Original Article

Evaluation of cardiovascular risk factors in patients with chronic kidney disease

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Abstract

Background: Patients with chronic kidney disease (CKD) have a high prevalence of cardiovascular risk factors. Cardiovascular disease is the leading cause of death in patients with CKD.

Aim: The aim of this study is to determine the prevalence of the various cardiovascular risk factors in CKD patients and compare with that of healthy controls.

Methods: A case-controlled study. The study sample included 94 diagnosed CKD patients above the age of 18 years without symptoms of cardiac disease and 70 controls. Fasting plasma glucose, lipid profile, creatinine, albumin, glomerular filtration rate and urinary albumin-creatinine ratio were estimated in participants. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 20.0.

Results: The cardiovascular risk factors found in CKD patients versus controls were hypertension (62.7% vs. 11.4%), diabetes (13.8% vs. 7.1%), dyslipidaemia (50.0% vs. 31.4%), obesity (14.9% vs. 20.0%), hypoalbuminaemia (19.1% vs. 0%), microalbuminuria (55.3% vs. 20.0%) and macroalbuminuria (21.3% vs. 0%). However, only the prevalences of hypertension ($P < 0.001$), hypertriglyceridaemia ($P = 0.007$), low high-density lipoprotein (HDL) ($P = 0.050$), hypoalbuminaemia ($P = 0.007$), microalbuminuria ($P < 0.001$) and macroalbuminuria ($P < 0.001$) were statistically significant. Patients on maintenance haemodialysis had higher prevalence of hypertension ($P = 0.018$) and hypoalbuminaemia ($P = 0.001$) than pre-dialysis patients.

Conclusion: Prevalences of hypertension, hypertriglyceridaemia, low HDL, hypoalbuminaemia, microalbuminuria and macroalbuminuria were significantly higher in CKD patients than in controls.

Keywords: Cardiovascular risk factors, chronic kidney disease, diabetes, dyslipidaemia, hypertension, macroalbuminuria, microalbuminuria, obesity

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INTRODUCTION

The prevalence of chronic kidney disease (CKD) has been on a steady increase globally.[1-4] In Nigeria, prevalence rates of 1.6%–45.5% have been reported among various populations.[5-7] Wachukwu *et al.* quoted a CKD prevalence of 1.6%–12.4% from several hospital-based studies in Nigeria. However, from a screening exercise carried out among members of a university community in Port

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Harcourt during the 2014 World Kidney Day, they derived a prevalence of 1.9% for patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.[5] Alebiosu *et al*. observed a CKD prevalence of 3.6% in Sagamu.[6] A higher prevalence of 19.9% among rural dwellers was given by Abioye-Kuteyi *et al*. and 45.5% among hospitalised hypertensive patients in Maiduguri was documented by Nwakwo *et al*.[7] Afolabi *et al*. reported a CKD prevalence of 10.4% defined by persistent low glomerular filtration rate (GFR) and 12.4% defined by persistent albuminuria among patients attending a family practice clinic in Ilesa.[7] Earlier stages of CKD have a much higher prevalence than kidney failure and are usually asymptomatic and not readily recognised.[1,4,5] CKD is an irreversible and progressive disease, and patients tend to present late with complications of CKD.[2,7] Cardiovascular disease (CVD) is a common complication of CKD and is the leading cause of death, accounting for 30%–50% of all deaths in CKD patients.[8-10] Amaresan documented that CVD mortality could be up to 30 times higher in CKD patients, particularly in end-stage renal disease (ESRD), than in the general population[9] and this increased cardiovascular risk begins early in the course of kidney disease.[9,11] Cardiovascular morbidity is reported to be 3–5 times higher in CKD than in the normal population.[12] The risk of a cardiovascular event is about 20 times higher for dialysis patients than for pre-dialysis patients, and overall mortality in haemodialysis patients in developed countries ranges from 13.3% to 25%.[12] The spectrum of CVD in CKD includes ischaemic heart disease (IHD) (angina, myocardial infarction and sudden cardiac death), cerebrovascular disease, peripheral vascular disease (PVD), cardiomyopathy and congestive heart failure.[1,8,9]

