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Research Article

Dyslipidemia in the Elevated Cadmium Exposure Population

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ABSTRACT
Excessive cadmium (Cd) exposure has been reported to cause alter and disorder lipid metabolism and lipid compounds in tissue and circulation. Cd-induced renal toxicity is caused from increased oxidative stress production at the cellular level and induced cell apoptosis. We examined the association of elevated Cd exposure with dyslipidemia, oxidative stress and chronic kidney disease (CKD) in 258 residents of the Cd exposure area. Elevated Cd exposure was significantly correlated with triglycerides/high-density lipoprotein-cholesterol (TG/HDL-C) ratio, malondialdehyde (MDA), N-acetyl-β-D-glucosaminidase (NAG) and negatively correlated with total antioxidants capacity (TAC) and estimated glomerular filtration rate (eGFR). Elevated Cd exposure may cause hypertriglyceridemia, low high-density lipoprotein-cholesterol (HDL-C), high TG to HDL-C ratio, oxidative stress and CKD. Our study demonstrated that excessive Cd exposure associated with hypertriglyceridemia, reduced HDL-C, elevated TG/HDL-C ratio, oxidative stress and CKD in residents of Cd contaminated area.

Keywords: Cadmium, hypertriglyceridemia, high-density lipoprotein-cholesterol, TG/HDL-C ratio, chronic kidney disease

INTRODUCTION

Cadmium (Cd) exposure is a one toxic metal contributed to organ dysfunction or damage. Its presence in the general environment or an industrial pollutant is a public health concern [1]. Environmental Cd contamination affected 13 villages of the district of Mae Sot in Tak Province, northwestern Thailand. Environmental Cd contaminated areas were caused from the two creeks running through the zinc mine as described in our recent studies[2- 4]. Acute toxicity is effectible for injuries to the lungs testes and liver[1,5]. Chronic exposure leads to renal insufficiency, end-stage renal failures, renal complications, airway obstruction diseases, emphysema, neurologic, bone disorders, urinary stone, immune-suppression, increased blood pressure, diabetic and cardiovascular diseases[1,3,5].

Kidney is the major organ for Cd-induced damage when Cd accumulates in the proximal tubule it causes renal tubular dysfunction or insufficiency and may progress to end stage of renal disease[1,5]. Cd-induced renal toxicity is caused from reactive oxygen species (ROS) formation at the cellular level[6], increased DNA damage[3] and induced cell apoptosis[7]. Our recent study demonstrated that elevated Cd exposure associated with increased oxidative stress and oxidative DNA damage in the population of Cd contaminated area[3]. The mechanisms of Cd induced oxidative stress toxicity are unclear. Cd does not generate free radicals but there is increased lipid peroxidation in various tissues after Cd exposure[8] and reduction in various antioxidants systems[9]. In animal studies, Cd can inhibit and disturb numerous enzymes and metabolic processes in lipid metabolism [10] and alter lipid compounds in tissue and circulation, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) to cause dyslipidemia[9-11]. Altered lipid profiles and/or dyslipidemia from the underlying etiology represent the pathogenesis of important degenerative diseases, including cardiovascular diseases and T2DM[12]. Therefore the aims of the present study to validate a possible association between increased Cd exposures with the alteration in lipids profiles in residents exposed to environmentally cadmium.

MATERIALS AND METHODS

This cross-sectional study was based on data of our health survey evaluation (during January 2010–January 2011). A total 534 volunteer subjects who were 30 years or older

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participated in this health survey evaluation. Two hundred fifty eight subjects were randomly selected from 13 Cd-contaminated villages and 276 subjects from non-Cd- contaminated villages in the same province were also randomly selected from the health survey evaluation as the control group. A questionnaire survey was conducted by trained health workers about demographic characteristics, occupational history, residency time, medical history of diabetes, hypertension, renal diseases, cancers, smoking and alcohol consumption. We excluded the 65 subjects with known end stage renal failure, cancer, infection and any life threatening diseases from the study. All participants provided written informed consent and agreed to participate and provide blood and urine samples for this study. Our study protocol was approved by the Ethic committees of Naresuan University (51 02 04 0043).

