

Research Article

Thyroid Function in 35 Patients with Gitelman Syndrome

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Objective. In this study, we aimed to analyze thyroid function and related risk factors for thyroid dysfunction in 35 patients with Gitelman syndrome (GS). **Methods.** This study included 35 patients with GS who were referred to West China Hospital of Sichuan University from Aug 2013 to Jan 2018. General patient characteristics were collected, and thyroid function was assessed. To evaluate the potential contribution of hypokalemia to thyroid dysfunction, 636 patients who were clinically diagnosed with primary aldosteronism (PA) during the same period were included as the control group; these patients were divided into a hypokalemia group ($N = 528$) and a normokalemia group ($N = 108$). Logistic regression was used to screen for significant determinants of thyroid dysfunction in the GS patients. **Results.** Patients with GS had a significantly different prevalence of subclinical hypothyroidism, hypothyroidism, and hyperthyroidism than patients with hypokalemic PA and normokalemic PA (28.6%, 2.9%, and 11.4% vs. 15.5%, 6.1%, and 0.7% vs. 8.3%, 4.6%, and 2.8%, $P < 0.001$). No significant difference was observed in the distribution of thyroid function between the hypokalemic PA group and the normokalemic PA group ($P > 0.05$). No significant differences were seen in the positive rates of thyrotropin receptor antibody (TRAb), thyroglobulin antibody (TGAb), and thyroid peroxidase antibody (TPOAb) among the three groups ($P > 0.05$). In the logistic regression, only sex (OR, 7.4; 95% CI, 1.555-35.479; $P = 0.012$) was significantly correlated with thyroid dysfunction in GS patients. **Conclusion.** GS is complicated with a greater rate of thyroid dysfunction than primary aldosteronism. The risk of thyroid dysfunction in female patients with GS is higher than that in male patients.

1. Introduction

Gitelman syndrome (GS) is an autosomal recessive hereditary disorder that is characterized by hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria [1]. Case reports have demonstrated that GS is associated with thyroid diseases and thyroid dysfunction [2–4], as described in a pedigree of patients with GS complicated by thyroid disease or dysfunction, reported by Liu et al. [2]. A 16-year-old teenager (the proband) was diagnosed with GS and Graves' disease [2], and his family members who carried SLC12A3 gene mutations without clinical manifestations of GS were also affected with subclinical hypothyroidism or thyroid autoantibodies [2]. Zhou et al. [3] reported a male patient with a 12-year history of Graves' disease (GD) who was finally diagnosed with GS. Aoi et al. [4] reported two GS patients who

were diagnosed using genetics and whose diseases were complicated by GD and autoimmune thyroid disease (AITD). Since according to multiple case reports, GS patients experienced thyroid dysfunction; it is necessary to verify this finding in additional GS patients.

It is generally recognized that thyrotoxicosis is the most common cause of hypokalemic periodic paralysis (HPP) in Graves' disease (GD), especially in Asian men [5]. Other studies have reported an association between HPP and other thyroid disorders, such as painless thyroiditis, toxic multinodular goiter (MNG), toxic thyroid adenoma, thyroid-stimulating hormone- (TSH-) secreting pituitary adenoma, and primary hypothyroidism [6–8]. Therefore, whether the thyroid dysfunction observed in GS is due to hypokalemia requires further investigation. In this study, we aimed to analyze thyroid function in 35 GS cases to determine the

potential influence of hypokalemia on thyroid dysfunction in GS compared with primary aldosteronism (PA) and to explore the risk factors of thyroid dysfunction in GS patients.

2. Materials and Methods

2.1. Patients. The data of patients with GS and PA were retrospectively collected. Patients with clinical symptoms, such as weakness, numbness, muscle pain, nocturia, palpitation, and chest pain, were referred to West China Hospital of Sichuan University from Aug 2013 to Jan 2018. Thirty-seven patients were clinically diagnosed with GS, and of these, nine were genetically diagnosed with GS. Two patients who underwent partial and total thyroidectomy due to thyroid adenoma and papillary thyroid cancer, respectively, were excluded. Thirty-five patients with GS were finally included in this study. 636 patients who were clinically diagnosed with PA from Dec 2008 to Dec 2018 were included as the control group. To evaluate the potential contribution of hypokalemia to thyroid dysfunction, PA patients with serum potassium levels lower than 3.5 mmol/L and between 3.5 mmol/L and 5.5 mmol/L were classified into the hypokalemic group ($N = 528$) and the normokalemic group ($N = 108$), respectively. Clinical data were retrospectively obtained from the medical records.

