Subclinical hyperthyroidism is the most prevalent thyroid dysfunction in older Italians and is associated with cognitive impairment

Ceresini G, Lauretani F, Maggio M, Ceda GP, Morganti S, Usberti E, Chezzi C, Valcavi R, Bandinelli S, Guralnik JM, Cappola AR, Valenti G, Ferrucci L. Thyroid function abnormalities and cognitive impairment in elderly people: results of the Invecchiare in Chianti study. J Am Geriatr Soc November 19, 2008. doi:10.1111/j.1532-5415.2008.02080.

SUMMARY

BACKGROUND The prevalence of overt and subclinical hypothyroidism in older populations is as high as 20%. Yet whether this affects health and functional status in older persons is uncertain. The aim of this study was to investigate thyroid function abnormalities in older persons and to explore the relationship between thyroid dysfunction and cognition.

METHODS The Invecchiare in Chianti, The InCHIANTI study, is a population-based study of persons living in the Chianti geographic area (Tuscany, Italy). The original study group comprised a total of 1453 persons whose age ranged from 20 to 102 years; representing 91.6% of the eligible population. The study was aimed at identifying measures clinicians could use to understand the causes of walking difficulties in older persons. Of the 1453 participants who had home interviews, 1343 (92%) donated a blood sample. Complete data on thyroid hormones and cognitive performance were available in 1208 participants who were not being treated with drugs known to interfere with thyroid function; also, 3 patients with dementia were excluded. The final study population for the study of thyroid dysfunction comprised 1171 subjects, 652 women (56%) and 519 men (44%). Blood and plasma samples collected in the morning after a 12-hour fast were analyzed for thyrotropin (TSH), free thyroxine (FT_4), and triiodothyronine (T_3). Global cognitive performance was assessed by the Mini–Mental State Examination (MMSE). A value less than 24 was considered to indicate cognitive impairment. Other information on demographics, smoking, and the use of medication were collected using standardized questionnaires. Weight, body-mass index (BMI), and the level of physical activity and exercise, nutrition and disease were also evaluated by standardized questionnaires. Participants were classified according to TSH and FT_4 and FT_3 concentrations into five categories: (1) overt hypothyroidism (TSH >4.68 μIU/ml, FT_4 <0.78 ng/dl); (2) subclinical hypothyroidism (TSH >4.68 μIU/ml, FT_4 = 0.77 to 2.19 ng/dl); (3) euthyroidism (TSH = 0.46 to 4.68 μIU/ml), (4) subclinical hyperthyroidism (TSH <0.46 μIU/ml, FT_4 = 0.77 to 2.19 ng/dl, FT_3 = 2.77 to 5.27 pg/ml); and (5) overt hyperthyroidism (TSH <0.46 μIU/ml, FT_4 >2.19 ng/dl, FT_3 >.27 pg/ml). Four patients with low T_3 syndrome with normal FT_3 and TSH levels were excluded from the analysis.

RESULTS Subclinical hypothyroidism was more prevalent in older than in younger participants (3.5% vs. 0.4%, P<0.03), as was subclinical hyperthyroidism (7.8% vs. 1.9%, P<002). Serum TSH and FT_3 declined with age in euthyroid participants, while FT_4 increased. Older participants (≥65 years) with subclinical hyperthyroidism had lower mean (±SD) MMSE scores than did euthyroid subjects (22.61±6.88 vs. 24.72±4.52, P<0.03). Participants with subclinical hyperthyroidism were, in an adjusted analysis, significantly more likely to have cognitive dysfunction (hazard rate [HR], 2.26; P = 0.003). Among 255 participants, 139

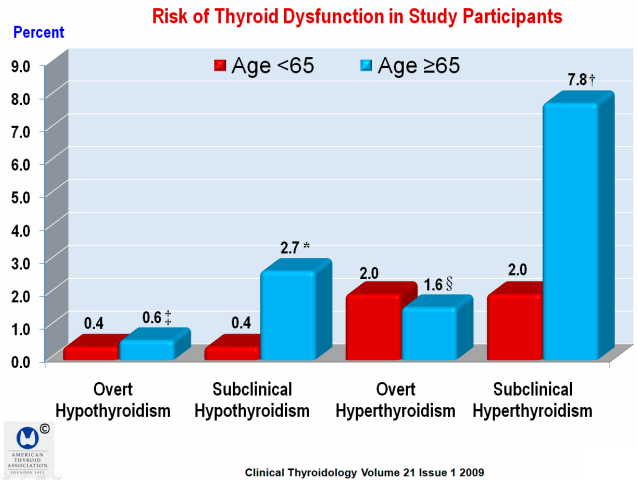

Figure 1. The risk of thyroid dysfunction in study participants younger than age 65 vs. participants 65 yr or older. 95% of the younger participants and 87% of the older participants were euthyroid. Subclinical hypothyroidism and subclinical hyperthyroidism were both more prevalent in older than in younger individuals, *P<0.03 and †P <0.002, respectively, while the prevalence of overt hypothyroidism and hyperthyroidism was similar in younger and older individuals. ‡P = 0.77, and §P = 0.93). Data from Ceresini et al.

