LEADING CAUSES AND POSSIBLE ENVIRONMENTAL CONTRIBUTORS FOR END STAGE RENAL DISEASE IN AL-MADINAH REGION IN SAUDI ARABIA

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Abstract

To find-out the leading causes and the possible environmental contributors for End Stage Renal Disease (ESRD) in Al-Madinah region, KSA.. 156 patients suffering from ESRD and 160 apparently healthy subjects of comparable age and sex were included. None of the participants was occupationally exposed to lead, cadmium and/or mercury. None affection of the control subjects with renal diseases was confirmed. Patients with undefined leading causes for ESRD (44) and an equal number of the control subjects were subjected to determine their blood levels of lead, cadmium and mercury. The study revealed that the main leading causes of ESRD in Al-Madinah region were hypertension, obstructive uropathy and diabetes mellitus. Environmental pollutants of lead (Pb) and cadmium (Cd) contributed to ESRD in Al-Madinah region particularly in urban areas. Mercury (Hg) was not a pollutant in Al-Madinah region. The study recommended early diagnosis and proper control of hypertension, obstructive uropathy and diabetes mellitus. It also recommended regular environmental monitoring for (Pb) and cadmium (Cd) levels and finds the sources of their elevations and efforts should be raised up to eliminate them.

Keywords: Environmental Pollutants, ERSD, Al-Madinah Region, KSA

Aim

The present study was conducted to find–out the most leading causes of ESRD and the role of nephrotoxic heavy metals in patients when no leading causes could be identified in Al-Madinah region.

Methods

A case control study was done in a private hospital and a charity kidney association that has a kidney dialysis center. 156 ESRD patients and 160 healthy subjects of comparable age and sex were included. A serum sample was taken from each of the patients and control subjects and was tested for lead, cadmium and mercury by using atomic absorption spectrophelometery. Urea and creatinin serum levels were also estimated using standard laboratory techniques.

Data were analyzed using SPSS-14, utilizing Students t test and the Chi square test as an appropriate. The adapted level of significance was 0.05. Correlations coefficient (r) was used to assess the presence of linear correlations.

Introduction

There has been a marked rise in the prevalence and incidence of end stage chronic kidney disease (CKD) in Saudi Arabia over the last three decades[(1)].

The first dialysis session in Saudi Arabia took place in 1971 and the first renal transplant in 1979. By the end of 2008, there were 10,203 patients on hemodialysis, 966 on peritoneal dialysis, and 7836 with functioning kidney grafts[2].

The over-all prevalence of CRF was 5.7 %[3]. This rise exceeds those reported from many countries. The enormous and rapid changes in lifestyle, high population growth, fast increase in life expectancy, and massive urbanization that has occurred over the last 3 decades combined to make the current CKD status different to what it was[1].

The major factors that influence the CKD status are the very high rate of diabetic nephropathy and shift in age demographics[4]. There are no available data about the possible environmental factors that may contribute to this rising prevalence in the general population of the kingdom of Saudi Arabia. Worldwide, one third of the patients with chronic renal failure had no obvious predisposing disease[4]. One of the silent leading causes of chronic renal failure is the chronic interstitial nephritis secondary to various nephrotoxins[5].

Heavy metals particularly; lead (Pb), cadmium (Cd) and mercury (Hg) are the most nephrotoxic environmental pollutants[6].

Chronic exposure to cadmium, (an industrial and environmental pollutant that is found in Tobacco smoke , fresh and canned fish and processed vegetable products), can cause both renal proximal tubular damage and decline in glomerular filtration rate (GFR) in humans; this has been confirmed in experimental models[7,8,9].

Cadmium nephropathy is characterized by low molecular weight (LMW) proteinuria due to diminished intrarenal uptake and catabolism of filtered proteins. In cadmium nephropathy, proximal tubular dysfunction persists until renal failure supervenes[10].

Although cadmium nephropathy has been observed in workers exposed to high levels of Cd, recent data suggest that relatively low levels of exposure in people living in polluted industrial areas increase the risk of tubular dysfunction[7].

Lead-induced nephropathy is well recognized in persons with a high level of exposure to lead[11-14].

The usual sources of lead are lead additives in motor fuels, lead water pipes, lead containing paints, smoking besides canned food and drinks[15].

Several epidemiologic studies have demonstrated a positive association between blood lead levels and the rate of the usual decrease in renal function that occurs with age in the general population[16-18].

