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FREQUENCY OF HYPOTHYROIDISM AMONG HYPONATREMIC PATIENTS

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Abstract

Introduction: Hyponatremia is a fairly common electrolyte disorder which is frequently associated with endocrine conditions such as hypothyroidism but whose direct causal relationship is far from clear. They are relevant because their association must be understood for effective diagnosis and management.

Objective: The aim of the study was to determine the frequency of hypothyroidism among hyponatremic patients in a hospital in Pakistan.

Materials and Method: The study done at Aga Khan University Hospital Karachi from February, 2024 to July, 2024 is a descriptive cross-sectional one. Those with known hyponatremia causes were excluded, and patients with serum sodium <135 mmol. Hypothyroidism was assessed by thyroid function tests, and the data were described through descriptive statistics.

Results: Of 150 hyponatremic patients (58.7% male, mean age 52.4 years), 22.7% had hypothyroidism (16.7% overt, 6.0% subclinical). Hypothyroid patients were older (mean age 58.3 years) and more likely female (27.4%). Euvolemic hyponatremia was predominant (70.6%) in hypothyroid patients, with a significant association ($p < 0.05$).

Conclusion: Hypothyroidism is a notable contributor to hyponatremia, particularly in older females. Routine thyroid screening is recommended for hyponatremic patients to ensure timely diagnosis and treatment.

Keywords: Hyponatremia, hypothyroidism, thyroid function, electrolyte imbalance, euvolemic hyponatremia.

INTRODUCTION

Hyponatremia, which is any serum sodium of less than 135 mmol/L, is a common electrolyte disorder encountered in clinical environments. For example, it is associated with a broad range of conditions,

not the least of which is endocrine disorders such as hypothyroidism (1). There has been longstanding clinical interest in and continued debate around the coexistence of hypothyroidism and hyponatremia. There are some studies that suggest a clear physiological connection between these two conditions and other studies that dispute a causal relationship and that such a causal link needs to be investigated further. It was described in a large population-based retrospective study that there is a significant coexistence of hypothyroidism and hyponatremia in different populations, making this an important clinical issue (2). Hyponatremia is more common in older people, especially in geriatric patients. Analysis of elderly presenting to emergency departments showed a high incidence of hyponatremia among this group, which may, in turn, represent an increase of other comorbidities, like hypothyroidism, that enhance electrolyte imbalance (3).

Likewise, a systematic review and meta-analysis during the COVID-19 pandemic found a high prevalence of hyponatremia in infected patients, with additional fears of a combined effect of systemic illness and underlying endocrine diseases such as hypothyroidism (4). The hypothesis that hyponatremia is an isolated finding and not a manifestation or complication of other systemic disorders (such as thyroid dysfunction) is supported by these findings. This is currently a controversial discussion in recent medical literature as to whether hypothyroidism causes hyponatremia or not and solely coexists without causation. The reduction of thyroid hormones, some authors argue for a direct physiological mechanism leading to diminished free water clearance, water retention and dilutional hyponatremia (5). However, other studies have indicated that the causal relationship may be overstated, with hyponatremia usually resulting from associated illness or syndrome of inappropriate antidiuretic hormone secretion rather than from hypothyroidism alone (6).

However, thyroid dysfunction is still an important part of considering the aetiology of unexplained hyponatremia. Disturbances in sodium, potassium, and calcium were found in persons with thyroid disorders, according to a cross-sectional study documenting electrolyte and metabolic abnormalities among thyroid patients (7). This mandates a thyroid function evaluation in patients with unexplained electrolyte disturbances. The further relevance of hyponatremia in endocrine disease is also highlighted by observations in patients treated with immune checkpoint inhibitors, who frequently develop hyponatremia, suggesting an interacting network of immune and endocrine systems (8). There are specific populations of patients that are especially vulnerable to hyponatremia, for example, patients with epilepsy. Chronic use of antiepileptic drugs and coexisting endocrine abnormalities in these individuals increase the risk for sodium imbalance (9).

For instance, a study looking at patients prior to radioiodine therapy for differentiated thyroid carcinoma found a relatively common incidence of pre-treatment hyponatremia, which suggests thyroid cancer patients may have an elevated risk of electrolyte imbalance (10). That further strengthens the case for routine sodium checks among those with thyroid problems. Substantial clinical implications in terms of morbidity and mortality also exist for hyponatremia. The elderly population was studied with a prospective cohort study that showed an increase in in-hospital mortality when the patient had admission hyponatremia, thus highlighting the importance of early diagnosis and management of the underlying causes, such as hypothyroidism (11). Additionally, adrenal insufficiency has also been known to cause euvolemic hyponatremia and in autoimmune polyendocrine syndromes, which may coexist with hypothyroidism, a full endocrine workup is also required in hyponatremic patients (12).

