Risk factors of cardiovascular disease among children with chronic kidney disease in Gaza strip

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ABSTRACT

Background: Chronic kidney disease (CKD) is increasingly recognized as a global public health problem. Cardiovascular disease (CVD) is a major cause of mortality in patients with mild-to-moderate CKD and end-stage renal disease. There is accumulating evidence that the increase in CVD burden is present in CKD patients prior to dialysis, due both to conventional risk factors and kidney-specific disease. Detection and initiation of treatment for CVD risk factors at early stages of CKD should be effective in reducing CVD events before as well as after the onset of kidney failure. **Materials and Methods:** The study sample consisted of a total of 112 subjects aged ≤12 years: 60 CKD patients and 52 healthy control individuals. All subjects were investigated for a group of CVD risk factors such as: Hypertension, diabetes, dyslipidemia, physical inactivity, body mass index (BMI), family history of CVD, hypoalbuminemia, albuminuria, anemia, Ca x P product, and inflammation in terms of C-reactive protein (CRP). **Results:** Patients (40 males and 20 females) were categorized into four CKD stages (2, 3, 4, and 5) where, Stage 4 had the highest frequency, followed by Stages 3, 5 and 2. Evaluation of the patients indicated that they were shorter, had lower weight and had higher systolic and diastolic blood pressure as compared with control subjects. Frequency of physical inactivity among patients was two-fold higher than controls (50% vs. 25%). The patients showed significantly higher levels of cholesterol (163.6±39.8 vs. 141.8±24.2 mg/dL, $P<0.0001$), triglycerides (145.5±67.1 vs. 82.9±39.8 mg/dL, $P<0.0001$), low-density lipoprotein (92.6±31.9 vs. 72.5±19 mg/dL, $P<0.0001$) and albumin/creatinine ratio (1792±3183 vs. 11.1±6.6 mg/g, $P<0.0001$). Moreover, the patients had lower levels of high-density lipoprotein (41.9±11.0 vs. 52.7±11.7 mg/dL, $P<0.0001$), hemoglobin (9.8±1.4 vs. 11.9±0.8 g/dL, $P<0.0001$) and albumin (4.6±0.6 vs. 4.8±0.2 g/dL, $P=0.012$). The CRP showed higher occurrence among patients (40% were positive for CRP). Calcium and phosphorus evaluation showed significantly lower calcium and higher phosphorus among patients. However, the difference in Ca X P product was not statistically significant. **Conclusions:** The study indicates that many of the CVD risk factors are associated with the different stages of CKD in children patients prior to dialysis, and that some of these factors are exacerbated as CKD progresses.

Key words: Cardiovascular disease, cardiovascular risk factors, children, chronic kidney disease

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INTRODUCTION

CKD disease is now being recognized as a major public health problem that is threatening to reach epidemic proportions over the next decade.[1] The annual incidence of end-stage renal disease (ESRD) in USA, UK and Europe is 33.6, 10, 13.5 per 100,000 population, respectively.[2]

CKD is defined as kidney damage for ≥3 months, as confirmed by kidney biopsy or markers of kidney damage, with or without a decrease in glomerular filtration rate (GFR) or GFR <60 mL/min/1.73 m^2 for ≥3 months, with or without kidney damage.[3]

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in patients with ESRD, both in dialysis and in transplant patients.[4] Approximately, 50% of mortality in the dialysis population is due to CVD and the risk of death from CVD is elevated 30-fold for patients with ESRD as compared with the general population.[5] Cardiovascular morbidity and even mortality seems to be prevalent also among children and adolescents with ESRD, despite much lower exposure to "classical" risk factors for atherosclerosis, diabetes, smoking, and hyperlipidemia.[6]

There is accumulating evidence that the increase in CVD burden is present in patients prior to dialysis, due to both conventional risk factors as well as those specific to kidney disease.[4] Risk factors for the increased prevalence of CVD in CKD include traditional factors: Age, sex, diabetes, hypertension, smoking, obesity and those specific to CKD: Blood pressure changes, fluid imbalance, anemia, calcium/phosphorus metabolism, malnutrition, hypoalbuminemia, hyperhomocysteinemia, inflammation, oxidant stress, insulin resistance, altered renin-angiotensin axis and endothelial dysfunction.[7]

