Clinical and Genetic Factors Associated With Thiazide-Induced Hyponatremia

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Abstract: Thiazide diuretics are associated with an increased risk of hyponatremia. The aim of this study was to investigate possible predictors of thiazide-induced hyponatremia. A total of 48 patients admitted to the ward or to the emergency department due to severe thiazide-induced hyponatremia (Na < 125 mEq/L) were enrolled in our study as the case group. Another 211 hypertensive patients with normal sodium levels after treatment with thiazide diuretics were selected as the control group. Twelve tag single nucleotide polymorphism markers were selected from the Potassium Channel, Inwardly Rectifying Subfamily J, Member 1 (KCNJ1) gene: rs1231254, rs2238009, rs1148058, rs675482, rs673614, rs12795437, rs2855800, rs2509585, rs3016774, rs881333, rs4529890, and rs7116606. Clinical and genetic parameters between patients with thiazide-induced hyponatremia and the control group were compared. Logistic regression was used to analyze data.

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The patients with thiazide-induced hyponatremia were older (P < 0.001), predominantly female (P = 0.008), had a lower mean body mass index (BMI) (P < 0.001), and more commonly used angiotensin II receptor antagonist (P < 0.001) and spironolactone (P = 0.007) compared with the control groups. Analysis with multivariate logistic regression revealed that age (odds ratio [OR], 1.13; 95% confidence interval [CI], 1.08–1.19, P < 0.001), female gender (OR, 4.49; 95% CI, 1.54–13.11; P = 0.006), BMI (OR, 0.80; 95% CI, 0.69–0.93, P = 0.003), and KCNJ1 rs2509585 C/T or T/T polymorphisms (OR, 5.75; 95% CI, 1.25–24.65, P = 0.03) were independent predictors for thiazide-induced hyponatremia.

Older female patients with lower BMIs and KCNJ1 rs2509585 C/T or T/T polymorphisms were more likely to develop thiazide-induced hyponatremia.

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INTRODUCTION

Thiazide diuretics are one of the most widely recommended first-line therapies for hypertension. Evidence from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial and other pivotal hypertension studies has suggested that thiazide-type diuretics significantly reduce stroke and cardiovascular events. However, there are concerns that thiazide diuretics may be linked to unfavorable side effects, such as new-onset of diabetes and electrolyte imbalance. Hypotension is a typical complication after thiazide diuretic treatment and is a potential cause of morbidity and mortality. This raises the question of what subgroup of patients is more susceptible to the adverse effects of this class of diuretics.

The Potassium Channel, Inwardly Rectifying Subfamily J, Member 1 (KCNJ1) gene encodes the renal outer medullary potassium channel (ROMK), which is highly expressed in the apical surface of epithelial cells in the thick ascending limb (TAL) and cortical collecting duct (CCD) of the kidney. Loss-of-function mutations in the human ROMK cause renal Na+ wasting. Whether, however, there is a link between genetic variation of KCNJ1 and thiazide-induced hyponatremia remains unknown.

Given the clinical recommendation of thiazide diuretics, especially for elderly hypertensive and resistant hypertensive patients, there should be careful monitoring of the incidence of hyponatremia after thiazide diuretic treatment. However,
clinical information concerning which patients are more susceptible to thiazide-induced hyponatremia is not conclusive, and the impact of genetic factors is unknown. For these reasons, this study aimed to investigate potential clinical and genetic predictors of hyponatremia following thiazide diuretic treatment. The results may support the individualization of anti-hypertensive treatment with thiazide diuretics and thus help prevent thiazide-induced hyponatremia.

MATERIALS AND METHODS

Patients

All patients who were sent to the emergency department or admitted to the hospital for hyponatremia at Taipei Veterans General Hospital, Taipei, Taiwan, were identified by computerized hospital registries. The cases of hyponatremia were coded according to the International Classification of Disease, Ninth Revision (ICD-9) 276.1. Thiazide-induced hyponatremia diagnosis was based on a history of thiazide diuretic use and a general absence of other factors known to impair water excretion. Patients with other possible factors known to impair water excretion, such as syndrome of inappropriate antidiuretic hormone secretion, heart failure, and thyroid or adrenocortical insufficiency, were excluded. Besides, patients presented with unstable vital signs or acute illness due to cardiovascular disease, infectious disease, malignancy, trauma, surgical condition, and other major systemic diseases were also excluded. We defined and included cases of thiazide-induced hyponatremia by taking histories and using systemic chart review. Furthermore, only patients who were admitted to the ward or sent to the emergency department due to severe thiazide-induced hyponatremia (Na < 125 mmol/L) were enrolled in our study. The control group was selected from those hypertensive patients who were prescribed thiazides on an out-patient basis at our hospital and had normal sodium levels after thiazide diuretic use.