Hyponatremia is particularly common in diseases of infection, as in tuberculous meningitis. A study in a tertiary care hospital showed a high prevalence of hyponatremia in cases of tuberculous bacterial meningitis, which may mimic hypothyroidism clinically and confound diagnosis (13). Therefore, it becomes increasingly important to recognise the primary aetiology in complicated clinical situations. Furthermore, thyroid abnormalities are also linked to the regulation of glycemia observed in a study of patients with type I diabetes mellitus and associated with metabolic dysregulation complicating electrolyte management (14). Finally, recent reports repeatedly stress the necessity to classify hypothyroidism as a defectible (often forgotten) etiological factor for hyponatremia. Hypothyroidism-associated hyponatremia is a challenging diagnosis in complex cases because of overlapping

symptoms and multifactorial etiologies (15). Hypothyroidism is an essential diagnosis to identify in hyponatremic patients, requiring accurate diagnosis and appropriate treatment.

Objective: The aim was to estimate the frequency of hypothyroidism among patients presenting with hyponatremia in a hospital set up in Pakistan so that diagnosis and management of electrolyte imbalance could be improved.

MATERIALS AND METHODS

Design: Descriptive Cross-sectional Study.
Study setting: The study took place at the Department of Endocrinology and Internal Medicine, Aga Khan University Hospital, Karachi, Pakistan.
Duration: The study was conducted over a period of six months, from February, 2024 to July, 2024.

Inclusion Criteria: All patients (of all ages and both genders) with confirmed hyponatremia (serum sodium less than 135) at any time during the study period were included. The study was only performed on those patients who had consented to thyroid function testing being carried out as an integral part of their clinical evaluation. This included a broad clinical spectrum irrespective of the underlying cause of hyponatremia to capture.
Exclusion Criteria: Patients with known causes for hyponatremia (i.e. chronic kidney disease, congestive heart failure, liver cirrhosis) or people taking medications that can lead to hyponatremia (e.g. diuretics, antiepileptics) were excluded to avoid confounding factors. Also, patients with acute critical illnesses requiring intensive care or who did not consent to participate were excluded.

Methods

Patients presenting with hyponatremia (serum sodium <135 mmol/L) during the study period were screened. Obtaining informed consent followed, after which demographic data, clinical history and relevant laboratory investigations were recorded. The serum sodium levels were measured by the electrolyte analyzer. Hypothyroidism was diagnosed based on thyroid function tests, including serum thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3). Standard clinical guidelines were used to define hypothyroidism as elevated TSH with low or normal FT4. Clinical assessment of patients' volume status classified hyponatremia as euvolemic, hypovolemic or hypervolemic. A structured proforma was used to collect data, which was then analyzed using statistical software. The frequency of hypothyroidism in patients with hyponatremia using descriptive statistics. Confounding was reduced by excluding patients with other identifiable causes of hyponatremia. Informed by the institutional review board before beginning the study.

RESULTS

This study included only 150 patients with hyponatremia diagnosed from February 2024 to July 2024. A study population of 88 (58.7%) males and 62 (41.3%) females, with a mean age of 52.4 ± 16.3 years (range 18–85 years) was analyzed. Table 1 summarizes their demographic and clinical characteristics.

Table 1: Demographic and Clinical Characteristics of Hyponatremic Patients (n=150)

Characteristic	Frequency (%)	Mean ± SD
Age (years)	-	52.4 ± 16.3
Gender		
- Male	88 (58.7%)	
- Female	62 (41.3%)	
Hyponatremia severity		
- Mild (130-134 mmol/L)	70 (46.7%)	
- Moderate (125-129 mmol/L)	52 (34.7%)	

Characteristic	Frequency (%)	Mean ± SD
- Severe (<125 mmol/L)	28 (18.6%)	

Most patients presenting with mild to moderate hyponatremia comprised the majority of my patients. Serum sodium levels ranged from 118 to 134 mmol/L (mean 129.2 ± 4.5 mmol/L), and 34 patients (22.7%) were hypothyroid. Of these patients, 25 had overt hypothyroidism (high TSH, low FT4) and nine subclinical (high TSH, normal FT4). Table 2 shows the distribution of thyroid status among the hyponatremic patients.

