REVIEW ARTICLE

Fluoride and hardness in groundwater of tropical regions - review of recent evidence indicating tissue calcification and calcium phosphate nanoparticle formation in kidney tubules

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Abstract: In many tropical environments, groundwater has high fluoride concentrations in addition to other ions such as Na^+ , Ca^{2+} , Mg^{2+} and PO_4^{3-} . These ions interact with one another and this geochemistry has a direct bearing on the health of the population living in such terrains. In the majority of cases, it is the groundwater that is used for drinking and the input of the above mentioned ions into the body often results in diseases such as dental and skeletal fluorosis, chronic kidney disease, soft and hard tissue calcification. Even though the actual input of the above mentioned ions into the body from drinking water as against diet, may be low, as reported in some studies, it may be high in people living in tropical terrains where agricultural productivity and nutrition is low and where the consumption of such water is high.

Keywords: fluoride, ionic interactions, kidney tubules, apatite crystallization.

INTRODUCTION

Tropical regions which cover approximately 40 % of the earth have some unique features in their geology, geochemistry and water quality. The climate plays a major role in bringing about these special features due to its extreme effects on rock weathering, nutrient depletion in soils, evaporation, evapotranspiration and concentration of many chemical species in groundwater. Interestingly, over 150 countries have at least half their landmass in the tropics and these countries represent more than 40% of the world's population of around 7.6 billion. The majority of these countries has poor agricultural productivity, water quality and associated health problems. Due to extreme changes in climate and rainfall, rock weathering is intense and soils are leached heavily. This results in poor agricultural productivity due to low nutrients (Fyfe *et al.*, 1983). The groundwater composition changes markedly during wet and dry seasons and in extreme cases the dissolved ions could reach very high levels exceeding the WHO recommended values several fold. The intimate association of the tropical population with the immediate geoenvironment results in several "geochemical diseases" on account of their origin in the geological environment (Dissanayake and Chandrajith, 1999; Dissanayake and Chandrajith, 2009a). Under the tropical environmental

conditions of high temperature, high rainfall alternating with very dry spells, element fractionation during rock weathering and soil formation result in heterogeneous distribution of chemical species in the geoenvironment. These geochemical provinces are unique in their chemistry and form an important facet of medical geology in tropical environments (Dissanayake, 1996; 2005a; Dissanayake and Chandrajith, 2009a; Chandrajith *et al.*, 2011b).

Fluoride is generally found in excessive amounts in the groundwater of these countries (Dissanayake, 2005b) and has a marked impact on the health of the population resulting in dental and skeletal fluorosis. Harinarayan *et al.* (2006) have shown that evidences of chronic fluoride intoxication associated with renal tubular dysfunction focusing on the possibility that fluoride toxicity may be responsible for both bone and kidney disease. Renal function, especially glomerular filtration rate is very sensitive to fluoride exposure (Ando *et al.*, 2001). In Sri Lanka, notably in some parts of the dry zone in the north central regions, a chronic kidney disease hitherto known as "of uncertain origin", persists in the areas of fluoride-rich groundwater coupled with water with high calcium and magnesium levels (Dissanayake and Chandrajith, 2007). This paper attempts to highlight the importance of groundwater with high levels of Ca^{2+} , Mg^{2+} , F^- and PO_4^{3-} used for drinking and its impact on the biogeochemical mechanisms leading to kidney tubular damage with the end result of chronic kidney disease (CKD).

Geochemistry of fluoride in groundwater

Fluorine is the most electronegative and chemically reactive element of all halides. It is highly reactive with all organic and inorganic substances, very often forming highly toxic compounds. It is abundant in silicate minerals at concentrations of about 650 mg/kg (Adriano, 2001). It has been shown that the geochemistry of the fluoride ion F^- (ionic radius 136 pm) is similar to that of the hydroxyl (OH^-) ion (ionic radius 140 pm) and hence there can be easy exchange between them. Fluorapatite [$\text{Ca}_5(\text{PO}_4)_3\text{F}$] and hydroxyapatite [$\text{Ca}_5(\text{PO}_4)_3\text{OH}$], are isomorphic end members of the solid solution series $\text{Ca}_5(\text{PO}_4)_3(\text{OH},\text{F})$. Hydroxyapatite, however, is the main mineral phase of

