

Environmental Lead Intoxication And Chronic Kidney Disease: A Review

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Abstract

The global burden of chronic kidney disease has reached epidemic proportions and it has been fuelled by the rising prevalence of diabetes and hypertension. A large percentage of patients especially in the developing countries have CKD on uncertain cause. Lead, a bivalent heavy metal is increasingly being recognized to play a role in the pathogenesis of hypertension and progressive renal disease. Lead poisoning detected by measuring blood lead levels can be prevented by the regulation of industrial production, dispersion and uses of lead. In the United States blood lead levels have been on the decline since the regulatory legislations came into effect in 1970. Even small concentrations of have been associated with adverse health effects from epidemiological studies. Whereas the type of large scale lead poisonings that were reported in the middle of the last century are now uncommon, chronic low level lead poisoning has correlated with the rate of hypertension and progressive renal disease. Clinicians should be alert to detect early lead poisoning, and commence treatments that have been shown to limit or reverse lead toxicity. The public health benefit of reducing environmental lead poisoning globally and especially in the developing countries with limited health resources make curbing environmental lead poisoning a very urgent need.

INTRODUCTION

The public health and economic burdens of Chronic Kidney Disease (CKD) continue to increase globally at an alarming rate with the incidence of End Stage Renal Disease (ESRD) estimated to be 7 % and prevalent population of 1.1 million that is expected to top 2 million by 2010 (1). It has been projected that the cost of renal replacement therapy will soon exceed 1 trillion dollars per annum globally at a patient per capita cost of over \$55,000 in the US (2). The majority of ESRD patients receiving dialysis or transplantation reside in the rich industrialized countries whereas in developing countries like India despite the cheaper cost of haemodialysis, that modality of treatment is largely unsustainable because of rampant poverty (3). Despite the high global disease burden and associated high morbidity, the causes of CKD in a high percentage of individuals remain largely elusive (4) especially in developing countries where the lack of modern diagnostic techniques and late presentation to nephrologists greatly limit the characterisation of kidney diseases. Those limitations have probably led to the misclassification of significant number of patients with the findings of bilaterally contracted kidneys as chronic glomerulonephritis. Several factors have been linked to the initiation and progression of CKD including diabetes,

hypertension, cigarette smoking, hyperlipidaemia, proteinuria and infectious agents and toxins. In recent times the important contribution of lead a bivalent heavy metal in the progression of renal disease is increasingly being recognized. There is the need for clinicians and public health worker to be aware of not only communicable and non-communicable diseases but also the contribution of environmental toxins that are fuelling the pandemic of CKD.

SOURCES OF LEAD POISONING

Environmental lead levels vary from place to place depending on a number of factors that includes proximity to a smelting factories and other industrial facilities that release lead into the environment (5). The industrialized countries experienced an epidemic of lead poisoning following the widespread use of lead salts in paints and petrol fuels necessitating legislations of laws that prohibited the use of lead salt additive. There has been a steady decline in the lead levels of the US population since the year 1970, presumably related to the changes in the industrial practice of using lead additives in gasoline, manufacture and use battery, ammunition, ceramics, cosmetics, paints and soldering of containers (6). The use of lead in gasoline as an antiknock agent accounts for the majority of the atmospheric lead as a result of emission from automobile exhaust. Whereas the

practice of use of lead as antiknock has been virtually eliminated in the US several other regions of the world have continued the practice. The use of lead free gasoline in the US has been responsible for the decrease in atmospheric lead levels and decrease in lead blood level (7). Lead paints used in construction and households pose significant risk of low dose lead poisoning with an estimated one million construction workers affected in the US alone (8). A recent report of severe lead poisoning in workers in a plastic industry where lead sulphate was used as lead stabilizer highlights the importance for surveillance of industrial workers and other people that maybe at risk of lead intoxication (9). Environmental lead gets into the body via the respiratory and gastrointestinal systems in the majority of cases while lead in gasoline has the additional ability of being capable of absorption through the skin. The enormous consequences of lead poisoning can be prevented by the elimination of potential sources of intoxication and by population surveys aimed at identification of occult cases of poisoning and their subsequent treatment.

