Correlation of Anemia, Secondary Hyperparathyroidism with Left Ventricular Hypertrophy in Chronic Kidney Disease Patients


Abstract

Aims: To demonstrate the correlation of anemia and intact parathormone with left ventricular hypertrophy in a cohort of Chronic Kidney Disease (CKD) patients in a tertiary care centre.

Methods: A cross-sectional study was done over 2 years on 230 renal failure patients (160 males, 70 females), aged 15-75 years, who had elevated serum creatinine and reduced GFR. The patients were assessed based on clinical history and a number of laboratory parameters including serum creatinine, calcium, iPTH level, Hb, Hct, GFR and LVMI.

Settings: Patients were seen as inpatients and outpatients in a tertiary care centre.

Results: In CKD stages I, II and III, 51% of the patients had anemia (Hb<11gm/dl), 16% of the patients had elevated iPTH, 79% of male patients and 71% of female patients had LVH. In Stage IV CKD, 55% of the patients had anemia, 25% of the patients had elevated iPTH, 74% of male patients and 100% of female patients had LVH. In stage V CKD, 76% of the patients had anemia, 31% of the patients had elevated iPTH, 77% of male patients and 96% of female patients had LVH. In all five stages, 78% of male patients and 71% of female patients with elevated iPTH had LVH, 81% of male patients and 90% of female patients with anemia had LVH. Systemic hypertension was present in 69% of the patients.

Conclusion: Anemia is widely prevalent in our cohort of CKD patients. Severity of anemia is correlated to LVH and secondary hyperparathyroidism in these patients.

INTRODUCTION

The association of anemia with Chronic Kidney Disease (CKD) has been recognized since the early 19th century. Moreover, various studies done over the years have shown not only a higher incidence of anemia, but also a significantly higher incidence of cardiac complications, particularly left ventricular hypertrophy in CKD patients. In fact, anemia has been cited as an independent risk factor for the development of left ventricular hypertrophy (LVH) in CKD patients. Also note worthy is the higher incidence of LVH, in CKD patients with elevated parathormone levels.

It is known that anemia is a strong predictor of development of LVH and morbidity and mortality in ESRD. The importance of anemia in ESRD dialysis patients was shown by the observation that decreases in hemoglobin (Hb) level of 1g/dl incrementally increased mortality by 18-25% and LVH by ~ 50%. In fact the role of anemia as a cardiac risk factor was shown in an evaluation of 246 patients in which it was found that every 0.5 gm/dl decrease in Hb increased the relative risk of left ventricular growth by 32% (P=0.04). Also in a prospective study of recombinant erythropoietin use in pre-dialysis patients; increase in mean Hb of 2.7g/dl was accompanied by a decrease in Left Ventricular Mass Index (LVMI) in almost all patients. This even in the absence of improved blood pressure control, confirmed the role of anemia in the genesis of LVH. And thus the role of recombinant erythropoietin for correction of anemia, which was shown to lead to the reversal of hypertrophy, came into significance.

The exact role of parathormone (PTH) as a cause of LVH in CKD patients is yet to be determined. Various theories proposed include vascular and visceral calcification, arteriolar wall thickening, myocardial interstitial fibrosis, and promotion of hyperlipidemia.
and hypertension due to the effect of PTH as possible aetiologies for the development of LVH in CKD patients. However, the correlation of anemia and PTH with LVH in CKD patients has not been studied adequately in the Indian context, and therefore the present prospective study was carried out.

**MATERIAL AND METHODS**

We undertook a prospective study over 2 years on 230 patients (160 males, 70 females) with varying severity of renal failure from the age group of 15 years - 75 years, who were either in-patients admitted in a tertiary care setting or attended Nephrology out-patient department for two years, and all of whom had elevated serum creatinine and reduced GFR. Of the 230 patients, there were 114 diabetics and 116 non-diabetics. The National Kidney Foundation has classified chronic kidney disease into five stages which is universally followed now – Stage I with GFR > or = 90 ml/min, Stage II with GFR between 60-89 ml/min, Stage III with GFR between 30-59 ml/min, Stage IV with GFR between 15-29 ml/min, and Stage V with GFR < 15 ml/min. However for the convenience of this study, we have grouped stages I, II and III together since they are mild renal failure, whereas Stage IV is moderate renal failure, and Stage V is severe renal failure requiring dialysis.

