Hypothyroidism-associated hyponatremia: Mechanisms, implications and treatment

Running title: Hypothyroidism and hyponatremia

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Abstract

Background: Patients with moderate to severe hypothyroidism and mainly patients with myxedema may exhibit reduced sodium levels (<135 mmol/L).

Summary: Aim of the short review is the presentation of the mechanisms of hyponatremia and of the available data regarding its implications and treatment in patients with hypothyroidism. Hypothyroidism is one of the causes of hyponatremia and thyroid-stimulating hormone determination is mandatory during the evaluation of patients with reduced serum sodium levels. The main mechanism for the development of hyponatremia in patients with chronic hypothyroidism is the decreased capacity of free water excretion due to elevated antidiuretic hormone levels, which are mainly attributed to the hypothyroidism-induced decrease of cardiac output. However, recent data suggests that the hypothyroidism-induced hyponatremia is rather rare and probably occurs only in severe hypothyroidism and myxedema. Other possible causes and superimposed factors of hyponatremia (e.g. drugs, infections, adrenal insufficiency) should be considered in patients with mild/moderate hypothyroidism. Treatment of hypothyroidism and fluid restriction are usually adequate for the management of mild hyponatremia and hypothyroidism. Patients with possible hyponatremic encephalopathy should be urgently treated according to current guidelines.

Conclusions: Severe hypothyroidism may be the cause of hyponatremia. All hypothyroid patients with low serum sodium levels should be evaluated for
other causes and superimposed factors of hyponatremia and treated accordingly.

Keywords: hyponatremia, sodium, hypothyroidism, antidiuretic hormone, myxedema
INTRODUCTION

Decreased thyroid hormone levels are usually associated with underlying thyroid disease (primary hypothyroidism), but occasionally may be caused by disorders of the hypothalamic-pituitary axis resulting in reduced secretion of thyroid-stimulating hormone (TSH) or thyrotropin-releasing hormone (TRH) (secondary or tertiary hypothyroidism). Patients with moderate to severe hypothyroidism and mainly patients with myxedema may exhibit reduced sodium levels (<135 mmol/L). Thus, hypothyroidism is one of the causes of hyponatremia and TSH determination is mandatory during the evaluation of patients with reduced serum sodium levels. Furthermore, the exclusion of hypothyroidism is one of the prerequisites for the diagnosis of the syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH).

Aim of this short review is the presentation of the mechanisms of hyponatremia and the available data regarding its implications and treatment in patients with hypothyroidism.

POSSIBLE MECHANISMS OF HYponATREMIA IN PATIENTS WITH HYPOTHYROIDISM

Acute hypothyroidism is usually seen in patients with differentiated thyroid cancer (papillary and follicular) who undergo preparation for radioiodine therapy, during which thyroid hormone treatment is withheld. In this setting of acute hypothyroidism, decreased glomerular filtration rate that can directly
decrease free water excretion by diminishing water delivery to the diluting segments is the most important mechanism of hyponatremia\(^9, 10\). In the setting of radioiodine treatment patients are instructed to follow low iodine diet and receive increased fluid intake. Additionally, radioiodine administration is associated with nausea and anxiety (which are very potent stimuli of antidiuretic hormone secretion) and these factors combined may contribute to hypothyroidism-associated hyponatremia\(^10\).

The main mechanism for the development of hyponatremia in patients with chronic hypothyroidism is the decreased capacity of free water excretion due to elevated ADH levels (Figure 1). The increase in ADH levels has been mainly attributed to the hypothyroidism-induced decrease of cardiac output, which stimulates the carotid sinus baroreceptors and induces the release of ADH\(^11-14\). Thus, hyponatremia in most of hypothyroid patients is the result of the inability to suppress maximally the secretion of ADH, which results in reduced water excretion\(^3, 15\). Indeed, it has been shown that the impaired water excretion in hypothyroidism is mediated through the upregulation of ADH-induced aquaporin-2 expression in the collecting tubules\(^15\).

