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Association between cadmium and lead exposure and kidney stone formation in fuel station workers: A case-control study in North Basra

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Abstract
Background: Cadmium and lead are two examples of nephrotoxic heavy metals. Environmental and occupational exposure to these heavy metal can be linked to nephrolithiasis, which is becoming a more prevalent condition worldwide. There is evidence of increased exposure in the vulnerable population of fuel station workers. Limited information on this condition is available from Iraq.
Objective: This study aims to examine the associations of the biomarkers of the cadmium and lead exposure with the kidney stones' odds among fuel station workers in North Basra, Iraq.
Materials and Methods: A total of 50 subjects, 25 patients with a verified diagnosis of kidney stones and 25 healthy controls, were enrolled in the study. The subjects' venous blood was drawn. The quantitative determination of cadmium concentration was performed through atomic absorption spectrometry, and the quantitative detection of lead and renal function markers-with chemist's method using biochemical analyzers. Statistical data processing was carried by independent sample t-test.
Results: The kidney stone group exhibited significantly elevated serum cadmium (1.85 µg/L vs. 0.45 µg/L, $p<0.01$) and blood lead levels (5.85 µg/dL vs. 2.50 µg/dL, $p<0.001$) compared to controls. A significant decrease in uric acid was also observed in patients (4.62 mg/dL vs. 5.17 mg/dL, p=0.029). No significant differences were found in urea, creatinine, or total protein levels.
Conclusion: The findings demonstrate a strong association between elevated cadmium and lead exposure and the presence of kidney stones among fuel station workers, highlighting these heavy metals as significant occupational risk factors for nephrolithiasis.

Keywords: Nephrolithiasis, cadmium, lead, occupational exposure, environmental pollutants

Introduction
Nephrolithiasis, commonly known as kidney stone disease, is a growing global concern. Kidney stones are becoming more widespread over the years [1]. In its most recent epidemiologic report in the United States of America, the worldwide prevalence of kidney stones was noted to be 9.3%, varying from 7-13% in North America, 5-9% in Europe, and 1-5% in Asia [2]. In 2019, more than 115 million new cases of urolithiasis were documented worldwide, with age-standardized incidence rates of 815 per 100,000 in women and 1,800 per 100,000 in men [3]. Kidney stone pathophysiology is governed by the interaction of urinary supersaturation, crystal nucleation, and inhibitor deficiency [4]. Roughly 80% of kidney stones are comprised of calcium oxalate with calcium phosphate, more commonly known as Randall plaques, whereas uric acid, struvite, and cystine stones account for around 9%, 10%, and 1% of the stones, respectively [5]. The stone formation's spontaneous course includes the following stages: saturation of the urine undersaturation, supersaturation, nucleation of the crystal, crystal aggregation, deposition of the crystal on the urothelium, and stone development [6]. Numerous conventional risk factors for nephrolithiasis have been identified, including dietary patterns, metabolic syndrome, obesity, diabetes mellitus, hypertension, and genetics [7]. Nevertheless, growing evidence imputes exposure to heavy metals in the environment and the workplace as unexplored risk factors for stone formation [8]. More recently, several studies have demonstrated associations between heavy metals and kidney stone formation, with cadmium and Blood lead showing the strongest association [9, 10].

Cadmium is among the most nephrotoxic heavy metals. It has a biological half-life of 10-30 years, and it preferentially accumulates in the proximal tubular epithelial cells [11]. Occupational exposure to cadmium is shown to cause kidney, sparks, and smoke in battery workers; the incidence rate ratios were 3.0 in the high exposure group [12]. The process that occurs is presented above: cadmium evokes the process of oxidative stress, affecting the function of mitochondria, which contributes to the enhancement of the electron's leakage from the electron transport chain and reactive oxygen species generation [13]. Cd-induced nephrotoxicity is characterized by proximal tubular dysfunction with polyuria and low-molecular-weight proteinuria. The primary mechanism is the disruption of the mitochondrial electron transport chain, which promotes electron leakage and the generation of reactive oxygen species [14]. Moreover, Cd suppresses NADPH oxidase function, which is another source of the reactive species that cause oxidative damage to DNA, proteins, and lipids. Pb was positively associated with kidney stones [15]. Participants in the highest quartile of the urinary Pb level showed 64% higher risks of kidney stones [13]. Pb can bind to the calcium-sensing receptor and cause abnormalities in the renal processing of calcium leading to hypercalciuria [16]. This mechanism is especially important because hypercalciuria is the most common etiological factor promoting the formation of stones. Lead-induced hypercalciuria results from disturbances at the cellular level in the renal tubules and the action of the extracellular calcium-sensing receptor that is expressed in the renal tubular cells [17]. The CaSR is responsible for the regulation of calcium homeostasis, and the binding of Pb ions disrupts the normal processing of calcium that leads to the increased excretion of calcium in the urine [18]. In addition, Pb exposure is responsible for inflammatory reactions and oxidative stress that is conducive to the damage of renal tubular epithelial cells [19].