All patients were evaluated at the hypertensive clinics of the hospital. Comprehensive histories and physical check-ups were conducted by a hypertension specialist. The following patient data were then collected: office blood pressure, body mass index (BMI), waist and hip circumference, and blood sampling. The study protocol was approved by the ethics committee of the hospital. All of the subjects agreed to participate and provided informed consent after being informed about the nature and purpose of the study.

Laboratory Measurements

Whole blood samples were drawn by venipuncture from the patients. The blood samples were centrifuged and the serum/plasma fraction was stored at −70 to −80 °C until it was thawed for analysis. Biochemical variables, including blood urea nitrogen (BUN), creatinine, sodium, and potassium, were measured using a dry multilayer analytic slide method in the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film Corporation, Minato-Ku, Tokyo, Japan).

Selection of Candidate Gene and Genotyping

This study evaluated the KCNJ1 gene. Single nucleotide polymorphisms (SNPs) of the KCNJ1 gene were selected using the HapMap SNP Database (http://hapmap.ncbi.nlm.nih.gov) and tag SNPs with minor allele frequencies >0.05 were chosen as the genotyping markers. Twelve tag SNPs from the KCNJ1 gene were investigated rs1231254, rs2238009, rs1148058, rs675482, rs673614, rs12795437, rs2855800, rs2509585, rs3016774, rs881333, rs4529890, and rs7116606.

Genomic DNA from peripheral white cells was isolated using the phenol/chloroform extraction method. Genotyping was carried out using matrix-assisted laser desorption ionization time-of-flight and mass spectrometry (Sequenom, MassARRAY, San Diego, CA) at the Academia Sinica National Genotyping Center in Taiwan. Automated genotype calling was performed, and the data were analyzed using Sequenom Typer software. SAS/Genetics software (Version 9.3, SAS Inc., Cary, NC) with a haplotype procedure was used to estimate haplotypes for the selected SNPs.

Power Calculation

Under the scenarios described below, the power of the genetic association study was calculated using the Genetic Power Calculator.20 We assumed that the prevalence of thiazide-induced hyponatremia was between 1% and 5% in a dominant-effect disease model. Given a genetic relative risk of 5 and a disease allele frequency of 0.1 to 0.2, the power of our analysis was 0.990 to 1.000. The power was increased to 0.997 to 1.000 when the genetic relative risk was increased to 6.

Statistical Analysis

All data were expressed using frequency (percentage), mean ± standard deviation, or median with interquartile ranges. Parametric continuous data (age, waist circumference, hip circumference, waist-hip ratio, height, body weight, BMI, BUN, Cr, and K) between patients with thiazide-induced hyponatremia and the control group were compared using Student’s t-test. Nonparametric data (Na) between patients with thiazide-induced hyponatremia and the control group were compared using the Mann–Whitney U test. Categorical variables were analyzed using Chi-square tests or Fisher Exact tests. Genotype frequencies between the cases and the controls in models of inheritance (additive model, recessive model, or dominant models) were compared. The associations were analyzed using Fisher Exact tests and rank-ordered according to the lowest P-value in these models. Bonferroni correction was applied for the multiple comparisons. Multivariate analysis was examined by logistic regression. The variables considered significant in the univariate analysis (P < 0.05) were entered into a multivariate logistic regression model. The logistic regression analyses were used to examine associations between haplotypes and risk of hyponatremia. Statistical analysis was performed utilizing SPSS software (Version 15.0, SPSS Inc., Chicago, IL).

RESULTS

Patients

A total of 48 patients who were admitted to the ward or sent to the emergency department due to severe hyponatremia after thiazide diuretic use were enrolled. Among these patients, 39 patients (81.3%) took hydrochlorothiazide, 7 patients (14.6%) took indapamide, and 2 patients (4.2%) took metolazone. The mean serum sodium level was 115.5 ± 7.1 mmol/L. Another 211 hypertensive patients who had been prescribed thiazides and maintained normal sodium levels (142.0 ± 2.4 mmol/L) were selected as the control group.

