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IMPACT OF OCCUPATIONAL CADMIUM EXPOSURE ON BIOLOGICAL BONE MARKERS IN WELDERS

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Abstract:

Objective: The exact mechanism of interference between cadmium and bone mineralization remains for further studies. Therefore this study aimed at assessing the associations between urinary cadmium levels as an indicator of body burden and osteoblastic and osteoclastic biological bone markers as an indicators of bone effects in middle aged welders. **Methods:** The studied population consist of a group of welders (n=30) selected from two welder shops in EL Manial and those who were engaged in welding work in Kasr Al-Aini hospital and matched control (n=20). All participants were subjected to occupational and medical history, creatinine-corrected urinary cadmium (U-Cd) as an indicator of the whole body burden and biochemical markers of bone turnover. Bone formation and bone resorption were assessed by measuring the N-terminal propeptide of type 1 procollagen (P_1NP) and C-telopeptide crosslaps of type I collagen (CTX-1) respectively. **Results:** U-Cd and CTX-1 were significantly higher in welders when compared to the controls. Further comparison of the exposed group(regarding U-Cd level ≤ 5 μg/ g cr and > 5 μg/ g cr) and control revealed statistically significant differences as regard U-Cd and CTX-1 in addition to statistically significant lower mean value of P_1NP only in the group of U-Cd > 5 μg/ g cr than that in control group.

On correlating U-Cd on one hand with duration of work, smoking index, CTX-1and P_1NP on the other, non significant correlation was found**. In conclusion** our study may confirm other studies which claim that Cd increase osteoclastic bone markers and hence has a direct bone effect.

Key words: welders, cadmium, bone formation marker(P_1NP), bone resorption. marker(CTX-1).

Introduction

Cadmium (Cd), a rare but widely dispersed element, is found naturally in the environment. It is released into the environment through mining and smelting, It is a highly corrosion-resistant metal used extensively in general industrial. One of the workers potentially exposed are cadmium alloy and cadmium-plate welders (ATSDR,2008).

Welding fumes and gases come from the base material, filler material, paints or coats covering the metal or the electrode and chemical reactions resulted from arc ultraviolet light and heat. Exposure to cadmium can occur when cutting, brazing, soldering, grinding or welding surfaces that are cadmium coated or plated. Welding fumes may also contain chromium, nickel, arsenic, asbestos, manganese, silica, beryllium, nitrogen oxides, phosgene, acrolein, fluorine compounds, carbon monoxide, cobalt, copper, lead, ozone, selenium, and zinc(American Welding Society,2002).

Exposure to welding fumes is associated with various health effects including different lung function abnormalities, metal fume fever, bronchial asthma, chronic obstructive pulmonary disease, pneumoconiosis and lung cancer(Wittczak et al, 2009).

Cadmium in welding fumes can be fatal in a short time. The diagnosis of acute Cd poisoning should be considered in any workman who has been occupied in high temperature welding in confined space(Yates and Goldman,1990).

Studies suggest that cadmium is associated with several clinical complications, primarily renal dysfunction and bone disease and some cancers(Jorup ,2002). The toxic effect of cadmium on bone became evident at the outbreak of Itai-itai disease in Japanese women. Recent studies indicate that relatively low exposure levels may also affect the skeleton (Alfvén et al. 2004; Jorup ,2002 and Staessen et al. 1999).

Although cadmium accumulates in bone, the bone disease that results from excessive cadmium exposure is believed to be secondary to changes in calcium metabolism due to cadmium-induced renal damage (ATSDR 1999).

The exact mechanism of interference between cadmium and bone mineralization remains to be discovered. Recently, a direct influence on osteoblast and osteoclast function seems as likely as the indirect influence via induction of renal dysfunction (Berglund M,2000).

Aim of the work

This study aimed at assessing the associations between urinary cadmium levels as an indicator of body burden and osteoblastic and osteoclastic bone markers as an indicators of bone effects in middle aged welders.

Subjects & Methods

Subjects

The studied population of the current work consist of 50 males.

The welders (n=30) were selected from two welder shops in EL Manial and those who were engaged in welding work in Kasr Al-Aini hospital. They frequently weld metals plated with antirust and anticorrosive(Cadmium is used frequently as a rust-preventive coating on steel). They were exposed to welding fumes either for the whole or for at least half the working day and used at least two welding processes, which were mainly manual metal arc welding and metal active gas welding.

All of them fulfilled the inclusion criteria of the study that necessitate working with welding on daily basis(minimally 8 hour/day except Friday or Sunday) for long duration of time(the minimal duration was 7years). All welders didn't use masks and worked in poorly ventilated work place.

