

Does Hypothyroidism Cause Hyponatremia?*

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Abstract

Background: According to most clinical guidelines hypothyroidism should be excluded as a cause in the analysis of euvolemic hyponatremia. Although this axiom has been well established in clinical practice, relatively little evidence supports a relation between hypothyroidism and hyponatremia. The current study was conducted to prove an association between hypothyroidism and the occurrence of hyponatremia. In addition, we sought to determine the effect of L-thyroxine replacement therapy on plasma sodium levels. **Methods:** Data from 2009 to 2011 were retrospectively reviewed. The database included blood samples in which both thyroid function and plasma sodium were determined. Regression analysis and ANOVA were performed to reveal an association between hypothyroidism and hyponatremia. **Results:** Linear regression analysis of plasma sodium on plasma TSH revealed no relationship ($R^2 = 0.005$). The corresponding gradient belonging to the regression line was -0.427 mmol/log plasma TSH ($p = 0.22$). No significant relation between plasma sodium and TSH concentration could therefore be found. 32 hypothyroid patients who were treated with L-thyroxine, were identified. No clear change in plasma sodium could be discerned with regression analysis (0.707 mmol/L per year, $p = 0.147$). **Conclusion:** Hypothyroidism is not a common cause of hyponatremia. Screening for thyroid function does not seem warranted in the initial analysis of a hyponatremic patient.

Keywords

Hyponatremia, Hypothyroidism

1. Introduction

Hyponatremia is a common electrolyte disturbance and analysis of hyponatremia has been topic of numerous

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guidelines. Most guidelines consider hypothyroidism to be a cause for hyponatremia [1]-[3]. More specifically in patients who are euvoletic and have high urine osmolality the differential diagnosis encompasses: syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypocortisolism and hypothyroidism. Proposed mechanisms for hypothyroidism induced hyponatremia include increase in vasopressin (ADH) release [4]-[7] and reduced renal glomerular filtration rate (GFR) [2] [8]-[17]. Changes in ADH or GFR are thought to diminish renal capacity for the excretion of free water, resulting in water retention and a hence hyponatremia [4]-[8] [18] [19]. Whether the increased vasopressin levels are a direct effect of low plasma thyroxin levels or secondary to reduced cardiac output due to hypothyroidism, is unknown [2] [3] [15] [17]. Relatively little epidemiological data supports the notion that hypothyroidism is an important cause of hyponatremia.

Several studies dispute the relationship between hypothyroidism and hyponatremia. Two small studies, one in thyroid ablated patients and another in congenital hypothyroid neonates found no significant difference in plasma sodium compared to euthyroid controls [20] [21]. Three larger studies in adults showed weak or no relation between the presence of hypothyroidism and hyponatremia [22]-[24]. Unfortunately none of the studies including adult subjects, investigated plasma sodium concentrations after supplementation of L-thyroxine. The present study was performed to examine the strength of the relationship between hypothyroidism and hyponatremia. In addition we set out to investigate the effect of L-thyroxine replacement therapy on plasma sodium concentration in hypothyroid patients.

2. Subjects and Methods

Data source: This study was carried out at the Maasstad hospital in Rotterdam, the Netherlands. Data were collected from a local database provided by the clinical laboratory. Samples were reviewed from the period spanning July 2009 to December 2011.

Study population: A cohort was retrospectively defined by searching the database for blood samples that contained plasma TSH, as well as plasma sodium and free serum thyroxin (fT4) concentration. With this search, information about birth date, gender, sample date was retrieved. The collected data were integrated into a new database (Access 2003, Microsoft). Hypothyroidism was defined as TSH > 4.0 mU/L and fT4 < 10.0 pmol/L. For the analysis of treatment with L-thyroxine on sodium concentration, treated patients were identified by a decrease in plasma TSH concentration on three consecutive measurements. It was assumed that a decline in TSH indicated response to L-thyroxine substitution therapy. From these patients all blood samples that contained plasma TSH and sodium measurement, were analysed. Review of subjects medical records verified use of substitution therapy with L-thyroxine.

Laboratory techniques: Plasma TSH and fT4 concentrations were determined by a homogeneous chemiluminescent immunoassay (LOCI[®] technology) and plasma sodium concentrations were determined by ion selective electrode. All measurements were performed on a Dimension Vista[®] 1500 (Siemens Healthcare Diagnostics, USA). The reference range was 0.4 - 4.0 mU/L for TSH, 10.0 - 24.0 pmol/L for fT4, and 135 - 145 mmol/L for sodium. The coefficients of variation (CV) were 3.5%, 3.3% and 3.6% for TSH concentrations of 0.75, 5.8 and 32.0 mU/L, respectively. For fT4 the CV's were 2.6%, 1.9% and 1.8% for concentrations of 14.0, 25.0 and 58.0 pmol/L, respectively. The CV's for sodium concentration of 125 and 150 mmol/L were both 1.0%.

