

# DISTRIBUTION OF PRURITUS AND ITS ASSOCIATION WITH SERUM PARATHORMONE LEVEL IN END STAGE RENAL DISEASE

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## Abstract

**Background:** Pruritus is a common manifestation in patients on hemodialysis. The aim of this study is to determine the distribution of pruritus and evaluate the association between pruritus and serum parathormone levels in chronic kidney disease patients on maintenance haemodialysis.

**Methods:** This analytic, descriptive, cross-sectional study was performed over 191 patients of maintenance haemodialysis in 2014. Information related to the patients including age, gender, residence, pruritus was extracted from questionnaires. Serum levels of intact parathormone were measured & data were analyzed.

**Results:** 68% of the patients had pruritus. The Mean  $\pm$  SD of serum parathormone was 53.25 $\pm$ 7.96 pg/ml in patients with pruritus and 81.91 $\pm$ 9.34 pg/ml in patients without pruritus. Our study showed that most patients with pruritus had normal serum parathormone levels and no significant association was found between pruritus and serum parathormone levels.

**Conclusion:** serum parathormone level may not play a role in uraemic pruritus in these patients.

**Keywords:** ESRD, parathyroid hormone, hemodialysis, pruritus.

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## Introduction

Chronic kidney disease (CKD) is important health problem and has a progressive course in most cases, and final results may be End Stage Renal Disease (ESRD). Various treatments have been considered for these patients, and one of the main options is hemodialysis (HD).<sup>1</sup> The incidence of CKD is increasing rapidly. According to the data of Bangladesh Renal Registry report almost twenty millions of Bangladeshi adults are suffering from various stages of CKD. One study showed that in Bangladesh approximately 100-120

patients per million populations (PMP) reach End Stage Renal Disease (ESRD) every year.<sup>2</sup> Rennke HG et al. showed that over 500 000 patients live with ESRD in the United State, of whom 72% have undergone long-term dialysis and 28% have received kidney transplantation.<sup>3</sup> Patients with CKD who are on treatment with HD suffer from various cutaneous lesions, which often annoy them. Another study in Bangladesh found that total 88% of study population had some form of skin disorder; pallor was the most common (82%), while xerosis (61%), pruritus (53%), pigmentation (37%) and bacterial infection

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(37%) were other common problems.<sup>4</sup> Banerjee S et al. stated that these cutaneous manifestations may be related to uremia, previous underlying disease, drugs and/or HD treatment.<sup>5</sup> One of the most common cutaneous manifestation seen in patients on HD is pruritus, the prevalence of which in patients with CKD is between 37% to 90%; this rate is about 80% in patients on HD.<sup>6</sup> The mechanisms of underlying uraemic pruritus are not exactly known and it appears that multiple combined factors integrate in the pathogenesis of this condition.<sup>7</sup> However, it may be associated to renal insufficiency, secondary hyperparathyroidism, xerosis, increased serum levels of magnesium, calcium, phosphate, aluminum, histamine, proliferation of nonspecific enolase-positive sensory nerves in the skin, hypervitaminoses A and iron deficiency anemia.<sup>8-10</sup> The pathophysiology of uraemic pruritus is complex and many uremic and nonuremic factors contribute to its development. Two hypotheses on the underlying pathophysiological mechanisms of uremic pruritus (UP) have been postulated - the immunohypothesis and the opioid hypothesis - and these have been strengthened somewhat by the results of clinical trials. The immunohypothesis considers uremic pruritus (UP) to be an inflammatory systemic disease rather than a local skin disorder.<sup>11-13</sup> The opioid hypothesis proposes that UP is partly a result of changes in the endogenous opioidergic system, with overexpression of opioid  $\mu$ -receptors in dermal cells and lymphocytes.<sup>14</sup> Overactivity of the opioid  $\mu$ -receptor (and concomitant downregulation of opioid  $\delta$ -receptors) might be caused by the increased serum  $\beta$ -endorphin to dynorphin ratio observed in patients with CKD and could explain the development of UP.<sup>15</sup> Parathormone and ions (e.g. calcium, phosphate and magnesium ions) have also been implicated in the pathogenesis of uremic pruritus, as itching frequently accompanies severe secondary hyperparathyroidism and an elevated calcium-phosphate product. Xerosis (dry skin) can facilitate the development of UP in patients with CKD. Abnormalities in calcium and phosphate metabolism in ESRD has been claimed to

provide an explanation for uraemic pruritus. Hyperparathyroidism with secondary hypercalcemia and skin calcification may stimulate mast cell degranulation with consequent release of histamine may play a role in uraemic pruritus.

