**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 68043

**Manuscript Type:** ORIGINAL ARTICLE

***Retrospective Cohort Study***

**Analysis of the incidence and influencing factors of hyponatremia before 131I treatment of differentiated thyroid carcinoma**

Cao JJ *et al*. Incidence and influencing factors of hyponatremia

Jing-Jia Cao, Can-Hua Yun, Juan Xiao, Yong Liu, Wei Wei, Wei Zhang

**Jing-Jia Cao, Can-Hua Yun, Juan Xiao, Yong Liu, Wei Wei, Wei Zhang,** Department of Nuclear Medicine, The Second Hospital, Cheeloo College of Medicine, Shandong University, Jinan 250033, Shandong Province, China

**Author contributions:** Cao JJ, Yun CH, Xiao J, Liu Y and Wei W contributed acquisition of data; Cao JJ, Yun CH and Xiao J contributed analysis of data, drafting the article; Zhang W conceived and designed the study; all authors have read and approved **t**he final manuscript.

**Corresponding author: Wei Zhang, MD, Professor,** Department of Nuclear Medicine, The Second Hospital, Cheeloo College of Medicine, Shandong University, No. 247 Road, Tianqiao District, Jinan 250033, Shandong Province, China. sdeyzhangwei@126.com

**Received:** May 11, 2021

**Revised:** August 3, 2021

**Accepted: November 15, 2021**

**Published online:**  **Abstract**

BACKGROUND

Hyponatremia is a common clinical electrolyte disorder. However, the association between hyponatremia and acute hypothyroidism is unclear. Acute hypothyroidism is usually seen in patients who undergo preparation for radioactive iodine therapy.

AIM

To analyze the incidence and influencing factors of hyponatremia in a condition of iatrogenic acute hypothyroidism in patients with differentiated thyroid cancer (DTC) before 131I treatment.

METHODS

The study group consisted of 903 DTC patients who received 131I treatment. The clinical data before and after surgery, as well as on the day of 131I treatment were analyzed. According to the blood sodium level before 131I treatment, patients were divided into the non-hyponatremia group and hyponatremia group. Correlations between serum sodium levels before 131I treatment and baseline data were analyzed. Univariate analysis and binary logistic regression were performed to identify the influencing factors of hyponatremia.

RESULTS

A total of 903 patients with DTC, including 283 (31.3%) males and 620 (68.7%) females, with an average age of 43.8 ± 12.7 years, were included in this study. The serum sodium levels before surgery and 131I treatment were 141.3 ± 2.3 and 140.5 ± 2.1 mmol/L, respectively (*P* = 0.001). However, the serum sodium levels in males and females before 131I treatment were lower than those before surgery. Patients aged more than 60 years and less than 60 years also showed decreased serum sodium levels before 131I treatment. In addition, the estimated glomerular filtration rate (eGFR) in males and females decreased before 131I treatment compared with those before surgery (*P* = 0.001). Moreover, eGFR in patients over 60 years and under 60 years decreased before 131I treatment, when compared with that before surgery. There were no significant differences in serum potassium, calcium, albumin, hemoglobin, and blood glucose in patients before surgery and 131I treatment (*P >* 0.05). Among the 903 patients, 23 (2.5%) were diagnosed with hyponatremia before 131I treatment, including 21 cases (91.3%) of mild hyponatremia and 2 cases (8.7%) of moderate hyponatremia. Clinical data showed that patients with mild hyponatremia had no specific clinical manifestations, while moderate hyponatremia cases were mainly characterized by fatigue and dizziness, which were similar to neurological symptoms caused by hypothyroidism and were difficult to distinguish. Correlation analysis showed a correlation between serum sodium before 131I treatment and the preoperative level (*r* = 0.395, *P* = 0.001). There was no significant correlation between blood sodium and thyroid-stimulating hormone (TSH) levels and urine iodine before 131I treatment (*r* = 0.045, *P* = 0.174; *r* = 0.013, *P* = 0.697). Univariate analysis showed that there were significant differences in age, sex, history of diuretic use, distant metastasis, preoperative blood sodium, blood urea nitrogen (BUN), eGFR, TSH and urinary iodine between the two groups (all *P <* 0.05). Logistic regression analysis showed that factors such as history of diuretic use, distant metastases, preoperative sodium and BUN were all influencing factors of hyponatremia. The Hosmer and Lemeshow test (*c2* = 2.841, *P* = 0.944) suggested a high fit of the model. Omnibus tests of model coefficients indicated the overall significance of the model in this fitted model (*P <* 0.05). Preoperative serum sodium was a significant factor associated with pre-131I therapy hyponatremia (OR = 0.763; 95%CI: 0.627-0.928; *P* = 0.007).

