

Original Article

A cross-sectional retrospective study to identify indicators for initiating thyroid hormone replacement therapy in patients with subclinical hypothyroidism

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Abstract: Subclinical hypothyroidism (SCH) is defined by elevated serum thyroid stimulating hormone (TSH) levels and normal levels of total or free thyroxine. SCH is associated with increased risk of cardiovascular morbidity and mortality, but convenient risk indicators are lacking. We aimed to identify reliable indicators of cardiovascular risk for determining initiation of thyroid hormone replacement therapy in SCH patients. This is a cross-sectional retrospective study. Medical records of 412 consecutive healthy subjects with SCH who underwent routine health check-ups at National Taiwan University Hospital between January 1, 2009 and December 31, 2009 were reviewed. Demographic, physical and clinical data were collected, including waist circumference, body mass index, thyroid function tests, fasting blood glucose, glycohemoglobin (HbA1c), and lipid profiles. Subjects were divided into three groups by HbA1c level: $\leq 5.6\%$, $5.7\%-6.4\%$, and $\geq 6.5\%$. National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) risk assessment was used to estimate cardiovascular risk. Group 3 had significantly higher fasting blood glucose ($P < 0.001$), postprandial glucose ($P < 0.001$), triglycerides ($P < 0.001$) and lower HDL-C ($P = 0.039$) than groups 1 and 2. HbA1c levels $> 5.7\%$ are associated with cardiovascular risk in SCH patients. HbA1c is an objective, convenient parameter for determining initiation of thyroid hormone replacement therapy in SCH patients with higher cardiovascular risk. Further studies are needed to demonstrate HbA1c capability for predicting cardiovascular risk in SCH patients and whether T4 treatment can improve outcomes.

Keywords: Subclinical hypothyroidism, HbA1c, cardiovascular risk, thyroid hormone replacement, hyperlipidemia

Introduction

Subclinical hypothyroidism (SCH) is defined as an elevated level of serum thyroid stimulating hormone (TSH) with normal levels of total or free thyroxine (T4) and triiodothyronine (T3). The American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE) guidelines state that the SCH definition only applies when thyroid function has been consistently stable with normal hypothalamic-pituitary-thyroid axis and no recent or ongoing illness [1]. SCH is common among otherwise healthy middle-aged and older adults [2]. Prevalence ranges between 4% and 15% in the general population and is about 20% in women aged 60 and older [3]. Causes include autoimmune thyroiditis (Hashimoto disease),

overtreatment of hyperthyroidism, certain medications, and recovery from non-thyroid illness [1].

Observational studies of the long-term consequences of SCH are conflicting [4]. Although patients with SCH are usually asymptomatic or have only mild symptoms [5], SCH is individually associated with hypercholesterolemia, atherosclerotic diseases, and cardiac dysfunction [2, 6]. SCH patients also have an increased risk for coronary heart disease, cardiovascular mortality, and incident ischemic heart disease [7-11]. Specifically, in a 10-year longitudinal study, the relative risk of all-cause mortality and cardiovascular disease-associated death in SCH patients was 1.30 (95% CI, 1.02-1.66) and 1.68 (95% CI, 1.02-2.76), respectively compared

Glycohemoglobin A1c and SCH

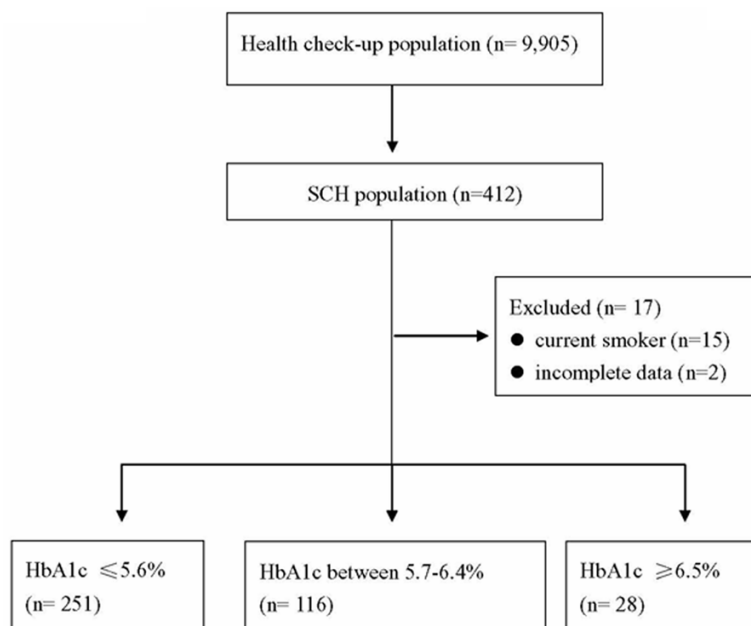


Figure 1. Schematic of study flow.