Blood and urine samples collection

Fasting venous blood was collected from all participants. Plasma glucose (Glu), blood urea nitrogen (BUN), TC, TG, HDL-C were measured by enzymatic method. Serum and urine creatinine (UCT) concentration was determined based on the Jaffe reaction using a Hitachi 912 auto-analyzer (Roche Diagnostic, Switzerland) at the laboratory of Medical Technology, Faculty of Allied health Sciences. LDL-C concentrations were calculated with Friedewald's formula in specimens with TG levels <400 mg/dl. TG/HDL-C ratio was calculated by TG divide by HDL-C concentrations (in mg/dl). Urine samples were collected in polyethylene bottles after physical examination, anthropometric measurements and blood taken. A 30-ml of urine sample from each subject was collected and divided into three aliquots (5-10 ml each), one for microscopic and other aliquots for cadmium, N-acetyl-β-D-glucosaminidase (NAG) and UCT.

Urinary Cadmium determination

Urinary Cd was determined by a graphite tube atomic-absorption spectrometer (Varian Model AA280Z, USA) at the Bangkok-Pathology Laboratory, a private reference clinical laboratory. Standards of low concentrations were freshly prepared by serial dilution with 20% (w/v) nitric acid. Bio-Rad lymphocheck urine control and Seronorm trace elements urine control (Nycomed As, Oslo, Norway) were performed for quality control of urine metal determination. Diammonium hydrogen phosphate was used as matrix modifier. Cd was measured at 228.8 nm by standard addition method. Cd concentration in urine was presented after correction for creatinine concentrations. The within-run assay coefficients of variation ranged from 2.8% to 13.6%. The external quality assurance program from the External Quality Assessment Scheme of Medical Sciences center of Thailand, laboratory measures were within 10% of reference means for urinary Cd ($r^2 = 0.97$).

Malondialdehyde (MDA) assay

MDA level was determined in serum samples by using the thiobarbituric acid substances (TBARS) assay, a spectroscopic techniques as our previously report[13]. The method is based on the reaction of one molecule of MDA with 2 molecules of TBA to yield a pink chromophore with absorption maximum at 532 nm.

Total antioxidants capacity (TAC) assay

The assay is based on the reaction of metmyoglobin with hydrogen peroxide to form ferryl myoglobin, a free radical species. Then, add with a chromogen of 2, 2'-amino-di-[3-ethylbenzthiazole sulphonate] to react with ferryl myoglobin to form a radical cation which has a relatively stable blue-green color that can be measured at 600 nm. Antioxidants in the added serum sample can suppress this color production to a degree proportional to their concentration. The assay was calibrated using 6-hydroxy-2, 5, 8-tetramethylchroman-2-carboxylic acid (Trolox) and the results were expressed as mmol/l trolox equivalent [14]. The within–run coefficient of variation for the TAC assay in control material assay was 4.8% (n=10).

Renal function

All participants had no clinically identified renal organ damage, defined as a serum creatinine level lower than 159.12 μmol/l (1.8 mg/dl) and serum BUN level lower than 7.14 mmol/l (20 mg/dl). Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) equation[15]. The formula is as: eGFR = 186 * [plasma creatinine $^{-1.154}$] * (age) $^{-0.203}$ * (0.742 if female) * (1.210 if African-American). Five eGFR stages were used: Stage I was normal eGFR (≥90ml/min/1.73 m^2); Stage II was mildly eGFR (60-89 mL/min/1.73 m^2); Stage III was moderately eGFR (30-59 ml/min/1.73 m^2); Stage IV was severely eGFR (<30 ml/min/ 1.73 m^2), and Stage V was end-stage renal disease: eGFR (<15 ml/min/1.73 m^2). An eGFR lower than 60 ml/min/1.73 m^2 (moderately eGFR) was defined as chronic kidney disease (CKD)[16].

Urinary NAG (UNAG) assay

Urinary NAG assay is base on enzyme NAG in urine which reacts with p-nitrophenyl-N-acetyl- β -D-glucosaminide substrate in sodium citrate buffer (pH 4.4) at 37 ºC to liberate p-nitrophenylate ion, then adding 2-amino-2-methyl-1-propanol (AMP) buffer (pH 10.25) into the reaction and measuring the reaction product with spectrophotometry at 405 nm [17]. The within–run and between-run coefficient of variation for NAG assay in control material assay was 3.14% and 4.11% (n=10).

Statistical analysis

The distributions of variables were expressed in arithmetic mean and standard deviation. Comparisons between groups were performed using the student's t-test. Bivariate correlations were performed by using Pearson correlation test. Odds ratios (OR) from logistic regression analysis were used to estimate the risk of hypertriglyceridemia, reduced HDL-C, elevated TG/HDL-C ratio, oxidative stress and CKD that was associated with elevated Cd exposure. The results of all analysis were evaluated for statistical significance using *p*-value <0.05 and the 95% confidence intervals (CI) by using the SPSS version 13.0 (SPSS, Chicago, IL).