CONCLUSION

The incidence of hyponatremia induced by 131I treatment preparation was not high. Preparation for radioactive iodine therapy was not a risk factor for the development of hyponatremia in thyroid cancer patients.

**Key Words:** Differentiated thyroid cancer; Hyponatremia; Incidence; Low iodine diet; Logistic regression analysis

Cao JJ, Yun CH, Xiao J, Liu Y, Wei W, Zhang W. Analysis of the incidence and influencing factors of hyponatremia before 131I treatment of differentiated thyroid carcinoma. *World J Clin Cases* 2021; In press

**Core Tip:** We analyzed the incidence and influencing factors of hyponatremia in patients with differentiated thyroid cancer (DTC) before 131I treatment. We evaluated 903 postoperative DTC patients who received 131I treatment. The results suggest that the incidence of hyponatremia induced by 131I treatment preparation was not high. The identified influencing factors of hyponatremia included history of diuretic use, distant metastases, preoperative sodium and blood urea nitrogen. Our findings may help to improve patient management during the preparation period for 131I treatment.

**INTRODUCTION**

Hyponatremia is a common clinical electrolyte disorder, with an incidence of about 15% to 30%[1]. Hyponatremia in chronic hypothyroidism is commonly seen in clinical practice. 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 (ADH) levels, which are mainly attributed to the hypothyroidism-induced decrease in cardiac output[2].

However, the association between hyponatremia and acute hypothyroidism is unclear[3]. Acute hypothyroidism is usually seen in patients with differentiated thyroid cancer (DTC) who undergo preparation for radioactive iodine (RAI) therapy. Before RAI therapy, it is suggested that treatment with thyroid hormone should be stopped to stimulate the uptake of 131I by thyroid follicular epithelium and DTC cells[4]. Moreover, a low iodine diet is usually associated with low solute intake that may contribute to the development of hyponatremia. Previous studies reported that severe hyponatremia occurred in patients before 131I treatment[5,6]. On the contrary, other studies showed that iatrogenic acute hypothyroidism after discontinuation of thyroid hormone had little effect on blood sodium concentration, and that insufficient sodium intake and low-iodine diet were not important causes of hyponatremia[3,7].

The incidence and influencing factors of hyponatremia before 131I treatment in China are still unclear. The purpose of this study is to investigate the incidence of hyponatremia and related influencing factors in patients after DTC surgery before 131I treatment (in a condition of iatrogenic acute hypothyroidism), in order to improve patient management during the preparation period for 131I treatment.

**MATERIALS AND METHODS**

***Study subjects***

A total of 1228 DTC patients treated with 131I from June 2017 to April 2020 were analyzed. All patients were confirmed to have DTC by pathology. Patients with thyroid stimulating hormone (TSH) not rising to 30 mIU/L after 4 wk of withdrawal of levothyroxine (L-T4), and with serum sodium levels lower than 136 mmol/L before and after DTC surgery were excluded from the study. The Institutional Review Board of the Second Hospital, Cheeloo College of Medicine, Shandong University approved this study (KYLL-2018[LW]013). All procedures complied with the Declaration of Helsinki for research involving human subjects. Written informed consent was obtained from each patient.

***Clinical data before 131I treatment***

All patients with DTC underwent L-T4 replacement therapy after surgery. After that, L-T4 was stopped 4 wk before 131I treatment. Enhanced computed tomography and oral Chinese herbal medicine were avoided during the low iodine diet. Morning urine and fasting blood samples were collected for laboratory examination on the day of 131I administration. The following indices were recorded, including serum sodium, potassium, calcium, free triiodothyronine (FT3), free thyroxine (FT4), TSH, urinary iodine, fasting glucose, hemoglobin, total protein, albumin, globulin, blood urea nitrogen (BUN), serum creatinine (SCR), and estimated glomerular filtration rate (eGFR). eGFR was calculated according to the simplified formula of MDRD. The data before and after surgery and before 131I treatment were examined in the same laboratory. All laboratory tests were measured on the VISTA 1500 systems (Siemens Diagnostics). The reference values for serum sodium were 137-147 mmol/L. Other data, including age, sex, body mass index, and systolic blood pressure were also collected before and after thyroid surgery and on the day of 131I administration. To minimize possible bias, patients with comorbid conditions (heart failure, acute and chronic kidney disease, and liver cirrhosis), or with intake of medications (such as diuretics) were strictly recorded.