Table 1 compares the baseline characteristics of the patients with thiazide-induced hyponatremia to those of the control group. The patients with thiazide-induced hyponatremia were older (77.5 ± 9.2 versus 53.9 ± 15.4 years, P < 0.001),
TABLE 1. Baseline Characteristics of the Patients With and Without Thiazide-Induced Hyponatremia

| Baseline characteristics                  | Thiazide-Induced Hyponatremia (n = 48) | Control (n = 211) | P-Value |
|------------------------------------------|----------------------------------------|-------------------|---------|
| Age, years                               | 77.5 ± 9.2                             | 53.9 ± 15.4       | <0.001  |
| Female, n, %                             | 27 (56.3%)                             | 75 (35.5%)        | 0.008   |
| Waist circumference, cm                  | 88.1 ± 11.3                            | 90.8 ± 11.2       | 0.21    |
| Hip circumference, cm                    | 96.3 ± 4.4                             | 100.2 ± 8.4       | 0.03    |
| Waist-hip ratio                          | 0.95 ± 0.06                            | 0.90 ± 0.08       | 0.005   |
| Height, cm                               | 159.0 ± 9.0                            | 163.9 ± 9.0       | 0.002   |
| BW, kg                                   | 59.9 ± 10.8                            | 73.0 ± 14.6       | <0.001  |
| BMI, kg/m²                               | 23.6 ± 3.9                             | 27.0 ± 4.0        | <0.001  |
| Concomitant medication                   |                                        |                   |         |
| ACEI, n, %                               | 5 (10.4%)                              | 9 (4.3%)          | 0.09    |
| ARB, n, %                                | 28 (58.3%)                             | 54 (25.6%)        | <0.001  |
| Alpha-blocker, n, %                      | 4 (8.3%)                               | 16 (7.6%)         | 0.86    |
| Beta-blocker, n, %                       | 19 (39.6%)                             | 99 (46.9%)        | 0.36    |
| CCB, n, %                                | 26 (54.2%)                             | 84 (39.8%)        | 0.07    |
| Spironolactone, n, %                     | 7 (14.6%)                              | 9 (4.3%)          | 0.007   |
| Laboratory study                         |                                        |                   |         |
| BUN, mg/dL                               | 17.4 ± 12.8                            | 13.8 ± 5.0        | 0.01    |
| Cr, mg/dL                                | 1.2 ± 0.8                              | 0.9 ± 0.3         | 0.001   |
| Na, mmol/L                               | 115.5 ± 7.1                            | 142.0 ± 2.4       | <0.001  |
| K, mmol/L                                | 3.4 ± 0.8                              | 4.0 ± 0.5         | <0.001  |

ACEI = angiotensin converting enzyme, ARB = angiotensin II receptor antagonist, BMI = body mass index, BUN = blood urea nitrogen, BW = body weight, CCB = calcium channel blocker, Cr = creatinine, K = potassium, Na = sodium.

predominantly female (56.3% versus 35.5%, P = 0.008), had higher waist-hip ratios (0.95 ± 0.06 versus 0.90 ± 0.08, P = 0.005), were lower in height (158.0 ± 9.0 cm versus 163.9 ± 9.0 cm, P = 0.002), were lower in body weight (59.9 ± 10.8 versus 73.0 ± 14.6 kg, P < 0.001), and had lower BMIs (23.6 ± 3.9 versus 27.0 ± 4.0 kg/m², P < 0.001) when compared with the control group. The patients with thiazide-induced hyponatremia used more angiotensin II receptor antagonist (58.3% versus 25.6%, P < 0.001) and spironolactone (14.6% versus 4.3%, P = 0.007) compared with the control group (Table 1).

In addition to the lower level of sodium (P < 0.001), these patients also had a lower level of potassium (3.4 ± 0.8 versus 4.0 ± 0.5 mmol/L, P < 0.001), and a higher level of blood urea nitrogen (17.4 ± 12.8 versus 13.8 ± 5.0 mg/dL, P = 0.01) and creatinine (1.2 ± 0.8 versus 0.9 ± 0.3 mg/dL, P = 0.001) than the control group (Table 1).

Thiazide-Induced Hyponatremia and KCNJ1 Gene

Table 2 summarizes the genetic information of the 12 SNPs from the KCNJ1 gene. All of these SNPs passed the Hardy–Weinberg equilibrium test. Minor allele frequency and genotype distribution of 7 SNPs of KCNJ1 were different in the patients with thiazide-induced hyponatremia compared with the control group (Table 2). There were more KCNJ1 rs1231254 A/T or T/T (case versus control = 44.7% versus 23.4%, P = 0.003), rs675482 C/C or C/T (case versus control = 84.8% versus 68.8%, P = 0.03), rs673614 A/G or G/G (case versus control = 85.4% versus 68.1%, P = 0.02), rs12795437 C/C (case versus control = 97.9% versus 85.0%, P = 0.02), rs2509585 C/T or T/T (case versus control = 40.4% versus 20.0%, P = 0.003), rs3016774 A/G or G/G (case versus control = 40.4% versus 24.9%, P = 0.03), and rs4529890 A/G or A/A (case versus control = 40.4% versus 25.2%, P = 0.04) in the patients with thiazide-induced hyponatremia than in the controls (Table 2). After Bonferroni correction, only rs1231254 and rs2509585 were shown to be significantly different between the 2 groups (Table 2).

