Analysis of Clinical Factors for the Determination of Optimal Serum Level of Thyrotropin After Recombinant Human Thyroid-Stimulating Hormone Administration

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Abstract

Purpose To determine the optimal levels of thyroid-stimulating hormone (TSH) levels after administration of recombinant human TSH (rhTSH) to patients with differentiated thyroid cancer (DTC), we have analyzed the clinical parameters that affected the degree of the increase in serum levels of TSH.

Methods We retrospectively analyzed 276 patients with differentiated thyroid cancer (DTC), post-thyroidectomy and remnant ablation. Pearson's correlation coefficient test was used to evaluate the correlation between serum levels of TSH after rhTSH stimulation and various clinical factors, including age, sex, height, weight, body mass index (BMI), body surface area (BSA), serum blood urea nitrogen, creatinine, and estimated glomerular filtration rate (GFR). Linear regression analysis was used to determine the predictors of the degree of increase in serum TSH level after rhTSH stimulation.

Results After the rhTSH injections, all subjects achieved TSH levels of >30 $\mu\text{U/mL}$, with a mean of 203.8 ± 83.4 $\mu\text{U/mL}$. On univariate analysis, age ($r=0.255$) and serum creatinine ($r=0.169$) level were positive predictors for higher levels of serum TSH after rhTSH stimulation, while weight ($r=-0.239$), BMI ($r=-0.223$), BSA ($r=-0.217$), and estimated GFR ($r=-0.199$) were negative predictors. Multiple linear regression analysis revealed that serum creatinine was the most powerful independent predictor for serum levels of TSH, followed by age, BSA, and BMI.

Conclusions An increment in serum TSH after rhTSH stimulation was significantly affected by age, BSA, BMI, and creatinine, with creatinine being the most powerful predictor. By understanding the difference in the increased levels of TSH in various subjects, their dose of rhTSH can be adjusted during scheduling for radioiodine ablation, or during follow-up (recurrence surveillance) after surgery and ablation.

Keywords Recombinant human thyroid-stimulating hormone · RhTSH · Thyrotropin · Differentiated thyroid cancer · Thyroid cancer

Introduction

Recombinant human thyrotropin (rhTSH), which is the thyrotropin alfa subunit, is synthesized using a genetically modified Chinese hamster ovary cell line, and is a valid alternative to thyroid hormone withdrawal (THW) during thyroid remnant ablation in patients who have received thyroidectomy for differentiated thyroid cancers (DTC), such as papillary or follicular cancer [1, 2]. In the follow-up for these patients, rhTSH is used in the preparation for radioiodine whole-body scanning. In addition, it is known that rhTSH-stimulated levels of serum thyroglobulin (Tg) have diagnostic significance in the detection of recurrence or metastasis after surgery and radioiodine ablation. The thyroid-stimulating effects of rhTSH are safe, effective, and can prevent the development of hypothyroidism-related side effects [3–5]. After intramuscular injection of rhTSH (0.9 mg) on 2 successive days (days 1 and 2), serum TSH concentrations typically peak in the following 24 h (day 3), and subsequently decrease considerably until day 5. However, several anthropometric parameters may affect the increase in serum TSH levels after rhTSH injection.

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Unfortunately, no controlled studies have been conducted to determine the levels of endogenous TSH that are needed for radioiodine ablation. Although studies using single-dose exogenous TSH suggest that maximal thyrocyte stimulation occurs at TSH levels between 51 and 82 $\mu\text{U/mL}$, TSH levels $>30\mu\text{U/mL}$ are typically considered adequate to increase the uptake of radioiodine in thyroid tumor cells during radioiodine ablation [6–8]. Thus, the 30 $\mu\text{U/mL}$ level has been accepted as the reference value for assessing the adequacy of TSH stimulation during ablation, or during follow-up after ablation. When two successive doses of rhTSH are administered, the vast majority of subjects achieve TSH levels of $>30\mu\text{U/mL}$, and some patients may reach levels $>500\mu\text{U/mL}$. These results indicate that it may be possible to lower the dose for each injection in some subjects, or that a single dose of rhTSH might be sufficient to achieve TSH stimulation [9]. Interestingly, several anthropometric and demographic parameters, including age, sex, height, body surface area (BSA), lean body mass, and renal function have been reported to influence peak levels of serum TSH after rhTSH injection, although conflicting results have also been reported in various studies [10–14]. Therefore, it is not clear whether the effect of rhTSH is mediated solely by the patient's body composition, or whether different clinical situations, such as ablation of remnant thyroid tissue or diagnostic testing after surgery (followed by radioiodine ablation), may also mediate the effect of rhTSH. Moreover, previous reports have typically evaluated patients from North American and European countries, which have large populations of obese or overweight persons. Subject characteristics inevitably vary among different ethnic populations, and the average body weight and height are higher in occidental populations compared with non-Western populations. Thus, there have been concerns regarding whether the factors that affect the degree of the increase in serum levels of TSH after rhTSH injection are different in occidental populations compared with non-Western populations.

