Prevalence of Environmental Acquired Cadmium Nephropathy among smokers

Thesis submitted for partial fulfillment of MD degree in internal medicine

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List of abbreviations

1N	…….	1 normal.
ACR	…….	Albumin/creatinine ratio .
ADPKD	…….	Autosomal dominant polycystic kidney disease.
AMD	……..	Anterior macular degeneration.
ATSDR	……..	Agency for Toxic Substances and Disease Registry
α1-M	…….	α1- microglobulin.
B-Cd	…….	blood cadmium.
BP	…….	blood pressure.
BAL	…….	British anti-lewisite.
β2-MG	…….	Beta 2 microglobulin.
Cadmibel	…….	Cadmium in Belgium study .
Cd	…….	Cadmium.
Cd-MT	…….	Cadmium-metallothionein complex.
Cr	…….	Creatinine.
CrCl	…….	Creatinine clearance.
CdO	…….	Cadmium oxide.
DEXA	…….	Dual-energy X-ray absorptiometry.
DBP	…….	Diastolic blood pressure.
DM	…….	Diabetes mellitus.
DMSA	…….	Dimercaptosuccinic acid.
eCrCl	…….	estimated creatinine clearance.
EDTA	…….	ethylene-diamine-tetraacetic acid.
eGFR	…….	estimated glomerular filtration rate.
ESRD	…….	End stage renal disease.
FAO	…….	Food and Agriculture Organization.
FF	…….	Filtration fraction.
GBM	…….	Glomerular basement membrane.
GFR	…….	Glomerular filtration rate.
HHS	…….	U.S. Department of Health and Human Services
HOPE	…….	Heart Outcomes Prevention Evaluation
HTN	…….	Hypertension
HS	…….	Highly significant
HUVS	…….	Hypo-complementemic urticarial vasculitis syndrome.
IARC	…….	International Agency for Research on Cancer.
IMN	…….	Idiopathic membranous nephropathy.
IRT	…….	Iron-regulated transporter.
JECFA	…….	Joint Expert Committee on Food Additives
Kg	…….	Kilogram.
Kim	…….	Kidney injury molecule.

LMW	…….	Low molecular weight protein.
LOAEL	…….	lowest observed adverse effect level.
LSD	…….	Least significant difference.
MRFIT Trial.	…….	Multiple Risk Factor Intervention
MT	…….	Metallothionein.
NAG	…….	N-acetyl-β-d-glucosaminidase.
NaOH	…….	Sodium hydroxide
NHANES Examination Survey.	…….	National Health and Nutrition
OSCAR factor study.	…….	Osteoporosis Cadmium as a Risk
OSHA Administration	…….	Occupational Safety and Health
PAD	…….	Peripheral arterial disease.
POD	…….	Point of departure .
PTWI	…….	Provisional tolerable weekly intake.
PY	…….	Pack-years.
RBP	…….	Retinol-binding protein .
RBPU	…….	Urinary retinol binding protein.
RPF	…….	Renal plasma flow.
S	…….	Statistically significant.
SBP	…….	Systolic blood pressure.
U-Alb	…….	Urine albumin.
U-Cd	…….	Urine cadmium.
WHO	…….	World Health Organization.
Xg in relation to gravity.	…….	A unit to measure centrifugation force
Yrs	…….	years.
ZIP	…….	ZRT/IRT - Related Protein.
ZRT	…….	Zinc –regulated transporter.

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INTRODUCTION

Up to date, there is no physiological function for cadmium, this raises the possibility of its potential biohazards **(Godt et al., 2006).**

Cadmium (Cd) is one of the most toxic elements to which man can be exposed at work or in the environment. Once absorbed, Cadmium is efficiently retained in the human body, in which it accumulates throughout life **(Bernard., 2008b).**

Cadmium is a cumulative nephrotoxicant that is absorbed into the body from dietary source (plants grown in contaminated soil, or fish from contaminated water) and cigarette smoking. The levels of Cd in organs such as liver and kidney cortex increase with age because of the lack of an active biochemical process for its elimination coupled with renal reabsorption (**Satarug et al., 2004**).

