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Ahmet Bahadir Ergin[1], James Bena[2] and Christian E Nasr[3]*

[1]Institute of Endocrinology, Diabetes, Health and Hormones, Panama City, USA
[2]Quantitative Health Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, USA
[3]Endocrinology & Metabolism Institute, Cleveland Clinic, Desk F20, 9500 Euclid Avenue, Cleveland, USA

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***Corresponding author:** Christian E Nasr, Endocrinology & Metabolism Institute, Cleveland Clinic, Desk F20, 9500 Euclid Avenue, Cleveland, USA, Tel: 216 3123211; Fax: 216 445 1656; E-mail: NASRC@ccf.org; cenasr@gmail.com

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Research Article

Hypothyroidism and Hyponatremia: Simple Association or True Causation

Abstract

Background: Hypothyroidism has been classically considered as a cause of hyponatremia. This causality has been controversial in clinical practice. The purpose of this study was to reexamine the association between thyroid state and serum sodium concentration in a large cohort of subjects

Methods: This was a chart review using electronic health records. The prevalence of the coexistence of hyponatremia and hypothyroidism as well as the magnitude of the correlation were investigated. All patients who were seen between September 1, 2005 and August 31, 2007 in Cleveland Clinic hospitals and out-patient clinics who had serum sodium and TSH. Main Outcome Measure was correlation between serum Na and TSH.

Results: There were 143,720 unique patients. A very small negative correlation was found between increasing TSH and blood sodium levels (r: -0.01, p<0.001, 95% CI (-0.02,-0.01)). All the patients who had hyponatremia in the setting of elevated TSH had 2 or more other factors known to cause hyponatremia.

Conclusion: There was only a negligible negative correlation between serum Na and uncomplicated hypothyroidism.

Introduction

Hyponatremia is the most common electrolyte abnormality encountered in ambulatory and hospital settings. Its frequency depends on multiple factors including the definition of hyponatremia, the frequency of testing, the healthcare setting, and the patient population [1]. Hyponatremia has an extensive list of etiologies including hypothyroidism which has been a common teaching point in text books and review articles to date [2,3]. Hyponatremia and hypothyroidism commonly coexist because both conditions are common. This coexistence, however, may not necessarily be causal. Contrary to the popular opinion about the association of hyponatremia and hypothyroidism, the magnitude of the effect of hypothyroidism on hyponatremia is yet to be well documented. The knowledge about the degree of correlation between severity of hypothyroidism and hyponatremia is also weak. Recently the strength of this association was disputed by a few number of smaller studies [4,5]. In the current study we aimed to shed light on the association between hypothyroidism and hyponatremia in a large cohort of patients. In order to do this, we examined the prevalence of the coexistence of hyponatremia and hypothyroidism as well as the magnitude of the correlation.

Materials and Methods

We performed a retrospective chart review of patients presenting to either the ambulatory clinics or in-patient units between September 1, 2005 and August 31, 2007. The study was approved by Cleveland Clinic Institutional Review Board.

Study population

Patients who had both serum sodium (Na) and serum thyrotropin (TSH) obtained previously were included in the study. For every patient, only the first sodium and first TSH were included. The values were then combined to include the closest two measures of sodium and TSH. 97% of the samples were taken the same day. This resulted in a dataset of 143,720 unique patients/pairs of observations. Categories for TSH and serum Na level levels were arbitrarily defined as in table 1. For further analysis, the data were dichotomized into inpatient vs outpatient, hypothyroidism vs. no hypothyroidism and hyponatremia vs no hyponatremia (normonatremia and hypernatremia). Hypothyroidism was defined as TSH >5 IU/L. We chose to use TSH as an index of hypothyroidism because it is accepted to be the most sensitive marker of thyroid function in the majority of cases. Moreover, most clinicians who relate hyponatremia to hypothyroidism point out to elevated TSH

