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

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Review Article

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Abstract

Introduction: Despite much research on chronic kidney disease of uncertain etiology (CKDu) in Sri Lanka the etiology and pathogenesis remains obscure. The fluoride level in the ground water in CKDu prevalent area was considered as one of the suspected etiological factor for the disease.

Methodology: A review was conducted through MEDLINE and Google Scholar databases for peer reviewed publications on ground water analysis related to CKDu areas globally.

Results: Groundwater plays as the primary source of drinking water in these disease prevalent areas. 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.

Conclusion: Therefore, urinary fluoride can be used as an early indicator of CKDu. Further, Fluoride toxicity occurs in 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; The Role of Water Quality in the Pathogenesis of CKDu with Respect to Fluoride

Abbreviations: CKD: Chronic Kidney Disease; WHO: World Health Organization; BIS: Bureau of Indian Standards; NCP: North-Central Province; ESRD: End Stage Renal Disease; GST: Glutathione-S-Transferase; GR: Glutathione Reductase; G6PD: Glucose-6-Phosphate Dehydrogenase; NKF: National Kidney Foundation; KHA: Kidney Health Australia.

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 many countries such as Sri Lanka [1], India [2], Egypt [3], ElSalvador [4], Nicaragua [5], Costa Rica [6] and some countries in Central America [7] there are a number of CKD patients. They are mainly in agricultural communities with low socioeconomic living standards and do not have the exact etiology 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 [8].

Drinking water has a great impact 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 [9]. Groundwater plays as the primary source of drinking water in water supply systems especially in community based systems, and a better quality can be assured in those small scale systems [10]. However, many developing countries encounter problems related to groundwater contamination with hazardous substances, including minerals and fluoride [11]. Similarly in the CKDu affected regions studies, the groundwater serves as the primary drinking water source [12]. This evidence gives some positive aspects for the fluoride as an etiological factor for CKDu.

Methodology

Medline database was searched using the search terms CKDu and Fluoride, Etiology of CKD unknown and global chronic kidney disease, CKDu in Sri Lanka. The search was carried out without restricting to a time limit. Published articles in peer reviewed journals in English language were included. Some Abstracts were reviewed for suitability and relevance by the author in order to gather the information. All co-authors reviewed the full papers and screened the cited references. The search resulted in more than 150 publications and about 80 of which were selected based on the full article. The possible involvement of fluoride in the pathogenesis of CKDu in Sri Lanka has been a much debated topic for several years, but evidence on the role of fluoride on CKDu is inconsistent. Many studies are based on ground water analysis, patient serum and urine analysis in the affected areas. Some work is concentrated on in vitro analysis of fluoride toxicity at cellular levels by cell culture studies. Based on the evidence it is advisable to study the preventive aspect of the disease with respect to the future victims. In this review the evidence favourable and unfavourable for the Fluoride as an etiological factor for CKDu will be summarized with recommendations.

Results

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 [13]. Drinking water is the commonest mode of Fluoride ingestion by humans [14]. Several studies have investigated groundwater fluoride in different regions and examined the groundwater quality for drinking [15]. In some region of India, 57% of the samples had fluoride concentrations higher than the WHO guideline value [16]. High levels of naturally occurring fluoride in groundwater sources in some parts of the dry zone in Sri Lanka has been reported, that is over 50% of wells have fluoride levels higher than 1.0 mg/L [17]. The fluoride content is also higher in deep wells compared to the shallow wells. And at least 20% of humans and domestic animals in these areas were affected by fluorosis diseases [18].

Therefore, it is important to consider the factors related to the water intake of an individual since it directly affects the fluoride intake. Water consumption of a person depends on temperature, humidity, exercise and the state of health. People living close to the equator the water consumption is relatively higher than the other parts of the world [19]. 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 [14,20]. 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. 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) [21]. 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 [22]. Because people in tropical countries consume more water than those in cold or temperate regions [23], the guideline fluoride concentration in drinking water in Thailand is 0.7 mg/L [24]. 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 and from other fluoride-related illness [25-28]. 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 [13]. 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 [29]. 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 [30]. Renal clearance of fluoride in healthy adults is directly related to the glomerular filtration rate and it is around 30-40 mL/min [31,32]. 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 [33].

Fluoride levels in the plasma can be increased in elderly people in general after about age of 45 years [34]. It was found that the mean urinary concentration of fluoride found to be decreased with increasing serum fluoride levels. This is either due to decreased excretion or due to increase releasing of deposited fluoride from bone [35,36]. However, among the elderly population between 40- 50 years of age, the deterioration of the kidney function could be the reason for decreased renal excretion of fluoride with decrease in glomerular filtration rate. As a result, serum fluoride level can be increased. This is generally related to the reduced eGFR [37]. Although a statistically significant difference ($p \leq 0.05$) between males and females was not observed, the mean serum fluoride concentration and urine fluoride concentration in male subjects were higher than those of females [38]. The incidence CKDu also much higher in male than female [39]. The gender related matters pertain to fluoride levels should be further investigated in different communities with respect to exposure and kidney function.

Role of kidney in Fluoride Metabolism and the Pathogenesis of CKDu

High concentrations of fluoride in drinking water adversely affect the human health [40,41]. Long term consumption of fluoride rich groundwater has become a widely discussed risk factor for (CKDu) [42,43]. 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 [44]. It is well established that fluoride exposure is associated with chronic renal failure in humans and animals in a dose dependent manner and are discussed in several recent reviews [45-47]. 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 [48]. 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 [49]. 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 [50]. High fluoride concentrations can also damage the nervous system [51], liver and kidneys [52,53]. 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 [53-55], 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 [53,56].

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 [53,56,57]. 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 [42,49,58]. 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 [59]. 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 [58]. When considering kidney injury associated with fluoride, effects on proximal tubular injury is more pronounced than glomerular injury according to experimental animal models [59]. 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 [60]. 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 [61].

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 [13,62]. The oxidative stress mediated mechanism of renal tissue injury in excess fluoride exposure is well documented based on in-vitro studies and animal studies [33,62]. Some studies have also indicated that fluoride can alter gene expression and induce cell apoptosis leading to organ damage [51,62]. 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 [63]. Fluoride induces oxidative stress, by increased production of ROS and free radicals, leading to excessive lipid peroxidation, and reducing antioxidant enzyme activities [64]. 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 [65]. In another experiment by (80) 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 [66]. 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 [66]. 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 [67]. In addition to apoptosis, necrosis also reported in mice tubular cells subjected to chronic fluoride exposure. Fluoride toxicity also activates pathways such as G-protein

activation, Cdc42 signaling, Rac signaling and RhoA signaling prominently [67]. 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 [68].

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 de-fluoridation 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) has 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 de-fluoridation 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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