2.2. Ethical Approval. The study protocol was approved by the Ethical Committee of West China Hospital of Sichuan University (2019-556) and was performed according to the principles in the Declaration of Helsinki.

2.3. Diagnostic Criteria. GS was diagnosed in accordance with the consensus and guidance established in 2017 [9]. Briefly, patients with chronic hypokalemia in the absence of potassium-lowering drugs, inappropriate renal potassium wasting, metabolic alkalosis, hypomagnesemia, hypocalciuria, high plasma renin activity, low or normal-low blood pressure, and normal renal ultrasound findings were clinically diagnosed with GS. Patients who were found to harbor biallelic-inactivating mutations in *SLC12A3* were genetically diagnosed with GS. Patients treated with laxatives or diuretics and those who abused alcohol or drugs were excluded. Patients with other extrarenal and renal causes of hypokalemia and transcellular shift of potassium, such as bronchodilator use and familial periodic paralysis, were excluded. Finally, patients with autoimmune diseases, such as Sjögren's syndrome, were also excluded.

PA was diagnosed in accordance with published guidelines [10]. Briefly, patients with a high plasma aldosterone (PAC, ng/dL)/renin (PRA, ng/mL/h) ratio (ARR) required one or more confirmatory tests to definitively confirm or exclude the diagnosis. PA was diagnosed when at least one of the confirmatory tests (captopril challenge test or saline infusion test) was positive.

2.4. Thyroid Function. The levels of free triiodothyronine (FT3, normal range 3.6-7.5 pmol/L), free thyroxine (FT4, normal range 12.0-22.0 pmol/L), thyroid-stimulating hormone (TSH, normal range 0.27-4.2 mU/L), thyroid peroxidase antibody (TPOAb, normal range < 34 IU/mL), thyroglobulin antibody (TGAb, normal range < 115 IU/mL),

and thyrotropin receptor antibody (TRAb, normal range < 3 IU/L) were measured using chemiluminescence immunoassay kits (Roche Kit, Cobas-e601 analyzer). The intra-assay and interassay coefficients of variation were all less than 5%.

Clinical hyperthyroidism was defined as the use of anti-thyroid medications, a history of hyperthyroidism or a TSH level < 0.27 mU/L, and an FT4 level > 22.0 pmol/L. Clinical hypothyroidism was defined as the use of levothyroxine treatment or a TSH level > 4.2 mU/L and an FT4 level < 12.0 pmol/L. Subclinical hypothyroidism was defined as a TSH level > 4.2 mU/L and a normal FT4 level between 12.0 and 22.0 pmol/L without administration of drugs for thyroid disease [11]. A TPOAb level > 34 IU/mL, a TGAb level > 115 IU/mL, and a TRAb level > 3 IU/mL were considered positive [11]. Patients with nonthyroidal illness, temporary changes in thyroid function due to subacute or painless thyroiditis, and thyroidectomy were not included. Patients with a clear history of hyperthyroidism due to Graves' disease were also included in the hyperthyroidism group for analysis, even though they had normal thyroid function or were treated with antithyroid drugs at the time of the study.

2.5. Statistical Analysis. Statistical analyses were performed with SPSS 22.0. For normal distributions, numerical variables were described as the means \pm standard deviations (SDs). For nonnormal distributions, numerical variables were presented as medians and quartiles. Categorical variables were described as counts. The Kruskal-Wallis test and one-way ANOVA were used to compare differences in laboratory tests among the three groups. Comparisons were performed using the chi-square test for categorical data. $P < 0.05$ was considered statistically significant. Univariate logistic regression was used to screen for significant determinants of thyroid dysfunction in GS patients. Factors such as sex, age, and the levels of serum magnesium, serum potassium, serum calcium, serum chlorine, TPOAb, and TGAb were included. Factors with an associated P value less than 0.05 were entered into a stepwise backwards conditional multivariable logistic regression analysis.