Gaza strip constitutes part of the Palestinian territories, with an area of 365 Km^2, lying on the coast of the Mediterranean Sea. Gaza strip is a highly populated area with a total population of 1,600,000 inhabitants.[8] Palestinian 2005 reports showed that the prevalence of renal failure was 4% with an incidence of 10.8 per 100,000.[9]

This study was undertaken in order to investigate the association between various risk factors of CVD and different stages of CKD in children patients without kidney replacement therapy in Gaza strip.

MATERIALS AND METHODS

The present study is a cross-sectional study that was conducted from the beginning of December 2008 to the end of March 2009. The study was carried out at the Nephrology Department of Abd El-Aziz El-Rantisy Specialized Pediatric Hospital in Gaza strip, Palestine.

The study population consisted of 112 subjects; divided as 60 CKD patients and 52 healthy control individuals. The control group was normotensive, non-diabetic children, with no history of renal or cardiovascular disease. Children in both control and patient groups were ≤12 and >1 years old. Regarding gender, males represented 40 (66.7%) of the patients and 28 (53.8%) of the controls, whereas females represented 20 (33.3%) of the patients and 24 (46.2%) of the controls. The age of the study population was divided into three main age groups. The age group 1–4 years represented 12 (20%) of the patients and 11 (21.2%) of the controls. Twenty (33.3%) patients and 22 (42.3%) controls belonged to the age group 5–8 years. Age group 9–12 years consisted of 28 (46.7%) patients and 19 (36.5%) controls.

Patients with kidney replacement therapy (hemodialysis, peritoneal dialysis or kidney transplantation), clinically overt inflammatory disease at the time of investigation, clinically significant overhydration or dehydration and those on anti-lipid drugs were excluded from the study.

The study ethical considerations were fulfilled through coordination with the Palestinian Ministry of Health and the approval of Helsinki Committee. Moreover, parents of the participants were given full explanation about the purpose of the study and assurance about the confidentiality of the information collected, and their written consent was obtained.

The levels of creatinine, urea, albumin, cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), phosphorus, calcium, hemoglobin, glucose and C-reactive protein (CRP) were based on laboratory investigations of blood samples collected after 12–14 h overnight fasting. LDL in mg/dL was calculated by Friedewald equation: [cholesterol – (HDL + triglycerides/5)]. Spot urine samples were tested for albumin/creatinine ratio (ACR). The ACR was calculated as: ACR (mg/g) = microalbumin in urine (mg/L) x 1000/creatinine in urine (mg/dL) x10.

Glomerular filtration rate was estimated for all participating subjects according to the Schwartz formula: GFR (mL/min/1.73m^2) = 0.55 × length/serum creatinine. Height, weight and blood pressure were measured for each participant. Body mass index (BMI) was also calculated for all subjects. Face-to-face interview questionnaire was used to obtain information about history of the disease (for patients), history of CVD in the patients' family and physical activity. According to the WHO, physical activity is defined as "any bodily movement produced by skeletal muscles that require energy expenditure," In the current study, physical activity was measured as recommended

by the US Department of Health and Human Services (2008).[10]

Sampling and processing

Blood samples were collected from patients and controls who agreed to participate in the study after overnight 12–14 h fasting. Five mL of blood was obtained from each subject and was divided into EDTA tube (1.0 mL) and plain tube (4.0 mL). A spot sample of morning urine in the fasting state was collected from each subject. Urine albumin, urine creatinine and CBC were done on the same day of collection. Serum samples were stored at -20ºC until the time of performing the analysis. All biochemical analyses were done in the laboratories of the Public Aid Hospital in Gaza.

Height, weight, BMI and blood pressure measurements

Height was measured to the nearest 1.0 cm and weight to the nearest 0.1 kg. BMI was calculated by dividing the weight in kilograms by the square of the height in meters. Blood pressure was measured in the right arm, with the subject in a relaxed, sitting position. The average of two measurements with a mercury sphygmomanometer was used for all subjects.