The matched control subjects (n=20) were selected from workers involved in cleaning services in Kasr Al-Aini. They were chosen so as to match the exposed personals in age, sex, body mass index (BMI), smoking index (SI) and socioeconomic standard. None of the control group had an occupational history of Cd exposure.

Methods

All studied group underwent an interview including full history taking with emphasising on occupational history, general and local examination. Smoking index was calculated as the number of packs per day X number of smoking years (Pack/ Year). Height and weight were measured and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Laboratory investigation

Urinary cadmium

A spot urine specimen was collected and stored at -20°C. Urinary cadmium was measured by graphite furnace atomic absorption (A ANALYST 100 atomic absorption Perkin-Elmer). We performed creatinine-corrected urinary cadmium values (urinary cadmium divided by urinary creatinine concentrations, expressed as

micrograms per gram) to account for between-participant differences in urine dilution. Urinary creatinine was measured using the Jaffe method with a Beckman ASTRA automated analyzer (Paschal et al, 2000).

Bone markers

Serum samples were obtained and stored at -70°C until assay. Biochemical markers of bone turnover were measured. Bone formation was assessed by measuring the N-terminal propeptide of type 1 procollagen (P_1NP), which is cleaved from procollagen during the formation of mature collagen in bone.

C-telopeptide crosslaps of type I collagen (CTX-1) is currently considered as one of the most sensitive markers of bone resorption and is released from bone type I collagen by cathepsin K, which is the key osteoclastic enzyme for systemic bone resorption(Garnero et al,2003 and Chopin et al,2007).

P_1NP was determined by Elecsys 1010/2010 total P_1NP serum kit (Roche Diagnostics, Mannheim, Germany), which employs the electrochemiluminescence immunoassay (ECLIA) technique. In healthy men, from age 40 to 65 years, The lower and upper reference limits of P_1NP based on the 95% CI of the back log-transformed data were 13.9 and 85.5 μg/L, respectively with mean (SD) concentrations of 38.1 (18.4) μg/L(Patrick Garnero et al,2008).

CTX-1 was determined by Elecsys 1010/2010 β-CrossLaps/serum kit (Roche Diagnostics, Mannheim, Germany), which also employs the ECLIA technique. The sensitivity of the assay is 0.01 ng/ml. The mean (SD) for men 30 to 50 years is 0.300 (0.142) ng/mL and for men 50 to 70 years is 0.200 (0.304) ng/mL.

Statistical analysis:

Results were evaluated for each group. Data were compared using Student t test. Analysis of variance (ANOVA) was used for multiple comparisons between the groups. Relations between U-Cd and different parameters were tested statistically using pearson correlation coefficient. The statistical significance was defined as P value<0.05. Computer based statistical package for social sciences(SPSS)for window9.1 program was used.

Results

This study was conducted on 30 male workers involved in welding with a duration of work (7-33years, mean=18.63±8.4) and matched control group of 20 male workers

never worked in welding. Regarding the clinical data among the studied population(not presented) 2 welders were hypertensive, 21 of them had conjunctivitis, 17 had chronic sinusitis,5 had generalized wheezes and 2 only had bone pains.

As evidence in table (1) there wasn't statically significant differences concerning age, BMI, SI in both welders and control group. Measured creatinine corrected urinary Cd (U-Cd) in welders ranged from 0.28-6.23μg/ g criatinine with a mean value of 3.75 ± 2.25 μg/ g cr. This value was significantly higher than that of the controls (range = 0.35-2.52μg/ g cr with a mean value of 1.06 ± 0.59). Similar finding were recorded among the welder as regard serum levels of crosslaps(CTX-1). The level of CTX-1 was higher among the exposed workers group than in control subjects (0.38 ± 0.09, 0.29 ± 0.04 respectively) with difference of statistical significance. The mean value of P_1NP was lower among welders than in control but not to the significant level, table (1).

Further comparison of the workers groups concerning the duration of work revealed that the U-Cd was higher in those with longer duration of work ≥ 20yrs than those < 20yrs (range= 4.27-6.23, 0.26-6.20 mean = 5.51 ± 0.79, 2.40 ± 2.06 respectively) with difference of statistical significance. While no statistical significant difference concerning age, BMI, SI, CTX-1and P_1NP between the same group table(2).

Regarding smoking habits among the welders (data not presented), the level of U-Cd was significantly higher in the smoker (mean = 4.55 ± 1.52) than non-smoker(mean = 2.84 ± 2.63) while no statistically significant difference concerning age, BMI, duration of work, crosslaps and P_1NP. Also there was significant increase in U-Cd in the smoker group of control compared with non smokers ($t = 3.96$ $P<0.05$).