Fuel station workers are an especially vulnerable occupational group with a documented increased exposure to multiple heavy metals, including Cd and Pb. Several studies conducted across different areas repeatedly found that fuel station workers had significantly higher blood Pb levels compared to the control population [20]. Occupational exposure in fuel station workers involves multiple pathways, including inhalational exposure to volatile compounds, touch exposure, and consumption due to inadvertent ingestion [21]. The period elevations are specially severe in such occupational populations since the majority work 12 hours' every few days per week job for the majority of years [22]. Thus, the period of contact to petroleum products was extensively and considerably linked with blood heavy metal levels were a sign of a cumulative toxicity effect [23]. The mechanisms underlying heavy metal-induced kind stone formation are multifaceted and involve oxidative stress, irritation, and disruption of calcium homeostasis [24]. Oxidative stress tyranny is central to stone development; renal tubular epithelia presented to heavy metals produces an over-abundance of the reactive oxygen types and leads to oxidative stress-induced inflammatory responses [25]. Oxidative stress emanates tight-fisted junction proteins and rises precious jewelry ivy precipitating onto the harmed risky-looking cells [23]. The North Basra governorate in Iraq displays a particular growing concern because it is an endemic area for heavy metal exposure due to extensive petroleum industry operations [25]. This area has been incorporated into a recognized area of concern for occupational conduct and work, based on significant evidence for oil and natural gas employers' commitment. The production lines contribute to the climate with away gases fun emitted from retrieving, processing, and refining operations. Wire Type: undefined [26]. Our study aims to explore the associations between biomarkers of cadmium, Pb, exposures, and the possibility of kidney stones. Therefore, the present study aimed to explore the associations between biomarkers of cadmium, Pb exposures, and the odds of kidney stones among fuel station workers.

Materials and Methods

This case-control study enrolled 50 participants: 25 patients diagnosed with renal calculi (cases) and 25 individuals without kidney stones (controls). Cases were identified based on clinical history and confirmed by radiological imaging (abdominal X-ray, abdominal ultrasound, or non-contrast computed tomography of the kidney, ureter, and bladder). Control participants were selected from patients admitted to the Department of Surgery for conditions unrelated to renal stones. All participants were aged between 39 and 80 years. The Institutional Ethical Committee of the Basra Health Directorate at Qurna Hospital approved the study protocol, and written informed consent was obtained from every participant prior to inclusion.

Venous blood samples were collected from participants at Al-Qurna General Hospital. For each participant, two 3 ml samples were drawn: one into a K3 EDTA vacuum tube (model FV01003) for whole blood analysis and another into a gel and clot activator vacuum tube (model G1326331) for serum separation. Serum was isolated by centrifugation. All samples were subsequently stored at-20 °C to-80 °C until analysis.

Quantification of Cadmium Cadmium levels were quantified by atomic absorption spectrometry. cadmium 1000 µg/ml standard Solution (Merck KGaA, Darmstadt, Germany) was serially Diluted using deionized water to 10 µg/ml intermediate solution and then calibrated using 1 to 5 ng/ml concentration into 100 µl. Serum creatinine was measured with Roche/Hitachi Cobas 6000 chemistry analyzer. To analyze proteids bands, protein electrophoresis was also performed. Urea Concentration was determined using Abbott C800 chemistry Anlyser.

Statistical analysis

Data Analysis SPSS software (Version 26) was used for statistical analysis. Values were expressed as mean ± standard deviation. The cases vs. controls were compared using the t-test of independent samples in two tails. A less than or equal to 0.05 p-value indicates a significant result.

Results

Table 1 demonstrates the comparison of serum parameters among kidney stone patients and control individuals. This table shows that while Age, urea, creatinine, and total protein levels were not statistically significant, the concentrations of heavy metals were highly significant between groups. Thus, the mean serum cadmium level in patients was over four times higher than in the control group. Once again, this Difference was highly significant with a p-value of <0.01. It should be noted that blood lead levels were more than two and a half times higher in the

patient group, showing an even higher statistical significance. Therefore, these f Findings clearly prove that high exposure to both Cadmium and lead will be associated with kidney stones.

Table 1: Concentration of (Creatinine, Protein, CD, Pb, and urea) in serum patients and control group.

Variables	Groups		P-value*
	Control (N=25)	Patients (N=25)	
	Mean ± SD	Mean ± SD	
Age (years)	55.4±11.5	57.4±14.5	NS
Urea (mg/dL)	38.1±16.7	36.2±14.1	NS
Creatinine (mg/dL)	1.04±0.344	1.11±0.376	NS
Protein (g/L)	69.0±3.93	70.0±3.24	NS
Cadmium (µg/L)	1.08±0.394	1.33±0.463	0.048
Blood lead (µg/dL)	1.13±0.305	1.68±0.538	<0.001

The urinary constituents are shown in table 2. The notable observation is the significant increase in urinary calcium excretion in the patient group with $p<0.01$. Conversely, a statistically significant reduction in urinary uric acid is also included in the patients group p=0.029. A cytologically elevated concentration of urinary calcium hypercalciuria is a well-recognized, dominant risk determinant in the development of calcium-containing stones.