Multivariate Analysis

The clinical parameters (age, sex, BMI, and the concomitant use of angiotensin II receptor antagonist and spironolactone) and genetic parameters (KCNJ1 rs1231254 and KCNJ1 rs2509585 polymorphisms) that were significantly different between the patients with thiazide-induced hyponatremia and the controls were entered into a multivariate logistic regression model. Since both BMI and waist hip ratio are obesity indexes, we used BMI in the model. Analysis with multivariate logistic regression revealed that age (odds ratio [OR], 1.13; 95% confidence interval [CI], 1.08–1.19, P < 0.001), female sex (OR, 4.49; 95% CI, 1.54–13.11, P = 0.006), BMI (OR, 0.80; 95% CI, 0.69–0.93, P = 0.003), and KCNJ1 rs2509585 C/T or T/T polymorphisms (OR, 5.75; 95% CI, 1.25–26.45, P = 0.03) were independent predictors for thiazide-induced hyponatremia (Table 3).

KCNJ1 Halotypes and Thiazide-Induced Hyponatremia

From the haplovie-generated linkage disequilibrium (LD) plot of KCNJ1 SNPs (Figure 1), there were 3 LD blocks distributed throughout the KCNJ1. The most significant SNPs from each LD block were selected. The haplotypes were constructed for rs1231254, rs2509585, and rs4529890 in this order. The degree of LD for these 3 SNPs is shown in Figure 1. There were 4 frequent haplotypes that cumulatively accounted for
98% of the observed haplotypes. ORs of each haplotype for the risk of thiazide-induced hyponatremia are shown in Table 4. Patients with T-T-A haplotype had an increased risk of thiazide-induced hyponatremia (OR, 2.27; 95% CI, 1.25–4.13, \( P = 0.015 \)) (Table 4).

### DISCUSSION

The main findings of the study are that both clinical and genetic factors were associated with thiazide-induced hyponatremia. In addition to older age, female sex, and lower BMI, \( KCNJ1 \) rs2509585 C/T or T/T polymorphisms were also found to be independent predictors for thiazide-induced hyponatremia. Genetic studies of thiazide-induced hyponatremia are still lacking, making this the first to report genetic markers of thiazide-induced hyponatremia.

Thiazide-induced hyponatremia is a common complication following thiazide treatment. Byatt et al recorded an
estimated incidence of 11% in 1 series of 114 geriatric patients, making it a potential cause of morbidity and mortality.11–13 Sonnenblick et al.12 reported 12 attributable deaths in a group of 129 cases of severe diuretic-related hyponatremia found by reviewing medical literature. Liamis et al.13 reported that even mild electrolyte disorders were associated with mortality. Since thiazide diuretics are one of the most widely recommended first-line therapies for hypertension, it is important to identify patients who are more susceptible to thiazide-induced hyponatremia.

The KCNJ1 gene encodes the ROMK, which is classified as an adenosine triphosphate-sensitive inward-rectifier potassium channel (Kir1.1 or KCNJ1). ROMK is highly expressed in the apical surface of epithelial cells in the TAL and CCD of the kidney.14–16 At the TAL, ROMK participates in a process critical for proper functioning of the furosemide-sensitive Na+/K+/Cl− cotransporter. This is the rate-determining step for salt reabsorption in the TAL.18 Previous studies using ROMK−/− mice demonstrated that 80% of NaCl absorption in the TAL was ROMK dependent.19 At the CCD, ROMK activity is tightly coupled to the amiloride-sensitive epithelial sodium channel, which is the final sodium reabsorption pathway in nephrons. In this study, KCNJ1 polymorphisms were found to be associated with thiazide-induced hyponatremia. The possible mechanism for this association may be related to the altered function of ROMK, which substantially contributes to salt reabsorption in the TAL and CCD. However, further studies are needed to confirm these findings.

