Serum Total Sialic Acid Level is Elevated in Hypothyroid Patients as an Atherosclerotic Risk Factor

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Background: Serum total sialic acid (TSA) concentration is regarded as an indicator of the risks of atherosclerosis and cardiovascular diseases. The association between SA levels and atherosclerosis risk factors has not been assessed in patients with thyroid diseases. *Methods:* Sixty newly diagnosed treatment-naive hypothyroid patients, 35 with subclinical and 25 with overt hypothyroidism, and 30 euthyroid individuals were analyzed. SA was measured in fasting blood samples, as were routine biochemical parameters, some atherosclerosis markers and carotid artery intima media thickness (CIMT). *Results:* Mean SA (38.1 ± 12.0 vs. 46.0 ± 15.8; $P = 0.019$) and CIMT (0.57 ± 0.06 vs. 0.62 ± 0.12; $P = 0.013$) were found to be higher in the patient group compared with the control group. Mean sialic acid was higher in overt hypothyroidism patients compared with subclinical hypothyroidism patients and the control group. No difference was found between the subclinical hypothyroidism group and the control group. Sialic acid level and CIMT had a positive correlation in both the entire population and the hypothyroidism group. The linear regression model established for mean CIMT level in the entire population showed that risk factors of LDL (B ± SE = 0.454 ± 0.206; $P = 0.030$), uric acid (B ± SE = 1.902 ± 0.686; $P = 0.007$), hs-CRP (B ± SE = 1.003 ± 0.380; $P = 0.010$), and SA (B ± SE = 2.419 ± 0.450; $P < 0.001$) were independent predictors of CIMT level. *Conclusion:* Sialic acid level is elevated in hypothyroid patients. However, this elevation is not related to thyroid hormone levels and autoantibodies. Correlations between SA and atherosclerosis indicators, such as CIMT, LDL, hs-CRP, and uric acid, in hypothyroid individuals suggest that SA may be an indicator of atherogenesis in these patients. J. Clin. Lab. Anal. 31: e22034, 2017.

Key words: atherosclerosis; carotid artery intima media thickness; hypothyroidism; sialic acid; uric acid

INTRODUCTION

Overt and subclinical hypothyroidism (SH) have been associated with atherogenesis (1,2). Moreover, hypothyroidism is frequently accompanied by risk factors for atherosclerotic cardiovascular disease (CVD), including elevated levels of low-density lipoprotein cholesterol (LDL-C) and apolipoprotein (Apo) B, decreased levels of high-density lipoprotein cholesterol (HDL-C) and Apo A1, and diastolic hypertension (3,4).

Efforts to identify new markers of atherogenesis have shown that serum total sialic acid (TSA) concentration is a possible indicator of atherosclerosis and cardiovascular diseases (5), as well as being associated with prolonged inflammatory responses (6).

Sialic acid (SA) is the monosaccharide found in the terminal end of substances in glycoprotein structure on the cell surface. N-substituted derivatives of neuraminic acid constitute almost the entire SA group, hence, it is also referred to as *N*-acetyl neuraminic acid. SA is usually found on inner or outer surfaces of the lysosomal membrane. Therefore, SA is the first biochemical molecule that allows for the intercellular

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relationships. This feature and its being negatively charged in physiological pH conditions are SA's main features responsible for its functions in the organism. SA is involved in tumor growth, autoimmune diseases, microbial invasion, and virulence pathogenesis. Glycoprotein or glycolipid sialylation or desialylation occur due to many factors and SA levels change in serum, urine, and body fluids. However, it is not yet clear which mechanisms are involved in the increase in SA (7).

Serum SA levels have been reported to be elevated in patients with coronary artery disease (CAD), type 1 and type 2 diabetes mellitus (DM), obesity, nonalcoholic fatty liver disease, and chronic renal failure, including patients on dialysis (8–10). Moreover, serum SA concentrations have been found to correlate with atherosclerotic risk factors, including blood levels of LDL-C, triglycerides (TG), HDL-C, fibrinogen, lipoprotein (a) (Lp(a)), and uric acid, as well as with albuminuria and carotid intima media thickness (CIMT) (11,12).

