

## Review Article

# Hyponatremia in Hypothyroid Disorders: Current Understanding

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## Abstract

The association of hyponatremia with primary hypothyroidism is well known but infrequent. Also in patients undergoing treatment for thyroid cancer, hyponatremia may arise. However, given the infrequency with which hyponatremia occur in patients with hypothyroidism, there are concerns that this may only be a coincidence. Here we review the available literature for the prevalence, pathologic mechanism and clinical implication of hyponatremia associated with hypothyroidism.

## ABBREVIATIONS

ANP: Atrial Natriuretic Peptide; ADH: Antidiuretic Hormone; CO: Cardiac Output; EDRF: Endothelial-Derived Relaxing Factor; PPV: Positive Predictive Value; RAAS: Renin-Angiotensin-Aldosterone-System; RAI: Radioactive Iodine Therapy; TSH: Thyroid Stimulating Hormone

## INTRODUCTION

Hyponatremia is the commonest electrolyte abnormality encountered in clinical practice and it is associated with variable morbidity, sometimes leading to serious clinical complications [1,2]. This disorder remains incompletely understood because of its association with numerous underlying disease states and multiple etiologies with differing pathophysiologic mechanisms [3]. Primary hypothyroidism had been a widely accepted clinical cause of hyponatremia [4]. However, because of the infrequency with which this occurs and lack of compelling evidence from observational data for a causal relationship, there is a growing concern that the presence of hyponatremia may only be a coincidence in hypothyroid patient, with only patients with myxedema being considered to likely have a causative association [5-7]. Despite these concerns, expert clinical guidelines include hypothyroidism as a potential cause of euvolemic hyponatremia that should be evaluated during management [3]. In addition to the general risk of hyponatremia associated with primary hypothyroidism, there has also been several reports of an increased risk of hyponatremia in association with thyroid cancer, which equally is an important clinical co-morbidity [8,9].

This review will focus on the prevalence of hyponatremia and pathophysiologic mechanisms of hypothyroid-induced-hyponatremia in different hypothyroid states and review available publications on this topic.

## PREVALENCE AND ASSOCIATION OF HYPONATREMIA WITH HYPOTHYROIDISM

Estimated prevalence of hyponatremia in hypothyroid patient is between 10% to 12.8% [10,11]. This relationship between hyponatremia and hypothyroidism though widely accepted has been challenged by some recent observational studies. In a study evaluating the relationship of serum sodium and thyroid stimulating hormone (TSH) in 33,912 patients who presented to a large city general hospital, the investigators found that in patients with hyponatremia, there was no difference between euthyroid subjects (11.4%) and hypothyroid subjects (12.8%) [11]. In another study of patients presenting in a primary care setting, the serum sodium levels of 999 newly diagnosed hypothyroid patients were compared with 4875 controls who had normal TSH values and noted a significant relationship between lower sodium concentration and hypothyroid status ( $P < 0.0001$ ) [12]. They also noted that in the hypothyroid group, every 10mU/l rise in TSH was associated with a 0.14mmol/l decrease in serum sodium; a change which though reached statistical significance ( $P < 0.0001$ ), they concluded was unlikely to be clinically relevant. An Australian study of 15,080 patients found that the prevalence of hypothyroidism was higher in the hyponatremic than normonatremic patients (4.7 versus 1.7%, respectively) and was statistically significant ( $P < 0.001$ ) [13]. However, this association was weak with a positive predictive value (PPV) of 5% for hypothyroidism. Strong evidence of hyponatremia associated with hypothyroidism has been mainly in case reports of patients with severe hypothyroidism. In one case, a patient with myxedema coma was noted to have severe hyponatremia with no additional etiologic factor recognized other than hypothyroidism, and serum sodium corrected after treatment with 3% saline solution and thyroxine replacement

[14]. In another report, a patient with hypothyroidism following thyroidectomy was admitted with severe hyponatremia after cessation of thyroid replacement, which was corrected with thyroxine replacement and hypertonic saline [15].

In addition to the general risk of hyponatremia associated with primary hypothyroidism, there have been several reports of an increased risk of development of hyponatremia in association with thyroid cancer in patients undergoing radioactive iodine therapy [8,9]. A retrospective analysis of 128 patients with thyroid cancer showed that only a few patients (3.9%) developed hyponatremia and none of them had sodium values below 130meq/l [16]. In a prospective cohort study of 30 patients which excluded patients with comorbidities that may contribute to hyponatremia, 26% of study population was found to have mild hyponatremia post radioactive iodine therapy (RAI) therapy [17]. In another prospective study that looked at 212 acutely hypothyroid patients with differentiated thyroid cancer, hyponatremia was uncommon in spite of the stress and nausea associated with radioiodine treatment and excessive fluid intake. In the patients with differentiated thyroid cancer, age, elevated creatinine and diuretic use were associated with development of hyponatremia [18].

## **PATHOPHYSIOLOGY**

Hyponatremia in hypothyroid patients have been reported to be associated with increased total body water and total body sodium, thus suggesting a key role for impaired water excretion in its development [19-21]. Though still incompletely understood, multiple pathophysiologic mechanisms are been implicated in the development of hyponatremia in hypothyroid patients; these mechanisms can be broadly divided into cardiovascular effects, renal effects and probable effect of antidiuretic hormone (ADH) [20,22]. Furthermore, other etiologic mechanisms associated in patients with thyroid cancer will be reviewed below.

