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Serum cadmium level of uterine fibroid patients in Korea

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Summary

Objective: The aim of this study is checking the blood level of cadmium (Cd) and lead in the patients with endometriosis or uterine leiomyomas. *Materials and Methods:* A total of 100 patients who underwent surgery for gynecological disease in the present tertiary teaching hospital were enrolled in this study. Twenty patients who underwent surgery for benign ovarian cysts were enrolled into the control group. Forty patients who underwent surgery for endometriosis and 40 patients who underwent surgery for leiomyoma were enrolled. Whole blood was collected by venipuncture in ordinary tubes after over eight hours of fasting. The Cd and lead levels were measured using graphite furnace atomic absorption spectrometry. *Results:* Blood lead and Cd levels were significantly higher in the leiomyoma group than in the control or endometriosis group. All participants were grouped into one of three groups according to their Cd level. Group 1 consisted of patients with Cd $\leq$ 0.05 ug/L (low quartile of the Cd level), group 2 included patients with 0.05 ug/L < Cd < 0.10 ug/L, and group 3 included patients Cd $\geq$ 0.10 ug/L (upper quartile of the Cd level). Age, parity, triglyceride levels, and lead levels had a significant correlation with Cd levels. The hemoglobin and high-density lipoprotein levels negatively correlated with Cd levels. *Conclusion:* Blood Cd level was elevated in leiomyoma patients, not in endometriosis patients. Blood lead and Cd levels showed significant positive correlation.

Key words: Uterine leiomyoma; Cadmium; Endometriosis.

Introduction

Uterine leiomyomas, also known as uterine fibroids, are well-known estrogen reactive tumors, similar to breast cancer or endometrial cancer. Because of their estrogen-dependent growth, connections between environmental disrupting substances and fibroids have been continuously suspected.

Cadmium (Cd) is a known metalloestrogen, which can act like estrogen or disturb estrogen metabolism inside the body through interactions with the estrogen receptors [1]. Cd exposure in ovariectomized rats led to increased uterine weight with accompanying proliferation of the endometrium [2] and Cd regulates progesterone synthesis in cultured granulosa cells [3]. Gao *et al.* reported Cd exposure in uterine leiomyoma cells and smooth muscle cells stimulated cell growth and resulted in non-genomic stimulation of the MAPK signaling pathway. They concluded that Cd exposure is a potential environmental risk factor for uterine fibroids [4]. Jackson *et al.* reported the association between heavy metals and endometriosis and uterine fibroids using the National Health and Nutrition Examination survey of a large population (n=1425). They reported an association between the Cd dose response and endometriosis but no association with lead or between Cd and uterine fibroids [5].

Lead is an established toxic and carcinogenic metal, like Cd; sources of exposure include inhalation of lead dust, ingestion of lead-based paint, and by ingestion of vegetables or fruits grown in contaminated soil [6]. Lead increases oxidative stress, affects endothelial function, promotes inflammation, and increases the risk of peripheral arterial disease, but the association between lead and uterine fibroids has not yet been evaluated. Some researchers reported potential anti-estrogenic effects of lead [7] and inhibition of the binding of estradiol to the estrogen receptor [8].

Nowadays, air pollution has become a serious problem due to the increase of industrial pollutants and local traffic in South Korea. In 2015, Seo *et al.* reported that the levels of blood lead and Cd in South Korea have been decreasing since 2008; however, the levels are still relatively high compared with those for the population of the United States of America, Canada, and Germany [9].

In this study, the authors examined the level of Cd and lead and endometriosis and uterine leiomyomas. They used the pathologic diagnosis after surgical biopsy for exact analysis. Given the estrogenic or anti-estrogenic effects of lead and Cd, they hypothesized that these heavy metals

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Table 1. — *Patient characteristics*