***Diagnosis of hyponatremia***

Hyponatremia was defined as serum sodium level ≤ 135 mmol/L. The diagnostic ranges of mild, moderate, and severe hyponatremia were 130-135, 125-129 and < 125 mmol/L, respectively. According to the serum sodium level before 131I treatment, the patients were divided into the non-hyponatremia group (blood sodium level > 135 mmol/L) and the hyponatremia group (blood sodium level ≤ 135 mmol/L).

***Statistical analysis***

SPSS 20.0 software was used for statistical analysis. The paired *t* test or Wilcoxon signed rank test was used for paired comparisons. Pearson or Spearman rank correlation was used for correlation analysis of data distribution. Descriptive analysis of the baseline characteristics of the hypothyroid patients were performed between the hyponatremia and non-hyponatremia groups. Univariate analysis was performed to evaluate the risk factors for hyponatremia. The binary logistic regression equation was established, and the factors with *P <* 0.05 in univariate analysis were included in the equation to further explore the influencing factors of hyponatremia. A *P* value < 0.05 was considered statistically significant.

**RESULTS**

***General information***

A total of 903 patients with DTC, including 283 (31.3%) males and 620 (68.7%) females, with an average age of 43.8 ± 12.7 years, were included in this study. The serum sodium levels before surgery and 131I treatment were 141.3 ± 2.3 and 140.5 ± 2.1 mmol/L, respectively (*P* = 0.001, Figure 1A). However, the serum sodium levels of males and females before 131I treatment were lower than those before surgery. The patients aged more than 60 years and less than 60 years also showed a decrease before 131I treatment (Figure 1B). In addition, eGFR in males and females decreased before 131I treatment compared with those before surgery (*P* = 0.001, Figure 1C). Moreover, eGFR in patients over 60 years and under 60 years decreased before 131I treatment, when compared with that before surgery (Figure 1D). There were no significant differences in serum potassium, calcium, albumin, hemoglobin, and blood glucose in patients before surgery and 131I treatment (*P >* 0.05).

***Incidence and clinical manifestations of hyponatremia***

Among the 903 patients, 23 (2.5%) were diagnosed with hyponatremia before 131I treatment, including 21 cases (91.3%) of mild hyponatremia and 2 cases (8.7%) of moderate hyponatremia. Clinical data showed that patients with mild hyponatremia had no specific clinical manifestations, while moderate hyponatremia cases were mainly characterized by fatigue and dizziness, which were similar to neurological symptoms caused by hypothyroidism and were difficult to distinguish (Table 1).

***Influencing factors of 131I sodium in blood before treatment***

Correlation analysis showed a correlation between serum sodium before 131I treatment and the preoperative level (*r* = 0.395, *P* = 0.001). There was no significant correlation between blood sodium and TSH levels and urine iodine before 131I treatment (*r* = 0.045, *P* = 0.174; *r* = 0.013, *P* = 0.697) (Table 2).

Univariate analysis showed that there were significant differences in age, sex, history of diuretic use, distant metastasis, preoperative blood sodium, BUN, eGFR, TSH and urinary iodine between the two groups (all *P <* 0.05) (Table 3).

Logistic regression analysis showed that factors such as a history of diuretic use, distant metastases, preoperative sodium and BUN were all influencing factors of hyponatremia (Table 4). The Hosmer and Lemeshow test (*c*2 = 2.841, *P* = 0.944) suggested a high fit of the model. Omnibus tests of model coefficients indicated the overall significance of the model in this fitted model (*P <* 0.05). Preoperative serum sodium was significantly associated with pre-RAI therapy hyponatremia (OR = 0.763; 95%CI: 0.627-0.928; *P* = 0.007).

**DISCUSSION**

In this study, the incidence of hyponatremia before 131I treatment was 2.5% (23/903). Among the 23 patients with hyponatremia, approximately 91% (21/23) had mild hyponatremia. In a prospective study of 212 patients after DTC surgery, the incidence of hyponatremia before 131I treatment was only 1.4% (3/212)[7]. Vannucci *et al* included 101 DTC patients who continued to withdraw thyroid hormone for about 2 wk and had a low iodine diet and found that the incidence of hyponatremia was 4% (4/101), of which approximately 75% (3/4) had mild hyponatremia[8]. Therefore, the incidence of hyponatremia caused by 131I treatment preparation is not high, and is mainly mild hyponatremia. Previous studies have reported that patients with severe hyponatremia during 131I preparation have an average withdrawal time of 4 wk for thyroid hormone, and the duration of low iodine diet is also more than 3 wk[3,5-6]. This study had similar 131I preparation before treatment. However, there were no severe hyponatremia patients in this study. Severe hyponatremia patients are reported to have different degrees of myxedema, which is combined with other underlying diseases, suggesting that the occurrence of severe hyponatremia may be due to other underlying diseases, rather than caused only by withdrawal of thyroid hormone or low iodine diet[5].

