Endocrine, *vol. 21, no. 2, 133–136, July 2003* 0969–711X/03/21:133–136/$25.00

Mortality Rate of Chronically Ill Geriatric Patients with Subnormal Serum Thyrotropin Concentration

A 2-yr Follow-up Study

Andrea Radácsi,[1] Orsolya Dohán,[1] Gábor Kovács,[1]
Wolfdieter Bernard,[2] Joachim Feldkamp,[3] Franz A. Horster,[3] and István Szabolcs[1]

[1]Division of Endocrinology, Department of Internal Medicine and Geriatrics, National Medical Center Budapest, Hungary; [2]Geriatric Hospital Elbroich, Düsseldorf, Germany; and [3]Department of Endocrinology, Heinrich Heine University, Düsseldorf, Germany

We investigated the natural course of subclinical thyroid dysfunctions in geriatric patients, especially regarding their association with mortality rate. Ninety-three randomly selected chronically ill geriatric patients 64–87 (median: 77) yr of age participated in the screening study with a 2-yr follow-up. Serum thyrotropin (thyroid-stimulating hormone [TSH]), free thyroxine, triiodothyronine, and antibodies against thyroid peroxidase were measured. During the follow-up, patients with suppressed TSH levels who were otherwise euthyroid (untreated) had a higher mortality rate than patients with normal TSH (5/8 vs 18/64; $p < 0.05$). The initial clinical state of these two subgroups did not differ significantly. Two-thirds of patients with treated hyperthyroidism died. The mortality rate of patients with initially subnormal but not suppressed TSH level was average and did not differ statistically from either the euthyroid or the hyperthyroid groups. Only 1 of 13 euthyroid patients with positive thyroid antibody titers developed a subsequent subclinical hypothyroidism. Subclinical hyperthyroidism was found to be associated with a higher mortality rate in chronically ill geriatric patients, which justifies screening for thyroid dysfunction and treatment of subclinical hyperthyroidism. In addition, a subnormal but measurable TSH was not indicative regarding the future development of hyperthyroidism. Finally, during the 2-yr follow-up, antibody positivity in the euthyroid cases did not prove to be predictive for the subsequent development of hypothyroidism.

Key Words: Geriatric patients; mortality; subclinical hyperthyroidism.

Introduction

Subclinical thyroid dysfunctions occur in 2–15% of elderly individuals *(1–8)*. In many investigators' opinion, however, it has yet to be proven that these dysfunctions are of clinical significance for the patient and require treatment *(9–13)*. Cross-sectional studies in elderly patients, however, show the association of subclinical thyroid disorders with hyperlipidemia, decreased myocardial contractility, depression, arrhythmias, and decreased bone mineral density (reviewed in refs. *14–16*). Longitudinal studies are rare; among people over 60 yr of age a low serum thyrotropin concentration was found to be connected with a threefold higher risk of developing atrial fibrillation in the subsequent decade *(17)*. In a recent study, Parle et al. *(18)* found an increased mortality rate in elderly subjects with reduced thyrotropin concentration. Interestingly enough, the mortality rate was the same for people with initially suppressed thyrotropin as for those with thyrotropin concentrations between 0.1 and 0.5 mU/L. Based on the published literature, the present longitudinal study is the second one to investigate the thyroid function–associated mortality of geriatric patients in the course of a follow-up.

Results

Ninety-three geriatric patients were screened for thyroid disorders and followed up for 2 yr as detailed in Materials and Methods and in Table 1. Of the 64 patients who were euthyroid at the initial screening, 18 died in the course of the follow-up. Forty-two patients remained euthyroid, one patient developed clinical hypothyroidism, another a subclinical hypothyroidism, and two had subnormal thyroid-stimulating hormone (TSH) level at the control investigation. Thirteen of the euthyroid patients had elevated positive AbTPO levels initially, but only one developed a subsequent subclinical hypothyroidism. Of the three clinically hyperthyroid and therefore treated patients, two died and the third is still undergoing methimazole treatment. Eight patients with initially suppressed TSH with normal free levorotatory thyroxine (FT_4) and triiodothyronine (T_3) (subclinical hyperthyroidism)

Received November 25, 2002; Revised February 10, 2003; Accepted February 11, 2003.

