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 T_4) and normal serum free triiodothyronine (free T_3). It is a clinically silent disorder that can only be diagnosed on laboratory basis. Overall prevalence of this disorder is 4% to 15%.[1-4] Prevalence of SCH is higher in females and in the elderly.[5,6] It is also common in patients with Down's syndrome, type 1 diabetes mellitus and other autoimmune disorders.[7,8] Among pregnant women 2.2% have subclinical hypothyroidism and thyroid autoantibodies are seen in more than half of them.[9] It's prevalence is more in areas with abundant iodine intake as compared to iodine deficient areas.[10]

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[11]. 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.,). The rising TSH found transiently during recovery from non-thyroidal illness is not included under subclinical hypothyroidism.

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.[12,13] During follow-up of over 20 years in Whickham survey,[11] 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[12] (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.[14] Spontaneous recovery has been described especially in patients with negative anti-thyroid antibodies or those with serum TSH less than 10 mIU/L.[15]

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 (T_4) 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

Online access
http://svimstpt.ap.nic.in/jcsr/apr-jun14_files/edi214.pdf
DOI: http://dx.doi.org/10.15380/2277-5706.JCSR.14.011

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.[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[18,19] especially in those with serum TSH greater than 10 mIU/L,[20] whereas some other studies have not shown any increased risk.[20,21] A meta-analysis[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.[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.[4] Several other randomized trials have shown reduction in serum total and LDL cholesterol in patients treated with T_4 versus those treated with placebo. One meta-analysis[24] of 13 studies concluded that serum total cholesterol and LDL cholesterol of patients with SCH improved with T_4 therapy. However, another smaller meta-analysis[25] of seven trials showed no significant effect of T_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_4 therapy especially if TSH is greater than 10 mIU/L. The factors that predict response of the lipids to T_4 therapy are greater elevation of TSH, insulin resistance, pre-therapy high cholesterol and type III dyslipidaemia.[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.[27] Mild thyroid failure can aggravate bipolar disorder, depression[28] and is associated with abnormalities of muscle function, nerve conduction.[29] Improvement is seen in some patients in cognitive and psychiatric functions after T_4 therapy.[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.[30]

Undetected SCH in pregnancy is a risk factor for miscarriage, low birth weight babies and possibly poor development outcome in off spring. In one study,[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_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.[16]

The fundamental clinical question regarding patients with SCH is whether they should be treated with T_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_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.[16]

Serum TSH 3-5 mIU/L is unlikely to indicate a clinically important abnormality, and T_4 therapy is controversial. In one study[32] improvement in cognitive and psychological functions was observed in T_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_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 T_4 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.

C. Srinivasa Rao,
V. Suresh,
Alok Sachan
Department of Endocrinology and Metabolism,
Sri Venkateswara Institute of Medical Sciences, Tirupati
e-mail: alok.sachan@yahoo.com

Received: 05 March, 2014.

Srinivasa Rao C, Suresh V, Sachan A. Subclinical hypothyroidism - when to treat? J Clin Sci Res 2014;3:81-4. DOI: http://dx.doi.org/10.15380/2277-5706.JCSR.14.011.

REFERENCES

1. Bemben DA, Hamm RM, Morgan L, Winn P, Davis A, Barton E. Thyroid disease in the elderly. Part 2. Predictability of subclinical hypothyroidism. J Fam Pract 1994;38:583-8.
2. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf) 1977;7:481-93.
3. Bagchi N, Brown TR, Parish RF. Thyroid dysfunction in adults over age 55 years. A study in an urban US community. Arch Intern Med 1990;150:785-7.
4. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526-34.
5. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol (Oxf) 1991;34:77-83.
6. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87:489-99.
7. Rubello D, Pozzan GB, Casara D, Girelli MF, Boccato S, Rigon F, et al. Natural course of subclinical hypothyroidism in Down's syndrome: prospective study results and therapeutic considerations. J Endocrinol Invest 1995;18:35-40.
8. Gray RS, Borsey DQ, Seth J, Herd R, Brown NS, Clarke BF. Prevalence of subclinical thyroid failure in insulin-dependent diabetes. J Clin Endocrinol Metab 1980;50:1034-7.
9. Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A, et al. Prevalence of thyroid deficiency in pregnant women. Clin Endocrinol (Oxf) 1991;35:41-6.
10. Szabolcs I, Podoba J, Feldkamp J, Dohan O, Farkas I, Sajgo M, et al. Comparative screening for thyroid disorders in old age in areas of iodine deficiency, long-term iodine prophylaxis and abundant iodine intake. Clin Endocrinol (Oxf) 1997;47:87-92.
11. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: A twenty-year follow-up of the Whickham survey. Clin Endocrinol 1995;43:55-68.
12. Huber G, Staub JJ, Meier C, Mitrache C, Guglielmetti M, Huber P, et al. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. J Clin Endocrinol Metab 2002;87:3221-6.

