

Thyroid Hormone Concentrations, Disease, Physical Function, and Mortality in Elderly Men

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Context: Physiological changes in thyroid hormone concentrations might be related to changes in the overall physical function in the elderly.

Objective: We determined to what extent thyroid hormone concentrations are related to physical function and mortality in elderly men.

Design: A longitudinal population study (the Zoetermeer study) was conducted. Mortality was registered in the subsequent 4 yr.

Participants: Four hundred three independently and ambulatory living men (aged 73–94 yr) participated.

Main Outcome Measures: The study examined the association between serum thyroid hormones and parameters of physical function as well as the association with mortality.

Methods: TSH, free T₄ (FT4) total T₄, T₃, rT₃, and T₄-binding globulin were measured. Physical function was estimated by the number of problems in activities of daily living, a measure of physical performance score (PPS), leg extensor strength and grip strength, bone

density, and body composition.

Results: Serum rT₃ increased significantly with age and the presence of disease. Sixty-three men met the biochemical criteria for the low T₃ syndrome (decreased serum T₃ and increased serum rT₃). This was associated with a lower PPS, independent of disease. Furthermore, higher serum FT4 (within the normal range of healthy adults) and rT₃ (above the normal range of healthy adults) were related with a lower grip strength and PPS, independent of age and disease. Isolated low T₃ was associated with a better PPS and a higher lean body mass. Low FT4 was related to a decreased risk of 4-yr mortality.

Conclusions: In a population of independently living elderly men, higher FT4 and rT₃ concentrations are associated with a lower physical function. High serum rT₃ may result from a decreased peripheral metabolism of thyroid hormones due to the aging process itself and/or disease and may reflect a catabolic state. Low serum FT4 is associated with a better 4-yr survival; this may reflect an adaptive mechanism to prevent excessive catabolism. (*J Clin Endocrinol Metab* 90: 6403–6409, 2005)

FEATURES OF AGING are in part similar to those of hypothyroidism. In both conditions basal metabolic rate decreases (1). Several changes in thyroid hormone concentrations occur during aging: serum TSH concentrations decrease in healthy elderly humans, serum total and free T₃ levels demonstrate a clear, age-dependent decline, whereas serum total and free T₄ (FT4) concentrations remain unchanged (2). These changes are often associated with a poor health status [reviewed by Mariotti *et al.* (2)]. Serum rT₃, an inactive metabolite of T₄, seems to increase with age (3). Together with the decrease in serum T₃ levels, this may indicate a decreased peripheral hepatic metabolism of iodothyronine during aging because liver type I deiodinase (D1) is important for both serum T₃ production and rT₃ clearance. However, evaluation of normal thyroid function in the elderly is complicated by an increased prevalence of nonthyroidal illness and by autoimmune subclinical hypothyroidism (4).

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Abbreviations: ADL, Activities of daily living; BMD, bone mineral density; CI, confidence interval; D1, type I deiodinase; FT4, free T₄; kp, kilopond; PPS, physical performance score; TBG, T₄-binding globulin.

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Thyroid hormones are known to regulate the metabolic thermostat by changing the basal metabolic rate. One may hypothesize, therefore, that physiological changes in thyroid hormone concentrations might be related to changes in the overall physical function in the elderly.

We determined in a cross-sectional setting to what extent thyroid hormone concentrations are related to age as well as several physical characteristics of aging in independently living, elderly men. In addition, we determined whether potential associations between thyroid hormone concentrations and age and physical status are due to the presence of disease. Finally, we determined the relation between serum thyroid hormones and 4-yr mortality.

Subjects and Methods

Subjects

A cross-sectional, single-center study was conducted in 403 independently living and ambulatory men, aged 73 yr and older. Only men were investigated to obtain a rather large population. Names and addresses of all male inhabitants 70 yr and older were obtained from the municipal register of Zoetermeer, a medium-sized town in the midwestern part of The Netherlands. A total of 1567 men were invited; 886 men did not respond to the mailed invitation in which it was mentioned that only subjects who lived independently and had no severe mobility problems could participate. After exclusion of subjects who did not live independently, subjects who were not physically or mentally able to visit the

study center independently, and subjects with severe systemic illnesses, 403 men participated (25.7%). Participants signed informed consent. The study was approved by the Medical Ethics Committee of Erasmus Medical Centre Rotterdam.