Author to whom all correspondence and reprint requests should be addressed: Dr. István Szabolcs, Division of Endocrinology, Department of Internal Medicine and Geriatrics, National Medical Center Budapest, POB 112, H-1389, Hungary, E-mail: szabolcs@hiete.hu

Table 1
Thyroid Function of Chronically Ill Geriatric Patients (n = 93) and Mortality Rate in a 2-yr Follow-up

Thyroid function (baseline)	Patients data[a]	Mortality rate	Cause of death
Euthyroid (TSH normal, 0.5–3.6 mU/L)	25 males, 39 females Median age: 77 yr (range: 64–87 yr) Clinical state: I, 11; II, 32; III, 21	18/64 (28%)	Cerebrovascular diseases: 9 Cardiovascular diseases: 2 Pneumonia: 5 Other: 2
Patients with subnormal but not suppressed TSH (>0.1 to <0.5 mU/L)	5 males, 8 females Median age: 76 yr (range: 69–87 yr) Clinical state: I, 3; II, 6; III, 4	5/13 (38%)	Cerebrovascular diseases: - Cardiovascular diseases: 3 Pneumonia: - Other: 2
Hyperthyroidism			
Subclinical (untreated)	2 males, 6 females Median age: 79 yr (range: 64–85 yr) Clinical state: I, 2; II, 3; III, 3	5/8 (62%)[b]	Cerebrovascular diseases: 1 Cardiovascular diseases: 2 Pneumonia: 2 Other: -
Clinical (treated)	0 males, 3 females Median age: 73 yr (range: 68–86 yr) Clinical state: I, 0; II, 2; III, 1	2/3 (67%)	Cerebrovascular diseases: - Cardiovascular diseases: - Pneumonia: 1 Other: 1
All cases	2 males, 9 females Median age: 78 yr (range: 64–86 yr) Clinical state: I, 2; II, 5; III, 4	7/11 (64%)[c]	Cerebrovascular diseases: 1 Cardiovascular diseases: 2 Pneumonia: 3 Other: 1
Hypothyroidism			
Subclinical (untreated)	0 males, 1 female Age: 74 yr Clinical state: II, 1	0/1 (%)	Cerebrovascular diseases: - Cardiovascular diseases: - Pneumonia: - Other: -
Clinical (treated)	1 male, 3 females Median age: 80 yr (range: 74–85 yr) Clinical state: I, 1; II, 2; III, 1	1/4 (25%)	Cerebrovascular diseases: - Cardiovascular diseases: - Pneumonia: - Other: 1
All cases	1 male, 4 females Median age: 80 yr (range: 74–85 yr) Clinical state: I, 1; II, 3; III, 1	1/5 (20%)	Cerebrovascular diseases: - Cardiovascular diseases: - Pneumonia: - Other: 1

[a]Clinical state: I, good health (Katz ADL: A-B); II, poor health (Katz ADL: C-D-E); III, bad health (Katz ADL: F).
[b]Mortality higher than in euthyroid patients: $\chi^2 = 3.865$; $p < 0.05$.
[c]Mortality higher than in euthyroid patients: $\chi^2 = 5.327$; $p = 0.02$.

were not treated; five patients died and three remained clinically euthyroid. Development of clinical hyperthyroidism in the nonsurvivors was not reported by any of the patients' doctors. Of the four patients with clinical hypothyroidism, one died and three are undergoing thyroxine treatment. The only patient with a subclinical hypothyroidism was euthyroid at the control after 2 yr. Of the 13 patients with initially subnormal but measurable TSH level, 5 died, in 6 patients the TSH became normal, and only 2 patients have persisting subnormal TSH. The initial clinical state of the euthyroid patients and those with subclinical hyperthyroidism or subnormal but measurable TSH did not differ significantly as semiquantitated by the Katz activities of daily living (ADL) scale *(19)*.

The mortality rates of the different subgroups are summarized in Table 1. Interestingly, the mortality of patients with subclinical hyperthyroidism (suppressed TSH) and the overall mortality of patients with hyperthyroidism (subclinical and treated clinical) were higher than that of euthyroid patients, whereas the mortality rate of patients with initially subnormal but not suppressed TSH was average and did not differ statistically from either the euthyroid or the hyperthyroid groups. The mortality rate of initially hypothyroid but subsequently treated patients was not higher than that of euthy-

reoid subjects; however, the low number of patients involved did not allow for statistical analysis and conclusions.