This study was performed to assess the efficacy of rhTSH injections on the peak levels of serum TSH in the Korean population, whose anthropometric parameters are markedly different from those in Western countries. We also evaluated the effects of various demographic and anthropometric parameters, such as age, sex, body weight, height, body mass index (BMI), BSA, serum blood urea nitrogen (BUN) levels, serum creatinine levels, and glomerular filtration rate (GFR) on the levels of serum TSH.

Materials and Methods

Patients

Data of 279 patients who underwent total thyroidectomy due to DTC were collected retrospectively in this study. All

patients underwent diagnostic radioiodine scanning for follow-up or radioiodine remnant ablation under rhTSH stimulation, while receiving TSH-suppressive thyroid hormone substitution. Each patient received two intramuscular injections of rhTSH (0.9 mg) on days 1 and 2, according to the standardized protocol provided by the manufacturer (Genzyme, Cambridge, MA, USA). Blood samples for TSH, BUN, and creatinine testing were taken during the 24 h after the second injection of rhTSH (day 3). In addition, anthropometric and demographic data were collected from each patient at the beginning of the study, including age, sex, height (cm), and weight (kg). Body mass index (BMI) was calculated as weight/height squared (kg/m^2), and BSA (m^2) was calculated using the DuBois formula ($\text{BSA}=0.20247 \times \text{weight} [\text{kg}]^{0.425} \times \text{height} [\text{m}]^{0.725}$) [15]. The GFR (mL/min/1.73 m^2) was estimated using the revised four-variable Modification of Diet in Renal Disease study equation: $\text{GFR}=175 \times [\text{serum creatinine}]^{-1.154} \times [\text{age}]^{-0.203} \times [\text{sex}] \times [\text{race}]$. The factor for sex was set to 0.742 for women and to 1 for men [16], and as all patients were of Asian origin, the factor for race was set to 1.

Two patients enrolled in the study group presented with high serum creatinine levels (1.91 mg/dL and 3.67 mg/dL), which both exceeded the mean creatinine level by more than 3 standard deviations (SDs). In addition, one patient presented with a high estimated GFR value (255.4 mL/min/1.73 m^2), exceeding the mean GFR by more than 3 SDs. Thus, these three outliers were excluded from the statistical analysis, which allowed us to analyze unbiased results in a sample of patients with normal or slightly impaired kidney function. Another one patient had a history of chronic hepatitis C and presented with an abnormal liver enzyme (AST, 89 IU/L; ALT, 179 IU/L), whereas other 275 patients presented with normal liver enzyme and had no history of liver disease. We included this one patient in statistical analysis. Therefore, the data from 276 patients were evaluated in the current study. This study was approved by the institutional review board of our hospital, and the need for written informed consent was waived.

TSH Measurements

Immunoradiometric assay commercial kits were used to measure serum TSH (TSH IRMA; B R A H M S, Hennigsdorf, Germany). In this method, seven calibrators, two controls, and patients' serum samples were incubated in two anti-thyrotropin antibodies (monoclonal, mouse) recognizing different binding sites on the antigen (TSH) are used in excess. One of them was labeled with iodine-125, the other was immobilized on the inner surface of the tube (coated tube system). The tubes were incubated on an orbital shaker (170–250 rpm) for 1 h at room temperature. Afterwards the remaining excess of iodine-125 labeled anti-thyrotropin

antibody was diluted and then completely removed. The tubes were washed twice, and the radioactivity in each tube was measured for 1 min in a gamma counter. TSH assay had a functional sensitivity of 0.07 $\mu\text{U/mL}$.