to risk in euthyroid patients [10]. However, even with evidence of cardiovascular risk, routine treatment of SCH is not recommended based on the idea that replacement therapy is justified only for those with TSH levels > 10 mU/L [12]. In contrast, the 2013 ETA Guideline for the management of SCH recommends a 3-month trial of L-thyroxine replacement therapy for younger SCH patients (≤ 70 y) with TSH levels < 10 mU/L and symptoms suggestive of hypothyroidism [13]. Replacement therapy with L-thyroxine for asymptomatic patients < 65-70 y with TSH levels > 10 mU/L is also suggested [13]. Furthermore, studies have revealed that SCH patients treated with T4 experienced a lower risk of heart failure and all-cause mortality [7-11]. The newest ATA and AACE guidelines [1] state that treatment should be considered for patients with TSH levels between the upper limit of the reference range (by individual laboratory) and 10 mU/L, particularly when symptoms suggest hypothyroidism, thyroperoxidase antibodies (TPOAbs) are present, or risk factors or evidence suggest atherosclerotic cardiovascular disease or heart failure. A study of women with TSH < 10 mU/L found that positive TPOAbs, classic cardiovascular risk factors or at least one symptom of hypothyroidism were present in 92% of SCH patients, suggesting that the 92% would be candidates for treatment based on the ATA/AACE guidelines [14]. However, T4

supplementation for SCH remains controversial due to insufficient evidence of effectiveness, especially among patients with TSH levels between 4.5 and 10 mU/L [5]. A randomized controlled trial showed no beneficial effects of thyroxine in elderly SCH patients based on cognitive function tests [15], while another controlled trial reported improvements in atherogenic lipoprotein profiles and carotid intima-media thickness after replacement therapy [16]. Thus, it remains to be determined whether T4 treatment improves SCH outcomes.

While an association between cardiovascular morbidity and mortality and SCH has been established [6-10], no reliable biochemical indicator has been available to determine the ideal time to initiate thyroid hormone replacement therapy in SCH patients. The only indication has been TSH levels. We hypothesized that risk scores determined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) risk calculation tool would help to identify cardiovascular risk factors in otherwise healthy subjects with SCH and, further, that results could be evaluated in conjunction with subjects' demographic and clinical variables to find associations between cardiovascular risk and potential indicators. The objective of the present study was to identify reliable indicators of cardiovascular risk to help identify patients who may require thyroid hormone replacement therapy.

Subjects and methods

Subjects

This cross-sectional retrospective study extracted and reviewed medical records of 412 consecutive SCH subjects from a total of 9,095 subjects who completed a routine health check-up at the Health Management Center, National Taiwan University Hospital, between January 1, 2009 and December 31, 2009. For

Glycohemoglobin A1c and SCH

Table 1. Baseline characteristics of the 395 patients with SCH

	Group 1 HbA1c < 5.7% (n = 251)	Group 2 5.7 ≤ HbA1c < 6.5% (n = 116)	Group 3 HbA1c ≥ 6.5% (n = 28)	P-value
Age, y	50.72±11.19	57.97±9.64 [†]	60.93±9.42 [†]	< 0.001*
Male	92 (36.7)	57 (49.1) [†]	16 (57.1) [†]	0.018*
BMI, kg/m ²	23.17±2.96	24.55±3.05 [†]	25.78±3.81 [†]	< 0.001*
Waist circumference, cm	83.55±7.7	87.49±8 [†]	90.63±8.73 [†]	< 0.001*

BMI = body mass index. Data were presented as mean ± standard deviation tested by one-way analysis of variance; gender was expressed as n (%) and tested by chi-square test. *Indicates a significant difference among the three groups, $P < 0.05$.

