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Original Article

Threshold effects between plasma total cholesterol level and the risk of sudden sensorineural hearing loss

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Abstract: Elevated serum total cholesterol (TC) level has been suggested to be a significant risk factor associated with the incidence of sudden sensorineural hearing loss (SSHL); however, the specific association between the two remains elusive. We aimed to investigate the specific association of serum TC levels with SSHL incidence. The present study was a secondary analysis of a large-scale matched case-control study, which was conducted in Korea between 2009 and 2012 using matched participants according to their propensity scores. Participants were divided into the SSHL group and the non-SSHL group, and their blood lipid profiles and clinical characteristics were recorded. The association between serum TC level and SSHL was evaluated using multiple logistic regression analysis, piecewise linear regression analysis, smooth curve fitting, and threshold effect analysis adjusted for potential confounders. We found that the serum TC concentration was significantly higher in the SSHL group compared with the non-SSHL group ($P<0.05$). The risk of developing SSHL increased significantly with increasing concentration of serum TC; however, this association could only be observed in the range of the TC concentration between 139 mg/dl and 280 mg/dl after adjusting for potential confounders. A steady incidence of SSHL was observed at TC level ranges below ≤139 mg/dl or over ≥280 mg/dl. In conclusion, we suggest that there is significant threshold effects between serum TC level and SSHL incidence. Lower serum TC levels may help reduce SSHL incidence; however, the individuals may not receive the further benefit of low serum TC in reducing the risk of SSHL if the TC levels are already below the threshold level of ≤139 mg/dl.

Keywords: Total cholesterol, sudden sensorineural hearing loss, threshold effect, lipid

Introduction

Sudden sensorineural hearing loss (SSHL) is a rapid decline in hearing, an audiologic emergency disease with an estimated incidence between 5 and 30 cases per 100,000 people each year [1-3]. SSHL significantly affects the patient's quality of life, and psychosocial-vocational activities. However, there is still a lack of an effective treatment regimen for the majority of patients with SSHL. Although about 30-60% of patients with SSHL exhibit spontaneous recovery within two weeks [4, 5], approximately 13% of these patients will eventually experience recurrent episodes of SSHL [6, 7].

Nevertheless, the underlying pathogenesis of SSHL remains elusive. Several etiological risk factors have been associated with the development of SSHL including blood vessel disorders, autoimmune diseases, and viral infections [2, 8-11]; however, the majority of patients with SSHL are categorized as idiopathic due to the unknown etiology. Recently, an association between blood lipids and SSHL has received increasing attention. Notably, elevated total cholesterol (TC), triglycerides, and low-density lipoprotein cholesterol (LDL-C) levels have also been significantly associated with SSHL [1, 12, 13]. Among the various causes responsible for SSHL, common hypotheses include the "lipids hypothesis". According to this hypothesis, elevated blood lipid levels may increase blood viscosity and contribute to atherosclerosis of the vessels supplying the cochlea, which is supplied by one to several terminal arteries with no collateral circulation, and lack of flow may promote hearing impairment [14]. Furthermore, Lee et al. noted that individuals with elevated levels of TC were more susceptible to SSHL

than those with normal levels of TC [1]. However, whether there is a concentration-dependent effect or threshold effect of TC levels, on the incidence of SSHL remains obscure.

Since adjusted TC levels may help reduce SSHL incidence, the hypothesis of this study was that there were concentration-dependent effects and threshold effects between plasma TC levels and SSHL incidence. Therefore, the present study aimed to investigate the association of plasma TC levels with the incidence of SSHL.

Materials and methods

Patient population

The present study was a secondary analysis of a large-scale matched case-control study, which was conducted in Korea between 2009 and 2012 [1]. A total of 324 consecutive patients diagnosed with unilateral SSHL at a University-affiliated hospital in Korea were selected. For each case, 3 subjects were matched as control subjects according to their propensity score. Thus, a total of 972 matched controls were included from the Korea National Health and Nutrition Examination Survey (KNHANES) between 2009 and 2010 [1]. The Institutional Review Board of Hallym University Sacred Heart Hospital approved the study. As participants were anonymous, the requirement of informed consent was therefore waived.

Patient demographic and clinicopathologic characteristics, including gender, age, body mass index (BMI), coexisting hypertension, diabetes, stroke, coronary heart disease (CHD), chronic renal failure (CRF) and dyslipidemia were carefully recorded. Blood lipid profiles included TC, triglycerides, high-density lipoprotein cholesterol (HDL-C) and LDL-C. Blood tests were performed between 6-8 a.m. in all the patients after an overnight fast [1]. For the study, the audiometric criterion of SSHL included a rapid unilateral sensorineural hearing loss of ≥30 dB over at least three contiguous frequencies occurring within 3 days. Pure tone thresholds were recorded at four pure tone frequencies.

