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Review

Is there a causal relationship between hypothyroidism and hyponatremia?

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***Abstract*:** Hyponatremia is one of the most common lab abnormalities seen in clinical practice. It has become widely accepted that hypothyroidism is a cause of euvolemic hyponatremia. The primary mechanism is thought to be due to impaired free water excretion and changes in sodium handling in the kidney. However, the clinical studies are conflicting and do not definitively confirm the association between hypothyroidism and hyponatremia. Therefore, if severe hyponatremia occurs in a patient without myxedema coma, other potential etiologies should be sought.

Keywords: electrolytes, hyponatremia, hypothyroidism, thyroid

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Introduction

Hyponatremia is one of the most common electrolyte abnormalities occurring in clinical practice. Severe acute hyponatremia can have devastating consequences, but even mild chronic hyponatremia can lead to adverse health effects. Mild hyponatremia has been shown to be associated with increased falls[1] as well as higher rates of osteoporosis[2] and fractures.[3,4] Determining the underlying cause of hyponatremia can be challenging and requires extensive laboratory evaluation. Hypothyroidism has been proposed to be one of the causes of euvolemic hyponatremia. However, the association between hypothyroidism and hyponatremia is neither clearly defined nor well understood. This review focuses on the available literature regarding thyroid and its possible association with hyponatremia.

Methods

Studies were identified through a comprehensive PubMed-based search using the search terms 'hypothyroidism' and 'hyponatremia' in the article title or abstract. Studies and case reports in which hypothyroidism was suspected but ultimately determined not to be the cause of hyponatremia were excluded. Given the limited studies in this area, there was no prespecified time frame.

Mechanisms

Several different mechanisms have been thought to explain the association between hypothyroidism and hyponatremia (Figure 1). Changes in vasopressin leading to impaired water excretion are postulated to be one of the primary mechanisms. The trigger for the release of vasopressin has been hypothesized to occur in multiple ways. Hypothyroidism leads to decreased cardiac output and increased peripheral vascular resistance.[5,6] The decrease in cardiac output is thought to cause baroreceptor-mediated release of vasopressin.[6] Hypothyroidism also results in the accumulation of interstitial mucopolysaccharides, which leads to decreased effective arterial blood volume and the release of vasopressin.[7] Increased vasopressin results in increased free water absorption. Impaired urinary dilution may also occur through an upregulation of renal aquaporin 2 channels.[8] Studies examining vasopressin levels in patients with hypothyroidism have been conflicting. In a study of 20 patients with severe hypothyroidism, vasopressin was shown to be elevated at baseline.[9] In addition, in 75% of participants, vasopressin failed to suppress with water ingestion.[9] However, in a study of eight patients with severe hypothyroidism, the hypothyroid patients had a significantly lower plasma vasopressin levels compared to normal controls.[10]

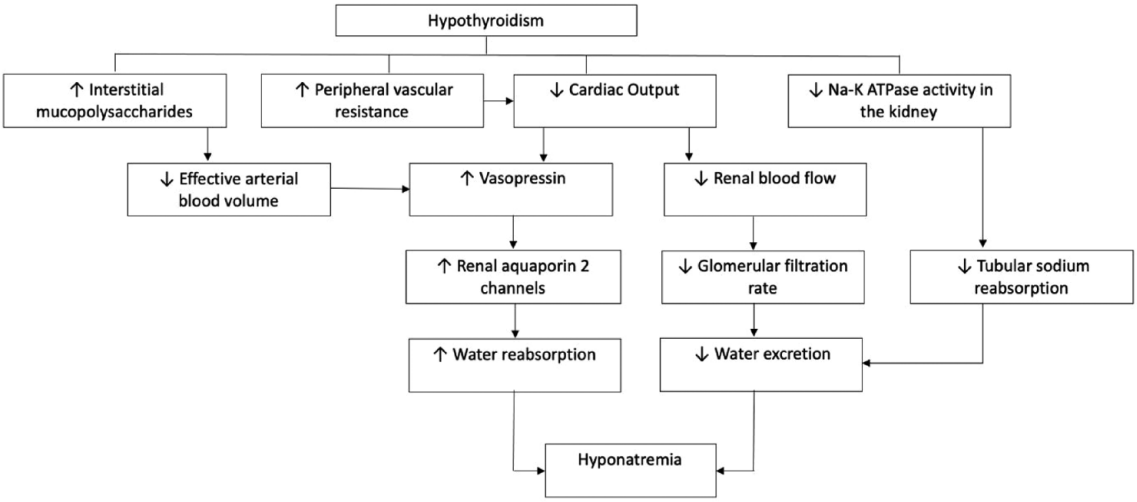

Figure 1. Proposed mechanisms for hypothyroidism-induced hyponatremia.

