International Journal of Hygiene and Environmental Health xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

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

Investigation of the relationship between low environmental exposure to metals and bone mineral density, bone resorption and renal function

A.C. Callan[a,c,*], A. Devine[b], L. Qi[d], J.C. Ng[d], A.L. Hinwood[c]

[a] School of Medical Sciences, Edith Cowan University, 270 Joondalup Drive, Joondalup WA 6027, Australia
[b] School of Exercise and Health Sciences, Edith Cowan University, 270 Joondalup Drive, WA 6027, Australia
[c] Centre for Ecosystem Management, Edith Cowan University, 270 Joondalup Drive, Joondalup WA 6027, Australia
[d] The University of Queensland, National Research Centre for Environmental Toxicology (Entox), 39 Kessels Road, Coopers Plains, Brisbane 4108, Australia

ARTICLE INFO

Article history:
Received 21 November 2014
Received in revised form 12 March 2015
Accepted 21 March 2015

Keywords:
Cadmium
Metals exposure
Bone density
KIM-1
Bone turnover
Menopausal

ABSTRACT

Environmental exposure to metals has been linked to adverse health outcomes. Exposure to cadmium has been associated with decreased bone density, an increased risk of osteoporotic fracture and possible renal dysfunction. Older women are a group at risk of renal and bone density impacts and exposure to metals may be an important risk factor for these health outcomes. This study was a cross sectional study of 77 women aged 50 years and above examining the relationship between metals exposure and renal and bone health. Urinary and blood metals concentrations, plasma creatinine, iron, ferritin and transferrin were measured in these subjects. Bone biomarkers assessed included the pyridinium crosslinks, pyridinoline and deoxypyridinoline measured by ELISA. Renal function was assessed using eGFR and KIM-1. Whole body, hip and lumbar spine bone mineral density was assessed using DEXA. Blood and urinary metals concentrations were generally low in the subjects, with a median urinary cadmium concentration of 0.26 μg/g creatinine (range <0.065–1.03 μg/g). Urinary cadmium was found to be a significant predictor of bone mineral density at whole body, lumber spine, total hip and femoral neck, with increasing urinary Cd concentrations associated with decreased bone density. Urinary cadmium and aluminium concentrations were positively correlated with bone resorption whilst blood zinc and mercury concentrations were negatively correlated. Urinary aluminium was positively correlated with KIM-1 concentrations, a marker of early kidney damage, however blood zinc concentrations were significantly negatively correlated with this biomarker. This study provides additional support for low cadmium exposure being of concern for the health of older women. Further investigation into the role of exposure to other metals on bone and renal health is warranted.

Introduction

Environmental exposure to metals can cause health impacts if exposure is at sufficiently high concentrations. It has been established that exposure to cadmium affects bone and renal health in older women; specifically increasing the risks of osteoporosis, fracture and renal dysfunction, especially in populations occupationally exposed or residing in close proximity to areas with known contamination (Jarup et al., 1998a; Kido et al., 1990). More recently, studies have demonstrated an increased risk of osteoporosis in older women whose urinary cadmium concentrations were lower than previously observed, <2 μg/g creatinine (Akesson et al., 2006; Wu et al., 2010). These effects have been confirmed by Gallagher et al. (2008) where lower concentrations of urinary cadmium, 0.5–1 μg/g creatinine, increased the odds (OR = 1.43) of diagnosed osteoporosis, compared with concentrations <0.5 μg/g creatinine and by a meta-analysis of 7 cross sectional studies (including Gallagher et al., 2008) that reported increasing odds ratios of osteoporosis associated with increased urinary cadmium (James and Meliker, 2013). Associations have also been observed between plasma zinc and lead and forearm T-scores in osteoporotic women (Sadeghi et al., 2014). In the NHANES III study of blood lead and cadmium, frailty was increased in those with increased lead concentrations (Garcia-Esquinas et al., 2015).

* Corresponding author at: School of Medical Sciences, Edith Cowan University, 270 Joondalup Drive, Joondalup WA 6027, Australia. Tel.: +61 8 6304 2349; fax: +61 8 6304 5509.
E-mail address: a.callan@ecu.edu.au (A.C. Callan).

http://dx.doi.org/10.1016/j.ijheh.2015.03.010
1438-4639/

Assessment of cadmium exposure is typically based on urinary cadmium concentration which is influenced by past exposure, current exposure, metabolism and diet. The mechanisms by which cadmium elicits negative health effects include direct effect on bone cells, skeletal formation and increasing resportion independent of the renal system (Bhattacharyya, 2009), and indirect effects via reduced calcium resorption from impaired renal function causing hypercalciuria leading to increased bone demineralisation (Schutte et al., 2008). Nambunmee et al. (2010) showed that at high cadmium concentrations in urine, effects on renal function were observed which accelerated bone resorption and reduced calcium resorption.