In terms of the relationship between the severity of hypothyroidism and serum sodium levels, the TSH levels in the hyponatremia group were significantly lower than those in the non-hyponatremia, which is consistent with the hypothesis that the higher the TSH level, the lower the blood sodium level. This result suggests that the occurrence of hyponatremia may not be related to the increase in TSH level. A previous study reported that serum sodium levels ranged from 132 to 144 mmol/L in hypothyroid patients (*n* = 999 cases) and from 134 to 144 mmol/L in patients with TSH in the normal range (*n* = 4875 cases), respectively, and there was no statistically significant difference in serum sodium levels between these two groups[9]. Although there was a trend of a 1.4 mmol/L decrease in serum sodium for every 100 mIU/L increase in TSH, the clinical correlation between the two groups could not be determined. Hammami *et al*[7] also reported that there was no significant correlation between TSH level and serum sodium level even in severe hypothyroidism patients with TSH levels of 140 to 192 mU/L.

In addition, it was found that the duration of a low-iodine diet was negatively correlated with the serum sodium level before 131I treatment, which indicates that the longer the duration of the low-iodine diet, the higher the serum sodium level. In this study, urinary iodine was used as an indicator of patients' iodine intake. However, we found that there was no correlation between urinary iodine and serum sodium level before 131I treatment. It was also reported that low-iodine diet is a factor affecting the occurrence of hyponatremia, mainly based on the strict management of patients with low-iodine diet, which is often accompanied by low or no sodium intake[10]. Our results showed that as the urine iodine level decreased, the blood sodium level did not have a linear downward trend. In addition, although there was a statistical difference in urinary iodine levels between the two groups (*P* = 0.037), it has limited significance in clinic practice. This is because only when the median urinary iodine concentration is lower than 50 µg/L, it can reflect the severity of the body’s iodine deficiency disorder. Therefore, serum sodium concentration may be affected only when a low iodine diet is accompanied by low sodium intake.

Our results showed that the preoperative serum sodium level was higher than before 131I treatment, implying that 131I treatment can cause a decrease in serum sodium level. Theoretically, chronic hypothyroidism is one of the causes of hyponatremia, but the mechanism of its occurrence is unclear[11]. Liamis *et al*[2] believed that the decreased cardiac output in patients with chronic hypothyroidism could lead to increased secretion of ADH, reabsorption of water, and increased excretion of sodium in the urine, leading to hyponatremia. Bautista *et al*[12] believed that thyroid hormones could affect the expression of electrolyte reabsorption channels in kidney cells, and long-term hypothyroidism could reduce the kidney's ability to reabsorb electrolytes such as sodium, calcium, potassium and magnesium, leading to hyponatremia. Montenegro *et al*[13] suggested that short-term and transient hypothyroidism may lead to a decrease in GFR and renal blood flow, which may in turn affect electrolyte reabsorption. In this study, we did not detect abnormalities in the levels of ADH and other hormones, but the preoperative eGFR was higher than after 131I treatment, indicating that the decrease in serum sodium level may be related to the decrease in eGFR.

Previous studies have suggested that age, sex, history of diuretic use and serum sodium level before surgery are all independent influencing factors of hyponatremia in DTC patients before 131I treatment[14-15]. In this study, we found that age and history of diuretic use were significantly different between the hyponatremia and non-hyponatremia groups by univariate analysis, but they were not identified as independent influencing factors in the multivariate analysis. We believe that age may have a common relationship with renal function. In theory, the efficiency of GFR gradually decreases with age, leading to an increase in BUN and an increased risk of hyponatremia[14]. The data in this study were also consistent with this theory. A previous study suggested that diuretics directly induced the release of ADH or increased the response of collecting ducts to ADH, leading to the occurrence of hyponatremia, which was more common in hospitalized patients with other etiologies[2]. However, in this study, diuretics had a relatively small effect on the occurrence of hyponatremia, which might be related to the age of the population. We found distant metastasis was an independent influencing factor for the occurrence of hyponatremia. Patients with distant metastasis can lead to the syndrome of dysregulation of ADH secretion, which leads to hyponatremia[15]. The main mechanism may be that the increase in ADH secretion phosphorylates aquaporin-2 on the cell membrane and promotes water reabsorption[3].

