Associations between urine cobalt and prevalence of kidney stones in American s aged ≥ 20 years old

Jia Wang (wangjiawch@163.com)
West China Hospital of Medicine: Sichuan University West China Hospital
Yunfei Xiao
West China Hospital of Medicine: Sichuan University West China Hospital
Shan Yin
West China School of Medicine: Sichuan University West China Hospital
Yunjin Bai
West China School of Medicine: Sichuan University West China Hospital
Jiahao Wang
West China Hospital of Medicine: Sichuan University West China Hospital
Jianwei Cui
West China Hospital of Medicine: Sichuan University West China Hospital

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Abstract

To determine whether urine cobalt is associated with the prevalence of kidney stones. We conducted a cross-sectional study of participants (≥ 20 years) involved in the National Health and Nutrition Examination Survey (NHANES) between 2007 and 2018. Urine cobalt level was divided into four groups: 0.02–0.22, 0.22–0.36, 0.36–0.58 and 0.58–37.40 ug/L. The independent correlation between urine cobalt and prevalence of kidney stones was determined by logistic regression analyses. Totally 10,744 participants aged over 20 years without pregnancy were eligible. Among them, 1,041 participants reported as ever having developed kidney stones. Patients with kidney stones developed significantly higher urine cobalt than the non-stone participants. The kidney stone patients were more likely to have smoking ≥ 100 cigarettes in life, hypertension, diabetes, cancer, and heavy activity. Multivariate logistic regression indicated a significantly positive relationship between urine cobalt level and occurrence of kidney stones (OR 1.059, 95%CI 1.018–1.102). Moreover, the outcome remained unchanged after some sophisticated factors were adjusted (OR 1.048, 95%CI 1.005–1.093), and the incidence of kidney stones rose with the increasing urine cobalt level [OR (95%CI) = 0.22–0.36 ug/L: 1.166 (0.955–1.422); 0.36–0.58 ug/L: 1.348 (1.108–1.640); 0.58–37.40 ug/L: 1.683 (1.382–2.044)]. Higher urine cobalt concentration is significantly related to an increased risk of kidney stones. However, more high-quality prospective studies are needed to elucidate the causal correlation between cobalt level and kidney stones.

1. Introduction

As one of the most common urinary system diseases, kidney stones develop in the renal pelvic, renal calyx, or the junction of the ureter and renal pelvic, and can lead to low back pain, lumbar distention, hematuria, urinary tract infection, and even renal failure. In the past 40 years, the incidence and prevalence rates of kidney stones have been increasing in both developed and developing countries regardless of age, gender, or race differences (Thongboonkerd 2019). For example, the incidence of kidney stones tripled from 3.2% in 1976–1980 to 8.8% in 2007–2010 in the USA (Kittanamongkolchai, Vaughan, Enders et al. 2018). Kidney stones can be treated by extracorporeal shock wave lithotripsy, ureteroscopic lithotripsy, percutaneous nephrolithotripsy or other surgical methods, but up to 50% of the patients suffer a higher recurrence rate than other types of urological diseases within 5 to 10 years after the first onset. Thus, the treatment of kidney stones already becomes a huge economic burden for the global public health system. In the USA, the total medical cost of kidney stones is more than 5 billion dollars per year, and the cost of clearing stones is far higher than that for prevention (Alelign and Petros 2018). Therefore, it is urgent to discover the risk factors of kidney stone formation and to develop prevention and early intervention strategies.

A variety of factors contribute to the formation of kidney stones, including genetics, environment, nutrition, gender, geographical location, climate, diet, and socioeconomic status (Howles and Thakker 2020). Reportedly, the distribution area of kidney stone patients is greatly close to the geological structure belt. Therefore, many studies support that trace elements are related to kidney stones. Although trace elements are essential for metabolic function and the optimal development of all organisms, trace

elements are also important mediators for the suffering from various diseases. In addition to the reported trace elements of zinc, iron, strontium and cadmium, cobalt (Co) is also associated with the development of kidney stones in animal models (Wahlqvist, Bryngelsson, Westberg et al. 2020). Co, one essential trace element in the human body, mainly comes from exposure to diet, the occupation environment, and medical equipment. It enters the body through the skin, respiratory tract and digestive tract, but is mainly excreted through urine (Wahlqvist, Bryngelsson, Westberg, et al. 2020). Co within the normal level undertakes many necessary physiological functions in the human body, such as up-regulation of erythropoietin and vitamin B12 formation. Various human activities affect the cobalt level in the body, including labor, drugs, malnutrition, alcohol intake, and diabetes (Daniel, Ziaee, Pradhan et al. 2010, Ren, Wang and Zhang 2017). Overexposure to or accumulation of Co in the body will induce potential toxicity and carcinogenicity, so Co is viewed as a carcinogen in many countries (Hutter, Wallner, Moshammer et al. 2016, Watson, Lewin, Ragin-Wilson et al. 2020). Excessive exposure to and ingestion of Co during working can lead to occupational diseases, such as hard mental lung disease, pulmonary edema, and papillary thyroid cancer (Hu, He, Tong et al. 2021, Thongprayoon, Krambeck and Rule 2020).