The increased cardiovascular morbidity and mortality in CKD is multifactorial and entails the interplay of traditional cardiovascular risk factors and non-traditional cardiovascular risk factors which are peculiar to CKD patients. Traditional cardiovascular risk factors are prevalent in CKD patients and include hypertension, diabetes mellitus, dyslipidaemia, older age, male gender, obesity, cigarette smoking and physical inactivity.[1,9,10] Non-traditional risk factors are also known as kidney-specific or uraemia-related risk factors.[8,9] They are the direct result of kidney disease itself and/or dialysis treatments and include anaemia, microalbuminuria/proteinuria, abnormal calcium-phosphate metabolism, inflammation, oxidative stress, extracellular fluid volume overload and hyperhomocysteinaemia, among others.[1,8-10]

CVD in CKD is potentially preventable and treatable. This study is undertaken to evaluate cardiovascular risk factors in CKD patients. Prompt management of these risk factors may reduce the rate of CKD progression and development of CVD.

METHODS

Subjects

This is an observational case–control study. The target population included diagnosed CKD patients (those with symptoms and signs of renal disease and/or GFR <60 mL/min/1.73 m^2 for ≥3 months, with laboratory or radiological evidence) of a tertiary hospital, above the age of 18 years without symptoms of cardiac disease.[2] Sample size was calculated based on a CKD prevalence rate of 3.6% in a Nigerian population[6] and was estimated at 60 using the formula $n = z^2pq/d^2$ and making allowance for an attrition rate of 10%. Ninety-four patients presenting to the haemodialysis unit who were about to start dialysis therapy and those who had already started dialysis therapy were included in the study. Those with acute renal failure or other acute conditions, diagnosed CVD and other chronic disorders were excluded from the study. Seventy controls, drawn from members of staff of the hospital and patients' relatives, with normal renal function and no history of CVD, diabetes, hypertension or other acute or chronic condition were also recruited. Approval was obtained from the Ethical Committee of the hospital, and informed consent was obtained from all participants. Demographic, social and medical data of participants were assessed with the use of questionnaires.

Definition of variables

The following definitions were used in this study.

Chronic kidney disease stages

The CKD stages are Stage 1 – eGFR ≥90 mL/min/1.73 m^2 with kidney damage, stage 2 – eGFR = 60–89.9 mL/min/1.73 m^2 with kidney damage, stage 3 – eGFR = 30–59.9 mL/min/1.73 m^2, stage 4 – eGFR = 15–29.9 mL/min/1.73 m^2 and stage 5 – eGFR <15 mL/min/1.73 m^2.[2]

Hypertension

It is defined as systolic blood pressure (BP) equal to or above 140 mmHg and diastolic BP equal to or above 90 mmHg.[13]

Type 2 diabetes

It is defined as a fasting plasma glucose (FPG) ≥7.0 mmol/L.[14]

Obesity

It is defined as body mass index (BMI) ≥30 kg/m^2.[13]

Dyslipidaemia

It is defined as any one or more of hypercholesterolaemia (plasma total cholesterol ≥5.2 mmol/L), hypertriglyceridaemia (plasma triglyceride ≥1.7 mmol/L), high low-density lipoprotein (LDL) (plasma LDL cholesterol ≥3.4 mmol/L) and low high-density lipoprotein (HDL) (HDL cholesterol <1.0 mmol/L in men and <1.3 mmol/L in women).[13]

Hypoalbuminaemia

It is defined as plasma albumin concentration below the lower reference limit (laboratory reference range = 35–52 g/L).

A urinary albumin-creatinine ratio (UACR) of <30 mg albumin/g creatinine (3.4 mg albumin/mmol creatinine) was regarded as normal. Microalbuminuria was defined as a UACR of 30–300 mg/g (3.4–33.9 mg/mmol) and overt albuminuria (macroalbuminuria) as a UACR of >300 mg/g creatinine (>33.9 mg/mmol).[7]

Physical examination

BP of each participant was measured with a mercury sphygmomanometer after 10 min of rest on two occasions. Participants were weighed bare footed and wearing light clothing on a weighing balance placed on a flat surface. Their heights were measured on a portable collapsible stadiometer, and BMI = weight/height^2 was calculated.