Statistical Analysis

Data were presented as mean $\pm$ SD. An independent two-sample *t*-test was used to evaluate whether a statistically significant difference existed between the means of the two groups. Univariate analysis was used to estimate the impact of age, sex, weight, height, BMI, BSA, BUN, and creatinine. Linear regression analysis was used to estimate the impact of estimated GFR on peak serum TSH at day 3, and Pearson's correlation coefficient *r* was calculated. Stepwise forward multiple linear regression analysis was used to determine the most powerful factor that affected serum levels of TSH after rhTSH stimulation. MedCalc Statistical Software version 13.2.2 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2014) was used for all statistical calculations, and results were considered statistically significant at *p* values <0.05.

Results

The patients' demographic characteristics are summarized in Tables 1 and 2. The median patient age was 48 years (mean, 47.6 $\pm$ 13.5 years; range, 19–81 years) and 233 patients (84 %) were women. The mean ages for men and women were not different (*p*=0.712). Anthropometric characteristics of the patients that we evaluated included height (160.9 $\pm$ 7.6 cm; range, 147.6–189.2 cm), weight (61.9 $\pm$ 11.1 kg; range, 41.0–99.0 kg), BMI (23.9 $\pm$ 3.5 kg/m²; range, 16.3–36.4 kg/m²), and BSA (1.65 $\pm$ 0.16 m²; range, 1.30–2.12 m²).

An increase in serum TSH of $\geq 30 \mu\text{U/mL}$ was achieved in all patients. The mean peak level of serum TSH on day 3 was 203.8 $\pm$ 83.4 $\mu\text{U/mL}$ (range, 48.6–711.1 $\mu\text{U/mL}$). Dichotomized by median value of serum TSH level of 188.65 $\mu\text{U/mL}$, we could divide into two groups of 138 (50 %) patients who had TSH level of over or under 188.65 $\mu\text{U/mL}$, respectively. There was significant difference in age (50.4 $\pm$ 14.4 years vs. 44.9 $\pm$ 11.9 years; *p*=0.0007), BMI (23.3 $\pm$ 2.8 kg/m² vs 24.4 $\pm$ 4.0 kg/m²; *p*=0.0079), BSA (1.62 $\pm$ 0.15 m² vs 1.67 $\pm$ 0.17 m²; *p*=0.0222), and weight (60.1 $\pm$ 9.4 kg vs 63.7 $\pm$ 12.3 kg; *p*=0.0068) between over and under TSH of 188.65 $\mu\text{U/mL}$ groups. And also, both serum BUN and creatinine seemed to be higher and estimated GFR lower in group with TSH over 188.65 $\mu\text{U/mL}$, although these differences did not reach statistical significance.

Eighty-one (29 %) patients received rhTSH for diagnostic whole-body scanning with radioiodine, and 195 (71 %) received rhTSH for radioiodine remnant ablation after surgery.

When data were classified by the purpose for rhTSH stimulation, the mean TSH in the radioiodine remnant ablation or adjuvant therapy group appeared slight lower compared with that in the diagnostic whole-body scan group, although this difference did not reach statistical significance (199.2 $\pm$ 84.3 $\mu\text{U/mL}$ vs 214.6 $\pm$ 80.7 $\mu\text{U/mL}$; *p*=0.1638) (Fig. 1a). When patients were classified by BMI, 96 (35 %) were obese ($\geq 25 \text{ kg/m}^2$), 62 (22 %) were overweight (25–23 kg/m²), 109 (39 %) were normal (23–18.5 kg/m²), and 9 (3 %) were underweight (<18.5 kg/m²). BMI increased significantly with increasing age (*r*=0.151; *p*=0.0123). Subgroup analyses of the BMI groups revealed that the mean TSH levels were significantly lower in obese patients compared with those in overweight or normal patients (182.1 $\pm$ 73.5 $\mu\text{U/mL}$ vs 214.9 $\pm$ 73.4 $\mu\text{U/mL}$, *p*=0.0068; 182.1 $\pm$ 73.5 $\mu\text{U/mL}$ vs 214.9 $\pm$ 93.5 $\mu\text{U/mL}$, *p*=0.0062, respectively) (Fig. 1b). When patients of each sex were compared, the peak levels of TSH in men (207.5 $\pm$ 74.4 $\mu\text{U/mL}$; range 63.1–379.3 $\mu\text{U/mL}$) were similar to those in women (203.1 $\pm$ 85.1 $\mu\text{U/mL}$, range 48.6–711.1 $\mu\text{U/mL}$, *p*=0.7474) (Fig. 1c).

