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Original Article

Internal Medicine Section

Prevalence and Clinical Characteristics of Hypothyroidism in a Population Undergoing Maintenance Hemodialysis

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ABSTRACT

Background: The prevalence of hypothyroidism in persons with chronic kidney disease is documented to be higher, compared to the normal population. However, no data is available about the prevalence rate of hypothyroidism among hemodialysis patients in Nepal.

Methods: A cross-sectional analysis was done on consecutive patients enrolled for maintenance hemodialysis in the Hemodialysis Unit of Gandaki Medical College Teaching Hospital, Pokhara, Nepal, during the period of one year (1st January 2011 to 31st December 2011). Total 64 subjects with end stage renal disease were recruited for the study. Thyroid function tests were performed at the time of starting regular hemodialysis. Classical symptoms and signs of hypothyroidism were assessed in all patients.

Results: Among the study subjects 17 (26.6%) had serum thyroid stimulating hormone levels above the laboratory reference range (>6.16 μIU/mL). Among them 12 (18.7%) patients had clinically significant symptoms or signs requiring thyroxin replacement. Cold intolerance, constipation, tingling sensation, dry skin, periorbital odema, pericardial effusion, pleural effusion and ascites were found at significantly higher rate in the hypothyroid patient group ($p<0.05$).

Conclusion: The diagnosis of hypothyroidism can be easily missed in the end-stage kidney disease population, because the symptoms of chronic kidney disease and hypothyroidism overlap. In our study we have found high prevalence of hypothyroidism. Clinicians should pay attention on this factor and screen routinely for thyroid disorders in the chronic kidney disease population.

Keywords: Chronic kidney disease, Thyroid disorder, Nepal

INTRODUCTION

End stage renal disease alters the hypothalamic-pituitary-thyroid hormone axis [1] in addition to the peripheral thyroid hormone metabolism [2].

Increased prevalence of goiter and thyroid gland volume have been reported in patients with end-stage renal disease (ESRD) [3,4] and there are also studies reporting increased prevalence of primary hypothyroidism among ESRD patients compared with the general population [5]. Thyroid hormone abnormalities have been reported among euthyroid patients with ESRD, including reduced total and free triiodothyronine (T3) and thyroxine (T4) levels [6]. The background for these abnormalities is unclear, however it has been postulated to be due to adaptive response to chronic nonthyroidal illness, uremia and protein malnutrition [7].

In ESRD patients, the symptoms of chronic kidney disease (CKD) and hypothyroidism overlap in many aspects, making it difficult to recognize primary hypothyroidism, unless one has a high level of suspicion.

In our research, we were exploring the burden of primary hypothyroidism in an ESRD population undergoing regular hemodialysis in Nepal. We were also trying to find answers as to, which are the typical symptoms or signs, more characteristic for hypothyroidism, which should prompt the physicians to do thyroid testing in this special population.

METHODS

Subjects

The study was performed on hemodialysis patients suffering from chronic kidney disease, enrolled for maintenance treatment at the Hemodialysis Unit in Gandaki Medical College Teaching Hospital (GMCTH, also known as Charak Hospital and Research Center), Pokhara, Nepal, during the period of 1st January 2011 to 31st December 2011.

A total of 64 subjects were enrolled. We invited all existing and new patients during the study period. Inclusion criteria were: age above 18 years, CKD stage 5 on hemodialysis, willing to consent for the study. Exclusion criteria: under treatment for thyroid disorders, unable to answer the questionnaire.

The study population's mean age was 47.2 ± 15.6 years. Female to male ratio is 1:3.3 (number of female subjects was 16 and male 48).

Ethical Considerations

Informed consent was taken from all the patients. The study protocol was approved by the institutional review board.

Laboratory Measurement

Blood for laboratory analysis was collected on the day of hemodialysis. In patients with AV fistula, the blood was drawn through the fistula needle immediately after insertion, before starting the hemodialysis procedure. In patients with double lumen catheter, the blood was drawn from the catheter, in similar way.

Thyroid function tests (thyroid stimulating hormone (TSH), free T4 and free T3 serum levels) were performed using ELISA method (Ranbaxy Diagnostics, India) in the central laboratory of GMCTH. The normal reference range for TSH, FT4 and FT3 was 0.39-6.16 μIU/mL, 0.8-2.0 ng/dL, 1.4-4.2 pg/mL respectively.

Questionnaire

Subjects were interrogated by a medical doctor and the presence or absence of nine symptoms of hypothyroidism were recorded. Periorbital odema was assessed by the same person. The presence

of pericardial or pleural effusion and ascites were assessed by ultrasound and echocardiography performed by experienced ultrasonographists.

STATISTICAL ANALYSIS

Statistical calculation was done using SPSS 14.0 software. All continuous variables are expressed as mean ± SD and proportions are expressed as a number (%). For comparing proportions we have used Chi-square test or Fisher`s exact test as appropriate.

