Science of the Total Environment 596–597 (2017) 1–11

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Biomarkers of chronic fluoride exposure in groundwater in a highly exposed population

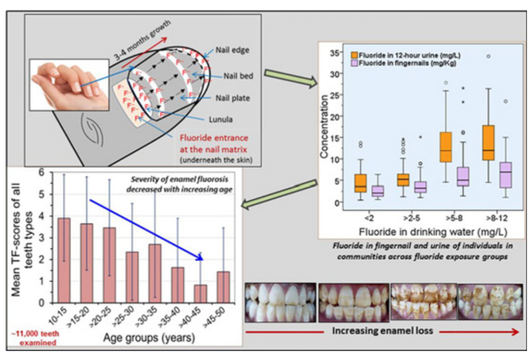
Tewodros Rango [a,*], Avner Vengosh [a], Marc Jeuland [b,e,f], Gary M. Whitford [c], Redda Tekle-Haimanot [d]

[a] Nicholas School of the Environment, Duke University, Durham, NC, USA
[b] Sanford School of Public Policy, Duke University, Durham, NC, USA
[c] Department of Oral Biology, College of Dental Medicine, Augusta University, Augusta, GA, USA
[d] Faculty of Medicine, Addis Ababa University, Addis Ababa, Ethiopia
[e] Institute of Water Policy, National University of Singapore, Singapore
[f] Duke Global Health Institute, Duke University, Durham, NC, USA

HIGHLIGHTS

- Relationships between F⁻ in water, fingernails, and urine; and enamel fluorosis (EF) were established.
- Fingernail F⁻ was assessed as a biomarker for EF in a high-F⁻ region for the first time.
- F⁻ biomarker levels were more related to children's EF than adults, indicating their greater F⁻ exposure⁻ during early childhood.
- Children's EF may be useful as a biomarker for other health effects that depend on early-life F⁻ exposure.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 8 February 2017
Received in revised form 29 March 2017
Accepted 4 April 2017
Available online 13 April 2017

Editor: F.M. Tack

Keywords:
Water quality
Biomarkers
Exposure timing

ABSTRACT

This study examined the relation between fluoride (F^-) concentrations in fingernail clippings and urine and the prevalence and severity of enamel fluorosis (EF) among Ethiopian Rift Valley populations exposed to high levels of F^- in drinking water. The utility of fingernail clippings as a biomarker for F^- exposure and EF was also assessed for the first time in a high-F^- region. The study recorded the EF status of 386 individuals (10 to 50 years old), who consume naturally contaminated groundwater with widely varying F^- concentration (0.6–15 mg/L). The mean F^- concentrations among residents of communities with primary reliance on groundwater were 5.1 mg/kg (range: 0.5–34 mg/kg) in fingernails and 8.9 mg/L (range: 0.44–34 mg/L) in urine. We show strong positive correlations between F^- in drinking water and 12-hour urinary excretion ($r = 0.74$, $p < 0.001$, $n = 287$), fingernail F^- content ($r = 0.6$, $p < 0.001$, $n = 258$), and mean individual measures of EF severity as measured using the Thylstrup and Fejerskov (TF) Index ($r = 0.42$, $p < 0.001$, $n = 316$). The data indicate that both fingernail and urine measures are good biomarkers for F^- exposure and EF outcomes, the latter being slightly more sensitive. Cases of moderate/severe EF were significantly more common among younger subjects (10 to 15 years old)

Abbreviations: ANOVA, Analysis of Variance; bw, body weight; BMI, body mass index; BEI, Biological Exposure Index; DDW, double deionized water; EF, enamel fluorosis; EARS, East African Rift System; F⁻, fluoride; IRB, Institutional Review Board; ISE, ion selective electrode; IQ, intelligence quotient; mg/L, milligram per liter; mg/kg, milligram per kilogram; mg/kg bw/day, milligram per kilogram body weight per day; HMDS, hexamethyldisiloxane; MCLG, Maximum-Contaminant-Level Goal; MUAC, mid-upper arm circumference; NOAEL, No-Observed-Adverse-Effects-Level; OLS, ordinary least squares; SMCL, Secondary-Maximum-Contaminant-Level Goal; SST, subscapular skinfold thickness; TISAB, total ionic strength adjuster buffer; TF Index, Thylstrup and Fejerskov Index; U.S. NRC, U.S. National Research Institute; U.S. EPA, U.S. Environmental Protection Agency; WHO, World Health Organization.

