An increase in secretion of thyroid-stimulating hormone (TSH) is the earliest biochemical sign of impending thyroid failure. The decrease in free thyroxine (fT4) below a critical individual value (set point) produces an increase in TSH by a negative feedback mechanism. TSH increases in an exponential manner in comparison with the decrease in fT4: a decrease in fT4 by a factor of 2 leads to an increase in TSH by a factor of about 100. Therefore, measurement of TSH is much more sensitive for the detection of minimal thyroid failure than is measurement of the thyroid hormones.

The syndrome of increased TSH in the presence of normal concentrations of circulating thyroid hormones is called subclinical hypothyroidism (SCH) (1–3). By definition, the peripheral thyroid hormone concentrations are within the normal laboratory ranges, but the mean values of fT4 and total T4 (TT4) are statistically decreased, fT4 at an earlier stage than TT4 (4). In SCH, measurement of tri-iodothyronine is not necessary, as it is always normal, except in patients with non-thyroid illnesses or those who are taking drugs that affect thyroid function.

The clinical relevance of this syndrome, its possible morbidity and the need for treatment remain matters of debate and have given rise to several controversies. Hypothyroidism is a graded phenomenon, extending from minimal thyroid failure to severe overt hypothyroidism. SCH may present with different grades of severity (4) and variable clinical or metabolic manifestations. The mildest form, with normal or slightly increased TSH concentrations (<6 mU/l; grade I) but an excessive response to thyrotrophin-releasing hormone, is asymptomatic in most patients and has few metabolic effects (“preclinical state”). This form is also associated with a low risk for developing overt hypothyroidism in the future (3, 5). The most severe form of SCH, with a marked increase in TSH (>12 mU/l; grade III), often presents with clinical symptoms and signs that increase in frequency according to the magnitude of the increase in TSH: some of the patients with this form, however, are nevertheless asymptomatic. This severe form is associated with a high risk for developing overt hypothyroidism in subsequent years (5). Two placebo-controlled double-blind studies in small groups of patients with SCH demonstrated an improvement of clinical signs and well-being in some patients who received treatment with l-thyroxine (6, 7). Even among patients exhibiting the same degree of thyroid failure, major differences may be observed between individuals in their clinical manifestations and the metabolic responses of the target organs, most probably because of individual differences of hormone action at the molecular level. The various peripheral hormone effects of SCH and minimal thyroid failure can be evaluated by assessing clinical scores, lipid metabolism, tests of myocardial contractility, muscular function and other parameters.

The paper from Michalopoulou et al. (8) in this issue of *European Journal of Endocrinology* reports a study in which the lipid profile in a selected group of patients with high-normal TSH and increased cholesterol were evaluated, with the aim of investigating the effect of thyroxine treatment. One hundred and ten consecutive hypercholesterolaemic patients with TSH concentrations in the high-normal or in the low-normal range were assigned randomly to groups to receive either 25 or 50 μg thyroxine per day for 2 months. There was a significant reduction in total cholesterol and low-density lipoprotein (LDL) cholesterol concentrations only in patients with high-normal TSH (2.0–4.0 mU/l) treated with the higher dose of thyroxine. A significant reduction in cholesterol was observed only in patients with positive thyroid antibody titres. The authors conclude that patients with autoimmune thyroiditis with high-normal TSH concentrations have subtle thyroid dysfunction leading to an increase in serum cholesterol. They assume that these subjects may have SCH at a very early stage, presenting with increased cholesterol concentrations, and that this group may possibly benefit from thyroxine treatment.

These results are in contrast to the current literature. Among 12 cross-sectional studies of lipids in patients with SCH, 10 described normal values for serum cholesterol concentrations. Cholesterol concentrations were not reduced significantly by thyroid hormone therapy in 10 longitudinal studies (1, 9). When data were analysed according to the severity of SCH, some studies showed that cholesterol and LDL cholesterol concentrations are increased only in the severe form of SCH and in overt thyroid failure (2, 4). In contrast to these results, the present study by Michalopoulou et al. (8) describes a significant reduction in cholesterol concentrations in a very mild form of SCH, with high-normal TSH concentrations. How might one explain these discrepant findings?
Lipid metabolism is highly dependent on various non-thyroid factors that are often not well defined or standardized in reported studies. These factors include a variety of dietary compounds, body mass index, sex, alcohol intake, drugs and hormones and, in particular, genetic effects such as familial hypercholesterolaemia. All studies on SCH have been performed with rather small groups of patients and have low statistical power to unmask confounding variables. A particular problem not considered in earlier studies is the strong influence of smoking on lipid metabolism, which is detected only in hypothyroidism in the subclinical and overt state, but not in euthyroid controls (10). These lipid-increasing factors could aggravate hypercholesterolaemia, potentiating the effect of mild hypothyroidism.

One important factor for all peripheral effects of thyroid hormones on target tissues is the wide individual variation mentioned above. Myocardial function (measured on the basis of systolic time intervals (4, 6, 10) or by myocardial scintigraphy (11)) can be abnormal in SCH in a few individuals and will be normalized by thyroxine treatment; in most other patients, however, these tests give results in the normal range and are not affected by therapy. Marked interindividual variations have also been observed for tests of skeletal muscle function, such as ankle reflex time and creatine phosphokinase and myoglobin concentrations (4, 7, 10, 11). There are thus major individual differences in metabolic responses, despite similar degrees of thyroid failure, and this may in part provide an explanation for the results of different studies reported in the literature. What are the practical consequences for the diagnosis and treatment of minimal thyroid failure? SCH is a frequent syndrome affecting about 7.5% of females and 3% of males (3, 4). This amounts to a population of 43 million people in western and eastern Europe and 14 million in the United States. By means of TSH screening (recently advocated for the population of women older than 40 years), this syndrome will be detected much more frequently in the future. Should SCH be treated in all these patients, even in its mildest form? In our opinion this is not justified and would not be cost-efficient. However, it may be possible to identify subgroups of patients who may derive major benefit from treatment and therefore the patients should be evaluated; TSH measurement should be repeated in order to exclude laboratory or spontaneous fluctuations. An initial staging should be performed that includes fT4, thyroid antibodies, cholesterol, LDL cholesterol, clinical score of hypothyroidism, ankle reflex time (if available), a general assessment of the risk for atherosclerosis and coronary heart disease, evidence of depression or unexplained infertility. After such evaluation, and on the basis of grading of the TSH concentration mentioned above, a decision can be made for the individual patient: patients with minimal or moderate TSH concentrations with no clinical or metabolic changes require no treatment, but annual follow-up; however, those with high TSH values or abnormal clinical or metabolic test results require lifelong treatment with l-thyroxine.

Subclinical hypothyroidism is an interesting syndrome for the study of the physiology of impending hypothyroidism at the pituitary and thyroid levels and the effects on peripheral target tissues. It illustrates the marked individual variations in response to thyroid failure, probably reflecting genetic differences at the molecular level, which, it is to be hoped, will be clarified in the future.

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References

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