RESULTS

Table 1 Comparison of general characteristics of the cadmium exposure with non-cadmium exposure population in Mae-Sot district, Tak province

Parameter	Cd exposure (n=258)	Non exposure (n=276)	*p*- value
Age (yr)	55.32 ± 12.07	54.07± 9.89	0.195
BMI (kg/ m^2)	22.14± 3.83	23.96± 3.98	<0.001
Systolic BP (mmHg)	129.12± 15.37	120.32 ± 11.04	<0.001
Diatolic BP (mmHg)	79.93± 10.18	77.87±6.59	0.006
Cd (µg/g CT)	9.76± 5.58	1.14± 1.18	<0.001
NAG (U/g CT)	6.45± 6.50	2.50± 2.86	<0.001
eGFR (ml/min/1.73 m^2)	56.65± 16.41	72.71± 19.67	<0.001
Glucose (mg/dl)	93.82± 23.22	88.09± 12.32	<0.001
BUN (mg/dl)	14.07± 4.37	11.78± 2.13	<0.001
CT (mg/dl)	0.97± 0.22	0.91± 0.17	0.001
TC (mg/dl)	199.2± 49.3	206.1± 35.1	0.065
TG (mg/dl)	181.9± 157.5	131.9± 62.6	<0.001
HDL-C (mg/dl)	44.1± 11.6	60.5± 16.5	<0.001
LDL-C (mg/dl)	118.6± 43.2	119.3± 30.3	0.844
TG/HDL-C ratio	4.93± 6.34	2.51± 1.75	<0.001
MDA (µmol/l)	6.35± 2.01	4.11± 1.06	<0.001
TAC (µmol/l Trolox equiv/l)	397.74±28.98	428.45± 34.61	<0.001
Smoking	142(55.0%)	28(10.1%)	<0.001
Alcohol drinking	120(46.5%)	28(10.1%)	<0.001

Data are mean±SD for all variables and n (%), *BP* blood pressure, *Cd* cadmium, *g CT* gram creatinine, *NAG* N-acetyl-β-D-glucosaminidase, *eGFR* estimated glomerular filtration rate, *BUN* blood urea nitrogen, *CT* creatinine, *TC* total cholesterol *TG* triglycerides *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *MDA* malondialdehyde, *TAC* total antioxidants capacity

A total of 258 residents (aged 55.32 ± 12.07 yrs) who lived in the cadmium-contaminated villages participated in this study and 276 residents (aged 54.07 ± 9.89 yrs) in the non-cadmium contaminated villages served as the comparison group. Out of the participants, 166 (31.1%) were male [113 (43.8%) were exposed] and 368 (68.9%) were female [145 (56.2%) were exposed]. The characteristics of the study population are shown in Table 1. Residents of Cd-exposed were significantly higher in BP, urinary cadmium, NAG, BUN, TG, TG/HDL-C ratio, MDA, smoking and alcohol consumption and lower in BMI, HDL-C, TAC and eGFR than residents of non Cd-exposed area ($p<0.05$). No significant difference in TC and LDL-C levels. Bivariate correlations demonstrated urinary cadmium levels showed the positive correlation with NAG (r = 0.293, p <0.001), MDA (r = 0.167, p 0.005), TG/HDL-C ratio (r = 0.163, p 0.007) and negative correlation with eGFR (r = -0.148, p = 0.017) and TAC (r = -0.244, p <0.001) while the other bivariate correlations were demonstrated in Table 2. We also analyzed the association of the elevation of Cd exposure and hypertriglyceridemia, reduced HDL-C, elevated TG/HDL-C ratio, increase oxidative stress and CKD after adjusting for BP, gender, age, smoking and alcohol drinking by using multiple logistic regression analysis. The risk of hypertriglyceridemia OR was 2.81 (95% confidence interval (CI): 1.72-4.60), elevated TG/HDL-C ratio OR = 3.78 (95% CI: 2.27-6.30), reduced HDL-C OR = 5.63 (95% CI: 3.33-9.53), increase oxidative stress OR = 4.48 (95% CI: 2.17-9.24), chronic kidney disease OR = 3.99 (95% CI: 2.36-6.71) after adjustment for smoking, alcohol drinking, gender and age as shown in Table 3 A-C.

