Original Research Article

Treating anaemia in chronic kidney disease improves cardiovascular outcome by improving left ventricular mass index

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ABSTRACT

Background: Chronic kidney disease (CKD) has a high global prevalence of 11 to 13% with majority in stage 3. This has increased the burden on health care. Anaemia is important and independent risk factor for adverse cardiovascular outcome in CKD.

Methods: Prospective observational study conducted over one year at KEM Hospital, Mumbai a tertiary care centre. Inclusion criteria were newly diagnosed patients with CKD above 18 years and excluded pregnant women, patients previously diagnosed as CKD, Ischemic heart disease and on maintenance haemodialysis. Complete haemogram, renal function tests, liver function tests, serum albumin, serum calcium, serum phosphorus, serum parathyroid hormone level, ECG and 2D Echocardiography were recorded. It was repeated at the end of one year after correcting Hb with human recombinant erythropoietin.

Results: In all 102 patients, anaemia and left ventricular mass index (LVMI) are negatively correlated with each other at the start and end of the study with a correlation coefficient (r) of -0.3 and 0.56 respectively. The change in haemoglobin and change in LVMI are also negatively correlated with correlation coefficient (r) of -0.65. All the correlations are statistically significant. There was a significant improvement in haemoglobin, and there was a significant decrease in LVMI in all the patients. There was a partial regression in left ventricular hypertrophy with partial correction of anaemia in these patients.

Conclusions: Anaemia and LVH in patients with CKD are negatively correlated. Treatment of anaemia with erythropoietin has been shown to induce a partial regression of LVMI.

Keywords: Anaemia, CKD, LVH, LVMI

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem affecting more than 50 million people, and more than 1 million of them are receiving kidney replacement therapy.1 CKD has a high global prevalence with a consistent estimated a global chronic kidney disease prevalence is between 11 to 13% with majority in stage 3.2 Chronic kidney disease is a global threat to health in general and for developing countries in particular, because therapy is expensive and life-long. Over 1 million people worldwide are alive on dialysis or with a functioning graft.3

Chronic diseases have become a major cause of global morbidity and mortality even in developing countries in recent past. CKD is a growing health problem in India; there is a rising incidence and prevalence of kidney failure, with poor outcomes and high cost. The incidence and prevalence of end-stage renal disease (ESRD) have doubled in the past 10 years and are expected to continue to rise steadily in the future with increasing incidence of
diabetes and hypertension, the two most common aetiologies of chronic kidney disease. Trivedi H et al found in kidney disease screening camps in a semi-urban population of Gujarat, India CKD was 20.93% and eGFR <60 mL/min/1.73 m² was noted in 8.29% (participants with known diabetes, stone diseases, hypertension, kidney/liver/cardiac disease, hepatitis, HIV, transplant recipients, pregnant women and those <18 years were excluded from this study). This study brings to light the underdetermined burden of CKD in India.

The majority of patients with CKD have anaemia, which can be severe unless it is treated with human recombinant erythropoietin (rHuEPO). Given the high prevalence of CKD and the decline in haemoglobin concentration with even modest reductions in kidney function, anaemia of CKD is a substantial public health burden.

The anaemia of CKD is also associated with an increased risk of morbidity and mortality principally due to cardiac disease and stroke and with an increased risk of hospitalization, hospital length of stay, and mortality in patients with CKD. In patients with end-stage renal disease, treatment of anaemia with recombinant human erythropoietin improves overall and cardiovascular event-free survival.

Risk factors for the development of LVH in patients with CKD principally include anaemia, hypertension, and ischemic heart disease. Anaemia has emerged as an important, independent risk factor for the development and progression of LVH in CKD, and of adverse cardiovascular outcomes, including mortality.

Left ventricular hypertrophy appears to regress with improvement in haemoglobin levels from less than 10 g/dL to levels up to about 12 g/dL. It does not appear that raising the haemoglobin further to normal levels leads to further regression of LVH or clinical improvement. This study was to study and confirm the same in Indian CKD patients there tertiary care centre.

METHODS

The prospective observational study design conducted over one year at KEM Hospital, Mumbai a tertiary care centre. The study was carried out after obtaining permission from institutional ethics board. Recently diagnosed cases of chronic kidney disease from medicine and nephrology ward and outpatient department were recruited for the study.