	Control (n=20)	Endometriosis (n=40)	Leiomyoma (n=40)
Age (years)	29.9 ± 5.3	31.0 ± 4.9	34.1 ± 3.9
Parity	0.65 ± 1.14	0.30 ± 0.72	0.35 ± 0.80
BMI (kg/m^2)	23.3 ± 8.10	21.2 ± 3.20 [a]	22.9 ± 2.92
Smoking (%)	5%	0%	0%
Menstrual cycle (day)	31.7 ± 5.48	30.4 ± 7.32	30.4 ± 6.05
Regular cycle (%)	70%	90%	90%
Hemoglobin (mg/dl)	13.5 ± 0.90[a]	12.5 ± 1.31	12.6 ± 1.75
Total cholesterol	166.4 ± 30.05[a]	174.5 ± 7.15	181.4 ± 21.70
Triglyceride	79.4 ± 36.11	71.1 ± 36.80	93.8 ± 66.01
High density lipoprotein	50.7 ± 17.65[a]	62.4 ± 13.30	65.0 ± 14.70

[a]$p < 0.05$, between control vs. leiomyoma, and leiomyoma vs. endometriosis. Data represented as mean ± standard deviation.

Whole blood was collected by venipuncture in ordinary tubes after the patients had fasted for over eight hours. The Cd and lead levels in whole blood were measured at the Occupational & Environmental Health Center of Korea, using graphite furnace atomic absorption spectrometry with a detection limit of approximately 0.03 µg/L. Individuals whose blood concentration fell below the detection limit were assigned a value of the detection limit divided by the square root of 2 [10]. Details of the Cd analysis have been reported previously [11].

The means and standard deviations of the demographic characteristics were calculated. The data obtained in three independent groups of subjects were compared by an inter-group *t*-test. The level of statistical significance was established at $p < 0.05$ for all statistical analyses. The calculations were performed using SPSS version 14.

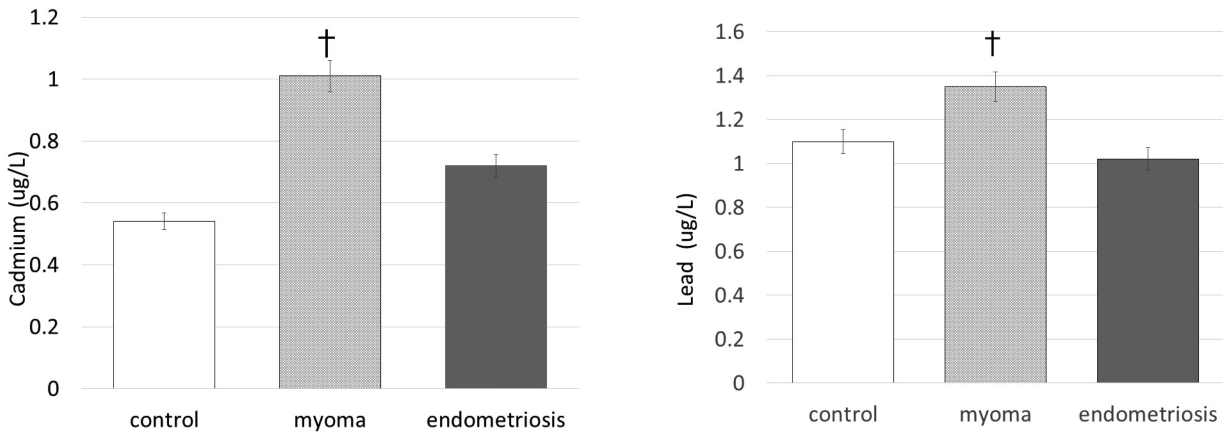

Figure 1. — Whole blood cadmium and lead levels in patients with endometriosis or leiomyoma. Blood cadmium and lead levels are significantly higher in patients with leiomyoma than those with endometriosis. Left (cadmium) and right (lead).

would be associated with endometriosis and uterine leiomyoma.

Materials and Methods

A total of 100 patients who underwent surgery for gynecological disease in the present tertiary teaching hospital were enrolled in this study. The protocol for the study was approved by the Ethics and Research Committee of the Catholic University of Korea and all study participants provided written informed consent. All participants were reproductive-aged women between 20 and 39 years of age.

Twenty patients who underwent surgery for benign ovarian cysts were enrolled into the control group. Forty patients who underwent surgery for endometriosis and 40 patients who underwent surgery for leiomyoma were enrolled.