Subjects and methods

Patients

The present study comprised 156 ESRD patients who were recruited from hemodialysis centers of Madinah National Hospital (MNH), and Al-Azhari Kidney Charity Centre during the period of the study (three months). Only patients on maintenance hemodialysis who were aged 16 years or more and who underwent hemodialysis for 6 months were enrolled in the study. Patients with any obvious chronic autoimmune diseases and those who had been hospitalized or had undergone surgery within the last 3 months before starting of the study were excluded. In addition, a questionnaire was arranged to survey patients who had a history of occupational exposure to lead or previous lead intoxication or those living in lead-contaminated areas also were excluded. Most of the patients has been undergone 4 hours hemodialysis, 3 times per week. Hemodialysis for these patients was carried out using single-use, hollow-fiber dialyzers equipped with modified cellulose, polyamide, or polysulfone membranes. Medical records of the ESRD patients were revised.

Controls

160 age and sex matched group of controls were randomly selected from those healthy subjects working in the same hemodialysis centers or visitors to MNH accompanying a relative during his / her visit to different patient clinics at MNH. Controls that had chronic illnesses or known to have an occupation that exposes them to environmental toxins were excluded by using the same questionnaires applied for the patient group. A random urine sample from each control subject was tested for albuminurea using Albustix to exclude renal disease subjects.

All subjects included in the study were interviewed for thorough history taking and physical examination.

Laboratory and Biochemical Procedures

Controlled group was subjected to urine Albustix to test for albuminuria in order to exclude renal disease.

Blood samples from each of the patients were collected in a glass tube from the arterial end of the vascular access immediately after initiating a 2-day hemodialysis at mid-week. From controls, blood samples were extracted from peripheral veins. All samples were centrifuged, and stored at −80° C for further analysis and measurement of blood lead, cadmium, mercury levels and biochemical data. Both groups were tested for blood hemoglobin, urea, creatinine and albumin. Serum high sensitivity C-reactive protein concentrations were measured by immunonephelometry.

The clearance of urea through dialysis was expressed as Kt/V, using the Daugirdas20 method. Abnormal high-sensitivity C-reactive protein level was defined as>3.0 mg/L, which corresponded to the level in patients on maintenance hemodialysis with an increased cardiovascular risk. Abnormal serum albumin level was defined as<3.5 g/dL,.

Blood lead, cadmium and mercury levels were measured using an electro-thermal atomic-absorption spectrometer (Spectra A-200Z; Varian, Lexington, Mass) [(19)]. Because most of lead exists in red blood cells, blood lead level is corrected by Zeeman Background Correction and L'vov platform hemoglobin (corrected blood lead level). In men, corrected blood lead level = blood lead level×14.0 /hemoglobin levels, in women, corrected blood lead level=blood lead level×12 /hemoglobin levels.

The mean blood levels were stratified into 2 equal groups: low blood lead levels and high blood lead level according to each matter range values.

Statistical analysis

Data were analyzed statistically by using Student's "t" test and the Chi square ($\chi 2$) test as appropriate. The adopted level of significance was 0.05. Correlation coefficient (r) was used to assess the presence of linear correlation between blood lead, cadmium and mercury levels and each of blood urea and serum creatinine levels[(20)].

Results

Table (1) displays characteristics of the studied groups. It shows that no significant difference did occur between patients and control subjects regarding the average age (t = 1.495), sex distribution ($\chi^2 = 0.023$) and residence ($\chi^2 = 0.455$).

Table (2) shows leading causes for chronic renal failure among patients and the control subjects. It shows that hypertension, obstructive uropathy and diabetes mellitus were associated with chronic renal failure in significant higher frequency than those in the control **subjects** (χ^2 = 24.426, 21.864 and 17.661 respectively) . Polycystic kidney did not occur among the control subjects while 13 chronic renal failure patients (8.4%) suffered from that

disease. Undefined leading causes for chronic renal failure were observed in 28.2% of the patients.

Table (3) shows residence and smoking habit among chronic renal failure patients with undefined leading causes and the control subjects. It shows that more than two thirds of the patients (70.45%) were living in urban areas compared to 36.36% of the control subjects. The difference was statistically significant (χ^2 = 10.276). The table sows also that smoking was reported by 50% of the chronic renal failure patients. Compared with 47.73% of the control subjects, the difference was insignificant (χ^2 = 0.045).

Table (1) : Characteristics of the studied groups.