DISCUSSION

Chronic Cd exposure leads to renal insufficiency, end-stage renal failures, renal complications[1,3,5]. We found that residents of Cd exposure area were significantly higher in Glu, BUN and CT levels but still in normal range while increased NAG and reduced eGFR levels. The results suggest that both NAG and eGFR were the better sensitive markers for renal dysfunction than BUN and CT. Increased Cd exposure caused increased oxidative stress and increased lipid peroxidation to increase 8-OHdG concentration as one of DNA damage products, it has been demonstrated in our recent study, and lower TAC levels in elevated Cd exposure population[3]. Mechanisms of Cd increased oxidative stress are uncertain. In a rat model, treatment with single dose of 30 nmol/kg Cd chloride caused carcinogenesis, lipid peroxidation overproduction, increased iron ion and H_2O_2 levels in Leydig cells of testis[18]. Many studies have tried to identify the mechanism(s) of Cd-increased oxidative stress. In Cd exposed cells, tissues and organs affects the thiol residue molecule to cause intracellular glutathione (GSH) and cellular antioxidant enzymes reductions to cause intracellular oxidative stress by ROS accumulation[19-21]. Mechanism of Cd substituting for zinc in the metabolic processes when metallothionein is present and displacement of endogenous iron and copper metals from the different cytoplasmic membrane increase metal ion concentrations to cause ROS overproduction via Fenton reactions[22-24]. These results support the idea

Table 2 Correlation of all variables among high urine cadmium levels

Correlation between parameters		Correlation coefficient	
		r	*P*- value
Cd/g CT	TG/HDL-C	0.163	0.007
	eGFR	-0.148	0.017
	NAG/gCT	0.293	<0.001
	MDA	0.167	0.005
	TAC	-0.244	<0.001
NAG /g CT	Age	0.257	<0.001
	eGFR	-0.505	<0.001
	TG/HDL-C	0.126	0.043
	Glu	0.212	<0.001
	BUN	0.187	0.003
	CT	0.183	0.003
	TC	0.132	0.034
	TAC	-0.213	<0.001
eGFR	BMI	0.445	<0.001
	TAC	0.153	0.014
	CT	-0.351	<0.001
Glucose	BUN	0.152	0.014
	CT	0.138	0.027
	HDL-C	-0.308	<0.001
	TG/HDL-C	0.160	0.010
BUN	CT	0.507	<0.001
	HDL-C	-0.149	0.017
	eGFR	-0.332	<0.001
	TG/HDL-C	0.134	0.031
TG	CT	0.123	0.048
	HDL-C	-0.374	<0.001
	TG/HDL-C	0.962	<0.001
	LDL-C	-0.161	<0.001
HDL-C	CT	-0.139	0.026
	LDL-C	0.164	0.008
	TG/HDL-C	0.962	<0.001
LDL-C	TG/HDL-C	-0.202	0.001
MDA	HDL-C	-0.139	0.021
	TAC	-0.171	0.004
Age	BMI	-0.310	<0.001
	BUN	0.258	<0.001
	CT	0.305	<0.001
	eGFR	-0.566	<0.001

that ROS and/or increased lipid peroxidation play the critical role in Cd-induced cells, tissues or organs damage and carcinogenesis.

Recent studies demonstrated significant imbalance in pro-oxidant/oxidant and antioxidant activities in patients with renal dysfunction[25,26] and have been found increased oxidative stress in the early stages of CKD. Increased oxidative stress from Cd exposure and from CKD stages accelerated the oxidative damage in the residents of Cd exposure areas. Oxidative stress is an extra risk factor that may accelerate atherosclerosis and glomerulosclerosis. Oxidative stress may cause inappropriate activation in vascular injury and the progression of atherosclerosis. The main atherosclerosis amplification occurs by direct oxidative damage the cellular components leading to defective cellular function, ageing and apoptosis by activation of signaling pathways[27].