At present, the available data about cobalt on the formation of kidney stones are scarce, and the specific interactions have not been clarified. Therefore, this study aims to analyze the relationship between urine cobalt concentrations and the prevalence of kidney stones.

2. Methods

2.1. Study population

All data were cited from National Health and Nutrition Examination Survey (NHANES) (https://www.cdc.gov/nchs/nhanes/index.htm), a database of studies designed to evaluate the nutritional status and health of adults and children in the USA. This database is the only population-based national survey, which aims at the control and prevention of diseases. The data in NHANES were acquired from different populations by using a complex probability sampling design through standardized interview, physical examination and sampling tests, and were analyzed to assess the health and nutritional status of non-institutionalized civilians in the USA. Since 1999, this database has been used by researchers for free and updated every two years.

We used six cycles of public NHANES data (2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, 2017–2018), which involved 59842 participants. Firstly, 25,072 participants under the age of 20 were excluded. Then the exclusion criteria were as follows: 1) pregnant participants (n = 372), 2) incomplete kidney stone questionnaire (n = 90), and 3) urine cobalt test missing (n = 23,564) (Fig. 1). Finally, 10,744 participants were admitted to this study.

2.2. Outcome and variables

The main indicator of interest was urine cobalt, which can be obtained from laboratory data. Urinary cobalt was measured to reflect the cobalt level in the human body. Urine cobalt level was equally divided into four types: <0.02–0.22, 0.22–0.36, 0.36–0.58, 0.58–37.40 ug/L (**Table 1**). However, no guidance on urine cobalt levels in the human body was found. Other continuous variables included age (≥ 20 years), poverty income ratio (PIR), and body mass index (BMI). Categorical variables included gender, age (20–34, 35–49, 50–64, ≥ 65), race, education level, marital status, PIR (≤ 1.3, 1.3–3.5, > 3.5%), BMI (< 25, 25–30, ≥ 30 kg/m^2), smoking (< 100 and ≥ 100 cigarettes in life), drinking (< 12 and ≥ 12 drinks/year); diabetes, high blood pressure (HBP), congestive heart failure (CHF), cancer, gout, vigorous activity, and moderate activity (all no, yes). Specifically, races included Mexican American, Other Hispanic, On-Hispanic black, Non-Hispanic white, and Other races. Education level included less than 9th grade, 9-11th grade, high school graduate, some college, and college graduate or above. Marital status was: married, widowed, divorced, separated, never married, and living with a partner (Table 2). PIR, drinking, and diabetes all involved missing data. HBP and diabetes are based on doctors' judgments. The focus of this study is the occurrence of kidney stones. The outcome variable of kidney stone prevalence can be extracted from the questionnaire data. When participants answered “yes" to the question "Have you ever had kidney stones?", we thought the person had kidney stones (Mao, Zhang, Xu et al. 2021).

2.3. Statistical analysis

The participants was divided by the quartiles of urine cobalt level into four groups (0.02–0.22, 0.22–0.36, 0.36–0.58, 0.58–37.40). The distributions of continuous variables and classified variables were clearly described by mean ± standard deviation (SD) and proportions respectively. Moreover, the clinical characteristics of all participants were evaluated by Chi-square analysis. Three multiple logistic regression models were built to analyze the correlation between urinary cobalt level and kidney stones (**Table 3**). In the non-adjusted model, no factor was adjusted. The minimally adjusted model was adjusted with age, gender, and race. Finally, the fully adjusted model was further adjusted with education level, marital status, smoking, alcohol, hypertension, diabetes, CHF, cancer, gout, vigorous activity, moderate activity, and BMI. All the above statistical analyses were completed with R (http://www.R-project.org; the R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc.). P less than 0.05 was considered statistically significant.