Although the relationships between SA and several diseases have been investigated, changes in SA levels have not been assessed in patients with thyroid function disorders. The potential relationships between hypothyroidism and atherosclerosis and between autoimmunity and inflammatory pathways in Hashimoto's thyroiditis suggest that serum SA levels may be influenced under such conditions. We therefore assessed SA levels in patients with hypothyroidism to determine the association between SA and certain atherosclerotic risk factors.

METHODS

Sixty newly diagnosed treatment-naive hypothyroid patients, including 35 with subclinical and 25 with overt hypothyroidism, and 30 euthyroid individuals, all aged 18–50 years, were included. Subjects known to have atherosclerotic CVDs (e.g., coronary artery disease, stroke, or peripheral vascular disease), any systemic disease (e.g., DM, chronic renal failure, or chronic liver failure), active or chronic infection, inflammatory diseases, or malignancies were excluded. Patients with elevated serum concentrations of thyroid-stimulating hormone (TSH) on at least two measurements and decreased free thyroxine (fT4) concentrations were regarded as having overt hypothyroidism, whereas those with elevated serum TSH but normal fT4 were regarded as having subclinical hypothyroidism (SH). A detailed medical history was obtained from each patient, including diseases and risk factors, and all underwent physical examinations. Systolic blood pressure (SBP), diastolic blood pressure (DBP), waist–hip ratio (WHR), weight, height, and body mass index (BMI) measurements were recorded.

The study was approved by the Local Ethics Committee and performed in compliance with the Declaration of Helsinki. All patients provided written informed consent prior to entry into the study.

Blood samples were obtained following a minimum fasting of 8 hrs. Serum concentrations of glucose, uric acid, total C, HDL-C, LDL-C, TG, very high-density lipoprotein cholesterol (VLDL-C), TSH, fT4, free triiodothyronine (fT3), anti-thyroglobulin (anti-T), and anti-thyroid peroxidase (anti-TPO) were measured, and a complete blood count including mean platelet volume (MPV) were assessed. Additionally, samples were stored at $-80°C$, and serum SA, homocysteine and high-sensitivity CRP (hs-CRP) levels were measured at the end of the study. SA (human sialic acid ELISA kit, Cusabio, College Park, MD) and Homocysteine EIA, Axis-Shield Diagnostics, Luna Place, The Technology Park, Dundee, Scotland) concentrations were measured by enzyme-linked immunosorbent assays (ELISA), and hs-CRP was measured by the nephelometric method. CIMT was measured with the General Electric Logic 5 Pro device using a 12 MHz probe, with all measurements performed by the same operator, as described previously (13). Bilateral (right and left CIMT) measurements were repeated five times at the posterior arterial wall and 1 cm distal to the main carotid artery bulb, with mean CIMT defined as the arithmetic mean of these measurements.

Statistical analysis

"SPSS (Statistical Program for Social Sciences) version 15.0 for Windows" software was used for the statistical analysis in this study. The normal distribution of the data was evaluated with the Kolmogorov–Smirnov test. Values with normal distribution were presented as mean $\pm$ standard deviation and values without normal distribution were presented as median (IQR). Categorical variables were presented as numbers and percentages. The student *t*-test was used for two group comparisons and the ANOVA test was used for three group comparisons of normally distributed numerical variables. The Mann–Whitney *U* test was used for two group comparisons and the Kruskall–Wallis *H* test was used for three group comparisons of nonnormally distributed numerical variables. The Bonferroni correction was applied to post hoc comparisons. Chi-square test and Fisher's exact chi-square test were used in comparison of categorical data. The multivariable linear regression model was established in order to determine independent predictors of CIMT levels. Risk factors correlated with CIMT and

$P < 0.250$ were included in the regression model. Logarithmic transformation was applied to nonnormally distributed risk factors before the multivariable linear regression analysis.

A value of $P < 0.05$ was accepted to be statistically significant.

