Editorial:

Subclinical hypothyroidism - when to treat?

Subclinical hypothyroidism (SCH) is defined biochemically as serum thyroid stimulating hormone (TSH) levels greater than the upper limit of the normal range, in presence of normal serum free thyroxine (free T₄) and normal serum free triiodothyronine (free T₃). It is a clinically silent disorder that can only be diagnosed on laboratory basis. Overall prevalence of this disorder is 4% to 15%. Prevalence of SCH is higher in females and in the elderly. It is also common in patients with Down’s syndrome, type 1 diabetes mellitus and other autoimmune disorders. Among pregnant women 2.2% have subclinical hypothyroidism and thyroid autoantibodies are seen in more than half of them. It’s prevalence is more in areas with abundant iodine intake as compared to iodine deficient areas.

The causes of subclinical hypothyroidism are same as those of overt hypothyroidism. Most of the patients have chronic autoimmune thyroiditis with high serum anti-thyroid peroxidase (anti-TPO) antibodies. Other causes include prior radioablation or anti-thyroid therapy for Graves’ disease, prior partial thyroidectomy, external radiation to neck, inadequate thyroxine replacement for overt hypothyroidism and drug-induced (e.g., iodide, lithium, amiodarone and iodine containing radiocontrast agents etc.).

A substantial proportion of patients with this condition eventually progress to overt hypothyroidism. The progression is related to initial serum TSH and to the presence of anti-TPO antibodies. During follow-up of over 20 years in Whickham survey, women with both high serum TSH and high thyroid autoantibody concentrations developed overt hypothyroidism at a rate of 4.3% per year, whereas women who had only high serum TSH or only high antibody concentrations developed overt hypothyroidism at rates of 2.6% and 2.1% respectively. In another study (n=82), the cumulative incidence of overt hypothyroidism was zero for those with initial TSH 4-6 mIU/L and 77% for those with initial serum TSH greater than 12 mIU/L after 10 years.

The underlying disease also may determine progression to overt hypothyroidism. Patients who have autoimmune disease, prior radioiodine therapy or high dose external radiotherapy are more likely to progress to overt disease. No progression is seen in those who have undergone thyroid surgery for indications other than hyperthyroidism or in those who had received external radiotherapy in childhood. Spontaneous recovery has been described especially in patients with negative antithyroid antibodies or those with serum TSH less than 10 mIU/L.

Though the term subclinical hypothyroidism means absence of clinical features, some patients may experience mild non-specific symptoms of hypothyroidism such as fatigue, constipation, weight gain, poor memory, among others. Data regarding the relationship between thyroxine (T₄) replacement and improvement in these symptoms are conflicting, probably due to differences among populations studied, age of patients, degree of TSH elevation and presence of antithyroid antibodies. Benefit of

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thyroxine replacement appears to be limited to patients with baseline TSH greater than 10 mIU/L. T4 replacement therapy given to patients with TSH less than 10 mIU/L does not result in any improvement in symptoms.\textsuperscript{16,17}

There are conflicting data regarding the association of SCH with cardiovascular risk factors. A few observational studies have shown increased prevalence of cardiovascular disease (CVD) and mortality\textsuperscript{18,19} especially in those with serum TSH greater than 10 mIU/L,\textsuperscript{20} whereas some other studies have not shown any increased risk.\textsuperscript{20,21} A meta-analysis\textsuperscript{22} of 15 studies showed an increase in prevalence and incidence of CVD mortality only in relatively younger population. There was no effect of SCH on CVD for those between 70-80 years; risk existed in younger than 70 years and positive protection was seen after 80 years of age.\textsuperscript{23} Serum total cholesterol and low density lipoprotein (LDL) cholesterol of subjects with TSH between 5.1 and 10 mIU/L has been reported to be greater than that seen in euthyroid subjects.\textsuperscript{4} Several other randomized trials have shown reduction in serum total and LDL cholesterol in patients treated with T\textsubscript{4} versus those treated with placebo. One meta-analysis\textsuperscript{24} of 13 studies concluded that serum total cholesterol and LDL cholesterol of patients with SCH improved with T\textsubscript{4} therapy. However, another smaller meta-analysis\textsuperscript{25} of seven trials showed no significant effect of T\textsubscript{4} replacement on serum total cholesterol, high density lipoprotein (HDL), LDL and lipoprotein (a) levels. It seems reasonable to infer that lipids improve with T\textsubscript{4} therapy especially if TSH is greater than 10 mIU/L. The factors that predict response of the lipids to T\textsubscript{4} therapy are greater elevation of TSH, insulin resistance, pre-therapy high cholesterol and type III dyslipidaemia.\textsuperscript{26}

Several reports suggest that SCH is associated with neuropsychiatric diseases. The life-time frequency of depression was found to be higher in subjects with SCH than those without SCH. It has also been observed that SCH may lower the threshold for the occurrence of depression.\textsuperscript{27} Mild thyroid failure can aggravate bipolar disorder, depression\textsuperscript{28} and is associated with abnormalities of muscle function, nerve conduction.\textsuperscript{29} Improvement is seen in some patients in cognitive and psychiatric functions after T\textsubscript{4} therapy.\textsuperscript{26} However, in a study among post-menopausal women, it was anti-TPO antibody and not TSH, which was found to be associated with depression.\textsuperscript{30}

Undetected SCH in pregnancy is a risk factor for miscarriage, low birth weight babies and possibly poor development outcome in offspring. In one study,\textsuperscript{31} a 7 point reduction in intelligent quotient was seen in children aged 7-9 years whose mothers had SCH at pregnancy compared with children of euthyroid mothers. T\textsubscript{4} replacement is suggested in pregnant women with TSH values above the trimester specific normal reference range and in women with SCH who wish to become pregnant.\textsuperscript{16}

The fundamental clinical question regarding patients with SCH is whether they should be treated with T\textsubscript{4} or not. As TSH level greater than 10 mIU/L predicts a higher rate of progression, most of the physicians prefer to start T\textsubscript{4} replacement. The experts also recommend treatment of patients with serum TSH greater than 10 mIU/L in view of data linking SCH with atherosclerosis, CVD and increased risk of progression to overt hypothyroidism.\textsuperscript{16}

Serum TSH 3-5 mIU/L is unlikely to indicate a clinically important abnormality, and T\textsubscript{4} therapy is controversial. In one study\textsuperscript{32} improvement in cognitive and psychological functions was observed in T\textsubscript{4} treated group compared to placebo treated group. Follow-up by TSH annually is a reasonable approach specially if anti thyroid antibodies are detected.

Large scale randomized studies showing any benefit in terms of improvement in serum lipids in patients with TSH of 5-10 mIU/L with T\textsubscript{4} treatment are lacking. Decision for therapy should be
individualized depending on age, presence of goitre, higher levels of antibodies, hypothyroid symptoms, progressive increase in TSH. Because of the effect of T₄ on growth and development, levothyroxine therapy for children and adolescents is also reasonable. Elderly persons older than 70 years of age, should not be considered for therapy in this category (TSH 5-10 mIU/L).

One simple approach is to start lowest dose necessary to normalise TSH typically with 25-50 μg/day. It avoids overtreatment in elderly or in patients with underlying cardiac disease. Young individuals with Hashimoto’s thyroiditis can be initiated on higher dosages, but dose should be titrated to maintain serum TSH in the range of 0.5-2.5 mIU/L.

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