Initial assessment included detailed clinical history with regard to duration of renal failure (in years), diabetes /hypertension if any, and whether the patients were on dialysis or erythropoietin replacement. Height, weight and blood pressure was noted in all patients. Laboratory tests including serum creatinine, Hb, Hct (by Coulter Counter), calcium, creatinine clearance (calculated according to creatinine clearance by Cockroft and Gault formula), and intact parathormone (iPTH) level (done by Chemiluminescence Immuno Assay) were also done. The NKF K/DOQI guidelines have recommended PTH target ranges for the progressive stages of CKD. The iPTH by the assay in normal individuals is < 70 pg/dl. For individuals upto Stage III, iPTH should be between 35-70 pg/dl, for those in Stage IV iPTH should be between 70-110 pg/dl, and for those in Stage V iPTH should be between 150-300 pg/dl. LVMI was calculated by using the ratio of LV mass to body surface area. Calculated by using the formula—— LV Mass = 0.8 x [LS(Vsd+LVIDd+LVPWd)3 - (LVIDd)3 + 0.6 gms by Daveroux. In this formula LVMI is calculated by subtracting the ventricular cavity from the ventricular mass to get the wall thickness and then multiplying this with specific gravity, other variables in the formula being correction factors. BSA calculated by V (height in cms) x (weight in Kgs) / 3600. Creatinine Clearance (Ccl) was calculated by using the formula of Cockcroft and Gault given below.

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\text{Creatinine Clearance (Ccl) was calculated by using the formula of Cockroft and Gault} \\
\text{calculated by using the formula of Cockroft and Gault (weight in Kgs) / 3600.}
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\text{Calculated by using the formula ——— LV Mass = 0.8 1.04} \\
\text{(LVSd+LVIDd+LVPWd)3 - (LVIDd)3 + 0.6 gms by Daveroux. In this formula LVMI is calculated by} \\
\text{subtracting the ventricular cavity from the ventricular mass to get the wall thickness and then multiplying this} \\
\text{with specific gravity, other variables in the formula being correction factors. BSA calculated by V (height in cms) x} \\
\text{(weight in Kgs) / 3600. Creatinine Clearance (Ccl) was calculated by using the formula of Cockroft and Gault} \\
\text{given below.}
\]

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\text{140 - Age x wt in Kg} \times 0.85 = \text{ml/min} \quad \text{For females}
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\text{72 x Sr Creatinine mg/dl}
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\text{NKF-DOQI Anemia work up target group guidelines suggested an Hb of 11 gm/dl (or a hematocrit of 33%)} \\
\text{after extensive evaluation of literature.}^{7}\text{Hence we took Hb < 11 gm/dl as anemia in CKD patients.}
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Chi square test has been applied to find if there is any relationship between the variables and odds ratio was calculated to determine the risk of abnormal values as compared to the normal values. P value < 0.05 is taken to be significant. Table 1 shows the demography of the patients with Chronic Kidney Disease.

**Table 1 : Demography of patients with CKD**

<table>
<thead>
<tr>
<th>Age</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-30</td>
<td>17</td>
<td>7.4</td>
</tr>
<tr>
<td>31-45</td>
<td>37</td>
<td>16.1</td>
</tr>
<tr>
<td>46-60</td>
<td>105</td>
<td>45.7</td>
</tr>
<tr>
<td>61-75</td>
<td>66</td>
<td>28.6</td>
</tr>
<tr>
<td>&gt;75</td>
<td>5</td>
<td>2.2</td>
</tr>
</tbody>
</table>

The commonest age group was 46 to 60 years (45.7%) with mean age being 53.55 years [Table 1]. Out of the 230 patients studied, 160 patients were males (69.6%) and 70 were females (30.4%). In this study, there were 49 patients in Stages I-III, 80 patients in Stage IV and 101 patients (43.9%) in Stage V.