However, reduced cardiac output is not the sole possible mechanism of hyponatremia in at least some patients with chronic hypothyroidism (Figure 1). Another contributing factor to increased ADH levels in patients with myxedema is the accumulation of interstitial mucopolysaccharides that results in fluid retention and decreased effective arterial blood volume leading to ADH-mediated water retention and reduced sodium levels\(^16, 17\). Additionally, some hypothyroid patients exhibit increased urine sodium concentration that points
to the diagnosis of SIADH and not to reduced cardiac output. Impaired renal function seems to play a role in the development of hyponatremia in patients with hypothyroidism. In these patients the impairment in kidney function [reduced glomerular filtration rate (GFR)], results in decreased water delivery to the diluting segments of the kidney and subsequently reduced capacity for water excretion. Moreover, a low iodine diet is usually associated with low solute intake that may contribute to the development of hyponatremia. Generally, low iodine diet is associated with the occurrence of hyponatremia especially in elderly patients (>65 years), in females, as well as in diuretic (thiazides)-treated individuals. Finally, a case report proposed salt-losing nephropathy as a possible mechanism of mild hyponatremia (serum sodium 134 mmol/l) in a hypothyroid patient with hypovolemic and multiple electrolyte abnormalities; it was proposed that thyroid hormone is essential for the expression of active transport pumps in the renal tubules, especially the Na\(^+\)-K\(^+\)-ATPase pumps, and hypothyroidism may be infrequently related with multiple electrolyte abnormalities associated with volume losses. Figure 1 describes the main pathogenetic mechanisms of chronic hypothyroidism-associated hyponatremia. In certain patients more than one of these mechanisms may co-exist.

**HOW REAL IS THE ASSOCIATION BETWEEN HYPONATREXIA AND HYPOTHYROIDISM?**

Generally, the association between hypothyroidism and hyponatremia is
rather week. A retrospective study showed that acute hypothyroidism in the setting of thyroid hormone therapy withdrawal in patients with differentiated thyroid cancer was associated with mild hyponatremia in only 3.9% of 128 patients, whereas none of the patients developed severe hyponatremia. Similarly, in a prospective analysis of 212 consecutive thyroid cancer patients a small difference was observed between pre- and post-isolation sodium levels (pre-isolation 139.5±2.3, post-isolation 137.8±3.0 mEq/l). Additionally, mild hyponatremia (≥130 mEq/l) was observed only in 18 patients (8.5%) and moderate hyponatremia (≥120 mEq/l) only in 4 (1.9%) patients. This prospective study also showed that in this setting serum sodium concentration may not need to be monitored, unless patients have “risk factors” for developing hyponatremia such as impaired renal function or are receiving diuretics. Additionally, increased age and female gender are associated with lower serum sodium concentration in the setting of acute hypothyroidism. Regarding chronic hypothyroidism, a retrospective analysis of data from 9012 patients admitted to an Emergency Medicine Department reported an increased prevalence of hyponatremia in patients having high TSH levels compared with patients having normal TSH levels (14% vs 9%, p<0.01). However, the difference in serum sodium concentration between these groups, although statistically significant, was rather non-clinically relevant (138 vs 139 mEq/L, p<0.01). Additionally, serum sodium concentration did not correlate with serum TSH levels; however, the most active free triiodothyronine (T3) correlated significantly with serum sodium levels. It should be mentioned that only patients with severe thyroid
dysfunction exhibited clinically relevant electrolyte abnormalities, including decreased serum sodium levels\textsuperscript{24}. Additionally, the incidence of hypothyroidism is low in patients with hyponatremia. In a series of patients with hyponatremia (n = 204, Na\textsuperscript{+} <130 mEq/L) hypothyroidism was evident only in two cases\textsuperscript{25}. Other authors reported that hypothyroidism was not a major cause of low sodium levels even in cases of unexplained hyponatremia\textsuperscript{26}.