The subjects were interviewed and examined by a single physician using a standard and validated survey. We divided the cohort into four groups according to the number of complaints or diseases present [0 ($n = 38$), 1 ($n = 87$), 2 ($n = 71$), and ≥ 3 ($n = 207$)]. Present diseases included mainly hypertension; cerebral, coronary, and peripheral atherosclerosis; mild congestive heart failure; chronic obstructive pulmonary disease; diabetes; and arthrosis. However, none of the subjects were treated for systemic, infectious, inflammatory, or malignant disorders at the time of the investigation.

Eight subjects who used amiodarone or corticosteroids were excluded from the analyses. Six subjects used thyroid hormone substitution and were also excluded from the analyses. A number of participants were taking medication for hypertension ($n = 96$), angina pectoris or a myocardial infarction more than 6 months ago ($n = 85$), mild congestive heart failure ($n = 28$), chronic obstructive pulmonary disease ($n = 40$), and diabetes ($n = 28$).

Four years after the initial investigation, 75 men (19%) had died (eight in the first year, 16 in the second year, 21 in the third year, and 30 men in the fourth year). None of the subjects were lost to follow-up.

Hormone measurements

Blood samples were collected in the morning after an overnight fast. Serum was separated by centrifugation and stored at -40°C . TSH was measured using an immunometric technique (Amerlite TSH-30; Ortho-Clinical Diagnostics, Amersham, UK). FT4 was measured using the Amerlite MAB FT4 assay (Ortho-Clinical Diagnostics). T_4 , T_3 , and rT_3 were all measured by in-house RIAs (5). T_4 -binding globulin (TBG) was measured by Dynotest RIA (Brahms, Berlin, Germany). Intra- and intervariability coefficients of all assays were less than 11%.

Subclinical hypo- and hyperthyroidism are defined as FT4 levels within the normal range (between 11 and 25 pmol/liter) and TSH levels, respectively, above ($\text{TSH} > 4.3 \text{ mU/liter}$) and below ($\text{TSH} < 0.4 \text{ mU/liter}$) the 95% confidence limits as determined for this assay in 447 healthy blood donors aged 19–69 yr.

Physical function

Activities of daily living (ADL). Self-reported disability or satisfaction in performing ADL was assessed by using a self-administered questionnaire modified from the Stanford Health Assessment Questionnaire as described by Pincus et al. (6). A high score denotes high impairment in ADL.

Physical performance

Lower extremity function, or physical performance, was assessed as described by Guralnik et al. (7), including measurements of standing balance, walking speed, and ability to rise from a chair. A summary physical performance scale (PPS) was created by summing the category scores for the walking, chair stand, and balance test. Mean scores of the three tests as well as the summary performance scale were comparable with subjects of the same age group investigated by Guralnik et al. (7).

Muscle strength

Isometric grip strength was tested using an adjustable handheld dynamometer (JAMAR, Horsham, PA) in the nondominant hand (8). Each test was repeated three times and the average, expressed in kiloponds (kp), was used in the analysis.

Isometric leg extensor strength was measured as described by Hsieh and Philips (9) and van den Beld et al. (10) using the Hoggan MicroFET handheld dynamometer. To obtain one measure of leg muscle strength, maximum leg extensor strength was defined as the maximum strength for the right or left leg in a position of 120 degrees. Statistical analyses were based on the physical unit measurement, moments, obtained by multiplying the maximum strength (newtons) and the distance of the dynamometer to the knee joint (meters).

Bone mineral density (BMD) and body composition

Total-body BMD was measured using dual-energy x-ray absorptiometry (Lunar, Madison, WI), as were hip BMDs at the femoral neck, trochanter, and Ward's triangle. In addition, total and trunk lean body mass and fat mass were measured (11, 12). Quality assurance including calibration was performed routinely every morning for dual-energy x-ray absorptiometry, using the standard provided by the manufacturer.

Body mass index was calculated as the weight in kilograms divided by the square of the height in meters.

Data analyses

Results are expressed, unless otherwise stated, as mean and SD. Variables, which were not normally distributed, were logarithmically transformed. Comparisons between groups were made by using ANOVA. Differences are given with corresponding 95% confidence intervals (CIs). Relations between variables were assessed using linear regression stated as linear regression coefficient (beta) and 95% CI. Multiple regression analysis was used to adjust for age and body mass index and determine the contribution of different independent variables to the dependent variable. Univariate general linear model was used to determine the significance between groups and adjust for covariates. Unless otherwise mentioned, all analyses are done after adjustment for age.