Statistical analysis: The statistic software SPSS (PAWS Statistics 18.0, Chicago, USA) was used for statistical analysis. Statistical significance was considered when $p < 0.05$. Because plasma TSH was non-linearly distributed data was log transformed. A linear regression analysis of plasma sodium concentration on the logarithm of plasma TSH concentration was performed. In addition samples were divided into three groups according to TSH concentration (see **Table 1**). For each group average age, sodium and fT4 concentrations were calculated. Analysis of variance (ANOVA) was used to compare mean sodium concentration in the three groups. Additional analysis was performed to determine the frequency of patients with sodium concentrations below 135 and below 120 mmol/L in each group. The proportions were compared with a Fisher's exact test. Linear regression of log plasma TSH against time was performed to verify the decline of TSH during L-thyroxine replacement therapy. In addition linear regression was performed on plasma sodium against time to determine whether plasma sodium changed as plasma TSH declined. To complete the analysis multiple linear regression of plasma sodium was performed with log plasma TSH and time as explanatory variables.

3. Results

A total of 328 blood samples were reviewed. These samples were taken from 270 patients. Of these patients 189

Table 1. The mean (SD) values for age, plasma fT4, and plasma sodium concentration according to plasma TSH concentration.

	No. of Blood Samples	Age (years)*	Total fT4 (pmol/L)*	Sodium (mmol/L)**	Sodium < 135 mmol/L (no[%])***	Sodium < 20 mmol/L (no[%])***
TSH range (mU/L)						
4.01 - 20.0	193	60.4 (16.4)	8.82 (1.0)	138.0 (2.8/0.20)	15 (=7.8%)	0
20.01 - 75.0	100	57.2 (19.5)	7.13 (1.9)	137.5 (3.0/0.30)	15 (=15%)	0
>75	35	47.6 (18.9)	5.25 (2.0)	137.5 (2.8/0.48)	5 (=14.3%)	0
Total	328	58.1 (18.0)	7.92 (1.9)	137.8 (2.9/0.16)	35	0

*Mean (SD); **Mean (SD/SE); ***Number (percentage).

were female and 81 were male. Mean age was 58.1 years, ranging from 0 to 95 years. The 328 samples were used for regression analysis. After logarithmic transformation of TSH, regression analysis revealed no significant correlation with plasma sodium concentration ($R^2 = 0.005$). The following equation emerged: $Y = 138.30 - 0.427X$ (**Figure 1(a)**). The regression coefficient appeared not to be different from 0 ($p = 0.22$). Assuming a significant difference was found, the relation would only predict a 0.427 mmol/L fall in plasma sodium when plasma TSH rises from 10 mU/L to 100 mU/L.

Data from the 328 samples were used for further analysis. When data was grouped by plasma TSH concentration, mean plasma sodium concentration ranged from 137.51 mmol/L in the highest to 137.98 mmol/L in the lowest Group 1 (**Table 1**). Analysis of variance (ANOVA) proved mean plasma sodium concentration not to be statistically significantly different ($p = 0.30$) across groups. Likewise mean plasma sodium only differed 0.47 mmol/L between the highest and lowest plasma TSH concentration. The percentage of patients with plasma sodium below 135 mmol/L increased from 7.8% in the group with lowest plasma TSH concentration, to 14.3% in patients with plasma TSH larger than 75 mU/L. A Fisher's exact test showed no significant difference between the 3 groups in proportions of samples that had a plasma sodium below 135 mmol/L ($p = 0.105$). None of the hypothyroid patients had a plasma sodium concentration below 120 mmol/L.

To evaluate the effect of L-thyroxine treatment on plasma sodium concentration, we selected patients for whom consecutive measurements of TSH, fT4 and sodium were available. We further refined the selection by reviewing only those cases that exhibited a decline in plasma TSH over time. Unfortunately in only 32 patients plasma sodium concentration was determined during follow-up at the out-patient clinic. Hypothyroidism in these patients was caused by auto-immune hypothyroiditis in 12 cases, iatrogenic hypothyroidism in 7 cases (5 due to ^{131}I -therapy, 1 due to hemistrulectomy and 1 due to radiotherapy), drug-induced hypothyroidism in 3 cases (1 due to amiodarone and 2 probably due to lithium) and in 10 patients the cause of hypothyroidism could not be elucidated from medical records. 27 out of 32 patients received L-thyroxine replacement therapy. The remaining 5 patients had spontaneous remission of their hypothyroid state. Out of the five untreated patients, 2 were diagnosed with drug induced hypothyroidism. In the remaining 3 patients no cause was documented. **Figures 1(b)-(c)** present plasma TSH and sodium concentration in time. Follow-up was limited to 650 days. Plasma TSH declined significantly over time, illustrating recovery from the hypothyroid state ($p < 0.001$). However plasma sodium did not change during follow-up ($p = 0.147$). Furthermore in a model with both time and log (TSH) as explanatory variables no significant regression coefficients were found ($p = 0.07$ and $p = 0.27$). Apparently within one patient substantial change in TSH over time was not accompanied by any change in plasma sodium concentration.