Further comparison of the exposed subgroup(regarding U-Cd level ≤ 5 μg/ g cr and > 5 μg/ g cr, as this level is the Biological Exposure Index which has been recommended by ACGIH) and control group was done using Analysis of Variance Test (ANOVA).The result showed statistically significant differences between the three groups as regard U-Cd and CTX-1, table (3). Post Hoc Test(data no presented) revealed statistically significant lower mean value of P_1NP (31.47 ± 9.17) in group with U-Cd > 5 μg/ g cr than that in control group (39.49 ± 12.19).However, both Cd subgroups had significantly higher U-Cd and CTX-1 levels than those of control subject.

Correlation coefficients of U-Cd levels in relation to the duration of work, smoking index, CTX-1 and P_1NP were shown in (Table 4).There was positive correlation concerning osteoclastic bone marker (CTX-1) although it didn't reach the significant level. Also non significant negative correlation was found regarding osteoblastic bone marker(P_1NP).

TABLE (1) Mean + SD of age, BMI, smoking index (SI), urinary cadmium(U-Cd), crosslaps (CTX-1) and P1NP in welders and control group .

	Welders n = 30	**Control n = 20**	**t**	**p**
	mean ± SD	mean ± SD		
Age (year)	44.56 ± 5.26	42.80 ± 3.75	1.38	n.s.*
BMI (Kg / m^2)	31.24 ± 5.05	29.88 ± 4.75	1.11	n.s.
SI (Pack. Year)	11.00 ± 16.57	9.50 ± 18.12	0.29	n.s.
U- Cd (μg/ g cr)	3.75 ± 2.25	1.06 ± 0.59	6.22	< 0.05
CTX-1 (ng / ml)	0.38 ± 0.09	0.29 ± 0.04	4.02	< 0.05
P_1NP (μg/ L)	35.16 ± 9.95	39.49 ± 12.19	- 1.32	n.s.

* n.s: non-significant P>0.05

TABLE (2) Mean ± SD of age, BMI, SI, U-Cd and bone markers in welders with duration of work < 20 yrs and ≥ 20 yrs.

	< 20 yrs Duration n = 17	**≥ 20 yrs Duration n = 13**	**t**	**p**
	mean ± SD	mean ± SD		
SI (Pack. Year)	8.82 ± 15.26	13.84 ± 18.38	0.79	n.s.
U- Cd (μg/ g cr)	2.40 ± 2.06	5.51 ± 0.79	5.69	< 0.05
CTX-1 (ng / ml)	0.39 ± 0.10	0.35 ± 0.08	- 1.07	n.s.
P_1NP (μg/ L)	37.18 ± 8.40	32.52 ± 11.48	- 1.23	n.s.

TABLE (3) Analysis of variance (ANOVA) test of mean ± SD of age, BMI, SI, U-Cd, CTX-1 and P_1NP in welders subgroups(Cd ≤ 5 and > 5) and control group.

	Cd ≤ 5 μg/ g cr **n = 16**	**Cd > 5** μg/ g cr **n = 14**	**Control n = 20**	**F**	**p**
	mean ± SD	mean ± SD	mean ± SD		
Age (year)	44.00 ± 4.24	45.21 ± 6.33	42.80 ± 3.75	1.07	n.s.
BMI (Kg / m^2)	32.59 ± 4.85	29.71 ± 4.99	29.68 ± 4.75	1.92	n.s.
SI (Pack/Year)	10.62 ± 12.36	11.42 ± 20.88	9.50 ± 18.12	0.05	n.s.
U- Cd (μg/ g cr)	1.95 ± 1.49	5.80 ± 0.41	1.06 ± 0.59	108.95	< 0.05
CTX-1 (ng/ ml)	0.34 ± 0.09	0.42 ± 0.08	0.29 ± 0.04	12.21	< 0.05
P_1NP (μg/ L)	38.38 ± 9.73	31.47 ± 9.17	39.49 ± 12.19	2.55	n.s.

TABLE (4) Correlation coefficient between U-Cd and duration of work, SI, CTX-1 and P_1NP in welders.

	r	**P**
Duration of work(years)	0.34	n.s.
SI (Pack/Year)	0.18	n.s.
CTX-1 (ng / ml)	0.35	n.s.
P_1NP (μg/ L)	-0.20	n.s.