Statistical analysis

Descriptive statistics were used to summarize patient demographic and clinicopathologic characteristics. Categorical variables were expressed as a number (percentage). For continuous variables, data were indicated as median (interquartile range). Unpaired t-test or Kruskal-Wallis rank sum test, Pearson chi-squared test or the Fisher's exact test, was performed between two groups comparison, as appropriate. Multiple logistic regression analysis was used to evaluate the association between plasma TC levels and the incidence of SSHL, with or without an adjustment for potential confounders. Adjusted criteria were the following: the criteria I adjusted variables producing a change in the regression coefficient ≥10% after introducting them into the basic model or removing them from the completed model; the criteria II adjusted variables including criteria I and variables yielding *P*-value <0.1 in univariate analysis as well as variables that were judged by clinical significance [16, 17]. Piecewise linear regression was applied to the test threshold effect of the TC on SSHL incidence with smooth curve fitting. The turning points were determined using trial and error, and then the optimal threshold that yielded the maximum model likelihood was selected. All statistical analyses were performed with R software (version 3.5.1). *P* values <0.05 were considered statistically significant.

Results

A total of 324 patients with SSHL and 972 matched control subjects with normal hearing from the KNHANES data were included in the present study (**Table 1**). No significant difference in patient demographics and clinicopathological characteristics were observed between the SSHL group and the non-SSHL group. However, the plasma TC concentration was significantly higher in the SSHL group than in the non-SSHL group (**Figure 1**, *P*<0.001). Moreover, diabetes, CRF, BMI, HDL-C, and triglycerides were found to be significantly positively correlated with SSHL as assessed by univariate analysis (**Table 2**).

In piecewise linear regression analysis (**Table 3**) and smooth curve fitting (**Figure 2**), significant threshold effects were observed between plasma TC level and the risk of SSHL. The risk of developing SSHL increased with increasing concentration of TC above the threshold point I (139 mg/dl) (odds ratio [OR], 1.07; 95% confi-

Table 1. Baseline characteristics and serum lipid profiles of the study participants

Characteristics	Sudden Sensorineural Hearing Loss	
	No (n=972)	Yes (n=324)
Age (year)	50 (38-60)	51 (39-60)
Gender, n (%)		
Female	520 (53.5)	162 (50.0)
Man	452 (46.5)	162 (50.0)
Hypertension, n (%)		
No	797 (82.00)	253 (78.09)
Yes	175 (18.00)	71 (21.91)
Diabetes, n (%)		
No	886 (91.15)	283 (87.35)
Yes	86 (8.85)	41 (12.65)
CHD, n (%)		
No	955 (98.25)	318 (98.15)
Yes	17 (1.75)	6 (1.85)
CRF, n (%)		
No	971 (99.90)	318 (98.15)
Yes	1 (0.10)	6 (1.85)
Stroke, n (%)		
No	959 (98.66)	316 (97.53)
Yes	13 (1.34)	8 (2.47)
Dyslipidemia, n (%)		
No	953 (98.05)	318 (98.15)
Yes	19 (1.95)	6 (1.85)
BMI (kg/m^2)	23.2 (21.1-25.2)	23.7 (21.6-26.2)
Triglyceride (mg/dl)	94 (66-131)	100 (69-156)
TC (mg/dl)	181 (159-202)	215 (194-241)
HDL-C (mg/dl)	53 (44-63)	55 (47-67)
LDL-C (mg/dl)	106 (86-123)	108 (87-132)

CHD, coronary heart disease; CRF, chronic renal failure; BMI, body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

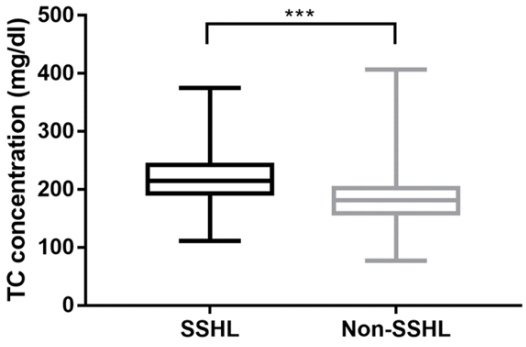

Figure 1. Comparison of plasma TC levels between the SSHL and the non-SSHL groups. Mean TC level was significantly higher in the SSHL group compared to that in the non-SSHL group. ***P<0.001. TC = total cholesterol level; SSHL = sudden sensorineural hearing loss.

dence interval [CI], 1.05-1.08; P<0.0001). The second threshold point was recorded at TC concentration of 280 mg/dl, after which no statistically significant difference was observed between increasing TC concentration and SSHL incidence (OR, 1.04; 95% CI, 0.99-1.09; P>0.05).