3. Results

From the NHANES 2007–2018 cycle, a total of 10,744 qualified participants were enrolled, including 1,041 (9.7%) participants with kidney stones and 9,703 (90.3%) participants without kidney stones. Considering the many factors identified to influence the formation of kidney stones, we examined the baseline characteristics of all participants (**Tables 1 and 2**). The kidney stone patients are likely to be 50–64 years old (38.61%), male (57.37%), non-Hispanic white (75.63%), and BMI ≥ 30 (46.81%). They all tend to have smoking ≥ 100 cigarettes in life (49.63%), hypertension (44.84%), diabetes (18.95%), cancer (16.32%) and heavy activity (81.23%). Compared with non-stone participants, kidney stone patients have a significantly higher urine cobalt level (0.65 ± 2.01 ug/L, p = 0.0032). Furthermore, the urine cobalt level

of kidney stone patients was equally divided into four groups (0.02–0.22, 0.22–0.36, 0.36–0.58, 0.58–37.40 ug/L), and the kidney stone prevalence of the highest cobalt group (11.29%) was more clearly elevated than the other three groups. Interestingly, the data also suggest that the lowest urine cobalt group (7.94%) accounted for the smallest proportion of kidney stones. In contrast, across all non-stone participants, people with 0.02–0.22 ug/L urine cobalt contributed to the highest proportion (92.06%), while people with 0.58–37.40 ug/L urine cobalt made up the smallest proportion (88.71%).

To further find out the risk factors associated with the prevalence, we constructed three logistic regression models to estimate the correlation between urinary cobalt concentrations and kidney stones (**Table 3**). Surprisingly, the prevalence of kidney stones always increased with the increasing urinary cobalt content in all the non-adjusted model, the minimally adjusted model and fully adjusted model. According to the quartiles of urinary cobalt, the trend test among the three models was still positively significant ($P < 0.00001$). When we almost equally made a full adjustment model into four categories by the quartiles of urine cobalt and compared these to the participants with 0.02–0.22 ug/L urine cobalt, we observed an increase in the likelihood of developing stones with the urine content rise (0.36–0.58 ug/L: OR 1.348, 95%CI 1.108–1.640; 0.58–37.40 ug/L: OR 1.683, 95%CI 1.386–2.044). Unfortunately, we found no significant difference in odds of kidney stones between 0.22–0.36 ug/L in urine content with the lowest one.

4. Discussion

As is well-known, kidney stone is a common and recurring disease seriously affecting human health, and causes increasing medical and economic burden. However, the specific pathogenesis of renal stones is still unclear. In addition to immune and inflammatory reactions, intestinal flora, and dietary regulation that significantly affect the stone formation process (Khan, Canales and Dominguez-Gutierrez 2021, Ticinesi, Nouvenne and Meschi 2019, Zhu, Liu, Lan et al. 2019), the role of trace elements in the occurrence and development of kidney stones has also attracted wide attention recently (Killilea, Westropp, Shiraki et al. 2015).

In this cross-sectional study, we used the public data from NHANES 2007–2018 cycles, which can symbolically represent the health of all residents in the USA. Results show that kidney stones are significantly associated with urinary cobalt ($P = 0.0032$). The prevalence of kidney stones grows gradually with the increase of urinary cobalt level. Additionally, the trend remains after adjustment for confounding factors.

To our knowledge, there is no direct experimental result to support this notion so far. Fortunately, many studies provide indirect evidence. Firstly, as for the mechanism of kidney stone formation, research shows that the increase of cobalt level can induce macrophage apoptosis, which leads to a decreased anti-inflammation ability and a higher risk of kidney stone formation (Xiao, Wu, Zhang et al. 2018). In addition, due to the higher incidence of thyroid cancer with increasing urine cobalt, more patients suffer from kidney stones (Edafe, Debono, Tahir et al. 2019, Murad and Eisenberg 2017, Royer, Mathieu and

Balsan 1970). Moreover, the vascular endothelial growth factor (VEGF) is reportedly an essential contributor to renal stones. Our results demonstrate that the urine cobalt concentration rises along with the increase of VEGF expression. VEGF may act through several pathways to initiate the pathogenesis of the stone disease. Therefore, VEGF may function as a signpost for preventing stone formation (Bi, Liu, Li et al. 2010, Loboda, Jazwa, Wegiel et al. 2005, Sato, Virgona, Ando et al. 2014). In a word, the urine cobalt concentration can be highly viewed as a potential indispensable indicator of kidney stone diagnosis.

However, there are few reports on correlation between cobalt and kidney stones. An animal model shows that some trace elements of calcium oxalate urolithiasis change in different trends, as urine calcium, copper, iron, and vanadium levels increase, while urine cobalt level decreases (Furrow, McCue and Lulich 2017). In our opinion, the differences with our results can be attributed to some reasons. First, the researchers regarded the calcium oxalate stones of dogs as study samples, and second, the sample size was not big enough to further prove the credibility and representativeness of the results. Hence, it is urgent to conduct a systematic and comprehensive prospective study to clarify the controversy.