[†]Indicates a significant difference from Group 1, $P < 0.05$.

the purposes of this study, SCH was defined as TSH levels between 4-10 mU/L and normal T3 and free T4 levels; subclinical hyperthyroidism was defined as < 0.4 mU/L, and euthyroid was defined as 0.4-4.0 mU/L. Patients were enrolled based on the following inclusion criteria: healthy subjects without known systemic diseases, including prior history of diabetes mellitus, not taking any medication that may affect thyroid function, and not pregnant or within first year of giving birth. Subjects who were current smokers or had a history of thyroid dysfunction (hypothyroidism or hyperthyroidism) were excluded from the study. After 15 current smokers and two subjects with incomplete data were excluded, the data of the remaining 395 subjects were included in statistical analysis (Figure 1).

Ethical considerations

The study protocol was reviewed and approved by the institutional review board of National Taiwan University Hospital. As this retrospective study was conducted using anonymous data without any link to personal information, informed consent was deemed unnecessary.

Data collection

Basic demographic information (age and sex), and physical data, including body height, body weight, body mass index (BMI), waist circumference, and systolic and diastolic blood pressure (SBP and DBP, respectively) were collected. History of pregnancy, thyroid disease, diabetes, dyslipidemia, hypertension, as well as smoking and drinking status were also ascertained. Laboratory tests were performed on fasting blood samples, included thyroid function tests (TSH, free T4), fasting glucose, HbA1c, triglycerides, total cholesterol, and high-density and

low-density lipoprotein cholesterol (HDL-C and LDL-C, respectively). Subjects were categorized into three groups according to HbA1c levels: Group 1, ≤ 5.6% (n = 251), Group 2, 5.7%-6.4% (n = 116), and Group 3, ≥ 6.5% (n = 28).

Risk score calculation

The NCEP ATPIII risk assessment tool (<http://hp2010.nhlbi.nih.gov/atpIII/calculator.asp>) uses recent data from the Framingham Heart Study to estimate 10-year risk of coronary heart disease (CHD; defined as myocardial infarction and coronary death) in adults aged 20 years and older who do not presently have heart disease or diabetes. The short-term (10-year) risk for developing CHD is determined using Framingham risk scoring, based on age, total cholesterol, HDL-C, SBP, treatment for hypertension, and cigarette smoking.

Statistical analysis

Mean and standard deviation (SD) were calculated for continuous variables with normal distribution. Median and inter-quartile range were reported for hs-CRP; count and percentage were estimated for gender. Differences in baseline characteristics between the three groups, including age, BMI and waist circumference, were tested by one-way analysis of variance (ANOVA). Bonferroni's correction was done for post-hoc tests when significant results were revealed by ANOVA. Chi-square test was applied to nominal data. Linear models adjusted for age, gender and BMI were implemented to evaluate differences in biochemical index among three HbA1c levels. Log transformation was applied to hs-CRP and NCEP risk score. All statistical assessments were evaluated at a two-sided alpha level of 0.05 using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC).

Glycohemoglobin A1c and SCH

Table 2. Differences in the clinical data by HbA1c level

	Group 1 HbA1c < 5.7% (n = 251)	Group 2 5.7 ≤ HbA1c < 6.5% (n = 116)	Group 3 HbA1c ≥ 6.5% (n = 28)	P_{adj}^1
SBP, mmHg	117.04±13.86	124.21±15.67	131.29±17	0.072
DBP, mmHg	68.92±9.31	73.92±10.1 [†]	78.54±10.74 [†]	0.002*
CRE, mg/dL	0.95±0.18	1.02±0.2	1.05±0.27	0.363
Free thyroxine, ng/dL	1.12±0.16	1.13±0.16	1.17±0.2 [†]	0.042*
Fasting glucose, mg/dL	88.55±7.36	98.39±11.82 [†]	127.79±31.58 ^{†,‡}	< 0.001*
2-hour postprandial glucose, mg/dL	110.00±27.56	129.53±38.82 [†]	221.14±60.99 ^{†,‡}	< 0.001*
HDL-C, mg/dL	53.14±12.14	51.74±12.25	44.32±10.49 ^{†,‡}	0.039*
LDL-C, mg/dL	111.91±27.41	124.9±30.6 [†]	120.89±32.73	0.003*
Triglyceride, mg/dL	105.47±63.14	128.79±75.26	185.82±81.74 ^{†,‡}	< 0.001*
Cholesterol, mg/dL	201.03±32.7	215.28±33.64 [†]	205.5±42.04	0.002*
Uric acid, mg/dL	5.55±1.48	6.28±1.38 [†]	6.11±1.55	0.019*
hsTSH, μ IU/mL	5.25±1.3	5.23±1.21	5.5±1.4	0.601
hsCRP ² , mg/dL	0.07 (0.04, 0.15)	0.09 (0.06, 0.19)	0.12 (0.04, 0.32)	0.760

SBP = systolic blood pressure, DBP = diastolic blood pressure, CRE = creatinine, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, hsTSH = high sensitive stimulating hormone, hsCRP = high sensitive C-reactive protein. Data were presented as mean \pm standard deviation; median (interquartile range) was reported instead for hsCRP.