A significant positive correlation was found between plasma TC level and the risks of SSHL without adjusting for potential confounding factors. Moreover, after adjusting for the variables according to adjustment I (BMI, CRF, diabetes, HDL-C, triglycerides and LDL-C) or adjustment II (gender, age, HDL-C, triglycerides, LDL-C, BMI, CRF and diabetes), the strength of this association did not change (**Table 4**). Higher levels of TC (139-280 mg/dl and >280 mg/dl) were significantly associated with higher risk of SSHL when compared to lower levels of TC (<139 mg/dl) with the OR and 95% CI of 4.59 (1.60-13.15) and 16.94 (4.59, 62.56), respectively (P for trend <0.0001).

Discussion

The present study indicated that plasma TC level was significantly associated with the risk of SSHL, with threshold effects. In order to prevent the incidence of SSHL, it may be appropriate to maintain plasma TC concentrations at lower levels, and the optimal control threshold could be achieved at 139 mg/dl.

SSHL, is an intriguing clinical emergency with a rapid decline in hearing and is defined as sudden hearing loss of ≥30 dB measured over at least three consecutive frequencies of pure tone audiometry and for at least 72 hours according to clinical practice guidelines [18]. Primarily, the condition is unilateral; however, bilateral cases are less than 1.7% of reported cases [19]. It can affect anyone at any age; however it predominantly occurs among elderly people. Although the specific etiology of SSHL remains to be completely elucidated, immunological disorders and viral infections have been considered as an underlying mechanism of pathogenesis for most cases with SSHL [2, 8]. Additionally, perilymph fistula may also play an etiological role in some cases of pancochlear hearing loss [20, 21]. Based on the theory that the cochlea is supplied only by the labyrinthine artery and is more susceptible

Table 2. Univariate analysis of possible influencing factors of the risk of sudden sensorineural hearing loss

Variables	Sudden Sensorineural Hearing Loss	
	OR (95% CI)	*P*-value
Age (year)	1.00 (1.00, 1.01)	0.3803
Gender, n (%)		
Male	Ref.	
Female	0.87 (0.68, 1.12)	0.2750
Hypertension, n (%)		
No	Ref.	
Yes	1.28 (0.94, 1.74)	0.1208
Diabetes, n (%)		
No	Ref.	
Yes	1.49 (1.01, 2.22)	0.0471
CHD, n (%)		
No	Ref.	
Yes	1.06 (0.41, 2.71)	0.9033
CRF, n (%)		
No	Ref.	
Yes	18.32 (2.20, 152.76)	0.0072
Stroke, n (%)		
No	Ref.	
Yes	1.87 (0.77, 4.55)	0.1689
Dyslipidemia, n (%)		
No	Ref.	
Yes	0.95 (0.37, 2.39)	0.9072
BMI (kg/m^2)	1.06 (1.02, 1.10)	0.0036
Triglyceride (mg/dl)	1.00 (1.00, 1.00)	0.0033
TC (mg/dl)	1.02 (1.02, 1.03)	<0.0001
HDL-C (mg/dl)	1.02 (1.01, 1.03)	0.0002
LDL-C (mg/dl)	1.00 (1.00, 1.01)	0.0955

CHD, coronary heart disease; CRF, chronic renal failure; BMI, body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 3. Threshold effect analysis of plasma TC on sudden sensorineural hearing loss using two-piecewise linear regression

Inflection point of TC (mg/dl)	Sudden Sensorineural Hearing Loss[a]	
	OR (95% CI)	*P*-value
Inflection point I		
<139	1.02 (0.96, 1.07)	0.5713
>139	1.07 (1.05, 1.08)	<0.0001
Inflection point II		
<280	1.07 (1.05, 1.09)	<0.0001
>280	1.04 (0.99, 1.09)	0.0875

[a]Adjustment II adjusts for: gender, age, BMI, diabetes, CRF, triglyceride, HDL-C and LDL-C. TC, total cholesterol; BMI, body mass index; CRF, chronic renal failure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

to hypoxic stress [14], previous studies have indicated that elevated blood lipids may prevent the blood supply to the cochlea due to increased plasma viscosity, which consequently leads to SSHL [1, 22].

Furthermore, Ballesteros et al. [13] found that lipid profile exhibited positive trends for the development of SSHL in a small study cohort of 99 patients with SSHL. Aimoni et al. [2] further reported hypercholesterolemia as a crucial risk factor for developing SSHL in a case-control study with 141 patients with SSHL and 271 controls. Similarly, Lee et al. [1] also found a significant positive correlation of increased TC with the incidence of SSHL. However, all these studies failed to further reveal the association between different levels of TC and the risk of SSHL.