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enamel in human teeth, a fact often used as an argument against the essentiality of fluoride to humans (Pauwels and Ahmed, 2007; Dissanayake and Chandrajith, 2009a). In general, the concentration of fluoride in groundwater is controlled by the solubility of CaF_2 , whereas the dissolution of Ca^{2+} in groundwater is controlled by the solubility of calcite and fluorite. The dissolution of calcite and fluorite is inversely proportional to each other, the activities of calcium, fluoride and carbonate being independent in groundwater (Rafique *et al.*, 2009; Kim *et al.*, 2012).

Due to the extreme changes of climate, weathering of rocks, minerals and degradation of soils takes place rapidly and passage of some chemical species into the aqueous medium takes place easily, thereby enriching the medium with abundant ions, a feature so typical of tropical environments. The leachability of fluoride from minerals such as carbonate concretions is controlled by pH of draining solutions, alkalinity, dissolved CO_2 and the pCO_2

in the soil (Figure 1). It is to be noted that the soil-water interaction and residence time of fluoride are two important factors that govern the fluoride concentration in water. Table 1 shows the average fluoride ranges in different types of water. The interaction dynamics of groundwater with rocks and minerals and associated fluoride concentration plays an important role and it has been noted that groundwater with long residence time is usually associated with deep aquifer systems and a slow groundwater movement as well (Figure 2) (Sivasankar *et al.*, 2016).

Figure 1: Mechanism for fluoride ingestion in arid and semi-arid areas (Modified from Ramesan and Rajagopalan, 1985).

Figure 2: Interaction dynamics of fluoride in groundwater (after Sivasankar *et al.*, 2016).

Table 1: Fluoride contents in different environmental components (after (Edmunds and Smedley, 2013).

Source	Range of fluoride (mg/L)
Rainfall	0.013-0.096
Surface waters (rivers)	0.06-0.18
Surface waters in high fluoride regions	0.6 -1281
Soil water	0.02-0.30
Geothermal springs	0.4-330
Groundwater crystalline basement rocks	<0.02- 20
Groundwater volcanic rocks	2.1- 250
Groundwater sediments and sedimentary basins	<0.1- 29

Fluoride as a nephrotoxin

It is well known that excessive fluoride concentrations in the groundwater can lead to dental and skeletal fluorosis among the population living in such terrains (Dissanayake, 2005a; 2000b). The map showing the distribution of fluoride in the groundwater of Sri Lanka clearly shows that the highest concentrations of fluoride are found in the dry zone regions (Figure 3a). Dental fluorosis is quite common among population living in such areas (Figure 4). Interestingly, the prevalence of chronic kidney disease of unknown etiology (CKDu) also coincides with the higher fluoride geochemical province (Figure 3b). Dissanayake (2005b), first suggested that it is the fluoride concentration and its interactions with other ions such as Ca^{2+} , Mg^{2+} and Na^{2+} that could trigger the onset of CKDu in Sri Lanka. In his paper several important observations and suggestions had been made as follows;

a. All areas affected by the CKDu were located in the dry zone and within this zone, areas with higher groundwater fluoride correlated with locations of high CKDu prevalence. This important correlation paved the way for further studies. The Hydrogeochemical Atlas of Sri Lanka produced by Dissanayake and Weerasooriya (1985), had already demarcated the “fluoride belt” of Sri Lanka at the boundary of the dry zone and the intermediate climatic zone.

b. The groundwater was more saline with high electrical conductivity indicative of an abundance of total dissolved solids.

c. The dry zone soils, due to the effect of drought and evaporation, tend to accumulate salts in the soil which then enrich the groundwater with many cations.

The important suggestion made by Dissanayake (2005b), notably the interaction of groundwater fluoride with other cations as a probable causative process for the CKDu, though doubted at first, gained gradual acceptance when further research studies were carried out with new data being published. It is now generally accepted that water hardness and fluoride together play a major role in the onset of CKDu (Dharmaratne, 2015).