However, this study has some limitations. For example, the sample size of patients with hyponatremia was small. Thus, the results of multivariate analysis may not be robust enough. However, considering that the incidence of hyponatremia was not high, the results still have a certain interpretability and reliability. In addition, the cause of hyponatremia was not further investigated in this study. Further studies with larger sample sizes, including prospective studies, are needed in the future to verify these results.

**CONCLUSION**

In conclusion, the incidence of hyponatremia was not high in patients with DTC. Preparation for radioactive iodine therapy was not a risk factor for the development of hyponatremia in thyroid cancer patients. Distant metastases, preoperative sodium and BUN were identified as influencing factors of hyponatremia.

**ARTICLE HIGHLIGHTS**

***Research background***

Hyponatremia in chronic hypothyroidism is commonly seen in clinical practice. However, the association between hyponatremia and acute hypothyroidism is unclear. Acute hypothyroidism is usually seen in patients who undergo preparation for radioactive iodine therapy.

***Research motivation***

The incidence and influencing factors of hyponatremia before 131I treatment in China are still unclear. This article will offer our center's experience of the management of thyroid cancer patients prior to 131I therapy.

***Research objectives***

To improve patient management during the preparation period for 131I treatment. The cause of hyponatremia was not further investigated in this study. Thus, further studies with larger sample sizes, including prospective studies, are needed in the future to verify these results.

***Research methods***

An observational study design was used in this clinical study. Patients with and without hyponatremia were studied by univariate and multivariate analysis. The sample size in this study was larger than those reported in previous publications.

***Research results***

The incidence of hyponatremia induced by 131I treatment preparation was not high (2.5%). Twenty-three (2.5%) patients were diagnosed with hyponatremia before 131I treatment, including 21 cases (91.3%) of mild hyponatremia and 2 cases (8.7%) of moderate hyponatremia.

***Research conclusions***

This study indicates that preparation for radioactive iodine therapy is not a risk factor for the development of hyponatremia in thyroid cancer patients.

***Research perspectives***

Measurement of sodium post-radioactive iodine therapy should be considered in patients.

**ACKNOWLEDGEMENTS**

We thank all medical staff and technicians of the Department of Nuclear Medicine, the Second Hospital, Cheeloo College of Medicine, Shandong University.

**REFERENCES**

1 **Corona G**, Giuliani C, Verbalis JG, Forti G, Maggi M, Peri A. Hyponatremia improvement is associated with a reduced risk of mortality: evidence from a meta-analysis. *PLoS One* 2015; **10**: e0124105 [PMID: 25905459 DOI: 10.1371/journal.pone.0124105]

2 **Liamis G**, Filippatos TD, Liontos A, Elisaf MS. MANAGEMENT OF ENDOCRINE DISEASE: Hypothyroidism-associated hyponatremia: mechanisms, implications and treatment. *Eur J Endocrinol* 2017; **176**: R15-R20 [PMID: 27484454 DOI: 10.1530/EJE-16-0493]

3 **Pantalone KM**, Hatipoglu BA. Hyponatremia and the Thyroid: Causality or Association? *J Clin Med* 2014; **4**: 32-36 [PMID: 26237016 DOI: 10.3390/jcm4010032]

4 **Haugen BR**, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016; **26**: 1-133 [PMID: 26462967 DOI: 10.1089/thy.2015.0020]

5 **Wolf P**, Beiglböck H, Smaijs S, Wrba T, Rasoul-Rockenschaub S, Marculescu R, Gessl A, Luger A, Winhofer Y, Krebs M. Hypothyroidism and Hyponatremia: Rather Coincidence Than Causality. *Thyroid* 2017; **27**: 611-615 [PMID: 28351291 DOI: 10.1089/thy.2016.0597]

6 **Kim SK**, Yun GY, Kim KH, Park SK, Choi HY, Ha SK, Park HC. Severe hyponatremia following radioactive iodine therapy in patients with differentiated thyroid cancer. *Thyroid* 2014; **24**: 773-777 [PMID: 24093878 DOI: 10.1089/thy.2013.0110]

7 **Hammami MM**, Almogbel F, Hammami S, Faifi J, Alqahtani A, Hashem W. Acute severe hypothyroidism is not associated with hyponatremia even with increased water intake: a prospective study in thyroid cancer patients. *BMC Endocr Disord* 2013; **13**: 27 [PMID: 23902827 DOI: 10.1186/1472-6823-13-27]