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levels in the clinical setting. Hyponatremia was defined as serum Na <133 mmol/l. A detailed chart review of these patients was performed to identify diseases and conditions that could contribute to low Na levels and would help explain the presence of hyponatremia in conjunction with hypothyroidism

Clinical assays

Serum TSH was measured by electrochemiluminescence immunoassay (Roche Modular Analytics E170 analyzer, Roche Diagnostics, Indianapolis, IN) at Cleveland Clinic laboratories. Intra-assay Coefficient of variance (CV) range was between 1.1 and 3%. Plasma Na was measured by ion selective electrode (Roche/Hitachi Modular P/Modular D analyzers (Roche Diagnostics, Indianapolis, IN) at Cleveland Clinic laboratories. Intra-assay CV range was between 0.31 and 0.32 %.

Statistical analysis

Frequencies and percentages were used to describe categorical factors while means and standard deviations were used for continuous variables. Data were plotted and normality was assessed graphically, since, given the sample size, normality tests would likely be overly sensitive to departures from normality. However, given the shape of the distributions, nonparametric methods were used. Spearman correlation estimates were developed for raw and categorized variables. Pearson chi-square tests were used to measure association between dichotomized values. All analyses were performed using SAS software (version 9.2).

Results

Patient demographics are described in table 2. In the overall cohort, nearly 64% of patients were female and almost 80% were Caucasian. Similar percentages were observed in the groups defined by patient status. The mean and median age in the cohort was 55 years. Inpatients had a mean age of 58 as compared to 54 in outpatients. The mean Na value in the entire patient population was 139.4 mmol/l, and this was similar in the outpatient and inpatient cohorts as seen in table 3. The mean TSH value was 2.67 mIU/L. Ninety-seven percent (139,452) of sodium measures were in the normal range and 85% of TSH measures were in the euthyroid category.

Of the 10,392 patients (7.2%) with hypothyroidism, 348 (3.3%) had hyponatremia including 319 mild, 25 moderate and 4 severe. There were no patients with severe hypothyroidism (TSH >50 mIU/L) and severe hyponatremia (Na<115 mmol/l). Ninety-five percent (n=358) of patients with severe hypothyroidism (n=374) had normal serum Na level (Na 133-145 mmol/l), 3% (14) had mild hyponatremia (Na 125-132 mmol/l) and only one had moderate hyponatremia (Na 115-124 mmol/l) (Table 4).

A statistically, albeit not clinically, significant negative correlation was observed between serum Na and TSH (r: -0.01, p<0.001, 95% CI (-0.02,-0.01)) (Table 5).

Because a large percentage of patients were in the normal range, sodium and TSH values were dichotomized for further

Table 1: Categories of thyroid status and sodium status.

TSH (mIU/l)	
<0.4	Hyperthyroidism
0.4-4.99	*Euthyroidism*
5.0-9.99	Mild hypothyroidism
10-49.99	Overt hypothyroidism
50+	Severe hypothyroidism
Sodium (mmol/L)	
<115	Severe hyponatremia
115-124	Moderate hyponatremia
125-132	Mild hyponatremia
133-145	*Normal serum sodium*
146-155	Mild hypernatremia
>155	Severe hypernatremia

Table 2: Patient characteristics.

	Total	Outpatient	Inpatient
Age			
N	143627	113525	30101
Mean (SD)	55.1 (18.4)	54.2 (17.9)	58.7 (19.4)
Median	55.7	54.7	60.1
Q1, Q3	43.4, 68.7	42.7, 67.2	46.4, 74.3
Range Gender	(0.2-104.5)	(0.2-104.5)	(0.2-101.4)
F	91873 (64.0%)	73456 (64.7%)	18417 (61.2%)
M	51749 (36.0%)	40066 (35.3%)	11682 (38.8%)
Missing or Unknown Ethnicity	5 (0.0%)	3 (0.0%)	2 (0.0%)
African American	19406 (13.5%)	12601 (11.1%)	6805 (22.6%)
Asian/Pac. Islander	1338 (0.9%)	1187 (1.0%)	151 (0.5%)
Caucasian	114736 (79.9%)	92815 (81.8%)	21920 (72.8%)
Hispanic/Latino	1731 (1.2%)	1440 (1.3%)	291 (1.0%)
Missing or Unknown	4177 (2.9%)	3618 (3.2%)	559 (1.9%)
Multi-Racial	33 (0.0%)	32 (0.0%)	1 (0.0%)
Native American	67 (0.0%)	53 (0.0%)	14 (0.0%)
Other	2139 (1.5%)	1779 (1.6%)	360 (1.2%)

