

Healthy Ashkenazi centenarians have higher serum TSH levels than healthy normal controls.

Atzmon G, Barzilay N, Hollowell JG, Surks MI, Gabriely I. Extreme longevity is associated with increased serum thyrotropin. *J Clin Endocrinol Metab* 2009;94:1251-4.

SUMMARY

BACKGROUND Recent studies indicate that serum thyrotropin (TSH) concentrations increase with age. It remains uncertain whether this is due to a decline in thyroid function or an alteration in the TSH set point in elderly persons or another as yet unidentified factor. As a consequence, some professional societies have recommended that elderly patients with elevated serum TSH levels be treated. The aim of this study was to determine whether the shift in serum TSH concentrations with aging extends to centenarians and to assess the relationship between the concentrations of TSH and free thyroxine (FT₄) levels in this group.

METHODS The study population was recruited from the previously described Longevity Genes Study at Albert Einstein College of Medicine, Bronx, NY. A group of 232 independently living Ashkenazi Jewish centenarians were recruited to participate in this study. The study group comprised 166 women with a median age of 97.8 years and 66 men with a median age of 97.6 years. Their medical history, demographic characteristics, and clinical data were obtained using a structured questionnaire. All subjects underwent a physical examination and provided a blood sample. Individuals with acute or debilitating medical conditions or a history of thyroid disease or subjects taking thyroid medications or with serum TSH levels less than 0.4 μIU/ml with or without FT₄ levels outside the reference limits were excluded from the study. A group of 188 younger, unrelated Ashkenazi Jews were recruited to serve as the Ashkenazi control group, of which 95 were women (median age, 69.7 years) and 93 were men (median age, 72.3 years).

To exclude the possibility of an ethnicity-related bias in the interpretation of the data, another control group was obtained from

the National Health and Nutrition Examination Survey (NHANES III) 1998 to 2002 data, which comprised all 605 subjects in the 60- to 79-year-old group who had serum TSH determinations and neither had thyroid disease nor were taking thyroid medications. All TSH and FT₄ analyses in the study subjects and the Ashkenazi controls were performed at the laboratories of Montefiore Medical Center, thus avoiding laboratory bias. However, because of

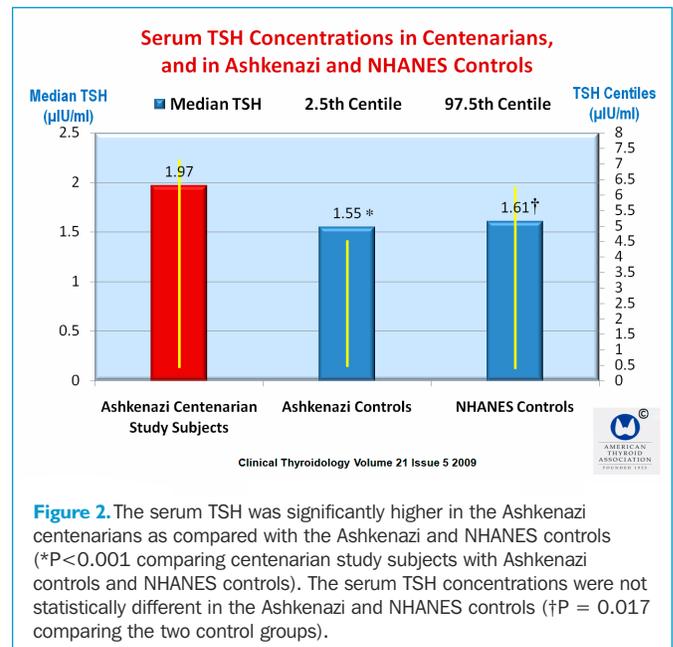


Figure 2. The serum TSH was significantly higher in the Ashkenazi centenarians as compared with the Ashkenazi and NHANES controls (*P<0.001 comparing centenarian study subjects with Ashkenazi controls and NHANES controls). The serum TSH concentrations were not statistically different in the Ashkenazi and NHANES controls (†P = 0.017 comparing the two control groups).