RESULTS

The research population was made up of 90 participants in total; 30 control, 35 subclinical hypothyroidism, and 25 overt hypothyroidism patients. Table 1 shows demographic and clinical findings related to the control group, the patient group, and subgroups. Accordingly, DBP level was higher in the patient group ($n = 60$) compared with the control group (70.2 ± 6.9 vs. 76.4 ± 10 mmHg; $P = 0.001$). In terms of lipid levels, total cholesterol (176.5 ± 31.4 vs. 203.6 ± 50.2 mg/dl $P = 0.002$), mean LDL-C (107.6 ± 25.9 vs. 128.8 ± 40.9 mg/dl $P = 0.004$), median TG (67 vs. 97.5 mg/dl $P = 0.008$), and median VLDL-C (13.5 vs. 19.5 mg/dl; $P = 0.01$) levels were higher in the patient group. Median homocysteine (13.2 vs. 18.5 μmol/l $P = 0.042$) was found to be higher in the patient compared with the control group. Mean sialic acid (38.1 ± 12.0 vs. 46.0 ± 15.8 μg/ml $P = 0.019$) and CIMT (0.57 ± 0.06 vs. 0.62 ± 0.12 mm $P = 0.013$) were found to be higher in the patient group compared with the control group.

Mean sialic acid was higher in overt hypothyroidism patients compared with subclinical hypothyroidism patients and the control group. No difference was found between the subclinical hypothyroidism group and the control group. Mean CIMT levels were similar in overt and subclinical hypothyroidism patients and higher compared with the control group (Table 1).

In the entire population, sialic acid level showed positive correlation with CIMT, age, total C, LDL-C, and hs-CRP levels. CIMT levels showed positive correlation with age, BMI, WHR, total C, LDL-C, TG, VLDL-C, uric acid, and hs-CRP levels (Table 2).

In hypothyroidism patients, sialic acid level showed positive correlation with CIMT, total C, and

TABLE 1. Demographic and clinical findings related to the whole patients and patients subgroup

			Patients		*P*-value			
Variables	Control $n = 30$	Patients $n = 60$	Subclinical H $n = 35$	Overt H $n = 25$	Control vs. patient	Control vs. SH	Control vs. OH	SH vs. OH
Gender, *n*(%)								
Female	25(83.3)	50(83.3)	29(82.9)	21(84.0)	0.999	0.959	0.947	0.908
Age (year)	32.5 ± 7.5	33.8 ± 9.8	34.4 ± 10.3	33 ± 9.3	0.483	0.393	0.829	0.588
SBP (mmHg)	111.7 ± 9.4	115.5 ± 12.3	115.4 ± 12.7	115.6 ± 12.1	0.106	0.185	0.181	0.958
DBP (mmHg)	70.2 ± 6.9	76.4 ± 10	76.9 ± 9.9	75.8 ± 10.5	0.001*	0.003*	0.020*	0.691
BMI (kg/m^2)	23.7 ± 3.9	27.1 ± 5.4	27.6 ± 5.9	26.4 ± 4.4	0.003*	0.003*	0.019*	0.402
WHR	0.83 ± 0.07	0.88 ± 0.09	0.88 ± 0.1	0.87 ± 0.07	0.025*	0.038*	0.050*	0.765
Glucose (mg/dl)	85.4 ± 6.4	86.7 ± 7.2	86.8 ± 7	86.5 ± 7.6	0.429	0.428	0.566	0.895
Uric acid (mg/dl)	4.2 ± 0.9	4.2 ± 1.2	4.3 ± 1	4.1 ± 1.5	0.676	0.499	0.994	0.613
Total C (mg/dl)	176.5 ± 31.4	203.6 ± 50.2	192 ± 37.5	219.8 ± 61.1	0.002*	0.078	0.003*	0.050*
HDL-C (mg/dl)	52.4 ± 10.4	51.1 ± 12.1	50.3 ± 11.3	52.2 ± 13.2	0.612	0.433	0.961	0.535
LDL-C (mg/dl)	107.6 ± 25.9	128.8 ± 40.9	118.3 ± 32	143.5 ± 47.7	0.004*	0.149	0.002*	0.017*
TG (mg/dl)	67(43–239)	97.5(41–399)	97(41–399)	106(44–374)	0.008*	0.031*	0.024*	0.453
Creatinine (mg/dl)	0.64 ± 0.11	0.70 ± 0.13	0.66 ± 0.11	0.75 ± 0.15	0.010*	0.468	0.003*	0.009*
hs-CRP (mg/dl)	0.06(0.01–0.74)	0.11(0.01–1.09)	0.12(0.02–1.09)	0.05(0.01–0.7)	0.033*	0.011*	0.025*	0.044*
Homocysteine (μmol/l)	13.2(8.4–43.1)	18.5(5.6–95.9)	12.2(5.6–50.7)	23.7(7.5–95.9)	0.110	0.104	0.009*	0.005*
TSH (μIU/ml)	1.4(0.5–3.5)	9.6(5–500)	7.2(5–19.1)	71.7(5.9–500)	0.042*	<0.001*	<0.001*	<0.001*
fT4 (ng/dl)	1.1 ± 0.2	0.8 ± 0.2	1.0 ± 0.1	0.6 ± 0.1	<0.001*	0.101	<0.001*	<0.001*
fT3 (pg/ml)	2.9 ± 0.5	2.7 ± 0.6	3.0 ± 0.3	2.2 ± 0.7	<0.001*	0.375	<0.001*	<0.001*
Anti-TG (IU/ml)	13.1(0.3–188)	156.8(14–20218)	144.6(14–5462)	164(50–20218)	0.056	<0.001*	<0.001*	0.144
Anti-TPO (IU/ml)	3.1(0.4–39)	706(2.7–19572)	83.1(2.7–16392)	971(5.7–19572)	<0.001*	<0.001*	<0.001*	0.045*
MPV (fl)	8.9 ± 1.0	8.6 ± 1.3	8.5 ± 1.1	8.6 ± 1.6	<0.001*	0.171	0.458	0.836
Sialic acid (μg/ml)	38.1 ± 12.0	46.0 ± 15.8	37.1 ± 15.5	58.2 ± 18.9	0.237	0.775	<0.001*	<0.001*
CIMT (mm)	0.55 ± 0.05	0.62 ± 0.12	0.63 ± 0.10	0.63 ± 0.14	0.019*	0.004*	0.003*	0.999