8 **Vannucci L**, Parenti G, Simontacchi G, Rastrelli G, Giuliani C, Ognibene A, Peri A. Hypothyroidism and hyponatremia: data from a series of patients with iatrogenic acute hypothyroidism undergoing radioactive iodine therapy after total thyroidectomy for thyroid cancer. *J Endocrinol Invest* 2017; **40**: 49-54 [PMID: 27507082 DOI: 10.1007/s40618-016-0525-6]

9 **Warner MH**, Holding S, Kilpatrick ES. The effect of newly diagnosed hypothyroidism on serum sodium concentrations: a retrospective study. *Clin Endocrinol (Oxf)* 2006; **64**: 598-599 [PMID: 16649984 DOI: 10.1111/j.1365-2265.2006.02489.x]

10 **Kim J**, Cho SG, Kang SR, Kwon SY, Cho DH, Cho JS, Song HC. Preparation for radioactive iodine therapy is not a risk factor for the development of hyponatremia in thyroid cancer patients. *Medicine (Baltimore)* 2017; **96**: e6004 [PMID: 28151897 DOI: 10.1097/MD.0000000000006004]

11 **Chaudhary N**, Warraich F, Warraich Z, Warraich S, Anwer F. Effect of Optimal Thyroid Replacement Therapy on Chronic Hyponatremia with Focused Review of the Evidence, Mechanisms, and Clinical Implications. *Cureus* 2019; **11**: e5813 [PMID: 31737455 DOI: 10.7759/cureus.5813]

12 **Bautista AA**, Duya JE, Sandoval MA. Salt-losing nephropathy in hypothyroidism. *BMJ Case Rep* 2014; **2014** [PMID: 24850556 DOI: 10.1136/bcr-2014-203895]

13 **Montenegro J**, González O, Saracho R, Aguirre R, González O, Martínez I. Changes in renal function in primary hypothyroidism. *Am J Kidney Dis* 1996; **27**: 195-198 [PMID: 8659492 DOI: 10.1016/s0272-6386(96)90539-9]

14 **Lee JE**, Kim SK, Han KH, Cho MO, Yun GY, Kim KH, Choi HY, Ryu YH, Ha SK, Park HC. Risk factors for developing hyponatremia in thyroid cancer patients undergoing radioactive iodine therapy. *PLoS One* 2014; **9**: e106840 [PMID: 25170831 DOI: 10.1371/journal.pone.0106840]

15 **Nagata T**, Nakajima S, Fujiya A, Sobajima H, Yamaguchi M. Prevalence of hypothyroidism in patients with hyponatremia: A retrospective cross-sectional study. *PLoS One* 2018; **13**: e0205687 [PMID: 30308047 DOI: 10.1371/journal.pone.0205687]

**Footnotes**

**Institutional review board statement:** The study was approved by the Institutional Review Board of the Second Hospital, Cheeloo College of Medicine, Shandong University (KYLL-2018[LW]013). All procedures complied with the Declaration of Helsinki for research involving human subjects.

**Informed consent statement:** Written informed consent was obtained from each patient.

**Conflict-of-interest statement:** All authors have no conflict of interest related to the manuscript.

**Data sharing statement:** The original anonymous dataset is available on request from the corresponding author.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review started:** May 11, 2021