Biochemical analyses

Serum urea, creatinine, albumin, cholesterol, triglycerides, HDL, phosphorus, glucose, urine albumin, and urine creatinine were analyzed manually using Stat Fax-1904 plus spectrophotometer (Awareness Technology Inc. Palm city- Florida-USA). Two levels of lyophilized multi-control sera: Normal and abnormal levels were analyzed with each run. Serum total calcium was analyzed using ion-selective electrode by Nova 10 electrolyte analyzer (Nova Biomedical, Waltham city- Massachusetts-USA). Four levels of controls: I, II, III and IV, were analyzed with each run. CRP was analyzed using semi-quantitative latex method; positive and negative controls were used in each run. Complete blood count (CBC) was measured using Cell-DYN 1800 cell counter (Abbott, Wiesbaden city-Germany). Three controls (R and D systems, Minneapolis city- Minnesota- USA): High, normal and low, were used in each run of CBC.

Statistical analyses

Data entry and statistical analyses were performed using SPSS (Statistical Package for Social Sciences) software package version 11. The variables were analyzed using descriptive statistics and independent samples *t*-test. Results were expressed as frequency or mean±SD. The results were statistically significant when the *P* value was less than 0.05.

RESULTS

Measurements carried out for patients and controls are presented in Table 1. Significantly decreased height (104.7±21.2 vs. 121.3±20.0, $P<0.0001$) and weight (18.9±9.2 vs. 26.2±10.2, $P<0.0001$) were observed in the patients as compared with controls. In contrast, there was a significant increase in the systolic (111.4±18.5 vs. 98.6±7.6, $P<0.0001$) and diastolic (70.3±17.6 vs. 63.9±5.6, $P=0.014$) blood pressure in the patients as compared with the controls. Patients showed significantly higher levels of urea (130.0±62.0 vs. 22.0±8.0, $P<0.0001$) and creatinine (2.57±1.51 vs. 0.47±0.11, $P<0.0001$). Albumin/creatinine ratio also showed significantly higher values in the patients as compared with the controls (1792±3183 vs. 11.0±6.0, $P<0.0001$). The wide variation in ACR values between patients is the reason behind the observed large SD of the mean (SD=3183 mg/g), since the ACR values depend on the type of kidney disease. Regarding GFR, the results revealed that patients had significant reduction in GFR (30.9±18.4 vs. 146.7±20.9, $P<0.0001$). As compared with the controls, the patients showed significantly higher levels of cholesterol (163.6±38.9 vs. 141.8±24.2, $P=0.0001$), triglycerides (145.5±67.1 vs. 82.9±35.7, $P<0.0001$) and LDL (92.6±31.9 vs. 72.5±19.0, $P<0.0001$). Meanwhile, the patients showed lower level of HDL (41.9±11.0 vs. 52.7±11.7, $P<0.0001$). The results also indicated a significant difference between the patients and controls

Table 1: The parameters tested for patients and controls

	Patients (*n*=60) Mean±SD	Control (*n*=52) Mean±SD	*P* value
Height (cm)	104.7±21.2	121.3±20.0	<0.0001
Weight (kg)	18.9±9.2	26.2±10.2	<0.0001
SBP (mmHg)	111.4±18.5	98.6±7.6	<0.0001
DBP (mmHg)	70.3±17.6	63.9±5.6	0.014
Urea (mg/dL)	130.0±62.0	22.0±8.0	<0.0001
Creatinine (mg/dL)	2.57±1.51	0.47±0.11	<0.0001
ACR (mg/g)	1792±3183	11.0±6.0	<0.0001
GFR (ml/min/1.73m^2)	30.9±18.4	146.7±20.9	<0.0001
Cholesterol (mg/dL)	163.6±38.9	141.8±24.2	0.0001
Triglycerides (mg/dL)	145.5±67.1	82.9±35.7	<0.0001
LDL (mg/dL)	92.6±31.9	72.5±19.0	<0.0001
HDL (mg/dL)	41.9±11.0	52.7±11.7	<0.0001
Hemoglobin (g/dL)	9.8±1.4	11.9±0.8	<0.0001
Albumin (g/dL)	4.6±0.6	4.8±0.2	0.012
Calcium (mg/dL)	9.2±1.4	10.3±0.4	<0.0001
Phosphorus (mg/dL)	5.7±1.3	5.2±0.5	0.006
Ca X P (mg^2/dL^2)	52.4±12.9	53.4±5.3	0.582