13. Rosenthal MJ, Hunt WC, Garry PJ, Goodwin JS. Thyroid failure in the elderly. Microsomal antibodies as discriminant for therapy. JAMA 1987;258:209-13.

14. Kabadi UM. Subclinical hypothyroidism: natural course of the syndrome during a prolonged follow-up study. Arch Intern Med 1993;153:957-61.

15. Díez JJ, Iglesias P, Burman KD. Spontaneous normalization of thyrotropin concentrations in patients with subclinical hypothyroidism. J Clin Endocrinol Metab 2005;90:4124-7.

16. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004 ;291:228-38.

17. Jorde R, Waterloo K, Storhaug H, Nyrnes A, Sundsfjord J, Jenssen TG . Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. J Clin Endocrinol Metab 2006;91:145-53.

18. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med 2000;132:270-8.

19. Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Arch Intern Med 2005;165:2460-6.

20. Boekholdt SM, Titan SM, Wiersinga WM, Chatterjee K, Basart DC, Luben R, et al. Initial thyroid status and cardiovascular risk factors: the EPIC-Norfolk prospective population study. Clin Endocrinol 2010;72:404-10.

21. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, et al. Thyroid status, cardiovascular risk, and mortality in older adults. JAMA 2006;295:1033-41.

22. Razvi S, Shakoor A, Vanderpump M, Weaver JU, Pearce SH. The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a metaanalysis. J Clin Endocrinol Metab 2008;93:2998-3007.

23. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev 2008;29:76-131.

24. Danese MD, Ladenson PW, Meinert CL, Powe NR. Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. J Clin Endocrinol Metab. 2000;85:2993-3001.

25. Villar HC, Saconato H, Valente O, Atallah AN. Thyroid hormone replacement for subclinical hypothyroidism. Cochrane Database Syst Rev 2007; :CD003419.

26. Meier C, Staub JJ, Roth CB, Guglielmetti M, Kunz M, Miserez AR, et al TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo- controlled trial (Basel Thyroid Study). J Clin Endocrinol Metab 2001;86:4860-6.

27. Haggerty JJ Jr, Stern RA, Mason GA, Beckwith J, Morey CE, Prange AJ Jr. Subclinical hypothyroidism: a modifable risk factor for depression? Am J Psychiatry 1993;150:508-10.

28. Haggerty JJ Jr, Prange AJ. Review Borderline hypothyroidism and depression. Jr Annu Rev Med 1995;46:37-46.

29. Biondi B, Palmieri EA, Lombardi G, Fazio S. Review Effects of subclinical thyroid dysfunction on the heart. Ann Intern Med 2002;137:904-14.

30. Pop VJ, Maartens LH, Leusink G, van Son MJ, Knottnerus AA, Ward AM, et al. Are autoimmune thyroid dysfunction and depression related? J Clin Endocrinol Metab 1998;83:3194-7.

31. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 2006;91:2587-91.

32. Pollock MA, Sturrock A, Marshall K, Davidson KM, Kelly CJ, McMahon AD, et al. Thyroxine treatment in patients with symptoms of hypothyroidism but thyroid function tests within the reference range: randomised double blind placebo controlled crossover trial. Br Med J 2001;323:891-5.