Table 3: Univariable summaries of TSH and sodium overall and within patient status.

	Total	Outpatient	Inpatient
Sodium (mmol/L)			
N	143627	113525	30101
Mean (SD)	139.4 (2.9)	139.6 (2.6)	138.9 (3.6)
Median	140.0	140.0	139.0
Q1, Q3	138.0, 141.0	138.0, 141.0	137.0, 141.0
Range	(104.0-174.0)	(106.0-169.0)	(104.0-174.0)
TSH (mIU/l)			
N	143627	113525	30101
Mean (SD)	2.67 (7.4)	2.7 (7.7)	2.7 (6.3)
Median	1.8	1.8	1.7
Q1, Q3	1.1, 2.8	1.2, 2.8	1.0, 2.8
Range	(0.0-715.9)	(0.0-715.9)	(0.0-307.9)

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analysis. Correlations in inpatients and outpatients were -0.03 and -0.01 respectively suggesting negligible clinical association between sodium and TSH in both groups.

Another subgroup analysis was then performed according to the TSH category to determine whether changes in sodium levels correlated with hypothyroid status. The mean sodium value in each TSH category is listed in table 6.

The difference in sodium levels between categories, being less than 1mmol/l, was not clinically relevant. Three hundred and forty nine patients were identified who had both hyponatremia and hypothyroidism. Almost all patients had 2 or more factors known to cause hyponatremia such as CHF (26%), CKD (16%), cirrhosis (7%), syndrome of inappropriate vasopressin secretion (4%), and drugs (diuretics, angiotensin converting enzyme inhibitors, opiate narcotics, and selective serotonin receptor inhibitors).

Table 4: Two way frequency table of categorized Sodium and TSH measures.

Sodium	TSH					
Frequency Percent	Hyper thyroidism	Euthy roidism	Mild Hypot hyroidism	Overt Hypot hyroidism	Severe Hypo thyroidism	Total
Severe Hyponatremia	0 0.00	13 0.01	2 0.00	2 0.00	0 0.00	17 0.01
Moderate Hyponatremia	17 0.01	184 0.13	20 0.01	4 0.00	1 0.00	226 0.16
Mild Hyponatremia	166 0.12	2134 1.49	230 0.16	75 0.05	14 0.01	2619 1.82
Normal Serum Sodium	6657 4.63	122788 85.49	7615 5.30	1948 1.36	358 0.25	139366 97.03
Mild Hypernatremia	91 0.06	1154 0.80	99 0.07	21 0.01	1 0.00	1366 0.95
Severe Hypernatremia	4 0.00	27 0.02	2 0.00	0 0.00	0 0.00	33 0.02
Total	6935 4.83	126300 87.94	7968 5.55	2050 1.43	374 0.26	143627 100.00

Table 5: Spearman correlation between Sodium and TSH.

Cohort	Variable 1	Variable 2	rho	95% CI	P value
Overall	TSH*	Sodium*	-0.01	(-0.02,-0.01)	<0.001
	TSH**	Sodium**	-0.01	(-0.02,-0.01)	<0.001
Outpatient	TSH*	Sodium*	-0.01	(-0.02,-0.00)	<0.001
	TSH**	Sodium**	0.00	(-0.01,0.00)	0.11
Inpatient	TSH*	Sodium*	-0.03	(-0.04,-0.02)	<0.001
	TSH**	Sodium**	-0.03	(-0.04,-0.02)	<0.001

* Continuous; ** Categorical

Table 6: Serum sodium by thyroid state.