* Corresponding author at: Nicholas School of the Environment, 205 Old Chemistry Building, Box 90227, Duke University, Durham, NC 27708, USA.
E-mail address: tg67@duke.edu (T. Rango).

http://dx.doi.org/10.1016/j.scitotenv.2017.04.021

Enamel fluorosis
East Africa

than older subjects (mostly >25 years old) ($p < 0.001$), consistent with their greater exposure to F^- during early childhood, which is the only period of life the enamel is at risk of fluorosis. In this younger population, EF may be useful as a biomarker for identifying individuals with other potential health effects that depend on a specific age window of susceptibility. The finding of exceptionally high F^- concentrations in water, fingernail clippings and urine in this region should motivate further investigations of other potential health consequences such as bone disease and abnormalities in the function of the neurological and endocrine systems.

1. Introduction

An estimated 200 million people worldwide are at risk of adverse health effects from exposure to high concentrations of naturally occurring fluoride (F^-) in drinking water sources (Edmunds and Smedley, 2005; WHO, 2006). As a result, F^- has been named one of the top ten chemicals of public health concern (WHO, 2016). Low concentrations (0.5–1 mg/L) of F^- in drinking water are anticariogenic and fluoridation of drinking water has been shown to be a safe and sound public health intervention (CDC, 1999; Ayoob and Gupta, 2006; WHO, 2006; U.S. DHHS, 2011). Chronic ingestion of drinking water with a F^- concentration higher than the optimum level, however, has been shown to increase the risk of mild enamel fluorosis (EF), a pre-eruptive, developmental disorder that results in hypomineralized enamel. The stage of EF progresses in dose-response manner from mild (scattered white spots and mottled enamel), to moderate (discolored enamel), to severe EF (discolored enamel with discrete or confluent pitting, fractures, or loss of enamel in the severest cases) (Thylstrup and Fejerskov, 1978; Rozier, 1994; Den besten and Li, 2011). The first 6–8 years of life is the only period during which EF can occur because by that time the enamel has completed its development (Pendrys, 1990, 1999). Skeletal fluorosis (SF) is a bone disorder that manifests as osteosclerosis, ligament calcification, bone deformity, osteoporosis, susceptibility to bone fractures, and chronic joint and bone pain (Boivin et al., 1989; Tekle-Haimanot, 1990; Wang et al., 1994; Teotia et al., 1998).

A recent U.S. National Research Council (U.S. NRC, 2006) review report raised several other potential health concerns related to high F^- exposure including altered biochemical and physiological processes, cardiovascular, reproductive, endocrine, gastrointestinal, neurological consequences, and bone fractures. Furthermore, excessive F^- exposure is emerging as a potential neurotoxic agent in that it has been linked to lower intelligence quotient (IQ) in children (Grandjean and Landrigan, 2014; Choi et al., 2012; Tang et al., 2008). The research on these various potential health effects is fairly new and the findings require validation through well-designed and well-conducted population-based studies.

