URINARY LEAD CONCENTRATION IN CHRONIC KIDNEY DISEASE PATIENT IN A TERTIARY CARE HOSPITAL IN SABAH, MALAYSIA

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ABSTRACT

Urine is frequently used as a biomarker to quantify lead (Pb) toxicity levels, especially in those affected with kidney disease. Presently, scientific knowledge on the association between urinary lead (UPb) concentration and renal profile is limited, which contradicts the evaluations of health-based Pb nephropathy. In the case of patients with chronic kidney disease (CKD) associated with long term Pb toxicity due to the accumulation of Pb in the kidneys, there is currently no complete explanation for high concentrations of UPb that could aggravate existing kidney disease. Furthermore, most studies have failed to adequately report the effects of UPb concentration and this has become an isolated screening practice in detecting the early signs of Pb nephropathy in patients. The objective of this cross-sectional study was to examine the concentrations of UPb and renal outcomes in CKD patients who were referred to the Nephrology Clinic at Queen Elizabeth Hospital, Sabah. Two hospitals were selected as the study population, namely Queen Elizabeth Hospital and Papar Hospital. Purposive Sample Method technique was used in the selection of samples with a minimum of 100 subjects required in total. Primary data on serum creatinine (SCr), blood urea nitrogen (BUN), diastolic blood pressure (BP), and demographic background was obtained during clinic visits as well as urine samples. The UPb concentration results and the primary data were analyzed using SPSS version 21 software to demonstrate the descriptive analysis of UPb concentration in the study group. The mean UPb concentration was 4.1±7.92µg/g for the CKD group and 3.8±2.93µg/g for the non-CKD group. A significant difference was observed in UPb concentration levels between the study groups, whereby the CKD group had higher UPb concentration levels than the non-CKD group (p-=0.002). However, there was no evidence of a relationship between UPb concentration and SCr concentration, BUN concentration, and diastolic BP in the CKD group in which the correlation was r=-0.123, r=0.101, r=0.127, respectively. Furthermore, no evidence was found of UPb accumulation in the CKD patients who had yet to start renal replacement therapy (RRT). As such, no reverse causation of Pb was evident in the CKD group. The possibility of Pb accumulation may potentially increase in a patient who has already started RRT or is no longer producing urine. Further larger scale studies are needed to demonstrate whether UPb concentration affects kidney function in society as a whole.

Keywords: urinary lead, chronic kidney disease, serum creatinine, blood urea nitrogen, diastolic blood pressure.

