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Anaemia as a Risk Factor for Cardiovascular Disease in Patients with Chronic Kidney Disease

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This study evaluated whether anaemia poses a cardiovascular risk and whether the risk is modified by the presence of chronic kidney disease (CKD). Anaemia was defined as haemoglobin concentration ≤11.0 for both males and females. The study population included 50 individuals with various chronic kidney diseases and/or with serum creatinine ≥200 μmol L^{-1}. Another 55 subjects with similar age and sex distribution but without kidney pathology were studied as controls. Thirty percent of the subjects had CKD with an estimated GFR (eGFR) of <60 mL/min/1.73 m^2, estimated with the modification of diet in renal disease (MDRD) equation and were more likely to be anaemic and nondiabetic, higher mean values for serum creatinine (CRT), lower values for haemoglobin (HB), haematocrit (HCT) and red blood cells (RBC). CKD subjects with anaemia had a higher prevalence of several cardiovascular (CVD) risk factors; age, male sex, diabetes and hypertension and lower haematological parameters and estimated GFR. However, they had higher total cholesterol (TC) and triglyceride (TG) level. In persons with CKD, anaemia poses a further cardiovascular risk as it increases some of the traditional cardiovascular risk factors.

Key words: Haematological parameters, lipid profile, GFR, cardiovascular disease

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INTRODUCTION

Chronic kidney disease (CKD) is a prevalent, worldwide condition and the number of patients affected continues to increase. In the United States, it is estimated that, by 2010, more than two million people will be afflicted with CKD (US Department of Health and Human Services, 2000). Although the most severe form of CKD is characterized by kidney failure and the need for renal replacement therapy (hemodialysis, peritoneal dialysis, or renal transplantation), many more patients are affected by less severe forms of CKD. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) defines CKD based on glomerular filtration rate (GFR) and divides the disease into five distinct stages. Regardless of the definition, anaemia is a common complication associated with CKD. Anaemia occurs early in the development of kidney disease and worsens with declining kidney function. Many studies have demonstrated an association between the subject's haemoglobin (Hb) concentration and kidney function (McCullough and Lepor, 2005; McFarlane *et al*., 2006).

CVD risk in patients with CKD involves traditional and nontraditional risk factors (Levin *et al*., 2002; Uhlig *et al*., 2003; Vlagopoulos and Sarnak, 2005). Traditional risk factors include diabetes, hypertension, obesity, dyslipidaemia, smoking, male gender and advanced age (Uhlig *et al*., 2003). Non-traditional risk factors include hyperhomocysteinaemia, hyperparathyroidism, hyperphosphataemia, endothelial dysfunction, diastolic dysfunction and anaemia (El-Atat *et al*., 2004).

Kidney failure is known to cause anaemia and most patients undergoing long-term dialysis require treatment with erythropoietin (McCullough and Lepor, 2005; McFarlane *et al*., 2006). Anaemia is associated with lower exercise tolerance (Canadian Erythropoietin Study Group, 1990), poorer quality of life (Levin *et al*., 1999) and left ventricular growth (Foley *et al*., 1998) among patients with chronic renal insufficiency and heart failure (Harnett *et al*., 1995) and among patients undergoing dialysis. A history of cardiac failure and left ventricular hypertrophy (LVH) are strong predictors of mortality and are present in approximately 40 and 70% of patients undergoing long-term dialysis in the United States, respectively (Foley *et al*., 1998). This suggests that the harmful effects of anaemia develop well before kidney function deteriorates to the point of requiring long-term dialysis. Recommendations for haemoglobin levels among patients undergoing long-term dialysis are 11 to 12 g dL^{-1}, (NKF-K/DOQI, 2001) although the optimal level remains unclear. The objectives of this study, therefore, were to: determine the prevalence of anaemia among subjects with CKD and identify the cardiovascular risk markers among CKD subjects with anaemia.