Other studies have questioned the direct correlation between hypothyroidism and hyponatremia. For example, a study including 33,912 patients reported no significant difference in serum sodium levels between euthyroid and hypothyroid patients\textsuperscript{27}. Additionally, no significant difference was shown in the proportion of euthyroid and hypothyroid patients with serum sodium concentration <135 mEq/L (11.4\% vs 12.8\%)\textsuperscript{27}. Another retrospective analysis from the Emergency Department or the Medical Intensive Care Unit of a University Hospital also showed not clinically significant alterations in serum sodium concentration in hypothyroid patients (mean serum sodium levels in hypothyroid group was 137.8 mEq/L and in euthyroid group was 137.4 mEq/L)\textsuperscript{28}. Additionally, the prevalence of hyponatremia was also similar in hypothyroid and in euthyroid individuals (19.7\% vs 20.7\%, p=NS)\textsuperscript{28}.

Moreover, no clinically relevant association between newly diagnosed hypothyroidism and decreased sodium levels was shown in a retrospective analysis (n=999), in which every increase in TSH by 10 mIU/L correlated with a decrease of serum sodium by only 0.14 mEq/L\textsuperscript{4}. Furthermore, studies in infants with congenital hypothyroidism did not show an association between
hypothyroidism and hyponatremia. Thus, in the cases of congenital hypothyroidism and hyponatremia, other causes of decreased serum sodium concentration (e.g. malnutrition, volume depletion, tubulopathies, SIADH) should be searched.

It has been suggested that the association between hyponatremia and hypothyroidism may at least be mediated by other comorbidities, including hypovolemia, nausea, infections, or drugs affecting water homeostasis, which may induce increased ADH secretion, water retention and hyponatremia. Thus, other causes of decreased sodium levels (including drugs) should be carefully excluded in patients with mild/moderate hypothyroidism and hyponatremia. Indeed, it has been suggested that hypothyroidism should be included in the differential diagnosis of hyponatremia only in patients with severe hypothyroidism (TSH levels >50 mIU/L) or with symptoms or signs of myxedema. However, clinicians should have in mind that severe hypothyroidism can exist with TSH levels below 50 mIU/L. Indeed, a significant negative correlation between age and TSH levels has been shown in thyroid cancer patients four weeks after the withdrawal of thyroxine therapy in preparation for radioiodine scan/treatment. Additionally, severe secondary hypothyroidism can be the cause of low thyroid hormones.

Patients with metastatic thyroid cancer may exhibit severe symptomatic hyponatremia if thyroxine treatment is stopped prior to the administration of radioactive iodine. However, low iodine diet associated with low solute intake, as well as the underlying neoplasia, may contribute to the
development of hyponatremia in these cases\textsuperscript{21}. Thus, serum sodium monitoring is crucial in patients with high risk of hyponatremia who are in low iodine diet\textsuperscript{22}.

Finally, hypothyroidism observed in patients with the polyglandular autoimmune syndrome type II is usually accompanied by adrenal insufficiency resulting in hyponatremia\textsuperscript{38}. Similarly, the simultaneous presence of glucocorticoid deficiency should be suspected in cases of secondary hypothyroidism\textsuperscript{5, 39}.

**CLINICAL IMPLICATIONS**

The assessment of the extracellular volume status is of vital importance in the evaluation of hyponatremia\textsuperscript{7}. Hypothyroidism-induced hyponatremia is usually euvolemic; thus, the presence of hypovolemia may suggest coexistent primary adrenal insufficiency or less frequently salt-losing nephropathy\textsuperscript{6}.

As aforementioned data clearly suggests, hypothyroidism should not be considered the sole cause of the low serum sodium in hypothyroid patients with TSH levels <50 mIU/L\textsuperscript{33}. In this setting, hypothyroidism should be considered as a possible superimposed factor and other causes of hyponatremia should be investigated. In euvolemic hypothyroid patients with TSH <50 mIU/ml, if no other obvious cause of hyponatremia can be identified after a thorough diagnostic work up and normonatremia has not been achieved after thyroid hormone replacement, the possibility of idiopathic
SIADH, which is not infrequently observed especially in the elderly, should be suspected. In these cases, careful and repeated monitoring for the presence of an occult tumor (particularly pulmonary) is essential.