Basically, there are three possible ways of cadmiu reabsorption: Gastrointestinal, pulmonary and dermal. The uptake through the human gastrointestinal is

approximately 5% of an ingested amount of cadmium, depending on the exact dose and nutritional composition **(Jin et al., 2002).**

The tobacco plant naturally accumulates relatively high concentrations of cadmium in its leaves. Thus, smoking tobacco is an important source of exposure, and the daily intake may exceed that from food in the case of heavy smokers. Cigarette smoking can cause significant increases in the concentrations of cadmium in the kidney, the main target organ for cadmium toxicity **(WHO, 2010).**

The major source of inhalative cadmium intoxication is cigarette smoke. The human lung resorbes 40–60% of the cadmium in tobacco smoke **(Godt et al., 2006).**

A 50 year-old average non-smoker has a cadmium body burden of 15 mg. While a comparable life-long smoker shows a value of 30 mg. Smokers generally have cadmium blood levels 4–5 times those of non-smokers **(Godt et al., 2006).**

Chronic exposure to Cd, an industrial and environmental pollutant, can cause both renal proximal tubular damage and decline in

glomerular filtration rate (GFR) in humans **(Thijssen et al., 2007).**

After pulmonary and/or gastrointestinal absorption, Cd binds to serum albumin and accumulates in the liver, where it is complexed to a metal-binding protein with a high affinity for Cd, metallothionein-1 **(Coyle et al., 2002).**

The Cd-metallothionein-1 complex reaches the kidney where it is filtered and accumulates in the proximal tubule, whose cells possess transporters for free and bound forms of Cd and interferes with the tubular function **(Ferarro et al., 2010).**

The main organ for long-term cadmium accumulation is the kidney. Here the half-life period for cadmium is approximately 10 years. A life-long intake can therefore lead to a cadmium accumulation in the kidney, consequently resulting in tubular cell necrosis **(Godt et al., 2006).**

Data from human studies suggested that there is a latency period of approximately 10 years of cadmium before clinical onset of renal damage, depending on intensity of exposure. However, subtle

alterations of renal function have been described after acute exposure in animals, and there are rare reports of renal cortical necrosis after acute high-dose exposure in humans **(ASTDR,2008).**

The earliest manifestation of Cd-induced renal damage is the increased urinary excretion of microproteins (molecular weight <40 kD). Among these proteins, β2-microglobulin, retinol-binding protein and alpha1-microglobulin have been the most validated for the routine screening of tubular proteinuria. The increased loss of these proteins in urine is a reflection of the decreased tubular reabsorption capacity **(Bernard .,2008b).**

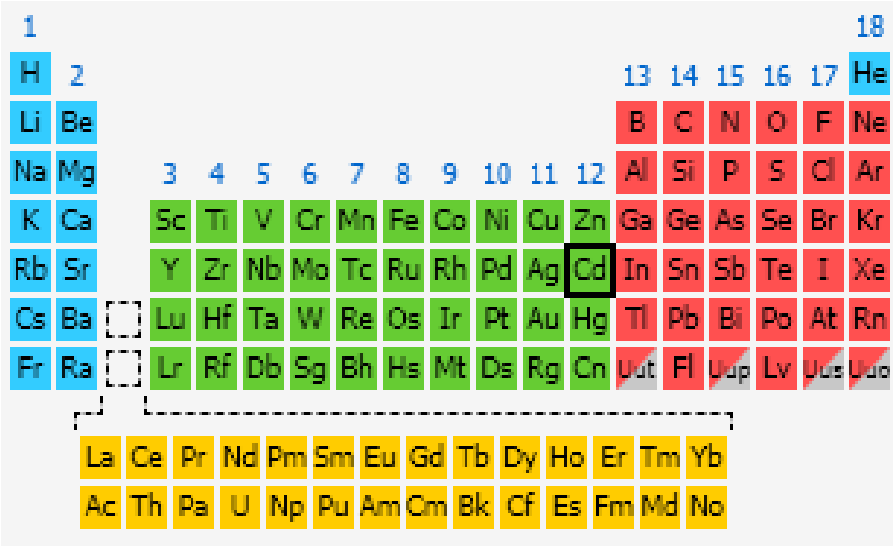
The abnormal urinary excretion of low molecular weight proteins, calcium, amino acid, phosphate and glucose observed in cadmium-exposed individuals share some similarities with Fanconi's syndrome, a genetic disorder of renal tubular transport (**Satarug et al., 2010).**

In general, the urinary cadmium level reflects the body burden over long-term exposure before the development of kidney damage, and blood cadmium is considered an indicator of recent exposure (**Satarug et al., 2010).**

Chapter(1)

Cadmium sources and health hazards

Cadmium (group IIB of the periodic table of elements) (see figure 1) is a heavy metal posing severe risks to human health. Till now , it could not be shown that cadmium has any physiological function within the human body. Interest has therefore risen in its biohazardous potential **(Godt et al., 2006).**



Figure(1): Cadmium in periodic table.