![FIGURE 1. Haploview-generated LD plot of KCNJ1 SNPs. We investigated 12 SNPs from the KCNJ1 gene, including rs1231254, rs2238009, rs1148058, rs675482, rs673614, rs12795437, rs2855800, rs2509585, rs3016774, rs881333, rs4529890, and rs7116606. There were 3 LD blocks distributed throughout the KCNJ1. LD = linkage disequilibrium, SNP = single-nucleotide polymorphisms.](image-url)
Clinical parameters that have been previously found to be associated with thiazide-induced hyponatremia are age, female sex, lower body weight, hypokalemia, and concurrent use of other medications that impair water excretion. However, these reported findings remain controversial because they were derived from case reports or case series that were limited by small sample sizes and lack of comparison groups.

Although a previous study showed that advanced age was not associated with higher hyponatremia prevalence, the current study, as well as others, found that more elderly patients were at greater risk to develop thiazide-induced hyponatremia. A number of hypotheses have been proposed to explain this correlation. Clark et al reported that healthy elderly subjects do not excrete free water as efficiently as younger people do. Elderly subjects with previous histories of thiazide-induced hyponatremia, and who have impaired urinary dilution capacity are more susceptible to thiazide-induced hyponatremia. Among these explanations, the most probable one is blunted prostaglandin synthesis, which may result from aging or the propensity of the elderly for polypharmacy, including nonsteroidal antiinflammatory agents. The predominance of thiazide-induced hyponatremia in elderly patients suggests that the decision to treat this group with thiazide should be made cautiously.

This study found a greatly increased risk of thiazide-induced hyponatremia in the elderly with lower BMI, which is consistent with previous studies. Since plasma sodium level is determined by the ratio between the total quantity of solutes and total body water, it is reasonable to assume that sodium concentration might change to a greater degree in subjects with smaller body sizes and less total body water.

The combination use of thiazide diuretics and angiotensin- converting enzyme or angiotensin II receptor antagonist was associated with thiazide-induced hyponatremia in previous studies. Rastogi et al reported that angiotensinogen converting enzyme use independently correlated with an increased risk of thiazide-induced hyponatremia. Kim et al reported 2 cases of severe hyponatremia following angiotensin II receptor antagonist combined with thiazide treatment. Similarly, Yamada et al reported 3 cases of severe hyponatremia in patients who received this therapy combination. Nakayama et al reported that the addition of low-dose thiazide diuretics to angiotensin II receptor antagonist treatment caused significant reduction in sodium level in elderly Japanese subjects. In this study, patients with thiazide-induced hyponatremia used more angiotensin II receptor antagonist than the control group. However, the combination use of angiotensin II receptor antagonist or other antihypertensives with thiazide treatment did not increase the risk of thiazide-induced hyponatremia after adjusting for other confounding factors.

There are some limitations that should be carefully considered in the current study. First, the sample size of patients with thiazide-induced hyponatremia was small because only patients with severe hyponatremia (Na < 125 mmol/L) were enrolled. We assumed that the prevalence of thiazide-induced hyponatremia was between 1% and 5% in a dominant-effect disease model. Given a genetic relative risk of 5.747, and a disease allele frequency of 0.128, the power of this study is very high (0.999–1.000). Second, although efforts were made to exclude other possible factors known to impair water excretion, such as syndrome of inappropriate antidiuretic hormone secretion, heart failure, and thyroid or adrenocortical insufficiency, there may have been other potential confounding factors not considered in the study. Third, the clinical parameters of the case and the control group were not matched. However, they allowed us to identify both the clinical and genetic predictors of thiazide-induced hyponatremia, and this genetic information was further confirmed by multivariate analysis controlling clinical factors. Fourthly, by a candidate genetic approach, we analyzed 12 tag SNPs in the KCNJ1 gene in the study, but comprehensive identification of the genetic markers for thiazide-induced hyponatremia may require future genome-wide association studies with large sample sizes. Finally, this study was mainly conducted using the hypertensive patients of the Han Chinese population in Taiwan. Further studies are needed to confirm these findings in other populations.

CONCLUSION

Patients of older age, female sex, lower BMI, and KCNJ1 rs2509585 C/T or T/T polymorphism were prone to developing severe thiazide-induced hyponatremia. This is the first study to report the genetic predictor of thiazide-induced hyponatremia. This study highlights the potential risk factors for symptomatic thiazide-induced hyponatremia and increases the understanding of the pathophysiology and awareness of thiazide treatment complications. With the current trend of thiazide diuretic usage in the treatment of hypertension, increased incidence of hyponatremia can certainly be expected in the future. The findings of the present study may help clinicians to better identify patients who are at risk for thiazide-induced hyponatremia in order to prevent the incidence of adverse reactions to diuretic therapy.

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