SH, subclinical hypothyroidism; OH, overt hypothyroidism; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WHR, waist–hip ratio; Total C, total Cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; VLDL-C, Very low-density lipoprotein cholesterol; hs-CRP, high-sensitive C-reactive protein; TSH, thyroid-stimulating hormone; fT4, free thyroxine; fT3, free triiodothyronine; anti-TG, anti-thyroglobulin; anti-TPO, anti-thyroid peroxidase; MPV, mean platelet volume; CIMT, carotid artery intima media thickness. *$P < 0.05$ was considered significant for statistical analyses.

TABLE 2. Demographic and Clinical correlations for sialic acid and CIMT

		Sialic acid		CIMT	
Group	Variables	*r*	*P*	*r*	*P*
All population	Sialic Acid	–	–	0.628	<0.001*
	CIMT	0.628	<0.001*	–	–
	Age	0.259	0.014*	0.431	<0.001*
	SBP	0.025	0.816	0.106	0.319
	DBP	0.132	0.216	0.200	0.059
	BMI	0.133	0.210	0.266	0.011*
	WHR	0.162	0.126	0.224	0.034*
	Glucose	0.171	0.106	0.152	0.153
	Total C	0.397	<0.001*	0.464	<0.001*
	HDL-C	0.119	0.263	0.072	0.502
	LDL-C	0.393	<0.001*	0.411	<0.001*
	TG	0.153	0.150	0.338	0.001*
	VLDL-C	0.095	0.374	0.279	0.008*
	Creatinine	0.033	0.758	−0.108	0.310
	Uric acid	0.193	0.068	0.425	<0.001*
	hs-CRP	0.280	0.008*	0.503	<0.001*
	Homocysteine	0.046	0.666	−0.027	0.804
	TSH	0.013	0.904	0.020	0.849
	fT4	0.019	0.857	−0.060	0.573
	fT3	0.159	0.134	0.116	0.275
	anti-TG	−0.092	0.388	−0.012	0.914
	anti-TPO	−0.123	0.250	−0.041	0.699
	MPV	−0.056	0.602	−0.168	0.113
Hypothyroidism	Sialic Acid	–	–	0.457	0.022*
	CIMT	0.457	0.022*	–	–
	Age	0.229	0.270	0.328	0.110
	SBP	0.179	0.391	−0.050	0.814
	DBP	0.092	0.661	−0.034	0.872
	BMI	0.176	0.399	0.083	0.694
	WHR	0.231	0.266	−0.066	0.755
	Glucose	0.360	0.077	−0.054	0.796
	Total C	0.676	<0.001*	0.699	<0.001*
	HDL-C	0.389	0.055	0.204	0.328
	LDL-C	0.693	<0.001*	0.639	<0.001*
	TG	0.212	0.308	0.470	0.018*
	VLDL-C	0.130	0.536	0.352	0.085
	Creatinine	0.242	0.244	−0.307	0.136
	Uric acid	0.199	0.340	0.512	0.009*
	hs-CRP	0.162	0.440	0.203	0.330
	Homocysteine	0.174	0.406	0.048	0.821
	TSH	0.163	0.436	0.128	0.543
	fT4	0.159	0.449	0.289	0.161
	fT3	0.050	0.814	0.001	0.995
	anti-TG	−0.203	0.330	−0.085	0.687
	anti-TPO	−0.020	0.923	−0.020	0.926
	MPV	0.180	0.390	−0.042	0.841