Cadmium is a toxic metal occurring in the environment naturally and as a pollutant emanating from industrial and agricultural sources. Food is the main source of cadmium intake in the non-smoking population. The bioavailability, retention and toxicity are affected by several factors including nutritional status such as low iron status **(Järup and Akesson, 2009).**

Cadmium is efficiently retained in the kidney (half-time 10-30 years) and the concentration in kidney tissue is proportional to that in urine (U-Cd). Cadmium is nephrotoxic, initially causing kidney tubular damage. Cadmium can also cause bone damage, either via a direct effect on bone tissue or indirectly as a result of renal dysfunction. After prolonged and/or high exposure the tubular injury may progress to glomerular damage with decreased glomerular filtration rate, and eventually to renal failure **(Järup and Akesson, 2009).**

Cadmium has been recognized as an occupational health hazard for many decades. In the general population, in the absence of specific industrial exposure, the main sources of exposure being food and tobacco smoke. During the last decade an increasing number of studies have found adverse health effects at much lower levels than in the earlier studies **(Järup and Akesson, 2009).**

Cadmium sources:

A.Non occupational sources of cadmium exposure(food and smoking):

Cigarette smoking is likely the most important source of cadmium exposure among smokers. Among non-smokers, consumption of specific foods is associated with increased urine cadmium concentration **(Adams et al ., 2011).**

1.Food as a major source of cadmium among non smokers:

Diet is the main source of environmental cadmium exposure in non-smokers in most parts of the world. Atmospheric deposition of airborne cadmium, mining activities and the application of cadmium containing fertilizers and sewage sludge on farm land may lead to the contamination of soils and increased cadmium uptake by crops and vegetables grown for human consumption.

Cadmium is present in virtually all foods, but the concentrations vary to a great extent, depending on type of food and level of environmental contamination. High concentrations of cadmium are present in molluscs and crustaceans. Also, high levels

are also found in offal products such as liver and kidney, especially from older animals.

Food from plants generally contains higher concentrations of cadmium than meat ,egg ,milk and dairy products. Among food from plants ,cereals such as rice and wheat, green leafy vegetables, potato and root vegetables such as carrot and celeriac contain higher concentration than other food from plants. The cadmium concentration in wheat is higher in the bran than in wheat flour**(Järup and Akesson, 2009).**

Based on estimation of cadmium intake, more than 80% of the food-cadmium comes from cereals, vegetables and potato **(Olsson et al., 2002)**. The average cadmium intake from food generally varies between 8 and 25µg per day **(Egan et al., 2007).**

The intake of cadmium may be higher in certain population with specific dietary habits. For example, vegetarians and high consumers of shell fish are groups that have a higher intake of cadmium than omnivores. Cadmium in drinking water contributes only to less than a few percent of the total cadmium intake **(Olsson et al., 2002).**

Analysis of dietary data among women with no reported history of smoking suggested that regular consumption of eggs , hot cereals, organ meats , tofu (curd made from mashed soya beans used chiefly in vegeterians), vegetable soups , leafy greens, green salad, and yams was associated with increased U-Cd. Consumption of tofu products showed the most robust association with U-Cd. U-

Cd was estimated to be 0.11 µg/g higher among women who consumed any tofu than among those who consumed none **(Adams et al ., 2011).**

Sunflower seeds, peanuts and flaxseed, accumulate cadmium from the soil in a manner similar to that of tobacco. Cadmium levels in sunflower kernels range from 0.2 to 2.5 mg/ kg. evidence for kidney effects, reflected by urinary beta 2 microglobulin (β2-MG) and N-acetyl-β-d-glucosaminidase (NAG) levels, was found among high consumers of sunflower seeds. These data may indicate that cadmium in sunflower kernels possess a high nephrotoxic potential **(Satarug et al ., 2010).**

In a study done by Huang et al. in Korea, intake of Cd from food was estimated at 7.07 µg /day or 0.12 µg/kg/day and was higher in males (8.25 µg/day, 0.13 µg/kg/day) than in females (6.37 µg/day, 0.11 µg/kg/day). As shown in table(1), major food stuffs responsible for Cd intake in this study were grains (32.8%), fish, and shellfish (23.8%), and vegetables (20.4%) **(Huang et al .,2013).**