Univariate linear regression analyses revealed that the peak level of serum TSH was negatively correlated with weight (*r*=−0.239; *p*=0.0001), BMI (*r*=−0.223; *p*=0.0002), BSA (*r*=−0.217; *p*=0.0003), and GFR (*r*=−0.199; *p*=0.0009). In contrast, the peak level of serum TSH was positively correlated with age (*r*=0.255; *p*<0.0001) and creatinine (*r*=0.169; *p*=0.0049) (Fig. 2). Further multiple linear regression analyses for age, weight, BMI, BSA, creatinine, and GFR were performed to assess the independent associations with peak serum TSH. Serum creatinine was the most powerful predictor (standardized β coefficient [β]=0.234; *p*=0.0001), followed by age (β =0.220; *p*=0.0002), BSA (β =−0.141; *p*=0.0198), and BMI (β =−0.126; *p*=0.0370) (Table 3).

Discussion

The use of rhTSH is common during radioiodine ablation of remnant thyroid tissue after surgery, as well as during the assessment for recurrence risk in the follow-up after DTC. Recently, the health insurance providers of various countries (including Korea) have chosen to reimburse the use of rhTSH during thyroid remnant ablation and in radioiodine scanning during follow-up. These changes have resulted in a rapid expansion in the use of rhTSH in many countries, where it has been applied with the same standard dosage and application protocol for rhTSH. However, this dosage and protocol was developed and prepared in Western countries, particularly in the USA, where anthropometric parameters in the general population are markedly different than in the Korean population. We observed wide variability in the degree of the increase in serum levels of TSH, and our peak levels of TSH were far higher than those that have been previously reported

Table 1 The demographic and laboratory characteristics of 276 patients who received recombinant human thyroid stimulating hormone

Characteristics	Mean±SD	Range	N (%)
Age (years)			
Gender	47.6±13.5	19.0–81.0	
Female			233 (84)
Male			43 (16)
Height (cm)	160.9±7.6	147.6–189.2	
Weight (kg)	61.9±11.1	41.0–99.0	
BMI (kg/m ²)	23.9±3.5	16.3–36.4	
<18.5			9 (3)
≥18.5 to <23			109 (39)
≥23 to <25			62 (22)
≥25			96 (35)
BSA (m ²)	1.65±0.16	1.30–2.12	
Serum creatinine (mg/dL)	0.84±0.18	0.46–1.49	
Serum BUN (mg/dL)	11.41±4.13	3.5–27.6	
Estimated GFR (mL/min/1.73 m ²)	81.3±17.6	34.0–155.5	
TSH (μU/mL)	203.8±83.4	48.6–711.1	
Purpose of rhTSH injection			
For ablation	199.2±84.3	48.6–512.6	195 (70.7)
For follow-up (stimulated Tg, DxWBS, etc.)	214.6±80.7	78.3–711.1	81 (29.3)

SD standard deviation, BMI body mass index, BSA body surface area, BUN blood urea nitrogen, GFR glomerular filtration rate, TSH the peak serum thyroid stimulating hormone level on day 3, after intramuscular injections of recombinant human TSH on days 1 and 2

Table 2 Patients' thyroid cancer-related clinicopathological characteristics

Characteristics	N (%)
Histology	
Papillary carcinoma	275 (99.6)
Follicular carcinoma	1 (0.4)
TNM stage	
I	114 (41.3)
II	2 (0.7)
III	125 (45.3)
IV	35 (12.7)
T stage	
T1	61 (22.1)
T2	6 (2.2)
T3	187 (67.8)
T4	22 (8.0)
N stage	
N0	57 (20.7)
N1a	155 (56.2)
N1b	64 (23.2)
M stage	
M0	274 (99.3)
M1	2 (0.7)

rhTSH recombinant human thyroid stimulating hormone, Tg thyroglobulin, DxWBS diagnostic radioiodine whole-body scintigraphy

[10, 11, 13, 14]. Therefore, we speculate that the standard dose of rhTSH can be lowered, or the standard injection protocol can be modified, if the patient has a small height and low body weight, as our results indicate that the levels of peak serum TSH are dependent upon anthropometric parameters. A number of previous studies have also attempted to demonstrate that anthropometric parameters can predict the peak level of TSH after rhTSH administration [10–14], although these were typically performed in Western countries. Thus, we evaluated the influence of a more extensive list of demographic and anthropometric parameters on the peak levels of serum TSH after rhTSH injection in a non-Western population.