ABSTRAK

KEPEKATAN PLUMBUM DALAM URIN DIKALANGAN PESAKIT BUAH PINGGANG DI HOSPITAL PAKAR SABAH, MALAYSIA

Urin adalah salah satu biomarker yang sering digunakan pada manusia untuk mengukur ketoksikan dari pendedahan kepada plumbum (Pb), terutama bagi kumpulan yang mengalami ginjal yang terjejas. Pada masa ini, pengetahuan saintifik mengenai hubungan diantara kepekatan urin plumbum (UPb) dan kesan toksik adalah kurang, dimana bertentangan dengan penilaian kesihatan terhadap kerosakan ginjal yang disebabkan oleh plumbum. Dalam kes pesakit yang mengidap penyakit ginjal yang kronik (CKD) yang dikaitkan dengan kesan jangka panjang pengumpulan Pb di ginjal, tidak ada penjelasan yang menyeluruh mengenai kepekatan UPb yang tinggi akan memburukkan lagi penyakit ginjal yang sedia ada. Selain itu, tidak banyak kajian yang dijalankan tentang kesan kepekatan UPb pada ginjal dan dengan itu menjadikannya isu terpencil. Oleh itu, objektif dalam kajian keratan rentas ini dilakukan untuk mengenal pasti kepekatan UPb pada pesakit ginjal kronik (CKD) yang dirujuk ke klinik nefrologi di Hospital Queen Elizabeth, Sabah. Terdapat dua hospital yang dipilih sebagai populasi kajian, iaitu di Hospital Queen Elizabeth dan Hospital Papar. Teknik persampelan purposif digunakan dalam pemilihan sampel untuk kajian ini dan jumlah minimum adalah 100 peserta dalam kajian ini. Data primer seperti serum kreatinin (SCr), darah urea (BUN), tekanan darah diastolik (BP) dan maklumat tentang latar belakang pesakit akan diperolehi semasa lawatan temujanji klinik pesakit dan pada masa yang sama sampel urin akan dikumpulkan. Keputusan kepekatan UPb dan data primer akan dianalisis dengan menggunakan perisian SPSS versi 21 untuk analisis statistik bagi mendapatkan analisis deskriptif kepekatan UPb dalam kumpulan kajian. Mean kepekatan untuk kumpulan CKD adalah 4.1±7.92µg/g and kumpulan bukan CKD adalah 3.8±2.93µg/g. Secara statistik terdapat perbezaan dari kepekatan UPb di antara kumpulan kajian di mana kumpulan CKD menunjukkan sedikit lebih tinggi daripada kumpulan bukan CKD (p-=0.002) namun, tiada bukti menunjukkan hubungan kepekatan UPb dengan SCr, BUN and julat BP diastolic dimana statistik hubungan menunjukkan masing-masing adalah r=-0.123, r= 0.101, r=0.127. Selain itu tiada bukti pengumpulan UPb bagi pesakit CKD yang masih belum dimulakan dengan terapi penggantian ginjal (RRT). Seperti juga tiada bukti yang menunjukkan kesan pengumpulan plumbum 'berbalik' yang berlaku dalam kumpulan CKD. Pengumpulan Pb mungkin berpotensi pada pesakit yang telah memulakan RRT atau tidak lagi menghasilkan urin. Kajian lanjut dalam skala besar adalah diperlukan bagi menunjukkan kepekatan UPb dalam mempengaruhi fungsi ginjal dalam masyarakat kita.

Kata kunci: urin plumbum, pesakit ginjal kronik, serum kreatinin, urea, tekanan darah diastolik

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LIST OF ABBREVIATION

AAS	-	Atomic Absorption Spectrometer
ASTDR	-	Agency for Toxic Substances and Disease Registry
ATP	-	Adenosine Triphosphate
BLL	-	Blood Lead Level
BLB	-	Body Lead Burden
BP	-	Blood Pressure
BUN	-	Blood Urea Nitrogen
CI	-	Confidence Interval
CKD	-	Chronic Kidney Disease
Corr Coef	-	Correlation Coefficient
df	-	Degree of Freedom
DMPS	-	Dimercaptopropane Sulfonate
DMSA	-	Dimercaptosuccinic Acid
EDTA	-	Ethylenediaminetetraacetic Acid
Fe2+	-	Ferrous Ion
FAO	-	Food and Agriculture Organization
GFR	-	Glomerular Filtration Rate
HSE	-	Health and Safety Executive
LMW	-	Low Molecular Weight
mmHg	-	Millimetre Mercury
Na+	-	Sodium Ion
NKF	-	National Kidney Foundation
Non-CKD	-	Non Chronic Kidney Disease
Pb	-	Lead
P value	-	Probability Under the Assumption of Hypothesis
QEH	-	Queen Elizabeth Hospital
RRT	-	Renal Replacement Therapy
SD	-	Standard Deviation
Upb	-	Urinary Lead

WHO	**-**	World Health Organization
µg/dl	**-**	Microgram per Decilitre
µg/g	**-**	Microgram per Gram

