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Evaluation of Selected Atherosclerosis Risk Factors in Women with Subclinical Hypothyroidism Treated with L-Thyroxine

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Abstract

Background. Subclinical hypothyroidism (SCH) is a common endocrine disorder, probably increasing cardiovascular (CV) risk. However, the relation between SCH and atherosclerosis risk factors remains unclear.

Objectives. The aim of the study was to evaluate selected atherosclerosis risk factors in women with SCH in comparison to a group of healthy women and women with overt hypothyroidism, as well as to investigate the influence of L-thyroxine replacement on those risk factors.

Material and Methods. The study group consisted of 187 obese women aged between 50 and 70 years: 100 women with SCH, 45 women with overt hypothyroidism and 42 women with TSH level in reference ranges. Anthropometric parameters were evaluated. Laboratory tests included thyroid hormones concentrations, lipid profile with apolipoproteins, CRP, homocysteine. Atherosclerotic indexes were calculated: LDL C/HDL C ratio, apoA1/apoB ratio and Castelli risk index. Women with hypothyroidism were given L-thyroxine treatment and after 6 months in euthyroidism the evaluation was repeated.

Results. Total cholesterol, LDL-cholesterol and triglycerides concentrations as well as LDL-C/HDL-C ratio and Castelli index were higher in SCH than in controls and decreased after L-thyroxine substitution. All of the calculated atherosclerosis indexes showed significant positive correlations with TSH concentration in SCH group. Also in this group the systolic and diastolic blood pressure decreased significantly after treatment.

Conclusions. Dyslipidemia in obese SCH women is not severe, but if untreated for many years, it may lead to atherosclerosis. Substitution therapy improves the lipid profile, changing the relations between protective and proatherogenic fractions of serum lipids, and optimises blood pressure (*Adv Clin Exp Med* 2016, 25, 3, 457–463).

Key words: risk factors, atherosclerosis, subclinical hypothyroidism, cardiovascular disease, L-thyroxine treatment.

Subclinical hypothyroidism (SCH) is defined as an elevated serum thyroid stimulating hormone (TSH) concentration in the presence of normal serum free thyroxine (fT4) and triiodothyronine (fT3) concentrations. This condition has been recently more commonly recognized due to thyroid function testing increase in primary care. The occurrence of SCH is estimated from 4% to 10% of the population, being diagnosed more frequently in women and elderly people [1, 2]. The importance of SCH results mainly from its sug-

gested influence on atherosclerosis development. Higher serum TSH could become easy to diagnose and eliminate cardiovascular (CV) risk factor, but the relationship between SCH and adverse CV outcomes are still uncertain. Although some interventional studies showed that L-thyroxine replacement therapy in SCH is able to improve most CV structural and functional surrogate markers [3–5], there is no clear evidence that restoration of euthyroidism in SCH reduces CV disease risk. Recent European Thyroid Associa-

tion Guidelines recommend individual approach to each patient [6].

The aim of the study was to evaluate selected atherosclerosis risk factors in women with SCH in comparison to a group of healthy women and women with overt hypothyroidism, as well as to investigate the influence of L-thyroxine replacement on those risk factors in SCH and overt hypothyroidism groups.

Material and Methods

The study group consisted of 187 postmenopausal women aged between 50 and 70 years (mean 61.2 ± 9.7 years), recruited in Endocrinological Outpatient Clinic in Bolesławiec in years 2005–2008. Written informed consent was obtained from each participant. The study protocol was approved by the ethical committee.

Specific anamnesis and general physical examinations were done. Exclusion criteria were drugs interfering with TSH, fT4, serum lipids and homocysteine (HCY) serum levels and other causes of elevated serum TSH concentration.

Body weight and height were measured. The BMI was calculated as body weight in kilograms divided by height in square meters (kg/m^2). Waist circumference was measured at the umbilical level, hip circumference was measured at the greater trochanter, waist-to-hip ratio (WHR) was also calculated. Blood pressure was measured on the left arm after 10 min of rest. Ultrasonography of the thyroid gland was performed with ALOKA apparatus, transducer frequency 7.5 MHz. Blood samples were drawn after an overnight fast (12 h) for plasma TSH, fT4, anti-thyroid peroxidase antibodies (TPO-Ab), triglycerides (TG), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), apolipoproteins – apoA1 and apoB, HCY, C-reactive protein (CRP).