		Sodium	
TSH Category	N	Mean	SD
Hyperthyroidism	6935	139.43	3.20
Euthyroidism	126300	139.44	2.84
Mild Hypothyroidism	7968	139.21	3.20
Overt Hypothyroidism	2050	138.86	3.34
Severe Hypothyroidism	374	138.42	2.91

Discussion

In this study we were able to show a very weak association between hyponatremia and hypothyroidism in the largest cohort of patients studied to date. The correlation estimate (r) being a very small number indicates that this was an artifact of the large sample size and the association between serum Na level and TSH was clinically negligible in both inpatients and outpatients. In other words, as hypothyroidism worsened serum Na level did not decrease accordingly. Moreover, patients who developed hyponatremia while in the hypothyroid state had at least 2 or more other etiologies that could have caused or contributed to hyponatremia.

Nevertheless, this study does not totally refute the relationship between hypothyroidism and serum Na level. We have shown that the effect of hypothyroidism on serum Na level was rather very small even in severe hypothyroidism. For example, none of the patients with severe hypothyroidism had severe hyponatremia and only very few patients had moderate hyponatremia compared to the majority of patients who had a normal serum Na level for the same high TSH level. Baajafer et al. showed that, after 5 weeks of thyroid hormone withdrawal in 128 thyroidectomized patients, none developed serum Na < 130 mmol/l. The average serum Na level difference between the euthyroid and hypothyroid states was only 1, 18 mmol/l [6]. Warner et al. investigated 999 newly diagnosed hypothyroid patients in an ambulatory setting and found that every 10 mIU/L increase in TSH was associated with only 0.14 mmol/l drop in serum Na level [5].

Among our ambulatory patients, the association between serum Na level and TSH was even smaller than inpatients and that association was practically negligible. Croal et al., investigated 3,567 patients with hypothyroidism and showed that the proportion of patients with a serum Na level of 135 mmol/l or lower was not significantly different between the euthyroid subjects (11.4%) and hypothyroid subjects (12.8%) [4]. Another study investigated 25 neonates with hypothyroidism. The serum Na concentration before treatment (139.1 mmol/l) did not change significantly 2 months after T4 replacement therapy (138.9 mmol/L) [7]. Finally, in a study of 10 hypothyroid patients with an average TSH of 250 mIU/L, none had a serum Na<135 mmol/l [8].

Despite the lack of correlation between hyponatremia and hypothyroidism based on the studies cited above, there is still a reasonably large literature supporting the relationship between the hyponatremia and hypothyroidism. When related publications were carefully reviewed one would notice that many times hypothyroidism was used interchangeably with myxedema or long complicated hypothyroidism.

The remedy to this confusion lies in understanding the pathophysiology of the real impact of hypothyroidism on serum Na concentration. Not only the degree of thyroid hormone deprivation itself but the duration and complications that develop secondary to prolonged hypothyroidism as well as lack of adequate Na intake can contribute to hyponatremia development albeit to a limited degree.

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Firstly, myxedema coma (MC), characterized by chronic TSH elevation, has been linked to the development of a mild decrease in serum sodium levels [9]. When published studies are carefully reviewed, it is clear that MC is generally not associated with severe serum Na changes. Derubertis et al. studied 16 patients with MC. Mean serum Na level was 136 mmol/l in MC patients compared with 140 mmol/l in control subjects who had similar demographic characteristics [10]. In another study investigating 20 MC patients, mean serum Na was 137 mmol/l in MC compared with 142 mmol/l after they were rendered euthyroid by thyroid hormone replacement [11]. Based on these studies, 4 to 5 mmol/l drop in serum sodium level can be expected in myxedema patients.

