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Original Research Article

Prevalence of anemia and cardiovascular diseases in chronic kidney disease patients: a single tertiary care centre study

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ABSTRACT

Background: Chronic kidney disease (CKD) is recognized as a global health issue having high mortality and morbidity rates putting a substantial burden on global resources. CKD has become a recognised independent risk factor for several adverse health outcomes including cardiovascular disease (CVD). Anaemia is an anticipated consequence as renal function declines, and can develop at any stage of CKD. There is a strong association between anemia and cardiovascular complications in CKD patients and many studies have proven that anemia plays a key role in worsening CVD in CKD patients. The objective of this study was to study the prevalence of anemia and cardiovascular diseases in CKD patients and establish an association between them.

Methods: This study was conducted between January 2008 and June 2008 for a period of six months at a Government tertiary referral institution in south India. During this period, all newly diagnosed cases of chronic kidney disease based on the National Kidney foundation definition were included in this study. All the patients were evaluated based on detailed history taking, clinical examination and laboratory investigations after an informed consent was obtained from them. Staging of CKD was done based on the national kidney foundation (NKF/KDIGO) staging system. GFR was estimated using the abbreviated MDRD (Modification of Diet in Renal Disease) formula.

Results: Of the 333 newly diagnosed CKD patients, a large majority (264, 79.28%) of the patients in the study presented in stage 5 CKD. The mean Hb in the study was 8.42±2.20 g/dl. Anemia was present in 90.39% while 25.53% had an Hb of <7g/dl. The prevalence of anemia increased from stage 3 (66.6%) to stage 5 (94.7%) and this correlation was statistically significant ($p<0.0005$). 167 (50.15%) were found to have some form of cardiovascular disease, of which 120 (71.86%) were males and 47 (28.14%) were females. 83.93% had left ventricular hypertrophy, 16.17% had ischemic heart disease and 7.78% had congestive heart failure. 56.3% of patients in the age group 41-60 years had cardiovascular disease. The correlation between cardiovascular disease and age was statistically significant ($p = 0.04139$). And it was found that cardiovascular disease was more common when the cause of CKD was Diabetic nephropathy (65.8%) and hypertensive nephrosclerosis (84.6%). The correlation between the cardiovascular disease and etiological diagnosis of CKD was statistically significant. ($p<0.0005$).Cardiovascular disease was present in 61.2 % of the study population with diabetes mellitus and in 56.4% of the study population with hypertension. The correlations between CVD and diabetes and hypertension were statistically significant. Cardiovascular disease was present in 61.2% of the study population with Hemoglobin <7 gm/dl, 41.7% with Hb between 7-11 gm/dl and the correlation between cardiovascular disease and the level of Hb was highly significant in CKD patients.

Conclusions: Thus there is a strong association between the clinical trial of anemia, CKD and CVD and prompt identification and management of common risk factors and adequate correction of anemia is necessary to slow progression of CKD and prevent cardiovascular events.

Keywords: Anemia in CKD, Cardiovascular disease in CKD, Clinical trial, Complications, Risk factors

INTRODUCTION

According to the Kidney Disease Improving Global Outcomes (KDIGO), CKD can be defined as either damage to kidneys or a glomerular filtration rate (GFR) of < 60 mL/min per 1.73 m^2 for a period of ≥ 3 mo, with implications for health. Kidney damage can be defined by structural (detected by imaging) or functional abnormalities of the kidneys with or without a decrease in GFR. These may be apparent as either pathological irregularities or as indicators of kidney damage which include albuminuria > 30 mg/d, urine sediment abnormalities and electrolyte and other abnormalities secondary to tubular disorders.[1]

Individuals with CKD are usually staged according to their GFR levels (Stage 1-5) and albuminuria category, with a higher stage representing lower GFR levels1. GFR category is assigned as G1 (>90 ml/min/1.73 m^2), G2 (60-89 ml/min/1.73 m^2), G3a (45-59 ml/min/1.73 m^2), G3b (30-44 ml/min/1.73 m^2), G4 (15-29 ml/min/1.73 m^2) and G5 (<15 ml/min/1.73 m^2). Albuminuria categories are A1 (<30 mg/24 hours), A2 (30-300 mg/24 hours) and A3 (>300 mg/24 hours).[1]