Inclusion criteria

Were newly diagnosed as chronic kidney disease those were above 18 years and willing to give informed consent. Following patients were excluded pregnant women, patients previously diagnosed as CKD, ischemic heart disease (IHD) and patients already on maintenance hemodialysis.

Procedure

These patients were provided with patient information sheet and a voluntary informed consent form. After explaining the nature of the study and the advantage, disadvantage and benefits patients willing to participate and follow up were enrolled in the study. Patients from all stages chronic kidney disease were included in the study irrespective of the aetiology of CKD and irrespective of the fact that they are on dialysis or not. The need for dialysis was decided by the treating nephrologists and no alteration would be done in the standard treatment. All the clinical details were entered in the prescribed proforma. Patients were asked detailed history including personal and past history.

Required physical and systemic examination was done and entered in the Proforma. Height and Weight were measured and body mass index was calculated. The baseline biochemical investigations i.e. complete haemogram, renal function tests, liver function tests, serum albumin, serum calcium, serum phosphorous, serum parathyroid hormone level and ECG. Haemoglobin and other baseline investigations were done once every month. ECG findings including Romhilt - Estes scoring were done to assess for left ventricular hypertrophy (LVH).

2-D Echo

2-D echocardiography in M-mode was done from the cardiology department of the hospital. The first echocardiogram was performed at the time of diagnosis left ventricular ejection fraction (LVEF), left ventricular end diastolic diameter, left ventricular posterior wall thickness, inter-ventricular diastolic thickness were noted.

Left ventricular mass (g) = 1.05 × [(LVDD + IVS + LVPW) - (LVDD)] - 13.6

Where 1.05 (g/cm³) is the specific gravity of the myocardium. The measurements were obtained at the peak of the R-wave on the ECG. The left ventricular mass index (LVMI, g/m²) was defined as left ventricular mass divided by body surface area (m²). Left ventricular hypertrophy is defined as an increase in the mass of the left ventricle, which can be secondary to an increase in wall thickness, an increase in cavity size, or both. LVH as a consequence of hypertension usually presents with an increase in wall thickness, with or without an increase in cavity size. This increase in mass predominantly results from a chronic increase in afterload of the LV caused by the hypertension. The ejection fraction is defined as the ratio of stroke volume to end-diastolic volume. It is most often computed as follows:

EF = [(EDV - ESV)/EDV] x 100 (%)
Where EF = ejection fraction, EDV = end-diastolic volume, and ESV = end-systolic volume.

Left ventricular mass index (LVMI), LVH was calculated based on Devereux et al formulae.

It was repeated at the end of one year after correcting Hb with human recombinant erythropoietin (rHuEPO) treatment.

**Statistical analysis**

The data was analyzed using paired t-test, Pearsons X2 and ANOVA F-test.

**RESULTS**

After fulfilling the inclusion criteria 102 patients were enrolled in the study. The peak incidence of chronic kidney disease was between 40 to 60 years of age with mean age 49±8.6 years. Mean age of male patients was 49.4±8.1 years. Mean age of female’s patients was 47.4±9.21 years. In this study, there were 8 (7.84%) patients in stage III, 33 (33.35%) patients in stage IV, and there were 61 (59.8%) patients in stage V. The aetiology of CKD in the study patients is shown in Table 1.

### Table 1: Causes of CKD.

<table>
<thead>
<tr>
<th>Pre-morbid condition</th>
<th>No of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>36 (35.29)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30 (29.42)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>20 (19.6)</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>6 (5.88)</td>
</tr>
<tr>
<td>Contrast induced nephropathy</td>
<td>3 (2.94)</td>
</tr>
<tr>
<td>Autosomal dominant polycystic kidney disease</td>
<td>1 (0.98)</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>2 (1.95)</td>
</tr>
<tr>
<td>Reno vascular</td>
<td>4 (3.92)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>102</strong></td>
</tr>
</tbody>
</table>

In this study we found 4 patients of diabetes, 2 patients of hypertension and 2 patients of unknown cause in stage III of CKD. We also found 4 patients of diabetes, 5 patients of hypertension and 20 patients of unknown cause, 2 patients of chronic glomerulonephritis, and 2 patients of chronic interstitial nephritis in stage IV of CKD. We also found 28 patients of diabetes, 23 patients of hypertension and 4 patients of unknown cause, 4 patients of chronic glomerulonephritis, 1 patients of chronic interstitial nephritis and 1 patient of autosomal dominant polycystic kidney disease (ADPKD) in stage V of CKD.