Over 25 countries worldwide have endemic environmental contamination with high levels of naturally-occurring F^- (Ayoob and Gupta, 2006). Ethiopia, is one of several countries with a substantial population living in the East African Rift System (EARS), a region that is extensively covered by volcanic materials, and that is known to be one of the global hotspots for high F^- contamination in groundwater (Rango et al., 2013, 2015; Žáček et al., 2015). Unlike surface water, groundwater supply to the local population is relatively safe from a microbiological perspective, and yet F^- leaching from volcanic aquifers that are characterized by complex lithology, and variation in depth coupled with unique geochemical processes, result in a wide range of F^- levels in groundwater (Rango et al., 2013). Concentrations in the Rift Valley wells typically range from ~1 to 10 times higher than the WHO standard of 1.5 mg/L, putting an estimated 10 million Ethiopians at risk of high F^- exposure in the region (Tekle-Haimanot, 2005; Rango et al., 2015).

The Rift Valley communities investigated in this study are mostly rural and predominantly rely on community-based groundwater wells used for drinking and cooking. This nearly exclusive sourcing, and the limited intake of F^- from other sources, provides a rare opportunity to generate a new and comprehensive dataset from a comparably homogenous population. Unlike previous work in the region, we have collected comprehensive data for a large sample of individuals that covers demographic variables, water quality measures, and multiple biomarkers, using well-designed methodologies, and sampling over a wide range of ages and exposures levels.

Biomarkers of F^- exposure can be evaluated using several biological tissues or fluids (i.e., teeth, bone, nail, hair, plasma, urine, and saliva) (Whitford, 2005; Rugg-Gunn et al., 2011). Urine is the main pathway of F^- elimination from the body, and excretion is proportional to total F^- intake (Whitford, 1996). Fluoride in plasma and other extracellular fluids is removed via uptake in bones and urinary excretion. In young children roughly 80% of absorbed F^- is retained within 24 h by calcified tissues; whereas in young to middle-aged adults, the retention is 30–50%, with the remainder being excreted in urine (Ekstrand et al., 1994; Whitford, 1996). In contrast to urine, F^- in fingernail clippings reflects the average plasma concentration of F^- that occurred over a protracted (1–2 week) period that represents past exposure roughly 3 to 4 months prior to collection (Levy et al., 2004; Whitford, 2005; Buzalaf et al., 2006; Buzalaf et al., 2012). Furthermore, once F^- is incorporated into nail at growth end, it will be unaffected by more recent F^- intake and physiological variables (Whitford, 2005). Fingernail analysis of F^- has previously been used to assess low-level exposures in communities with fluoridation of water, tooth paste, salt, and milk use (e.g., Buzalaf et al., 2011; Lima-Arsati et al., 2010; de Almeida et al., 2007; Buzalaf et al., 2006; Pessan et al., 2005; Levy et al., 2004; Whitford et al., 1999), but epidemiological studies that evaluate the suitability and sensitivity of this biomarker in populations with endemic fluorosis are virtually absent.

Our study aims to assess the concentrations of F^- in fingernail clippings and urine and relate them to the degrees or stages of EF in individuals of different ages with large differences in their chronic exposures to F^- Since the timing of well installations has varied across communities (10–56 years), as well as prior use of low F^- surface waters before the wells, the study also offers suggestive evidence on the importance of timing of exposure (early F^- exposure in childhood or later) in influencing EF severity and prevalence. We also investigated the relationship between F^- and Ca (calcium), Mg (magnesium), and Al (aluminum) in water and urine, given that these are known to influence exposure by binding with F^- in the digestive system and body fluids (Whitford, 1994; Sauerheber, 2013) and since these minerals play a significant role in tooth and bone formation. This work lays a foundation for follow-up studies in developing biomarkers to better understand a range of F^--related disorders that affect bones, joints, cartilage, and other non-mineralized tissues. There is a need to better understand such potential effects because these could add to already significant public health challenges that are facing affected populations in many parts of the world.

2. Materials and methods

2.1. Study area and population

The study area in the Ethiopian Rift Valley (Fig. S1) is part of the Great East African Rift Valley, which bisects the northeastern side of the African continent. The rift floor and the plateaus to the east and west that border the Rift floor have average altitudes of 1600 m and