Suitable defluoridation methods need to be introduced at the household level. In vitro studies can be recommended with the reported factors and preventive measures with antioxidants and other Fluoride absorbing methods.

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