The prediction of Dissanayake (2005b), “*The abundance of high fluoride in all areas and dissolved solids in the groundwater, and the high saline nature of*

the water may well turn out to be a major factor in the incidence of CRF”, is now gaining credence. Fluoride-rich groundwater geochemistry, as shown by Dissanayake (2005b), is therefore of paramount importance in the study of the aetiology of CKDu.

The importance of fluoride as a geochemical marker for CKDu was further discussed by Dissanayake and Chandrajith (2017). It is known that the kidney, with the exception of the pineal gland, is exposed to high concentrations of fluoride than all other soft tissues in the human body. Damaged kidneys accumulate more fluoride resulting in further damage to kidney, bone and other organs (Connett, 2012). It has also been observed that those who suffer from CKD in tropical countries also have a tendency to develop bone disease, mainly skeletal fluorosis. Lantz *et al.* (1987) reported a case of fluoride intoxication related to potomania of Vichy water, a highly mineralized water containing 8.5 mg/L of fluoride. They observed a relationship between osteosclerosis and end-stage renal failure and concluded that the long duration of high fluoride intake and the absence of other causes of renal insufficiency suggested a causal relationship between fluoride intoxication and renal failure. Fluoride has consistently been underestimated for its toxic effects mainly because of the proponents of water fluoridation emphasizing the supposed benefits of fluoride to dental health. At an optimum level, fluoride may have beneficial effects, but at higher concentrations, the detrimental effects notably in teeth, bones and kidneys are remarkably high (Çiftçioglu *et al.*, 1999; Harinarayan *et al.*, 2006). Significantly, even at low doses, fluoride is known to interact with cellular systems including oxidative stress and modulation of intracellular redox homeostasis and some others emphasizing the toxicity of fluoride to human beings (Cittanova *et al.*, 1996). Fluoride could be more genotoxic at lower doses than at higher doses when ingested through drinking water (Podder *et al.*, 2011). It should be remembered that the largest input of fluoride into the human body comes from drinking rather than diet and air. This fact is of extreme importance in tropical dry regions of the world where millions of people use fluoride-bearing water as their drinking water source. It should however be mentioned that tea is a source of fluoride and this may provide an additional input to the human fluoride intake (Chandrajith *et al.*, 2007).

Figure 3:(a) Map showing the distribution of fluoride in groundwater (Chandrajith *et al.*, 2012); (b) areas with high prevalence of endemic kidney diseases and (c) average temperature variation in Sri Lanka.

Figure 4: A case of dental fluorosis in Sri Lanka.

The determination of the exact dose of fluoride that is effective in the triggering of physiological imbalances and how other interactive chemical species such as Na^+ , Ca^{2+} and Mg^{2+} control the critical dose needs further extensive research (Dissanayake and Chandrajith, 2017). Experiments had been carried out in order to characterize some subcellular determinants of fluoride cytotoxicity and to determine whether sub-toxic fluoride exposure affects tubular cell vulnerability to superimposed ATP depletion and nephrotoxic attack (Zager and Iwata, 1997). They concluded that (a) fluoride induces dose-dependent cytotoxicity in cultured human proximal tubular cells, (b) this occurs via Ca^{2+} and phospholipase A2- (PLA2) dependent mechanisms, (c) partial cytosolic PLA2 depletion subsequently results and (d) sub-toxic fluoride exposure can acutely increase cell resistance to further attack.

Quadri *et al.* (2018) pointed out that in India alone, 21 out of 35 states has endemic fluorosis due to high fluoride contamination from groundwater. Kidneys are also known to be badly affected due to their susceptibility to fluoride toxicity and to their unique anatomy and function.