RESULTS

TSH Levels among the Subjects

The mean TSH level in the whole group was 5.16 ± 5.74 μIU/mL. Based on the TSH levels, the subjects were classified into three groups: low TSH (TSH ≤ 0.38 μIU/mL, Group 1), normal TSH (TSH 0.39-6.16 μIU/mL, Group 2) and high TSH (TSH ≥ 6.17 μIU/mL, Group 3) [Table/Fig-1]. Data analysis has showed, that 3.13% patients had lower range TSH levels, 70.3% had normal TSH and 26.6% of patients had high TSH levels. The mean thyroid function values are displayed in [Table/Fig-1]. Among patients with high (≥ 6.17 μIU/mL) TSH levels, 3 had normal range fT4 and fT3 levels, considered as subclinical hypothyroidism, the rest of the subjects had low fT4 levels (fT4 < 0.8 ng/dL), considered as hypothyroid subjects. Among the 17 patients in the hypothyroid group, 12 (18.7%) patients had clinically significant symptoms or signs requiring thyroxin replacement.

The female to male ratio did not change significantly in the different groups, compared to the ratio found in the study population.

	Group 1 (TSH ≤ 0.38 μIU/mL)	Group 2 (TSH 0.39-6.16 μIU/mL)	Group 3 (TSH ≥ 6.17 μIU/mL)
n	2 (3.13%)	45 (70.3%)	17 (26.6%)
Female/Male ratio	1/1	12/33	3/14
Mean age (years)	45 ± 14.1	48.7 ± 17.9	42.1 ± 13.5
Mean TSH level (μIU/mL)	0.16 ± 0.19	2.92 ± 1.59	11.32 ± 7.26
Mean fT4 level (ng/dL)	1.15 ± 0.07	1.18 ± 0.39	0.73 ± 0.30
Mean fT3 level (pg/mL)	2.5 ± 1.13	2.60 ± 0.67	1.54 ± 0.74

[Table/Fig-1]: Clinical characteristics of the patient groups based on TSH level

Clinical Symptoms and Signs Associated with Hypothyroidism

The classical symptoms and signs of hypothyroidism were accessed and analysed in the euthyroid and hypothyroid groups, as seen in [Table/Fig-2]. All symptoms were found present in both groups, but there are differences in the prevalence. Using Chi-square test and Fisher`s exact test, as appropriate, we have compared the symptom prevalence between the two groups. Among the symptoms, cold intolerance, constipation, dry skin, tingling sensation and muscle pain or weakness were significantly more prevalent in the hypothyroid group. Among the signs, periorbital odema, pericardial and pleural effusions and ascites were significantly more prevalent in the hypothyroid group.

More than half of the patients with any kind of effusions eg. pleural, pericardial or ascites, had elevated TSH.

DISCUSSION

In our study we have found high prevalence of primary hypothyroidism in a dialysis patient population. There are no population-based data about the prevalence of thyroid disorders in Nepal. According to reports from developed countries, the prevalence of primary hypothyroidism (TSH > 6 μIU/mL) is 7.5% in women and 2.8% in men [8], and it is reported to be 5% in multiple populations [9]. One recent Indian population-based study done in

	Euthyroid group (TSH 0.39-6.16 μIU/mL)	Hypothyroid group (TSH ≥ 6.17 μIU/mL)	P-value	OR (95% CI)
Symptoms				
Fatigue	16/45 (35.6%)	10/17 (58.8%)	NS	2.59 (0.82-8.12)
Cold intolerance	2/45 (4.4%)	10/17 (58.8%)	<0.0001	30.71 (5.52-170.76)
Constipation	13/45 (28.9%)	10/17 (58.8%)	<0.05	3.52 (1.10-11.23)
Dry skin	16/45 (35.6%)	12/17 (70.6%)	<0.01	4.35 (1.30-14.57)
Tingling sensation	4/45 (8.9%)	9/17 (52.9%)	<0.001	11.53 (2.84-46.78)
Poor concentration/ memory	8/45 (17.8%)	5/17 (29.4%)	NS	1.93 (0.53-7.02)
Muscle pain/ muscle weakness	10/45 (22.2%)	8/17 (47.1%)	<0.05	3.11 (0.95-10.16)
Anxiety/ Depression	9/45 (20.0%)	5/17 (29.4%)	NS	1.66 (0.47-5.9)
Hair loss	3/45 (6.7%)	1/17 (5.9%)	NS	0.875 (0.08-9.04)
Signs				
Periorbital odema	7/45 (15.6%)	13/17 (76.5%)	<0.0001	17.64 (4.44-70.16)
Pericardial effusion	7/45 (15.6%)	9/17 (52.9%)	<0.01	6.11 (1.75-21.27)
Pleural effusion	3/45 (6.7%)	9/17 (52.9%)	<0.001	15.75 (3.48-71.27)
Ascites	6/45 (13.3%)	7/17 (41.2%)	<0.05	4.55 (1.25-16.57)

[Table/Fig-2]: Symptom prevalence in the euthyroid and hypothyroid groups
Note: NS: not significant

Cochin on 971 adult subjects, the prevalence of hypothyroidism was 3.9%, and prevalence of subclinical hypothyroidism was 9.4% [10].