Discussion

The main finding of the present study is the association of an increased mortality rate of chronically ill geriatric patients with suppressed TSH levels in the course of a 2-yr follow-up. Low TSH in geriatric patients is caused either by nonthyroidal illnesses or by thyroid dysfunction *(20,21)*. Most investigators, however, define hyperthyroidism as suppressed TSH, whereas in nonthyroidal illnesses, TSH levels may be low but remain measurable *(22)*.

The clinical state of our chronically ill geriatric patients as semiquantitated by the Katz ADL scale was similar to that of patients with suppressed and subnormal but measurable TSH. Therefore, we believe that the increased mortality rate found in patients with suppressed TSH was associated not with their nonthyroidal clinical state but, rather, with their subclinical hyperthyroidism. If so, there is good reason (1) to screen chronically ill geriatric patients for thyroid dysfunction with sensitive TSH measurement, and (2) to investigate and treat further patients with established clinical as well as subclinical thyroid dysfunction. The screening can be performed either by the family doctor or—as in our study—on admission to a geriatric hospital regardless of the reason for admission. Previously we showed that screening at the time of admission is justified because we found no case of a normalization of a suppressed TSH in the course of the hospital stay *(23)*.

In the debate on whether or not to treat subclinical hyperthyroidism, our study may serve as a further argument in favor of those who recommend treatment *(24–26)* as compared with those who do not *(9–13)*. At the same time, our data do not support the findings of Parle et al. *(18)*, who found excess mortality not only in their geriatric patients with suppressed (<0.1 mU/L) but also in those with subnormal but measurable (0.1–0.5 mU/L) TSH. Unfortunately, they did not report follow-up TSH measurements of the survivors. In our study, on the one hand, the mortality rate of patients with subnormal TSH did not differ statistically from either the euthyroid or the hyperthyroid group. On the other hand, none of the survivors from these subgroups developed hyperthyroidism in the course of the follow-up; however, most of the subnormal TSH levels did become normal. Based on these findings, we believe that a subnormal but measurable TSH in a chronically ill geriatric patient does not indicate hyperthyroidism, and even if caused by the non-thyroidal illness of the geriatric patient, it is not predictive of a higher risk of mortality.

Finally, antibody positivity in our euthyroid geriatric patients was not predictive of the future development of hypothyroidism. This supports, for the first time in a longitudinal study, previous cross-sectional data that the overall high occurrence of antibody positivity in old age is a nonspecific finding, and there is no reason to use antibody measurements in the first-line thyroid screening of elderly subjects *(27,28)*.

We wish to stress, however, that these conclusions are valid only for chronically ill elderly subjects; in the "healthy" elderly population it is possible that there is no association between the rate of mortality and subclinical thyroid dysfunctions.

Materials and Methods

Chronically ill patients from a geriatric hospital ($n = 93$ [33 males, 60 females]; median age: 77 yr) were screened after informed consent for thyroid dysfunction and reinvestigated (if alive) 2 yr later. In the case of patients who had died, information about time and cause of death were obtained from the patients' doctors. Data on the patients' age, gender, clinical state, and cause of death are detailed in Table 1. Only patients surviving at least 6 mo after the initial investigation were included in the study. The area from where the patients came is moderately iodine deficient (median iodine excretion: 70 μg/g of creatinine). All patients were undergoing rehabilitation treatment after a cerebrovascular accident or hip prothesis implantation. Two-years of follow-up was chosen because of the advanced age, impaired health status, and relatively low life expectancy of the patients investigated.

Serum TSH (sensitive two-site immunoradiometric assay; functional sensitivity *[29]* of the assay: 0.04 mU/L), FT_4, and T_3 levels were measured by Corning-magic assays (Medfield, MA) (normal ranges: TSH = 0.5–4.0 mU/L, FT_4 = 13–27 pmol/L, T_3 = 1.3–2.9 nmol/L; interassay CV = 3.5, 3.4, and 5.9%, respectively). AbTPO were measured by IMMUtest anti-TPO radioligand assay (Henning, Berlin, Germany); interassay CV was 4.0%. AbTPO values >100 kU/L were considered to be positive. Thyroid dysfunctions were defined as follows: clinical hyperthyroidism: suppressed (<0.1 mU/L) TSH and elevated FT_4 or T_3; subclinical hyperthyroidism: suppressed (<0.1 mU/L) TSH and normal FT_4 and T_3; subclinical hypothyroidism: elevated TSH and normal FT_4 and T_3; clinical hyperthyroidism: elevated TSH and low FT_4 or T_3. Based on their nonthyroidal clinical state, the patients' biologic and psychosocial function was semiquantitated by the Katz ADL scale *(19)*. The severity of the clinical state of the patients as semiquantified by the Katz ADL was as follows: good health, $n = 17$; poor health, $n = 46$; bad health, $n = 30$. The χ^2 test was used to detect correlation between the mortality of the patients and their thyroid function.