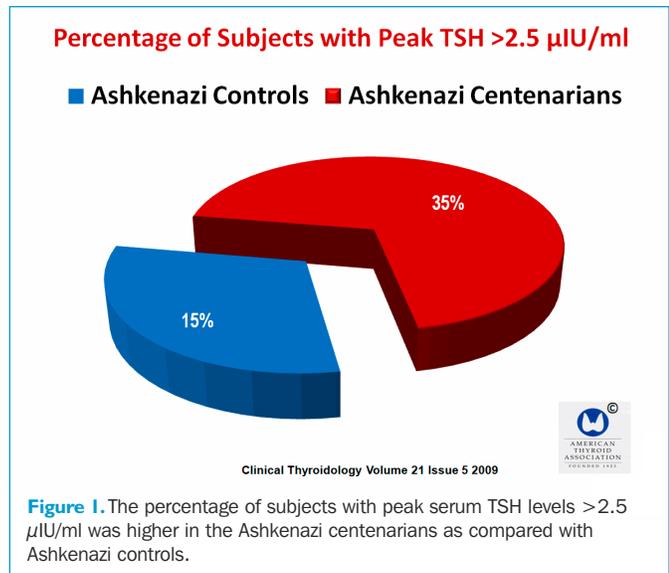


Figure 1. The percentage of subjects with peak serum TSH levels >2.5 μIU/ml was higher in the Ashkenazi centenarians as compared with Ashkenazi controls.

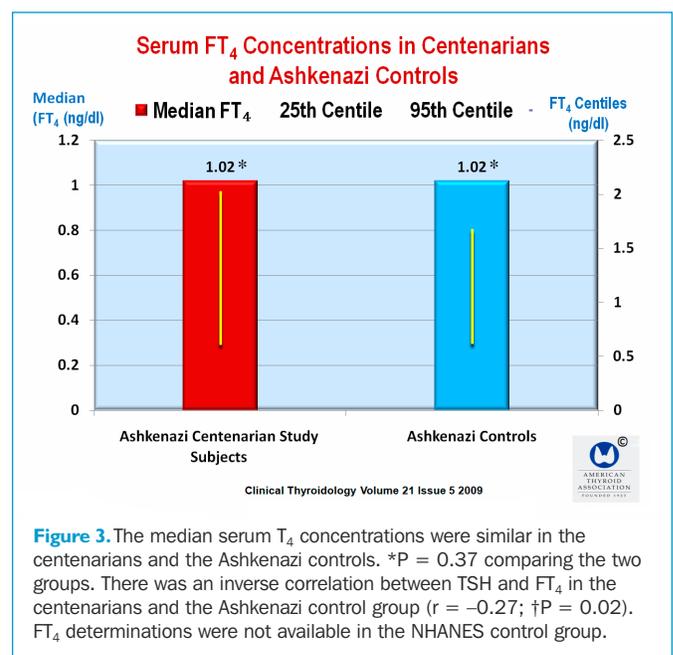


Figure 3. The median serum T₄ concentrations were similar in the centenarians and the Ashkenazi controls. *P = 0.37 comparing the two groups. There was an inverse correlation between TSH and FT₄ in the centenarians and the Ashkenazi control group (r = -0.27; †P = 0.02). FT₄ determinations were not available in the NHANES control group.

logistic and technical issues, serum TSH was analyzed in 232 centenarians and 185 controls, and serum FT₄ was analyzed in 137 centenarians and 172 controls, but only 97 centenarians and 150 controls had both serum TSH and FT₄ analyzed. In addition, antithyroid antibody levels were not determined in the study population because of insufficient availability of serum.

RESULTS The TSH was greater than 2.5 μIU/ml in 15.4% of the controls and 35.2% of the centenarians (Figure 1). Serum TSH was significantly higher in the Ashkenazi centenarians (median, 2.5 and 97.5 centiles) [1.97 (0.42 to 7.15 μIU/ml)] as compared with the Ashkenazi controls [1.55 (0.46 to 4.55) μIU/ml] and the NHANES controls [1.61 (0.39 to 6.29) μIU/ml]; (P<0.001), as well as the TSH levels in the individuals older than 80 years in NHANES III (1.9 μIU/ml).

The median serum TSH concentrations were similar in the Ashkenazi [1.55 [0.46 to 4.55 μIU/ml] and NHANES [1.61 [0.39 to 6.29] μIU/ml]) control groups (P = 0.018) (Figure 2). The TSH distribution did not differ significantly between the

Ashkenazi and NHANES control groups (P = 0.17), but the TSH distribution in the centenarians was significantly shifted to higher serum concentrations as compared with Ashkenazi and NHANES control groups (P = 0.01 and P = 0.002, respectively). Although the frequency distribution curves for TSH appeared similar in shape, the curves shifted to higher TSH concentrations in the centenarians, including the peak TSH level.

The median serum FT₄ concentrations were similar in the centenarians (1.02 [0.62 to 2.02] ng/ml) and Ashkenazi control group (1.02 [0.63 to 1.67] ng/ml) (P = 0.37) (Figure 3). There was an inverse correlation between TSH and FT₄ in the centenarians (r = -0.27; P = 0.02) and the Ashkenazi control group (r = -0.17; P = 0.47). However, FT₄ determinations were not available in the NHANES group. A stepwise regression model demonstrated that none of the medications that centenarians were taking had any significant effect on TSH levels.

