



AGE RELATED FT3/FT4 RATIO AS POSSIBLE INDICATOR OF CHRONIC DISEASE AND CANCER DEVELOPMENT: A PILOT STUDY

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Abstract – Background: Age-related physiological aging is associated with mild deficiency of thyroid function or subclinical hypothyroidism (sHT), especially in the elderly. Furthermore, in areas with high risk of pollution (Naples and Caserta known as “Terra dei Fuochi”, Italy), thyroid disorders are increasing and basically correlated with neoplastic development, probably due to environmental contamination. This study sets out to understand the relationship between the levels of free triiodothyronine (FT3) and thyroxine (FT4) with longevity, chronic disease and cancer development.

Patients and Methods: This cross-sectional observational pilot study recruited 80 subjects >85 years old, living in Campania (Southern Italy). 40 of them are healthy subjects (have not physical and mental disabilities) while others 40 subjects have cancer and often co-morbidities like chronic metabolic diseases. In both groups thyroid function parameters were measured in the frame of a comprehensive geriatric assessment.

Results: TSH and FT3 levels were statistically different in the 2 groups: (A) TSH low, FT3 high; (B) TSH high level, FT3 low. These two groups showed a different FT3/FT4 ratio: there were significantly two folds higher in the control group A (5.0) than in group B (2.6) ($p=0.031$).

Conclusions: Age-related subtle thyroid function due to high levels of FT3 seems to be related to longevity in the subject aged > 85 years. Also, further study in a large number of subjects needs to validate that the FT3/FT4 ratio could be predictive of the predisposition to the development of cancer, chronic diseases and the degree of disability.

KEYWORDS: Thyroid, Sub clinic hypothyroidism, Longevity, Goiter, Levotiroxina.

INTRODUCTION

Different studies suggest that a decreased thyroid activity might be advantageous in oldest-old subjects and that subclinical thyroid hyperfunction may be detrimental¹.

Thyroid gland disorders are very prevalent and underestimated in older people than young people. Since co-morbidities can hide the symptoms, it is often difficult to make a precise diagnosis of thy-

roid malignancy². Age-related physiological aging is associated with mild deficiency of thyroid function or subclinical hypothyroidism (sHT); moreover, it is characterized by high level of thyroid stimulating hormone (TSH) and/or normal values of thyroxine T4 (FT4) and triiodothyronine T3 (FT3) free, frequently demonstrated in the elderly female³. Several authors have shown a correlation between high serum TSH level and geriatric disease like diabetes, hyperlipidemia, cardiovascular, neurological and cancer⁴.



The association between chronic illness and sHT is not yet completely clear and especially for older people (> 85 years) the literature is discordant. In high-risk areas of Campania Region (the area of the Province of Naples and Caserta known as the “Terra dei Fuochi”), thyroid disorders including cancer are increasing, probably due to environmental contamination, not only heavy metals but mainly TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) and PCB (3,3', 4,4', 5-pentachlorobiphenyl). These molecules are released by the combustion of materials which, accumulating in the soil and inserting in the food chain, may compromise the endocrine function of the thyroid gland. It is known that TSH is elevated in a subset of patients with thyroid cancer, but to date, the literature is low about the evidence that the abnormal level of the TSH could be influencing the cancer development. Furthermore, it could be possible that elevated levels of FT3 and FT4 may also be correlated with malignancy. A study has shown that FT4 is elevated in patients with thyroid cancer odd's ratio (OR) of 1.73⁶ while in another study this correlation has been found for total T3⁷. However, the optimal age-related TSH reference intervals have remained poorly defined. It is largely a consequence of the difficulties associated with enrolling large numbers of participants into multiple age partitions across adulthood and adequately excluding occult thyroid disease, which are both essential components of the traditional, direct approach to establishing age-related reference intervals. To the best of our knowledge, there is no evidence-based hypothesis, which explains this relationship between FT3/FT4 ratio and cancer development.

We aimed to investigate changes in thyroid hormone status in two groups of subjects aged > 85 years who lived in high environmental risk so called “Terra dei Fuochi”.