¹P-values were estimated by a linear model adjusting for age, gender and BMI. ²Log transformation was applied. *Indicates a significant difference among the three groups, $P < 0.05$. [†]Indicates a significant difference from Group 1, $P < 0.05$. [‡]Indicates a significant difference from Group 2, $P < 0.05$.

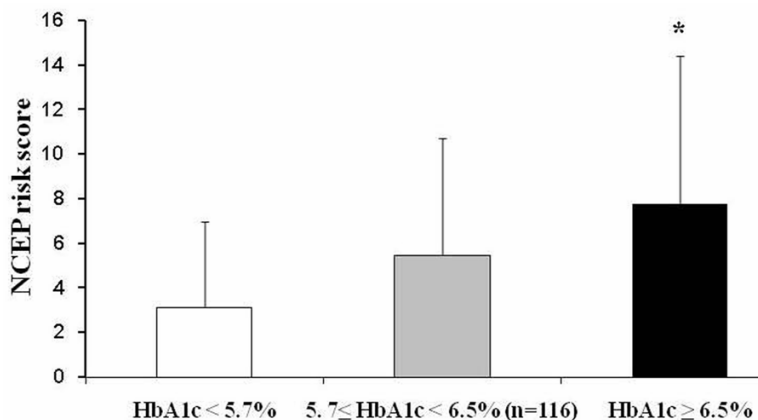


Figure 2. National Cholesterol Education Program (NCEP) score in 395 patients. Data were presented as mean \pm standard deviation. Linear model based on log-transformed data adjusting for age, gender and BMI was implemented. Asterisk indicates significant difference from “HbA1c < 5.7%” group ($P = 0.022$).

Results

Baseline demographic, anthropometric and clinical characteristics

The baseline features of 395 patients in the three groups are summarized in **Table 1**. Subjects with HbA1c < 5.7% were younger ($P < 0.001$) with a lower BMI and waist size (both P

< 0.001), and a greater proportion were female ($P = 0.018$) as compared to those with HbA1c \geq 5.7%. No differences were found in these features between group 2 (5.7-6.4%), and group 3 (\geq 6.5%).

Biochemical indices

Differences were found between the three groups in SBP, DBP, CRE, fasting and postprandial blood sugar, HDL-C, LDL-C, triglycerides, cholesterol, uric acid, hs-CRP and NCEP risk scores (data not shown). However, the differences in SBP, CRE and hs-

CRP disappeared after controlling for the effects of age, gender and BMI (**Table 2**).

Groups 2 and 3 had higher DBP ($P = 0.037$ for group 2; $P = 0.007$ for group 3), fasting glucose ($P = 0.002$ for group 2 and $P < 0.001$ for groups 3), and 2-hour postprandial glucose ($P < 0.001$ for groups 2 and 3) than subjects in group 1. Group 2 subjects had higher LDL-C ($P = 0.001$),

cholesterol ($P < 0.001$) and uric acid level ($P = 0.024$) than group 1. Group 3 also had higher free thyroxin ($P = 0.017$) and triglyceride ($P < 0.001$), and lower HDL-C ($P = 0.034$) than group 1. Subjects with HbA1c 5.7%-6.4% shared many similarities in biochemical indices with those with HbA1c above 6.5% (Group 3), except in the level of fasting glucose ($P < 0.001$), post-prandial glucose ($P < 0.001$), HDL-C ($P = 0.011$) and triglyceride ($P = 0.001$).

NCEP risk scores are displayed in **Figure 2**. Higher risk scores were found among patients with HbA1c $\geq 6.5\%$ compared to scores of patients in the HbA1c $< 5.7\%$ group ($P = 0.022$). Although higher risk scores were reported for group 2, which had HbA1c between 5.7% and 6.4%, the difference in risk scores between the two remaining groups with lower HbA1c levels disappeared after controlling for the effects of age, gender and BMI (**Figure 2**).