**First decision:** July 8, 2021

**Article in press:**

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

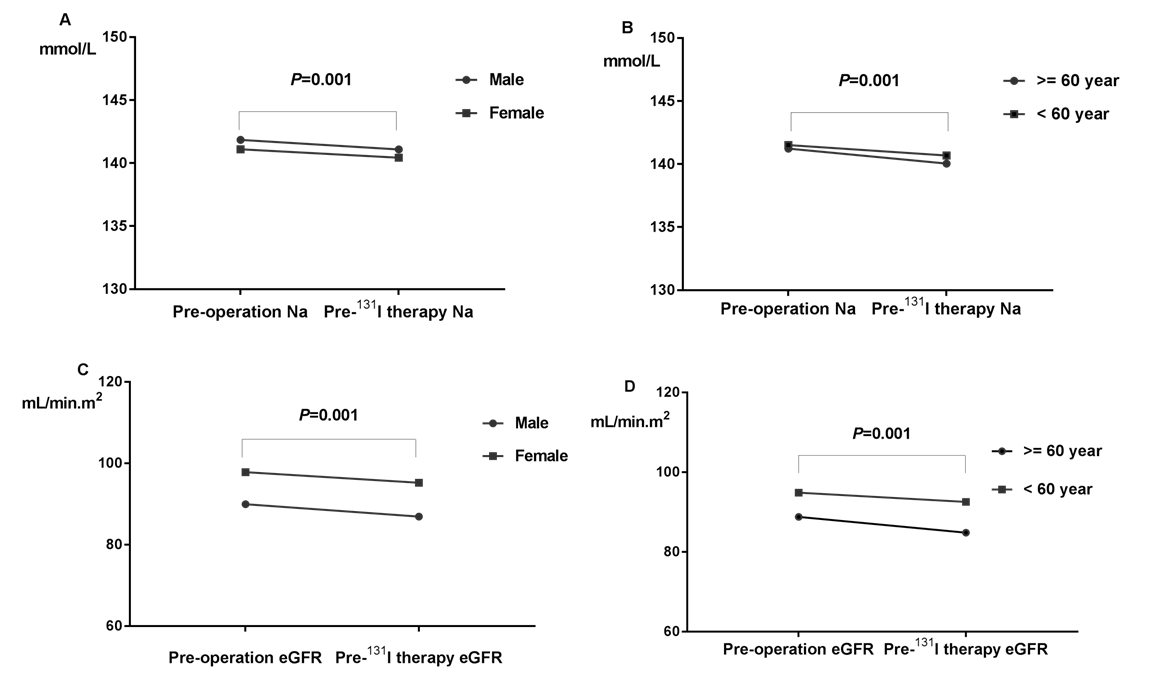
Grade C (Good): 0

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** Qutbi M **S-Editor:** Wang LL **L-Editor:** Webster JR **P-Editor:** Wang LL

**Figure Legends**



**Figure 1 Comparison of serum sodium and eGFR levels before surgery and 131I treatment.** A: The serum sodium levels in males and females before 131I treatment were lower than those before surgery; B: The serum sodium levels in patients aged more than 60 and less than 60 years showed a decrease before 131I treatment; C: The eGFR in males and females decreased before 131I treatment compared with that before surgery; D: The eGFR in patients over 60 and under 60 years decreased before 131I treatment compared with that before surgery.

**Table 1 Clinical data of the patients with hyponatremia before 131I treatment**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patients** | **Age (yr)** | **Gender** | **Pre-operation sodium (mmol/L)** | **Pre-131I therapy sodium (mmol/L)** | **Potentially hyponatremia-inducing drugs** | **Potentially hyponatremia-inducing comorbidities** |
| 1 | 75 | Male | 138 | 134 | Diuretic, ACEI | DM, adenocarcinoma of lung |
| 2 | 71 | Male | 140 | 135 | Diuretic, ARB | None |
| 3 | 71 | Male | 140 | 133 | None | None |
| 4 | 64 | Male | 141 | 134 | Diuretic | None |
| 5 | 64 | Male | 141 | 135 | None | None |
| 6 | 64 | Male | 144 | 133 | None | None |
| 7 | 63 | Male | 136 | 134 | Diuretic, ACEI | None |
| 8 | 53 | Male | 140 | 135 | None | DM |
| 9 | 52 | Male | 138 | 135 | None | DM, coronary heart disease |
| 10 | 47 | Male | 144 | 135 | None | None |
| 11 | 45 | Male | 138 | 135 | None | Adrenocortical hypofunction |
| 12 | 38 | Male | 136 | 131 | None | None |
| 13 | 31 | Male | 136 | 128 | None | DM |
| 14 | 69 | Female | 140 | 129 | None | RI, CHD, old cerebral infarction |
| 15 | 49 | Female | 136 | 135 | None | None |
| 16 | 47 | Female | 142 | 135 | None | None |
| 17 | 42 | Female | 140 | 135 | None | None |
| 18 | 42 | Female | 140 | 134 | None | None |
| 19 | 41 | Female | 137 | 132 | None | DM, diabetic nephropathy |
| 20 | 35 | Female | 145 | 135 | None | None |
| 21 | 35 | Female | 138 | 134 | None | None |
| 22 | 33 | Female | 142 | 135 | None | Chronic hepatitis B |
| 23 | 32 | Female | 138 | 133 | None | None |

DM: Diabetes mellitus; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CHD: Coronary heart disease; RI: Renal insufficiency.