Therefore, in the present study, to prevent the risk of developing SSHL and to accurately evaluate the impact of the TC level on SSNL and the optimal control threshold of TC for individuals, a secondary analysis was conducted based on a previous study [1]. This previous study included a well-matched case-control study using the method of propensity score matching to reduce the selection bias. The plasma TC level remains statistically significantly associated with the incidence of SSHL after adjustment for the potential confounding risk factors in this study. Not only a TC concentration-dependent effect was found (TC concentration from 139 mg/dl to 280 mg/dl), but also two threshold effects were observed in this study. The most important benefit of identifying the threshold effect is that it can assist in lipid control. Notably, by maintaining plasma TC at lower levels, the risk of developing SSHL could be prevented. However, if the TC concentration is already below 139 mg/dl, this study indicated that

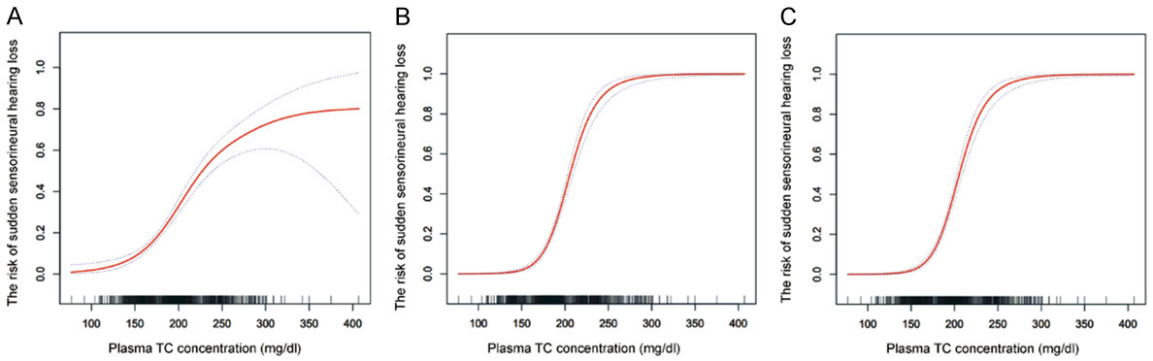

Figure 2. The smooth curve fitting shows the association between the risk of SSHL and plasma TC concentrations in the crude (A), model I (adjusted for BMI, diabetes, CRF, triglyceride, HDL-C and LDL-C) (B), and model II (adjusted for HDL-C, triglycerides, LDL-C, BMI, CRF, diabetes, gender and age) (C). The fitting curves of model I and model II are similar. Dotted lines represented the upper and lower 95% confidence intervals. SSHL = sudden sensorineural hearing loss; TC = total cholesterol level; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; BMI = body mass index; CRF = chronic renal failure.

Table 4. Multivariate regression analysis of plasma TC with the risk of sudden sensorineural hearing loss

Parameter	Sudden Sensorineural Hearing Loss					
	Non-adjust		Adjust I[a]		Adjust II[b]	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
TC (mg/dl)						
<139	Ref.		Ref.		Ref.	
139-280	5.51 (1.99, 15.25)	0.0010	4.68 (1.64, 13.35)	0.0039	4.59 (1.60, 13.15)	0.0045
≥280	30.15 (9.17, 99.11)	<0.0001	17.90 (4.89, 65.55)	<0.0001	16.94 (4.59, 62.56)	<0.0001
P for trend	<0.0001		<0.0001		<0.0001	

[a]Adjustment I adjusts for: BMI, diabetes, CRF, triglyceride, HDL-C and LDL-C. [b]Adjustment II adjusts for: gender, age, BMI, diabetes, CRF, triglyceride, HDL-C and LDL-C. TC, total cholesterol; BMI, body mass index; CRF, chronic renal failure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

there was no need to pursue an even lower TC level. Since TC concentration between 139 and 280 mg/dl have been associated with a rapid increase in the risk of SSHL (**Figure 2B, 2C**), people who are within this TC level could obtain a higher "cost-benefit ratio" from TC control.

To the best of our knowledge, the present study is the first to reveal the association between different plasma TC levels and the risk of SSHL. The present study does have its own strengths and limitations. Strengths of this study include the large sample size of consecutive patients with SSHL and well-matched covariates between the patients and the control. However, several limitations are worth noting. First, the study participants were recruited from a single center in East Asia, thus whether the results of this study apply to other regions needs further evaluation. Secondly, some potential confounders such as smoking, patient occupation and lipid-lowering drugs use were not included in this study, as these variables were not available from the data.

Conclusions

The findings of the present study indicated a significant association of increased plasma TC level with an increased risk of developing SSHL. Furthermore, two significant threshold effects at 139 mg/dl and 280 mg/dl, respectively were observed. Consequently, for reducing the risk of SSHL, it may be crucial to control the concentration of plasma TC below 139 mg/dl; however, individuals with plasma TC level between 139 and 280 mg/dl can still significantly benefit from TC control for reducing the risk of SSHL.

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Disclosure of conflict of interest

None.

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