Based on our results, serum creatinine (a surrogate marker of renal function) was the most powerful independent predictor of peak levels of serum TSH, although age, BSA, and BMI were also significant predictors. Interestingly, human pituitary TSH is metabolized in the liver, and is also eliminated by the kidneys [17, 18], and therefore it has been suggested that renal function may influence the course of serum TSH clearance over time. Over et al. [13] have reported that the peak levels of TSH on day 3 and day 5 after rhTSH injection were higher in elderly subjects, and that the peak level of TSH was negatively correlated with GFR. They hypothesized that this result was due to decreasing renal clearance in elder subjects. However, this correlation was not significant after multivariate analysis, although this could be influenced by the relatively small number of enrolled patients ($n=112$). Mean serum

Fig. 1 Independent *t*-test analyses of the thyroid stimulating hormone (TSH) levels after recombinant human TSH injections. Patients ($n=276$) were grouped according to (a) the purpose of the rhTSH injection, (b) body mass index (BMI), and (c) sex

creatinine levels in their study (0.7 ± 0.14 mg/dL) were somewhat lower than those in our study (0.84 ± 0.18 mg/dL), which indicates that their study group contained fewer subjects with impaired renal function. Montesano et al. [12] have also tested the impact of renal function on peak levels of TSH, although they too did not find a statistically significant correlation. However, they included only 98 of 311 patients in their subgroup analyses and measured TSH on day 5 after rhTSH injection, which might have affected the accuracy of their analysis. More recently, Hautzel et al. [11] have reported that serum creatinine had the second greatest impact on peak serum TSH levels after rhTSH injection, with BSA having the greatest impact. As predicted, the mean values for weight, height, and BSA (calculated using the DuBois formula with

weight and height) were far higher in their study, compared with those in our patient group (weight, 78.6 ± 19.4 kg vs 61.9 ± 11.1 kg; height, 1.70 ± 0.09 m vs 1.61 ± 0.08 m; BSA, 1.89 ± 0.24 m² vs 1.65 ± 0.16 m²). In addition, their ranges for patient weight, height, and BSA were broader than those in our study (weight, 42–175 kg vs 41–99 kg; height, 1.47–2.02 m vs 1.48–1.89 m; BSA, 1.42–3.01 m² vs 1.30–2.12 m²). Thus, their results may have reflected a higher impact for BSA (vs serum creatinine) compared with that observed in our study. In our study, BUN and estimated GFR (which represents renal function) did not predict the peak levels of TSH after univariate and multivariate analyses. This observation can be attributed to an intrinsic property of the Modification of Diet in Renal Disease formula, which has been reported to provide inaccurate GFR estimations among subjects without renal impairment [19, 20].

Although our study analyzed a more comprehensive list of variables, in a relatively large sample size, our results were similar to those of previous studies for most parameters. For example, our results regarding age corroborated the data of previous reports [11–13]. Over et al. [13] have previously hypothesized that any effects that were apparently exerted by altered renal function, or altered metabolism in fat or lean mass compartments, might ultimately be caused by age-related changes. Our results (supplementary data) partially support this hypothesis, as age significantly correlated with creatinine levels with positive correlation coefficient ($r=0.123$; $p=0.0420$). However, the BMI reflecting fat or lean mass compartments also positively correlated with age ($r=0.151$; $p=0.0123$), whereas the BMI was negatively correlated with serum TSH level. These results mean that the serum creatinine level (renal function) is more influential in correlation between age and serum TSH level than BMI, and is consistent with the final results of this study; creatinine is the most influential factor for peak levels of serum TSH after rhTSH injection. Regarding BSA, our results are in agreement with the results of Vitale et al. [14] and Hautzel et al. [11].