Specimen collection

After 10–12 h overnight fast and observing aseptic procedure, freshly voided spot mid-stream urine was collected from each participant in a plain bottle for determination of UACR. Ten millilitre of venous blood was drawn from the antecubital fossa of each participant into a fluoride oxalate bottle for FPG analysis, an ethylenediaminetetraacetic acid bottle for analysis of lipids and a plain bottle for the estimation of serum creatinine and albumin. Plasma/serum was separated from blood cells after centrifugation at 2500 g for 10 min, harvested with a clean Pasteur pipette and stored at −20°C.

Laboratory analysis

Urine and serum creatinine concentrations were analysed using the kinetic Jaffe method,[15] and the serum value obtained was used to calculate the eGFR of each participant using the abbreviated Modification of Diet in Renal Disease formula: 32788 × (serum creatinine in μmol/L)$^{-1.154}$ × (age)$^{-0.203}$ × 1.210 (if black) × 0.742 (if female). Estimation of FPG was done using the colorimetric glucose oxidase method, urine and serum albumin by the bromocresol green method, HDL cholesterol by precipitation technique, total cholesterol and triglyceride by enzymatic method[15] and LDL cholesterol was calculated using the Friedewald's formula.[16]

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, Illinois, USA). Frequencies and percentages were obtained for categorical variables. Differences in proportions were analysed using the Chi-squared test. The means of continuous variables were compared using unpaired Student's *t*-test and expressed as mean ± standard deviation. Pearson correlation statistics were used to assess the relationship between variables. $P \leq 0.05$ was considered statistically significant in all the analyses.

RESULTS

The study sample included 164 participants composed of 94 CKD patients and 70 controls. The CKD patients were composed of 40 (42.6%) males and 54 (57.4%) females, whereas the controls consisted of 41 (58.6%) males and 29 (41.4%) females. The clinical characteristics of the study sample are shown in Table 1. CKD patients were older ($P = 0.001$) and had higher B*P* values than controls ($P < 0.001$).

Compared to controls, CKD patients had a higher prevalence of hypertension ($P < 0.001$), hypertriglyceridaemia ($P = 0.007$), low HDL ($P = 0.050$), hypoalbuminaemia ($P = 0.007$), microalbuminuria ($P < 0.001$) and macroalbuminuria ($P < 0.001$) [Table 2].

Details of the biochemical parameters of CKD patients compared with those of controls using the Student's *t*-test are summarised in Table 3. Serum creatinine and triglyceride and UACR of CKD patients were significantly higher ($P < 0.001$ for all), and their eGFR ($P < 0.001$) and serum albumin ($P = 0.023$) were lower than that of controls. There was a negative correlation between eGFR and age of CKD patients ($r = -0.358$, $P = 0.007$) and controls ($r = -0.346$, $P = 0.021$) [Table 4].

Table 1: Comparison of physical characteristics of chronic kidney disease patients and controls

Characteristic	Mean±SD		*P*
	CKD patients (*n*=94)	Controls (*n*=70)	
Age (years)	47.4±14.9	38.6±12.7	0.001*
Waist circumference (cm)	88.7±12.5	86.3±12.4	0.299
BMI (kg/m^2)	24.2±4.8	25.9±5.5	0.091
Systolic BP (mmHg)	130.1±22.6	116.2±11.9	0.0001*
Diastolic BP (mmHg)	81.2±15.4	73.7±7.8	0.001*

*Statistically significant ($P \leq 0.05$). SD: Standard deviation, BMI: Body mass index, CKD: Chronic kidney disease, BP: Blood pressure

Table 2: Prevalence of cardiovascular risk factors in patients and controls

Risk factor	Frequency (%)		*P*
	CKD patients (*n*=94)	Controls (*n*=70)	
Hypertension	59 (62.7)	8 (11.4)	<0.001*
Diabetes mellitus	13 (13.8)	5 (7.1)	0.372
Obesity	14 (14.9)	14 (20.0)	0.615
Dyslipidaemia	47 (50.0)	22 (31.4)	0.183
Hypercholesterolaemia	22 (23.4)	9 (13.0)	0.355
Hypertriglyceridaemia	26 (27.7)	3 (4.3)	0.007*
Low HDL	44 (46.8)	18 (25.7)	0.050*
High LDL	30 (31.9)	19 (27.1)	0.799
Hypoalbuminaemia	18 (19.1)	0	0.007*
Microalbuminuria	52 (55.3)	14 (20.0)	<0.001*
Macroalbuminuria	20 (21.3)	0	<0.001*