In chronic kidney disease (CKD), there is elevated serum parathormone (PTH) concentration secondary to derangement of serum calcium ( $\text{Ca}^{++}$ ), serum phosphate ( $\text{PO}_4^{-}$ ) and vitamin D metabolism. Generally, hyperphosphatemia, hypocalcemia and decreased calcitriol production can all increase the PTH production and hyperplasia of parathyroid cells, finally resulting in secondary hyperparathyroidism.<sup>12</sup> Impairment of renal excretion of PTH metabolites also play a role in the development of increase serum PTH level in CKD. Hyperparathyroidism can stimulate mast cells to release histamine and increase deposition of Ca and Mg salts on the skin. However, not all patients with severe hyperparathyroidism have pruritus. In addition, in some of the studies, no association has been found between serum levels of PTH and cutaneous proliferation and number of mast cells.<sup>16</sup>

### Materials and methods

This descriptive-analytic, cross-sectional study was conducted on 191 patients who were on HD for more than 3 months at the Department of Nephrology in Dhaka Medical College Hospital (DMCH), National Institute of Kidney Diseases and Urology (NIKDU) and Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, in 2014. Data were collected from questionnaires regarding age, gender, residence and pruritus. History of taking significant drugs (such as opioids, steroid, anticonvulsants, chloroquine), patients who were previously diagnosed as a case of AIDS, internal malignancy, hypothyroidism, hyperthyroidism, lymphoma, polycythaemia rubra vera, psychiatric illness, skin diseases (such as scabies, psoriasis, eczema, tineasis), patients with clinically detectable jaundice and patients with sign symptom of hypothyroidism or hyperthyroidism (Weight gain or loss, persistent diarrhoea or constipation, heat or cold

intolerance, croaky voice) were excluded as a case. iPTH was measured by the enzyme-linked immunosorbent assay. Data were analyzed by the chi-square test, Fisher’s exact test and Student’s unpaired T-test with SPSS-16 software. A P-value less than 0.05 were considered as being statistically significant.

**Result**

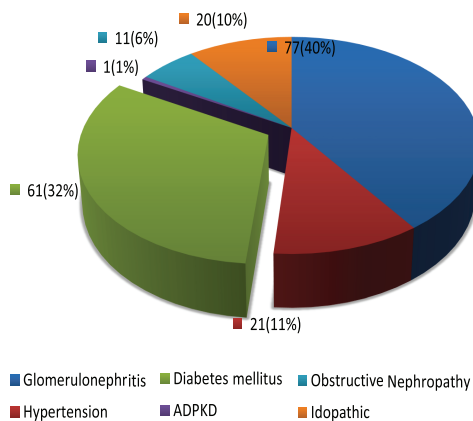
Total 191 patients on HD were studied. Majority of the patients aged between 35 and 55 years, from urban areas, were male, [Table 1]. Pruritus was found in only 129 patients (68 percent). This study found that serum parathormone level was low ,normal and high in 28.8 percent, 49.7 percent and 21.5 percent of study subjects, respectively ; and it was not significantly associated with pruritus [Table 5].