CKD has become recognized as a key independent risk factor for several adverse health outcomes including cardiovascular disease (CVD) so much so that many studies have shown that CKD patients are more likely to die from cardiovascular disease than to develop end stage renal disease (ESRD).[2]

Anaemia is an anticipated consequence as renal function declines, and generally begins to develop before ESRD. The severity of anemia increases with declining kidney function. There is a strong association between anemia and cardiovascular complications. Specifically to LVH development and is an independent predictor of consequent cardiac morbidity and mortality among patients with ESRD.[2]

Here we have attempted to study the prevalence of anemia and cardiovascular diseases in CKD patients and establish an association between them.

METHODS

This study was conducted between January 2008 and June 2008 for a period of six months at a Government tertiary referral institution in south India. During this period, all newly diagnosed cases of chronic kidney disease based on the national kidney foundation definition were included in this study.[2] All the patients were evaluated based on detailed history taking, clinical examination and laboratory investigations after an informed consent was obtained from them. Staging of CKD was done based on the National Kidney Foundation (NKF/KDIGO) staging system.[1] GFR was estimated using the abbreviated MDRD (modification of diet in renal disease) formula.[3]

RESULTS

Of the 333 newly diagnosed CKD patients, a large majority (264, 79.28%) of the patients in the study presented in stage 5 CKD. Only 18.03% in stage 4, 2.7% in stage 3and none in stages 1 or 2 (Table 1).

Table 1: CKD stage at presentation.

CKD stage	Number	Percentage
3	9	2.70
4	60	18.02
5	264	79.28
Total	**333**	**100.00**

Table 2: Hemoglobin distribution.

Hemoglobin (g/dl)	Number	Percentage
>11	32	9.61
7-11	216	64.86
<7	85	25.53
Total	333	100.00

The mean Hb in the study was 8.42±2.20 g/dl varying withing a range of 4g/dl to 16.8 g/dl. Anemia was present in 90.39% while 25.53% had a Hb of <7 g/dl (less than the recommeneded cutoff). Mean Hb was 9.167 g/dl in stage 3, 10.195 g/dl in stage 4 and 7.993 in stage 5. The prevalence of anemia increased from stage 3 (66.6%) to stage 5 (94.7%) and this correlation was statistically significant (p<0.0005) (Table 2, 3).

Table 3: Stage wise distribution of hemoglobin levels.

Hemoglobin (g/dl)	Stage 3 CKD	Stage 4 CKD	Stage 5 CKD
>11	3 (33.3%)	15 (25%)	14 (5.3%)
7-11	2 (22.2%)	40 (66.7%)	174 (65.9%)
<7	4 (44.4%)	5 (8.3%)	76 (28.8%)
Total	**9 (100%)**	**60 (100%)**	**264 (100%)**

p <0.0005.

Table 4: Correlation of cardiovascular disease with age.

CVD	>20 years	21-40 years	41-60 years	>60 years
Yes	6 (27.3%)	53 (45.3%)	89 (56.3%)	19 (52.8%)
No	16 (72.7%)	64 (54.7%)	69 (43.7%)	17 (47.2%)
Total	**22 (100%)**	**117 (100%)**	**158 (100%)**	**36 (100%)**

Among the 333 patients included in the study, 167 (50.15%) were found to have some form of cardiovascular disease, of which 120 (71.86%) were males and 47 (28.14%) were females. 83.93% had left

ventricular hypertrophy, 16.17% had ischemic heart disease and 7.78% had congestive heart failure. 8 patients had ischemic heart disease or congestive heart failure or both in addition to left ventricular hypertrophy.

Table 5: Correlation between cardiovascular disease and etiological diagnosis.

