CLINICAL STUDY

Increased reverse triiodothyronine is associated with shorter survival in independently-living elderly: the Alsanut study

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Abstract

Objective: Increased reverse triiodothyronine (T₃) used to be described as a part of euthyroid sick syndrome (ESS). It was demonstrated to be associated with increased mortality in acutely ill patients. It can also be found with low or normal T₃ in non-severely ill subjects but its significance remains unclear.

Patients and design: The Alsanut study included a representative sample of 440 independently-living subjects aged 65 or over constituted between January 1988 and September 1989. Past and current medical history and nutritional data were collected at inclusion. Baseline thyroid hormone (TSH, FT₄, FT₃ and rT₃) serum levels were measured. Life status was determined on 1 December 2005.

Results: Of the 374 elderly subjects included in the final analysis, 52 had abnormal TSH (43 with hyperthyroidism, nine with hypothyroidism) and 80.7% had died by 1 December 2005. There was no statistical difference in survival between subjects according to thyroid function ($P=0.54$). Of the 322 elderly subjects with normal TSH, mortality rate was 81.1%. ESS was found in 3.4%, whereas 8.1% of the participants displayed elevated rT₃ with normal FT₃. Time to death was strongly related to rT₃ ($P<0.0001$) and FT₃ ($P<0.0001$) in a univariate analysis. After adjusting for other confounding variables, rT₃ was the only thyroid hormone associated with shorter survival ($P=0.014$).

Conclusions: rT₃ was the only thyroid hormone associated with shorter survival in a representative population of independently-living elderly. In these subjects, isolated elevated rT₃ might be an equivalent of ESS, reflecting declining health.

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Introduction

Acute and severe chronic non-thyroidal illnesses are frequently associated with non-specific disturbances of thyroid function tests called 'euthyroid sick syndrome' (ESS) (1, 2). This syndrome is characterized by a constant decrease in tri-iodothyronine T₃ and free T₃ (FT₃) serum concentrations. It can be associated with more variable disturbances of the other thyroid parameters, such as an increase in reverse T₃ (rT₃), a decrease in T₄ and free T₄ (FT₄), and even a decrease in TSH concentrations in the most severe forms (3, 4).

Substantial data suggest that there are probably several kinds of ESS, depending on the type of associated diseases, severity or acute, or chronic form. In acute ESS, it was shown that the decrease in T₃ and the increase in rT₃ are related to mortality (5–10). In non-acutely ill elderly, T₃ and rT₃ are often decreased and increased respectively, but many questions remain as to whether these disturbances are due solely to aging or to poor health status (11, 12).

Alsanut was an epidemiological study conducted in the late 1980's that aimed at determining the prevalence of thyroid dysfunction and ESS in 440 independently-living elderly (13). It individualized a group of subjects who displayed elevated rT₃ with FT₃ and TSH within normal ranges. They were characterized by lower energy intake, older age, and lower cholesterol level. Sixteen years later, the mortality data were collected in this population to explore the relationship between baseline clinical and biological characteristics and survival, with a focus on rT₃.

Subjects and methods

Subjects

The representative sample of independently-living subjects aged 65 or over in Bas-Rhin (northeastern France) who were included in the Alsanut study was constituted as previously published (13). Briefly, subjects were randomized based on electoral lists with

stratification on age, gender, and settlement (rural versus urban). Deceased persons and those refusing to participate in the study or give a blood sample were replaced by a subject with the same characteristics taken from an additional list. Inclusion in the study was spread over a period of 20 months from January 1988 to September 1989.

A total of 440 subjects accepted to participate in the study. They were subsequently interviewed by an investigator and completed a questionnaire on their medical history (diabetes, cardiac failure, hypertension, cerebrovascular disease, ongoing neoplastic disease), current treatment, smoking status, and mean energy and nutrients intake on a 3-day food record. Body mass index was calculated for each person.

No subject was undergoing corticosteroid therapy. Seven subjects taking amiodarone were excluded from the final analysis, as well as 13 others who were on synthetic thyroid hormones or antithyroid drugs.

