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Deleterious role of trace elements – Silica and lead in the development of chronic kidney disease

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HIGHLIGHTS

- Environmental risk-factors of CKDu studied using Indian sub-district as case-study.
- High CKDu rate in sub-district linked to high silica and borderline lead exposure.
- Silica and lead exposure occurs via chronic contaminated groundwater consumption.
- Silica's nephrotoxicity via renal tubular-cell apoptosis explained for first-time.
- Lead nephrotoxicity-direct & indirect (causing skeletal ailments thus NSAID abuse).

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ABSTRACT

Chronic-Kidney-Disease of Unknown-etiology (CKDu) has been reported in developing-countries like Sri-Lanka, India and Central-America without sparing the Indian sub-district (namely Canacona) located in south-Goa. The disease etiology is unlinked to common causes of diabetes and hypertension and assumed to be environmentally induced due to its asymptomatic-nature and occurrence in groundwater relying communities. This study aimed to understand environmental risk-factors underlying CKDu-etiology using Indian sub-district (Canacona) as case-study. Biochemical-analysis of CKDu-affected and non-affected individual's blood and detailed hydro-geochemical analyses of CKDu-affected and non-affected region's groundwater (drinking-water)were conducted. Trace geogenic-element-silica was highly dominant in affected-region's groundwater, thus its nephrotoxic-potential was analysed via in-vitro cytotoxicity-assays on human-kidney-cell-lines. All CKDu-affected-subjects showed increased-levels of serum-urea (52.85 mM),creatinine (941.5 μM),uric-acid (1384.5 μM), normal blood-glucose (4.65 mM), being distinct biomarkers of environmentally-induced CKD-'chronic-tubulo-interstitial-nephritis'. Affected-subjects reported high blood-lead levels (1.48 μM)suggesting direct-nephrotoxicity resulting in impaired blood-clearance and also exhibits indirect-nephrotoxicity by disrupting calcium-homeostasis causing skeletal-disorders and prolonged-consumption of NSAID's (pain-alleviation), indirectly causing renal-damage. Affected-region's groundwater was acidic (pH-5.6), resulting in borderline-lead (9.98 μgL^{-1}) and high-silica (115.5 mgL^{-1})contamination. Silica's bio-availability (determining its nephrotoxicity) was enhanced at groundwater's acidic-pH and Ca-Mg-deficient-composition (since these cations complex with silica reducing bioavailability). Silica exhibited renal-proximal-tubular-cytotoxicity on long-term exposure comparable with affected-region's groundwater silica-levels, by apoptosis-mediated-cell-death resulting in tubular-atrophy, interstitial-fibrosis and irreversible renal-damage (CKD). Thus this study provides novel-insights into nephrotoxic-potential of trace-geogenic-element-silica in CKDu causation. It highlights direct-indirect nephrotoxicity exhibited by lead at low-levels

Abbreviations: APHA, American Public Health Association; APHA, American Public Health Association; A498, Kidney carcinoma cell line; BMI, Body Mass Index; BIS, Bureau Of Indian Standards; CTN, Chronic Tubulo-interstitial Nephritis; CKD, Chronic Kidney Disease; CKDu, Chronic Kidney Disease of Unknown etiology; DMEM, Dulbecco's Modified Eagle's Medium; FACS, Fluorescence Activated Cell Sorting; FITC, Fluorescein isothiocyante; GFR, Glomerular Filtration Rate; ICP-MS, Inductively Coupled Plasma Mass spectrometer; HEK, Human Embryonic Kidney cells; MTT, 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide; NSAID's, Non-Steroidal Anti-Inflammatory Drugs; PI, Propidium Iodide; SiO2, Silica; TDS, Total Dissolved Solids; WHO, World Health Organization.

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due to its bio-accumulative-capacity. Silica's nephrotoxic-potential can be considered when deciphering etiology of CKDu-problem in developing-countries (relying on groundwater).

1. Introduction

Chronic Kidney disease (CKD) is a global health problem and the 12th leading cause of death worldwide (Jha et al., 2013) with common risk-factors being diabetes and hypertension (Vassalotti et al., 2016). However, recently, a growing concern has aroused about a new-form of CKD not caused by these risk-factors termed as CKD of unknown-etiology (CKDu) (Jayatilake et al., 2013). It is prominent in developing-countries like Sri-Lanka (Wanigasuriya, 2014),India (Singh et al., 2013)and some central-American countries (Costa-Rica, Nicaragua, Panama and El-Salvador) (Correa-Rotter et al., 2014). This disease affects kidney's tubular-interstitium belonging to the type-chronic tubulo-interstitial nephritis (CTN) (Mackensen and Billing, 2009), caused by chronic exposure to environmental-toxins like heavy-metals (lead, arsenic, cadmium),mycotoxins, pesticides (diazinon) (Weaver et al., 2015). Heavy-metals cause nephrotoxicity at high-exposure levels, but it can cause toxicity even at low-levels on chronic exposure due to bio-accumulation and decreased clearance rate from the kidneys (Ferraro et al., 2010).