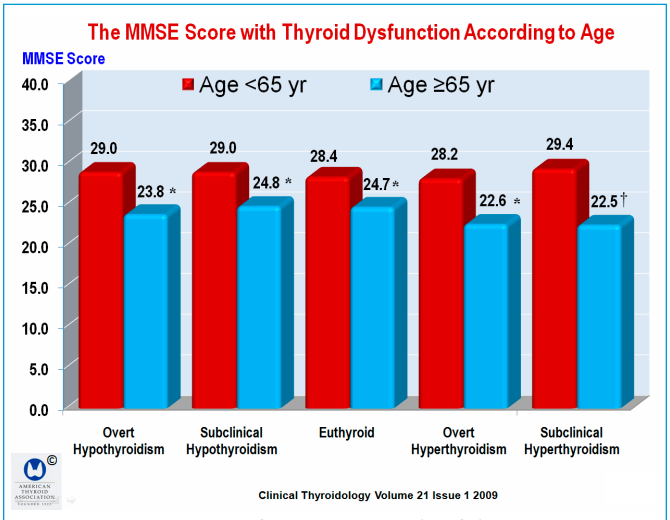

Figure 2. The Mini–Mental State Examination (MMSE) scores were significantly lower in participants age 65 or older as compared with younger participants. *P <0.03, †P = 0.002, from age-adjusted linear or logistic-regression models, as appropriate. Older participants (≥65 yr) with subclinical hyperthyroidism had lower mean (±SD) MMSE scores than did euthyroid subjects (22.61±6.88 vs. 24.72±4.52, P<0.03). Participants with subclinical hyperthyroidism were, in an adjusted analysis, significantly more likely to have cognitive dysfunction (hazard rate [HR], 2.26; *P = 0.003). Data are from Tables 1 and 2 in Ceresini et al.

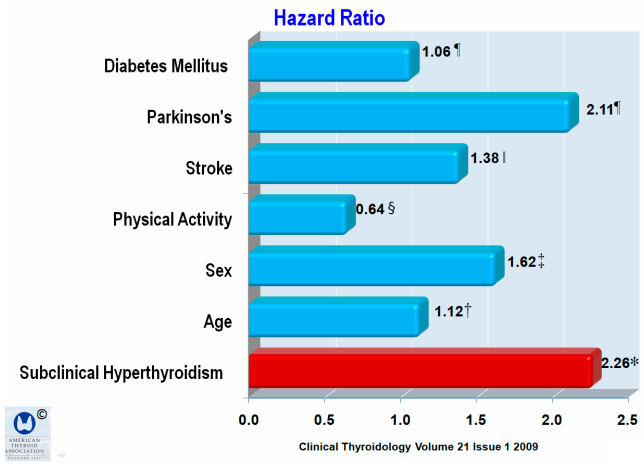

Figure 3. Multivariate regression analysis relating subclinical hyperthyroidism to the risk of having low Mini–Mental State Examination (MMSE) score <24 (considered to indicate cognitive impairment) *P = 0.003, †P = <0.001, ‡P= .05, §P =0.006, γP = 0.01, ¶P = 0.6. Data from Table 3 in Ceresini et al.

women (53%) and 116 men (46%) were younger than 65 years, 243 were euthyroid (95%), and 1 each had overt hypothyroidism (0.4%) and subclinical (0.4%) hypothyroidism (Figure 1). Five participants (2%) had subclinical hyperthyroidism and five (2%) had overt hyperthyroidism (Figure 1). Of the 916 participants aged 65 or older (513 women and 403 men), five (0.6%) had overt hypothyroidism, 25 (2.7%) had subclinical hypothyroidism, and 800 (87%) were euthyroid, 71 (7.8%) had subclinical hyperthyroidism, and 15 (1.6%) had overt hyperthyroidism (Figure 1). Subclinical hypothyroidism and subclinical hyperthyroidism were thus both more prevalent in older than in younger individuals (P<0.03 and P<0.002, respectively) while the prevalence of overt hypothyroidism was similar in younger and older individuals (P = 0.77; Figure 1). The MMSE score, adjusted for age, sex and other potential confounders was significantly lower in subclinically hyperthyroid than in euthyroid participants (22.61±6.88 vs. 24.72±4.52, P<0.03; Figure 2). Multivariate regression analysis found the hazard ratio of having cognitive impairment associated with subclinical hyperthyroidism versus euthyroidism was 2.26 (P<0.003) (Figure 3).

CONCLUSION Subclinical hyperthyroidism is the most prevalent thyroid dysfunction in older Italian persons and is associated with cognitive impairment.

COMMENTARY

The prevalence of overt and subclinical hypothyroidism in elderly populations is as high as 20% (1). With aging, the prevalence increases 1% or 2% in iodine-deficient geographic areas and up to 7% or 8% in iodine-sufficient areas (1). However, inconsistent findings have been found in epidemiologic studies investigating the relationship between subclinical hypothyroidism and cognitive dysfunction (2). In the present study, the odds of having poorer cognitive function were greater for subclinical hyperthyroidism than for stroke, diabetes mellitus, and Parkinson's disease. Thus, in this large population-based study, the overall prevalence of thyroid dysfunction tended to be higher in older than in younger persons, with subclinical hyperthyroidism being the most highly prevalent condition associated with cognitive deterioration. A study from the Netherlands found that subclinical hyperthyroidism in the elderly increased the risk of dementia and Alzheimer's disease. A recent study by Samuels et al. (3) found mild decrements in health status and mood in when subclinical hypothyroidism was induced in a blinded, randomized fashion. More importantly, there were independent decrements in working memory, which suggested to the authors that subclinical hypothyroidism specifically impacts brain areas responsible for working memory. Whether treating the subclinical hyperthyroidism—or for that matter, subclinical hypothyroidism—would ameliorate cognitive dysfunction is unknown, but some studies suggest this might not be the case (4). However, other cross-sectional or longitudinal observations have failed to demonstrate an association between thyroid dysfunction and cognition (2, 5). Still, there is a high prevalence of autoimmune thyroid disorders in patients with Alzheimer's disease (6), and other studies have found an association between autoimmune-associated subclinical hyperthyroidism and dementia (7). This intriguing observation by Ceresini et al. will certainly spark further investigation.

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