Biological data

For each subject a blood sample was taken in the morning at inclusion. TSH, thyroid hormones (free T_4 (FT_4), free T_3 (FT_3), and reverse T_3 (rT_3)), total and high density lipoprotein (HDL) cholesterol, and prealbumin serum concentration were measured. TSH and thyroid hormones were assayed using radioimmunological commercial kits (Behringwerke AG, Marburg, Germany for TSH; Amerlex MAB, Kodak diagnostic, UK for FT_4 ; Amerlex M, Kodak diagnostic, UK for FT_3 ; and Biodata, Montecelio, Italy for rT_3). Normal ranges that had been determined on subjects from various European centres were provided by the manufacturer. They were 0.4–4.5 mU/l for TSH; 13.2–28.8 nmol/l for FT_4 ; 3.3–8.22 nmol/l for FT_3 ; and 0.14–0.53 nmol/l for rT_3 . Total cholesterol and HDL cholesterol were assayed using the caloric enzymatic method (CHOP-PAP) on a Hitachi 737 analyser. Normal ranges were 1.25–1.85 g/l (males) and 1.35–2.10 g/l (females) for total cholesterol, more than 0.40 g/l (males) and more than 0.50 g/l (females) for HDL cholesterol, and 220–350 mg/l (males), and 200–300 mg/l (females) for prealbumin.

Technical problems concerning biological data led to the exclusion of 18 subjects.

Mortality data

The registry offices of the towns where the subjects were born were consulted to determine if the subjects were living or had died after 1 December 2005. This information was not available for 28 subjects leading to their exclusion from the final analysis. Dates of death were collected but cause of death could not be assessed in this way.

Statistical analysis

Unless otherwise stated results are expressed as mean $\pm$ s.d. Because of its markedly skewed distribution, TSH was natural-log transformed before analysis. The Pearson's product-moment correlation coefficient was used to evaluate the association among continuous variables. The study population was further divided into three tertiles based on serum rT_3 levels. The intergroup comparisons were determined by ANOVA test. Cumulative survival was analyzed using the Kaplan–Meier method, with every continuous variable divided into tertiles. Multivariate survival analyses were performed with a Cox model. They were adjusted first for age and sex, and other major confounding factors (total and high-density lipoprotein cholesterol levels, prealbumin level, systolic and diastolic blood pressure, body mass index, smoking status, pre-existing disease such as diabetes mellitus, ischemic heart disease, cardiac failure, cerebrovascular disease, and cancer) based on literature data or univariate survival analysis ($P < 0.05$) were subsequently added to the multivariate models. The relative strength and interdependence of these relationships were investigated by an automatic backward stepwise selection. Hazard ratios (HRs) with a 95% confidence interval were used to estimate the relative risk of death. HRs are expressed by a 1-unit increase in the parameter at baseline. Receiver operator characteristic (ROC) curve analysis were carried out for different parameters (age, total cholesterol, HDL cholesterol, prealbumin, TSH, and thyroid hormones) using occurrence of death versus non-occurrence as the outcome measure. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Thyroid status and its relationship with mortality

Of the 374 persons included in the study, 322 had normal TSH levels between 0.4 and 4.5 mU/l. Forty three subjects had TSH levels below 0.4 mU/l (between 0 and 0.39 mU/l) with normal FT_4 in 34 subjects corresponding to subclinical hyperthyroidism. TSH was above 4.5 mU/l in nine subjects (between 5.5 and 45 mU/l), with normal FT_4 in three of them reaching the criteria for subclinical hypothyroidism. The characteristics of the three groups, defined according to TSH levels, did not differ significantly (data not shown).

On this whole sample, survival was not associated with FT_4 ($r = 0.007$; $P = 0.89$) and TSH ($r = -0.043$; $P = 0.4$) levels. Conversely, a significant correlation existed with rT_3 ($r = -0.288$; $P < 0.001$) and FT_3 levels ($r = 0.200$; $P < 0.001$). Kaplan–Meier analysis did not show any significant difference in survival between the three groups defined by TSH levels ($P = 0.54$) or by FT_4

levels ($P=0.80$), unlike FT₃ ($P<0.001$) and rT₃ ($P<0.001$; data not shown).