CVD	CGN	DIAB. NEPH	HTN NEPH	Non-GLOM	Undetermined
Yes	79 (46.2%)	48 (65.8%)	22 (84.6%)	9 (29%)	9 (27.3%)
No	91 (53.8%)	25 (34.2%)	4 (15.3%)	22 (71%)	24 (72.7%)
Total	**170 (100%)**	**73 (100%)**	**26 (100%)**	**31 (100%)**	**33 (100%)**

p<0.0005; CGN - chronic glomerulonephritis; DIAB. NEPH - Diabetic nephropathy; HTN NEPH - hypertensive nephropathy; NON-GLOM - non glomerular diseases.

The prevalence of cardiovascular disease in the study population was studied and it was found that 56.3% of patients in the age group 41-60 years had cardiovascular disease. Only 27.3% of the patients below 20 years had an associated cardiovascular disease. This correlation between cardiovascular disease and age was statistically significant (p = 0.04139).

Table 6: Correlation between cardiovascular disease and diabetes mellitus.

Cardiovascular disease	Diabetic mellitus	
	Yes	**No**
Yes	49 (61.2%)	118 (46.6%)
No	31 (38.8%)	135 (53.4%)
Total	80 (100%)	252 (100%)

p = 0.02273.

Table 7: Correlation between cardiovascular disease and hypertension.

Cardiovascular disease	Hypertension	
	Yes	**No**
Yes	159 (56.4%)	8 (15.7%)
No	123(43.6%)	43 (84.3%)
Total	**282 (100%)**	**51(100%)**

Table 8: Correlation between cardiovascular disease and hemoglobin levels.

Cardiovascular disease	Hemoglobin (g/dl)		
	<7	**7-11**	**>11**
Yes	52 (61.2%)	90 (41.7%)	25 (78.1%)
No	33 (38.8%)	126 (58.3%)	7 (21.9%)
Total	85 (100%)	216 (100%)	32 (100%)

P< 0.00004.

The prevalence of cardiovascular disease in the study population with respect to the etiological diagnosis of CKD was studied and it was found that cardiovascular disease was more common when the cause of CKD was Diabetic nephropathy (65.8%) and hypertensive nephrosclerosis (84.6%). The correlation between the cardiovascular disease and etiological diagnosis of CKD was statistically significant (p<0.0005).

Table 9: Correlation between cardiovascular disease and CKD stage.

Cardiovascular disease	Chronic kidney disease		
	Stage 3	**Stage 4**	**Stage 5**
Yes	4 (44.4%)	32 (53.3%)	131 (49.6%)
No	5 (55.6%)	28 (46.7%)	133 (50.4%)
Total	**9 (100%)**	**60 (100%)**	**264 (100%)**

p= 0.82286.

Some form of cardiovascular disease was present in 61.2 % of the study population with diabetes mellitus and in 48.6% of the study population without diabetes mellitus. This correlation between presence of cardiovascular disease and diabetes mellitus in CKD patients was statistically significant (p = 0.02273).

Cardiovascular disease was present in 56.4% of the study population with hypertension and in 15.7% of the study population without hypertension. This correlation between the presence of cardiovascular disease and hypertension in CKD patients was highly significant (P<0.0005).

Cardiovascular disease was present in 61.2% of the study population with Hemoglobin <7 gm/dl, 41.7% with Hb between 7-11 gm/dl and the correlation between cardiovascular disease and the level of Hb was highly significant in CKD patients. P<0.0005 but there was a paradoxical increase in percentage of patients with cardiovascular disease among those with value more than 11g/dl (78.1%). Whether an association exists between increased incidence of cardiovascular disease and higher values of Hb above 11g/dl in patients with CKD cannot be commented upon because of the lesser number of patients in this group.

There was no significant correlation between the presence of cardiovascular disease and CKD stage at presentation in the study population.

DISCUSSION

The NKF defines anemia as hemoglobin of less than 13.5 g/dL in men and less than 12.0 g/dL in women. Although anemia may be diagnosed in patients at any stage of CKD, there is a strong correlation between the prevalence of anemia and the severity of CKD4. In our study too, anemia was estimated to be present in 90.39% of people with any stage of CKD. The prevalence of anemia increased with stage of CKD, from 66.6% at stage 3 to 94.7%% at stage 5. A similar trend has been reported by several other authors consistent with the known pathogenesis of CKD.