### **Cardiovascular effects**

Patients with hypothyroidism could have up to 30-50% decrease in their cardiac output (CO) due to bradycardia, decreased ventricular filling and decreased cardiac contractility [13,17,23]. Also, hypothyroidism is associated with increased peripheral vascular resistance likely due to endothelial dysfunction from decrease in the release of endothelial-derived relaxing factor (EDRF) that leads to increased contraction of endothelial cells [24,25]. These hemodynamic alterations lead to reduced renal blood flow, decreased glomerular filtration and thus reduction in free water formation. Furthermore, decreased cardiac output in hypothyroidism may lead to significant depression in effective arterial pressure sufficient enough to stimulate ADH release via baroreceptor mechanism causing decrease in free water excretion [3].

### **Renal effects**

Functional reduction of up to 40% in glomerular filtration rate (GFR) which resolves after thyroid hormone replacement has been found in hypothyroid patients. The potential mechanisms of reduction in GFR include decrease in cardiac output, renin-angiotensin-aldosterone-system (RAAS) activity dysregulation and decrease systemic release of atrial natriuretic peptide (ANP)

level [26,27]. Hypothyroidism also influences renal tubular functions. A Study which compared hypothyroid patients to euthyroid patients and patients with chronic kidney disease showed that hypothyroid patient had decrease in proximal sodium reabsorption and increase in distal sodium reabsorption with reduced maximal urine flow and free water clearance that was similar to patient with chronic kidney disease [28].

### **Effect of ADH**

Though impaired water excretion seems to underlie the development of hyponatremia in patients with hypothyroidism, its association with ADH as a possible causative factor is weak [29]. In a study of eight patients with myxedema, two of whom had hyponatremia at the basal state, the investigators noted they had mild urinary diluting defect along with appropriately suppressed ADH and concluded that the impaired water excretion was due mainly to an ADH-independent mechanism [30]. Another study evaluating the role of ADH in impaired water excretion in five hypothyroid patients, found that they had low ADH which did not decrease further with water loading suggesting that there was impaired release and/or metabolism of ADH in hypothyroidism [31]. Of note, an earlier study had shown elevated ADH level which failed to completely respond to water loading in a majority (75%) of patients with myxedema [32]. In this same study, a small number of patient who had suppressible ADH with impaired water excretion suggesting a non-ADH mediated renal mechanism.

### **Hyponatremia in patients with thyroid cancer**

Several factors have been implicated to play a role in development of hyponatremia in thyroid cancer patients undergoing treatment with radioactive iodine (RAI). Prior to starting RAI therapy, patients are counseled to adhere to low iodine diet, but instead have been known to inadvertently follow a low sodium diet by omitting iodized salt and other food that contain salt which may likely lead to hyponatremia especially if a mild defect or renal excretion of free water coexists [33-35]. In addition, patients are asked to increase oral intake of fluids post treatment to flush out the iodine, which may further exacerbate hyponatremia in certain patients [35]. Also, nausea and stress associated with RAI therapy can also favor lowering of serum sodium by directly stimulating the release of vasopressin [36]. Finally, the induced hypothyroidism, which occurs in preparation for radioactive therapy, may have added effect by the various mechanisms detailed above.

## **DISCUSSION**

Clinically significant hyponatremia is rare in patients with hypothyroidism, with most reported cases being in patients with severe longstanding hypothyroidism or myxedema [9,16]. Hypothyroidism with impaired water excretion leading to hyponatremia has mainly been seen in patients with severe hypothyroidism who typically are elderly and most times meeting criteria for myxedema coma [3]. In patients with hypothyroidism presenting with euvolemic hyponatremia, other etiologic should be sought, with high index of suspicion for hypothyroidism reserved for cases with no other discernable etiologies or in patients with clinical features of severe hypothyroidism.

Hyponatremia associated with treatment of thyroid cancer patients occur in a small subset of patients. The limited studies that are available with the exception of a few case reports, show that the prevalence of hyponatremia is low (3.9-4%) in this setting and when hyponatremia occurred, it was mild [8,9]. In reported cases, development of hyponatremia was associated with age, elevated creatinine and diuretic use. Given the low incidence of hyponatremia in this subset of population, sodium concentration need not be routinely monitored during treatment unless patients have associated risk factors like old age, diuretic usage, pretreatment hyponatremia or impaired renal function [18].

## CONCLUSION

Though primary hypothyroidism causes hyponatremia, this association is infrequent. When patients with elevated TSH present with euvolemic hyponatremia, a recent expert guideline suggests that other diagnosis instead of hypothyroidism should be considered except in the few elderly patients with severe hypothyroidism especially myxedema coma [3]. These differential diagnoses include Syndrome of inappropriate ADH secretion, Glucocorticoid deficiency, and primary polyuria.

Hyponatremia occurring in association with RAI therapy for thyroid cancer seems to be mild with limited clinical significance and routine monitoring of these patients does not seem to be warranted unless they fall in the high-risk group of patients.

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