Characteristics of euthyroid subjects according to rT₃ and FT₃ levels

Three hundred and twenty-two subjects with normal TSH level were included in the following analysis, 168 males and 154 females with a mean age of 76.3 ± 7.4 years. Their characteristics are summarized in Table 1. Briefly, 33 (10.2%) subjects suffered from diabetes and 115 (35.7%) from hypertension. A history of stroke, cardiac failure, or ischemic heart disease was noted in 21 (6.5%), 33 (10.2%), and 44 (13.7%) people respectively. Fifteen (4.7%) persons had been treated for neoplastic disease, 113 (35.1%) subjects were active or former smokers.

Mean TSH and FT₄ at inclusion were 1.29 ± 0.68 mU/l and 20.24 ± 3.69 nmol/l respectively. Two hundred and eighty-eight subjects (89.4%) had normal FT₃ and rT₃ levels. Eleven (3.4%) participants had low FT₃ (between 1.85 and 3.23 nmol/l) corresponding to the definition of ESS, with normal rT₃ levels in seven, and rT₃ above the normal range (between 0.68 and 1.50 nmol/l) in four. Twenty-six subjects (8.1%) had elevated rT₃ (between 0.54 and 1.50 nmol/l) with normal FT₃. The remaining biological data are reported in Table 1.

On 1 December 2005, 261 (81.1%) subjects had died and 61 (18.9%) were alive. Median survival was 2755 ± 352 days ($\sim 7.5 \pm 1.0$ years). It was significantly shorter for participants with isolated elevated

rT₃ or low FT₃ compared with those with normal hormone levels ($P=0.001$). Eighteen (5.6%) died within 1 year of the inception, 24 (7.4%) between 1 and 2 years, 29 (9%) between 2 and 3 years, 25 (7.8%) between 3 and 4 years, and 226 (70.2%) after 4 years or later.

Subject characteristics by rT₃ tertile

The population was divided into three tertiles based on rT₃ serum concentrations: the lowest tertile, less than 0.31 nmol/l ($n=104$); the middle tertile, 0.31 to 0.41 nmol/l ($n=109$); and the highest tertile, more than 0.41 nmol/l ($n=109$).

The characteristics of these three groups are shown in Table 2. Increasing age and FT₄ concentrations were noted throughout the rT₃ tertiles, whereas an inverse relationship between energy intake, cholesterol concentrations, prealbuminemia, and rT₃ serum levels was found. Ischemic heart disease was more frequently reported by subjects with the highest rT₃ levels.

Relation between baseline parameters and survival

In a Kaplan–Meier analysis, shorter survival was significantly related to increased rT₃ ($P<0.0001$; Fig. 1, part A) and decreased FT₃ ($P<0.0001$; Fig. 1, part B), whereas there was no relation with TSH and FT₄ ($P=0.328$ and 0.169 respectively). Other variables significantly associated with early death in univariate analysis were advanced age ($P<0.0001$), male gender

Table 1 Characteristics of subjects by reverse triiodothyronine (T₃) and free T₃ level.

