Doctoral Thesis

SUBCLINICAL HYPOTHYROIDISM AS A CARDIOVASCULAR RISK FACTOR

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Controversy remains as to the risk of cardiovascular disease (CVD) associated with subclinical hypothyroidism (SCH) defined as an increased serum thyrotropin TSH concentration with normal free thyroxine and triiodothyronine levels. Substantial evidence indicates altered cholesterol and lipoprotein metabolism in SCH when serum TSH is above 10 mUI/L. Observed abnormalities include elevated plasma levels of total cholesterol (TC) and low density lipoprotein-cholesterol (LDL-C); the altered TC/high density lipoprotein-cholesterol (HDL-C) and LDL-C/LDL-C ratios suggest a potential accelerated risk for CVD. The influence of SCH on lipids is directly proportional to the degree of TSH elevation and becomes more significant with the progression from SCH to overt disease, thereby accelerating any propensity to atherosclerosis. Although many clinicians may tend to ignore SCH with TSH levels <10 mUI/L, it is apparent that an enhanced CV risk could apply to these individuals, perhaps compounded by insulin resistance and amplified by the co-presence of other risk factors such as endothelial dysfunction and elevated C-reactive protein.

Therefore, the aim of our study was to evaluate subclinical hypothyroidism as a cardiovascular risk factor, to assess the association between SCH and CHD, the dyslipidemia and morphological/functional cardiac changes at patients with subclinical hypothyroidism and the effect of the LT_4 treatment on those changes.

In the first part of our study we aimed to analyse the natural course of SCH, quantify the incidence of overt hypothyroidism and evaluate the risk factors for the development of definitive thyroid failure in our patients. Thirty-five patients (29 women and 6 men) over age 30yr. with SCH were followed-up for 36 months with repeated determinations of TSH and FT_4. Subscilical hypothyroidism was defined as a TSH level of 4.5 mU/L or greater, and was further classified

according TSH levels (stage 1: 4.5-6.9 mUI/L; stage 2: 7.0-9.9 mUI/L; stage 3: >10 mUI/L) Nine patients developed overt hypothyroidism and 12 showed normalisation of their TSH values, 14 remained with SCH. Kaplan-Meier analysis showed that the development of definitive thyroid failure was significantly related to the presence of symptoms of hypothyroidism ($P<0.0001$), goiter ($P<0.0001$), positive thyroid antibodies ($P<0.005$) and mainly low normal free T_4 ($P<0.0001$) and high TSH ($P<0.0001$) concentrations at baseline. A stepwise Cox regression analysis showed that the only significant factor for progression to overt hypothyroidism was serum TSH concentration ($P<0.0001$).

In conclusion, TSH concentration is the most powerful predictor for the outcome of SCH. Subjects with mildly elevated TSH had a low incidence of overt hypothyroidism. We recommend follow-up with clinical and biochemical monitoring in these patients. Our data suggests that patients with mildly elevated TSH (4.5-9.9 mUI/L) have a low risk of developing overt hypothyroidism and a great probability of normalizing their TSH values over time. We recommend follow-up with clinical and biochemical monitoring in these patients. However, patients with higher levels of TSH should be treated with LT_4 because the risk of overt hypothyroidism is definitely elevated. These opinions are in agreement with the recommendations by an expert committee in a recently reported scientific review and guidelines for diagnosis and management of SCH.

In the second part of our study, we evaluated the association between SCH and CVD. There have been large epidemiological studies examining the association between thyroid dysfunction and cardiovascular disease. In particular, it is uncertain if SCH is a risk factor for cardiovascular disease. SCH has been associated with systolic and diastolic cardiac dysfunction and an elevated cholesterol level, but data on cardiovascular outcomes are limited. We investigated 69 patients, 35 with SCH and 34 euthyroid subjects, with baseline TSH measurements and 24 months follow-up data to determine whether SCH was associated with coronary heart disease. We examined the prevalence of CHD in subjects with subclinical thyroid dysfunction. In our prospective, analytical study we examined the risk of coronary heart disease events. Subjects with SCH (n=35) had a significantly higher prevalence of CHD than euthyroid subjects (n=34) (age and other cardiovascular risk factors adjusted) prevalence odds ratio, 1.7; 95% confidence interval (CI), 0.9-3.4 for TSH:4.5-6.9 mUI/L, P:0.24; OR, 2.2, 95% CI, 1.2-3.8, for TSH:7.0-9.9 mUI/L, P:0.02; OR, 3.2, 95% CI, 1.8-8.9 for TSH over 10 mUI/L, P:0.01.