### Table 2: Correlation of haemoglobin and LVMI.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Mean</th>
<th>N</th>
<th>Correlation/ Coefficient (r)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb Baseline</td>
<td>7.65±1.52</td>
<td>102</td>
<td></td>
<td>-0.3</td>
<td>0.002</td>
</tr>
<tr>
<td>LVMI Baseline</td>
<td>218.64±31.29</td>
<td>102</td>
<td></td>
<td>-0.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb At 1 Year</td>
<td>8.61±1.06</td>
<td>102</td>
<td></td>
<td>-0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVMI At 1 Year</td>
<td>205.75±30.88</td>
<td>102</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb At 1 Year - Hb baseline</td>
<td>0.95±1.46</td>
<td>102</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMI At 1 Year - LVMI baseline</td>
<td>12.89±33.11</td>
<td>102</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hb - Haemoglobin; LVMI - left ventricular mass index.

### Table 3: Correlation of improvement of anaemia with change in LVMI In all patients.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Mean</th>
<th>N</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average SBP</td>
<td>144.78±7.14</td>
<td>102</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Average SBP at 1 year</td>
<td>145.06±6.22</td>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average DBP</td>
<td>87.41±4.79</td>
<td>102</td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>Average DBP at 1 year</td>
<td>87.37±4.96</td>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average Hb</td>
<td>7.65±1.52</td>
<td>102</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average Hb at 1 year</td>
<td>8.61±1.06</td>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMI</td>
<td>202.47±53.45</td>
<td>102</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>LVMI at 1 year</td>
<td>190.4±37.1</td>
<td>102</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SBP - Systolic Blood pressure; DBP - Diastolic Blood pressure; LVMI - left ventricular mass index.

The overall prevalence of LVH was 80.4%, and was increasingly higher with declining renal function: 25% in stage 3, and 58% and 100% in stages 4 and 5, respectively.
There was a significant trend for a stepwise increase in left ventricular hypertrophy in Patients with increasing stage of CKD. Figure 2 is showing different left ventricular parameters in different CKD stages. Table 2 is showing correlation of haemoglobin and LVMI. Table 3 is showing correlation of improvement of anaemia with change in LVMI in all patients.

In all 102 patients, anaemia and LVMI are negatively correlated with each other at the start and end of the study with a correlation coefficient (r) of - 0.3 and 0.56 respectively. The change in haemoglobin and change in LVMI are also negatively correlated with correlation coefficient (r) of - 0.65. All the correlations are statistically significant. There was no significant difference in blood pressure in patients overall. But there was a significant improvement in haemoglobin, and there was a significant decrease in left ventricular Mass index in all the patients. There was a partial regression in left ventricular hypertrophy with partial correction of anaemia in these patients.

**DISCUSSION**

This study dealt with spectrum of chronic kidney disease in adults so patients with age less than 18 years were excluded from the study. The peak incidence of chronic kidney disease was between 40 to 60 years of age with mean age 49±8.6 years. Mean age of male and females patients was 49.4±8.1 years and 47.4±9.21 years respectively. In the study conducted by Rajapurkar et al for the Indian CKD registry, the overall age was 50.1±14.6 years and the females were younger by 2.5 years. In the study conducted by Agrawal SK et al at AIIMS, New Delhi the mean age of patients with chronic kidney disease was 42.3±12.54 years. The age of the study population ranged from 19 to 65 years with a mean age of 47.6±13.4 years in the study done by Jesuorobo et al in Nigeria (males 47.8±10.7 females 46.1±12.6 years). The study included 60 (58.82 %) males and 42 (31.18%) females which are different from study conducted by Rajapurkar et al, which included 70% males and 30% females. This difference in gender can be explained by the large group of male patients in there society who reach the health care facility earlier as compared to females. The study conducted by Agrawal SK et al at AIIMS had 56.16% were male and 43.84 % as females Jesuorobo et al study in Nigeria also had similar finding with 60 % males and 40% females. These findings are similar to the finding in this study.