Results

Serum hormones and their relation with age

Mean age of this population was 77.8 yr (range 73–94 yr). Mean age did not differ between the groups with no to three or more diseases.

As shown in Table 1, within the population of elderly men, serum rT_3 concentrations were significantly positively related with age, whereas TSH and FT4 concentrations were not. There was a tendency in this population for TBG levels to increase and T_3 levels and T_3 to TBG ratio to decrease with age. Although T_4 levels were positively related with age in this population (Table 1), none of the subjects had T_4 levels above the range of healthy adults ($>138 \text{ nmol/liter}$). However, 53 subjects had T_4 levels below the range of healthy adults ($<64 \text{ nmol/liter}$). All the relations described in Table 1 were independent of the presence of disease.

Subclinical hyper- and hypothyroidism

One subject with newly discovered overt hypothyroidism and two subjects with newly discovered overt hyperthyroidism were excluded from further analyses.

Six subjects met the biochemical criteria for subclinical hypothyroidism ($\text{TSH} > 4.3 \text{ mU/liter}$ and FT4 between 11 and 25 pmol/liter), and 44 subjects met the biochemical criteria for subclinical hyperthyroidism ($\text{TSH} < 0.4 \text{ mU/liter}$

TABLE 1. Relations of the thyroid hormones with age in a population of elderly men

	All subjects		
	β	SE	P value
TSH (mIU/liter)	-0.01	0.01	0.24
FT4 (pmol/liter)	0.05	0.04	0.23
T_4 (nmol/liter)	0.68	0.23	0.003
T_3 (nmol/liter)	-0.006	0.003	0.07
rT_3 (nmol/liter)	0.005	0.001	<0.001
TBG (mg/liter)	0.11	0.06	0.06
T_4 to TBG ratio	0.06	0.01	0.71
T_3 to TBG ratio	-0.01	0.001	0.07

and FT4 between 11 and 25 pmol/liter). Age did not differ between the euthyroid and subclinically hypo- or hyperthyroid groups.

Subjects with subclinical hyperthyroidism had by definition normal FT4 levels. However, within this normal range, subjects with TSH levels less than 0.4 mU/liter had slightly higher FT4 levels than subjects with normal TSH levels (17.5 ± 0.46 vs. 16.5 ± 0.17 pmol/liter, $P = 0.05$). T_3 levels did not differ between these groups.

It should be stressed that, although we classified subjects with TSH less than 0.4 mU/liter and normal FT4 levels as having subclinical hyperthyroidism, this does not necessarily mean that they all have subclinically increased thyroid function. Serum TSH may also be decreased by high age, illness, or drugs (see below). If we used the more conservative cut-off serum TSH level of 0.1 mU/liter, only six patients met the criteria for subclinical hyperthyroidism.

Serum hormones and their relation with the presence of disease

Subjects who met the biochemical criteria for subclinical hyperthyroidism had significantly more diseases, compared with euthyroid or subclinical hypothyroid subjects (2.34 ± 0.16 vs. 2.08 ± 0.06 vs. 1.26 ± 0.53 , $P < 0.05$)

Summarized values of the hormone measurements as well as the values in the groups divided according to the number of diseases present (for etiology, see *Subjects and Methods*) are presented in Table 2. Only serum rT₃ concentrations differed among the four groups, with the highest levels in the group with three or more diseases.

According to the normal ranges in healthy adults, 137 subjects had normal T_3 and rT₃ levels (Fig. 1, group A); 123 subjects had T_3 levels within the normal range and rT₃ levels above the normal range (>0.32 nmol/liter, group B); 63 subjects had T_3 levels below (<1.35 nmol/liter) and rT₃ levels above the normal range, which is characteristic for the low T_3 syndrome or nonthyroidal illness (group C); and 66 subjects had T_3 concentrations below and rT₃ concentrations within the normal range (group D).

Subjects with the biochemical criteria for the low T_3 syndrome were significantly older than those without low T_3 and high rT₃ (Fig. 1). Furthermore, these subjects had significantly more diseases than the other subjects [2.35 (95% CI 2.09; 2.61) vs. 2.06 (95% CI 1.94; 2.17), $P = 0.04$]. After adjustment for age, there remained a trend toward significance ($P = 0.07$).