Discussion

Because SCH has been associated with cardiovascular morbidity and mortality [6-10], this study was undertaken to identify a reliable biochemical indicator to determine the ideal time to initiate thyroid hormone replacement therapy in SCH patients. Results of the present study revealed that older adults with higher HbA1c levels ($> 5.7\%$) demonstrated higher cardiovascular risk scores via the NCEP risk calculation tool, which utilizes patient age, total cholesterol, HDL-C, SBP, treatment for hypertension, and cigarette smoking. Thus, HbA1c may provide an objective and convenient parameter by which to identify SCH patients who exhibit higher cardiovascular disease risk and should receive thyroid hormone replacement.

The present study and previous studies show that cardiovascular risk increases with increasing age. In agreement with our findings, the Rotterdam study [17] revealed that SCH is a strong indicator for atherosclerosis and myocardial infarction in women aged 55 years and older. Similarly, Rodondi et al. [18] found SCH to be associated with an increased risk of heart failure among older adults aged 70 to 79 years. Two other studies conducted in Chinese populations corroborated vascular risk in SCH subjects. Jian et al. [19] provided evidence that both SCH and high normal TSH were independent risk factors for hypertension in middle-

aged to elderly Chinese women. A cohort study conducted in a different geographic region of Taiwan also showed that SCH was associated with increased risk for all-cause and cardiovascular mortality, especially in subjects over 65 years of age [10]. In contrast, however, a meta-analysis of 15 studies with 2500 SCH subjects and 26,500 euthyroid subjects showed that SCH was only associated with increased ischemic heart disease and cardiovascular and all-cause mortality in individuals younger than age 65, which suggests that increased cardiovascular risk may only be present in younger SCH patients [20]. Additionally, the Leiden 85-Plus Study observed that individuals older than 85 years with abnormally high TSH actually had a prolonged life span [21]. Also, a randomized controlled trial among elderly subjects with SCH found no evidence to support treating these patients with T4 replacement to improve cognitive function even though 82% and 84% achieved euthyroidism at 6- and 12-month intervals, respectively [15]. The reasons behind these rather divergent results are unclear but may be related to study design and participants' characteristics other than age.

Abdominal obesity is associated with multiple cardiometabolic risk factors, such as dyslipidemia and elevated blood glucose, as well as the development of cardiovascular disease [22]. The association between dyslipidemia and increased cardiovascular risk also is well-established [3]. At the same time, thyroid function and overt hypothyroidism also are associated with lipid profiles and dyslipidemia as a result of reduced numbers of LDL receptors in the liver and reduced excretion of LDL-C [3, 12]. Both total cholesterol and LDL-C concentration correlate positively with TSH levels independent of individuals' thyroid status [12]. In the present study, the groups with the higher cardiovascular risk scores also had higher LDL-C and cholesterol levels and greater waist circumference than SCH subjects with lowest risk scores. For Asian populations, abdominal obesity is defined by NCEP ATP III criteria as a waist circumference greater than 90 cm in men or 80 cm in women and decreasing waist circumference increased the crude prevalence of the metabolic syndrome from 12.2% to 19.7% in Asian subjects using that criteria [23]. Among Asian SCH subjects in the present study, mean waist circumference measures for men and women were 87.5 cm and 83.6 cm, respective-

ly; while in group 3 ($\text{HbA1c} \geq 6.5\%$), which had the highest cardiovascular risk scores, with the mean waist circumference as 90.6 cm, which matched the measurements that define abdominal obesity in Asians, and also the largest waist circumference among three groups. As such, waist circumference is a convenient parameter for measuring abdominal obesity as an important predictor of adverse cardiovascular outcomes [21], making it especially useful in assessing individuals with SCH.