The expected decrease in serum sodium level in severe and prolonged hypothyroidism can be explained by reduced cardiac output increased peripheral resistance, and reduced volume delivery to the kidneys causing a decline in glomerular filtration rate (GFR). Reduced GFR results in water retention and increased renal sodium excretion by decreasing sodium and net volume delivery to the distal diluting segment of the nephron [10,12]. Reduction in GFR was suggested to be responsible by another study in which hyponatremia was documented in 45 % of 22 patients with elevated creatinine levels and hypothyroidism [13]. Continuous water retention and loss of sodium in the urine can also create a negative sodium balance. In these studies in which reduction in serum sodium was documented, reduced GFR was reported as well. In the absence of reduced GFR, hypothyroidism would not be expected to cause reduction in serum Na. Although clinical picture of complicated hypothyroidism or myxedema and syndrome of inappropriate antidiuretic hormone secretion can be similar, real mechanism appears to be completely different. The effect of inappropriate antidiuretic hormone in the setting of hypothyroidism was studied and refuted by many studies [10,11,14].

When increased sodium excretion is not compensated by adequate sodium intake, further reduction in serum Na can develop. This was investigated both in humans and animal studies [15,16]. In one study, thyroid cancer patients had one week of iodine deficient diet in thyroid withdrawal protocols and the change in mean serum Na level was 1mmol/l [16]. Longer duration of salt restriction may have caused a larger change in Na. When rats were treated chronically with either propylthiouracil or thiouracil, they developed a negative sodium balance, lost weight and eventually died if given a diet deficient in sodium long enough [15].

Low aldosterone levels in hypothyroid patients were demonstrated in a few studies [17,18] albeit clinical merit in these studies were rather small. Marks et al. showed incremental response of aldosterone to thyroid replacement [17]. In another study, reduced aldosterone was thought to be related to exaggerate Na excretion [18]. Changes in aldosterone levels were reversed by treatment with thyroxine. Nevertheless, since no patient in these studies had hyponatremia one can infer that the renin-aldosterone system is not a predominant regulator of serum Na level.

Reduced cortisol levels also have also been shown to affect serum Na level by inducing ADH secretion [19] and this is a serious consideration in the differential diagnosis of hyponatremia in the presence of hypothyroidism. Despite all the elegant descriptions of the pathophysiology of serum Na level changes in hypothyroidism, these reported changes were not at all clinically significant. Only in MC was a mean reduction in serum Na level of 5 mmol/l noted. Patients with hypopituitarism may also be at high risk for significant Na drop due to lack of both thyroid hormone and cortisol [20].

The strength of this study is that it is the largest reported cohort of patients looking at the association of serum Na and TSH. Limitations of our study can be listed as follows: limitations inherent to retrospective study design, lack of T4 value on most patients, inability to exclude patients who were already on treatment for hypothyroidism and patients who were acutely unwell in which the low or raised TSH values could have been the result of non-thyroidal illnesses or recovery from it, respectively. Keeping these in mind a subgroup analysis was performed for ambulatory patients and in-patients and no significant difference was found. Since, we only compared TSH and sodium values, we could have potentially missed patients with central hypothyroidism but those are generally rare.

We found no clinically relevant relationship between hypothyroidism and hyponatremia in varying degrees of hypothyroidism from mild to severe. Based on our literature review, severe hypothyroidism, if not prolonged, does not seem to cause hyponatremia as long as sodium intake is not restricted due to reduced mental status or low iodine/salt diet. A mild to moderate decrease in serum sodium may be expected only when signs of prolonged severe hypothyroidism develop such as peripheral edema, reduced GFR, and changed mental status as seen in MC. Even then, clinicians should not expect a large drop in serum Na level. When moderate to severe hyponatremia is encountered, concomitant etiologies of hyponatremia should be sought in addition to hypothyroidism.

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