TABLE 2. Descriptive values of the thyroid hormones in a population of elderly men in the total group as well as divided by the number of diseases

	All subjects		No diseases		One disease		Two diseases		Three or more diseases	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
TSH (mU/liter)	1.16	1.06–1.27	1.42	0.84–2.00	1.17	0.95–1.38	1.21	0.92–1.49	1.10	0.99–1.21
FT4 (pmol/liter)	16.6	16.3–16.9	16.6	15.6–17.5	15.9	15.3–16.5	17.1	16.2–17.9	16.7	16.3–17.1
T ₄ (nmol/liter)	80.6	79.0–82.0	75.6	70.7–80.6	78.7	75.0–82.4	81.4	77.5–85.2	82.0	79.8–84.1
T ₃ (nmol/liter)	1.43	1.41–1.45	1.41	1.33–1.48	1.47	1.42–1.52	1.43	1.38–1.48	1.42	1.38–1.45
rT ₃ (nmol/liter)	0.33	0.32–0.34	0.31	0.29–0.34	0.31	0.29–0.32	0.33	0.31–0.35	0.35 ^a	0.33–0.36
TBG (mg/liter)	18.0	17.6–18.4	17.2	15.8–18.5	18.1	17.2–19.0	18.1	17.1–19.0	18.1	17.5–18.7
T ₄ to TBG ratio	4.65	4.55–4.76	4.62	4.34–4.91	4.46	4.26–4.67	4.66	4.39–4.92	4.74	4.59–4.90
T ₃ to TBG ratio	0.084	0.08–0.09	0.085	0.079–0.091	0.083	0.080–0.087	0.084	0.078–0.089	0.084	0.077–0.092

^a Differences between groups, $P < 0.01$.

Serum hormones and their relation with physical characteristics

The 44 subjects with subclinical hyperthyroidism had a significantly lower lean body mass than euthyroid and subclinically hypothyroid subjects [50.6 kg (95% CI 49.1; 52.3) vs. 51.6 (95% CI 51.1; 52.1) and 58.4 kg (95% CI 52.4; 64.4), $P < 0.05$] and slightly lower bone density values. This latter relation seemed to be explained through the first relation because after adjustment for lean body mass, the trend with bone density was no longer present. No other significant differences in physical characteristics were observed between these groups.

Among the four groups illustrated in Fig. 1, there was a significant difference in PPS, independent of age. Subjects with low T_3 and high rT₃ concentrations had the lowest PPS, whereas subjects with low T_3 and normal rT₃ had the highest scores. Furthermore, lean body mass was significantly higher in this latter group. The other parameters did not significantly differ between the groups.

However, considering the values of the physical characteristics in Fig. 1, there seemed to be a trend that subjects with high rT₃ levels have lower scores of these physical characteristics. Therefore, we repeated the analyses dividing subjects into two groups: one group with elevated rT₃ concentrations (>0.32 nmol/liter) and one group with normal rT₃ levels. After adjusting for age, it appeared that PPS, muscle strength (leg extensor strength and isometric grip strength), and lean body mass were significantly lower in subjects with high rT₃ concentrations. Because the number of diseases was higher in this group, we also adjusted for disease. Although the strength of the relations became slightly less, the direction of the relations remained similar (Table 3).

Independent of age and disease, increasing serum FT4 concentrations, within the normal range, were related to lower PPS [$\beta = -0.11$ point/(nanomoles per liter) (95% CI -0.18 ; -0.03), $P = 0.006$] and isometric grip strength [$\beta = -0.24$ kp/(nanomoles per liter) (95% CI -0.53 ; -0.11), $P = 0.004$]. Figure 2 shows the correlation between rT₃ and FT4 concentrations. This relation is independent of T_3 levels and has a correlation coefficient of 0.62 ($P < 0.001$).