Characteristics	Chronic Renal Failure (n = 156)	Control group (n = 160)	Tests of significance
Age (years) :			
Range	28 – 63	28 – 63	t = 1.495
Mean ± SD	44.6 ± 10.4	44.6 ± 10.4	
Sex :			
Males No. (%)	106 (67.95)	110 (68.75)	χ^2 = 0.023
Females No. (%)	50 (32.05)	50 (31.25)	
Residence :			
Urban No. (%)	48 (30.77)	59 (36.9)	χ^2 = 0.445
Rural No. (%)	108 (69.23)	101 (63.1)	

Table (2) : Leading causes for chronic renal failure among patients and the control subjects.

Leading causes	Chronic Renal Failure (n = 156) No.	%	Control (n = 160) No.	%	χ_1^2
Hypertension	35	22.4	6	3.8	24.426*
Obstructive uropathy	29	18.6	4	2.5	21.864
Diabetes Mellitus	29	18.6	6	3.8	17.661*
Polycystic kidney	13	18.4	0	0.0	---
Gout	6	8.4	6	3.7	0.0002
Undefined	44	28.2	138	86.3	108.966*

* Significance at p < 0.05.

Table (3) : Residence and smoking habit among chronic renal failure patients with undefined leading cause and the control subject.

	Chronic Renal Failure (n = 44)		Control (n = 44)		χ^2
Residence :					
Urban No. (%)	31	(70.45)	16	(36.36)	10.267*
Rural No. (%)	13	(29.55)	28	(63.64)	
Smokers No. (%)	22	(50.00)	21	(47.73)	0.045
Non smokers No. (%)	22	(50.00)	23	(52.27)	

* Significant at p < 0.05.

Table (4) : Averages of blood levels of lead, cadmium and mercury in chronic renal failure patients and the control subjects by residence.

Heavy metals and Residence	CRF (n = 44)		Control (n = 44)		t_1
	n	Mean ± SD	n	Mean ± SD	
Lead :					
Urban	31	22.7 ± 3.8	16	13.2 ± 2.3	7.91*
Rural	13	17.2 ± 3.3	28	10.9 ± 4.1	5.25*
t		4.82*		3.71*	
Cadmium :					
Urban	31	0.9 ± 0.3	16	0.5 ± 0.2	5.44*
Rural	13	0.7 ± 0.2	28	0.3 ± 0.1	4.37*
t		2.58*		3.71*	
Mercury :					
Urban	31	0.8 ± 101	16	0.6 ± 0.2	0.982
Rural	13	0.6 ± 0.8	28	0.5 ± 0.2	0.450
t		0.90		1.41	

t : Tested difference between two arithmetic means in urban and rural residence.
t_1 : Tested difference between two arithmetic means in CRF patients and control subjects. CRF = Chronic renal failure. * = Significant at $p < 0.05$.

Table (5) : Correlations between blood levels of the heavy metals (Lead, cadmium and mercury) and each of serum urea and creatinine levels.

Heavy metals	Serum urea (mg/dl)		Serum creatinine (mg/dl)	
	r	t	r	t
	(n = 44)		(n = 44)	
Lead (ug/dl)	0.543	3.224*	0.501	2.996*
Cadmium (ug/dl)	0.601	3.534*	0.698	4.036*
Mercury (ug/dl)	0.21	0.136	0.049	0.315

* Significant at $p < 0.05$.

Table (4) displays average of blood levels of lead, cadmium and mercury among chronic renal failure patients and the control subjects according to residence. It reveals that whatever the residence, the averages of the blood levels of lead and cadmium were significantly higher among chronic renal failure patients compared to the control subjects. Averages of blood levels of mercury in chronic renal failure patients did not differ from those of the control subjects whether living in urban or rural areas (t= 0.491 and 0.00 respectively). Averages of blood lead and cadmium levels were significantly among residence in urban areas compared to those in rural areas whether they suffer from chronic renal failure or not.

Table (5) shows correlations between blood levels of the heavy metals (lead, cadmium and mercury) and each of serum urea and creatinine. Blood mercury level did not correlate with neither serum urea nor serum creatinine (r = 0.021 and 0.049 respectively).