This difference in this study and the Rajapurkar et al study was found mainly because of the small number of patients in this study and the fact that they were taken from a tertiary care hospital were patients are referred mainly for dialysis, transplant and further management. In Mujais et al study the percentage of patients in stage V were less due to the total number of patients were very high (1182) and patients in stage V on dialysis were excluded. Most common cause of CKD was diabetes mellitus in this study followed by hypertension and then patients with undetermined cause. In the Study conducted by Rajapurkar et al and GK Modi et al most common cause of chronic kidney disease was diabetes mellitus and followed by hypertension which was consistent with this study. In the study conducted by Mittal et al the most common cause of chronic kidney disease was chronic glomerulonephritis followed by diabetes mellitus and
chronic interstitial nephritis. The difference in this and this study can be explained by the fact that this study had collected data from May 1994 to April 1995 and data was published in 1997. India is experiencing a rapid health transition with large and rising burdens of chronic diseases, which are estimated to account for more of all deaths and more of disability adjusted life years. Even in rural India, chronic non-communicable diseases are emerging as the leading cause of death. India leads the world with the largest number of diabetics earning the term of “diabetes capital of the world”.

There has been an alarming rise of diabetes mellitus and diabetic nephropathy in the last 2 decades in developing countries like India. This has led to the shift of paradigm of causes of CKD towards non-infectious causes like diabetes and Hypertension. According to the first annual report published by the CKD registry of India involving 13, 151 patients, diabetes and hypertension were major causes of CKD in India accounting for 28.5% and 16.2% respectively, as in other parts of the world. In the present study there is a progressive decline of haemoglobin with decline in renal function as estimated by increase in stage of CKD.

In the study conducted by Khanam S et al in Bangladesh too there was a significant decrease in haemoglobin with increasing stage of chronic kidney disease i.e. with declining GFR. The results were consistent with this study. In the study done by Aztor BC et al there too the haemoglobin levels decrease with declining renal function. The results of this study too were similar to the present study. The Average haemoglobin was less in this study that is explainable by the poor nutritional status of Indian CKD patients. The recurrent infection in developing countries and CKD in particular and chronic inflammation also suppresses the bone marrow for production of Haemoglobin in these patients.

Left ventricular hypertrophy was seen in 80.4% of patients in this study. 25% of patients in stage III were having LVH, 58% of patients in stage IV of patients were having LVH and 100% of patients in stage V were having LVH. In the study by Chen et al LVH was seen in 62.5% of patients in CKD, there were 44.4% of patients in stage III were having LVH, 61% of patients in stage IV of patients were having LVH and 83.9% of patients in stage V were having LVH. The higher percentage of patients with LVH is mainly due to higher no of patients in Stage V (59.8 % vs. 30.5 %) of CKD in this study in whom the prevalence of LVH is higher. This difference is mainly because of the small no of patients in this study (102) and large number of patients in the study by Chen et al. (285) has led to a selection bias of patients in different stage of CKD. Daniel et al study demonstrated that LVH was already high in CKD stage 3 (56%) and increased progressively along with the decline in eGFR, attaining the greatest prevalence in patients with eGFR <15ml/min (90%) (Stage V). Paolletti et al and Levin et al also documented a similar trend and this clearly suggest that in patients with CKD, LVH occurs earlier than expected and is already present well before the onset of overt uraemia.

In this study LVEF <55% was seen to progressively increase as the stage of CKD advances from stage 3 to 5. In the study by Chen et al similar results were found as the prevalence of LVEF < 55% and a stepwise decrease in the LVEF corresponding to advancement in CKD from stage 3 to 5. In this study there is significant trend for a stepwise increase in left ventricular mass index (LVMI) corresponding to the advancement in chronic kidney disease from stage 3 to 5.18 In the study by Jesuoro DE, Estimated glomerular filtration rate correlated negatively with left ventricular mass index and also emerged the strongest predictor of LVMI in patients with CKD accounting for 24.1% of the variation in LVMI. In the study done by Chen et al the trend was the same as in this study except for the fact that it had lower values of LVMI probable because of Higher Haemoglobin values in their study which is one of the important negative determinants of LVMI.