The analysis of the third national survey in the United States revealed, that among patients with chronic kidney disease, the prevalence of hypothyroidism increases with lower levels of glomerulus filtration rate (GFR), in subjects with GFR <30 mL/min/1.73m^2 the prevalence was 23.1% [11]. In another cross-sectional analysis in Italy, the prevalence of subclinical hypothyroidism was found to be 17.9% in persons with GFR <60 mL/min/1.73m^2 [12].

In our study among the 64 hemodialysis patients, 17 (26.6%) had elevated TSH, and only 3 of them was considered as subclinical hypothyroidism based on the normal fT4 levels.

In our dialysis patient population the female:male ratio was 1:3.27, and there is no significant difference in the ratio among the euthyroid and hypothyroid groups. In most studies the hypothyroidism is reported to be more frequent in women (in general population, not in CKD population).

It is common to find the classical symptoms and signs both in the euthyroid and hypothyroid individuals. However, they will be found more frequently among the hypothyroid people. In the Colorado Thyroid Survey constipation and cold intolerance were the symptoms associated significantly with the disease state [13].

There are multiple factors leading to thyroid abnormalities in patients with CKD. Due to reduced deiodinase activity, tissue and circulating levels of the active form of T3 are low in kidney failure [14]. Because of reduced renal excretion, inorganic iodide generated by residual deiodinase activity accumulates in stage 4 and 5 CKD, which in turn dampens thyroid hormone synthesis. On the other hand, accumulation of toxic uremic solutes alters the central (hypothalamic) control of the pituitary gland, and the TSH response to thyrotropin-

releasing hormone is subnormal in these patients [15]. In contrast, the thyroid–pituitary feedback loop seems to remain intact, because steady-state plasma TSH remains substantially normal and TSH undergoes the expected rise after thyroidectomy in these patients [16]. Central effects apart, toxic uremic solutes inhibit protein binding of thyroxin [17]. Furthermore, studies in the last decade showed that systemic inflammation [6,18] and metabolic acidosis [19] might alter thyroid function in CKD patients.

The kidney contributes to the iodine clearance primarily through glomerular filtration. Serum iodine concentrations are high in CKD but are not correlated with the degree of kidney failure [20]. Elevation of serum iodine levels result in prolongation of the Wolff–Chaikoff effect [21]. Iodine excess has been linked to increased prevalence of goiter and hypothyroidism reported in CKD [14, 22]. A high exposure to iodine facilitates the development of hypothyroidism in CKD patients [23]. Some authors have reported that a restriction of dietary iodine in uraemic patients on HD can correct the hypothyroidism avoiding the need for hormone replacement with levothyroxine [24].

Undiagnosed and untreated hypothyroidism is posing danger on CKD patients in many ways. First, ESRD patients have a well-recognized increased risk of cardiovascular disease that begins early in the course of CKD and results in 10-fold or higher cardiovascular mortality rates after the start of renal replacement therapy [25]. Hypothyroidism itself is also a risk factor for cardiovascular disease [26], thus adding to the existing risks. However hypothyroidism is a modifiable risk factor, hence should be recognized and treated on time. Second, hypothyroidism impairs myocardial function [27]. In CKD patients, cardiac function can be already challenged by fluid overload, overt hypertension, anemia, etc., leading to cardiac failure. Hypothyroidism can worsen the situation. Third, certain neurobehavioral and neuromuscular dysfunctions are also associated with hypothyroidism, e.g. depression, memory loss, cognitive impairment and peripheral nerve dysfunction [28-30]. The prevalence of depression in dialysis patients is high [31], and hypothyroidism can contribute to its development. Fourth, hypothyroidism is associated with anemia, approximately 20-60% of patients with hypothyroidism are also diagnosed with anemia [32]. It can have various etiologies, and can manifest as normocytic, microcytic or macrocytic anemia [33]. In patients on maintenance hemodialysis, erythropoietin resistance is a common problem, and hypothyroidism should be also ruled out together with the other well-known causes. Last but not least, symptoms of hypothyroidism can further decrease the quality of life of CKD patients, which is already much affected due to the kidney disease and uremia.

Recent studies suggest that thyroid hormone replacement in CKD patients with subclinical hypothyroidism could slow down the rate of decline of renal function and thus may delay reaching end-stage renal disease [34, 35].

CONCLUSION

In our study, we have found high prevalence of subclinical and clinical hypothyroidism among hemodialysis patients, 26.6% of the study subjects had TSH levels above the reference range.

It was also shown that cold intolerance, constipation, dry skin and the presence of tingling sensation were much more common among patients with high TSH levels. Those subjects who also had serous effusions (pleural, pericardial or peritoneal) had a very high chance to have high TSH levels.

The diagnosis of hypothyroidism can be easily missed in the ESRD population, because the symptoms of CKD and hypothyroidism overlap. Timely diagnosis and treatment of hypothyroidism may prevent deterioration of patient condition and prolong survival.

Knowing the high prevalence, clinicians should pay attention on this factor and screen routinely for thyroid function disorders in the CKD population.

LIMITATIONS

1. Selection bias – not all incident hemodialysis patients were included, and among the population not all patients who would need dialysis can afford it.
2. Small sample size.
3. Only a small geographical area was covered, thus not representative of the whole country.

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