Discussion

The finding that the undefined leading causes for chronic renal failure was encountered in more than a quarter of patients (28.2%), agrees with many authors [21,22] but disagrees with others[23-25]. Discrepancies in the detectability rates of leading causes of ESRD in different areas or countries are dependent on the comprehensiveness of the diagnostic

approach and facilities as well as awareness with the relevant local environmental hazards[26]. According to Nordfors et al. and Choi et al., hypertension and diabetes mellitus are the main leading causes for ESRD in USA[27,28]. These data were confirmed by the annual United States Renal Data 2011[29]. The present work added obstructive uropathy as a leading cause of equal frequency or even more with diabetes mellitus. This high frequency of obstructive uropathy among patients with ESRD was contrary with the finding of Norris and Agodoa (2005) as well as Warren et al. (2004)[30,31]. This might be explained on the basis of the high prevalence of multiple types and sizes of renal stones associated with different pictures of renal strictures in the studied area. a matter that was supported by the observation that more than two thirds of the ESRD (69.23%) were living in rural areas. According to El Minshawy , obstructive uropathy related to schistosomiasis is more powerful renal failure inducer compared to other reasons of obstructive uropathy[22]. This might be attributed to an associated immune complex nephritis exerting a synergistic effect towards chronic renal failure[32].

The estimated high frequencies of ESRD with undefined leading causes has triggered thinking of chronic interstitial nephritis which might be incidious, symptomless and often presenting as secondary hypertension or unexplained chronic renal failure[5]. Thijssen et al. postulated that environmental pollutants might be the underlying cause for such chronic interstitial nephritis[8]. In this work; whether in the urban or the rural residence, the averages of blood lead levels among ESRD patients were not only significantly higher than those of the control subjects, but also far beyond the normal limit (15µg/dl)[24]. According to Weeden (1992), blood lead level over 15 µg/dl is associated with lead-induced organ damage[12]. The significant positive correlation between blood lead level and each of serum urea and creatinine pointed to amenability of renal tissue to lead-induced damage. This was in line with Kim et al. who reported that the increased body lead burden contributes to a significant portion of chronic renal failure[18].

The finding that urban inhabitants had significant higher averages of blood lead levels compared to rural ones should indicate more environmental pollution with lead in urban areas as none of the studied groups was occupationally exposed to lead. Moreover, frequencies of smokers among urban and rural inhabitants in this study were nearly equal. According to Nuyts et al. and Staessen, leaded-gasoline used for motor running is the main source for environmental pollution in urban areas due to traffic overcrowding. Rural areas are less exposed due to fewer number of running cars[14,16].

In the present study, the significant higher averages of blood cadmium levels among chronic renal failure patients compared to the control subjects, agree with Järup et al. and Ferraro et al.[7,10]. This in addition to the significant positive correlation between blood cadmium level and each of serum urea and creatinine reflect the role of cadmium exposure in the occurrence of chronic renal failure. Also, the observed significant higher averages of blood cadmium levels among urban inhabitants compared to rural ones might reflect more environmental pollution in urban areas. This was in line with Francis et al.[9] Hallan and Orth incriminated smoking while Milman et al. incriminated the more consumption of tinned fish and vegetables[33,34]. However the equal rates of smoking in urban and rural areas excluded smoking from being the main source of cadmium pollution in urban areas.

In this study, the averages of blood mercury levels among chronic renal failure patients and the control subjects were < 1 µg/dl which is the cut-off level for toxicity as determined by WHO (1977)[35]. The observed apparently higher mercury levels in chronic renal failure patients compared with control subjects might be explained on the basis that, kidneys in patients with chronic renal failure are not yet able to clear the accumulated body mercury from whatever source resulting in the slight higher blood mercury concentration[36]. The slight elevation of blood mercury level is a result not a cause as confirmed by the lack of

correlation between blood mercury levels and each of the serum urea and creatinine (table 5). Therefore, mercury might not be an environmental pollutants in Al-Madinah region.

Conclusion

The well defined leading causes for chronic renal failure in Madinah Region, KSA., were hypertension, diabetes mellitus and obstructive uropathy. Urban areas were significantly more affecting by environmental pollutions. We attribute pollution in urban areas to heavy traffic by all kinds of cars and preferred use of the majority of population to the caned and preserved food and drinks.

Recommendations

The following might minimize the occurrence of chronic renal failure:

1- The health care strategy should emphasize early case finding and proper control of hypertension, diabetes mellitus and obstructive uropathy.
2- There should be regular environmental monitoring of heavy metals particularly lead and cadmium levels.
3- Sources of detected pollutants should be periodically investigated and should be treated or eliminated.
4- Industrial or service activities associated with environmental pollution with heavy metals should be away from the residential areas
5- Lead-free gasoline should be made the only available engine fuel and its use should be generalized.

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