BURDEN OF PROBLEM

The non-specific manifestations of lead intoxication and the fact that not many laboratories have the capacity for assessing lead contribute in making the estimates of the health burden of lead poisoning difficult to ascertain. Reports from the US account for the majority of the available data. The Adult Blood Lead Epidemiology and Surveillance (ABLES) report of the Centre for Disease Control (CDC) showed that in 1994–97 period 20 % of the 20,000 samples per quarter that were examined had blood lead levels greater than 25 micrograms per decilitre (10). Such a level of lead poisoning of short duration can be treated and the clinical consequences reversed but high level poison (greater than 80 microgram per decilitre) or protracted low level exposure tend to lead to progressive disease. Defining elevated Blood Lead Level (BLL) as concentrations greater than 10 µg /dl for all ages the National Health and Nutrition Examination Survey (NHANES) reported the overall prevalence of elevated BLL for the US population was 0.7 % down from 2.2 % in the 1991–94 survey. In that survey the largest decrease in elevated BLL was 11.2 % to 3.1 % among non-Hispanic black children aged 1–5 years. The NHANES findings for the period 1976–80 to 1991–94 showed a steep decline (from 77.8 % to 4.4 %) in the percentage of children aged 1–5 years with blood lead level greater than 10 µg / dl (11,12). In the US BLL are higher in certain populations notably children from ethnic

minorities, children from low-income families and those resident in older homes (11). Among the ethnic groups non-Hispanic blacks and Mexican Americans had higher percentages of 1.4 and 1.5 % respectively than the non-Hispanic whites 0.5 % (13). The decreasing blood lead in the US adult population was further highlighted in a report that showed the mean levels fell 41 % from 0.13 µmol/L in 1988–94 to 0.08 µmol/L in 1999–2002 and that the percentage of adults with blood lead greater than 10 µmol /L has fallen by 79 % over the same periods (14). Whereas it is convenient to dichotomise BLLs into elevated and normal, the reality is that there does not appear to exist a threshold below, which the adverse effects of lead exposure experienced (15).

CAUSALITY RELATIONSHIP BETWEEN LEAD POISONING AND CKD

Several studies have demonstrated relationship between the levels of environmental lead exposure and the prevalence of hypertension, hyperuricaemia, gout, and peripheral arterial disease (16,17,18). Acute high dose lead intoxication can cause proximal tubular damage manifesting as aminoaciduria, renal glycosuria and hyperuricaemia as a result of reduced uric acid excretion (19). Chronic low dose lead poisoning on the other hand is associated with increased urinary excretion of low molecular weight proteins and lysosomal enzymes (20). Munter et al analysed the results of NHANES III with over 15,000 individuals in a cross sectional general population survey and reported an association between lead exposure even at low levels to hypertension and chronic kidney disease (21). The development and the progression of Chronic Kidney Disease (CKD) have been associated with environmental lead burden in the general population and at individual level. In their study Lin et al demonstrated that chelation therapy for lead was beneficial in slowing the progression of renal insufficiency for up to one year after treatment (22). The inverse reciprocal relationships between the measured blood lead levels and glomerular filtration rate had for some time been an issue of speculation as to which comes before the other. Since the kidneys excrete lead, it is quite possible that the observed increased blood lead in chronic kidney disease patient maybe as a result impaired urinary excretion of the metal. Indeed renal impairment has been reported to cause impaired lead excretion especially in individuals with chronic lead exposure (23). Studies in the past 2 decades have addressed the controversy by showing that higher blood lead levels in individuals with renal impairment are the cause rather than the consequence of

reduced glomerular filtration rate. The Cadmibel study group in Belgium reported that the estimated glomerular filtration rates were reduced in the general population by 13 mls/min in men and 30mls/min in women for a 10 fold increase in blood lead level (₂₄). In a cohort of middle aged and older men of whom the majority were 774 Caucasians who had low level chronic lead exposure in the Normative Aging Study, Kim et al demonstrated an acceleration of the age related impairment of kidney function. They reported that a 10 fold increase in blood lead resulted in a 7 $\mu\text{mol/L}$ increase in serum creatinine equivalent to the predicted increase in serum creatinine for 20 years of normal ageing (₂₅). Sanchez –Fructuoso et al had in their study of 296 subjects/patients without history of lead exposure reported normal body lead in renal failure patients of known aetiology but elevated lead levels in 56 % of renal failure patients of unknown aetiology (₂₆). The study highlighted the hypothesis that lead poisoning may be an important factor in the pathogenesis of CKD especially in the group without identifiable cause of the disease.