*Statistically significant ($P \leq 0.05$). HDL: High-density lipoprotein, LDL: Low-density lipoprotein, CKD: Chronic kidney disease

Table 3: Biochemical parameters of patients and controls

Parameter	Mean±SD		*P*
	CKD patients (*n*=94)	Controls (*n*=70)	
Serum creatinine (μmol/L)	451.9±528.3	99.5±24.0	0.0001*
eGFR (mL/min/1.73 m^2)	43.2±37.2	91.3±35.6	0.0001*
Fasting plasma glucose (mmol/L)	5.4±2.7	4.5±1.4	0.063
Triglyceride (mmol/L)	1.4±0.8	0.9±0.3	0.0001*
HDL (mmol/L)	0.7±0.2	0.8±0.2	0.380
LDL (mmol/L)	3.2±1.0	3.4±0.5	0.372
Total cholesterol (mmol/L)	4.7±1.2	4.6±0.5	0.401
Serum albumin (mmol/L)	40.3±7.2	42.9±1.9	0.023*
UACR (mg/g)	325.0±616.0	16.1±28.8	0.001*

*Statistically significant ($P \leq 0.05$). UACR: Urinary albumin creatinine ratio, eGFR: Estimated glomerular filtration rate, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SD: Standard deviation, CKD: Chronic kidney disease

Table 4: Correlation of estimated glomerular filtration rate with clinical variables in patients and controls

Variable	CKD patients (*n*=94)		Controls (*n*=70)	
	r	*P*	*r*	*P*
Age	−0.358	0.007*	−0.346	0.021*
Systolic BP	−0.264	0.073	0.234	0.126
Diastolic BP	−0.201	0.176	0.180	0.241
Waist circumference	0.045	0.764	−0.193	0.210
BMI	−0.096	0.519	−0.291	0.055

*Statistically significant ($P \leq 0.05$). *r*: Correlation coefficient, BP: Blood pressure, BMI: Body mass index, CKD: Chronic kidney disease

Twenty-four (25.5%) CKD patients were already on regular dialysis while 70 (74.5%) had not commenced haemodialysis. Majority of the CKD stage 5 patients were on maintenance haemodialysis. Prevalences of the various cardiovascular risk factors in pre-dialysis and haemodialysis CKD patients are outlined in Figure 1. Patients on haemodialysis had insignificantly lower prevalences of dyslipidaemia ($P = 0.776$) and obesity (0.616). They had higher prevalences of hypertension ($P = 0.018$), hypoalbuminaemia ($P = 0.001$), microalbuminuria (0.103), macroalbuminuria (0.164) and diabetes (0.992) [Figure 1]. However, only the prevalences of hypertension ($P = 0.018$) and hypoalbuminaemia ($P = 0.001$) attained statistical significance between the two groups. Hypertension had the highest prevalence in haemodialysis patients while dyslipidaemia had the highest prevalence in pre-dialysis patients [Figure 1].

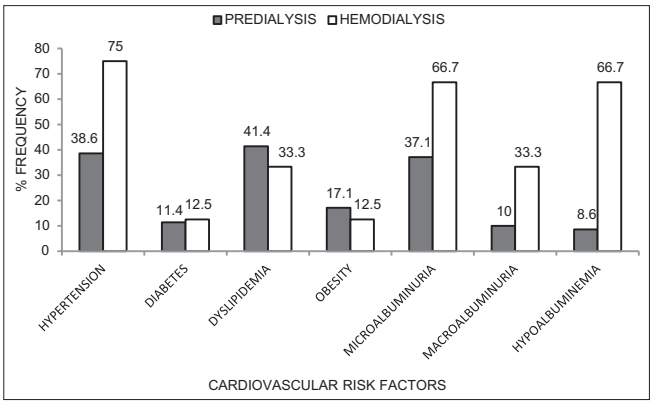

Figure 1: Prevalence of cardiovascular risk factors of pre-dialysis and haemodialysis chronic kidney disease patients