In this study, all subjects had a normal or subnormal rise in vasopressin in response to hypertonic saline infusion.[10] Therefore, the impaired water excretion observed in hypothyroidism may also occur via vasopressin-independent processes.

The kidney plays a key role in the water and sodium homeostasis. In hypothyroidism, decreased cardiac output leads to decreased renal blood flow and reduced glomerular filtration rate (GFR).[6] Tubular sodium and water excretion were similar in hypothyroid patients compared to those with a similar degree of renal insufficiency.[11] Therefore, the changes observed may be a consequence of the reduction in GFR. In addition, hypothyroidism causes decreased Na-K-ATPase pump activity in the kidney with a reduction in tubular sodium reabsorption.[12] All these changes ultimately contribute to water retention and altered sodium handling leading to hyponatremia. Many questions remain with regard to the pathophysiologic link between hypothyroidism and hyponatremia.

Clinical studies

The clinical data regarding the association between thyroid and sodium levels are poor. Clinical studies, excluding case reports, are summarized in Table 1. There have been several studies that have concluded that hyponatremia, especially severe hyponatremia, is uncommon in patients with hypothyroidism.[13] In a large retrospective review of 33,912 patients, sodium levels were similar in euthyroid and hypothyroid patients, suggesting that the association is more coincidence than causal.[14] Studies conducted in the emergency department and the primary care setting have demonstrated that although hyponatremia is more common in patients with elevated thyroid stimulating hormone (TSH) values, serum sodium levels do not correlate with TSH levels.[15,16] This could be because most of the patients had normal sodium levels and therefore, when TSH and sodium was analyzed as a continuous variable, a strong correlation could not be found. A single-center, retrospective analysis found that in 98.88% of patients with hypothyroidism and hyponatremia, there was a potential alternative cause for the patient's hyponatremia, with no cases of clinically relevant hyponatremia ($Na < 130$ mmol/L) attributable to hypothyroidism alone.[17] The results suggest that hyponatremia is oftentimes multifactorial in hypothyroid patients with moderate to severe hyponatremia. A study of 100 patients with hyponatremia associated with altered mental status found only eight patients with hypothyroidism requiring replacement, indicating that hypothyroidism is not a common cause of severe unexplained hyponatremia.[18] Although there was not a significant association between hypothyroidism and hyponatremia in newly diagnosed hypothyroid patients, every 10 mU/L rise in TSH was associated with a 0.14 mmol/L decrease in sodium, suggesting that only the most severe cases of hypothyroidism result in clinically significant hyponatremia.[16] A retrospective, cross-sectional study of 71,817 patients also concluded that the prevalence of overt hypothyroidism was higher for more severe hyponatremia, even after adjusting for potential confounders.[19]

However, patients with severe hypothyroidism will often have other electrolyte derangements and organ impairments that can impact sodium levels. Therefore, it can be challenging to draw meaningful conclusions regarding the effect of the thyroid hormone alone. A study of 10 patients with severe hypothyroidism undergoing a levothyroxine absorption test concluded that despite having a very elevated TSH and decreased GFR, hyponatremia was not observed in these patients.[20] Therefore, even in severe hypothyroidism, in the absence of myxedema coma, hyponatremia may not be seen.

The pediatric population can potentially further our understanding, given that adults have many factors which can affect their sodium handling, including medications, variable sodium intake, and comorbidities such as hypertension and obesity. There have been case reports of hyponatremia in pediatric patients with hypothyroidism.[21–23] However, these cases were often confounded by comorbid conditions such as acute illness or brain injury. In a study of 32 neonates with congenital hypothyroidism detected on screening, there were no cases of hyponatremia and no significant changes in sodium after thyroid hormone replacement.[24] These results suggest that hyponatremia is uncommon in patients with hypothyroidism alone.