Mortality

After adjustment for age, serum FT4 concentrations, within the normal range, were significantly related with an increased risk of 4-yr mortality [relative risk 1.27 (95% CI 1.01–1.60)]. Serum TSH and T_3 were not related to mortality

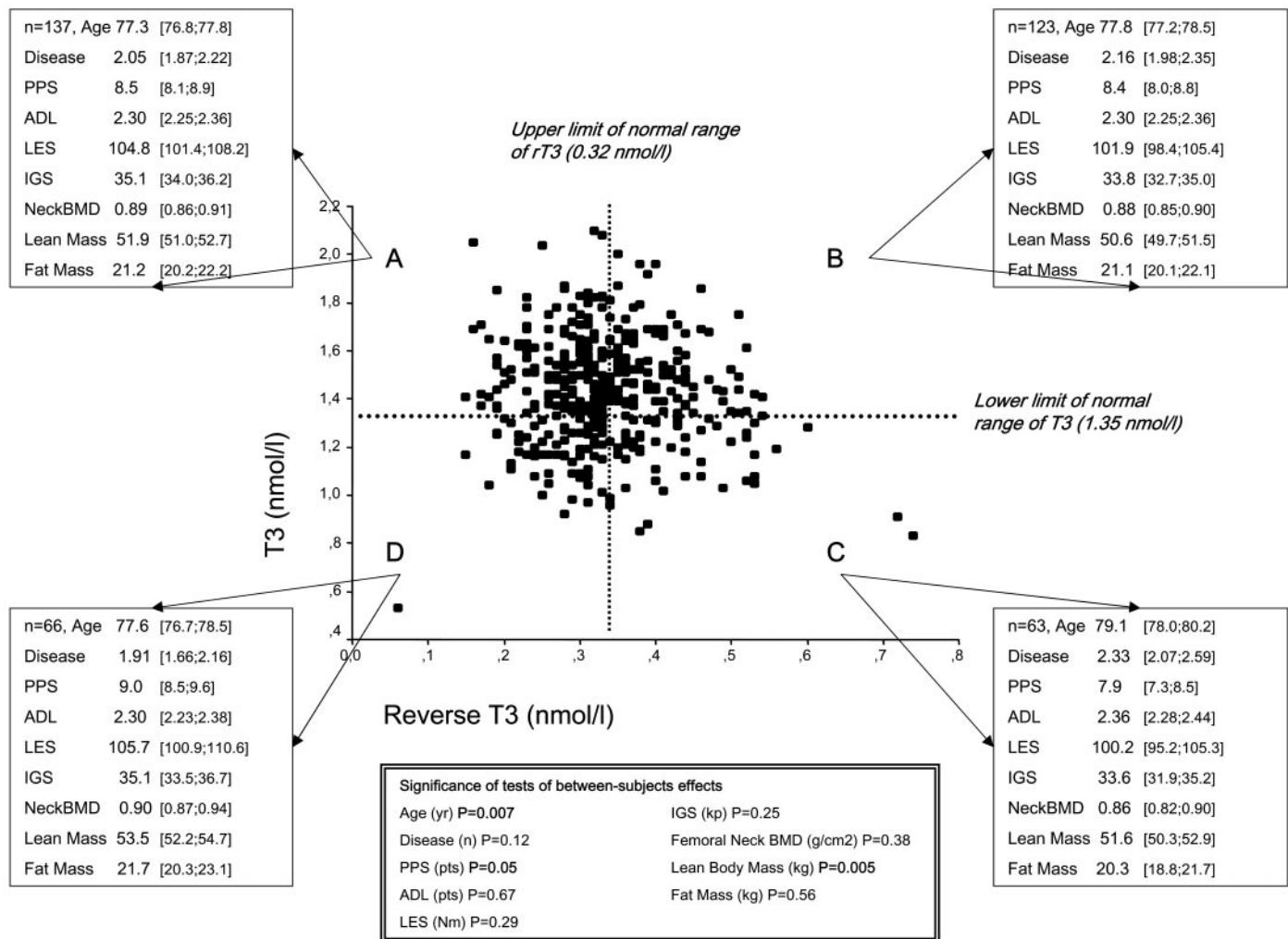


FIG. 1. Overview of the values of T_3 and rT_3 within a population of 403 elderly men. The spotted lines indicate the normal values of T_3 and rT_3 . LES, Maximum leg extensor strength; IGS, isometric grip strength.

nor was the T_3 to TBG ratio. Subjects with the low T_3 syndrome did not have a higher 4-yr mortality risk than subjects without this syndrome. Also, subjects with subclinically hypo- ($n = 6$) or hyperthyroidism ($n = 44$) did not show a higher 4-yr mortality than euthyroid subjects. The relation between FT4 concentrations and mortality was independent of the presence of disease and parameters of physical function.