Cadmium is stored and retained in the kidney and the liver for decades (10–30 years) (Jarup et al., 1998b), with peak cadmium concentrations reached in the kidney between 40 and 60 years of age (Satarug et al., 2003). Small amounts of cadmium are released over time and biological cadmium concentrations in urine are proportional to the amount stored (Akerstrom et al., 2013). Blood concentrations reflect short term cadmium concentrations and urinary cadmium reflect lifetime exposures, with the skeleton only containing very small amounts of cadmium (Jarup, 2003).

For women, menopause increases the rate of bone loss due to higher bone turnover (Riggs et al., 1998). Prior to menopause, women are at an increased risk of gastrointestinal absorption of cadmium when iron stores are low. As the iron requirements of women decrease at menopause, the absorption of dietary cadmium will also decrease, however, health effects arising from exposure may occur at this time as it coincides with peak renal cadmium (Vahter et al., 2004). It is therefore important to assess the health effects associated with cadmium exposure in this population group. The simultaneous exposure to other metals, through diet for example, or increased blood metals concentrations through endogenous release of metals through age related bone resorption may confound the results of studies of cadmium exposures and therefore also need to be considered.

Pyridinium crosslinks of collagen are excreted in urine and can be measured as a specific biomarker of bone resorption (McLaren et al., 1992). Kidney Injury Molecule 1 (KIM-1) has been suggested to be a prodromal biomarker of kidney damage, and a means to sensitively detect early kidney tubular injury (Ichimura et al., 1998; van Timmeren et al., 2007). However, to date there are few reports of ranges of KIM-1 in individuals without kidney disease and limited investigation of the utility of this biomarker as an indicator of renal effects of low cadmium exposure (Pennemans et al., 2011; Ruangyuttikarn et al., 2013). This study has combined the measurement of metals exposure, biomarkers of bone and kidney disease, and bone mineral density to investigate the relationship between exposure to metals and these outcomes in Australian women aged 50 years and above.

Materials and methods

Subjects

This study was a cross sectional study of metals exposure in non-smoking women aged 50 years and above in Western Australia. Seventy seven West Australian women were recruited via email or paper-based flyers at the university, sporting clubs, leisure centres, retirement villages and age specific organisations. Exclusion criteria included current smokers, those taking medication, or with a condition known to affect bone metabolism, a diagnosis of osteoporosis or a previous osteoporotic fracture; or currently or within last year taking medication for osteoporosis apart from calcium or vitamin D; steroid use; clinical diagnosis of diabetes and renal insufficiency. All procedures followed were in accordance with institutional guidelines. The present study was conducted in accordance with the Declaration of Helsinki and all procedures involving human subjects were approved by Edith Cowan University Human Research Ethics Committee (#6879). All participants provided written informed consent. All data was collected between October and December 2011.

Questionnaire

Participants completed a questionnaire that included questions relating to demographic information, smoking history and exposure to environmental tobacco smoke, characteristics of the home (including recent renovations), employment history, medical history including menopausal status, lifestyle factors and other activities that may increase metals exposure.

Dietary assessment

The questionnaire contained a food frequency component which listed a range of food items, including those known to be sources of dietary metals exposure (Callan et al., 2014) and requested that participants state the frequency with which they typically consumed these items (in portions per week or per month). Total fish and seafood consumption per month was estimated by adding the reported frequencies of consumption of each type of fish, with weekly values multiplied by 4 to generate a monthly frequency. In addition, participants completed a 24 h diet record using household measures which was reviewed by a dietitian for completeness. These data were analysed using FoodWorks Professional Edition (version 7, Xyris Software, QLD) with intake of macro and micronutrients calculated.

Urine sample

First morning void urine samples were collected midstream into a 60 mL sterile plastic container and aliquoted before being stored at −20 °C until analysis of metals and other biomarkers.

Blood sample

Venous blood samples were collected into two 6 mL NH Trace Elements Sodium Heparin vacuettes (Greiner Bio-One, Austria). One tube of whole blood was stored at −20 °C prior to analysis of metals. The second tube was centrifuged immediately at ≥1300 RCF for 15 min at room temperature and the plasma extracted and stored at −20 °C prior to analysis.

Biochemistry

Plasma iron, ferritin and transferrin were measured using standard methods (Pathwest, Department of Health WA). Urine creatinine was measured by the Jaffe reaction using a discrete analyser (Labmedics/Thermo Fisher Aquakem 250, ChemCentre WA).

Urine pyridinoline and deoxypyridinoline, markers of type I collagen resorption were measured in duplicate by ELISA (Microvue PYD, Quidel, USA) (Gomez et al., 1996) according to manufacturers' instructions (Quidel, ns.). Kidney Injury Molecule-1 (KIM-1) was quantified in duplicate in urine samples using Milliplex® Human Kidney Toxicity Panel 4 with magnetic beads (Millipore) on the Luminex® xMAP® platform using standard techniques. Estimated glomerular filtration rate (eGFR) was calculated for each participant using the Modification of Diet in Renal Disease (MDRD) study equation (Levey et al., 2006):

Please cite this article in press as: Callan, A.C., et al., Investigation of the relationship between low environmental exposure to metals and bone mineral density, bone resorption and renal function. Int. J. Hyg. Environ. Health (2015), http://dx.doi.org/10.1016/j.ijheh.2015.03.010