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CHAPTER 1

INTRODUCTION

1.1 Introduction

The harmful effects of exposure to lead (Pb) have been well documented and studied for centuries. Pb is one of the more beneficial and inexpensive metals. It has been extracted since the Roman era (500 BCE) and used for many generations in a wide range of applications. The demand for this metal peaked during the period of 20th century industrialization in developed countries. This has resulted in Pb continuing to exist ubiquitously in the environment in most countries. In industry, the usage of Pb is noted in activities such as mining, smelting, and manufacturing for commerce. Up until now it has been widely used in more than 900 different industries (Karrari, Mehrpour and Abdollahi, 2012), including the manufacture of buildings, lead-acid batteries, piping systems, ornaments, paint, ceramic ware, home utensils, cosmetics, and still in leaded fuel (Jan *et al.*, 2015) in several countries. Due to its extensive usage, Pb concentration is relatively high in the environments in many cities of the developing and developed countries (Osman *et al.*, 2005). Particular areas that are highly contaminated are districts and agricultural zones (Bibi *et al.*, 2015; Payus, 2015; Ali, 2004). The rapid increase in the amount of Pb in the environment has raised concern about the effect on living organisms, especially in relation to the physical surroundings and global public health associated with environmental contamination (Tchounwou *et al.*, 2012). Concern is primarily focused on those who are vulnerable to this form of pollution.

While clinical Pb poisoning is reported mainly from occupational contamination, the widespread use of Pb could expose the general population to the same toxic dose levels of Pb (Skerfving and Bergdahl, 2015). The prevalence of Pb exposure rates and the outcome severity in the general population may differ regardless of populations within the same countries (World Health Organization, 2010). In most countries, Pb has been established as a poisonous and toxic element in the human body (Karrari, Mehrpour and Abdollahi, 2012) particularly if it exceeds the action level. Evidence also has shown that exposure to Pb, even in a small but significant amounts can cause chronic disease of the vital organs.

As such, the occupational hazards of Pb have been extensively studied due to its association with chronic disease and morbidity (Batuman and Wedeen, 2014). However, in recent decades, there is an increasingly significant body of literature on the association of Pb exposure in the general population and the incidence of chronic kidney disease (CKD) as discussed by Muntner et al. (2003) and Chung et al. (2014). These studies show that the blood lead level (BLL), even at low levels, is related to elevated serum creatinine (SCr) and hypertension and has led to a decline in the renal function in susceptible groups. Several epidemiologic researchers have also demonstrated an association between chronic Pb toxicity with age, gender, ethnicity, residential location (Liu *et al.,* 2012) and the renal profile that was used for Pb exposure monitoring (Buser *et al*., 2016). There is a growing consensus that Pb may contribute to renal failure and hypertension in the general population. Many studies have reported cases associated with renal profile leading to reduced renal function to the baseline. Several studies have indicated that Pb plays an essential role in contributing to the progression of kidney-related diseases (Yu, 2004; James, 2015; Soderland *et al*., 2010; Karrari, Mehrpour, and Abdollahi, 2012; Evans and Elinder, 2011 and Huang *et al*., 2013). These findings suggest that long-term exposure to low Pb levels causes Pb nephropathy, especially in those from developed countries (Spector *et al.,* 2011). Several studies have also emphasized that significant Pb nephropathy may have consequences for the tubulointerstitial region, which may alter the kidney's physiological function and lead to kidney failure in the long term (Bergdahl *et al.,* 1997). Similar findings were made by Evans and Elinder (2011), who concluded that there is excellent anecdotal evidence that Pb nephropathy may initiate tubular fibrosis after prolonged or high absorption of Pb in the kidneys. According to Soderland et al. (2010) and James (2015), acute or high exposure to Pb regardless of the source may also have implications for the kidneys, possibly leading to nephrotic syndrome. In nephrotic syndrome, the mitochondria become swollen causing the formation of fibrillary aggregates due to the lead-protein complex. This in turn causes the formation of a nuclear inclusion body, a disorder known as Fanconi Syndrome. As a result, the kidneys may lose the ability to remove waste including Pb, especially in the case of the CKD patients. Generally, this can lead to bioaccumulation of Pb in the kidneys (Rango *et al.,* 2015) and a high concentration of Pb in the urine.

Previous studies have also demonstrated that Pb exerts nephrotoxicity, which is reflected in the Pb concentration in the kidneys, and which is usually detected in the urine during late stage kidney disease (Chaumont *et al*., 2012). Moreover, inefficient excretion of these toxins in CKD patients may lead to further accumulation in the kidneys thus causing toxicity effects that will aggravate the existing disease (Rango *et al*., 2015). However, rather than necessarily pointing to renal function, this result may also due to the fact that the kidneys of the CKD patients may inefficiently filter these toxic elements. The remaining Pb circulating in the blood will be transferred and absorbed by the bone and other compartments in the body (Barbosa *et al*., 2005).

