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Does TSH Directly Affect PCSK9, a Regulator of LDL Receptors, in Euthyroid Subjects?

Stephen W. Spaulding

Kwakernaak AJ, Lambert G, Kobold ACM, Dullaart RPF. Adiposity blunts the positive relationship of thyroid-stimulating hormone with proprotein convertase subtilisin-kexin type 9 levels in euthyroid subjects. Thyroid. October 29, 2012 [Epub ahead of print]. doi:10.1089/thy.2012.0434.

SUMMARY

Background

Patients with altered thyroid function may display a variety of lipid abnormalities, but the precise mechanisms involved are poorly understood. The protein PCSK9 (proprotein convertase subtilisin/kexin type 9) binds to low-density lipoprotein (LDL) receptors on the cell surface of hepatocytes, and targets them for lysosomal degradation, which raises the LDL cholesterol (LDL-C) level by impairing clearance. Recently, two monoclonal antibodies against PCSK9 were shown to acutely lower LDL-C levels in clinical studies (1,2). The current paper reports an initial exploration of possible relationships between the circulating level of PCSK9 and lipids, TSH, and FT_4.

Methods

The subjects were recruited by advertising in Groningen newspapers. Any candidate who was pregnant, smoked, consumed more than three drinks per day, took any medication other than oral contraceptives, had a history of thyroid disease or had thyroid abnormality on physical examination was excluded, as was anyone with a history of diabetes, hypertension, clinically manifest cardiovascular disease, or substantial liver or renal abnormalities. The paper reports results on fasting samples from 74 subjects, of whom 10 were obese (body-mass index [BMI, the weight in kilograms divided by the square of the height in meters], 30.2 to 35.2) and 31 were women. Four subjects (all non-obese) had positive anti-TPO or anti-Tg antibody levels. Insulin sensitivity, measured by the Homeostasis Model Assessment (HOMA), was calculated based on insulin and glucose levels. Apolipoprotein B (ApoB), total cholesterol, and high-density lipoprotein cholesterol (HDL-C) and triglyceride levels were measured, and non-HDL-C and LDL-C levels were calculated. PCSK9 levels were measured by sandwich enzyme-linked immunoabsorption. Most of the data are provided only as medians and interquartile values. Between-group differences were assessed using chi-squared or nonparametric Mann–Whitney U tests; Spearman's rank correlation coefficient was used to assess univariate differences between obese and non-obese subjects; and multiple linear regression was used to assess the contributions and interactions between multiple variables.

Results

The obese and non-obese groups did not differ in their TSH, FT_4, PCSK9, non-HDL-C, LDL-C, or ApoB levels. In the non-obese group, the PCSK9 level displayed a moderate linear correlation with the TSH level ($r = 0.285$, $P = 0.023$) When the data from both obese and non-obese groups were combined to assess univariate relationships, the PCSK9 level correlated with insulin, total cholesterol, non-HDL-C, LDL-C, ApoB, and triglyceride levels. When the non-obese group was analyzed separately, the same correlations were found, except that the correlation with insulin was no longer significant. In contrast, in the obese subjects, PCSK9 levels correlated only with insulin and HOMA levels. Interestingly, however, TSH levels in the obese subjects did correlate significantly with BMI. If obesity was expressed simply as a dichotomous variable (BMI either < or >30), multiple regression analysis on the data from all 74 subjects indicated a significant interaction between TSH and BMI, after accounting for the direct effects of age, sex, FT_4, TSH, and obesity.

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Remarkably, none of the lipid parameters showed any correlation with the FT_4 level.

Conclusions

In euthyroid non-obese subjects, the circulating level of PCSK9 correlated linearly with the TSH level. In the entire group of 74 subjects, the PCSK9 level showed univariate correlations with total cholesterol, non-HDL-C, LDL-C, ApoB, and triglyceride levels. In the obese euthyroid subjects, the TSH level was positively associated with the BMI.

ANALYSIS AND COMMENTARY

The modest association observed between PCSK9 and TSH levels in this selected group of 64 non-obese subjects was not found in the small group of 10 obese subjects. Larger studies that include the assessment of other factors known to affect the variables studied, and that include more overweight and obese individuals, will be required in order to better evaluate associations of PCKS9 with TSH. (It is unfortunate that T_3 levels were not measured and that only a single measurement of FT_4 and TSH was made). Even so, it seems that PCSK9 will need to be added to the growing list of genes thought to link lipid and thyroid metabolism. Clinical studies show that the circulating level of PCSK9 responds promptly to fasting and to cholesterol depletion. One important factor that regulates PCSK9 is SREBP-2 (sterol regulatory element binding protein 2), a transcription factor that integrates signals from many pathways, including thyroid hormone. (I also note in passing that the PCSK9 gene contains a potential thyroid hormone receptor binding site [AGTGGAGGTAGGTGA] upstream of the transcription start site]). Despite such theoretical connections of PCSK9 with thyroid hormone levels, we must face the fact that this study reports that the PCSK9 level is associated with TSH, and not with FT_4. It is clear that functional TSH receptors are expressed in many tissues in addition to the thyroid and that some clinical studies on euthyroid subjects have found direct associations between TSH and cholesterol LDL-C and non-HDL-C levels (3). Several clinical papers suggesting a direct action of TSH on hepatic hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase were recently reviewed in Clinical Thyroidology (4). What is more, a direct association of BMI with TSH—but not with FT_4—was recently reported in a study of the National Health and Nutrition Examination Survey (NHANES) database (5). I look forward to further studies that assess how overt thyroid dysfunction affects PCSK9, and I hope that a specific mechanism that connects the level of TSH with that of PCSK9 will be uncovered.

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