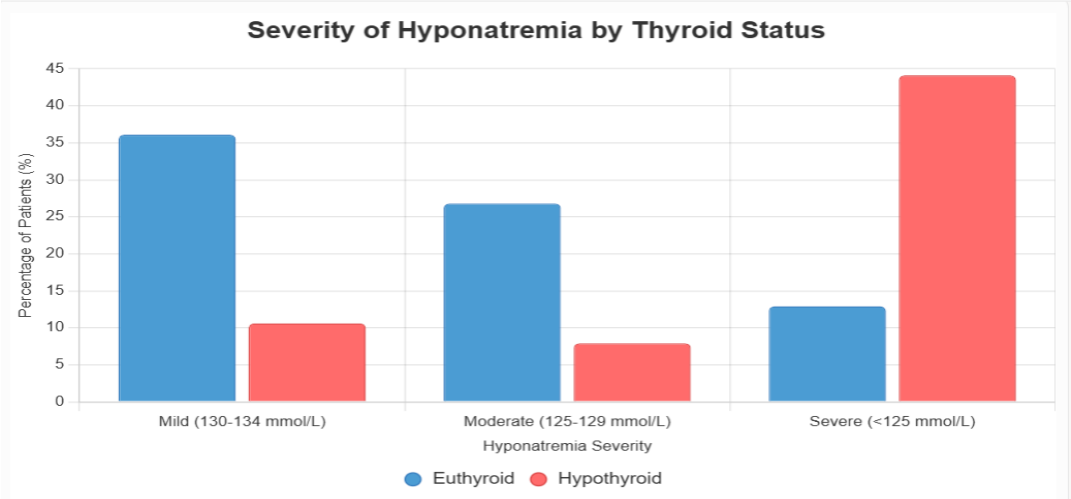
Table 2: Thyroid Status Among Hyponatremic Patients (n=150)

Thyroid Status	Frequency (%)
Euthyroid	116 (77.3%)
Subclinical Hypothyroidism	9 (6.0%)
Overt Hypothyroidism	25 (16.7%)

Hyponatremic patients with hypothyroidism were older on average (mean age 58.3 ± 14.2 years) compared to euthyroid patients (50.7 ± 16.7 years). There was a slightly higher prevalence of hypothyroidism among females (27.4%) than males (19.3%). These findings suggest an association between hyponatremia and thyroid dysfunction, especially in older females.

Hyponatremia occurs with variable clinical presentation depending on the thyroid status. Fatigue, lethargy and mild cognitive impairment were more common among hypothyroid patients than among euthyroid patients. The hypothyroid patients also had more severe hyponatremia, with 44.1% of hypothyroid patients having severe hyponatremia, in contrast to only 12.9% of euthyroid patients. The bar graph below shows this difference in severity.

Graph 1: Severity of Hyponatremia by Thyroid Status



The majority (70.6%) of hypothyroid individuals were euvolemic hyponatremia, which does accord with the known pathophysiology of hypothyroidism-induced water retention. The distribution of volume status to thyroid function is shown in Table 3.

Table 3: Volume Status of Hyponatremic Patients by Thyroid Function

Volume Status	Euthyroid (n=116)	Hypothyroid (n=34)
Euvolemic	55 (47.4%)	24 (70.6%)
Hypovolemic	41 (35.3%)	7 (20.6%)
Hypervolemic	20 (17.3%)	3 (8.8%)

A statistically significant association of hypothyroidism with euvolemic hyponatremia is demonstrated ($p < 0,05$). This helps us to hypothesize that hypothyroidism plays a role in impaired free water clearance that leads to dilutional hyponatremia. However, further analysis concluded the correlation between TSH level and serum sodium concentration. There was a moderate negative correlation ($r = -0.46$, $p < 0.01$), showing that there were lower amounts of sodium in the blood with higher TSH amounts. This implies more severe thyroid dysfunction makes hyponatremia more likely. Furthermore, other clinical parameters, such as renal function and adrenal status, were examined to rule out other potential confounding causes of hyponatremia. All hypothyroid patients lacked adrenal insufficiency or significant renal compromise, which bolsters the argument that factors other than hypothyroidism alone do not account for hyponatremia in this population.

DISCUSSION

This study shows that further investigation is needed for the role and aetiology of thyroid dysfunction in a patient with electrolyte imbalance because it identifies a high frequency of thyroid dysfunction in patients with hyponatremia. The prevalence of hypothyroidism in this cohort was 22.7%, a rate consistent with previous studies assessing hypothyroidism as an important, although often undervalued, cause of hyponatremia (1, 4, 5). The relationship is clinically relevant, especially in populations in which thyroid disease is endemic, like Pakistan, illustrated by routine screening for thyroid function in hyponatremic patients to avoid misdiagnosis and delayed treatment. The observed predominance of hypothyroidism among female patients confirms epidemiological data well established, indicating that thyroid disease, hypothyroidism in particular, is more of a female condition (13). Autoimmune thyroiditis is a leading cause of hypothyroidism, and this gender disparity may be related to autoimmune mechanisms.