The serum TSH, fT4 and TPO-Ab levels were measured by immunofluorescence (Immulite 1000; DPC). The levels of TC, TG and HDL-C were measured with a colorimetric method (Flexor E, Vitalab). LDL-C was calculated by means of the Friedewald equation. ApoA1, apoB and CRP were measured with the use of nephelometric methods (Siemens) and HCY with enzyme conversion immunoassay (AxSYM test, Abbott).

For each patient atherosclerotic indexes were calculated: LDL-C/HDL-C ratio, Castelli risk index (TC-HDL-C/HDL-C) and apoA1/apoB ratio.

The patients were divided into subgroups based on the thyroid function tests:

- One hundred women with SCH, with fT4 in reference ranges and TSH level above $4.0 \mu\text{IU}/\text{mL}$ (ranged from 4.1 to $12 \mu\text{IU}/\text{mL}$ with mean value

$8.6 \pm 4.0 \mu\text{IU}/\text{mL}$). All patients after confirming SCH received L-thyroxine therapy and were observed for 6 months. During that time all became euthyroid and the examinations were repeated.

S1 – SCH women before treatment, S2 – the same group after treatment.

- Forty-five women with overt hypothyroidism, TSH level over $10 \mu\text{IU}/\text{mL}$ (mean value 44.6 ± 21.6) and fT4 below $0.8 \text{ ng}/\text{mL}$. All patients after confirming hypothyroidism received L-thyroxine therapy and were observed for 6 months. During that time all became euthyroid and the examinations were repeated.

H1 – women with hypothyroidism before treatment, H2 – the same group after treatment.

- Forty-two healthy women with TSH level in reference ranges – 0.4 to $4.0 \mu\text{IU}/\text{mL}$ (mean value 1.5 ± 0.8) and normal fT4 in reference ranges – 0.8 to $1.9 \text{ ng}/\text{dL}$ (mean value $1.3 \pm 0.2 \text{ ng}/\text{dL}$).

C – control group.

Variables were described with the use of elements of descriptive statistics and included: minimum and maximum value, mean and standard deviation.

Planned comparisons between two of three pairs of independent continuous variables were made with the Mann-Whitney *U* test. The 5% significance level was set to each individual comparison, than the whole family of comparisons as in multiple comparisons, i.e. the Bonferroni correction to adjust the significance level was not applied. This approach has more power to detect true differences [7].

Differences between dependent continuous variables were evaluated by the Wilcoxon signed-rank test.

In order to examine the correlation between the analyzed indices, Spearman's rank correlation coefficient was calculated.

Results

Thyroid Function

As a result of subgroups definition, before treatment TSH concentrations were significantly higher in SCH and overt hypothyroidism groups than in controls. After treatment TSH levels decreased significantly and showed no difference with TSH in controls (Table 1).

RR, BMI, WHR

In the group with SCH, systolic and diastolic blood pressure (RRs, RRd) decreased significantly after treatment (mean RR: $144.4/87.1 \text{ mm Hg}$ in S1

Table 1. TSH and fT4 concentrations before and after treatment

Group	TSH ($\mu\text{IU/mL}$)	fT4 (ng/dL)
S1 (X \pm SD)	8.6 ± 4.0 ^{1) 3)}	1.1 ± 0.2 ^{1) 3)}
S2 (X \pm SD)	1.9 ± 1.0 ¹⁾	1.4 ± 0.3 ^{1) 3)}
H1 (X \pm SD)	44.6 ± 21.6 ^{2) 5)}	0.6 ± 0.2 ^{2) 5)}
H2 (X \pm SD)	1.4 ± 0.9 ²⁾	1.6 ± 0.3 ^{2) 6)}
C (X \pm SD)	1.6 ± 0.8 ^{3) 4)}	1.3 ± 0.2 ^{3) 4) 5) 6)}

X – mean value; SD – standard deviation; S1 – SCH group before treatment; S2 – SCH group after treatment; H1 – group with overt hypothyroidism before treatment; H2 – group with overt hypothyroidism after treatment; C – control group; statistically significant differences between groups ($p < 0.05$): ¹⁾ S1 and S2; ²⁾ H1 and H2; ³⁾ S1 and C; ⁴⁾ S2 and C; ⁵⁾ H1 and C; ⁶⁾ H2 and C.

vs. 138.3/84.2 mm Hg in S2). RRs and RRd were also higher in S1 group in comparison to controls, but the difference was not statistically significant. RRs, RRd were significantly higher in H1 group than in control group. After treatment with L-thyroxine

RRs and RRd decreased and there was no difference between groups H2, S2 and controls (Table 2).