MATERIALS AND METHODS

This study was conducted between August 2007 and March 2008. Fifty consecutive patients with various chronic kidney diseases and/or with serum creatinine ≤ 200 μmol L^{-1} from the medical unit and the diabetic clinic of the Tamale Teaching Hospital, in the Northern Region of Ghana were recruited for this study. The aetiology of the chronic kidney disease (CKD) ranged from diabetic nephropathy, 25(50%) patients; chronic glomerulonephritis, 4(8%) patients; adult polycystic kidney disease, 1(2%) patient; hypertensive nephropathy, 6(12%) patients and chronic kidney disease with unknown aetiology, 14(28%) patients. Another 55 subjects with similar age and sex distribution without chronic kidney disease were studied as controls. The participation of the respondents who are all indigenes of Ghana was voluntary and informed consent was obtained from each of them. The study was approved by the local Committee on Human Research Publication and Ethics.

Sample collection and preparation

Biochemical analysis: Venous blood samples were collected after an overnight fast (12-16 h). About 7 mL of venous blood was collected. Three milliliter was dispensed into vacutainer® plain tubes and 2 mL into fluoride oxalate tubes. After centrifugation at 500 g for 15 min, the serum and plasma were stored at -80°C until assayed. Serum biochemistry was performed with ATAC® 8000 Random Access Chemistry System (Elan Diagnostics, Smithfield, RI, USA). Parameters that were determined include: fasting blood sugar (FBS) (mmol L^{-1}), serum creatinine (CRE) (μmol L^{-1}) and serum lipid profile [(total cholesterol (mmol L^{-1}), HDL (high density lipoprotein) (mmol L^{-1}), LDL (low density lipoprotein) (mmol L^{-1}), VLDL (very low density lipoprotein) (mg dL^{-1}) and triglycerides (mmol L^{-1})]. The methods adopted by the automated instrument for the determination of the above parameters are according to the reagent manufacturer's instruction-JAS™ diagnostics, Inc. (JAS Diagnostics, Inc. Miami Florida, USA). The rest of the blood was dispensed into K_2 EDTA (dipotassium ethylene diamine tetra acetic acid) anticoagulant tubes for haematological tests. Full blood counts (FBC) were run on the samples using CELL DYN 1800 (Abbot Diagnostics Division, Abbot Laboratories. Abbot Park, USA).

Urinalysis: Early morning urine was collected in plastic containers from the respondents and urine protein was determined using the dip-stick qualitative method (CYBOW™ DFI Co Ltd, Gimhae-City, Republic of Korea).

Anthropometric variables: Anthropometric measurements included height to the nearest meter without shoes and weight to nearest 0.1 kg in light clothing. Subjects were weighed on a bathroom scale (Zhongshan Camry Electronic Co. Ltd, Guangdong, China) and their height measured with a wall-mounted ruler. BMI was calculated by dividing weight (kg) by height squared (m^2).

Estimation of GFR: The 4v-MDRD (4 variable modification of diet in renal disease) renal function equation was used to estimate the GFR of both subjects and controls using serum creatinine.

$$4v\text{-}MDRD = 186 \times SCr^{-1.154} \times age^{-0.203} \times (1.212n \text{ if black}) \times (0.742 \text{ if female})$$

Blood pressure: Blood pressure was taken by trained personnel using a mercury sphygmomanometer and stethoscope. Measurements were taken from the left upper arm after subjects had been sitting for >5 min in accordance with the recommendation of the American Heart Association (Kirkendall *et al*., 1967). Duplicate measurements were taken with a 5 min rest interval between measurements and the mean value was recorded to the nearest 2.0 mmHg.

Cut-offs: Anaemia was defined as haemoglobin ≤11.0 g dL^{-1}; hyperglycaemia ≥6.1 mmol L^{-1}; hypertriglyceridaemia ≥1.7 mmol L^{-1}; low HDL <2.2 mmol L^{-1}; LDL ≥160 mmol L^{-1}; total cholesterol ≥5.2 mmol L^{-1}.

Statistical analysis: The results are expressed as Means±SEM. Unpaired t-test was used to compare mean values of continuous variables and χ^2 was used to compare discontinuous variables. Correlation was assessed by the Pearson's rank method. A level of $p<0.05$ was considered as statistically significant. GraphPad Prism version 5.00 for windows was used for statistical analysis (GraphPad software, San Diego California USA, www.graphpad.com).