Discussion

We found in a population of independently living, elderly men that a substantial number of subjects (one third of the population) had T_3 levels below the normal range of healthy adults. Half of these subjects also had elevated rT_3 levels, which is characteristic for the low T_3 syndrome or nonthyroidal illness. This group had a higher age, more diseases,

TABLE 3. Relations between normal and elevated rT_3 concentrations with physical performance in elderly males

	Age adjusted		Age and disease adjusted	
	Normal rT_3	High rT_3	Normal rT_3	High rT_3
Physical performance (pts)	8.69 (8.37–9.01)	8.21 (7.87–8.54) ^a	8.65 (8.33–8.97)	8.25 (7.92–8.58)
Activities of daily living (pts)	10.6 (10.0–11.2)	10.8 (10.2–11.4)		
Max. LES (Nm)	105.1 (102.3–107.9)	101.3 (98.5–104.2) ^b	104.9 (102.1–107.6)	101.6 (98.7–104.5)
Isometric grip strength (kp)	35.1 (34.2–36.0)	33.7 (32.8–34.7) ^a	35.0 (34.1–35.9)	33.8 (32.9–34.8)
Lean mass (kg)	52.4 (51.7–53.1)	50.9 (50.2–51.7) ^c	52.4 (51.7–53.1)	50.9 (50.1–51.7)
Fat mass (kg)	21.4 (20.6–22.2)	20.8 (20.0–21.6)		
Neck BMD (g/cm)	0.89 (0.87–0.91)	0.87 (0.85–0.89)		

Max. LES, Maximum leg extensor strength; pts, points; Nm, physical unit measure (maximum strength in newtons multiplied by the distance of the dynamometer of the knee in meters).

^a $P < 0.05$.

^b $P < 0.10$.

^c $P < 0.001$.