**Table 2 Factors associated with pre-131I therapy serum sodium level**

|  |  |  |
| --- | --- | --- |
|  | **Correlation *r*** | ***P* value** |
| Age(yr) | 0.087 | 0.009 |
| TSH(mIU/L) | 0.045 | 0.174 |
| Tg(ng/mL) | -0.028 | 0.402 |
| Urinary iodine(µg/L) | 0.013 | 0.697 |
| Pre-operation serum sodium(mmol/L) | 0.395 | 0.001 |
| Blood urea nitrogen(mmol/L) | 0.028 | 0.401 |
| eGFR(mL/min m2) | -0.073 | 0.027 |

**Table 3 Baseline characteristics of the hyponatremia group and non-hyponatremia group before 131I treatment**

|  |  |  |  |
| --- | --- | --- | --- |
| **Items** | **Hyponatremia group** | **Non-hyponatremia group** | ***P* value** |
| Sex (*n,* %) |  |  | 0.008 |
| Male | 13 (56.5) | 270 (30.7) |
| Female | 10 (43.5) | 610 (69.3) |
| Age (yr) | 50.5 ± 14.2 | 43.6 ± 12.7 | 0.01 |
| Body mass index (kg/m2) | 22.2 ± 3.3 | 23.1 ± 4.3 | 0.348 |
| Systolic blood pressure (mmHg) | 129.9 ± 21.1 | 124.5 ± 18.1 | 0.161 |
| History of ACEI or ARB (*n,* %) |  |  | 0.42 |
| Yes | 3 (13.1) | 69 (7.8) |  |
| No | 20 (86.9) | 811 (2.2) |  |
| History of diuretics (*n,* %) |  |  | 0.015 |
| Yes | 4 (17.4) | 35 (4.1) |  |
| No | 19 (82.6) | 845 (95.9) |  |
| Distant metastasis (*n,* %) |  |  | 0.014 |
| Yes | 6 (26.1) | 77 (8.8) |  |
| No | 17 (73.9) | 803 (91.2) |  |
| Hemoglobin (g/L) | 141.1 ± 19.5 | 144.2 ± 18.4 | 0.52 |
| Fasting blood glucose (mmol/L) | 5.2 (4.6, 7.2) | 5.1 (4.8, 5.6) | 0.267 |
| Pre-operation serum sodium (mmol/L) | 139.5 ± 2.6 | 141.3 ± 2.3 | 0.001 |
| Pre-131I therapy serum sodium (mmol/L) | 133.6 ± 1.9 | 140.6 ± 1.8 | 0.001 |
| Serum potassium (mmol/L) | 4.3 ± 0.3 | 4.2 ± 0.3 | 0.462 |
| Serum calcium (mmol/L) | 2.3 ± 0.1 | 2.2 ± 0.1 | 0.062 |
| Blood urea nitrogen (mmol/L) | 4.7 ± 2.1 | 3.8 ± 1.2 | 0.043 |
| Serum creatinine (µmol/L) | 78.7 ± 13.3 | 74.4 ± 16.4 | 0.271 |
| Urinary iodine (µg/L) | 83.1 (52.9, 100.3) | 93.1 (54.5, 203.1) | 0.037 |
| Total protein (g/L) | 77.1 ± 5.9 | 76.9 ± 4.4 | 0.865 |
| Albumin (g/L) | 46.6 ± 4.2 | 47.9 ± 2.8 | 0.155 |
| Globulin (g/L) | 30.5 ± 4.1 | 29.1 ± 3.7 | 0.077 |
| eGFR (mL/min m2) | 81.8 ± 11.4 | 88.8 ± 15.3 | 0.029 |
| TSH (mIU/L) | 99.5 ± 28.5 | 130.6 ± 59.4 | 0.001 |
| FT3 (pmol/L) | 2.8 ± 0.4 | 2.9 ± 0.6 | 0.594 |
| FT4 (pmol/L) | 2.1 ± 1.2 | 1.8 ± 1.2 | 0.27 |

DM: Diabetes mellitus; ACEI: Angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

**Table 4 Logistic regression analysis of factors associated with hyponatremia development**

|  |  |  |  |
| --- | --- | --- | --- |
| **Items** | ***β*** | OR **(95%CI)** | ***P* value** |
| Gender (male) | -0.647 | 0.524 (0.203, 1.354) | 0.182 |
| Age (yr) | 0.007 | 1.007 (0.965,1.050) | 0.762 |
| Distant metastasis (*n*) | 1.193 | 3.296 (1.112, 9.770) | 0.031 |
| History of diuretics (*n*) | -1.212 | 0.298 (0.090,0.988) | 0.048 |
| TSH (mIU/L) | -0.009 | 0.991 (0.980,1.002) | 0.101 |
| Urinary iodine (µg/L) | -0.011 | 0.989 (0.98,0.998) | 0.075 |
| eGFR (mL/min m2) | -0.032 | 0.969 (0.934,1.005) | 0.09 |
| Pre-operation Na (mmol/L) | -0.271 | 0.763 (0.627, 0.928) | 0.007 |
| Blood urea nitrogen (mmol/L) | 0.420 | 1.521 (1.094, 2.115) | 0.013 |