**Table-I**

*Basic demographic variables of the study population.*

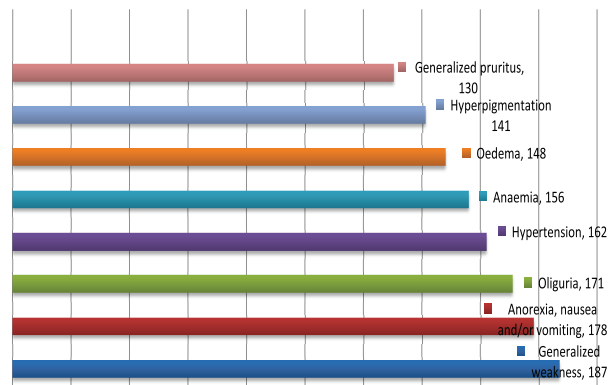
Variable	Data	Frequency	Percentage
Age	Below 35 yrs	41	21.5
	35-55 yrs	86	45.0
	Above 55 yrs	64	33.5
Sex	Male	113	59.2
	Female	78	40.8
Residence	Rural	65	34.0
	Urban	126	66.0

Majority of the patients aged between 35 and 55 years, from urban areas, were males.



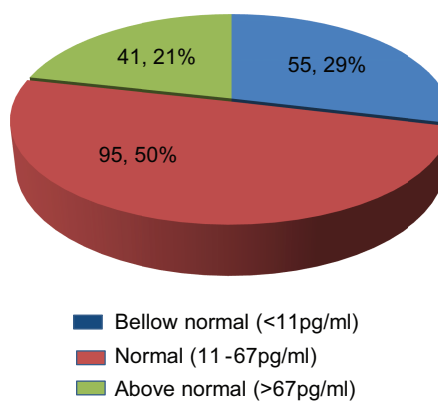
**Fig.-1:** Etiology of CKD

Figure-1 shows the etiology of the CKD in the study subjects. Glomerular disease (77, 40%) was the most prevalent cause, followed by diabetes mellitus (61, 32%) and hypertension (21, 11%).



**Fig.-2:** Clinical features of CKD

Figure 2 shows the clinical features of the patients under study. Generalized weakness was the most common clinical feature found in 187 (98%) patients. Other common features were gastrointestinal symptoms (anorexia, nausea and vomiting), oliguria, hypertension, anaemia, oedema and hyperpigmentation found in 178 (93%), 171 (90%), 162 (85%), 156 (82%), 148 (78%) and 141 (74%) respectively. Pruritus was found in 129 patients (68%).



**Fig.-3:** Serum parathormone level

Figure 3 shows the serum parathormone level of the study subjects in three categories. Serum parathormone level was low (<11 pg/ml), normal (11 – 67 pg/ml) and high (>67 pg/ml) in 55 (28.8 percent), 95 (49.7 percent) and 41 (21.5 percent) study subjects, respectively.

**Table-III**  
*Association of serum parathormone level with pruritus.*

Serum parathormone	Total	Pruritus		Odds ratio	95 percent CI	p-value*
		Present (n <sub>1</sub> =129)	Absent (n <sub>2</sub> =62)			
Below normal (< 11 pg/ml)	55(28.8%)	34(17.8%)	21(11.0%)	0.52	0.26 – 1.04	0.06 <sup>ns</sup>
Normal (11- 67 pg/dl)	95(49.7%)	69(36.1%)	26(13.6%)	1.19	0.66 – 2.17	0.56 <sup>ns</sup>
Above normal (>67 pg/ml)	41(21.5%)	26(13.6%)	15(7.9%)	0.79	0.38 – 1.63	0.53 <sup>ns</sup>

\*Chi-square test<sup>ns</sup> -Not significant.

Table- 5 shows the serum parathormone level of the study subjects in three categories. Serum parathormone level was low (<11 pg/ml), normal (11 – 67 pg/ml) and high (>67 pg/ml) in 55 (28.8 percent), 95 (49.7 percent) and 41 (21.5 percent) study subjects, respectively. No significant association was found between serum parathormone level and pruritus.