DISCUSSION

Among the traditional risk factors, hypertension and diabetes are major causes of CKD[6,7] and both can result in accelerated atherosclerosis.[9,10] Fifty-nine (62.7%) CKD patients, compared to 8 (11.4%) controls, in this study had hypertension ($P < 0.001$). Kidney disease has been documented to have a 5-fold higher prevalence among hypertensives compared with normotensive individuals.[7] Several reports indicate that hypertension is present in 43%–85% of CKD patients and account for about 25% of CKD causes in Nigeria.[2,6,7] Ulasi *et al.* reported a high prevalence of 85.2% in CKD patients. Iliou and Fumeron also documented a prevalence of 25% in CKD and 80% in haemodialysis patients.[12] Similar prevalence of 75% was observed in haemodialysis patients in this study. Hypertension in CKD is usually severe, and it increases pressure overload on the heart. It is a strong predictor of left ventricular hypertrophy (LVH), cardiac dilatation, cardiac failure and IHD.[9,12] It has been demonstrated that hypertensive patients with stage 2–3 CKD have an increased risk of new or recurrent cardiovascular events[11] and poor control of hypertension has been associated with increased risk of cardiovascular morbidity and mortality.[13] There is also a blunting of the physiological nocturnal 'dip' in BP which increases the risk for LVH and CVD.[1,9,13] Lowering BP has been proven to decrease the rate of CKD progression and reduce cardiovascular morbidity and mortality.[10]

Thirteen (13.8%) CKD patients, compared to 5 (7.1%) controls, in this study were diabetics. From a study done

in Nigeria by Alebiosu *et al*., diabetes accounted for 13.1% of the causes of CKD.[6] Similar prevalences of diabetes in healthy individuals as well as in CKD patients in Port Harcourt and other areas of Nigeria and Africa have been reported.[14,17,18] Afolabi *et al*. reported that the prevalence of kidney disease is 3 times higher in diabetic patients than in those without diabetes.[7] Diabetes is associated with many risk factors for atherosclerotic CVD including albuminuria/proteinuria, endothelial dysfunction, increased oxidant stress and dyslipidaemia.[9,10] CKD patients with diabetes have been shown to have a higher prevalence of coronary artery stenosis and higher cardiovascular mortality compared to non-diabetic CKD patients.[9,10] There is also a higher prevalence of increased carotid intima-media thickness and increased aortic stiffness (both of which independently predict cardiovascular mortality) in diabetic CKD than either diabetes or non-diabetic CKD alone.[10] Tight diabetic control not only slows progression of diabetic nephropathy but is also associated with a lower risk of macrovascular disease including IHD and PVD.[9,10]

In this study, estimated creatinine clearance was observed to reduce progressively as age increased, both in CKD patients and in healthy controls. Similar findings have been documented in previous studies.[5,19,20] Kidney function naturally declines with increasing age,[6] and the incidence of CKD has been documented to be 6–10 times higher in individuals between 70 and 90 years of age than in those between 30 and 50 years.[5] Cardiovascular morbidity and mortality in CKD patients also increase with age.[11] Oluyombo *et al*. noted that increasing age was associated with increased prevalence of CKD and clustering of cardiovascular risk factors.[20] Age has been shown to independently predict cardiovascular events in CKD patients.[7] Elderly patients (>60 years) with ESRD have been reported to have a higher incidence of CVD.[9]

CKD patients in this study had significantly higher prevalence of hypertriglyceridaemia and low HDL than controls. Prevalence of hypercholesterolaemia and high LDL was insignificantly higher in CKD patients than in controls. Overall prevalence of dyslipidaemia in CKD patients was 50%. High prevalence of dyslipidaemia has been observed in CKD, and it increases with severity of renal impairment.[11] Adejumo *et al*. recorded prevalences of 60% and 67.1%, respectively, from two studies in Southern Nigeria, which are higher than the 50% from this study.[21,22] CKD patients have a unique pattern of lipid disorders characterised by low HDL, high triglyceride levels, normal or slightly elevated LDL, marked oxidation of LDL, increased small, dense LDL, increased very LDL, increased intermediate-density lipoprotein, low apolipoprotein (Apo) A1 and Apo-A2, elevated Apo-B and Apo-C3, decreased Apo-A2 to Apo-C3 ratio, high lipoprotein (a) levels and lipoprotein remnants.[9,12,14,21] The pattern of dyslipidaemia observed in this study was low HDL (46.8%) which was the most frequent, high LDL (31.9%), hypertriglyceridaemia (27.7%) and hypercholesterolaemia (23.4%). Adejumo *et al*. also identified low HDL as the most prevalent type of dyslipidaemia in CKD patients.[21] Chijioke *et al*. reported higher prevalences for low HDL (75.8%), hypertriglyceridaemia (81.7%) and hypercholesterolaemia (90.8%), but hypercholesterolaemia was the most common dyslipidaemia that was noted.[23] The abnormal pattern of lipid disorders observed in CKD patients is mainly due to reduced activity of lipoprotein lipase and hepatic triglyceride lipase. This inhibits the uptake, and subsequent catabolism and clearance, of triglyceride-rich, apolipoprotein B-containing lipoproteins by the liver and peripheral tissues, resulting in increased levels of these atherogenic lipoproteins in the circulation.[9,11] Dyslipidaemia is a major risk factor for cardiovascular morbidity and mortality.[11,21]