3. Results

3.1. Biochemical Characteristics of the Included Subjects. The biochemical features of 35 patients with GS are summarized in Table 1. Their serum potassium (K^+) concentration ranged from 1.3 to 2.9 mmol/L with inappropriate renal potassium wasting (15.9-180.5 mmol/day); the serum magnesium (Mg^{2+}) concentration in these patients ranged from 0.2 to 0.9 mmol/L, and 5 patients had a normal serum Mg^{2+} concentration (normal range 0.7-1.0 mmol/L). Their calcium excretion varied from 0.1 to 9.6 mmol/day (normal range 2.5-7.5 mmol/day). All patients demonstrated high plasma renin activity that ranged from 4.5 to 12.0 ng/mL/h (normal range 0.1-0.8 ng/mL/h). The pH ranged from 7.37 to 7.52.

As shown in Table 2, the mean age of patients in the GS group was 36.6 ± 15.4 years, which was lower than the mean ages of patients in the normokalemic PA group (51.9 ± 11.7 years) and the hypokalemic PA group (48.4 ± 12.1 years) ($P < 0.05$). As expected, all patients in the GS group had

TABLE 1: Biochemical features in 35 patients with Gitelman syndrome.

Biochemical feature	GS patients	Normal range
Serum electrolyte levels		
K ⁺	2.5 ± 0.3	3.5-5.5 mmol/L
Mg ²⁺	0.5 ± 0.2	0.7-1.0 mmol/L
Ca ²⁺	2.1 ± 0.2	2.1-2.7 mmol/L
Concomitant urinary electrolyte excretions		
K ⁺	57.5 (42.1, 85.9)	40-80 mmol/day
Ca ²⁺	0.4 (0.2, 1.2)	2.5-7.5 mmol/day
Plasma renin activity	12.0 (12.0, 12.0)	0.1-0.8 ng/mL/h
Blood gas analysis (room air)		
pH	7.45 ± 0.03	7.35-7.45
BE	4.0 ± 2.3	-3 to +3 mmol/L

GS: Gitelman syndrome; K⁺: serum or urinary potassium; Mg²⁺: serum magnesium; Ca²⁺: serum or urinary calcium; BE: base excess.

higher plasma renin activity in the supine position 12.0 (12.0, 12.0) ng/mL/h compared with patients in the normokalemic PA group 0.1 (0.1, 0.2) ng/mL/h and patients in the hypokalemic PA group 0.1 (0.1, 0.3) ng/mL/h. The serum magnesium level in the GS group was much lower than that in the hypokalemic PA group (0.5 ± 0.2 mmol/L vs. 0.9 ± 0.1 mmol/L, $P < 0.05$) and the normokalemic PA group (0.5 ± 0.2 mmol/L vs. 0.9 ± 0.1 mmol/L, $P < 0.05$), as shown in Table 2. The aldosterone level in the hypokalemic PA group was much higher compared with that in the GS group (30.2 (21.3, 38.6) ng/dL vs. 20.8 (15.7, 28.8) ng/dL, $P < 0.05$) and the normokalemic PA group (30.2 (21.3, 38.6) ng/dL vs. 16.8 (14.3, 20.6) ng/dL, $P < 0.05$).

3.2. Thyroid Dysfunction in the Three Groups. In the GS group, the percentages of patients with euthyroidism, subclinical hypothyroidism, hypothyroidism, and hyperthyroidism were 57.1% (20/35), 28.6% (10/35), 2.9% (1/35), and 11.4% (4/35), respectively, which were significantly different from the percentages in the hypokalemic PA group (77.7%, 15.5%, 6.1%, and 0.7%) and the normokalemic PA group (84.3%, 8.3%, 4.6%, and 2.8%) (adjusted $P = 0.002$ and adjusted $P < 0.001$), as shown in Figure 1. No significant difference was observed in the distribution of thyroid function between the hypokalemic PA group and the normokalemic PA group ($P > 0.05$). In the univariate logistic regression analysis, only sex (OR, 7.4; 95% CI, 1.555-35.479; $P = 0.012$) was significantly correlated with thyroid dysfunction in GS patients. The risk of thyroid dysfunction was 7.4 times higher in female GS patients than in male patients.

3.3. Thyroid Autoimmune Dysregulation in GS Patients. The positive rates of TRAb, TGAb, and TPOAb were 0% (0/19), 10.0% (2/20), and 13.0% (3/23), respectively, in the GS group, 5.5% (7/128), 10.4% (21/202), and 12.3% (26/211), respectively, in the hypokalemic PA group, and 0% (0/23), 18.2% (6/33), and 15.2% (5/33), respectively, in the normokalemic PA group; these data are shown in Table 2. No significant dif-

ferences were found in the positive rates of TRAb, TGAb, and TPOAb among the three groups ($P > 0.05$).