One of the interesting findings of our study is that, there was no difference in the mean levels of serum TSH of the first ablation group and the follow-up group. This result might indicate that serum levels of TSH after rhTSH injection are not influenced by the amount of remnant thyroid tissue or the residual tumor burden of the thyroid cancer, unlike in THW. More importantly, our results indicate that the desired level of serum TSH after rhTSH injection can always be achieved using rhTSH alone. There have been several reports stating that levels of serum TSH are not always sufficiently increased after THW in thyroid cancer patients. Even after several weeks of withdrawal, TSH levels may not increase sufficiently in cases of persistent thyroid hormone production by large thyroid remnants or functionally active metastases, such as hypothalamic or pituitary dysfunction, long-term steroid administration as prophylaxis against tumor compression of key

Fig. 2 Linear regression analyses of the relationship between various parameters and peak serum levels of thyroid stimulating hormone (TSH) after recombinant human TSH injections. The clinical and demographical factors we evaluated were (a) age, (b) weight, (c) body mass index (BMI), (d) body surface area (BSA), (e) serum creatinine, and (f) estimated glomerular filtration rate (eGFR)

anatomical structures, or unusually slow response, particularly among the elderly [21–24].

In our study, mean peak level of serum TSH was distinctively higher ($203.8 \pm 83.4 \mu\text{U/mL}$) than previous studies [10,

11, 13, 14]. These results may have great implications, because some reported that very high levels of serum peak TSH might stimulate persistent tumor masses, although the duration of this action appears to be short [25–27].

Table 3 Multiple linear regression analysis of independent predictors for peak serum levels of thyroid stimulating hormone

Dependent variable	Independent predictors	Standardized β coefficient	t	p
Peak serum TSH	Age	0.220	3.718	0.0002
	BMI	−0.126	−2.096	0.0370
	BSA	−0.141	−2.344	0.0198
	Serum creatinine	0.234	3.955	0.0001

BMI body mass index, BSA body surface area, TSH thyroid stimulating hormone

Therefore, it is important to achieve adequate levels of serum TSH within several days, thereby facilitating an adequate uptake of radioiodine and avoiding an excessive stimulation of the tumor mass. Dichotomized by the median value of serum TSH (188.65 $\mu\text{U/mL}$), age was significantly higher in high TSH ($\geq 188.65 \mu\text{U/mL}$) patients, and BMI, BSA, and weight were significantly lower in those patients. Although it was not significantly different, both serum BUN and creatinine were higher in high TSH patients, and estimated GFR was lower in those patients. These results have given the clues for adjusting personalized rhTSH dose to achieve adequate levels of serum TSH. In addition, Tg is known to be one of the most accurate predictors for disease recurrence among patients with thyroid cancer. Valle et al. [28] have reported that the majority of patients with detectable Tg levels ($\geq 0.2 \text{ ng/mL}$) exhibit a continuous increase in TSH and Tg throughout the 4 weeks of THW. They suggested that a TSH cutoff of $>30 \mu\text{U/mL}$ is unable to identify many of the patients that eventually exhibit a stimulated Tg level ($\geq 2 \text{ ng/mL}$) throughout the 4 weeks of THW. They also suggested a cutoff level of $>80 \mu\text{U/mL}$ or $>100 \mu\text{U/mL}$ would provide a more reliable predictor for patients whose final Tg exceeds 2 ng/mL . Interestingly, Tg levels could be affected by TSH levels after rhTSH injection, as well as after THW. Therefore, if the rhTSH dose for each patient could be personalized, over-stimulation of the tumor mass (due to high TSH) could be avoided, and this would also allow for more accurate Tg testing during the follow-up. Based on our results, taking into account the serum creatinine, age, BSA, BMI, etc. of subjects, this hypothesis would be feasible. Further studies are needed to evaluate this hypothesis.

In conclusion, serum creatinine is the most powerful predictor for peak levels of serum TSH after rhTSH injection, although age, BSA, and BMI also significantly predicted peak levels of serum TSH. As we observed that the factors that influence the pharmacokinetics of TSH decline over time, we believe it is possible to calculate an appropriate dosage of rhTSH to obtain optimal levels of TSH in each patient, particularly in populations where anthropometric parameters are different and more homogenous compared with those in Western countries.

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Conflict of Interest Seung Hyun Son, Sang-Woo Lee, Ji-hoon Jung, Choon-Young Kim, Do-Hoon Kim, Shin Young Jeong, Byeong-Cheol Ahn, and Jaetae Lee declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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