Discussion

Cadmium (Cd) is one of the most toxic elements to which man can be exposed at work or in the environment. Even in the twenty-first century, welding is still a common and a highly skilled occupation. Cadmium is one of the hazardous agents associated with welding processes(Meo and Al-Khlaiwi ,2003).

Once Cd is absorbed, it accumulates in the human body throughout life. Cd is primarily toxic to the kidney, especially to the proximal tubular cells. Also it causes bone demineralization, either through direct bone damage or indirectly as a result of renal dysfunction(Bernard ,2008).

Using U-Cd was adopted in many studies investigating Cd body burden. World Health Organization WHO(1992) proposed a health base limit of 10μg/g cr while the American Conference of Governmental Industrial Hygienists (ACGIH) (2007)has recommended a new Biological Exposure Index (BEI) of 5 μg/g cr for cadmium in urine. In the current study the mean concentration of U-Cd in welders were significantly higher than that of their matched referents(3.75+2.25 versus 1.06+0.59).It may be attributed to the higher exposure levels particularly without usage of protective equipments(masks)and working in badly ventilated work places. This is in accordance with the results reported by Botta C et al(2006) who found that blood and urinary concentrations of Cd, Co, Cr, Ni, and Pb were higher in the welders than in the control group. It was reported that the Urinary cadmium of39-year-old patient worked as a welder was 25 micro g/g creatinine(Nogué S et al,2004). Yassin and Martonik in 2004 have reported urinary Cd levels ranging from 0.01 to 15.57 μg/L in the US working population.

Because of the fact that Cd accumulate inside the body, beside that our workers were exposed to welding fumes on daily basis during their work, it was not surprising to have significant higher value of U-Cd among the group with longer duration of work. A positive non-significant correlation was found between the duration of exposure and U-Cd levels. Actually there is multiple confounders which affect the body burden of cadmium(U-Cd), rather than the occupational exposure, such as renal dysfunction and person's susceptibility in addition to the age, BMI, smoking and environmental exposure.

Proximal tubule represents the primary target of Cd induced nephrotoxicity (Thévenod, 2003). If the kidney's cadmium binding sites all become saturated after chronic high-level exposure, renal

dysfunction results(due to increased free cadmium within the cell)and urine cadmium levels increase dramatically. The ability of an individual to synthesize or utilize metallothionein, Cd binding proteins, after exposure to cadmium affects person's susceptibility (Lu et al., 2005).

The levels of cadmium increase with age(ATSDR,2008).A positive significant correlation was found between age and blood-Cd levels(Tobias Alfvén,2002). Further, Higher cadmium levels were also associated with a lower BMI(Andy Menk et al,2009).

Tobacco smoke may be one of the most common sources of Cd in the general population(Anetor JI et al,2008). Concerning our work, a significant increase in U-Cd was noticed between smokers and non-smokers(data not presented) in both welders and reference group. Similar significant difference was reported by Patricia et al in 2009. Mannino et al. (2004) mentioned that clinicians should be aware that smokers in general will have higher urinary cadmium than non-smokers since tobacco smoke is a major source in non-occupationally exposed persons.

Bone is continuously being remodelled in a process by which osteoclasts resorb bone tissue and osteoblasts produce new bone matrix that is subsequently mineralised. Bone loss occurs when the balance shifts toward excess resorption (Vis M et al,2003).

Exposure to Cd has been associated with the alteration of bone metabolism and the development of osteoporosis(Lovesque M,2008).It was reported that although cadmium accumulates in bone, the bone disease that results from excessive cadmium exposure is believed to be secondary to changes in calcium metabolism due to cadmium-induced renal damage (ATSDR 1999).However, The mechanisms of bone damage caused by cadmium (Cd) exposure have not been fully clarified. Little information is available about the direct effects of Cd on bone(Kazantzis .2004).

It was mentioned that cadmium decreases bone density indirectly through renal tubular dysfunction and the bone damage related to cadmium exposure occurred later than renal dysfunction (Qian et al, 2007).However, Schutte et al(2008) found that even in the absence of renal tubular dysfunction, cadmium increases bone resorption suggesting a direct osteotoxic effect.

Several markers have been described to measure bone metabolism. C-telopeptide crosslaps of type I collagen (CTX-1),a

marker for osteoclastic activity, is currently considered as one of the most sensitive markers of bone resorption (Chopin et al,2008).On the other hand, procollagen type I N-terminal propeptide (P_1NP) is a marker of bone formation(a marker for osteoblastic activity).