in terms of hemoglobin (9.8±1.4 vs. 11.9±0.8, $P<0.0001$) and albumin (4.6±0.6 vs. 4.8±0.2, $P=0.012$). The results revealed that patients had significantly lower calcium than controls (9.2±1.4 vs. 10.3±0.4, $P<0.0001$). In contrast, patients had significantly higher phosphorus as compared with controls (5.7±1.3 vs. 5.2±0.5, $P=0.006$). The difference in the Ca x P, however, was not significant.

CRP among patients and controls was measured by qualitative and semi-quantitative latex method. Table 2 illustrates the frequency of positive and negative CRP in the subjects of the two groups.

Participants from both groups were investigated for some traditional CVD risk factors including diabetes, hypertension, physical inactivity, BMI, and family history of CVD. As shown in Table 3, no diabetic children were encountered in the study population. Hypertension was obvious in the patient group. Physical inactivity (PA) was higher in patients than control group. Physical activity is classified into two categories: "Inactive" refers to no PA beyond baseline activities of daily living or less than 150 minutes/week of moderate-intensity PA and "Active" refers to ≥150 minutes/week of moderate/high-intensity activity.

Table 2: C-reactive protein among patients and controls

CRP titer	Patients (*n*=60) no. (%)	Control (*n*=52) no. (%)
Negative		
<6 mg/dL	36 (60.0)	49 (94.2)
Positive		
6 mg/dL	3 (5.0)	3 (5.8)
12 mg/dL	13 (21.7)	–
24 mg/dL	6 (10.0)	–
48 mg/dL	2 (3.3)	–

Table 3: Traditional cardiovascular (CVD) risk factors among patients and controls

Traditional CVD risk factors	Patients No. (%)	Controls No. (%)
Diabetes		
Yes	0 (0.0)	0 (0.0)
No	60 (100.)	52 (100)
Hypertension		
Yes	28 (47.0)	0 (0.0)
No	32 (53.0)	52 (100)
Physical inactivity		
Inactive	30 (50.0)	13 (25.0)
Active	30 (50.0)	39 (75.0)
BMI*		
Normal weight	10 (16.7)	13 (25.0)
Underweight	50 (83.3)	39 (75.0)
Family history of CVD		
Yes	22 (37.0)	20 (38.0)
No	38 (63.0)	32 (62.0)

**BMI: Body mass index. Normal weight=18.5–24.9 BMI (kg/m^2). Underweight <18.5 BMI (kg/m^2)*

Body mass index is divided into groups as recommended by the WHO: Underweight <18.5 kg/m^2, Normal weight 18.5–24.9 kg/m^2, overweight 25–29.9 kg/m^2, obesity ≥30 kg/m^2, morbid obesity >40.0 kg/m^2.[11] Accordingly, the results showed that the majority of patients were underweight. The percentage of patients with family history of CVD was of nearly equal percentage of controls.

The patients were classified into 1 to 5 stages according to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI), New York-USA. NKF-KDOQI has provided evidence-based clinical practice guidelines for all stages of chronic kidney disease (CKD) and related complications since 1997. Twelve patients couldn't collect urine because of difficulty in their urine voidance; the 12 cases belonged to Stage 4 and 5 of CKD. Four patients (in Stage 3) had normal ACR while other patients had abnormal ACR (albuminuria). Figure 1 shows the percent distribution of the patients in each stage of CKD. The highest number of the patients belonged to Stage 4 followed by Stage 3, Stage 5, and then Stage 2. Stage 1 was not encountered in the studied sample.