Characteristics	Total ($n=322$)	Normal FT ₃ and rT ₃ ($n=285$)	Isolated elevated rT ₃ ($n=26$)	Low FT ₃ ($n=11$)	<i>P</i> value*
Age (years)	76.3 ± 7.4	75.8 ± 7.4	80.1 ± 6.4	79.4 ± 6.1	0.007
Sex (M/F)	168/154	147/138	15/11	6/5	0.83
Death (%)	261 (81.1)	225 (78.9)	25 (96.1)	11 (100)	0.03
Median time to death (days)	2755 ± 352	2918 ± 407	1036 ± 210	1348 ± 550	0.001
BMI (kg/m ²) ^a	26.8 ± 6.1	27.0 ± 6.3	26.3 ± 3.7	24.5 ± 5.6	0.38
Diabetes (%)	33 (10.2)	31 (10.9)	1 (3.8)	1 (9.1)	0.52
Cancer (%)	15 (4.7)	14 (4.9)	2 (7.7)	0 (0)	0.59
Cerebrovascular disease	21 (6.5)	14 (4.9)	5 (19.2)	2 (18.2)	0.005
Cardiac failure (%)	33 (10.2)	23 (8.1)	9 (34.6)	2 (18.2)	0.0001
Ischemic heart disease (%)	44 (13.7)	37 (13.0)	5 (19.2)	3 (27.3)	0.27
Hypertension (%)	115 (35.7)	97 (34.0)	17 (65.4)	1 (9.1)	0.001
Smokers (%)	113 (35.1)	99 (34.7)	10 (38.5)	4 (36.4)	0.93
Energy intake (kcal/day)	1877 ± 515	1902 ± 517	1632 ± 499	1809 ± 342	0.03
Total cholesterol (g/l)	2.24 ± 0.49	2.28 ± 0.43	2.04 ± 0.53	1.74 ± 0.39	0.0001
HDL cholesterol	0.51 ± 0.16	0.51 ± 0.16	0.49 ± 0.13	0.48 ± 0.13	0.59
Prealbuminemia (mg/l)	228.1 ± 54.8	232.4 ± 51.8	208.1 ± 62.6	165.6 ± 67.8	0.0001
TSH (mU/l)	1.29 ± 0.68	1.27 ± 0.65	1.40 ± 0.83	1.62 ± 0.86	0.16
FT ₄ (nmol/l)	20.24 ± 3.69	19.90 ± 3.21	24.74 ± 4.29	21.63 ± 6.28	0.0001
FT ₃ (nmol/l)	5.17 ± 1.00	5.26 ± 0.92	5.07 ± 0.97	2.96 ± 0.41	0.0001
RT ₃ (nmol/l)	0.38 ± 0.15	0.35 ± 0.09	0.66 ± 0.14	0.57 ± 0.41	0.0001

BMI, body mass index; HDL, high-density lipoprotein; TSH, thyreostimulin hormon; FT₄, free T₄; FT₃, free T₃; RT₃, reverse T₃. **P* value evaluating intergroup comparisons were determined by ANOVA test.

^aBody mass index was calculated as weight in kilograms divided by height in meters squared.

Table 2 Characteristics of subjects divided into three tertiles according to reverse triiodothyronine (T₃) level.

Characteristics	Lowest tertile rT ₃ <0.31 (n=104)	Middle tertile rT ₃ =0.31–0.41 (n=109)	Highest tertile rT ₃ >0.41 (n=109)	P value*
Age (years)	73.6±6.2	75.9±7.3	79.3±7.5	0.0001
Sex (M/F)	53/51	61/48	54/55	0.61
Death (%)	65 (62.5)	92 (84.4)	104 (95.4)	0.0001
Median time to death (days)	4726±1030	2693±525	1700±624	0.0001
BMI (kg/m ²) ^a	26.1±4.7	27.5±8.3	26.9±4.4	0.23
Diabetes (%)	12 (11.5)	11 (10.1)	10 (9.1)	0.85
Cancer (%)	5 (4.8)	6 (5.5)	4 (4.4)	0.80
Cerebrovascular disease	2 (2.1)	9 (8.2)	10 (9.2)	0.07
Cardiac failure (%)	8 (7.7)	9 (8.2)	16 (14.7)	0.18
Ischemic heart disease (%)	9 (8.7)	13 (11.9)	22 (20.2)	0.04
Hypertension (%)	33 (31.7)	39 (35.8)	43 (39.4)	0.50
Smokers (%)	39 (37.5)	39 (36.1)	35 (32.1)	0.69
Energy intake (kcal/day)	2026±579	1847±470	1766±459	0.001
Total cholesterol (g/l)	2.32±0.37	2.25±0.47	2.14±0.48	0.02
HDL cholesterol	0.53±0.17	0.49±0.17	0.51±0.14	0.23
Prealbuminemia (mg/l)	235.3±53.8	232.7±56.8	216.5±52.4	0.02
TSH (mU/l)	1.30±0.65	1.27±0.70	1.32±0.69	0.86
FT ₄ (nmol/l)	18.20±3.03	20.38±3.27	22.37±3.53	0.0001
FT ₃ (nmol/l)	5.19±0.90	5.31±1.05	5.00±1.03	0.08
RT ₃ (nmol/l)	0.25±0.05	0.36±0.03	0.53±0.16	0.0001

BMI, body mass index; HDL, high density lipoprotein; TSH, thyreostimulin hormon; FT₄, free T₄; FT₃, free T₃; RT₃, reverse T₃. *P value evaluating intergroup comparisons were determined by ANOVA test.