The acute thyroid hormone withdrawal prior to radioactive iodine (RAI) treatment can result in hyponatremia and a significant decline in sodium.[25,26] However, there have also been other studies in which there was a minimal change in blood sodium concentration.[27,28] In a study examining 903 patients with differentiated thyroid cancer undergoing RAI, only 2.5% of patients developed hyponatremia.[29] Among the patients who developed hyponatremia, 91.3% were mild and asymptomatic with sodium levels in the 130–135 mmol/L range.[29] These results were corroborated in a study of 212 thyroid cancer patients in which 1.9% patients developed moderate hyponatremia (sodium $\geqslant$120 mEq/L).[27] These studies demonstrate that the incidence of hyponatremia prior to RAI treatment is low and mild in most cases. It could be that chronic hypothyroidism results in hyponatremia. Therefore, hyponatremia is not appreciated in patients undergoing thyroid

Table 1. Summary of relevant clinical studies.

Author	Study design	Study population	Conclusions
Pediatric studies			
Asami and Uchiyama[24]	Single-center, prospective, cohort study	32 neonates with congenital hypothyroidism	No significant difference in serum sodium concentrations between congenital hypothyroidism neonates compared to control neonates.
Adult studies			
Baajafer *et al.*[13]	Single-center, retrospective, cohort study	188 patients with hypothyroidism	No significant correlation between TSH and sodium levels in the hypothyroid state compared to euthyroid state to the hypothyroid state ($r = 0.06$, $p = 0.6$).
Cao *et al.*[29]	Single-center, retrospective, cohort study	903 patients with differentiated thyroid cancer	No significant correlation between sodium and TSH levels and urine iodine before ^{131}I treatment ($r = 0.045$, $p = 0.174$; $r = 0.013$, $p = 0.697$).
Ching *et al.*[20]	Single-center, retrospective, chart review	10 ambulatory patients with TSH > 100 mIU/mL	In patients with severe hypothyroidism (median TSH 193 mIU/mL), none had serum sodium below the normal range.
Croal *et al.*[14]	Single-center, retrospective, cohort study	33,912 patients	No significant difference in rates of hyponatremia between hypothyroid patients compared to euthyroid patients (12.8% *versus* 11.4%).

(Continued)

Table 1. (Continued)

Author	Study design	Study population	Conclusions
Dayrit *et al.*[28]	Single-center, retrospective, chart review	30 patients with differentiated thyroid cancer	No significant correlation between pre-RAI sodium concentration and TSH ($r = 0.055$, $p = 0.775$) or post-RAI sodium concentration and TSH ($r = -0.159$, $p = 0.401$).
Hammami *et al.*[27]	Single-center, prospective, cohort study	212 thyroid cancer patients acutely hypothyroid for RAI scan	No significant correlation between post-isolation sodium concentration and TSH concentration ($r = 0.03$, $p = 0.69$).
Nagata *et al.*[19]	Multicenter, retrospective, cross-sectional study	71,817 patients	Significant increase in rates of patients with hypothyroidism with worsening severity of hyponatremia ($p < 0.001$).
Schwarz *et al.*[15]	Single-center, retrospective, cohort study	9012 patients admitted to the emergency department	Significant difference in rates of hyponatremia between patients with high TSH compared to patients with normal TSH (14% *versus* 9%, $p < 0.01$).
Vannucci *et al.*[26]	Single-center, retrospective study	101 patients with differentiated thyroid cancer	Significant difference in the sodium level evaluated before total thyroidectomy compared to sodium level on the day of RAI therapy (140.7 ± 1.6 *versus* 138.7 ± 2.3 mEq/L, $p = 0.012$)
Warner *et al.*[16]	Single-center, retrospective, cohort study	999 newly diagnosed hypothyroid patients presenting to primary care clinics	No significant difference in rates of hyponatremia in hypothyroid patients compared to control patients ($p = 0.17$).

RAI, radioactive iodine; TSH, thyroid stimulating hormone.

hormone withdrawal due to the acute changes in thyroid hormone levels. A variety of factors including age, preoperative serum sodium level, and history of diuretic use are risk factors for hyponatremia.[27] In addition, the low-iodine diet that thyroid cancer patients undergo in preparation for RAI treatment can contribute to the development of hyponatremia. Therefore, the hyponatremia seen prior to RAI therapy is likely multifactorial rather than solely due to hypothyroidism.

Conclusion

Hyponatremia and hypothyroidism are common diagnoses. Therefore, their simultaneous co-occurrence is not surprising. It is challenging to establish causality given that, in many situations, the etiology of hyponatremia is likely multifactorial. Although there are proposed mechanisms that explain how hypothyroidism leads to hyponatremia, clinical studies have not consistently demonstrated this relationship. Therefore, if hyponatremia occurs in patients with hypothyroidism in the absence of myxedema coma, other etiologies for hyponatremia should be evaluated.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Julie Chen: Writing – original draft.

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