Study participants were mostly obese or overweight (mean BMI over 30). There was no significant difference in BMI and WHR between groups before and after treatment and in comparison to control group (Table 2).

Serum Lipids and Atherosclerosis Indexes

TC and LDL-C concentrations were higher in S1 and H1 groups than in controls and decreased significantly after L-thyroxine substitution. After 6 months of treatment both parameters were lower in S2, H2 than in controls (statistically significant only TC in S2). TG concentration was also higher in S1 and H1 than in controls (but significantly only in group with overt hypothyroidism) and decreased after treatment, but the differences between S1 and S2, as well as H1 and H2 did not reach statistical significance. HDL-C levels were lower in S1 and H1 than in the control group and decreased after treatment in both groups (Ta-

Table 2. Characteristic of the groups before and after the treatment with L-thyroxine

Group	BMI (kg/m^2)	WHR	RRs (mm Hg)	RRd (mm Hg)	V thyroid (mL)	TPO-Ab (IU/mL)
S1 (X \pm SD)	30.1 ± 5.7	0.9 ± 0.1	144.4 ± 2.0 ¹⁾	87.1 ± 9.8 ¹⁾	12.9 ± 12.3	225 ± 356.7
S2 (X \pm SD)	30.5 ± 5.9	0.9 ± 0.1	138.3 ± 18.8 ¹⁾	84.2 ± 10.4 ¹⁾		
H1 (X \pm SD)	31 ± 5.7	0.9 ± 0.1	152.3 ± 22.2 ^{2) 3)}	90.9 ± 9.4 ^{2) 3)}	12.8 ± 16.7	471.7 ± 446.6
H2 (X \pm SD)	30.9 ± 5.7	0.9 ± 0.1	138 ± 20.8 ²⁾	84.9 ± 9.3 ²⁾		
C (X \pm SD)	29.9 ± 5.1	0.9 ± 0.1	141.7 ± 15.8 ³⁾	84.5 ± 9.6 ³⁾	14 ± 9.2	78.5 ± 232.1

X – mean value; SD – standard deviation; RRs – systolic blood pressure; BMI – body mass index; RRd – diastolic blood pressure; WHR – waist-hip ratio; V thyroid – thyroid volume; S1 – SCH group before treatment; S2 – SCH group after treatment; H1 – group with overt hypothyroidism before treatment; H2 – group with overt hypothyroidism after treatment; C – control group; statistically significant differences between groups ($p < 0.05$): ¹⁾ S1 and S2, ²⁾ H1 and H2, ³⁾ H1 and C.

Table 3. Serum lipids and apolipoproteins concentrations before and after treatment

Grupa	TC (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	TG (mg/dL)	ApoA1 (g/L)	ApoB (g/L)
S1 (X \pm SD)	228.8 ± 45.5 ¹⁾	53.1 ± 16.8 ³⁾	145.6 ± 42.6 ¹⁾	151.2 ± 74.5	1.3 ± 0.4 ³⁾	0.9 ± 0.3
S2 (X \pm SD)	204.6 ± 35.4 ^{1) 4)}	51.1 ± 11.3 ⁴⁾	125.9 ± 32.7 ¹⁾	137.7 ± 64.4	1.4 ± 0.4 ⁴⁾	0.9 ± 0.3
H1 (X \pm SD)	266 ± 68.4 ^{2) 5)}	57.2 ± 16.9 ²⁾	176.4 ± 61.6 ^{2) 5)}	174.1 ± 78.4 ⁵⁾	1.3 ± 0.5 ⁵⁾	1 ± 0.4
H2 (X \pm SD)	213.6 ± 36.7 ²⁾	51.7 ± 11.9 ²⁾	132.6 ± 33.5 ²⁾	146.5 ± 80.3	1.4 ± 0.3 ⁶⁾	0.9 ± 0.3
C (X \pm SD)	223.1 ± 42.3 ^{4) 5)}	57.9 ± 12.8 ^{3) 4)}	136.3 ± 38.8 ⁵⁾	136.3 ± 56.3 ⁵⁾	1.6 ± 0.4 ^{3) 4) 5) 6)}	1 ± 0.3