4. Discussion

The present study was undertaken to further characterise the relation between hypothyroidism and the occurrence of hyponatremia. No statistically significant correlation between plasma TSH and sodium concentration was found in a retrospectively identified cohort of patients frequenting the Maastad hospital in Rotterdam, the Netherlands. Numerous publications associate hypothyroidism with the occurrence of hyponatremia. However, very few reports investigated the strength of this association. Despite convincing epidemiological evidence recent clinical guidelines and reviews still consider hypothyroidism a cause for hyponatremia [1]-[3]. The most

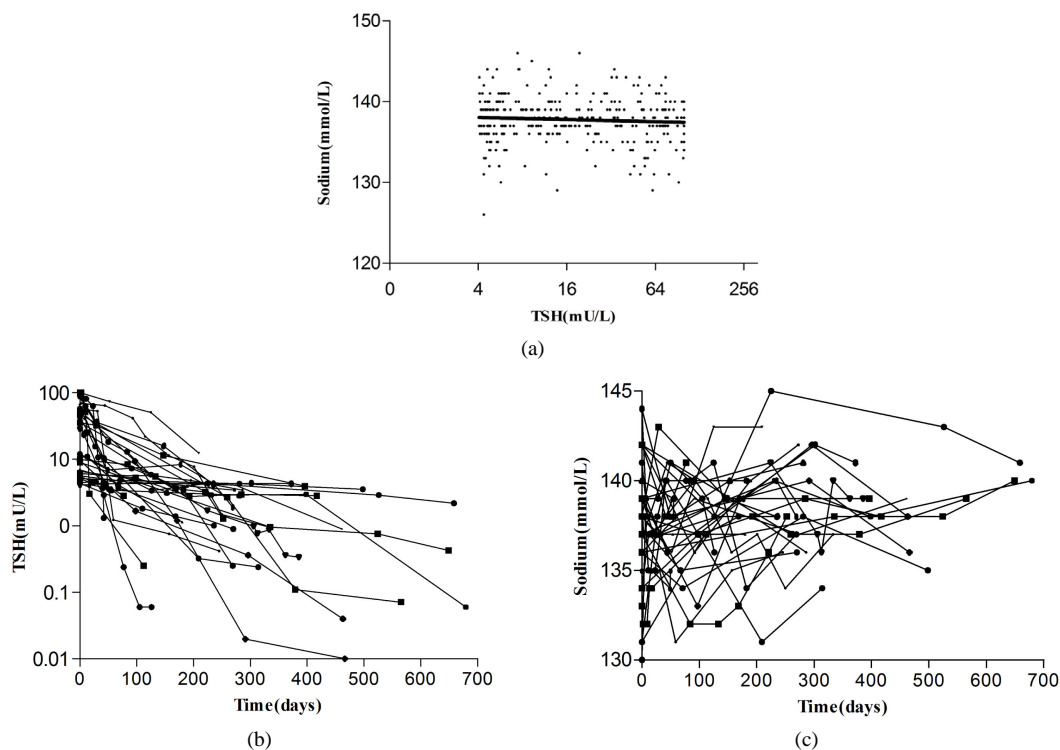


Figure 1. The relationship between plasma TSH and sodium concentration. (a) Plasma sodium concentration was plotted against TSH concentration for 328 blood samples; (b) Plasma TSH was plotted against time for 32 hypothyroid patients; (c) Plasma sodium concentration was plotted against time for the same 32 patients as presented in (b).

compelling evidence for a causal relation between hypothyroidism and hyponatremia comes from old, relatively small studies in humans and rats [4]-[8] [18] [19]. These studies report that hypothyroidism causes an impairment in renal excretion of free water [4]-[8] [18] [19] and hence a diluting hyponatremia. One proposed mechanism is a serum osmolality independent elevation of plasma antidiuretic hormone (ADH) concentration due to hypothyroidism [4]-[7]. It remains unclear whether increased ADH was a direct result of a low plasma thyroxin concentration or secondary to a decrease in cardiac output during a hypothyroid state. Although hypothyroid induced heart failure is rare [17], a decreased cardiac output causing hypovolemia with a baroreceptor-mediated, nonosmotic ADH release has been proposed in severe hypothyroidism [2] [3] [15]-[17]. Unfortunately, a rise in ADH has not been consistently found and some studies report no such relation [8] [18] [19].