**RESULTS**

Systemic hypertension with BP>140/90mmHg was present in 69% of the patients (males 38% and females 31%) and were on various antihypertensive medications.

Among 101 patients in Stage V, majority of the patients (76%) had anemia with Hb < 11 gm/dl with 55% of the patients having an Hb% of 7.1-11 gm%. Similarly, this was observed with the 80 patients in Stage IV. Majority of the patients (55%) had anemia with 42.5% of the patients having an Hb% of 7.1-11 gm%. Among forty nine patients in Stages I-III, 25 patients (51%) had anemia.

With regard to the prevalence of cardiovascular diseases in CKD patients, in Stage V, out of 74 male patients, 57 patients (77%) and out of 27 female patients, 26 patients (96%) had LVH (P < 0.05). 23 out of 44 patients (52%) had systolic dysfunction. In Stage IV, out of 58 male patients, 43 patients (74%) and all of the 22 female patients had LVH. And out of 53 patients, 27 patients (51%) had systolic dysfunction. In Stages III-IV, out of 28 male patients, 22 patients (79%) and out of 21 female patients, 15 patients (71%) had LVH. Out of 32 patients, 20 patients (62.5%) had systolic dysfunction. As per Table 3, 82% of male patients with Hb < 7 gm/dl, 80% of male patients with Hb between 7.1-11 gm/dl and 68% of male patients with Hb > 11 gm/dl had LVH. Similarly among female patients, 91% of the patients with Hb < 7 gm/dl, 89% of the patients with Hb between 7.1-11 gm/
dl, and 63% of the patients with Hb > 11 gm/dl had LVH. Thus we see that with a higher hemoglobin level, the incidence of LVH is lesser.

With regard to the prevalence of hyperparathyroidism in CKD patients, we found that 30 out of 96 patients (31%) in Stage V, 15 out of 60 patients (25%) in stage IV, and 7 out of 43 patients (16%) in Stages I-III had elevated iPTH values between 70-300 pg/dl (Table 2). As per Table 4, 35 out of 45 male patients (78%) with elevated iPTH values between 70-300 pg/dl had LVH as compared to 68 out of 95 male patients (72%) with iPTH values in the normal range (<70 pg/dl). Also, majority of the female patients, 5 out of 7 patients (71%) with elevated iPTH values had LVH (Table 4).

**DISCUSSION**

Chronic kidney disease which leads to anemia manifests as cardiac failure, exercise intolerance, defective cognitive functions etc. Anemia associated with CKD is typically normocytic and normochromic. Anemia is seen early in the course of CKD, the decline in hemoglobin concentration starting at levels of Ccl of around 70 ml/min among men and 50 ml/min among women, and progressing relentlessly so that closer to ESRD, majority of the patients with CKD have anemia. However, the onset of renal anemia may occur at Stage II or III CKD except in patients with diabetes mellitus. In our cohort of patients, 51% of the patients in stages I-III, 55% of the patients in stage IV, and 76% of the patients in stage V had anemia, with an Hb < 11 gm/dl. Patients with GFR<30 ml/min are at 1.9 times more risk of having Hb<11 gm/dl as compared to patients with GFR>30 ml/min. P value is 0.04 (<0.05), which is significant (Table 3). The etiology of anemia in CKD is multifactorial and varies between patients. But the primary underlying defect is erythropoietin deficiency. Anemia may in fact contribute to the progression of renal disease through hypoxia and oxidative stress. And since anemia of CKD is often inadequately monitored and treated, the European Best Practice Guidelines (EBPG) have
recommended giving recombinant human erythropoietin (rHuEPO) as soon as Hb concentration falls below 11gm/dl, after ruling out other causes of anemia such as iron and/or vitamin deficiency. Our observational study highlights the importance of the diagnosis and management of anemia with erythropoietin therapy in the Indian CKD patients.