Exclusion criteria were a combined diagnosis of endometriosis and leiomyoma. Hemoglobin, blood chemistry, and blood samples for heavy metals were checked in the outpatient department. Patient characteristics are listed in Table 1. Height and weight were measured in the outpatient department with the participants wearing light clothing and no shoes. Body mass index was calculated as weight (in kilograms) divided by the square of height (in meters).

Results

The mean age and parity were not significantly different among the groups. The mean body mass index was significantly lower in the endometriosis group than in the other groups. The preoperative mean hemoglobin level was higher in the control group than in the other groups. In lipid profiles, triglyceride levels were not different among the groups but high-density lipoprotein levels and total cholesterol levels were significantly higher in the endometriosis and leiomyoma groups than in the control group (Table 1).

Blood lead and Cd levels were significantly higher in the leiomyoma group than in the control or endometriosis group (Figure 1). The authors analyzed the correlation between some parameters and the whole blood Cd level using the Pearson correlation coefficient. All participants were grouped into one of three groups according to their Cd level. Group 1 consisted of patients with Cd ≤ 0.05 ug/L (low quartile of the Cd level), group 2 included patients with 0.05 ug/L < Cd < 0.10 ug/L, and group 3 included patients Cd ≥

Table 2. — *Cadmium levels and patient characteristics*

	Lower quartile Cd ≤ 0.05 μg/L (n=25)	Cd = 0.06~0.99 ug/L (n=48)	Upper quartile Cd ≤ 1.0 μg/L (n=27)	Correlation coefficient
Age (years)	28.6 ± 5.01	31.5 ± 5.28	33.7 ± 4.55	0.99[a]
Parity	0.32	0.35	0.51	0.88[a]
BMI (kg/m^2)	21.4 ± 3.2	23.0 ± 5.8	21.7 ± 2.3	0.03
Menstrual cycle length (day)	31.0 ± 3.7	30.0 ± 6.1	31.5 ± 8.7	0.02
Dysmenorrhea (%)	72 %	87.5 %	81.4 %	0.02
Hgb (mg/dl)	13.4 ± 0.84	13.0 ± 1.11	11.73 ± 1.95	0.91[a]
Lead (ug/dl)	1.05 ± 0.75	1.16 ± 0.46	1.25 ± 0.43	0.99[a]
Total cholesterol (mg/dl)	175.5 ± 29.0	178.5 ± 26.1	171.6 ± 24.0	0.31
Triglyceride(mg/dl)	78.3 ± 34.8	80.5 ± 35.2	87.9± 82.0	0.91[a]
High density Lipoprotein(mg/dl)	63.8 ± 15.4	61.7 ± 13.8	59.0 ± 17.7	0.99[a]
Low density lipoprotein(mg/dl)	104.1 ± 35.3	93.9 ± 23.8	97.8 ± 6.8	0.37

[a] *$p < 0.05$ vs. other groups.*

0.10 ug/L (upper quartile of the Cd level). The Pearson correlation coefficient was calculated and the relationships between the parameters were analyzed (Table 2). Age, parity, triglyceride levels, and lead levels had a significant correlation with Cd levels. The hemoglobin and high-density lipoprotein levels negatively correlated with Cd levels.

The authors analyzed Cd and leiomyoma characteristics, but blood Cd and lead levels were not significantly correlated with the total number of fibroids, average fibroid size, largest fibroid size, or the total volume of the fibroids.

Discussion

Cd is a toxic heavy metal, which is known to have many hazardous effects on human health. Cd is widely used in industrial processes. In polluted areas, Cd was emitted and contaminated the soil and is found in house dust. The route of human exposure is through contaminated food or water or inhalation of polluted air or tobacco smoke [12]. Health hazards of Cd include pneumonitis, damage to the kidney microtubules, increased risk of renal stones, interference in ovarian steroidogenesis, embryo toxicity, implantation failure, enhanced mammary development, loss of bone density and mineralization, and testicular necrosis [12, 13]. In gynecology, Cd is known as a metalloestrogen, an endocrine disrupting chemical. Cd affects the production of progesterone and testosterone. In low dose exposure, ovarian progesterone biosynthesis is stimulated, but in high dose exposure, Cd inhibits progesterone synthesis [14].