A rise in the blood urea nitrogen (BUN) and SCr is a good predictor of CKD risk (Shlipak and Day, 2013) and the elevation can be a significant clinical indication of Pb nephropathy reflecting that the renal function is starting to deteriorate. Such cases were reported by Patrick (2006) and Lai *et al*. (2008) who noted that, following renal profile such as BUN and SCr, Pb toxicity was seen to increase and this was reflected in the decrement of renal function. In this study, the scenario that affects the concentrations of SCr, BUN and diastolic blood pressure (BP) parameters due to influences of concentration of UPb is expected to lead to significant differences in the study population. Although UPb concentration could explain the association or influence the concentrations of SCr, BUN and BP, several other confounders may affect the relationship and need to be taken into account.

1.2 Problem Statement

Sabah is currently expanding economically in line with its growing population. It is also expected that non-communicable diseases such as diabetes mellitus and hypertension, which have a high attribution in the Malaysia population will account for more than half of the primary CKD for patients requiring dialysis. Every year this disease keeps on increasing. In 2014, there were 34,767 CKD patients depending on dialysis in Malaysia a two-and-a-half-fold increase from 13,356 in 2005. While the new intake of CKD dialysis patients was only 3,167 in 2005, this more than doubled to 7,055 in 2014. The incidence of CKD patients who experienced advanced CKD were 234 and 1,155 per million population in 2014. 61% of the new patients had diabetes mellitus as the primary renal disease, and this has been the major cause of end-stage renal disease since 2004. Moreover, hypertension was

the second primary renal disease in 18% of the new patients between 2013-2014 (Leong *et al,* 2014). These studies, however, were either retrospective or were not adjusted for other confounding factors that could affect the progression of renal function. These factors include sociodemographics and lead toxicity, which are to be included in the renal profile in the study despite the fact that lead has also been associated with the development of diabetes, hypertension secondary to nephropathy and unknown etiology (Huang, 2013; Evans and Elinder, 2011; Sanchez 1996).

A correlation between UPb concentration and renal outcome has been widely observed in the general populations of other developing countries such as United States. Although further evidence is needed to illustrate the mechanisms, findings from several studies suggest a potential role of Pb in inducing renal outcomes. Therefore, a comprehensive understanding of Pb excretion through urine may help to understand the harmful mechanisms, and thus may lead to the discovery of novel diagnostic, prognostic, and treatment approaches for Pb nephropathy. A greater understanding of Pb toxicity, including Pb nephropathy and the role of kidney outcomes may provide useful information on the prevention of Pb exposure and its adverse effects. However, the relationship between UPb concentration in CKD patients and the declining ability of the kidneys to remove Pb in the urine (which can increase renal profile due to bioaccumulation of Pb in the kidneys) is still uncertain.

In previous studies linking low levels of environmental Pb exposure and the development of renal disease in the general population in Europe and the United States, BLL and bone Pb have been shown to have positive associations with kidney outcomes (ATSDR, 2007; Huang, 2013). The associations between increased creatinine clearance and high Pb concentration measures also have been previously reported (Weaver *et al.*, 2003). In a similar study, Melanie (2015) also noted a significant positive association between renal outcomes and UPb. In relation to the general population, some studies found evidence that increased UPb concentrations (Tsai *et al.,* 2017) were associated with declining glomerular filtration rates (GFR), while another study claimed that the increased concentration of UPb was associated with estimated glomerular filtration rate (eGFR) increment (Buser *et al.,* 2016; Zheng *et al.,* 2015). The question remained whether there is 'reverse

causality' whereby reverse causation specifically increased Pb concentration as a result of reduced kidney excretion and this is most prominent in populations with CKD (Spector *et al.*, 2011). At this point, loss of kidney function regardless of the cause in the CKD group can be a potential explanation for the accumulation of Pb in the body, which may cause either an increase or decrease in Pb excretion via the urine. In this regard, a hypothesis that suggests that the increase of SCr, BUN, and BP should correspondingly increase with UPb levels in the CKD population is supported by Batuman and Wedeen (2014). In a clinical setting, chronic Pb nephropathy can represent an increase in SCr and BUN.