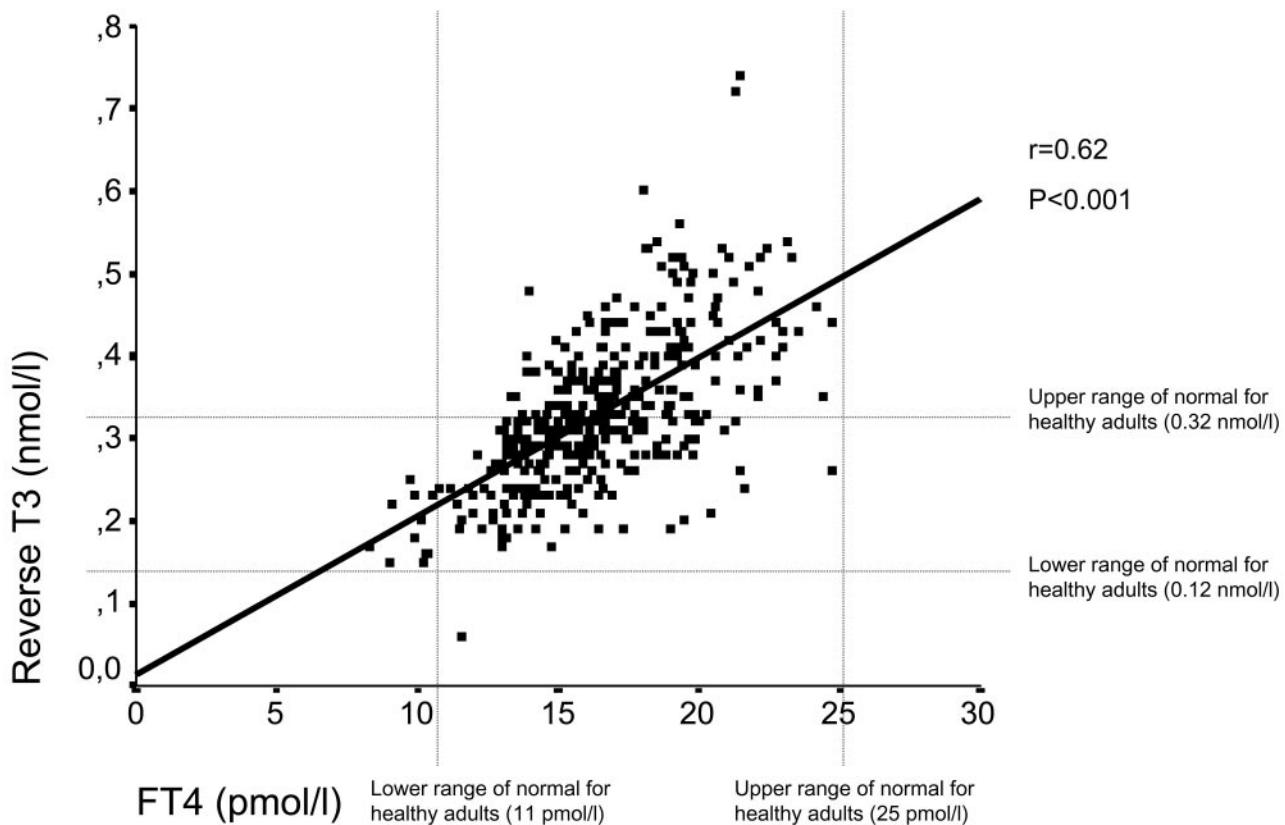


FIG. 2. Correlation between rT_3 and FT4 concentrations in 403 elderly men. r , Correlation coefficient.

and a lower physical performance. Subjects with isolated low T_3 levels (and normal rT_3 concentrations) had the best physical performance and the highest lean body mass. Furthermore, subjects with high rT_3 concentrations (independent of the T_3 level) had worse physical performance scores and lower grip strength. These high rT_3 levels (above the normal range of healthy adults) were accompanied by high FT4 levels (within the normal range). Low FT4 concentrations were related to a decreased risk of 4-yr mortality.

In agreement with previous studies, serum rT_3 concentrations increased with age in our population, whereas approximately one third of this population had T_3 levels below the normal range of healthy adults (2). Serum total T_4 levels increased with age in our population. This relation could not be explained through an increase in TBG levels. It has to be mentioned, however, that T_4 levels were never above the normal range of healthy adults in our population. In contrast, T_4 levels were below this normal range in 53 subjects.

These changes in thyroid hormone concentrations may be explained by a decrease in peripheral (hepatic) thyroid hormone metabolism with aging. First, aging may be accompanied by a decreased activity of D1, which in turn leads to a decrease in serum T_3 , due to a reduced peripheral conversion of T_4 to T_3 , and an increase in serum rT_3 levels due to a reduced rT_3 degradation in the liver (13, 14). In addition, a reduced selenium intake may contribute to a decreased D1 activity in the elderly because selenium deficiency is known to reduce the expression of the D1 selenoprotein (15). Second, the observed increase in rT_3 levels with aging may in part be

explained by a reduced hepatic uptake of rT_3 . However, both an impaired D1 activity and a decreased hepatic uptake of thyroid hormones may also be due to disease or a poor nutritional state rather than aging itself. The extent to which the changes in thyroid hormone concentrations and their relations with physical characteristics in this elderly population were due to the aging process *per se* or the presence of (nonthyroidal) illness was investigated by examining these relations before and after adjustment for the presence of disease (see below).

We determined whether changes in serum thyroid hormone concentrations were related to characteristics of the aging process, like physical functional status. Thyroid hormones are known to play an essential role in many biological processes in essentially every tissue. This is illustrated by the clinical symptoms in hypothyroidism and thyrotoxicosis. We hypothesized, therefore, that changes in peripheral thyroid hormone metabolism in the elderly might be related to changes in physical functional status.

As mentioned above, nonthyroidal illness is associated with an increase in serum rT_3 concentrations (16, 17). Interestingly, in this population a relatively large proportion of the subjects met the biochemical criteria for the low T_3 syndrome, which is decreased serum T_3 and increased serum rT_3 . It needs to be emphasized that the investigated population was relatively healthy and that subjects with systemic infectious, inflammatory, and malignant disorders were excluded. Known morbidity included mainly hypertension, atherosclerotic disease, congestive heart failure, chronic ob-