3.4. Hypomagnesemia Is Not Associated with Thyroid Dysfunction in GS Patients. GS patients with serum magnesium levels lower than 0.67 mmol/L and serum magnesium levels that ranged from 0.67 to 1.04 mmol/L were classified into the hypomagnesemia group ($N = 30$) and the normomagnesemia group ($N = 5$), respectively. Thirteen patients in the hypomagnesemia group and two patients in the normomagnesemia group exhibited thyroid dysfunction. No significant difference was observed between the two groups in the occurrence of thyroid dysfunction by chi-square test ($P = 0.889$).

3.5. Angiotensin II Is Not Associated with Thyroid Dysfunction in GS Patients. GS patients were divided into the high angiotensin II ($N = 17$) and low angiotensin II groups ($N = 18$) according to the median value. Ten patients in the high angiotensin II group and five patients in the low angiotensin II group exhibited thyroid dysfunction. No significant difference was found between the two groups in the occurrence of thyroid dysfunction by chi-square test ($P = 0.064$).

4. Discussion

In this study, we discovered that patients with GS had a high incidence of thyroid dysfunction, including 28.6% (10/35) with subclinical hypothyroidism, 2.9% (1/35) with hypothyroidism, and 11.4% (4/35) with hyperthyroidism. This prevalence of thyroid dysfunction was significantly higher than that in the general population of China (the prevalence of subclinical hyperthyroidism and subclinical hypothyroidism was 0.46% and 5.46%, respectively) [12]. This prevalence was also higher than the reported prevalence in the US and Korea [13, 14]. Published studies have shown that the prevalence of subclinical hypothyroidism, hypothyroidism, and hyperthyroidism was 8.5%, 0.4%, and 0.1%, respectively, according to the US Colorado thyroid disease prevalence survey [13]. Moreover, in Korea, the prevalence of subclinical hypothyroidism and subclinical hyperthyroidism was 3.3% and 2.6%, respectively, [14].

Fujimura et al. [15] investigated the clinical and genetic characteristics of 185 Japanese patients with GS diagnosed by genetic testing. They found that 4 (4.3%) of 94 cases exhibited thyroid dysfunction: 2 (2.1%) had hyperthyroidism, while 2 (2.1%) had hypothyroidism [15]. Unfortunately, they did not present data on subclinical thyroid dysfunction, which was high in the present study, and did not mention the issue of previously diagnosed thyroid disease and those who were under treatment for thyroid disease. To date, no other cohort study on GS and thyroid dysfunction could be found.

The most prominent characteristic of GS is hypokalemia. To study the impact of hypokalemia on thyroid dysfunction in GS patients, PA patients with and without hypokalemia were used as control groups. The results showed that the distribution of thyroid function in the GS group was

TABLE 2: Comparison of the general characteristics of patients with GS and PA.

	GS	Hypokalemic PA	Normokalemic PA
N	35	528	108
Age (years)	36.6 ± 15.4* ^{†‡}	48.4 ± 12.1 [‡]	51.9 ± 11.7
Sex (M/F)	16/19	229/299	37/71
Serum K ⁺ (mmol/L)	2.5 ± 0.3* ^{†‡}	2.7 ± 0.5 [‡]	3.8 ± 0.2
Serum Mg ²⁺ (mmol/L)	0.5 ± 0.2* ^{†‡}	0.9 ± 0.1	0.9 ± 0.1
Renin activity (ng/mL/h)	12.00 (12.0, 12.0)* ^{†‡}	0.1 (0.1, 0.3)	0.1 (0.1, 0.2)
Angiotensin II (ng/L)	110.7 (88.3, 177.4)* ^{†‡}	57.8 (48.1, 68.3)	57.8 (51.8, 66.0)
Aldosterone (ng/dL)	20.8 (15.7, 28.8)* ^{†‡}	30.2 (21.3, 38.6) [‡]	16.8 (14.3, 20.6)
TSH (mU/L)	2.4 (1.8, 4.8)	2.6 (1.7, 4.0)	2.3 (1.5, 3.2)
TGAb (positive/N)	2/20	21/202	6/33
TPOAb (positive/N)	3/23	26/211	5/33
TRAb (positive/N)	0/19	7/128	0/23

GS: Gitelman syndrome; PA: primary aldosteronism; serum K⁺: serum potassium; TSH: thyroid-stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; TPOAb: thyroid peroxidase antibody; TGAb: thyroglobulin antibody; TRAb: thyrotropin receptor antibody. [†]*P* < 0.05 compared with hypokalemic PA; [‡]*P* < 0.05 compared with normokalemic PA; **P* < 0.05 compared across groups.