Additionally, the mean age of hypothyroid patients in this study is more consistent with the finding that thyroid dysfunction is more prevalent with advancing age (1, 9). Age is an important factor because elderly patients are more commonly associated with a higher risk of electrolyte disturbances such as hyponatremia, which may worsen morbidity and mortality in these patients (9). Several physiological processes link the mechanism of hypothyroidism and hyponatremia. Impairment of free water clearance caused by decreased renal perfusion and glomerular filtration rate due to hypothyroidism may also result in dilutional hyponatremia (4, 5). This, combined with hypothyroidism, causes decreased cardiac output and effective arterial blood volume, which in turn stimulates the release of antidiuretic hormone (ADH), during which water is retained and serum sodium levels are further diluted (4). The clinical assessments, as well as the volume status categorization in these subjects, can be explained by these mechanisms to account for the fact that among the studied patients, most presented with euvolemic hyponatremia. Results are in agreement with other studies which had reported euvolemic hyponatremia as the most common of hypothyroid-related hyponatremia cases (14).

The negative correlation reported between TSH levels and serum sodium concentration indicates (s) further evidence of a dose-dependent effect of thyroid hormone deficiency on sodium homeostasis. Low sodium levels were seen with higher TSH levels, which meant those with more severe hypothyroidism also had more profound hyponatremia. Early diagnosis and control of hypothyroidism might prevent the aggravation of severe hyponatremia and its deleterious consequences. Nevertheless, there are some authors who believe that hypothyroidism per se can't always be the cause of hyponatremia, namely when it comes to mild or subclinical hypothyroidism and that other conditions or drugs might also play a role (4, 6). Nevertheless, the present investigation was designed in a way that the exclusion criteria would restrict the confounding effects so as to strongly support the conclusion that hypothyroidism itself was an important variable.

These findings have clinical implications. While hyponatremia can be asymptomatic (no symptoms), signs and symptoms may include generalized fatigue, lethargy, confusion and, in severe cases, seizures. Diagnosis can be hard, especially when these symptoms overlap with hypothyroid manifestations (14). This reminds clinicians that hyponatremic patients, which especially includes euvolemic status and lack of other causes of sodium imbalance, must remain at high index of suspicion

for thyroid dysfunction. Thyroid hormone replacement early in life has been shown to correct hyponatremia through a reversal of the pathophysiological disturbances underlying hyponatremia (1, 5). The prevalence of hypothyroidism for hyponatremic patients is compared with studies in other clinical settings, and the results show a slight difference in hypothyroidism prevalence in patients with hyponatremia. For instance, Chu et al. (1) found a slightly higher nationwide prevalence of hypothyroidism in hyponatremic patients compared to the results, which could be attributed to larger scale and more diverse patient populations.

However, regional studies like Alqahtani et al. (5) and Lee et al. (14) have focused on metabolic derangements in thyroid patients, and this further highlights the association. These provide distinctive differences in different geographic and demographic regions and also show the varied study outcomes on the basis of various geographic, demographic and methodological factors, which clearly emphasizes the requirement for localized data to guide clinical practice. The relationship with hypothyroidism, hyponatremia and comorbid conditions is yet another important aspect. Patients with other more common etiologies of hyponatremia, such as heart failure, liver cirrhosis or renal disease, were excluded. However, many hypothyroid patients may have subtle or undiagnosed comorbidities that lead to abnormal electrolyte balance. Furthermore, the clinical picture may be complicated by the interplay between hypothyroidism and other endocrine disorders (such as adrenal insufficiency) (10). This study rules out adrenal insufficiency, thus isolating hypothyroidism. However, a complete endocrine evaluation is recommended in hyponatremic patients, especially when clinical suspicion continues to exist despite initial workup.

The results of the study have to be contextualized, and the study's limitations must be acknowledged. The findings are limited to other populations and healthcare settings by being a single-centre, cross-sectional study. Additionally, the precision of prevalence estimates might also be affected by a relatively small sample size. The study also did not examine the long-term outcomes or the response to thyroid hormone therapy, which would help determine the prognosis and treatment of hypothyroid-related hyponatremia. These are areas that future research could focus on, such as prospective cohort studies with more participants and longer follow-ups.

CONCLUSION

The prevalence of hypothyroidism was 22.7% among patients, with this being one of the causes of hyponatremia. A strong association between thyroid dysfunction and electrolyte imbalance is seen with hyponatremia in patients, and thyroid status should be evaluated when other common causes have been excluded. The predominantly euvolemic nature of hyponatremia in hypothyroid patients signifies the role of disturbed water clearance and elevated levels of antidiuretic hormone in the pathophysiology. Timely identification and management of hypothyroidism have the ability to effectively rectify the hyponatremia and prevent complications. Since women are more likely and older people more likely to be hypothyroid, clinicians should suspect hypothyroidism in these populations. Routine thyroid function assessment in this and other hyponatremic patients is desired for early diagnosis and optimization of care. More research, including future larger-scale and longitudinal studies, is encouraged to further validate these findings and treatment outcomes.

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