### Discussion

One hundred and ninety one patients of chronic kidney disease (CKD) Stage 5 on maintenance haemodialysis (HD) were included in this study. Majority of cases aged between 35 and 55 years (45%). The age distribution was similar to that of the previous study conducted in Bangladesh which was a descriptive, cross sectional study done regarding the prevalence of Chronic Kidney Disease.<sup>17</sup> One hundred and thirteen (59.2%) were males and seventy eight (40.8%) were females. (Table 1) Similar sex distribution was found in the study on CKD patients in Bangladesh.<sup>17</sup>

One hundred and fifteen (60.2%) were urban and 76 (39.8%) were rural. (Table 1) Similar distribution of residence was found in a study on patients on maintenance haemodialysis, in urban and rural areas of Bangladesh.<sup>18, 19</sup>

Glomerular disease (77, 40%) was the most prevalent cause of chronic kidney disease (CKD), followed by diabetes mellitus (61, 32%) and hypertension (21, 11%). No cause could be identified in 20 patients (10%). (Fig 1) Similar etiological distribution in a study on patients on maintenance haemodialysis, in urban and rural areas of Bangladesh, respectively.<sup>18, 19</sup> In these study, obstructive nephropathy and adult

polycystic kidney disease were found in 5% and 2% cases respectively, and no cause could be identified in 16 patients (8%). In our study, obstructive nephropathy and adult polycystic kidney disease were found in 6% and 1% cases respectively. (Fig 1)

Generalized weakness was the most common clinical feature found in 187 (98%) patients. Other common features were gastrointestinal symptoms (anorexia, nausea and vomiting), oliguria, hypertension, anaemia, oedema and hyperpigmentation found in 178 (93%), 171 (90%), 162 (85%), 156 (82%), 148 (78%) and 141 (74%) patients respectively. Pruritus was found in 129 patients (68%). (Fig 2) Similar clinical features were observed on CKD (stage 5) patients on maintenance haemodialysis in Iran, which found pruritus in 60% of study population. Same distribution of clinical features also found in Bangladesh among nondialytic patients with Chronic Kidney Disease.<sup>21</sup>

In previous studies the reported prevalence of pruritus has been higher (84%), while in some other studies, it has been lower than that in our study.<sup>22</sup> It was higher than that found by another study on CKD patients in Bangladesh (53 percent).<sup>4</sup> Inclusion of only stage-5 patients in this study may explain this discrepancy. Pruritus was observed in 58.8% of the patients by Szepietowski et al., 41.9% by Akhiani et al. and 70% by Yazdanpanah et al. from Japan.<sup>23-25</sup> These differences may be due to the prevailing climatic conditions. Comparison of these results shows that, generally, more than half of the patients complained of pruritus in most studies.



Serum parathormone level was below normal (<11 pg/ml), normal (11 – 67 pg/ml) and above normal (>67 pg/ml) in 55 (28.8 percent), 95 (49.7 percent) and 41 (21.5 percent) study subjects, respectively (Table 1). Similar metabolic profile was found in nondialytic CKD patients in Bangladesh.<sup>21</sup> Ramin Tajbakhsh et al. found serum parathormone concentration below normal in 55%, normal in 9.16% and above the normal limit in 35.83% of the patients on maintenance haemodialysis.<sup>20</sup> Nonjudicious frequent use of active vitamin D may be responsible for this discrepancy.

In this study, no significant association was found between pruritus and serum parathormone. In some other study, there was a significant association between serum PTH levels and pruritus.<sup>26</sup> In the study by Yazdanpanah et al., the serum PTH level was normal in 60% of the patients of ESRD and 84% of them complained of pruritus.<sup>25</sup> They found a significant difference in the serum PTH levels in patients with and without pruritus. In addition, Ramin T et al. also reported that the serum PTH level in HD patients with pruritus was significantly higher than in those without pruritus.<sup>20</sup> In the present study, contrary to the three previous studies, the serum PTH concentration in patients with and without pruritus showed no significant difference (P = 0.53) (Table 1). This finding is similar to the results of some other studies in which no significant association was found between pruritus and serum PTH levels.<sup>24, 27-28</sup>

### Conclusion

Hemodialysis (HD) is one of the mainstays in the treatment of ESRD patients. Disturbance of serum parathormone (PTH) levels are observed in these patients. One of the most common cutaneous manifestations in patients on hemodialysis is pruritus. The aim of this study is to determine the distribution of pruritus and evaluate the association between pruritus and serum parathormone levels in patients on maintenance haemodialysis.

In our study pruritus was found in 68% of patients on maintenance haemodialysis (HD). No significant association was found between serum parathormone level and pruritus.

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