Children suffering from renal impairments also have some symptoms of dental and skeletal fluorosis suggesting a link between fluoride and renal anatomy/physiology (Quadri *et al.*, 2018). A screening of 156 patients with childhood nephrotic syndrome, 32 of them had significantly high levels ($p < 0.05$) of fluoride in urine (4.01 ± 1.83 mg/L) and serum (0.1 ± 0.013 mg/L). Various sub-cellular ultrastructural changes including nuclear disintegration, chromosome condensation, cytoplasmic ground substance lysis and endoplasmic reticulum blebbing were noted. Increased levels of apoptosis were also observed in the high fluoride group compared to the normal fluoride group.

The significance of the above mentioned observations may be applicable to the large number of CKDu patients in the dry zone of Sri Lanka. Dharmaratne (2015), noted the following features associated with the Sri Lankan CKDu;

- Fluoride excretion rate is considerably lower in children than adults, leading to renal damage of children living in areas with high fluoride.
- Adults who had renal damage due to fluoride in childhood are vulnerable to CKDu with continued consumption of

Table 2: Fluoride (mg/L) and hardness (mg/L) in CKDu effected and no-effected regions (*calculated using Ca and Mg values).

Region	Fluoride	Hardness	Reference
CKDu regions			
Girandurukotte	0.64	217	Chandrajith <i>et al.</i> (2011a)
Nikawewa	1.21	336	"
Medawachchiya	1.42	324	"
Padaviya	0.62	443	"
Kebithigollawa	1.00	345	Lapegue (2000)
Gomarakadawala	1.00	466	"
5 CKDu endemic regions	1.00	215*	Rango <i>et al.</i> (2015)
Medawachchiya	0.97	230	Wasana <i>et al.</i> (2016)
Medawachchiya/Maderigiriya	0.60	223*	Levine <i>et al.</i> (2016)
Girandurukotte	0.73	148	Wickramarathna <i>et al.</i> (2017)
Wilgamuwa	1.48	279	"
Nikawewa	1.12	428	"
Non-CKDu regions			
3 non-endemic regions	0.05	19.4*	Rango <i>et al.</i> (2015)
Matale	0.20	259*	Chandrajith <i>et al.</i> (2015)
Haguranketha	0.25	79.9	Abeywickrama <i>et al.</i> (2016)
Panama	0.44	6.69	Chandrajith <i>et al.</i> (2014)
Jaffna	0.38	503*	Chandrajith <i>et al.</i> (2016)
Mannar	0.41	476*	Bandara <i>et al.</i> (2018)

water from the same source.

- Patients with chronic renal insufficiency are at an increased risk of chronic fluoride toxicity.
- High content of fluoride in groundwater paves the way to excess fluoride in local food crops, consequently adding more fluoride to the systems of the consumers.
- People who work outdoors for prolonged periods consume excess water and tea, and are subjected to additional doses of fluoride in their system.

Water hardness and kidney disease

A noteworthy feature of the spatial distribution of CKDu in Sri Lanka is its prevalence in regions of high fluoride groundwater and high water hardness (Chandrajith *et al.*, 2011a; Chandrajith *et al.*, 2011b) (Table 2). Most natural water supplies in the dry zone of Sri Lanka contain dissolved calcium and magnesium carbonates and silicates (Dissanayake and Chandrajith, 1999). The interactions of fluoride with Ca^{2+} , Mg^{2+} , PO_4^{3-} and Na^+ appear to have a controlling effect on the onset of CKDu, depending on their dosage (Chandrajith *et al.*, 2011a) and saturation factors. Both geochemical and biochemical influence by these chemical species do exert a marked effect on the etiology of the kidney disease. While water hardness alone could not be a causative agent for CKDu, their combined and synergistic effect, mainly due to the controlling effects on solubility and precipitation, could however, be a rate determining step in the mechanism of the disease onset.

Several studies have shown an inverse relationship between drinking water magnesium level and heart disease (Rylander *et al.*, 1991; Yang, 1998; Leurs *et al.*, 2010;

Knezović *et al.*, 2014) although its effect on kidney disease remains to be studied in greater detail. The increase of $\text{Ca}^{2+}/\text{Mg}^{2+}$ ratio in drinking water is also attributed to the occurrence of urolithiasis (Yang *et al.*, 2016). The studies of Dharma-wardana *et al.* (2015) and Dharma-wardana (2018) highlighted the importance of groundwater ionicity noting that fluoride may contribute to CKDu by its high rank in the Hofmeister series (Zhang and Cremer, 2006) for denaturing of proteins of the kidney membrane. They also suggested that while the increase of hardness (below a threshold) correlates with good health, any ionicity increase above a threshold would correlate with disease.