SBP, Systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WHR, waist–hip ratio; total C, total Cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; VLDL-C, very low-density lipoprotein cholesterol; hs-CRP, high-sensitive C-reactive protein; TSH, thyroid-stimulating hormone; fT4, free thyroxine; fT3, free triiodothyronine; anti-TG, anti-thyroglobulin; Anti-TPO, anti-thyroid peroxidase; MPV, mean platelet volume; CIMT, carotid artery intima media thickness. *$P < 0.05$ was considered significant for statistical analyses.

LDL-C levels. CIMT levels showed positive correlation with total C, LDL-C, TG, and uric acid levels (Table 2).

The linear regression model (method: backward) established with risk factors with a *P*-value lower than 0.250 according to correlation analysis for mean CIMT level in the entire population showed that risk factors of LDL ($B \pm SE = 0.454 \pm 0.206$; $P = 0.030$), uric acid ($B \pm SE = 1.902 \pm 0.686$; $P = 0.007$), hs-CRP ($B \pm SE = 1.003 \pm 0.380$; $P = 0.010$), and sialic

acid (B ± SE =2.419 ± 0.450; $P < 0.001$) were independent predictors of CIMT level (Table 3). Accordingly, an increase of 1 unit in sialic acid level leads to an increase of 2.419 in CIMT level.

DISCUSSION

In this study, we found that SA levels were higher in hypothyroid patients than in controls. We also observed that SA levels were positively correlated with CIMT, total-C, hs-CRP, and LDL-C concentrations. Furthermore, we found that SA is an important independent predictor of CIMT together with LDL-C, hs-CRP, and uric acid.

Many studies to date have demonstrated a robust relationship between elevated SA levels and cardiovascular diseases, with SA levels being predictive of cardiovascular mortality and cerebrovascular diseases (5). Moreover, SA levels are higher in patients with than without a history of myocardial infarction (14) and hypercholesterolemia (15,16). Elevated serum SA levels have been associated with carotid atherosclerosis, independent of other risk factors (17). Serum SA levels may be used to screen populations for atherosclerotic processes (5,18,19).

Many studies support the correlations we observed among atherogenic risk factors, including CIMT, SA, uric acid, homocysteine, and hs-CRP. For example, SA levels were found to be higher in patients with than without type 2 DM, with SA concentrations positively correlated with cardiovascular risk factors such as Apo B, LDL-C, TG, and uric acid (12). In a study conducted with obese individuals, Yerlikaya et al. (20) showed that SA levels were elevated in obesity and SA correlated with conventional KVH risk factors such as hs-CRP and LDL-C cholesterol. In addition, CRP and SA levels were shown to be positively correlated in patients with a history of myocardial infarction (21).