References

1. Brochmann, H., Bjoro, T., Gaarder, P. I., Hanson, F., and Frey, H. M. (1988). *Acta Endocrinol.* **17,** 7–12.
2. Parle, J. V., Franklyn, A., Cross, K. W., Jones, S. C., and Sheppard, M. C. (1991). *Clin. Endocrinol.* **34,** 77–83.
3. Sundbeck, G., Lundberg, P. A., Lindstedt, G., Svanborg, A., and Eden, S. (1991). *Aging (Milano)* **3,** 31–37.

4. Gochiot, B., Schlienger, J. I., Grunenberger, F., Pradignac, A., and Shapin, R. (1994). *Eur. J. Endocrinol.* **30,** 244–252.
5. Chuang, C. C., Wang, S. T., Wang, P. W., and Yu, M. L. (1998). *Gerontology* **44,** 162–167.
6. Knudsen, N., Jorgensen, T., Rasmussen, S., Christihansen, E., and Perrild, H. (1999). *Clin. Endocrinol. (Oxf.)* **51,** 361–367.
7. Ayala, C., Cozar, M. V., Rodriguez, J. R., Silva, H., Pereira, J. L., and Garcia-Luna, P. P. (2001). *Med. Clin. (Barc.)* **117,** 534–535.
8. Danbaek, L. and Jorgensen, L. M. (2001). *Ugeskr. Laeger.* **163,** 5665–5668.
9. Utiger, R. D. (1994). *N. Engl. J. Med.* **331,** 1302, 1303.
10. Wallace, K. and Hofmann, M. T. (1998). *Geriatrics* **53,** 32–38.
11. Koutras, D. A. (1999). *Thyroid* **9,** 311–315.
12. Drinka, P. J. (1999). *Geriatrics* **54,** 55–58.
13. Lerch, M., Meier, C., and Staub, J. J. (1999). *Ther Umsch* **56,** 369–373.
14. Samuels, M. H. (1998). *Thyroid* **8,** 803–813.
15. Toft, A. D. (2001). *N. Engl. J. Med.* **345,** 512–516.
16. Sawin, C. T. (2002). *Thyroid* **12,** 501–503.
17. Sawin, C. T., Geller, A., Wolf, P. A., et al. (1994). *N. Engl. J. Med.* **331,** 1249–1252.
18. Parle, J. V., Maisonneuve, P., Sheppard, M. C., Boyle, P., and Franklyn, J. A. (2001). *Lancet* **358,** 861–865.
19. Katz, S., Ford, A. B., Roland, W., Moskowitz, R. W., Jackson, B. A., and Jaffe, M. W. (1963). *JAMA* **185,** 914–919.
20. Szabolcs, I., Ploenes, C., Bernard, W., and Herrmann, J. (1990). *Horm. Metab. Res.* **22,** 298–302.
21. Szabolcs, I., Kovács, Z., Gönczi, J., et al. (1995). *Eur. J. Endocrinol.* **133,** 294–299.
22. Saller, B., Broda, N., Heydarian, R., Gorges, R., and Mann, K. (1998). *Exp. Clin. Endocrinol. Diabetes* **106,** 29–33.
23. Radácsi, A., Bernard, W., Feldkamp, J., Horster, F. A., and Szabolcs, I. (2000). *Exp. Clin. Endocrinol. Diabetes* **108,** 290–293.
24. Jayme, J. J. and Landenson, P. W. (1994). *Trends Endocrinol. Metab.* **5,** 79–82.
25. Surks, M. I. and Ocampo, E. (1996). *Am. J. Med.* **100,** 217–223.
26. Fatourechi, V. (2001). *Mayo Clin. Proc.* **76,** 413–416.
27. Szabolcs, I., Bernard, W., and Horster, F. A. (1995). *J. Am. Geriatr. Soc.* **43,** 670–673.
28. Mariotti, S., Sansoni, P., Barbesino, G., et al. (1992). *Lancet* **339,** 1506–1508.
29. Spencer, C. A., Takeuchi, M., and Kazarosyan, M. (1996). *Clin. Chem.* **42,** 140–145.