Wickramarathna *et al.* (2017), who studied the etiological factors associated with CKDu in the dry zone of Sri Lanka observed that hardness reached values as high as 516 mg/L in some groundwater in affected regions. The mean hardness of groundwater in all samples taken during the pre-monsoon period was 181 mg/L indicating very hard water. Their studies clearly indicated a close association of CKDu with the synergistic effect of high water hardness and high fluoride in groundwater. The importance of high water hardness in the etiology of CKDu was also highlighted by Herath *et al.* (2017). They observed that 26.9% of well water in dry zone of Sri Lanka was soft, 15.0% moderately hard, 15.8% hard and 42.2% very hard. This close association of fluoride with water hardness further emphasizes the importance of the latter in the etiology of CKDu. The climate change impact is expected to enhance fluoride accumulations in groundwater, in particular through the decrease of rainfall and increase of evaporation (Pauwels *et al.*, 2011). The non-prevalence of CKDu in the northern regions of Sri Lanka underlain

by limestones, possibly due to the non-availability of fluoride caused by the precipitation of CaF_2 in view of the abundance of calcium. Further, the hard metamorphic rocks carrying fluoride-bearing minerals are only found at considerable depths.

Effect of calcium, magnesium and phosphate ions on CKDu

Given the scenario where groundwater fluoride, water hardness and phosphates are high, and also in view of the fact that the vast majority of people in tropical dry terrains use this groundwater as their drinking water source, Ca^{2+} , Mg^{2+} and PO_4^{3-} assume importance in health. Blaine *et al.* (2014) reviewed the renal control of the above mentioned chemical species in view of their importance in many biological and cellular functions, with kidneys playing a central role in the homeostasis of the ions. Renal excretion balances the gastrointestinal absorption when the contents of these ions decline significantly, gastrointestinal absorption, bone resorption and renal tubular reabsorption increase to normalize their levels. Renal regulation becomes an important determinant of plasma ion concentration since it occurs through glomerular filtration and tubular re-adsorption and/or secretion. The fine adjustment of urinary excretion to balance the net intake maintains the whole body balance of Ca^{2+} , Mg^{2+} and PO_4^{3-} under physiological conditions. In the case of Sri Lanka, PO_4^{3-} levels in groundwater are high due to the alarmingly excessive application of phosphate fertilizers (Dissanayake and Chandrajith, 2009b; Rubasinghe *et al.*, 2015). Since the drinking water of the affected population of the dry zone of Sri Lanka consume large quantities of such water, their body burden of the ions may be excessive and which may have a significant impact on kidney tubular damage. This may not be too significant in temperate countries where the input if these ions may be much lower.

Magnesium as a neglected element in CKD

It has been clearly stated above that water hardness and fluoride levels in the groundwater in combination with phosphates could be a cause for CKDu in tropical dry terrains. While the importance of calcium in kidney diseases has been discussed at length in many studies, magnesium, which is also an integral component of hard water has been grossly underestimated for its role in the etiology of CKDu. Magnesium plays a major role in cardioprotectivity and shows an antagonistic biochemical behavior towards calcium. The $\text{Ca}^{2+}/\text{Mg}^{2+}$ ratio in both groundwater and in the body tissues appear to be of paramount importance in controlling the homeostasis of these two species. The high levels of drinking water fluoride can increase the levels of two kidney damage markers, N-acetylglucosaminidase (NAG) and γ -glutamyltransferase (γ -GT) in urine in children (Xiong *et al.*, 2007). The CKDu of the dry zone of Sri Lanka is a slow progressing disease and the investigations on histopathology of kidney patients indicated a tubulointerstitial disease present mainly as focal to diffuse fibrosis, accompanied by varying degrees of sclerotic vascular lesions resulting in high frequency of glomerular sclerosis and collapse (Nanayakkara *et al.*,

2014).