LEAD POISONING AND ESSENTIAL HYPERTENSION

The association between blood lead level and hypertension appears to be stronger for the black race than the white (₁₉). Hypertension is more prevalent starts earlier and is associated higher rates of end organ damage in the African American than their White counterparts. The excess end organ damage in African Americans compared to the Whites has been linked to genetically and /or environmentally determined exaggeration in the profibrotic mechanisms such as the renin angiotensin system (RAS) and the transforming growth factor beta (₂₇). It is quite likely that lead maybe one of such environmental determinants of organ damage in hypertensive subjects. The development of adverse effects of lead exposure has some genetic contributions as some studies have suggested that alleles of the delta –amino levulinic acid dehydratase gene are among the molecular determinants of lead toxicity (₂₈). It has been hypothesised that hypertension may exist in two forms namely the salt resistant and salt sensitive forms. Whereas the salt resistant type has a normal renal autoregulation and normal renal functions the salt sensitive form is more likely to be seen in blacks with hyperuricaemia or gout and chronic low level lead intoxication, deranged renal vascular auto regulation and a tendency for progressive renal disease (₂₉).

LABORATORY DIAGNOSIS OF LEAD

POISONING

Measurement of blood lead levels is the most common method of assessing environmental lead exposure in the community. It however is considered to reflect acute better than chronic lead exposure since 99 % of the blood lead is carried by the red blood cells that have a definite life span of 3 months. Zinc dependent delta amino levulinic acid dehydratase (ALAD) activity that is important in heme synthesis is inhibited by lead leading to the formation protoporphyrins. Free Erythrocyte Protoporphyrin (FEP) and Zinc Protoporphyrin (ZPP) levels both measure the adverse effect of lead exposure on haeme synthesis and can be used instead of blood lead level to determine lead exposure. Urinary and hair lead levels are not as accurate and do not correlate as well as does blood lead levels to the total lead burden measured by ethylenediaminetetraacetic acid (EDTA) –lead mobilization test or X –ray fluorescence (20). The bone is the main reservoir of lead with upto 95 % of the total lead body burden borne therein with a half-life that runs into decades (₃₀).

PREVENTION OF LEAD TOXICITY TO THE KIDNEY

Whereas a lot of attention has been focused on the prevention of such initiation factors for the progression of chronic kidney disease such as hypertension and diabetes especially in the developed countries less recognition has been given globally to the important and largely preventable exposure to lead (₃₁). Lead poisoning poses a serious public health problem especially in the developing countries and emerging economies of the world where efforts at reducing lead poisoning has not been as pronounced as in the developed countries. Despite the obvious benefits of the legislations to curtail the use of lead in the US lead poisoning remains a huge public health problem as a result of continued usage and the previous widespread dispersion of the heavy metal in the environment (₃₂). Chelation therapy has been reported to be beneficial to subjects with lead associated kidney disease as it improves the glomerular filtration rate. 2,3 Dimercaptosuccinic acid (DMSA, succimer) has found clinical use in childhood and adulthood lead poisoning but discontinuation of the lead exposure must be ensured before its use. Ascorbic acid that is readily available in citrus fruits and in vitamin C supplements has been shown to reduce blood lead levels in animal experiments. Considering the safety of modest doses of vitamin C we recommend that it should be taken by lead exposed individuals considering that there is nothing to lose

but a lot to gain. Physicians should consider the inclusion of vitamin C supplementation into the armamentarium of agents such as aspirin, statins, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) to stem the rising tide of CKD and hypertension because of its potential not only as an antioxidant but also for its salutary effect on blood lead concentration. Global, and regional action plans at curtailing the carefree attitude in the use of lead containing products such as batteries, gasoline, and paints should put in place.

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