^aBody mass index was calculated as weight in kilograms divided by height in meters squared.

($P=0.047$), history of ischemic heart disease ($P=0.01$), heart failure ($P=0.001$), and stroke ($P<0.0001$), low total ($P<0.0001$) and HDL cholesterol levels ($P=0.02$), and low prealbuminemia ($P<0.0001$).

In multivariate analysis (adjusted for age and gender), increased rT₃ ($P<0.001$) and low FT₃ ($P<0.001$) remained associated with shorter survival. This association disappeared for FT₃ ($P=0.34$) after adjustment for other variables associated with early death in a univariate analysis, whereas it remained unchanged for rT₃ ($P=0.001$; Table 3, model A). In a full model including rT₃ ($P=0.014$), early death was also significantly related to low caloric intake ($P=0.016$), low prealbuminemia ($P=0.002$), decreased total ($P=0.005$) and HDL cholesterol ($P=0.035$), and history of ischemic heart disease ($P=0.054$), stroke ($P=0.037$), and diabetes ($P=0.019$; Table 3, model B). It is noteworthy that the association between rT₃ and survival was stronger after exclusion of participants with low FT₃ serum levels ($P<0.0001$).

To test if the association between rT₃ and survival was due to increased short term mortality, subjects who died within 1, 2, and 3 years of inception were subsequently excluded from analysis. The results did not change when subjects who died within 1 or 2 years of inception were excluded ($P=0.003$ and 0.001 respectively in multivariate analysis). Conversely, they were significantly modified after the exclusion of the 71 subjects who died within 3 years of inception since association between survival and baseline rT₃ in the remaining subjects completely disappeared in multivariate analysis ($P=0.199$).

Predictive value of rT₃ for mortality

A ROC curve was created to evaluate the predictive value of rT₃ and other variables significantly associated with shorter survival in multivariate analysis (Fig. 2). The area under the curve was the highest for rT₃. With the restrictive upper normal value of 0.53 nmol/l used in our study, its specificity was 98.4%, whereas sensitivity was only 11.5%. The value of 0.38 nmol/l, corresponding to the mean of rT₃ in the population gave a specificity of 85.2% and a sensitivity of ~51%.

Discussion

In a population of independently-living elderly euthyroid subjects, the Alsanut study demonstrated a significant relationship between rT₃ and shorter survival while taking into consideration other critical factors such as age, gender, medical history, nutritional parameters, and energy intake. Conversely, FT₃, FT₄, and TSH were not associated with survival in these subjects after adjustment for confounding variables.

Apart from the most severe clinical pictures of hypo- and hyperthyroidism, conflicting data exist on whether or not thyroid dysfunction is associated with increased all-causes mortality (14–17). Major methodological differences (populations' age; length in years of follow-up; co-morbidities considered in the statistical analysis; etc.) could explain these contradictory results. Similarly, recent meta-analysis did not allow formal conclusion of this possible association (18, 19). In our study, there was no significant difference in survival between subjects according to thyroid function.

Figure 1 Cumulative survival by tertile of baseline reverse T_3 (RT_3) (part A) and free (FT_3) (part B) serum concentrations (Kaplan–Meier analysis). RT_3 lowest tertile correspond to serum concentrations lower than 0.31 nmol/l, middle tertile to concentrations between 0.31 and 0.41 nmol/l, and the highest tertile concentrations greater than 0.41 nmol/l. FT_3 lowest tertile correspond to serum concentrations lower than 3.16 nmol/l, middle tertile to concentrations between 3.16 and 4.10 nmol/l, and the highest tertile to concentrations greater than 4.10 nmol/l.

However, the relatively small size of our sample prevents us from adding any reliable proof to this debate.