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 of CKD patients, 78% of male patients and 71% of female patients in stages I-III, 74% of male patients and 100% of female patients in Stage IV, and 77% of male patients 96% of female patients in stage V had LVH. This is in accordance with another study in which 74% of the patients exhibited baseline LVH by the time they reached ESRD. We also found that 52% of the patients in stage V, 51% of the patients in stage IV and 62% of the patients in stages I-III had systolic dysfunction which was due to LVH and could aggravate cardiovascular mortality.

Thus we see a higher prevalence of both anemia and LVH in CKD patients. In fact while looking at the subgroups, CKD patients with severe anemia clearly have a higher prevalence of LVH, as seen in our study where 82% of the male patients and 91% of the female patients with severe anemia (Hb < 7 gm/dl) had LVH. As the hemoglobin progressively improved, the risk of developing LVH became less. This finding is in accordance with other clinical trials that have demonstrated that partial correction of anemia leads to improvement in the cardiac index and oxygen transport that can arrest or reverse LVH progression. Hyashi et al. who looked at predialysis population reported that the baseline LVMI of patients with Hct <25% was 140.6 ± 12.1 gm/m² (n=9). After 4 months of therapy, Hct levels had increased to 32.1% ± 1.8% while LVMI had decreased to 126 ±10.0 gm/m². Similar progressive improvements were seen after 12 months, when mean Hct levels had increased to 39.1% ± 2.4% and LVMI had decreased to 111.2 ± 8.3 gm/m². This underscores the importance of adequately addressing anemia in predialysis stages and its implications in the management of cardiovascular disease. The impact of anemia as a mortality risk multiplier along with CKD and cardiac failure is reported in a large number of studies.

With regard to the effect of PTH on LVH, various studies have shown that hyperparathyroidism increases the cellular binding of Ca²⁺, and also activates fibroblasts and can disrupt myocardial metabolism. This hypertrophic effect of PTH and dysregulated calcium phosphorus product contributes to cardiovascular disease in HD patients with secondary hyperparathyroidism. Secondary hyperparathyroidism can lead to anemia through bone marrow fibrosis, which in turn can lead to LVH. In one of our recent publications from South India, significant secondary hyperparathyroidism and very high calcium phosphorus product were less frequently seen compared to studies from developed countries. In our study 78% of male patients and 71% of female patients with iPTH values between 70-300 pg/dl had LVH, which is in accordance with the study done by Rostand and Druke. And since secondary hyperparathyroidism begins in the early stages of CKD, it is important to monitor iPTH levels from the early predialysis phase through ESRD, and make early interventions in the predialysis phase itself which will lead to the amelioration of cardiovascular morbidity and mortality in ESRD. Systemic hypertension was present in 69% of our study population on drug therapy. However, because of the paucity of multicentre Indian studies, we do not know the prevalence of secondary hyperparathyroidism in Indian CKD in its various stages, and thus more prospective longitudinal studies are required.

The common causes of morbidity and mortality in CKD patients are cardiovascular disease and infection. The treatment of anemia also improves immune functions.

Our study has some inherent limitations such as the lack of follow up of the whole cohort to assess the mortality, and we did not study the impact of hyperlipidemia, homocysteine levels, inflammatory status or the severity of hypertension.

However, the study clearly underscores the importance of anemia as a frequent complication of CKD and its severity correlated with left ventricular hypertrophy, and secondary hyperparathyroidism in a cohort of south Indian patients.

CVD is in fact, the leading cause of death in end-stage renal failure representing 43-52% of overall mortality. Thus patients with CKD should be considered in the highest risk group for subsequent CVD events, and control of the risk factors including appropriate adaptive parathyroid hyperplasia and iPTH should be adequately addressed. And since anemia has been found to be an independent risk factor for LVH, it is imperative that anemia be treated in patients with CKD complicated by cardiac muscle remodeling to obtain a target hematocrit of at least 33% as specified in the clinical practice guidelines of the National Kidney Foundation. Dialysis Outcomes Quality Initiative (NKF DOQC).

**References**


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**Announcement**

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