structive pulmonary disease, diabetes, and arthrosis. Independent of the presence of disease, subjects who met the biochemical criteria for the low T_3 syndrome had a lower physical function. It appeared, however, that not only subjects with the low T_3 syndrome but all subjects with isolated high rT_3 (and $FT4$) concentrations (groups B and C in Fig. 1) had a lower physical function. To examine the potential influence of disease on the associations found, the following analyses were made. First, the increase in rT_3 levels with age was independent of the presence of disease. Second, the decrease in physical functional status with age was independent of disease (data not shown). Third, when we adjusted for the presence of disease, similar linear regression coefficients were obtained for the relations between rT_3 (and $FT4$) and physical characteristics, this despite the observation that rT_3 levels were slightly higher in subjects with the presence of several diseases or complaints. This may indicate that rT_3 levels may reflect an individual's physical functional status, partially independent of disease. Increasing rT_3 levels could then represent a catabolic state, eventually preceding an overt low T_3 syndrome. In this respect, nutritional status may also be a determinant of rT_3 concentrations because caloric deprivation is also accompanied by an increase in rT_3 levels (3). A substantial number of subjects had low T_3 levels, remarkably without accompanying high rT_3 levels. Because T_3 and rT_3 changes in nonthyroidal illness are usually concordant, it seems unlikely that isolated low T_3 levels are due to nonthyroidal illness. The higher physical performance scores and lean body mass in subjects with isolated low T_3 levels support this. Although Mariotti *et al.* (18) carried out a different study protocol, they support the finding of an age-dependent reduction of peripheral thyroid hormone metabolism at least partially independent of associated nonthyroidal illness.

A small number of subjects met the biochemical criteria for subclinical hypothyroidism, compared with previous findings in older populations (19). However, it should be realized that our population consisted entirely of males, and subclinical hypothyroidism is less prevalent in males than females. The relatively low number of subjects with subclinical hypothyroidism may also be due to selection of relatively healthy elderly subjects. This would suggest that subclinical hypothyroidism is associated with significant morbidity and mortality. Although subclinical hypothyroidism is indeed associated with increased cardiovascular morbidity (20), in very old subjects, it is associated with reduced mortality (19). Lean body mass was significantly lower in subjects with subclinical hyperthyroidism, compared with subjects with subclinical hypothyroidism. Due to the small number of subjects with subclinical hypothyroidism, the power of the analyses involving this group is very small.

A relatively large number of subjects (44, 11%) were identified with subclinical hyperthyroidism using a TSH cut-off level of 0.4 mU/liter. In a substantial number of these subjects, the low TSH concentrations may be explained by the age-related decline in serum TSH as well as by nonthyroidal illness. If the more stringent and generally accepted TSH cut-off level of 0.1 mU/liter was used, only six subjects (1.5%) were identified with subclinical hyperthyroidism.

Recently it has been described that in a population-based

study, subclinical hyperthyroidism predicts mortality (21). We could not confirm these results. However, higher $FT4$ levels, within the normal range (independent of TSH levels), were associated with a higher risk of 4-yr mortality. This relation appeared to be very strong and independent of, for example, disease bone density and specific medication known to influence thyroid function. Although no definitive conclusions can be made, it should be mentioned that we were not informed about the possible subsequent development of overt hyperthyroidism during 4-yr follow-up in the population studied. Also, no information about autoimmune thyroid antibodies was available. Our findings are in agreement with a recent study by Gussekloo *et al.* (19), who were informed about the development of overt thyroid dysfunction. They also found that low $FT4$ levels were associated with a longer life span in a population of men and women aged older than 85 yr. Unlike their findings, we did not find an association between elevated TSH levels and a lower mortality. This might be due to the low prevalence of elevated TSH levels in our population. Although serum rT_3 concentrations were also inversely related to parameters of physical ability, they did not predict mortality. Remarkably the presence of nonthyroidal illness, associated with a number of diseases, was not predictive of mortality.

In conclusion, in a population of independently living elderly men, serum rT_3 concentrations increase with age and the presence of disease. In this relatively healthy population, a large proportion met the biochemical criteria for the low T_3 syndrome. Higher $FT4$ and rT_3 concentrations are associated with a lower physical functional status. Higher serum rT_3 concentrations may result from a decreased peripheral metabolism of thyroid hormones due to the aging process itself and/or disease and may reflect a catabolic state. The inverse relations between T_3 and physical performance and lean body mass and between $FT4$ and mortality may indicate that a lower activity of the thyroid hormone axis is beneficial during the aging process. Possibly it serves as an adaptive mechanism to prevent excessive catabolism.

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