RESULTS

The mean age of the 50 participants included in this study was 48.23 years, with 56% of participants being males. The demographic and clinical characteristics of study population are as shown in Table 1. Apart from the haematological parameters (haemoglobin (HB), Haematocrit (HCT) and RBC) and GFR which were significantly decreased as compared to the control, lipid fractions (TC, TG, HDL and LDL), fasting blood sugar and blood pressure were significantly increased when the CKD subjects were compared to the control group.

Table 1: Demographic and clinical characteristics of study population

Parameters	Control	CKD subjects	p-value
Age (years)	34.74±2.15	48.23±2.510	<0.0001
BMI (kg m^{-2})	24.66±0.80	25.41±0.900	0.5270
SBP (mmHg)	120.70±1.82	140.40±3.850	<0.0001
DBP (mmHg)	70.21±1.21	90.32±2.610	<0.0001
PRT	0.04±0.02	1.17±0.260	<0.0001
HB (g dL^{-1})	12.45±0.19	9.79±0.440	<0.0001
HCT (%)	34.67±0.51	30.10±1.430	0.0023
RBC (k μL^{-1})	4.60±0.07	3.64±0.160	<0.0001
TC (mmol L^{-1})	4.54±0.14	5.32±0.300	0.0159
TG (mmol L^{-1})	1.53±0.08	2.07±0.190	0.0086
HDL (mmol L^{-1})	1.27±0.05	1.37±0.090	0.3337
LDL (mmol L^{-1})	107.70±4.84	131.50±10.53	0.0372
AI	2.40±0.12	3.21±0.230	0.0019
FBS (mmol L^{-1})	5.31±0.17	7.10±0.400	<0.0001
CRE (μmol L^{-1})	105.90±3.97	341.60±68.32	0.0004
GFR (mL/min/1.73 m^2)	103.10±8.69	66.54±8.500	0.0037

BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, PRT: Proteinuria, HB: Haemoglobin, HCT: Haematocrit, TC: Cholesterol, HDL: High Density Lipoprotein, TRIG: Triglyceride, LDL: Low Density Lipoprotein, AI: Artherogenic Index, CRE: Creatinine, GFR: Glomerular Filtration Rate, FBS: Fasting Blood Sugar, RBC: Red Blood Cell

Approximately 30% of the subjects had an estimated GFR (eGFR) of <60 mL/min/1.73 m^2. The distribution of anaemia and other variables according to eGFR is shown in Table 2. Compared to subjects with an eGFR ≥60 mL/min/1.73 m^2, those with an eGFR <60 mL/min/1.73 m^2 were more likely to be anaemic and nondiabetic. Subjects with eGFR <60 mL/min/1.73 m^2 also had higher mean values for serum creatinine and lower mean values for haematological parameters (HB, HCT and RBC). The mean values of LDL cholesterol, HDL cholesterol and total cholesterol did not appear to vary significantly with estimated GFR (Table 2).

The baseline characteristics of the CKD cohort are shown in Table 3, stratified by the presence or absence of anaemia. Subjects with anaemia had a higher prevalence of several CVD risk factors, including older age, diabetes and hypertension. Subjects with anaemia as expected also had lower values for haematological parameters (HB, HCT and RBC) and eGFR. Also, they had higher total cholesterol levels compared with subjects without anaemia. The mean values of LDL cholesterol and HDL cholesterol did not appear to vary significantly in the absence of anaemia.