X – mean value; SD – standard deviation; S1 – SCH group before treatment; S2 – SCH group after treatment; H1 – group with overt hypothyroidism before treatment; H2 – group with overt hypothyroidism after treatment; C – control group; HDL-C – HDL cholesterol; LDL-C – LDL cholesterol; TG – triglycerides; statistically significant differences between groups ($p < 0.05$): ¹⁾ S1 and S2, ²⁾ H1 and H2, ³⁾ S1 and C, ⁴⁾ S2 and C, ⁵⁾ H1 and C, ⁶⁾ H2 and C.

Table 4. Atherosclerosis indexes before and after treatment

Group	LDL-C/HDL-C	Castelli risk index	apoB/apoA1
S1 (X ± SD)	2.9 ± 1.2 ²⁾	3.6 ± 1.3 ²⁾	0.7 ± 0.2
S2 (X ± SD)	2.6 ± 0.8	3.1 ± 0.9	0.7 ± 0.2
H1 (X ± SD)	3.2 ± 1.3 ^{1) 3)}	4 ± 1.7 ³⁾	0.9 ± 0.3 ^{1) 3)}
H2 (X ± SD)	2.6 ± 0.8 ¹⁾	3.3 ± 1.0	0.7 ± 0.2 ¹⁾
C (X ± SD)	2.5 ± 0.8 ^{2) 3)}	3 ± 0.9 ^{2) 3)}	0.6 ± 0.2 ³⁾

X – mean value; SD – standard deviation; S1 – SCH group before treatment; S2 – SCH group after treatment; H1 – group with overt hypothyroidism before treatment; H2 – group with overt hypothyroidism after treatment; C – control group; statistically significant differences between groups ($p < 0.05$): ¹⁾ H1 and H2, ²⁾ S1 and C, ³⁾ H1 and C.

ble 3). There was also a significant positive correlation between fT4 and HDL-C concentrations in S1 and H2 groups (p -values 0.02 and 0.004, respectively) – data not shown.

ApoA1 concentration was significantly lower in each group with subclinical and overt hypothyroidism before and after treatment in comparison to the control group. L-thyroxine treatment did not influence significantly the apoA1 level in any group. ApoB concentrations in examined groups did not differ significantly (Table 3).

LDL-C/HDL-C ratio was in SCH group significantly higher than in the controls. It also decreased after treatment, the difference before and after L-thyroxine substitution was not statistically significant (S1 vs. S2); however, the value between S2 and controls did not differ significantly. In the group with overt hypothyroidism, the LDL-C/HDL-C ratio was significantly higher before treatment than in the controls and after treatment. Castelli risk index (TC-HDL-C/HDL-C) was significantly higher in S1 and H1 than in the controls, but the treatment decreased it only insignificantly. L-thyroxine substitution influenced apoB/apoA1 ratio only in the group with overt hypothyroidism (Table 3). All of the calculated atherosclerosis

indexes showed statistically significant positive correlations with TSH concentration in S1 group (p -values for LDL-C/HDL-C: 0.002, Castelli risk index: 0.02, apoB/apoA1: 0.03). There were also statistically significant negative correlations between fT4 and two indexes - LDL-C/HDL-C and Castelli risk index in S1 group (p -values 0.03 and 0.02, respectively) – data not shown.

Homocysteine

HCY concentration was the highest in the group with overt hypothyroidism before treatment, but the differences between groups and after treatment were not significant (Table 5). There was also no correlation between HCY and TSH or fT4 (data not shown).

CRP

CRP concentrations were higher before treatment both in SCH and overt hypothyroidism groups than after 6 months of L-thyroxine replacement and in comparison to controls, but the differences were not statistically significant (Table 6). There were no significant correlations between CRP and TSH or fT4 (data not shown).