Furthermore, our result suggests that the proportions of obesity, smoking, and older people in kidney stone patients are growing gradually, and these types of patients are likely to have lower content of adiponectin (Achari and Jain 2017, Chełchowska, Gajewska, Maciejewski et al. 2020, Higham, Bostock, Booth et al. 2018, Kadowaki, Yamauchi, Kubota et al. 2006, Komiyama, Wada, Yamakage et al. 2018). The decline of adiponectin, an adipocytokine with the ability of anti-inflammation and anti-lipid peroxidation, contributes to a relatively high risk of stone diseases. In a word, adiponectin plays a potential role in stone formulation. Moreover, heavy activity can accelerate the loss of body fluid and urine concentration, so the urine cobalt level increases with the rising prevalence of kidney stones (Mao, Zhang, Xu, et al. 2021).

As we all know, the main types of kidney stones recognized by researchers are calcium oxalate, calcium phosphate, uric acid, cystine, and infectious stones (Bostanghadiri, Ziaeefar, Sameni et al. 2021). Analysis of the nature and composition of the stones indicates that the stones contain many trace elements (e.g. Fe, Zn, Sr, Se, Cd, and Co) in addition to the major elements (e.g. Ca, P, K, Na, Mg). The contents of trace elements in different types of stones and different parts of the same stone may differ (Keshavarzi, Yavarashayeri, Irani et al. 2015). Currently, the cobalt level in the human body can be observed through many objective indicators, of which urinary cobalt is the most feasible and economical one. Urinary cobalt can reflect the exposure of the human body to cobalt and can be used to detect human cobalt content (Junqué, Grimalt, Fernández-Somoano et al. 2020, Kettelarij, Nilsson, Midander et al. 2016). Over-accumulation of cobalt in the human body may cause kidney stones, hard metal lung disease, pulmonary edema, papillary thyroid carcinoma, allergic dermatitis, and other severe diseases (Knoop, Görgens, Geyer et al. 2020, Lantin, Vermeulen, Mallants et al. 2013, Leyssens, Vinck, Van Der Straeten et al. 2017, Van Der Meeren, Lemaire, Coudert et al. 2020). Cobalt is mainly excreted through urine. Therefore, the temporary storage and excretion of cobalt through the kidneys affect the external morphology of crystal formation and accelerate or slow down crystallization, probably causing the formation of kidney stones (Killilea, Westropp, Shiraki, et al. 2015). The above results suggest the

potential role of urinary cobalt in calcium oxalate urolithiasis and prompts us to further analyze the relationship between urinary cobalt and kidney stones and to explore the possible etiology and pathophysiology of stone formation. These results also contribute to formulating safer and more effective standardized measures to prevent and treat kidney stones. Moreover, urinary cobalt content can reflect human exposure to cobalt, so it may provide a basis for developing a comprehensive cobalt exposure guide in the future and plays a critical role in the prevention and screening of kidney stones.

The major advantage of this study is that the representative population includes a multi-ethnic population from the USA. The large sample size also allows us to conduct in-depth analysis. However, there are some limitations and deficiencies. Firstly, due to the feature of the cross-sectional study, we cannot determine whether higher or lower urinary cobalt concentrations will affect the changes in kidney stone disease over time, and cannot assess the causal relationship between the two. Secondly, the data do not include information such as the size, quality, or type of kidney stones, and we were not permitted to conduct deeper analysis. In addition, we excluded pregnant women, because pregnancy has some effects on urinary cobalt content and kidney stones formation (Reinstatler, Khaleel and Pais 2017). Therefore, the findings of this study cannot be applied to this type of population. Finally, we do not rule out the biases caused by other potential confounding factors that were not adjusted here, such as food intake, and sleep hours.

5. Conclusion

The increase of urinary cobalt content is closely related to kidney stones. Nevertheless, more high-quality prospective studies are needed to elucidate the causal correlation between cobalt and kidney stones.

Declarations

Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Author Contribution

(I) Conception and design: J Wang, Shan Yin; (II) Administrative support and supervision: J Wang; (III) Collection and assembly of data: YF Xiao, JH Wang, JW Cui; (IV) Data analysis and interpretation: Shan Yin, YJ Bai;(V) Manuscript writing: YF Xiao; (VI): Final approval of manuscript: all authors.

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Ethics approval

This study was done using Public Data from the National Center for Health Statistics (NCHS) program, the National Health and Nutrition Examination Survey (NHANES). The data have been de-identified and not been merged or augmented in a way that has compromised the privacy of the participants. Therefore, the study requires no further approval and follows ethical guidelines.

Consent to participate

Participant data were obtained from the publicly available NHANES, so no additional consent was obtained.

Data availability statements

Data available in a publicly accessible repository that does not issue DOIs. Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

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Figures

Figure 1

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