In multivariate analysis, the risk of CHD was higher among those with high TSH levels (TSH: 7.0-9.9 mUI/L, HR, 2.49, 95% CI, 1.17-5.3, P:0.02 and TSH over 10 mUI/L, HR, 3.27, 95% CI,

1.59-6.34, P<0.01. Among the 56 participants without CHD at baseline, the HR for incident CHD events was higher among those with TSH values over 7.0 mUI/L (TSH: 7.0-9.9 mUI/L, HR, 1.6, 95% CI, 1.0-2.6, P:0.04; TSH over 10 mUI/L, HT, 2.5, 95% CI, 1.3-5.3, P<0.01). The increased risk of coronary heart disease events remained significant after further adjustment for standard cardiovascular risk factors.

Subclincal hypothyroidism is associated with an increased risk of CHD events among adults with a TSH level of 7.0 mUI/L or greater. Subclinical hypothyroidism may be an independent risk factor for coronary heart disease. Further investigation is warranted to assess whether SCH causes or worsens CHD.

The significance of dyslipidemia in SCH and the effect of thyroid substitution on lipids remains controversial. The third chapter of our study aimed to assess the association of SCH with lipid abnormalities and to quantify the effect of LT_4 therapy on serum lipids profiles. Serum lipids parameters of 41 patients with SCH (mean TSH, 11.9±3.1 mUI/L) who received LT_4 therapy for 50 wk. (mean dose 86.7±5.5 µg daily) and 35 patients with SCH (mean TSH, 9.1±1.1 mUI/L) and without treatment with levothyroxine were evaluated in an analytical study. Individual LT_4 replacement was performed based on TSH monitoring, resulting in euthyroid TSH levels (1.6±1.2 mUI/L). Lipid concentrations were measured before and after treatment. In the LT_4 group (n=41) total cholesterol and LDL were significantly reduced (-25 mg/dl, 9.9%, P<0.0001, respectively -7 mg/dl, 4.2%, P:0.02); also HDL decreased after treatment (-4 mg/dl, 6.7%, P:0.03). Patients with high pre-treatment total cholesterol (>240 mg/dl) showed a significant reduction in both total cholesterol (273±16 vs. 242±15 mg/dl, P<0.01) and LDL-C (187±18 vs. 171±18 mg/dl, P<0.01) levels. Similar, pronounced changes were observed in a subgroup of patients with pre-treatment levels of TSH >10mUIL (cholesterol, 235±24 mg/dl vs. 213±19 mg/dl, P<0.01; LDL-C, 141±16 vs. 140±18 mg/dl, P:0.05).

Our study suggests that physiological LT_4 replacement in patients with SCH has a beneficial effect on total cholesterol and LDL-C levels.

SCH has negative metabolic effects in affected patients and physiological, TSH guided LT_4 treatment determines a definite improvement in plasma lipoprotein profile and we therefore suggest replacement therapy in patients with mild thyroid failure and hypercholesterolemia, in particular in the presence of other cardiovascular risk factors.

Thyroid hormone is an important regulator of cardiac function. Overt hypothyroidism is accompanied by intrinsic myocardial changes reflected by alterations in contractility and relaxation, causing decreased cardiac contraction, cardiac output, heart rate and left ventricular

compliance as well as increase in total peripheral resistance, which may be responsible for increased prevalence of hypertension in overt hypothyroidism. Although there is no clear evidence that SCH causes clinical heart disease, changes in thyroid status are associated with changes in several cardiac parameters manifested by left ventricular dysfunction at rest and systolic dysfunction on effort, an enhanced risk for atherosclerosis and myocardial infarction. These cardiovascular abnormalities have been shown to regress with LT_4 therapy.