Table 5. Homocysteine concentrations before and after treatment

Group	Homocysteine (HCY)(μmol/L)
S1 X ± SD	13.0 ± 3.2
S2 X ± SD	13.6 ± 4.1
H1 X ± SD	15.2 ± 3.4
H2 X ± SD	14.4 ± 7
C X ± SD	13.5 ± 4.4

X – mean value; SD – standard deviation; S1 – SCH group before treatment; S2 – SCH group after treatment; H1 – group with overt hypothyroidism before treatment; H2 – group with overt hypothyroidism after treatment; C – control group.

Table 6. CRP concentrations before and after treatment

Group	hsCRP (mg/L)
S1 X ± SD	2.7 ± 1.8
S2 X ± SD	2.6 ± 2.6
H1 X ± SD	2.6 ± 1.8
H2 X ± SD	2.3 ± 2.1
C X ± SD	2.1 ± 1.9

X – mean value; SD – standard deviation; S1 – SCH group before treatment; S2 – SCH group after treatment; H1 – group with overt hypothyroidism before treatment; H2 – group with overt hypothyroidism after treatment; C – control group.

Discussion

SCH is a common finding, often causing a treatment dilemma in endocrine practice. European guidelines recommend a L-thyroxine substitution in younger patients (< 65 years), especially with some symptoms suggestive of hypothyroidism, with goiter, after hemithyroidectomy or with serum TSH > 10 mU/L. However, patients with TSH < 10 mU/L and lack of complaints might be also monitored without treatment [6]. Such ambiguity arises from unanswered questions, including whether SCH increases CV risk or mortality and whether it negatively influences metabolic parameters.

Our patient group was classified to a category, where no clear indications are given – aged 50–70 years, with median TSH 8.6 ± 4.0 μ IU/mL, without obvious symptoms of hypothyroidism. The most important reason to treat such individuals would be to improve their metabolic profile, especially taking into consideration obesity affecting most of them. We assessed the influence of SCH on clinical and laboratory markers of CV risk as well as the changes of those parameters after treatment with L-thyroxine. The limitation of our study is the number of patient groups, because the examined parameters (such as body weight or serum lipids) are influenced by many other factors, especially lifestyle. That might be the reason why some correlations did not reach statistical significance, but some tendencies were observed.

The first examined CV risk factor was blood pressure. It was higher in SCH group than in controls, and interestingly enough both RRs and RRd decreased significantly after the treatment (Table 2). Before L-thyroxine supplementation mean RRs value was over 140 mm Hg – allowing us to diagnose hypertension, and after 6 months it fell below this limit. Our results correspond with many other studies in this field. Adrees et al. observed a reduction of blood pressure and intima media thickness together with a normalization of glomerular filtration rate in SCH women treated 18 months with L-thyroxine, suggesting its hemodynamic effect [8]. Dernellis et al. showed that hypothyroidism is connected to aortic stiffness, and hormone replacement therapy eliminated hypertension in 50% of patients [9]. The role of hypothyroidism, even subclinical, in hypertension development probably stems from increasing the systemic arterial resistance and influence mostly RRd. Even the elevation of TSH in normal ranges might be related to higher blood pressure [10].

The second measured parameter was BMI and WHR. Most of the patients in our study were obese or overweight, and there was no significant differ-

ence between SCH vs. control or overt hypothyroidism group (Table 2). Hormone substitution did not influence body weight or WHR. In contrast to our results, there are some studies showing that elevated TSH, even in upper reference ranges, may lead to weight gain [11]. Also Knudsen et al. observed a positive correlation between TSH and BMI; however, this relationship disappeared when BMI exceeded 30 kg/m² [12]. Authors explain that when BMI reaches the limit of obesity, lifestyle factors like diet or physical activity have a greater influence on body weight than thyroid hormones. The European Thyroid Association declares: “There is no evidence for a favorable effect of L-thyroxine therapy on body weight in obese subjects with serum TSH levels < 10 mU/L and normal fT₄ concentrations” [6]. Our results remain in accordance with this claim.