High incidence of CKDu-cases have been reported in few-villages of Canacona sub-district of south-Goa, India for the past two decades (The Hindu, 2007; DNA, 2010). In the quest of finding the cause(s) of this CKDu-disease, a joint-team from NIOH(National Institute of Occupational-Health)and ICMR (Indian Council of Medical-Research)in 2005, checked for role of ochratoxin, arsenic and cadmium (in water and food)in the etiology but nothing conclusive was obtained (Saiyed et al., 2005). Hence we took the challenge to decipher the etiology of this endemic mysterious-form of CKDu, which is unknown till-date, thus analyse the environmental risk-factors of global CKDu-problem.

The study-region comprised of two villages in Canacona with high-incidence of CKDu-Ponsulem and Chaudi, located in the vicinity of a non-operational granite mine, bearing geographical-coordinates:15°5′ 17″ N and 74°5′ 64″ E, average elevation of 10 m above mean sea-level. The climate is tropical with three seasons-winter (December–February), Summer (March–May)and Monsoon (June–September), average temperature:27.3 °C - 40.6 °C and annual precipitation of 2995 mm (Nadaf, 2009a). The geology of this CKDu-endemic study-region comprises of older-trondhjemitic sodium-plagiogranitic gneiss, while the flanking non-endemic CKDu-region has greenschists-metabasites. The granitic-gneiss is intruded by younger granites exposed (mining-sites) in the Chaudi village (Fernandes and Widdowson, 2009). The drainage is dendritic consisting of west-flowing rivers draining into the Arabian Sea, viz. Talpona (flowing through CKDu-endemic granitic-belt)and Galgibagh, Saleri river (flowing through metabasitic-formations) (Nadaf, 2009b) (Fig. S1).

In the present study, the authors hypothesized that chronic exposure to trace geogenic element-silica and nephrotoxic heavy-metals through prolonged consumption of groundwater could be the causative-agents for this endemic CKD. Silica is the most abundant constituent of the earth's-crust but not easily bioavailable (hence trace-element)causing pulmonary-silicosis (respiratory-disorder)on long-term exposure, with CKD as a complication. The toxicity is assumed to be exhibited by silica travelling through blood-stream and depositing in the kidney causing inflammation and fibrosis (Steenland et al., 2001). It demonstrated certain amount of nephrotoxicity in animal-models but its nephrotoxic mechanism in humans is unknown. Hence one objective (aim) of the study was to check its nephrotoxic effect (mechanism) on human kidney cell-lines (as it was not explored before)over a short-term and long-term exposure via in-vitro cytotoxicity assays. Since silica demonstrated tremendous amount of nephrotoxic potential on long-term exposure it was presumed to be a potential causative agent for this endemic-CKD on prolonged exposure through consumption of silica contaminated groundwater (being a prime drinking source in this rural sub-district). Thus authors hypothesized an alternate exposure-route (not reported before)to silica to be groundwater (primary-route being air)since the granite-mine has been non-operational for long, thus CKDu-endemic region's groundwater could get contaminated with excess silica through Acid-mine drainage (AMD)from the granite-mine into this aquifer. Silica's bioavailability increases at an acidic-pH, hence the acidic groundwater from the mine could have drained to the neighbouring CKDu-endemic region's granitic-aquifer (silica-rich) causing excessive leaching of silica resulting in high-exposure on consumption. Therefore another objective (aim) of the study was to conduct a complete hydro-geochemical screening of the CKDu-endemic region's groundwater for various environmental-toxins (specifically silica and heavy-metals), analyse physiochemical-factors affecting the bioavailability and subsequent nephrotoxicity of newly-emerging toxins (silica)and relate them to the etiology of the CKDu-disease. Since the etiology is unlinked to common risk-factors (diabetes and hypertension), various biochemical-markers, indicative of the type of renal-damage induced were analysed in blood of CKDu-affected and control subjects in-order to relate the damage detected to the dominant environmental-nephrotoxin.

2. Materials and methods

2.1. Study design

This study was approved by the Government of Goa through Directorate of Health-Services, Panaji, Goa (Reference No: DHS/Sp.Cell/Sect/8/1119). It also complies with The Code of Ethics of the World Medical Association (Declaration of Helsinki)and ethical approval was granted by Institutional Human-Ethics Committee of BITS-Pilani, India (Reference No: IHEC/11M/2)and Institutional Ethics Committee of Goa Medical Hospital (Dated 20th July 2015); head hospital of Goa.

A detailed-list of Canacona sub-district's CKD-affected patients were obtained from two main hospitals in Goa-Apollo Victor hospital and Canacona Health Centre. On analysis it was found that 142 from a combined total of 180 patients were hailing from Canacona sub-district, from which 80% of the patients (n = 114)were residents of two villages - Ponsulem and Chaudi, were grouped under study-group 1 and their area of residence clubbed as study-area 1. The remaining 28 patients hailing from scattered villages of the sub-district namely Cola, Poinguinim and Anvali were grouped under non-endemic study-group 2 and their area of residence -study-area 2. For true-controls, volunteers from two healthy villages of the sub-district namely Molorem and Endrem were randomly chosen and grouped under study-group 3 with their