From Table 4, using participants without anaemia and CKD as the reference group, participants with

Table 2: Demographic and biochemical characteristics of study population stratified by the presence or absence of CKD

Parameters	Total (50)	GFR stratification >60 (35)	<60 (15)	p-value
Demographics				
Age (years)	48.23±2.51	48.00±3.08	48.73±4.48	0.8934
Male	56.00	54.00	60.00	0.7645
Medical history and examination				
Diabetes (%)	44.00	57.00	13.00	0.0053
Hypertension (%)	38.00	37.00	40.00	1.0000
Mean SBP (mmHg)	140.40±3.85	141.80±4.66	137.00±6.98	0.5725
SBP≥140 mmHg (%)	52.00	48.60	40.00	0.7582
Mean DBP (mmHg)	90.32±2.61	90.45±3.42	90.00±3.63	0.9375
DBP≥90 mmHg (%)	58.00	51.40	53.30	1.0000
Mean body mass index (kg m^{-2})	25.41±0.89	26.32±1.09	23.30±1.46	0.1241
Laboratory values				
Mean serum creatinine (μmol L^{-1})	341.60±20.32	94.42±17.95	901.8±35.10	<0.0001
Mean hemoglobin (g dL^{-1})	9.79±0.44	10.05±0.50	9.19±0.88	<0.0001
Anaemia (%)	54.00	53.30	54.30	0.0138
Mean haematocrit (%)	30.09±1.43	31.10±1.63	27.74±2.86	<0.0001
Mean RBC (k μL^{-1})	3.64±0.16	4.09±0.17	3.00±0.34	<0.0001
Mean LDL cholesterol (mg dL^{-1})	131.50±10.53	143.20±13.73	104.20±12.20	0.0899
LDL cholesterol >160 (%)	24.00	31.40	6.00	0.0787
Mean HDL cholesterol (mmol L^{-1})	1.37±0.09	1.37±0.11	1.37±0.18	0.9981
HDL cholesterol <2.2 (%)	88.00	91.40	80.00	0.3476
Mean total cholesterol (mmol L^{-1})	5.12±0.23	5.34±0.29	4.64±0.34	0.1623
Total cholesterol >5.2 (%)	46.00	54.30	26.60	0.0215

Table 3: Demographic and biochemical characteristics of study population stratified by the presence or absence of anaemia

Parameters	No anaemia	Anaemia	p-value
Demographics			
Age (years)	46.04±3.53	50.73±3.57	<0.0001
Male	56.50	58.50	0.0456
Medical history and examination			
Diabetes (%)	40.04	52.30	0.0015
Hypertension (%)	43.40	54.44	0.0028
Mean SBP (mmHg)	140.80±6.31	140.00±4.76	0.9169
SBP≥140 mmHg (%)	43.40	55.50	0.5709
Mean DBP (mmHg)	91.14±3.66	89.60±3.76	0.7725
DBP≥90 mmHg (%)	52.20	55.55	1.0000
Mean body mass index (kg m^{-2})	25.73±1.34	25.14±1.23	0.7467
Laboratory values			
Mean serum creatinine (μmol L^{-1})	304.5±89.20	371.70±101.6	<0.0001
Mean hemoglobin (g dL^{-1})	12.33±0.21	7.62±0.50	<0.0001
Mean haematocrit (%)	38.01±0.66	21.97±1.73	<0.0001
Mean RBC (k μL^{-1})	4.39±0.08	3.01±0.22	<0.0001
Mean LDL cholesterol (mg dL^{-1})	114.8±11.09	145.70±16.77	0.1449
LDL cholesterol >160 (%)	30.40	18.50	0.5077
Mean HDL cholesterol (mmol L^{-1})	1.20±0.12	1.51±0.13	0.0999
HDL cholesterol <2.2 (%)	91.30	85.20	0.6740
Mean total cholesterol (mmol L^{-1})	4.81±0.32	5.58±0.50	0.0015
Total cholesterol >5.2 (%)	30.40	41.00	0.0358
GFR (mL/min/1.73 m^2)	97.61±14.67	82.76±15.46	0.0042

Table 4: Cardiovascular risk factors stratified by anaemia and CKD

Parameters	- Anaemia - CKD	-Anaemia +CKD	+Anaemia -CKD	+Anaemia +CKD
Elevated SBP	7(43.7)	3(42.8)	8(47)	3(37.5)
Elevated DBP	9(56.2)	3(42.8)	7(41.2)	5(62.5)
Obesity-BMI	6(37.5)	0(0.00)	3(17.6)	2(25)
Hypercholesterolaemia	6(37.5)	1(14.3)	13(76.5)	3(37.5)
Hypertriglyceridaemia	8(50)	4(57.1)	7(41.2)	4(50)
Low HDL	3(18.7)	3(42.8)	4(23.5)	3(37.5)
Hyperglycaemia	5(31.2)	4(57.1)	8(47.0)	3(37.5)
Renal insufficiency	5(31.2)	7(100)	1(5.8)	8(100)

BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HDL: High Density Lipoprotein, Column 1: Those without anaemia and CKD (n = 16); Column 2: Those with only CKD (n = 7); Column 3: Those with only anaemia (n = 17) and Column 4: Those with both anaemia and CKD (n = 8)

only CKD were particularly at risk of developing hypertriglyceridaemia, low HDL, diabetes, renal insufficiency and less likely to develop obesity. Those with only anaemia were at risk of developing hypercholesterolaemia, low HDL, diabetes and less likely to develop obesity and renal insufficiency. Subjects with both anaemia and CKD were at particularly high risk for developing hypertension, low HDL, diabetes and renal insufficiency.

From the pearson rank correlation analysis in Table 5, there are significant positive correlations between the various haematological parameters (HB, HCT and RBC) and between SBP and DBP (hypertension) among the control group and subjects with CKD. There was generally no significant correlation among the various haematological parameters in relation to creatinine (CRE) within the control group as opposed to the negative but significant correlation among the haematological parameters in relation to CRE among the subjects with CKD. CRE in relation to GFR and FBS gave negative but significant correlation within the CKD subjects. Among the control group, it is only CRE in relation to GFR that indicates such a correlation. With the exception of HDL in relation to AI which showed a significant negative correlation, all other lipid fractions showed a significant positive correlation in relation to AI among both the

Table 5: Pearson correlation coefficients of clinical variables and demographic characteristics for chronic kidney disease (upper right-hand side) and control group (lower left-hand side)

Variables	AGE	BMI	SBP	DBP	PRT	HB	HCT	CHOL	TRIG	HDL	LDL	AI	CRE	GFR	FBS	RBC
AGE		0.24	0.28	0.19	-0.16	0.17	0.14	-0.04	0.21	-0.07	-0.09	0.00	0.03	0.11	-0.08	0.06
BMI	0.14		0.19	0.23	0.16	-0.09	-0.10	-0.21	-0.13	-0.11	-0.18	-0.11	-0.06	0.28	0.08	-0.13
SBP	0.37**	0.39**		0.76***	0.10	0.10	0.12	-0.06	0.02	-0.09	-0.10	0.05	-0.02	0.06	-0.18	0.13
DBP	0.19	0.43**	0.63***		0.03	-0.02	-0.01	-0.16	0.03	-0.25	-0.16	0.02	0.11	0.06	-0.12	0.01
PRT	0.54***	-0.05	0.23	0.05		-0.03	-0.03	-0.06	-0.16	0.01	-0.03	-0.03	-0.17	0.07	-0.06	0.01
HB	-0.24	-0.08	0.25	0.08	-0.18		0.99***	-0.16	0.12	-0.10	-0.21	0.02	-0.30*	0.20	-0.06	0.92***
HCT	-0.26	-0.03	0.25	0.08	-0.16	0.96***		-0.15	0.13	-0.13	-0.20	0.06	-0.32*	0.24	-0.06	0.95***
CHOL	-0.11	0.27*	-0.07	0.16	-0.21	-0.11	-0.09		0.01	0.32*	0.96***	0.57***	-0.24	0.19	0.17	-0.15
TRIG	-0.15	0.23	0.20	0.10	-0.15	0.25	0.28*	0.40**		-0.43**	-0.17	0.46**	0.22	-0.10	-0.06	0.14
HDL	-0.19	0.04	-0.07	-0.03	-0.09	-0.01	0.03	0.05	-0.27*		0.29*	-0.52***	-0.03	-0.06	0.06	-0.10
LDL	-0.04	0.23	-0.07	0.10	-0.15	-0.16	-0.13	0.72***	0.17	-0.20		0.55***	-0.24	0.17	0.20	-0.19
AI	0.18	0.20	0.26	0.26	-0.03	0.00	-0.04	0.23	0.47***	-0.75***	0.34*		-0.16	0.19	0.02	0.08
CRE	0.08	0.27	0.14	-0.01	-0.12	0.13	0.13	0.10	0.17	0.23	0.00	0.01		-0.70***	0.29*	-0.29*
GFR	-0.33*	-0.4**	-0.30*	-0.15	-0.05	0.18	0.18	-0.18	-0.19	-0.09	-0.08	-0.08	-0.78***		0.34*	0.21
FBS	0.00	0.10	-0.05	-0.03	-0.04	-0.12	-0.04	0.07	-0.08	0.02	0.07	0.05	0.06	-0.07		-0.02
RBC	-0.31*	-0.02	0.14	-0.04	-0.27*	0.83***	0.88***	-0.08	0.21	0.07	-0.09	-0.10	0.15	0.14	-0.01	

*Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.001 level (2-tailed), ***Correlation is significant at the 0.0001 level (2-tailed). BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, PRT: Proteinuria, HB: Haemoglobin, HCT: Haematocrit, CHOL: Cholesterol, HDL: High Density Lipoprotein, TRIG: Triglyceride, LDL: Low Density Lipoprotein, AI: Artherogenic Index, CRE: Creatinine, GFR: Glomerular Filtration Rate, FBS: Fasting Blood Sugar, RBC: Red Blood Cell

control group and CKD group. GFR also indicated a significantly positive correlation with FBS only within the CKD group as shown in Table 5.

DISCUSSION

In this study, the subjects were older, more anaemic and had reduced estimated GFR (eGFR) compared to the controls (Table 1). This is in conformity with the findings of other studies (Coresh *et al*., 2002; National Kidney Foundation, 2002). These parameters together provided a greater cardiovascular (CVD) risk among the CKD study population compared to the controls. These findings are consistent with recent data which showed that CVD is independently associated with kidney function decline (Elsayed *et al*., 2007). As shown in Table 1, the CKD subjects had proteinuria which is an indication of increased protein excretion and hence a classical marker of declining kidney function (Levey *et al*., 2003). Physiologically normal persons usually excrete routinely undetectable amounts of protein in the urine. Increased excretion of albumin is a sensitive marker for chronic kidney disease and may be due to diabetes, glomerular disease and hypertension. Reduced kidney function is also associated with increased levels of inflammatory factors (Hsu *et al*., 2002; Muntner *et al*., 2004; Shlipak *et al*., 2003); abnormal apolipoprotein levels (Muntner *et al*., 2004); elevated plasma homocysteine (Muntner *et al*., 2004; Shlipak *et al*., 2003); enhanced coagulability (Shlipak *et al*., 2003); anaemia (Hsu *et al*., 2002); left ventricular hypertrophy (Levin *et al*., 1999); increased arterial calcification (Raggi *et al*., 2002); endothelial dysfunction (Blacher *et al*., 2003) and arterial stiffness (London *et al*., 2003). The mechanisms by which these and other factors interact to increase the risk of adverse outcomes remains unclear but are the focus of ongoing investigations (Muntner *et al*., 2004).

When CKD subjects were stratified according to the absence or presence of anaemia, those with anaemia had a higher prevalence of several cardiovascular risk factors including increased age, male gender, diabetes and hypertension and reduced kidney function (low eGFR). This is consistent with the findings of Thomas *et al*. (2005) who stated that the risk of cardiovascular disease in patients with moderate to severe renal impairment may be attributed, in part, to the high burden of traditional risk factors (such as diabetes, hypertension and dyslipidaemia) in this population. However, recent evidence suggests that anaemia may also represent a significant additional risk for cardiovascular disease in patients with CKD. Certainly, anaemia in CKD identifies patients at increased risk for hospitalization and premature death. Furthermore, these subjects had higher total cholesterol and triglyceride levels with normal values for the other lipid fractions. The high serum triglycerides observed among this cohort is partly consistent with the findings of Locatelli *et al*. (2003) who observed that CKD-related lipid disorders mainly consist of increased serum triglyceride levels (due to an enhanced production and accumulation of triglyceride rich lipoproteins, such as very low-density lipoproteins and intermediate-density lipoproteins due to low clearance). However, Locatelli *et al*. (2003) also observed low high density lipoprotein cholesterol levels and increased amounts of small low-density lipoproteins which are inconsistent with the observations made in this study. These cholesterol fractions activate proinflammatory pathways, thereby promoting artherogenesis and endothelial dysfunction (Snively and Gutierrez, 2004).