Magnesium is known to play a very important role in over 300 enzymatic reactions and transport processes and synthesis of proteins DNA and RNA (De Francisco and Rodríguez, 2013). They showed that Mg deficiency is a risk factor for several common metabolic diseases, whereas Mg supplementation and mild hypermagnesemia might have beneficial effects in CKD patients with regard to calcification and mortality. Significantly, in CKD patients, cardiovascular disease is the leading cause of death (Foley *et al.*, 1998). Patients with CKD undergoing dialysis have 2 to 5 fold more coronary artery calcification than age-matched individuals. The calcifications take place in the intimal and medial vessel layer and this plays a major role in cardiovascular disease and mortality in CKD patients (De Francisco and Rodríguez, 2013).

The input of Ca^{2+} and Mg^{2+} into the body in the population living in tropical dry regions and consuming hard water is not known to any degree of certainty, though it can be expected that in view of the high frequency of consumption of hard water, the input of Ca^{2+} and Mg^{2+} into the body may be high. This needs further study, supported by geochemical mapping of Ca^{2+} and Mg^{2+} and their ratios in the groundwater. In the dry zone of Sri Lanka where the CKDu prevalence is high, the average Mg^{2+} content in the groundwater is 35.7 mg/L as compared to the Mg^{2+} content of 9.65 mg/L in wet zone where the CKDu incidence is insignificant (Rubasinghe *et al.*, 2015). This indicates the need for a detailed study of Mg and its role in CKDu.

Nanocrystal formation in kidney tubules

The geochemistry of the groundwater with high concentrations of Ca^{2+} , Mg^{2+} , F^- and PO_4^{3-} and the large consumption of such water is conducive for the precipitation of nanocrystals of calcium phosphate as either hydroxyapatite or fluorapatite or as its mixtures. These nanocrystals of calcium phosphate are formed in pathological calcifications as well as during stone formation. Even though many theories have been put forward as to how the nanocrystals form in the human tissues (Miller *et al.*, 2004), the exact mechanism is still being debated. Yiu *et al.* (2015) reviewed the mechanism that cause biocalcification. They discussed a recent computer model indicating a possible cause of spontaneous tubular calcium phosphate crystal formation, specifically at the descending loop of Henle, due to an increase in plasma phosphate, or a decrease in phosphate fractional re-adsorption in the proximal tubule (Robertson, 2015). They also report a study by Linnes *et al.* (2013), who showed a greater incidence of tubular plugging, in which some stone formers (brushite and apatite) exhibited severe plugging, calcium phosphate supersaturation being a major factor associated with plug formation. A study by Martel *et al.* (2014) has shown that mineralizing tissues contain polyphosphate nanoparticles that may serve as a source of inorganic phosphate for apatite formation following treatment with alkaline phosphatase. Martel *et al.* (2014) believe that monitoring the level of apatite particles found in body fluids may allow us to determine the general state of vascular calcification and predict the progression of

certain pathologies like end-stage renal disease.

The human kidney tissues obtained from end-stage chronic kidney disease or renal cancer patients contained round, multilamellar mineral particles of 50 to 1500 nm whereas no particles were observed in healthy controls (Wong *et al.*, 2015). They observed that these nanoparticles were composed of polycrystalline calcium phosphate similar to the mineral found in bones. The nanoparticles were deposited in the extracellular matrix surrounding the convoluted tubules, collecting ducts and loops of Henle as well as within the cytoplasm of tubule delineation cells (Figure 5). Recent studies on calcium phosphate nanoparticle formation in kidney tubules (Figure 6) open up new avenues of research on the impact of groundwater chemistry on chronic kidney diseases in tropical geoenvironments where the water is abundant in dissolved solids including Ca^{2+} , Mg^{2+} , PO_4^{3-} , Na^+ and F^- , formation of nanocrystals with a higher fluoride content could be

envisaged. For example, when drinking water has very high fluoride levels, a reaction can take place (Thole, 2011) as given below;

The calcium deca-fluoride so formed is very hard and brittle and is unsuitable for the bone structure and will certainly have a debilitating effect on the kidney.