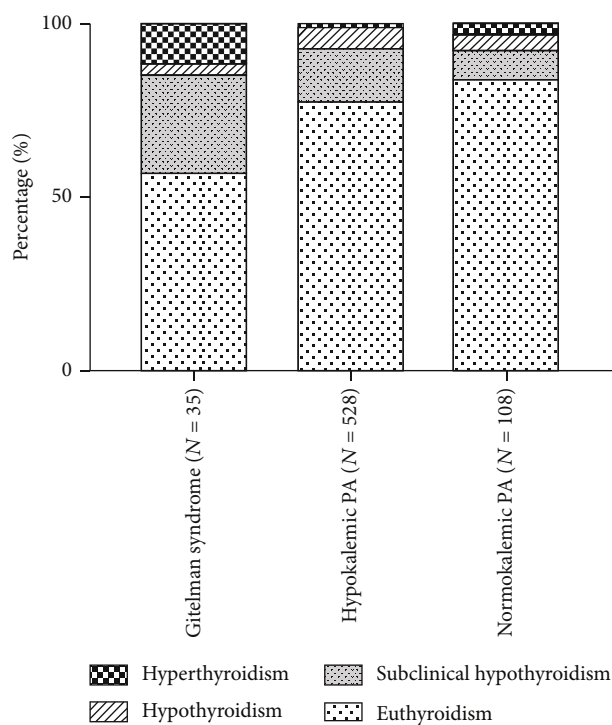


FIGURE 1: Distribution of thyroid function among the three groups.

significantly different than that in the normokalemic PA group and the hypokalemic PA group. No significant difference was observed in the distribution of thyroid function between the hypokalemic PA group and the normokalemic PA group. The probable explanations for this finding might be that (1) the hypokalemia in the GS group was congenital, while in the PA group, it was acquired. Whether sustained inherited hypokalemia affects thyroid function in GS patients requires further study; or (2) other factors instead of hypokalemia affected thyroid function in these GS patients.

The GS patients also exhibited hypomagnesemia. In animal experiments, thyroid-deficient animals conserved magnesium much more efficiently than rats with either euthyroidism or hyperthyroidism, although the serum magnesium levels in thyroid-deficient rats were similar to those in euthyroid rats [16]. Studies have shown that patients with hyperthyroidism had lower levels of serum Mg²⁺ than patients with euthyroid function [17, 18]. The use of methimazole for the treatment of hyperthyroidism due to GD leads to an increase in serum Mg²⁺ concentration [18]. In our study, 30 (85.7%) GS patients exhibited hypomagnesemia. We compared the occurrence of thyroid dysfunction between the hypomagnesemia group and the normomagnesemia group. Nevertheless, no significant difference was found. This negative result still requires further confirmation by studies with larger sample sizes.

It has also been shown that the rat thyroid expresses the angiotensin II receptor subtype 1, AT1, but not the other subtype, AT2 [19]. Angiotensin II acts on AT1 to produce aldosterone. GS patients have high levels of angiotensin II, which might affect thyroid function by acting on AT1 receptors in thyroid cells. We compared the rate of thyroid dysfunction in GS patients in the high angiotensin II and low angiotensin II groups (divided by the median value) and found no difference in thyroid dysfunction between these two groups.

Patients with GS and Sjögren's syndrome (SS) have been reported in the literature [20–23]. In these patients, both acquired [20] and inherited GS [21–23] were reported. Kim et al. reported a case of acquired GS associated with primary SS and suggested the presence of circulating autoantibodies to sodium-chloride cotransporter (NCCT), which led to GS [23]. SS and AITDs may frequently coexist in clinical practice [24]. In a recent study of the characteristics of SS in a Chinese population, 332 (11.1%) patients had thyroid disease, including hyperthyroidism (1.2%), hypothyroidism (6.0%), and subacute thyroiditis (3.9%) [25]. In our study, we did not find manifestations of SS in any of the 35 GS patients. Since a relationship among GS, SS, and thyroid disease has been

reported, we still need to exclude SS in GS patients in future studies.

