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Editorial

Subclinical Hypothyroidism in Elderly: Who should be Treated?

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Editorial

Subclinical Hypothyroidism (SCH) is defined as elevated serum Thyroid Stimulating Hormone (TSH) level with normal Free Thyroxine (FT4) and Free Triiodothyronine (FT3). Prevalence of SCH increases with age, which is estimated to be 1-6% in general population and 7-18% in older adults [1]. There is growing body of evidence that TSH levels shift towards higher concentration as part of normal ageing. Therefore, high prevalence of SCH in older adult should be partly due to overestimation from failure to use age-specific reference range for TSH. Surks MI et al., reanalyzed NHANES III data and reported that median and 97.5 centile of TSH levels progressively increased with age [2]. The 97.5 centile (upper limit of normal reference range) of TSH were 3.56 and 7.49 mIU/L for age group 20-29 year and 80 year and older, respectively. Authors estimated that approximately 70% of older adults diagnosed with SCH due to TSH greater than 4.5 mIU/L were considered euthyroid when their age specific reference range were used for SCH diagnosis. It's important to note that analysis of NHANES III data also showed progressively decreased prevalence of anti-thyroid antibodies with age in individuals with TSH greater than 4.5 mIU/L [2]. These findings suggest that the age related progressive shift in TSH distribution curve is most likely physiological and may not represent higher prevalence of thyroid dysfunction. Increase in age-related TSH may be due to higher TSH set point or reduced TSH bioactivity [1].

Up to 2-6% of patients with SCH progress to overt hypothyroidism every year [3]. It's important for clinicians to be aware that not all patients with SCH eventually develop overt hypothyroidism. A significant proportion of patients with SCH revert back to euthyroidism spontaneously with higher rates of reversion in individuals with lower TSH concentrations, negative TPO antibodies and homogenous echotexture on thyroid ultrasound [4]. Prevalence of thyroid autoantibodies also increases with age and risk of SCH progression to overt hypothyroidism is approximately four times higher in patients with elevated anti-thyroid antibodies [5]. The known risk factors of SCH progression are baseline TSH level, old age, female sex and the presence of thyroid autoantibodies [1].

Untreated SCH is associated with higher comorbidities and complications in general population, but data in older adults is conflicting [6-14]. Analysis of participants (mean age 85 year) of Cardiovascular Health Study All Stars Study showed no associations between SCH and mortality [7]. Interestingly, an observational, population-based follow-up study showed association of elevated TSH levels with lower mortality in 85 year or older subjects [8]. One study demonstrated better mobility, cardiorespiratory fitness and walking ease in individuals with TSH level 4.5-7.0 mIU/L compared to patients with TSH 7.0-20 m IU/L and euthyroid subjects [9]. A meta-analysis of 15 studies involving a total of 2,531 individuals with SCH and 26,491 euthyroid subjects showed higher cardiovascular morbidity and mortality in individuals with SCH [10]. Compared to euthyroid subjects, patients with SCH demonstrated 57% increased relative risk for incidence of ischemic heart disease and 37% increased relative risk for cardiovascular death. However, these associations were only noted in studies involving subjects younger than 65 year.

Contrastingly, there are multiple studies that showed increased morbidity and mortality in elderly with SCH. Emerging data, however, suggest that most of these associations are more likely to be present in patients with elevated anti-thyroid antibodies, TSH greater than 10 mIU/L and underlying Congestive Heart Failure (CHF) [11-14]. Patients with TSH greater than 10 mIU/L have shown to have a higher prevalence of metabolic syndrome, higher incidence of heart failure events and significant changes in echocardiographic parameters such as greater increase in left ventricular mass and changes in diastolic function compared to euthyroid subjects [12, 13]. An analysis of NHANES III data showed 44% increased mortality in individuals with SCH and congestive heart failure compared with euthyroid individuals [11]. Mortality was neither increased nor decreased in SCH patients without CHF. Postmenopausal women with SCH and elevated anti-thyroid antibody levels have shown strong associations with coronary and aortic atherosclerosis [14].

Even with higher prevalence of SCH in older adults, treatment with thyroxine replacement is controversial. A randomized controlled trial showed no significant improvement in cognitive function in elderly subjects (>65 year of age) with SCH after 12 months of thyroxine therapy [15]. Anderson et al. showed beneficial effects of levothyroxine treatment on myocardial infarction, cardiovascular death and all-cause mortality exclusively in patients with SCH who are younger than 65 year [16]. A randomized, double-blind, placebo-controlled trial involving subjects aged ≥65 years with SCH (TSH 4.6 to 19.99 mIU/L) showed no significant difference in carotid intima media

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thickness and maximum plaque thickness after a median 18.4 months of levothyroxine treatment, which resulted in normalization of TSH [17]. Moreover, Grossman A et al. showed, in a case control study, 19% increased mortality risk with levothyroxine treatment in 65 year or older patients with SCH and TSH <10 mIU/L [18]. On the other hand, some studies showed self-reported improvement in symptoms, improved memory and somatic complaints and significant decrease in LDL as well as apolipoprotein B with levothyroxine treatment of patients with SCH [19-21].

Based on currently available evidence, we believe that patients with SCH and TSH >10 mIU/L may benefit from thyroxine replacement. For patients with milder elevation of TSH in range 4.5-10 mIU/L, clinicians should personalize treatment plan and exercise caution while starting levothyroxine. Levothyroxine treatment may be considered in presence of anti-thyroid antibodies and/or concurrent CHF. In other patients, conservative follow up with close monitoring of thyroid function tests should be favored. Older patients with SCH must be informed regarding conflicting and unclear evidence on benefits of levothyroxine therapy and their opinion should be sought prior to formulating management plan.

When levothyroxine is initiated, patient should be closely monitored with serial thyroid function tests and for clear evidence of improvement in hypothyroid symptoms. Thyrotoxicosis is more prevalent in older adults taking levothyroxine and is associated with significant morbidity in the elderly, particularly increased risk for atrial fibrillation and progressive bone loss [22]. In individuals 60 year or older, TSH level of ≤ 0.1 mIU/L was associated with threefold higher risk for atrial fibrillation during a 10 year follow up period [23]. Older patients with SCH should be started on levothyroxine at low dose of 25 mcg/day and the dose should be slowly titrated to achieve the target TSH of 4-6 mIU/L. Combination treatment with levothyroxine and liothyronine is controversial and should be avoided in elderly patients with SCH [24]. Above reviewed literature underscores the importance of a large, randomized, placebo controlled trial to study the effects of levothyroxine therapy on CV morbidity and mortality, all-cause mortality, cognitive function and quality of life in elderly patients with SCH.

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