CONCLUSION Ashkenazi centenarians have significantly higher median serum TSH levels than younger Ashkenazi controls.

COMMENTARY

The findings in this study are both very important and very intriguing. The data in this study demonstrate that centenarians have significantly higher median serum TSH concentrations than younger Ashkenazi controls. Moreover, the TSH distribution in the centenarians was shifted toward higher TSH levels, further emphasizing the fact that the majority of the centenarian population had higher serum TSH values as compared with the Ashkenazi control group. Furthermore, the NHANES data in all 605 subjects in the 60- to 79-year-old group were used to form an additional control group to avoid an ethnicity-related effect on serum TSH concentrations that might be overlooked if only the Ashkenazi control group were used in the study. In fact, the median serum TSH concentrations and distributions were comparable in the Ashkenazi and NHANES controls, verifying that the results were not biased by the ethnicity of the centenarians and Ashkenazi controls. Furthermore the serum TSH determinations for the centenarian and Ashkenazi control populations were performed at the same laboratory, excluding laboratory-related bias.

An earlier analysis of the TSH distribution in the U.S. population (NHANES III) (1) found a progressive increase in the median serum TSH concentrations with aging. A more recent study by Surks and Hollowell (2) demonstrated that the serum TSH distribution progressively shifts toward higher concentrations with age and that the prevalence of subclinical hypothyroidism may be significantly overestimated unless an age-specific range for TSH is used. In another study, Boucai and Surks (3) found that the reference limits for TSH differ between races and with age, and that the use of race- and age-specific reference limits decreases misclassification of patients with decreased or raised TSH in an urban practice. In the current study, the median TSH concentrations in the centenarian study group (1.97 μIU/ml) was higher than that in Ashkenazi or NHANES controls, including controls older than 80 years in NHANES III, demonstrating that the progressive population increase in serum TSH with aging includes centenarians. The findings by Surks and Hollowell

support the findings in other studies that demonstrate an elevated serum TSH concentration in people with extreme longevity. For example, a study by Ravaglia et al. (4) of 44 healthy Northern Italian subjects ranging in age from 90 to 107 years, found that the study subjects had higher serum TSH levels (P<0.01) with lower free triiodothyronine/FT₄ ratios as compared with younger subjects. However, Surks and Hollowell state that the data in their study should be interpreted with caution because the reported studies have smaller numbers of subjects, some living in areas of variable iodine deficiency, and have different genetic backgrounds; thus the study by Surks and Hollowell should not be extrapolated to populations outside the United States.

Why there is a progressive increase in serum TSH concentrations with aging, including centenarians, remains uncertain. The authors suggest that this could be the result of several phenomena, including age-related alterations in TSH glycosylation, atrophic nonautoimmune thyroid changes, or an altered negative feedback set point. Moreover, they acknowledge that it is possible that the same FT₄ and TSH concentrations in aging individuals might have been present at a younger age.

Whether patients with subclinical hypothyroidism should be treated remains a subject of great controversy. Surks and Hollowell underscore two recent meta-analyses that provide conflicting views concerning the influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease. One study (5), designed to investigate whether age and sex influence the prevalence, incidence, and mortality of ischemic heart disease in people with subclinical hypothyroidism found that the incidence and prevalence of ischemic heart disease were higher in individuals with subclinical hypothyroidism as compared with euthyroid participants, but this held only for those younger than 65 years of age and not for subjects age 65 years or more.

Another meta-analysis (6) of subclinical thyroid dysfunction and the risk for coronary heart disease and mortality found that the relative risk (RR) for subclinical hypothyroidism for coronary heart

disease was 1.20 (95% confidence interval (CI), 0.97 to 1.49), and risk estimates were lower when higher-quality studies were pooled (RR, 1.02 to 1.08) and were higher among participants younger than 65 years (RR, 1.51 [95% CI, 1.09 to 2.09] for studies with a mean participant age less than 65 years and 1.05 [95% CI, 0.90 to 1.22] for studies with a mean participant age of 65 years or older). In an accompanying editorial, Ladenson (7) opined that, on the basis of these studies, the independent risk for coronary heart disease posed by subclinical hypothyroidism seems to be very modest, if it exists at all, and that only an appropriately powered prospective, randomized, controlled, double-blind interventional trial of thyroxine therapy for subclinical

hypothyroidism can answer this question with the certainty that patients and their physicians deserve—which is feasible and should be done.

In accord with the comments by Ladenson, Surks and Hollowell concluded that until these issues are settled by future research, it seems prudent not to routinely treat elderly patients with levothyroxine because they are found to have a minimal increase in serum TSH. This is sound advice coming from strong evidence.

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