TABLE 3. Independent predictors of CIMT level in the entire population

		95% C.I.		
Variables	B ± SE	Lower	Upper	*P*
LDL-C	0.454 ± 0.206	0.044	0.864	0.030*
Uric acid	1.902 ± 0.686	0.536	3.267	0.007*
hs-CRP	1.003 ± 0.380	0.247	1.76	0.010*
Sialic acid	2.419 ± 0.450	1.525	3.314	<0.001*
Model Summary: Adjusted $R^2 = 0.572$; $P < 0.001$				

B ± SE: Regression Coefficients ± Standard Error; 95% CI= 95% Confidence intervals

CIMT, carotid artery intima media thickness; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitive C-reactive protein. *$P < 0.05$ was considered significant for statistical analyses.

Atherosclerotic risk markers (11), including CIMT (0.74 vs. 0.66 mm) and SA concentration, were higher in 53 hemodialysis (HD) patients than in controls. Moreover, the SA concentration was positively correlated with hs-CRP, Lp(a), and CIMT in these patients indicating that serum SA level is associated with inflammation and accelerated atherosclerosis in patients with HD. In addition to malondialdehyde, a marker of oxidative stress, SA levels were higher in patients with CAD, as determined by coronary angiography, than in patients with normal angiography results (22). Furthermore, a cross-sectional study showed that LDL-C, total C, TG, Apo B, protein bound SA, and hs-CRP levels were significantly higher in prehypertensive than in normotensive individuals, with protein bound SA concentration positively correlated with hs-CRP and LDL-C concentrations. These findings suggest that SA and hs-CRP may be cardiovascular risk factors in prehypertensive individuals (23). It remains unclear, however, whether elevated SA levels represent the natural course of CVD or whether there is an etiological association. Further prospective studies are necessary to provide evidence for the use of SA as a marker of CVD.

The mechanism of the relationship between elevated serum SA levels and CVD remains unclear. However, three possible mechanisms have been proposed. The first suggests that serum SA levels are correlated with those of fibrinogen (24). The second mechanism is based on finding that SA concentrations in LDL-C are 40–75% lower in patients with coronary atherosclerosis than in healthy individuals. This lower LDL-C concentration may cause lipids to accumulate in endothelial and smooth muscle cells and macrophages (25). In addition, the higher SA content of LDL-C is a determining factor in LDL-C catabolism, with the catabolism of SA-poor LDL-C being more difficult in humans (26). According to the third mechanism, the contribution of inflammatory cells [monocytes, macrophages] to the atherosclerotic process increases SA levels (24). Therefore, higher serum SA levels indicate both an active atherosclerotic process and increased thrombogenic activity (7).

Many studies show that SA is high in CVD and associated with conventional risk factors. However, to the best of our knowledge, the number of studies investigating SA and CIMT association is very limited (11, 17, 27). For example, Tseke et al. (11) showed that there was a positive correlation between SA and CIMT in HD patients. In the present study, we showed a positive relationship between SA and CIMT as well. Moreover, we found that SA was the most powerful factor among factors that predict risk for CIMT (it was found that an increase of 1 unit in sialic

acid level led to an increase of 2.419 in CIMT level). This shows us that measurement of SA might provide information about CV risk as reliably as conventional CV risk indicators, maybe even more.

The fact that no relationship was found between SA and TSH, fT4, fT3, and thyroid autoantibody levels strongly suggests that there is no relationship between elevated SA and hypothyroidism and Hashimoto's thyroiditis and the correlation of SA with LDL-C, hs-CRP, and CIMT strongly suggests that elevated SA is related to atherosclerosis.

The cross-sectional design of the study was our main limitation. The re-evaluation of atherogenetic indicators following the establishment of euthyroidism with treatment could have provided more valuable results. In addition, the question whether sialic acid levels would represent a better biomarker of cardiovascular risk than the established biomarkers remains unanswered by this study design.

In conclusion, measurement of TSA is a simple and practical method. SA correlates well with conventional atherosclerosis markers and therefore might be an indicator of atherosclerosis in patients with hypothyroidism. However, further studies are needed to conclude whether sialic acid is superior to other atherosclerosis markers and make a suggestion to use it for this purpose.

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