The values of cholesterol, triglycerides, HDL, and LDL at different stages of CKD in the patients are presented in Figure 2. Generally, the results showed a gradual increase in the levels of cholesterol (160.3±50.8, 166.9±48.6, 155.2±28.8, and 186±25.7 mg/dL), triglycerides (117.7±8.0, 120.3±64.5, 153.4±54.7, and 204±99.2 mg/dL), and LDL (96.7±40.8, 97.3±40.0, 83±22.3, and 109±22.6 mg/dL) in Stages 2, 3, 4 and 5, respectively. On the other hand, HDL generally showed a gradual decrease as CKD progressed (39.7±12.8, 45.6±7.5, 41.5±13.2, and 36.1±5.8 mg/dl) in Stages 2, 3, 4 and 5, respectively.

Figure 3 showed general decrease in hemoglobin (10.0±1.7, 10.5±1.2, 9.4±1.3, and 9.2±1.8 g/dL), total serum calcium (9.6±1.1, 9.8±1.4, 8.8±1.2, and 8.3±1.2 mg/dL) in Stages 2, 3, 4 and 5, respectively. The results of albumin (4.6 g/dL) were stable at different stages of CKD, while ACR fluctuated between stages (1657±3480, 951±2121, 2521±3090, and 868± 209 mg/g in Stages 2, 3, 4 and 5, respectively). The results showed gradual increase of phosphorus (4.5±0.4, 5.3±0.7, 6.0±1.4, and 7.2±1.2 mg/dL) and Ca x P product (43.6±7.1, 52.6±12.8, 52.6±13.7, and 59.2±11.4 mg^2/dL^2) in Stages 2, 3, 4 and 5, respectively.

Distribution of CRP in the different stages of CKD is

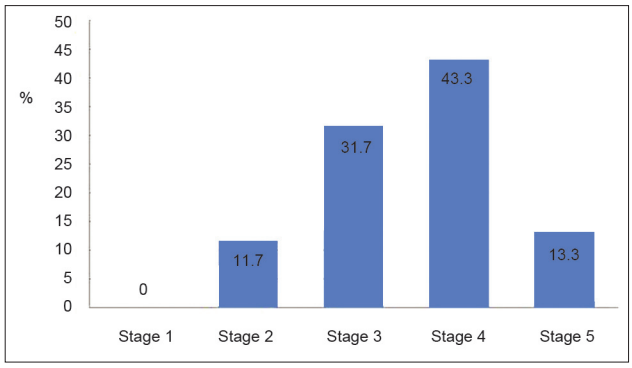

Figure 1: Distribution of chronic kidney disease stages among patients

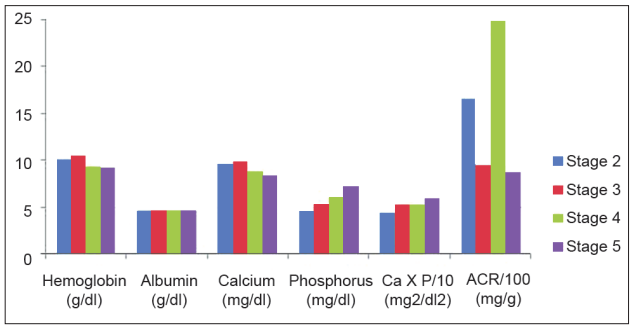

Figure 3: Relation between hemoglobin, albumin, calcium, phosphorus, Ca x P, and albumin/creatinine ratio with stages of chronic kidney disease

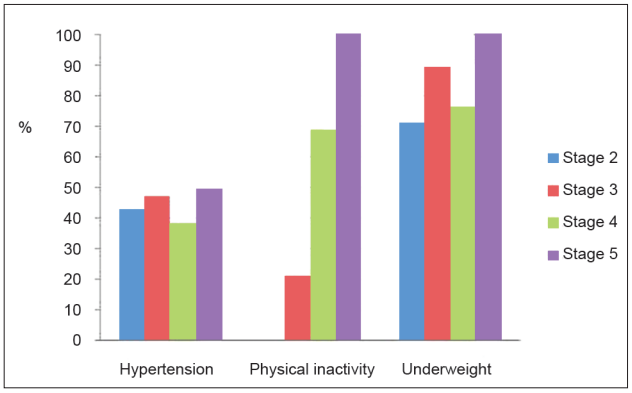

Figure 5: Distribution of some traditional cardiovascular disease risk factors with respect to chronic kidney disease stages

illustrated in Figure 4. The results showed that Stage 5 had the highest percentage of CRP-positive patients.