Cd is thought to interact with estrogen receptors in uterine cells from in vitro or animal data [2] but human observational data has not correlated with animal data. Jackson *et al.* reported the dose-response association between Cd and endometriosis, but no association was observed between Cd and uterine fibroids or between mercury and endometriosis or fibroids [5]. They used the National Health and Nutrition Examination Survey where the diagnosis of endometriosis and uterine fibroids is self-reported, not confirmed through medical records. The accuracy of the diagnosis and the possibility of combined disease were not investigated. In the present study, the authors used operation records and pathologic diagnoses.

The precise mechanism and pathophysiology of Cd in uterine fibroids remains to be elucidated. Byrene *et al.* [15] reported that Cd interaction with amino acids induces structural changes that mimic those induced by estradiol binding. Nasiadek *et al.* reported Cd bioaccumulation induces oxidative stress and lipid peroxidation in the uterus of rats and that Cd accumulates in the uterus in a dose- dependent manner. However, Cd concentration was significantly lower in leiomyoma than in normal tissue [16]. Cd in uterine fibroids cells activates the growth factor receptors EGFR, HGFR, and VEGF-R1 upstream of MAPK and these effects were not observed in normal uterine smooth muscle cells. Brama *et al.* suggested that Cd inhibits the binding of estradiol to estrogen receptor alpha [17] but many authors reported Cd acts like an estrogen, affecting the uterus not only through estrogen receptor binding, but also through extra-receptor mechanisms.

In the present results, blood Cd levels had a positive correlation with age, parity, and lead and triglyceride levels. Hemoglobin concentration and high-density lipoprotein levels negatively correlated with blood Cd levels. Increased age and parity are known risk factors for developing uterine fibroids [18]. The incidence of uterine fibroids by age 35 was 60% among African-American women and increased to over 80% by age 50. In Caucasian women, there was a 50% incidence by age 35, which increased to 70% by age 50. Age and parity were also the greatest contributors to blood and urinary Cd [19]. Increased parity is related to increased levels of Cd in the placenta, blood, and urine because the heavy metal absorption rate is increased during pregnancy [20]. In general, Cd in the blood, urine, and kidneys is higher in women than in men because of lower iron stores or increased risk of iron deficiency in women [12]. An iron deficient state upregulates metal transporter 1, an intestinal iron transporter which mediates the uptake of iron or Cd [21]. An increased Cd level with age and parity reflects the bioaccumulation effect of Cd. Blood Cd reflects both recent and cumulative exposure and Cd has more than a ten-year half life in humans. The national geometric mean of blood Cd level for adults is 0.38 μg/L and a geometric mean blood Cd level of 1.58 μg/L for New York City smokers has been reported [12]. In Korea, the mean blood Cd level in the adult population was 0.86 μg/L and the blood lead level was 1.99 μg/dl in 2011 [9].

In the present study, blood lead levels had a positive correlation with Cd levels. In the general population, the routes of lead and Cd exposure are through ambient air, especially in areas near emission sources, certain foods, smoking, soil, or drinking water [6, 12]. The positive association between lead and Cd suggest a co-exposure source of these toxic metals. The percentage of smokers was very low in this study and the main co-exposure route might be through contaminated air born dust or water. Increased lead and Cd levels were associated with the risk of atherosclerosis, chronic kidney disease, or low bone mass [6, 12]. Both toxic metals have nephrotoxicities and accumulate in the body resulting in chronic exposure. They inactivate the oxidation-reduction pathway, increase reactive oxygen species, and increase lipid peroxidation [22]. Cd and lead levels showed some correlation with metabolic syndrome and the odds ratio of a high triglyceride to HDL-C ratio was significantly increased in the high blood Cd groups [23].

In conclusion, blood Cd and lead levels were significantly higher in patients with leiomyoma than in the patients with endometriosis or the control group. Blood lead levels positively correlated with Cd levels, suggesting co-exposure. Further study is needed regarding the major exposure route of Cd or lead and their effects on the female reproductive system.

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