Other frequently reported changes in hypothyroidism are increased systemic vascular resistance, reduction in glomerular filtration rate (GFR) and reduction in renal blood flow (RBF) [2] [8]-[17]. A reduction in GFR and RBF could conceivably be another mechanism for the diminished renal excretion of free water [8] [10] [25]. A reduction in GFR results in a decreased delivery of urinary filtrate to the distal tubular diluting segment [8] [25] and hence a diminished capacity to generate electrolyte free water [15]. However, one could argue that reduction in GFR and RBF are manifestations of a diminished cardiac output rather than a direct effect of hypothyroidism on the kidney.

In accordance with the above mentioned studies our study showed that hyponatremia, defined as plasma sodium concentration smaller than 135 mmol/L, was more prevalent as hypothyroidism was more severe. However statistical significance was not reached. No such correlation was found for severe hyponatremia, when plasma sodium concentration was below 120 mmol/L. In fact no hypothyroid patients had plasma sodium concentrations below this extreme. Possibly the absence of a robust relation between hyponatremia and hypothyroidism is caused by the relative rarity of severely hypothyroid patients in our dataset. Since previous studies selectively investigated patients with myxedema [5] [19] the relationship between hypothyroidism and hyponatremia could become more overt.

Few studies question the relationship between hypothyroidism and hyponatremia. A small study in 32 neonates with a congenital hypothyroidism (CH) did not show hyponatremia in any of the neonates [20]. Plasma

sodium concentration was identical in hypothyroid neonates compared to an age-matched controls. In addition two months of L-thyroxine replacement therapy did not result in a significant increase in plasma sodium concentration in the hypothyroid neonates [20]. Another study in 188 thyroid-ablated patients showed no significant correlation between plasma TSH levels and plasma sodium during the transition from euthyroid to hypothyroid state [21]. Three observational studies have been performed showing weak or no relation between hypothyroidism and hyponatremia. A study in 33.912 patients showed an equal distribution of plasma sodium in euthyroid and hypothyroid patients [22]. A second study in 15.080 patients found that hypothyroidism was significant more common in patients with hyponatremia compared to patients with normonatremia (4.7% versus 1.7%) [23]. They computed a positive predictive value of 5% for finding hypothyroidism in hyponatremic patients. However considering the weak association the authors advised to always investigate other causes of hyponatremia [23]. In a third study sodium concentrations from 999 newly diagnosed hypothyroid patients referred to the hospital were compared with 4.750 control patients [24]. A significant relation was found between plasma levels of TSH and sodium. It appeared that within the hypothyroid group every 10 mU/l rise in TSH was associated with a decrease of 0.14 mmol/L in plasma sodium concentration. This finding relates well to our current results. We further elaborated on these studies by assessing the effect of L-thyroxine replacement therapy on plasma sodium concentration. If hypothyroidism causes hyponatremia, treatment of hypothyroidism would be expected to raise plasma sodium concentration. Even if overt hyponatremia was initially absent, treating hypothyroid state might be expected to significantly raise plasma sodium concentration lending further support to the idea that hypothyroidism is causally related to the occurrence of hyponatremia. Unfortunately only few patients could be included in the analysis of L-thyroxine replacement therapy. Plasma sodium concentration is not regularly determined in our outpatient clinic while monitoring the effect of L-thyroxine replacement therapy. From the 32 patients eligible for analysis no relation between plasma sodium and TSH concentration could be elucidated.

Before starting this study one of the drawbacks seemed to be the possibility of confounding by indication. Cases were identified from the hospital laboratory database. These cases are not a reflection of the general population. Most likely the indication to determine TSH was either the presence of symptoms reflecting thyroid disease or the need for biochemical workup in the context of hyponatremia. Since hypothyroidism per se does not necessarily warrant analysis of plasma sodium, the number of samples including measurement of both TSH and sodium could be skewed towards the second indication. Such a bias could conceivably lead to an over representation of patients in whom low plasma sodium was the reason to determine plasma TSH concentration and hence suggest a relation. Yet our study proved otherwise. Since no significant relation between plasma TSH and sodium was found, confounding by indication showed not to be the case. In addition a previous study included only incident hypothyroid patients and found similar relations as presented here [24].

In summary, we conclude that although hypothyroidism is still a common investigated cause in the analysis of hyponatremia, there remains little evidence supporting this approach.

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