Table 3A Impact of the association of elevated cadmium exposure with variables

Variables	Elevated cadmium exposure		
	OR	95% CI	*P-value*
Hypertriglyceridemia	2.81	1.72-4.60	<0.001
Chronic kidney disease (CKD)	3.99	2.36-6.71	<0.001
Elevated oxidative stress	4.48	2.17-9.24	<0.001
BMI	0.97	0.91-1.04	0.414
Drinking	5.81	3.11-10.86	<0.001
Smoking	6.23	3.33-11.64	<0.001
Systolic BP	1.09	1.06-1.12	<0.001
Diastolic BP	0.95	0.92-1.00	0.010
Age	1.00	0.97-1.02	0.704
Gender	2.35	1.35-4.09	0.002

Table 3B Impact of the association of elevated cadmium exposure with variables

Variables	Elevated cadmium exposure		
	OR	95% CI	*P-value*
Elevated TG/HDL-C ratio	3.78	2.27-6.30	<0.001
Chronic kidney disease (CKD)	3.90	2.30-6.23	<0.001
Elevated oxidative stress	4.29	2.07-8.89	<0.001
BMI	0.97	0.90-1.04	0.377
Drinking	6.65	3.47-12.76	<0.001
Smoking	6.03	3.19-11.37	<0.001
Systolic BP	1.09	1.06-1.12	<0.001
Diastolic BP	0.95	0.92-1.00	0.013
Age	1.00	0.97-1.02	0.681
Gender	2.66	1.52-4.68	0.001

Table 3C Impact of the association of elevated cadmium exposure with variables

Variables	Elevated cadmium exposure		
	OR	95% CI	*P-value*
Reduced HDL-C	5.63	3.33-9.53	<0.001
Chronic kidney disease (CKD)	3.83	2.23-6.59	<0.001
Elevated oxidative stress	3.52	1.63-7.59	0.001
BMI	0.95	0.88-1.02	0.162
Drinking	5.36	2.82-10.22	<0.001
Smoking	6.59	3.40-12.79	<0.001
Systolic BP	1.08	1.05-1.11	<0.001
Diastolic BP	0.95	0.92-1.02	0.024
Age	0.99	0.97-1.02	0.633
Gender	1.57	0.89-2.79	0.128

In this study, we propose one hypothesized to cause dyslipidemia that may come from oxidative stress induced insulin resistance. Many research studies reported that increased oxidative stress plays a major role in the pathogenesis of insulin resistance[28,29] by insulin signals disruption and adipocytokines dysregulation[28,30]. The evidences indicate that ROS overproduction induces insulin resistance and confirm by insulin resistance was ameliorated by antioxidant tempol in Ren-2 transgenic rats[31]. In insulin resistance individuals demonstrated by dyslipidemia, called the lipid triad comprises with hypertriglyceridemia, lower HDL-C levels and increased small, dense, low density lipoprotein cholesterol (sdLDL-C) commonly found in type 2 diabetes patients[32]. Insulin inhibits lipolysis, so insulin resistance will cause lack of insulin function, leading to increase free fatty acid in circulation and concurrent with reduced lipoprotein lipase activity to cause increased chylomicron remnant rich TG[33]. In animal experimental models, Cd exposure may alter TC, TG, HDL-C and LDL-C metabolism both in serum and tissue concentrations to cause dyslipidemia [9-11]. Increased oxidative stress, reduced TAC, hypertriglyceridemia, reduced HDL-C levels and higher TG/HDL-C ratio occurred in the residents of Cd exposure areas. The TG/HDL-C ratio has been demonstrated as a marker to estimate insulin resistance[34]. These results may

indicate that residents with Cd exposure were in the insulin resistance state as higher in TG/HDL-C ratio. After adjustment for covariates, higher OR for hypertriglyceridemia, low HDL-C, high TG/HDL-C ratio, oxidative stress, CKD, and were presence with elevated cadmium exposure. Many recent studies demonstrated that Cd exposure is higher risk for cardiovascular diseases, hypertension, T2DM and cancer[4,35-37]. Our present study elucidates the association of cadmium body burden and dyslipidemia (hypertriglyceridemia and lower HDL-C but not LDL-C or TC) in the residents with Cd exposure. They are at higher risk for all degenerative diseases and concomitant CKD may cause future morbidity and mortality. Today, Cd contamination areas still cause health problems. Environmental protection, consumption and lifestyle are warranted to protect further exposure. Limitation of our study was not the direct insulin assay for using insulin resistance calculation. In conclusion, this human-based study demonstrated the association of increased Cd exposure with hypertriglyceridemia, low HDL-C, high TG/HDL-C ratio, oxidative stress and CKD. Our results suggested that increased oxidative stress from elevated Cd exposure and concurrent CKD are significant in the development of cardiovascular disease, hypertension, T2DM and degenerative diseases.

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DECLARATION OF INTEREST

No conflict of interest

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