Figure 5 shows the frequency of some traditional CVD risk factors including hypertension, physical inactivity and BMI in various CKD stages. In general, there is a progressive increase in hypertension with CKD stages. Physical inactivity was also increased as CKD developed. Obesity, as a traditional risk factor, was not present since most of the patients were underweight; results showed there is a progressive weight loss with the development of CKD.

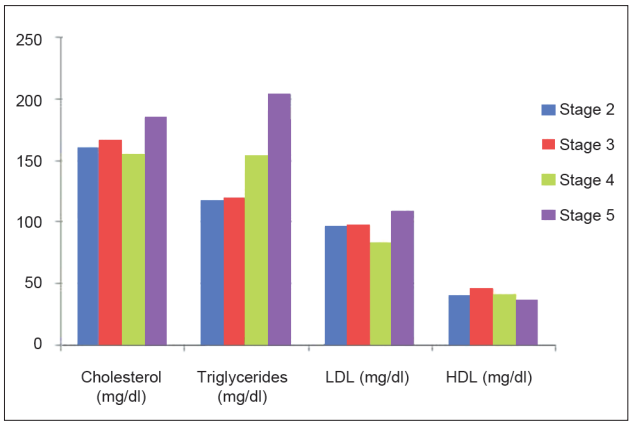

Figure 2: Relation between lipid profile and chronic kidney disease stages

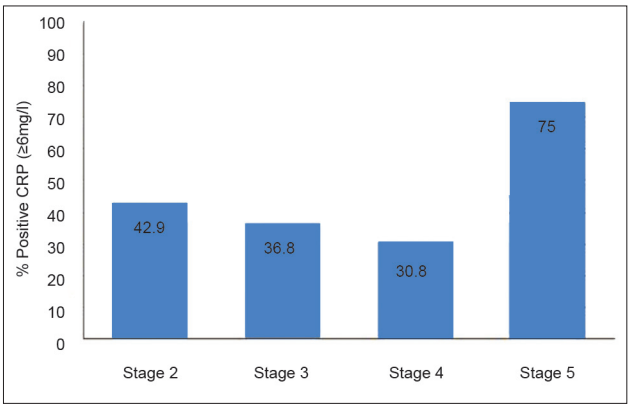

Figure 4: C-reactive protein with respect to the chronic kidney disease stages

DISCUSSION

Patients enrolled in this study could be classified into four stages of CKD (Stage 2, 3, 4 and 5). Stage 4 presented with the highest incidence, followed by stage 3, then stage 5 and stage 2. The decreased presentation of Stage 5 in the study population is due to initiation of hemodialysis or peritoneal dialysis for many of Stage 5 patients and in some cases death of the patients before reaching Stage 5. Absence of Stage 1 and reduced number of Stage 2 patients in the study population is due to low number of patients in these stages referred and hospitalized in the Nephrology Department, because the disease in such early stage is asymptomatic and criteria of kidney impairment are very mild, especially in Stage 1. Unfortunately, no data regarding the prevalence of CKD stages is available in our population to compare the study findings with. This is due to underreporting of such diseases in Gaza strip. The National Health and Nutrition Examination Surveys in 1999–2004 in the USA estimated higher prevalence of Stage 3 followed by Stages 2 and 1, while Stage 4 represented the lowest prevalence, whereas Stage 5 was excluded.[12] The study of Annear *et al*. indicated

that Stage 3 had higher prevalence followed by Stages 4 and 5.[13] Essig *et al*. in their study on early CKD stages (1, 2 and 3) found that Stage 3 had higher distribution followed by Stages 2 and 1.[14]