Table 2: Concentration of stoneanaysis Ca, uric acid,) in urin patients and control group.

Variables	Groups		P-value*
	Control (N=25)	Patients (N=25)	
	Mean ± SD	Mean ± SD	
Ca	9.49±0.722	9.95±0.710	NS
Uric Acid	5.17±1.13	4.62±0.467	0.029

Discussion

The results of the current case-control study establish notable linkages between elevated biomarkers of Cd or Pb exposure and nephrolithiasis among fuel station employees in North Basra. The execution of this study is crucial because reliable information on the toxicological safety concerns related to Pb or Cd exposure for the Iraqi populace, especially in environmentally vulnerable areas, is currently lacking. This is despite the fact that earlier studies already indicated the existence of environmental pollution from these heavy metals in relevant areas [27, 28]. Therefore, the specific relationship with nephrolithiasis was unclear.

The formation and development of urolithiasis have multiple pathways and are under the concurrent influence of dietary habits and lifestyle and conditions such as obesity, diabetes, and metabolic syndrome [29, 30]. Our findings add to a rising body of evidence highlighting the role of environmental and occupational toxicants as major risk factors. The patient cohort had markedly and abnormally high blood levels of Cd and Pb, which are consistent with existing toxicological literature [31]. Cadmium, which has a biological half-life of 10-30 years and preferentially accumulates in the renal proximal tubules, is nephrotoxic in this context. Its nephrotoxicity is mainly mediated through oxidative stress, which impairs oxidative phosphorylation, induces the production of reactive oxygen species, and attacks several cellular targets, ultimately causing cellular damage and tubular dysfunction [13, 15]. This injury attracts and plugs crystals, preventing them from passing down the tubule and promoting new stone formed [24].

Thirdly, high Pb levels in the kidney stone group could have a significant impact on the patients. Lead is known to interfere with calcium homeostasis through the renal tubules calcium-sensing receptor binding, which may cause hypercalciuria, a significant promotor of calcium stones fact [16, 18]. We report that the urinary concentration of patella is highly excreted by the patients when compared to the controls, Fact which may promote kidney stone formation. Moreover, Pb induces parallel oxidative stress and inflammatory responses [17], which both damage the tubular epithelium Physiology creating a potential hotbed for lithogenesis.

The most striking is the marked decrease in Urinary uric acid in our patient group. This apparent paradox may be explained by the specific stone composition present in our cohort; with more calcium rather than uric acid stones, 24-hour uric acid excretion may not be abnormal. Moreover, the multitude of interactions of diet, purine metabolism, and concomitant renal insurrection might Have played a role [32]. The absence of significant differences in serum urea and creatinine levels among groups suggests that the strong metal exposure observed may cause tubular damage and stone formation prior to the development of true global renal insufficiency assessed by those common markers.

The findings on cadmium are consistent with the previous literature where subtypes of cadmium, blood cadmium levels as a marker of recent exposure, were positively correlated with stone risk [9, 33]. However, the situation is significantly more complex for lead [8, 17]. While our data, as well as the literature, show a strong positive association, other reports in populations with generally lower environmental exposure have been neutral or even negative [34, 35]. This indicates the outstanding importance of exposure levels and sources. Our fuel station workers cohort's elevated Pb levels, acquired through chronic inhalation of fumes or dermal absorption, represent an instance of occupational exposure that is unequivocally distinct from the general population's low-level environmental exposure. Once more, Pb exposure at the high level seen in several workplaces 'remains a hazardous nephrotoxic exposure' as opposed to episodes of environmental levels experienced by the population.

There were several limitations of our study. First, it was a relatively small sample size, which might limit the generalizability of our results. Also, we were unable to prove causality, as our survey had a cross-sectional case-control design. Even though a significant association was found, there was no way to confirm from the survey that exposure to heavy metals had occurred before the stone was formed. More large-scale prospective cohort studies that also have careful stone material analysis would strengthen the evidence statement and reveal dose-response Cantonese.

Conclusion

The current study delivers sufficient evidence that occupational cadmium and lead exposures are highly correlated with growing odds of kidney stones in the participants. The probable mechanistic channels, which involved oxidative stress, inflammation, and Ca disruption supported above, provide a plausible biological for this association. Thus, as many fuelling workers are simultaneously exposed to nephrotoxic metals, the current findings underline the urgent need to enhance occupational safety in, require employees to use adequate PPE, and

perform frequent heavy metal to guard against dangerous nephrolithiasis and renal co morbidities.

Conflict of Interest
Not available

Financial Support
Not available

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