Comparison of correlation of anaemia and LVMI in different studies

In this study was found a negative correlation between haemoglobin and LVMI with a correlation coefficient (r) of -0.3. The haemoglobin levels of the study population had a negative correlation with LVMI which was statistically significant. This finding is similar to a previous report by Ulasi et al in Nigeria in which a strong relationship was found between anaemia and the prevalence of LVH in patients with chronic renal failure. Anaemia has been consistently associated with cardiovascular morbidity and LVH in the ESRD population and the results of this study are consistent with those in the literature. In the study done by Chen et al which got published in 2012 found a negative correlation between LVMI and albumin, haemoglobin [correlation coefficient (r) of -0.212], calcium, and ACE inhibitors and/or ARB use. Zehnder et al studied the course of left ventricular hypertrophy was in anaemic haemodialysis patients treated with recombinant human erythropoietin (rHuEPO). At baseline, haemoglobin (Hb) was 8.6±0.7 g/dl, left ventricular muscle mass index (LVMI) 222.7±41 g/m² and blood pressure (BP) 146.4±10/81.6±6 mm Hg. Hb rose to 11.4±1.2 g/dl (p less than 0.001); LVMI decreased to 155.4±25.1 g/m² (p less than 0.001); BP remained unchanged (146.8±16.9/81.2±7.8 mm Hg) at the end of the study. The results of this study were consistent with this study.

Ayus et al studied the effects of erythropoietin on left ventricular hypertrophy in adults with severe chronic renal failure and haemoglobin <10 g/dl at The University of Texas health science centre at San Antonio, Texas USA found that LVMI decreased in anaemic patients receiving rHuEPO (142±56 versus. 157±56 g/m) P = 0.007, with an increase in haemoglobin (11.3±1.9 versus.

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9.1±0.7 g/dL) P = 0.001.23 There were no changes in LVMl or haemoglobin level among controls. After adjusting for confounders and change in haemoglobin, receipt of rHuEPO was associated with a significant reduction in LVMl (P = 0.01). Results of this study were also similar to this study. Hayashi et al the regression of left ventricular hypertrophy (LVH) on echocardiography in nine pre-dialysis patients with chronic renal failure after a partial correction [target Haematocrit (Hct) 30%] and normalization (target Hct, 40%) of the Hb with rHuEPO treatment. Twenty-four hour ambulatory blood pressure monitoring was also performed. The administration of rHuEPO significantly increased Hct to the target values. The rate of renal failure progression did not change during rHuEPO treatment for 12 months (Cr, from 6.2±2.0 to 5.5±2.1 mg/dL). The left ventricular mass index (LVMl) tended to decrease after a partial correction of anaemia (Hct, 32.1%±1.8%) at 4 months, whereas it tended to significantly decrease after normalization of Hct (Hct, 39.1%±2.4%) at 12 months (baseline, 140.6±2.1 mm²/g; partial correction, 126.9±10.0 mm²/g; normalization, 111.2±8.3 mm²/g). All patients had received antihypertensive medication before rHuEPO administration, and additional drugs were also required in four cases during the study. As a result, a good overall blood pressure control was obtained without any adverse effects on the circadian blood pressure rhythm. Results of this study were also consistent with this study. In this study however in sub group analysis of one group of patients (diabetes mellitus) when the blood pressure was significantly higher at the end then at the base line, despite a significant increase in haemoglobin there was no significant decrease in the LVMl. In the study done by Zehnder et al the group of patients who had higher BP values (158.9±8.86.5±5.3 versus 140.0±9.579.2±6.8 mm Hg, p less than 0.01), and the period with Hb values above 10 g/dl was shorter (14.5±2.4 versus 17.8±2.4 months, p less than 0.05). These patients failed to show a significant decrease in LVMl. The result of this sub group explains that this finding in this study was similar to the study by Zehnder et al which in both the studies was similar.

CONCLUSION

Haemoglobin and renal function were inversely related; as the renal function (i.e. the GFR) declined there was simultaneous decrease in haemoglobin. Left ventricular function progressively declines as the Stage of CKD advances as evident by increase no of patients with reduced ejection fraction, increase in the incidence of patients with left ventricular hypertrophy and increase in left ventricular mass index. Anaemia is a significant factor affecting left ventricular hypertrophy in patients with chronic kidney disease and both are negatively correlated. Treatment of anaemia with erythropoietin has been shown to induce a partial regression of left ventricular mass. However there are many other factors including hypertension and micro-inflammation which influences this condition and needs to be kept in control for an improvement in Left ventricular hypertrophy.

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Ethical approval: The study was approved by the institutional ethics committee

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