The attribution of hyponatremia to hypothyroidism is a diagnostic challenge for clinicians, even in cases of myxedematous coma, since myxedema crisis is often induced by an underlying infection, respiratory or central nervous system illness, or drugs (e.g. sedatives or antidepressants), which are all well-established causes of hyponatremia. It is also possible that myxedema and hyponatremia may have a common underlying cause (e.g. amiodarone).

Hypothyroidism also frequently coexists with diabetes mellitus, which is associated with hyponatremia through several underlying mechanisms. Additionally, in hyperglycemic states, it is imperative to correct the serum sodium concentration for the degree of hyperglycemia. Another important step in the approach of any patient with hyponatremia is to exclude the possibility that the decreased serum sodium levels are due to an artifact.

Potential causes of pseudohyponatremia in patients with hypothyroidism are dyslipidemia (especially if diabetes mellitus coexists) and hypergammaglobulinemia (in hypothyroidism of autoimmune origin). Consequently, hyponatremia of multifactorial origin may be seen in patients with hypothyroidism and the presence of common causes or superimposed factors should be meticulously investigated.

**TREATMENT OF HYponATREMIA IN HYPOThYROIDIC PATIENTS**
In most cases, hyponatremia associated with hypothyroidism is usually mild; thus, thyroid hormone replacement and moderate fluid restriction are generally enough to correct serum sodium levels. More severe hyponatremia is mainly observed in patients who have severe hypothyroidism usually accompanied by altered mental status. It should be emphasized that the neurological picture of myxedema and hyponatremic encephalopathy is often extremely difficult to be distinguished. In this case, urgent treatment of hyponatremia may be indicated to determine whether the low serum sodium levels is contributing to the patient’s neurological symptoms\textsuperscript{45}. It has been proposed that treatment of hyponatremia in such emergent cases should be attempted with water restriction and normal saline, especially when only in patients with serum sodium concentration is $<$120 mEq/L, while in patients with higher serum sodium levels water restriction is usually adequate. More aggressive treatment (hypertonic saline solution plus furosemide) should be used cautiously to avoid inadvertent correction of hyponatremia with its devastating consequences (osmotic demyelination syndrome)\textsuperscript{46}.

However, taking into account the rarity of hypothyroidism-related hyponatremia and the lack of relative studies, we believe that therapy of this entity should not be deviated from the principles of treating hyponatremia of any cause\textsuperscript{45, 47, 48}. Specifically, normal saline should not be administered in patients with suspicious hyponatremic encephalopathy because no significant change or even a decrease in serum sodium levels can be observed\textsuperscript{49, 50}. On the contrary, in cases of severely symptomatic hyponatremia, administration of 100 mL of 3% NaCl (2 mL/kg body weight) should be immediately given. If
it is needed, up to two additional infusions at 10-min intervals may be given\textsuperscript{45}. Normal saline should be restricted only in the rare cases of hypothyroidism-induced hypovolemic hyponatremia\textsuperscript{50, 51}.

**CONCLUSIONS**

The hypothyroidism-induced hyponatremia is rather rare and probably occurs only in severe hypothyroidism. Even in myxedema coma, however, other possible causes and superimposed factors of hyponatremia (e.g. drugs, infections, adrenal insufficiency) should be considered.
AUTHOR DISCLOSURE STATEMENT

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**FIGURE LEGEND**

*Figure 1.* Implicating mechanisms of hyponatremia in patients with chronic hypothyroidism. The most important mechanisms are shown with bold letters and the rare mechanisms are shown with dashed lines.

ADH = antidiuretic hormone; SIADH = syndrome of inappropriate antidiuretic hormone secretion; GFR = glomerular filtration rate


22. Li JH, He ZH, Bansal V & Hennessey JV. Low iodine diet in differentiated thyroid cancer: a review. *Clin Endocrinol (Oxf)* 2016 **84** 3-12.


Implicating mechanisms of hyponatremia in patients with chronic hypothyroidism. The most important mechanisms are shown with bold letters and the rare mechanisms are shown with dashed lines.