The study showed that the patients were shorter, had lower weight and had higher systolic and diastolic blood pressure. This result is congruent to the results of Litwin *et al*. who found that the patients were significantly smaller and lighter and had higher blood pressure than control subjects.[6] Other studies have indicated that CKD in growing children leads to a state of impaired growth due to altered metabolic status and defective growth hormone action,[15] and that high blood pressure is a leading cause of CKD in adults and contributes to the worsening of CKD in children.[16]

The present study showed that there is an association between hypertension and CKD. Forty-seven percent of patients had a history of hypertension and were treated with anti-hypertensive drugs. The relationship between hypertension and progression of CKD was clear within stages of CKD since the frequency of hypertensive patients gradually increased through Stages 2, 3 and 5. The results are in agreement with those of other authors who found an association between hypertension and CKD and showed that hypertension was frequent in all stages of CKD.[17-20] The link between CKD and hypertension is primarily through the renin-angiotensin system where, these hormones are released in response to chronic kidney damage and can contribute to a patient's hypertension by stimulating both salt retention as well as constriction of blood vessels.[21] An analysis of blood pressure in the North American Pediatric Renal Transplant Cooperative Study (NAPRTICS) database estimated the prevalence of hypertension among children with CKD as being close to 50% and demonstrated that renal function in hypertensive children with CKD deteriorated significantly more rapidly than in normotensive children, and raises the possibility that improved blood pressure control may be one method of slowing the progression of CKD in this population.[22] Another study that was carried out on CKD adult patients not receiving renal replacement therapy showed that 76% of patients had history of hypertension.[23] Locatelli *et al*. found out that hypertension plays a major role in determining cardiac damage at all stages of CKD, including the dialytic phase.[24]

Half of the patients of the present study were physically inactive. With respect to CKD stages, the results showed that all cases in Stage 2 were active, inactivity was increased in Stages 3 and 4, and in Stage 5 all cases were inactive. This indicates a positive correlation between physical inactivity and CKD progression. Stein *et al*. reported in their study that physical inactivity was associated significantly with CKD.[25] Moreover, Shlipak *et al*. stated that low physical activity is a predictor of cardiovascular mortality in persons with CKD.[26]

In terms of BMI, the results showed that the frequency of underweight among patients was higher than controls. CKD stages in the study revealed that the frequency of underweight increased as GFR declined through Stages 2, 4 and 5. Our results are in agreement with those Litwin *et al*.[6] Other studies, however, reported contradictory results, where they reported that obesity was a risk factor for CKD progression and that there was an increase in BMI as GFR declined.[27,28] Variation in the results may be because we studied the presence of obesity in our study population who are already suffering from CKD and not CKD as a sequel to obesity. Additionally, the prevalence of underweight in both the controls and patients may reflect the nutritional status or behavior of our children population.

In examining family history of CVD as a risk factor of CVD in the study population, the results indicated that there was no difference between patients and controls, since they had nearly equal percentages of subjects with family history of CVD. This observation confirms the involvement of genetic factor(s) in causing CVD.

In the general population, high plasma concentrations of LDL cholesterol, low concentrations of HDL cholesterol, and to some extent high total triglyceride concentrations are associated with increased atherosclerotic CVD risk.[29] There seems to be a gradual shift to the uremic lipid profile as kidney function deteriorates.[30] Uremic lipid profile shows dyslipidemia with elevated cholesterol and triglyceride and decreased HDL. Elevated plasma LDL cholesterol concentration is common in nephrotic syndrome but is not a typical feature of patients with advanced CKD.[31] Our study showed significant increase in total cholesterol, triglycerides and LDL in the patients as compared with the controls. The results also revealed significantly lower level of HDL in the patients. A gradual shift to the uremic lipid profile as CKD progresses was evident in the CKD stages of the present study. This finding is in agreement with other studies that assessed the association between CKD and some CVD risk factors including dyslipidemia.[18,20,23,24]

Elevation of albuminuria is associated with high risk of development of clinical nephropathy and CVD events.[32] More than one method can be used to determine urine albumin excretion.[33] In the present study, ACR in spot morning urine samples was used to measure albuminuria.