One strength of this study was that we analyzed thyroid function in a cohort of GS patients, which is different from previous case reports. Another strength was that we included a large sample size of hypokalemic PA and normokalemic PA patients as control groups, which helped us determine the impact of hypokalemia on thyroid dysfunction in GS patients. Through a comparison with PA, which is also a hypokalemic disease, we did not find that hypokalemia affected thyroid function in GS patients.

The present study also had some limitations. TRAb was detected in only 19 (54.3%) GS patients, TGAb was detected in 20 (57.1%) GS patients, and TPOAb was detected in 23 (65.7%) GS patients. Therefore, we could not identify whether high thyroid dysfunction in GS patients was due to AITD. Zhou et al. summarized the data of 18 patients with GS complicated by AITD from nine papers and found that 13 had GD, 3 had Hashimoto's thyroiditis (HT), and two had antibody-positive AITD [3]. However, case reports cannot reflect real-world situations. In our study, we did not find that the positive rates of TPOAb and TGAb were related to thyroid dysfunction in GS patients. We speculated that thyroid dysfunction in GS patients was caused by factors other than AITD. However, additional studies are needed to clarify the detailed mechanisms of thyroid dysfunction in GS patients.

In conclusion, the situation of GS patients may be complicated by thyroid dysfunction. Thyroid dysfunction is more common in GS patients than in PA patients, and the risk of thyroid dysfunction is higher in female GS patients than in male patients.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no competing interests.

Authors' Contributions

Hong Zhou and Yan Ren contributed equally to this manuscript.

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References

- [1] I. Kurtz, "Molecular pathogenesis of Bartter's and Gitelman's syndromes," *Kidney International*, vol. 54, no. 4, pp. 1396–1410, 1998.
- [2] S. Liu, J. Ke, B. Zhang, C. Yu, Y. Feng, and D. Zhao, "A novel compound heterozygous variant of SLC12A3 gene in a pedigree with gitelman syndrome co-existent with thyroid dysfunction," *Endocrine Practice*, vol. 24, no. 10, pp. 889–893, 2018.
- [3] H. Zhou, X. Liang, Y. Qing et al., "Complicated Gitelman syndrome and autoimmune thyroid disease: a case report with a new homozygous mutation in the SLC12A3 gene and literature review," *BMC Endocrine Disorders*, vol. 18, no. 1, p. 82, 2018.
- [4] N. Aoi, T. Nakayama, Y. Tahira et al., "Two novel genotypes of the thiazide-sensitive Na-Cl cotransporter (SLC12A3) gene in patients with Gitelman's syndrome," *Endocrine*, vol. 31, no. 2, pp. 149–153, 2007.
- [5] C. Z. D. Molin and D. J. Trevisol, "Persistent severe hypokalemia: Gitelman syndrome and differential diagnosis," *Brazilian Journal of Nephrology*, vol. 39, no. 3, pp. 337–340, 2017.
- [6] A. Vijayakumar, G. Ashwath, and D. Thimmappa, "Thyrotoxic periodic paralysis: clinical challenges," *Journal of Thyroid Research*, vol. 2014, Article ID 649502, 6 pages, 2014.
- [7] N. Kadeeja, N. Senthilnathan, S. Viswanathan, and R. Aghoram, "Sporadic hypothyroidism-related hypokalemic paralysis: diagnosis in a resource-poor setting," *Journal of Family Medicine and Primary Care*, vol. 6, no. 4, pp. 862–864, 2017.
- [8] U. Sinha, N. Sengupta, K. Sinharay, and P. K. Sahana, "Recurrent hypokalemic paralysis: an atypical presentation of hypothyroidism," *Indian Journal of Endocrinology and Metabolism*, vol. 17, no. 1, pp. 174–176, 2013.
- [9] A. Blanchard, D. Bockenhauer, D. Bolignano et al., "Gitelman syndrome: consensus and guidance from a kidney disease: improving global outcomes (KDIGO) controversies conference," *Kidney International*, vol. 91, no. 1, pp. 24–33, 2017.
- [10] J. W. Funder, R. M. Carey, F. Mantero et al., "The management of primary aldosteronism: case detection, diagnosis, and treatment: an endocrine society clinical practice guideline," *The Journal of Clinical Endocrinology and Metabolism*, vol. 101, no. 5, pp. 1889–1916, 2016.
- [11] J. R. Garber, R. H. Cobin, H. Gharib et al., "Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association," *Endocrine Practice*, vol. 18, no. 6, pp. 988–1028, 2012.
- [12] X. Liu, C. Zhang, Z. Meng et al., "Waist circumference and subclinical thyroid dysfunction in a large cohort of Chinese men and women," *Endocrine Practice*, vol. 24, no. 8, pp. 733–739, 2018.
- [13] G. J. Canaris, N. R. Manowitz, G. Mayor, and E. C. Ridgway, "The Colorado thyroid disease prevalence study," *Archives of Internal Medicine*, vol. 160, no. 4, pp. 526–534, 2000.
- [14] J. W. Hong, J. H. Noh, and D. J. Kim, "Association between subclinical thyroid dysfunction and depressive symptoms in the Korean adult population: the 2014 Korea National Health and Nutrition Examination Survey," *PLoS One*, vol. 13, no. 8, article e0202258, 2018.
- [15] J. Fujimura, K. Nozu, T. Yamamura et al., "Clinical and genetic characteristics in patients with Gitelman syndrome," *Kidney International Reports*, vol. 4, pp. 119–125, 2018.
- [16] C. McCaffrey and G. A. Quamme, "Effects of thyroid status on renal calcium and magnesium handling," *Canadian Journal of Comparative Medicine*, vol. 48, no. 1, pp. 51–57, 1984.
- [17] R. Moncayo and H. Moncayo, "The WOMED model of benign thyroid disease: acquired magnesium deficiency due to physical and psychological stressors relates to dysfunction of oxidative phosphorylation," *BBA Clinical*, vol. 3, pp. 44–64, 2014.