Conversely, our results concerning the association between survival and rT_3 in euthyroid subjects certainly deserve much more attention. RT_3 is an isomere of T_3 with no demonstrated biological activity. It results from the transformation of T_4 through inner ring deiodination by types 1 and 3 deiodinases in peripheral tissue. By contrast outer ring deiodination by types 1 and 2 deiodinases leads to activation of T_4 into T_3 (20, 21). Clinical studies illustrated that rT_3 serum concentrations increase with age (1, 12, 13), the presence of multiple diseases (12), and may be influenced by energy intake (despite conflicting results) (13, 22). However,

whether these variations should be taken into account is still unknown.

Increased rT_3 is usually considered as a part of ESS. This entity is characterized by a constant decrease in T_3 serum concentrations, and variable abnormalities of other thyroid hormone levels (4). It is secondary to severe acute (e.g., septic shock, myocardial infarction) (8, 9) or chronic (e.g., cancer, advanced acquired immunodeficiency syndrome) (23–25) diseases and it has been demonstrated to be a predictor of increased mortality (6, 18). As expected in our population of independently-living non-severely ill people, ESS was rare, occurring in only 3.4%. The one-step method used for FT_3 measurement in our study has been criticized because it tends to underestimate FT_3 concentrations in ESS, compared with the reference method that is equilibrium dialysis (26). Consequently, the number of participants with ESS might be even lower in our study, and we can be sure that subjects with normal FT_3 serum levels did not have ESS.

Despite normal FT_3 , 26 participants had increased rT_3 levels (>0.53 nmol/l, the upper normal range used in our study), accounting for 8.1% of the assessable subjects. At baseline, they had older age, lower energy intake, and lower cholesterol levels compared with other participants (13). Similarly, Van den Beld identified more than 25% of healthy independently-living elderly men with a similar hormone profile in a study with a less restrictive upper normal range (12). He showed that these people with isolated increased rT_3 had lower physical performance. Thus, in addition to classically defined ESS, elevated rT_3 appears far from rare in non-severely ill subjects and seems to be associated with a poor global health status.

In acutely ill patients, rT_3 was described as an independent parameter predictive of mortality, as after acute myocardial infarction or in patients hospitalized in intensive care (8, 9). In independently-living subjects, mortality data are weak. Only Van den Beld evaluated this parameter in his study and did not find an association between increased rT_3 and shorter survival (12). However, he showed an association between low FT_4 and 4 year survival. Conversely in our study, rT_3 was the only thyroid hormone associated with survival in non-severely ill elderly. With the restrictive upper normal range of 0.53 nmol/l used in our study, rT_3 has a specificity as high as 98.5% in predicting early death, whereas its sensitivity is quite low at 11.4%.

Our results appear reliable given the quality of the initial selection of subjects, which was carefully done by stratification and randomization in an epidemiological view, giving a perfectly representative sample of the elderly Alsatian population. Additionally, the long follow-up makes it possible to interpret these results over the long term. No definite explanation can be advanced to differentiate our results and Van den Beld's. The main difference between the two populations resides in the fact that he included only men, whereas

Table 3 Factors associated with all-causes mortality (Cox regression).

Variable	Model A ^a		Model B ^a	
	Hazard ratio (95% CI) ^b	P value	Hazard ratio (95% CI) ^b	P value
Age (year)	1.087 (1.066–1.109)	<0.001	1.093 (1.071–1.115)	<0.001
Sex (M/F)	0.812 (0.619–1.065)	0.113	0.674 (0.504–0.903)	0.008
RT ₃ (nmol/l)	2.858 (1.504–5.434)	0.001	2.345 (1.185–4.640)	0.014
Prealbumin (mg/l)	0.996 (0.993–0.999)	0.005	0.996 (0.993–0.998)	0.002
Total cholesterol (g/l)	0.598 (0.415–0.863)	0.006	0.598 (0.417–0.858)	0.005
HDL cholesterol (g/l)	0.348 (0.139–0.874)	0.025	0.365 (0.143–0.930)	0.035
Stroke (y/n)	1.623 (1.023–2.576)	0.040	1.641 (1.031–2.611)	0.037
Energy intake (kcal/d)	–	–	1.000 (0.999–1.000)	0.016
Ischemic heart disease (y/n)	–	–	1.428 (0.995–2.050)	0.054
Diabetes (y/n)	–	–	1.641 (1.086–2.481)	0.019

^aCox regression model adjusted for age and sex, and stepwise selection among covariates that predicted death in univariate survival analysis ($P < 0.10$) (model A) or stepwise selection among all available covariates (model B).