The present study was the first to show that HbA1c levels between $\geq 6.5\%$ were significantly associated with higher NCEP risk scores. Thus, along with older SCH patients and those with a large waist circumference, SCH patients with higher HbA1c levels may also tend to have other cardiovascular risk factors, such as obesity, higher blood pressure, and dyslipidemia. HbA1c reflects biochemically average glycemia over a period of several months, and the American Diabetes Association (ADA) criteria indicate that an HbA1c $\geq 6.5\%$ is indicative of diabetes, whereas HbA1c between 5.7% and 6.4% denotes pre-diabetes [24], and both are known cardiovascular disease risk factors [21] and are included in the constellation of diseases that represent metabolic syndrome [6, 19]. Although individuals with a history of diabetes were excluded from the present study, the HbA1c levels suggest that 29.4% of the patients had pre-diabetes and 7.1% had diabetes. However, the healthy patients with SCH analyzed in the present study could not be diagnosed with diabetes as their blood was only analyzed once. In some studies, fasting blood glucose, HbA1c, and prevalence of diabetes were not significantly different between patients with SCH and euthyroid controls [25], but other studies found higher fasting blood glucose and higher prevalence of diabetes in SCH subjects [9]. Maratou et al. [26] reported that subjects with SCH had greater insulin resistance than euthyroid patients, and that difference may help to explain the increased risk of cardiovascular disease in SCH subjects.

Thyroxine replacement therapy improved insulin sensitivity and plasma glucose in SCH patients [27]. Another study that examined effects of L-T4 treatment in SCH patients reported a positive correlation between TSH and HbA1c, and normalization of TSH levels decreased fasting insulin, fasting and post-

prandial blood glucose, C-reactive protein (CRP) and lipids [28]. This demonstrates strong support for treating SCH in patients who need glucose regulation as well as for addressing increased risk of cardiovascular disease in SCH patients. In multiple cohorts with more than 25,000 participants, subclinical thyroid dysfunction was found to be a heterogeneous entity with varying levels of cardiovascular risk based on TSH levels [29]; increased risk of heart failure events were found in participants with both higher TSH (> 10 mU/L) and lower TSH (< 0.10 mU/L) TSH levels. Therefore, it is not surprising that the American College of Cardiology and American Heart Association guidelines [30] advise measuring thyroid function in adult patients with heart failure. However, it is surprising that the guidelines do not recommend a TSH threshold or a level at which treatment should be initiated to correct subclinical thyroid dysfunction. A review study found no consensus on the clinical significance and treatment of mild SCH (TSH 5-9 mU/L) and tacit agreement between investigators that treatment should be individualized [31]. Among the reviewed studies, the factors shown to influence treatment included age; risk of progression to overt disease; cognitive, metabolic and cardiovascular risk factors; quality of life and presence of comorbidities. In younger SCH patients with TSH levels < 10 mU/L and symptoms suggestive of hypothyroidism or those that are asymptomatic but with TSH levels > 10 mU/L, the 2013 ETA Guideline L-thyroxine replacement therapy [13]. Based on our results and the absence of a suitable indicator for thyroid hormone replacement in SCH, HbA1c levels may represent a convenient indicator for initiating treatment in individuals with SCH as individuals with higher HbA1c levels had significantly higher NCEP risk scores, which was consistent with greater cardiovascular risk factors, including obesity, higher blood pressure, and worse lipid profile. Further studies are necessary to evaluate the predictive value of HbA1c levels with respect to cardiovascular risk as well as to examine whether T4 treatment can improve outcomes in SCH patients.

The present study has certain limitations that warrant mention. First, this study was cross-sectional in nature and lacked prospective follow-up of subjects for evaluating cardiovascular outcomes. Although we might hypothesize that

SCH subjects have an increased cardiovascular risk in association with the presence of identified clinical risk factors, future multicenter studies with large cohorts and a sufficient follow-up period are required to establish this notion. Finally, while SCH subjects may potentially reduce their cardiovascular risk through initiation of thyroid hormone replacement therapy, a randomized controlled trial is needed to evaluate this possibility.

In conclusion, older age, large waist circumference, and HbA1c levels > 5.7% may identify SCH patients with higher cardiovascular risk that may benefit from initiating thyroid hormone replacement. Based on the findings of the present study, we would suggest that replacement therapy must be implemented for SCH patients with HbA1c \geq 6.5%, is highly recommended for patients with HbA1c between 5.7%-6.4%, and is optional for patients with HbA1c < 5.7%. Further prospective studies are needed to determine the significance of the clinical factors associated with risk and the capability of HbA1c for predicting cardiovascular risk in SCH patients, as well as to investigate whether T4 treatment can reduce risk and improve outcomes in this population.

Disclosure of conflict of interest

None.

Authors' contribution

Dr. Pei-Chi Chen provided helpful discussion and wrote the manuscript. Dr. Chih-Yuan Wang performed the data analysis, provided discussion, and reviewed/edited the manuscript.

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