The role of nanobacteria as nuclei for the formation of calcium phosphate nanoparticles has been studied extensively (Çiftçioglu *et al.*, 1999; Cisar *et al.*, 2000). Self-replicating nanobacteria and their association with calcium phosphate nanoparticle formation in kidney tubules, particularly in CKDu patients in tropical countries would pave the way for an entirely new biogeochemical pathway for kidney diseases.

Figure 5: General scheme of the biological consequences of fluoride exposure on mammalian cells (after Barbier *et al.*, 2010).

Figure 6: Calcium phosphate (apatite) deposition in kidney tubules.

CLIMATE CHANGE, WATER QUALITY AND CKD

Climate change is a scientific fact and this has led to a significant rise of 0.80°C – 0.90°C in global mean temperature over the last century. With ensuing heat waves and heat stress human health is increasingly affected directly as well as indirectly. One of the consequences of climate-related extreme heat exposure is dehydration and volume loss, leading to kidney ailments (Roncal-Jimenez *et al.*, 2016). Heat stress and recurrent dehydration has been linked to the high prevalence of CKD of uncertain etiology, recognized in Central America, termed Mesoamerican nephropathy (Crowe *et al.*, 2013; Glaser *et al.*, 2016; Roncal-Jimenez *et al.*, 2016). Several experimental and epidemiological studies have shown that the disease may be a type of heat stress nephropathy (HSN) and that this could be an example of a disease that is accelerated by global warming (Roncal-Jimenez *et al.*, 2016).

Figure 3c illustrates the relationship of Sri Lankan CKDu and heat distribution in the country. While the correlation of temperature and CKDu incidence is seen in many parts of the dry zone, some parts of Sri Lanka, notably the northern regions have little or no CKDu. This indicates that apart from heat stress, other factors such as groundwater geochemistry play a major role in the etiology of CKDu. A marked effect of climate change in the tropical environments is the change in water quality. The high evaporation rates increase the concentrations of many dissolved ions including F^- , Ca^{2+} , Na^+ , Mg^{2+} and PO_4^{3-} in the groundwater and which would almost certainly have a detrimental effect on the health of the people living in the areas concerned, when consumed such water in large quantities. Global changes in F^- concentrations in groundwater were studied by Amini *et al.* (2008) who

noted that spatial and temporal heterogeneities of fluoride concentrations in groundwater are large. It is known that fluoride-rich groundwaters are associated with rocks of low Ca^{2+} contents, high pH conditions where sodium bicarbonate dominates the groundwater composition. Further, residence time, soil conditions, evapotranspiration and precipitation influence the fluoride concentrations in the groundwater. All these factors are affected by climate change when ambient temperature increases (Watts *et al.*, 2017). The impact of increasing fluoride levels especially in tropical regions is very high leading to fluoride-related diseases (Figure 7).

CONCLUSIONS

With climate change in tropical countries, the groundwater quality changes frequently due to high evaporation, evapotranspiration, pH changes and variations in soil chemistry. Fluoride is a chemical species that is found in abundance in the groundwater of tropical regions and medical evidence points to fluoride having a marked effect on human and animal health. Dental and skeletal fluorosis, apatite formation in kidney tubules, calcification of arteries, are such diseases where fluoride plays a major role. Coupled with heat stress caused by increases of global temperature, ionic interactions in groundwater used as a drinking source, precipitation of calcium phosphate nanoparticles takes place aided by nano-bacteria and this could result in kidney diseases in tropical regions. Biomineralogy clearly plays a major role in the new field of Medical Geology. With further advances in instrumentation, notably in transmission electron microscopy, the study of nanocrystal formation in the human body affecting arteries, kidney tubules etc. will almost certainly provide a better understanding of some human diseases.

Figure 7: Regions with fluoride concentration in the groundwater exceeding WHO guidelines for drinking water of 1.5 mg/L.

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