The results showed that there was association between CKD and increased level of ACR. Macroalbuminuria (ACR >300 mg/g) was predominant in the patients followed by microalbuminuria (ACR=30–300 mg/g), while few patients (8.3%) had normal albuminuria (ACR <30 mg/g). Albuminuria showed irregularity between stages of CKD, i.e., ACR levels fluctuated between stages. This irregularity can be attributed to the cause of the renal disease, since albuminuria varies according to the cause of the renal disease.[34] Our findings are congruent with other studies, which suggested that albuminuria is a common feature in CKD and is related to the underlying glomerular or interstitial damage.[7,18] Several investigators have shown that there is a continuous association between the level of albuminuria and the risk for CVD, and thus, macroalbuminuria or clinical proteinuria is associated with a higher risk for CV morbidity and mortality than microalbuminuria. The presence of macroalbuminuria is a clear manifestation of overt nephropathy and is associated with faster deterioration of kidney function.[35-37]

Anemia has been shown to be significantly associated with left ventricular hypertrophy (LVH) in both dialysis patients and patients with early CKD, suggesting that anemia is primarily implicated in the development of LVH in CKD.[38,39] Anemia is a potentially modifiable risk factor; its treatment seems to have a more beneficial effect on LVH regression if it is given as early as possible during the course of CKD and before patients have reached ESRD.[24] In the present study, the majority of patients were anemic and the results showed a continuous decrease of hemoglobin in Stages 3, 4 and 5, which indicates an association between anemia and CKD progression in the study population. These results are congruent with that of other authors who found an association between CKD and low hemoglobin or hematocrit in predialysis CKD patients.[23,24] Goicoechea *et al*. in their study on CKD patients, and after a mean follow-up of 22.3 months, found that some of the patients had a cardiovascular event; the patients who suffered from cardiovascular event were older, more anemic, and had higher pulse pressure.[17]

With respect to stages of CKD, the results showed a gradual decrease in total calcium and a progressive rise in phosphorus levels as CKD progresses. The levels of Ca x P product also showed continuous increase in Stages 2, 3, 4 and 5. This finding of calcium–phosphorus metabolism indicates the association of progressive nephron loss with phosphorus retention and hypocalcemia in pre-dialysis patients.

Hypercalcemia can develop when patients (mainly in late stages of CKD and dialysis) are given calcium and/or vitamin D and due to increased levels of parathyroid hormone (PTH), which increases calcium and phosphorus ion product. Hyperparathyroidism along with hyperphosphatemia and increased calcium phosphate ion product are identified as independent CVD risk factors.[40] The results of the present study are in accordance with Zehnder *et al*. study, which showed that serum phosphorus and PTH concentrations were elevated among patients and indicated that calcium–phosphate disorders were important CVD risk factors in CKD.[41]

Regarding CRP, the results showed that patients had higher percentages of positive CRP (CRP>6 mg/L) than controls. Stage 5 had the highest percentages of CRP-positive patients with percentages decreasing through Stage 2, stage 3 and then stage 4. The rise in inflammatory state of CKD (especially in stage 5) may be due to an increase of uremia (which is a state of chronic inflammation), reduced renal clearance of cytokines, and accumulation of advanced glycation end products.[42,43] Inflammation and increased level of CRP in patients with CKD was also observed in other studies, which reported that patients with CKD had elevated levels of CRP.[20,23]

There is a growing evidence that inflammation probably plays a key role in the initiation and progression of the atherosclerotic process.[44] High serum concentrations of markers of systemic inflammation (including C-reactive protein and interleukin-6) have been associated with atherosclerosis.[42,43]

In conclusion the present study showed a significant association between a number of CVD risk factors and CKD stages prior dialysis. These factors included hypertension, dyslipidemia, physical inactivity, anemia, albuminuria, hypoalbuminemia, and inflammation.

Identification of those risk factors among patients with CKD is potentially useful for raising awareness of the relationship between CKD and CVD, and should encourage clinicians to evaluate their CKD patients for those factors which are useful in monitoring the progression of the disease and predicting the future outcomes. Moreover, amelioration and treatment of CV risk factors at earlier stages of CKD may be effective in reducing CVD events both before and after the onset of kidney failure.

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