However, several studies have shown that it is still unclear that UPb has the closest relationship with the renal effects of Pb: Sommar *et al.* (2014) assumed that the significant correlation or differences in UPb concentration in the CKD and non-CKD patients was due to the different GFR between the study groups. It should also be noted that an underlying assumption of this study is that the accumulation of Pb in the urine is due to renal impairment. This affects the remaining healthy structure in the kidneys, mainly the tubulointerstitial region in the CKD group resulting in high Pb in the urine. Pb nephropathy that is associated with CKD may be relevant to describe Pb in directly inducing kidney decline due to reverse causation rather than exposure to Pb pollution. Nevertheless, the mechanism by which reverse causation causes the kidneys to be unable to eliminate the accumulating Pb, thus leading to declining kidney function has not been fully defined, especially in the CKD population. In the case of non-CKD patients, Pb is removed from the body very deliberately, with urinary excretion being the primary route of Pb elimination (Klotz and Goen, 2017) indicating that healthy functioning kidneys can reduce Pb concentration. This statement is supported by Jin (2018), whose group results show that higher eGFR in a healthy person may increase urinary excretion of Pb. Both groups seem to have had high Pb levels in the urine regardless of the renal function. There have been limited studies on the impact of UPb concentration in the CKD population. This study could, therefore, shed new light on the use of UPbs as biomarkers especially among the CKD population.

Additional knowledge on the physiological effects of Pb on the kidneys is required. However, very few studies have been conducted on the association between UPb concentration and kidney outcomes, particularly among the working

population. It is a neglected area of study, whereby potential preventable factors that play an essential role in the progression of chronic renal diseases are still be identified. To date, there is no recommendation on a baseline UPb concentration in the general population, or the CKD population, as well as a lack of consensus on the reference range (ASTDR, 2007; Pohl *et.al.*,2017; Jin *et. al.*,2018; Skerfving and Bergdahl, 2015).

Pb and CKD have been widely studied in western countries. Lead Toxicity Surveillance Programs have also has been widely carried out in other countries, but not in Malaysia. The use of UPb in renal profiles for kidney function in determining the risk of CKD is limited in our country. According to Orr and Bridges (2017), the exposure of cells to Pb can affect the structure and lead to alterations in cell mitochondria. The tissue becomes swollen causing the outer membrane to rupture in the renal area and this affects the efficiency of the kidney function resulting in the elevation of BUN and SCr levels (Ahmed et. al., 2008). Analysis of SCr and BUN is essential in evaluating the kidney function, mainly the GFR. However, evaluation of the change in GFR from the increasing SCr concentration is still not possible due to the decrements in glomerular filtration. These do not usually show any significant rise proportionate to the increase in the SCr concentrations in the early stages. At this point, a 50% decrement in the GFR can appear in the absence of measurable change in the SCr excretion (ATDSR, 2007). Therefore, since there are insufficient data to accurately define the relationship between UPb concentration in CKD patients, the need to relate this to Pb nephropathy has become less important. Moreover, there is no baseline data available on UPb which would clarify a level at which action should be taken, hence policymaking steps need to be taken. The outcome of this study may be the presentation of vital information on baseline Pb concentration levels to an environmental agent such as the World Health Organization (WHO) (Cascio, 2011) or Jabatan Alam Sekitar (JAS) in Malaysia to create and maintain a healthy environment. This study may also explain the effect of Pb bioaccumulation on renal function and changes in the renal tubules. Such information may assist the Ministry of Health to develop new prognostic and diagnostic tests mainly for susceptible populations such as those with CKD. Control of Lead at Work Regulations 2002 Approved Code of Practice and guidance is the one of the policy example that can be refer to manage the risks from lead only in the workplace but not practicable for general population. To date, only a small