- [18] M. Klatka, E. Grywalska, M. Partyka, M. Charytanowicz, and J. Rolinski, "Impact of methimazole treatment on magnesium concentration and lymphocytes activation in adolescents with Graves' disease," *Biological Trace Element Research*, vol. 153, no. 1-3, pp. 155–170, 2013.
- [19] M. Montiel and E. Jiménez, "Characterization of angiotensin II receptors (binding and mRNA) in the rat thyroid gland," *Journal of Molecular Endocrinology*, vol. 20, no. 3, pp. 299–304, 1998.
- [20] E. Mishima, T. Mori, E. Sohara, S. Uchida, T. Abe, and S. Ito, "Inherited, not acquired, Gitelman syndrome in a patient with Sjögren's syndrome: importance of genetic testing to distinguish the two forms," *CEN Case Reports*, vol. 6, no. 2, pp. 180–184, 2017.
- [21] Y. C. Chen, W. C. Yang, A. H. Yang, S. H. Lin, H. Y. Li, and C. C. Lin, "Primary Sjögren's syndrome associated with Gitelman's syndrome presenting with muscular paralysis," *American Journal of Kidney Disease*, vol. 42, no. 3, pp. 586–590, 2003.
- [22] X. Gu, Z. Su, M. Chen, Y. Xu, and Y. Wang, "Acquired Gitelman syndrome in a primary Sjögren syndrome patient with a SLC12A3 heterozygous mutation: a case report and literature review," *Nephrology (Carlton)*, vol. 22, no. 8, pp. 652–655, 2017.
- [23] Y. K. Kim, H. C. Song, W. Y. Kim et al., "Acquired Gitelman syndrome in a patient with primary Sjögren syndrome," *American Journal of Kidney Disease*, vol. 52, no. 6, pp. 1163–1167, 2008.
- [24] C. Baldini, F. Ferro, M. Mosca, P. Fallahi, and A. Antonelli, "The association of Sjögren syndrome and autoimmune thyroid disorders," *Frontiers in Endocrinology (Lausanne)*, vol. 9, p. 121, 2018.
- [25] D. Xu, S. Zhao, Q. Li et al., "Characteristics of Chinese patients with primary Sjögren's syndrome: preliminary report of a multi-centre registration study," *Lupus*, vol. 29, no. 1, pp. 45–51, 2020.