The principal finding of this study is that anaemia and elevated serum creatinine (Scr) could confer a risk of developing adverse CVD as they modified the predisposing factors in participants who have CKD. The combination of anaemia and CKD confers a particularly high-risk group for adverse outcomes. Several, but not all, studies have suggested that anaemia may be a risk factor for adverse outcomes in different populations and that the risk may be modified by the presence of CKD (Abramson *et al*., 2003; Al-Ahmad *et al*., 2001; Jurkovitz *et al*., 2003). For example, in atherosclerosis risk in communities (ARIC), anaemia was an independent risk factor for CVD outcomes (Sarnak *et al*., 2002) and the combination of anaemia and CKD conferred a synergistic risk for cardiovascular risk factors compared with each risk factor alone (Abramson *et al*., 2003; Jurkovitz *et al*., 2003) as confirmed by this study (Table 4). Similarly, in a secondary analysis of the studies of left ventricular dysfunction (SOLVD), a randomized controlled trial that enrolled patients with an LV ejection fraction ≤35%, lower GFR and lower HCT were independent risk factors for all-cause mortality; however, the combination conferred a synergistic risk (Al-Ahmad *et al*., 2001).

The association between increased risk of CHD and high serum creatinine in patients with anaemia might be explained by an impairment in the physiologic mechanisms of adaptation to maintain the oxygen supply to the tissues in the presence of anaemia. These mechanisms of adaptation are both non-haemodynamic and haemodynamic (Metivier *et al*., 2000). Nonhemodynamic mechanisms include increased erythropoietin production to stimulate erythropoiesis and increased oxygen extraction. In normal resting conditions, the non-haemodynamic factors can almost entirely compensate for the haemoglobin (Hb) deficit (Metivier *et al*., 2000). However, in the setting of kidney disease, erythropoietin production is impaired and therefore, the only non-haemodynamic mechanism of compensation is an increase in oxygen extraction, which has a limited effect (London, 2001).

Besides that, a strong association has been established between anaemia, CKD and cardiovascular disease through both direct and indirect effects on the heart, leading to impaired left ventricular (LV) function, LV dilatation, heart failure and death (Culleton *et al*., 1999; Shulman *et al*., 1989). It is widely known that patients with a GFR <60 mL/min per 1.73 m^2 are much more likely to have anaemia (Astor *et al*., 2002) and the prevalence and severity of anaemia increase with declining renal function (Astor *et al*., 2002) as confirmed by this study. Anaemia, together with the hypertension, which was also common in the CKD subjects (Table 1), are both known as traditional risk factors for CVD.

When subjects with only CKD were compared to the reference group (Table 4); the subjects were at risk of developing hypertriglyceridaemia, low HDL, diabetes, renal insufficiency and less likely to develop obesity. This is in agreement with the study of Muntner *et al*. (2004) and Longenecker *et al*. (2002) whose studies showed that patients with CKD were more likely to have elevated triglyceride values and lower HDL-C values.

CONCLUSION

In patients with CKD, anaemia is primarily a risk factor for CVD. Furthermore, the presence of anaemia and CKD confers a particularly high-risk group. Although true biologic interaction is rare and the duration of kidney disease, which could explain the observed association, is unknown, the magnitude of the effect may warrant, if these results are confirmed, aggressive prevention strategies of progression of kidney disease and early treatment of anaemia. Clinical trials studying the effect of early treatment of anaemia in patients with kidney disease are necessary, however, before suggesting a change in guidelines.

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