In the current work, eosteoclastic activity marker (CTX-1) among Cd exposed group showed a significant increase particularly among the group of U-Cd>5 μg/ g cr rather than in those with U-Cd<5 μg/ g cr (0.42 ± 0.08, 0.34 ± 0.07 respectively) versus 0.29 ± 0.04 in control.

Several studies show consistent associations between various bone biomarkers and the urinary excretion of Cd (used to assess Cd body burden)(Bernard ,2008).

Schutte et al(2008) studied the association of cadmium exposure with specific markers of bone resorption they concluded that in the absence of renal tubular dysfunction, environmental exposure to cadmium increases bone resorption in women, suggesting a direct osteotoxic effect. Further, Nambunmee et al (2009) studied urinary and blood cadmium in 412 Cd exposed population in relation to bone formation and resorption markers. They found that both genders had high levels of blood and urinary cadmium and high levels of the markers for bone resorption in a dose-response relationship to urinary cadmium. Moreover, Agneta Akesson et al(2006) showed clear associations between increasing cadmium body burden and increasing bone resorption marker. They added that the associations persisted even in the group of lowest cadmium exposure. They suggested a direct effect of cadmium on osteoclasts, resulting in increased its marker. Such stimulation of bone resorption has been demonstrated in animal studies (Brzoska and Moniuszko-Jakoniuk,2004, Regunathan et al,2003). On the other hand, Wallin et al(2005) mentioned that there were no significant associations between U-Cd and Biochemical markers in serum of osteoblastic and osteoclastic activity.

On correlating CTX-1 and U-Cd, non significant positive correlation was found. This can be explained by the presence of many confounders that may affect the level of bone markers as age, ethnicity, body mass index, calcium intake, and physical inactivity (Yuanyuan Wang et al,2005). Also, as Cadmium accumulates in bone and is associated with osteoporosis, other bone-seeking trace elements, such as chromium, lanthanum, strontium and zinc, are of concern because of low level environmental

or occupational exposure(Jorup L,2002). Regarding the duration of exposure >20Y or <20Y both osteoclastic(CTX-1) and osteoblastic (P_1NP)bone markers hadn't statistically significant difference which could be due to the same mentioned confounders.

Since bone mass is maintained constant by the balance between osteoclastic bone resorption and osteoblastic bone formation, alterations in osteoblast proliferation and differentiation may disturb the equilibrium of bone remodelling(Lovesque M,2008).

Concerning the levels of osteoblastic bone marker(P_1NP) in the current study, there wasn't statistically significant difference between exposed and reference group. Further analysis for our data revealed significant reduction of P_1NP in the group with U-Cd>5 μg/ g cr compared by control. Moreover, P_1NP level was negatively correlated (r = -0.20)with U-Cd levels although this correlation didn't reach the level of significance.

No available human studies to support our finding, but it was reported that increasing concentrations of Cd in osteoblast culture medium reduced cell viability in a time- and concentration-dependent manner, suggesting that Cd accumulates in osteoblasts (Lovesque M et al,2008). In addition, Xiao Chen et al(2009)studied the effects of cadmium on osteoblasts in vitro and stated that Cd could inhibit bone formation at high concentrations. .

The mechanisms by which Cd affect osteoblast are not fully understood. Coonse et al(2007) identified a role for apoptosis in cadmium-induced toxicity in bone cells. Other researcher found that chronic Cd exposure exacerbated the uncoupling between bone formation and resorption in ovariectomized rats(Uriu et al,2000).

Contrary to our finding, several studies showed no association between cadmium and bone formation markers(Agneta Åkesson et al 2006, Wallin et al 2005, Nambunmee et al 2009). On the other hand, Aoshima et al. (2003) showed increased levels of bone formation markers in patients with Itai-itai compared with controls.

Conclusions &Recommendations

This study showed that our exposed group had increased body burden of cadmium as revealed from the high U-Cd compared to their controls. Although the mean values were below BEI stated by ACGIH, exposed personnel experienced a condition of sub-clinical bone affection as evident from increased ostoclastic bone markers confirming the potential toxic effects of welding fumes.

Our study may confirm other studies which claim that Cd increase osteoclastic bone markers and hence has a direct bone effect. Also, higher cadmium levels may cause reduction in osteoblastic bone marker. However, further larger scale studies are needed for more clarification of this issue and mechanisms of toxicity. Indeed, more researches on cadmium is necessary to ascertain that these associations are truly causal and not secondary to another factor and to reveal true environmental and occupational exposure limits.

Moreover, the study recommends a probably planed program for health promotion of welders that include pre-employment and periodic medical examination, health education and stressing on the use of personal protective equipment.

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