In the fourth chapter of our study, we evaluated fifteen patients with SCH (mean TSH, 9.3±4.5 mUI/L) and ten subjects with euthyroidism that served as controls (mean TSH, 1.6±0.7 mUI/L) over a period of 50 wk., by Doppler-echocardiography, and re-evaluated after 50 wk. of LT_4 substitutive therapy (mean dose, 79 µg daily). Mean plasma TSH was significantly higher in patients with SCH (9.3±4.5 vs. 1.6±0.7 mUI/L), whereas serum free T_4, although in the normal range were significantly lower (11.7±1.5 vs. 15.6±2.5 pmol/l, $P<0.005$). Blood pressure and heart rate did not differ from control values. Echocardiogram examination showed slight abnormalities of the left ventricular morphology (LVEDD was shortened, 45±1 vs. 48±1.8 mm, P:0.0001) and a significant reduction in the systolic function in the patient group (RVS, 1495±197 vs. 1262±192 dyn/secxcm^5, P:0.007; PEP, 6.9±0.2 vs. 5.01±0.3 (ms)^2, P:0.001; PEP/LVET, 0.71±0.03 vs. 0.58±0.03, P:0.001). In contrast, Doppler derived indices of diastolic function showed significant prolongation of the isovolumic relaxation time (94.4±7 vs. 84.3±8 msec, P:0.002), increased A wave (55.6±7 vs. 48.4±3.8 cm/sec, P:0.02) and reduced early diastolic mitral flow velocity /late diastolic mitral flow velocity ratio (1.38±0.3 vs. 1.57±0.3, P:0.001).

In the subgroup of 15 patients, thyroid hormone profile was normalised after 50 wk. of treatment and changes in the left ventricular morphology were also noticed (LVEDD, 45±1 initial vs. 48.2±1.6 mm, final, P:0.001). Systolic function was significantly enhanced as compared with pre-treatment values (RVS, 1495±197 vs. 1355±98 dyn/secxcm^5, P:0.02; PEP, 6.9±0.2 vs. 5.4±0.5 (ms)^2, $P<0.001$; PEP/LVET, 0.71±0.03 vs. 0.60±0.04, $P<0.0001$). Assessment of diastolic function showed significant shortening of isovolumic relaxation time (IVRT, 94.4±7 vs. 84.4±3 msec, $P<0.0001$), reduction of A wave (55.6±7 vs. 50.4±4 cm/sec, P:0.02) and increase of early diastolic mitral flow velocity/late diastolic mitral flow ratio (E/A, 1.38±0.3 vs. 1.58±0.1, P:0.0007). These findings indicate that subclinical hypothyroidism affects systolic but mostly diastolic function, and that these abnormalities may be reversed by LT_4 substitutive therapy.

As a final conclusion of our study, we may say that subclinical hypothyroidism could be considered an independent risk factor for coronary heart disease. A causal relationship between SCH and cardiovascular disease is biologically plausible, and patients with initial TSH values

over 7 mUI/L have an increased risk of developing cardiovascular disease. Subclinical hypothyroidism is associated with hypercholesterolemia (especially in patients with initial cholesterol values over 240 mg/dl and TSH over 10 mUI/L), left ventricular diastolic and systolic dysfunction, changes that are reversible with LT_4 substitutive therapy. Our study was a transversal one and it does not necessarily follow that treatment of subclinical hypothyroidism will reduce the risk of cardiovascular disease. To demonstrate such a benefit would require a large clinical trial with a long follow-up period. Until such a study is conducted, evidence based management of subclinical hypothyroidism will be based on epidemiological studies and on clinical trials with surrogate cardiovascular endpoints.

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