The beneficial effect of SCH treatment in our study was shown in the area of serum lipids. At the beginning of the observation, patients with SCH presented an intermediate TC, LDL-C and TG profile between euthyroidism and overt hypothyroidism. It is consistent with the data from large epidemiologic studies, where TC, LDL-C and TG levels were confirmed higher in people with SCH vs. controls [1]. Interestingly, some works provide evidence that relationship between SCH and dyslipidemia is more pronounced in women [13, 14]. Most importantly, the treatment intervention in our study caused significant reduction of serum TC (mean decrease of 24.2 mg/dL) and LDL-C (mean decrease 19.7 mg/dL) as well as statistically insignificant decrease of serum TG (13.5 mg/dL) (Table 3). Similarly, Meier et al. showed a reduction of serum LDLc by 0.33 mmol/L and of TC by 0.24 mmol/L after 12 months of L-thyroxine replacement [15] and Razvi et al. – reduction of 7.3% of LDL-C concentration and 5.5% of TG concentration [3]. There is reliable data suggesting that such changes in LDL-C concentration may improve CV outcomes [16]. Another significant factor is the relation between atherosclerotic cholesterol fractions to atheroprotective HDL-C. We calculated LDL-C to HDL-C ratio and Castelli risk index (LDL-C and VLDL to HDL, value over 4 suggests high CV risk). Both of those parameters were significantly higher in groups with overt and subclinical hypothyroidism than in the controls. As in the case of the mentioned dyslipidemia, SCH group presented an intermediate state between overt hypothyroidism and euthyroidism (Table 4). Interestingly, there was a significant correlation between TSH and LDL-C/HDL-C and TSH with Castelli risk index in SCH group before treatment. L-thyroxine substitution brought some improvement in atherosclerosis indexes; however, the de-

crease was only statistically significant in overt hypothyroidism group in LDL-C/HDL-C ratio. Some authors reported a similarly beneficial influence of hormone therapy on LDL-C/HDL-C ratio [17], but others failed to show such relations [18]. As for atheroprotective HDL particles, their concentration was lower in both hypothyroidism groups vs. controls in our study. Surprisingly, HDL-C level fell even lower after the treatment, which remains in contrast to the general advantageous effect of L-thyroxine therapy on lipid profile. The possible explanation might be the decrease of TC level. Moreover, the relations between LDL and HDL cholesterol improved after treatment, so we can conclude that decrease of HDL-C in this situation does not cause negative effect on CV profile.

A case-control INTERHEART study emphasized the influence of apoB/apoA ratio on CV risk in every ethnic and age group [19]. In our study apoA1 concentration was significantly lower in groups with subclinical and overt hypothyroidism than in controls and tended to increase after treatment (Table 3). ApoB concentration did not differ significantly among the studied groups. The proatherogenic apoB/apoA ratio was the highest in patients with overt hypothyroidism and the lowest in euthyroid group (Table 4). Once again, SCH group presented intermediate profile among studied groups. There was a significant correlation between apoB/apoA ratio and TSH level in SCH group before treatment. However, L-thyroxine treatment caused a significant decrease of this index only in the group with overt hypothyroidism, not in SCH group. The data concerning this problem in literature is scarce. According to Turhan et al., there was no difference in apoB concentration between SCH and control group [18], while

some authors reported not only higher apoB level, but also its positive correlation with TSH in SCH patients [17]. The observations concerning apoA1 are also unclear. In some studies L-thyroxine substitution caused increase of apoA1 level [20], while in some it remained unchanged [21].

Generally, most of the authors note a positive influence of thyroid hormone supplementation on lipid profile in patients with SCH. Our work remains consistent with this statement. The reported changes in absolute values may not be very large, but the relations between protective and proatherogenic factors changed in a beneficial way and they seem to be more important in predicting CV risk.

Hiperhomocysteinemia, which is an independent CV risk factor, was also reported to be associated with SCH [22]. However, some studies denied this correlation [23]. We did not observe differences in HCY concentration between SCH and control group or significant changes after treatment (Table 5). Probably, a greater effect of factors such as age, body weight and vitamin B status limited the influence of SCH on HCY.

We also observed no clear association between SCH or thyroid hormone substitution in SCH with CRP concentration. Therefore, our results are similar to some large studies [24, 25]. Those findings imply that SCH probably does not play any important role in inflammation associated with atherosclerosis.

Summarizing, our results indicate that SCH in postmenopausal women causes a negative effect on CV risk, mainly due to increase of blood pressure and disturbances in serum lipid profile. Treatment with L-thyroxine may reverse some of those phenomena.

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