Prevalence of obesity in CKD patients (14.9%) was observed to be lower than that of controls (20.0%). Adejumo *et al*. also noted that CKD patients had a lower prevalence of obesity (18.4%) compared to controls (21.1%) and attributed this to malnutrition and chronic inflammation in CKD patients.[22] Similar findings were also observed by Oluyombo *et al*. who documented lower prevalence of obesity in CKD patients (4.8%) than in controls (8.3%).[20]

Hypoalbuminaemia is known to be a potent risk factor for cardiovascular mortality and is associated with faster decline in GFR and adverse cardiovascular events.[9,20,22] Prevalence of hypoalbuminaemia observed in this study was 19.1% in CKD patients, but none of the controls had hypoalbuminaemia. Adejumo *et al*. reported a higher prevalence of 35.5% in CKD patients and similar findings in controls.[22] Agaba and Agaba quoted a much higher prevalence of 43.2%.[24] Hypoalbuminaemia may be due to proteinuria resulting from the underlying glomerular damage, malnutrition, expansion of plasma volume and reduced albumin synthesis in favour of increased synthesis of positive acute phase proteins due to inflammatory response.[9]

Fifty-five percent and 21% of total CKD patients in this study had microalbuminuria and macroalbuminuria, respectively. Twenty percent of controls had microalbuminuria, and none had macroalbuminuria. Oluyombo *et al*. recorded prevalences of 17.4% and 17.5%, respectively, among

individuals in semi-urban communities in South-West Nigeria.[20] CKD patients with microalbuminuria have a higher prevalence of cardiovascular risk factors including dyslipidaemia, hypertension, obesity and insulin resistance than those without microalbuminuria.[1] In their study, Fraser *et al.* observed that albuminuria had significant positive associations with male gender, lower eGFR, diabetes and high-sensitivity C-reactive protein.[25] Microalbuminuria/proteinuria is associated with endothelial dysfunction, increased vascular permeability, inflammation and abnormalities in the coagulation and fibrinolytic pathways and may portend increased severity of end-organ damage[1] and increased risk of CVD.[12,25] Microalbuminuria has been documented to be an adverse prognostic indicator for CVD events (including myocardial infarction, stroke and CVD death) and all-cause mortality in CKD patients.[1,25]

Prevalence of cardiovascular risk factors has been observed to be increased in CKD patients. Most of them are modifiable. Early diagnosis and prompt management of these risk factors have been reported to reduce major atherosclerotic events and rate of progression to ESRD in CKD patients.[21,22] Lifestyle modification, BP and lipid-lowering medications will be beneficial in reducing cardiovascular risk in these patients.[21]

CONCLUSIONS

Compared to controls, CKD patients were older, had higher mean BP and had a higher prevalence of hypertension, hypertriglyceridaemia, low HDL, hypoalbuminaemia, microalbuminuria and macroalbuminuria. Patients on maintenance haemodialysis had a higher prevalence of hypertension and hypoalbuminaemia but had lower prevalence of dyslipidaemia and obesity than pre-dialysis patients. Early detection, prompt and intensive management of these cardiovascular risk factors will go a long way to slow down the progression of CKD and reduce cardiovascular morbidity and mortality.

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Conflicts of interest

There are no conflicts of interest.

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