While anemia in CKD can result from multiple mechanisms - iron, folate, or vitamin B12 deficiency; gastrointestinal bleeding; severe hyperparathyroidism, systemic inflammation, and shortened red blood cell survival-decreased erythropoietin synthesis is the most important and specific etiology causing CKD-associated anemia. The more important fact though is that in CKD patients, irrespective of the stage, anemia predicts a poor prognosis and is associated with increased mortality compared with those individuals with preserved hemoglobin (Hb).[4]

Cardio vascular disease (CVD) is emerging as the most common cause of death in patients with end stage renal disease (ESRD). 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, malnutrition, hypoalbuminemia, hyperhomocysteinemia, inflammation, oxidant stress, insulin resistance, altered renin angiotensin axis and endothelial dysfunction.[5] In this study there was a statistically significant correlation between age and presence of cardiovascular disease with 56.3% of the CKD patients in the age group of 41-60 years having some form of cardiovascular disease as opposed to only 26% in the age group of <20 years having CVD. Cardiovascular disease was present in 61.2 % of the study population with diabetes mellitus and in 56.4% of the study population with hypertension. The correlations between CVD and diabetes and hypertension were statistically significant.

The high burden of CVD in CKD cohorts, and vice versa, is a reflection of the fact that both disease processes share similar risk factors. Having one disease increases an individual's risk of having the other; the combination of both is associated with a higher mortality than either disease alone6. Among the cause of deaths, cardiovascular disease (CVD) is emerging as the most common cause of death in patients with End Stage Renal disease (ESRD). Age adjusted CVD mortality is about 30 times higher in ESRD than in the general population. The risk of dying of cardiac complications is 65 times higher in dialysis patients between 45-54 years and 500 times higher than the general population in the younger cohort. This multifold increased CVD risk may be related to the primary disease causing chronic kidney disease (CKD) eg: diabetes mellitus (DM), hypertension (HT) and /or presence of one or more of associated risk factors like anemia, dyslipidemia etc.[5]

Left ventricular hypertrophy (LVH) is a common finding and a strong adverse prognostic factor which has not been previously analyzed in Indian patients. Left ventricular abnormalities are very highly predictive of future cardiovascular events and death in Indian CKD patients regardless of age, diabetes mellitus, hypertension, hyperlipidemia, smoking and coronary heart disease. In our study too, 50% of the study population had some form of cardiovascular disease, with 83.3% of them having LVH, followed by Ischemic heart disease (16.17%) and congestive cardiac failure (7.78%).

Epidemiological and observational data suggest that Hb levels are an important determinant of outcomes in patients with CKD and CVD. Anemia is associated with CKD progression, an increased risk of developing CVD and decreased survival.[6] The anemia of CKD increases morbidity and mortality from cardiovascular complications which may lead to further deterioration of renal function and the establishment of a vicious cycle termed the cardio renal anemia syndrome.[2]

In an observational study it was demonstrated that each 10 g/L drop in hemoglobin, leads to a 20%-40% increased risk of developing heart failure, LVH or mortality in those patients on long-term dialysis.[2] In our study too, cardiovascular disease was present in 61.2% of the study population with Hemoglobin <7 gm/dl, 41.7% with Hb between 7-11 gm/dl, which was statistically significant.

Thus, based on the current body of literature, we can safely conclude that anemia is associated with poorer outcomes in patients with CVD and CKD, and that in turn, CVD and CKD are closely related. Since anemia plays a key role in worsening the outcomes of both these disease states, there is increased focus on adequate correction of anemia with erythropoietin. The complexity and the intricacies of the relationship between CKD, CVD and anemia however require further research.[6]

CONCLUSION

Chronic kidney disease (CKD) is now recognized as a risk factor of both end-stage renal disease (ESRD) and independently cardiovascular disease (CVD). Anemia, a predictable complication of CKD, plays a key role for worsening both CKD and cardiac performance in a vicious circle. Thus an increased awareness of an unmistakable association between CKD, CVD and

anemia, prompt identification of the common risk factors as well as aggressive treatment for anemia with erythropoietin have been recommended to help slow the progression to ESRD and prevent cardiac events in CKD patients.

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