^bHR for each additional unit increase of the continuous variables or compared with the reference category for dichotomized variables (female sex, no stroke, no ischemic heart disease, no diabetes mellitus).

ours was composed of both genders. Van den Beld's subjects were also probably in better health since none of them were treated for systemic, infectious, inflammatory, or malignant disorders at the time of investigation contrary to ours (13). Otherwise, the mean age of the participants is similar, the size of the two samples is comparable, and the results are based on a single hormone measurement at inclusion in both studies.

Finally, although we suggested previously that rT₃ could be a reliable hormonal parameter to appreciate nutritional status (13), we can now propose that elevated rT₃ may reflect more than simply the nutritional status but rather a poor overall health status given the relationship between survival and rT₃. This is supported by the relation between rT₃ and survival resulting from increased short-term mortality, since it disappears after exclusion of the subjects who died within 3 years of inception. We can support Van den Beld's hypothesis that isolated elevated rT₃ may be a catabolic state preceding ESS (12). We could also hypothesize that this condition might not be a pre-stage but rather an equivalent of ESS in the independently-living elderly. Unfortunately, the design of our study does not formally answer this question. A prospective evaluation of subjects with the highest rT₃ levels would certainly help to verify whether they develop true ESS throughout standardized biological follow-up and whether death occurs earlier compared with control subjects.

The mechanisms that could explain isolated elevated rT₃ remain to be identified. One can hypothesize that they may be at least partly similar to those involved in ESS. These mechanisms remain unclear (reduced activity of type 1 deiodinase (1, 9, 21), clearance of T₃ and rT₃ by the liver (12), tissular transport of thyroid hormones, nuclear, and post-transcriptional phenomena (4, 27)...). Several are in fact probably involved, depending on the underlying disease, and prove that ESS is a heterogenous condition. To explain isolated elevated rT₃, it could be hypothesized, for example, that

the reduced hepatic clearance of rT₃ would appear before, or would be predominant, at this stage on the reduced activity of type 1 deiodinase, which also leads to decreased FT₃. Other mechanisms than those leading to non-thyroidal illness are thought to be involved. As previously mentioned, they may be related to age and energy intake which impact on rT₃ concentrations. However, according to our results, others are also probably independent of the aging process or nutritional parameters.

Apart from rT₃, most other variables associated with survival in our study were previously reported.

Figure 2 Receiver operating characteristic curves of the biological markers significantly associated with shorter survival in a multivariate analysis. The area under the curve is 0.34 (95% confidence interval [CI], 0.27–0.40) for total cholesterol, 0.40 (95% CI, 0.32–0.49) for high density lipoprotein (HDL) cholesterol, 0.37 (95% CI, 0.29–0.44) for prealbumin, 0.38 (95% CI, 0.31–0.45) for free T₃ (FT₃) and 0.75 (95% CI, 0.69–0.81) for reverse T₃ (RT₃).

Nevertheless, the link with nutritional data must be emphasized. Low energy intake, prealbuminemia, and both HDL and total cholesterol were strong predictors of early death in a multivariate analysis including adjustment for BMI. Several authors have published conflicting results on total cholesterol in free-living elderly. Most studies pointed out hypocholesterolemia as an independent predictor of mortality (28, 29), whereas others did not (30). Some investigations also underlined the close link between usual nutritional markers such as prealbumin or albumin, cholesterolemia, and health status (31–33). Our study provides additional arguments to these observations. Nevertheless, it should be noted that according to the ROC curve created with our results, rT_3 was the best parameter to predict shorter survival among those tested.

In conclusion, our study demonstrates a strong association between rT_3 and survival in a population of independently-living elderly subjects regardless of other confounding factors. This 'high rT_3 syndrome' might precede an overt 'low T_3 syndrome' or might be an equivalent of it in the non-severely ill elderly. Thus, rT_3 could deserve to be assessed in elderly subjects with normal TSH. Additional studies are nevertheless necessary to confirm these results and explore the pathophysiological pathways that could lead to elevated rT_3 .

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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