Both groups are selected as below: group A is represented by completely autonomous subjects who are not affected by disabling chronic conditions and neoplastic disease. On the other hand, group B consists of patients who are not self-sufficient and who suffer from severe chronic and disabling diseases, including cancer. We tried to verify in enrolled patients: (i) whether circulating levels of thyroid hormones reduce with aging; (ii) whether their reduction is associated with adequate aging quality (extreme longevity, chronic disease and cancer development); (iii) if both groups show differences in FT3/FT4 and FT3/TSH ratio.

PATIENTS AND METHODS

PATIENTS

We investigated changes in thyroid hormone status in 80 subjects aged > 85 years who lived in high environmental risk so called “Terra dei Fuochi”. They were enrolled in two groups:

- Case group A: 40 healthy geriatric subjects (26 females, 14 males);
- Control group B: 40 subjects (26 females, 14 males), who are affected by cancer and additional co-morbidities like chronic hypertension and need both walking-assistances and/or psycho-motory supplies.

This retrospective work was performed in compliance with the Ethical values laid down by the Declaration of Helsinki, and informed consent agreed by each patient.

METHODS

Thyroid function parameters (FT3, FT4 and TSH) were measured in the frame of a comprehensive geriatric assessment. Serological FT3, FT4 and TSH were measured with an immunometric assay performed on the Elecsys Analyzer (Roche Diagnostics, Basel, Switzerland).

STATISTICAL ANALYSIS

All analysis was performed in Microsoft Excel using the basic program. *p*-values were extrapolated by Welch test.

RESULTS

The mean value of measured FT3, FT4 and TSH has been reported in Table 1 for both groups. All mean values were in normal range except for FT3 higher in group A and TSH higher in group B.

- Group A: FT3 4.14 (IC 3.95-4.32); FT4 1.26 (IC 1.05-1.46) and TSH 2.01 (IC 1.73-2.29);
- Group B: FT3 3.15 (IC 3.61-4.42), FT4 1.64 (IC 1.34-1.94) and TSH 4.01 (IC 3.61-4.42).

We found that age was significantly associated with decreased levels in FT4 between groups A and B ($p < 0.001$; $p = 0.018$, respectively) but not with FT3 and TSH ($p = 0.700$). Statistically significant differences were found for FT3/FT4 ratio between groups: the age-related decline in values was significantly lower in the control group A than in the case group B ($p = 0.031$).

Furthermore, FT3/TSH is also significant, but this data needs to be verified on a larger number of subjects, because TSH levels suffer from multiparametric variability⁸.

Moreover, the finest age-related TSH reference intervals still have remained weakly defined. This is mostly an effect of the difficulties to enrolling great numbers of adult patients and adequately excluding occult thyroid disease.

TABLE 1. Mean values of TSH, FT3 and FT4 serum level in two groups.

Analyses (Normal Range)	Group A		Group B		p-value
	Value	Ratio*	Value	Ratio	
FT3 (2.0-3.5 pg/mL)	4.14 ^{\$}	4.97	3.15	2.56	<i>p=0.031 calculated on FT3/FT4 ratios</i>
FT4 (0.7-2.2 ng/mL)	1.26		1.64		
TSH (0.4-4.5 IU/mL)	2.01	2.45	4.01 ^{\$}	0.86	<i>p=9.4x10⁻¹² calculated on FT3/TSH ratio</i>

*Ratio FT3/FT4; \$Out of normal range, in bold.

DISCUSSION

The findings from this study have important interpretative implications. Our results denote that age-associated changes in thyroid function might represent a physiological mechanism directly contributing to the aging process through a resetting of the hormonal milieu, which may promote longevity and successful aging rather than an adaptation to the need of reducing the catabolic processes, heavy metals storage and oxygen consumption. This conceptual model is in agreement with previous studies showing that elderly subjects with low serum FT4 and FT3 concentrations had longer survival, especially in the presence of normal reverse T3 concentrations⁹.

If confirmed, this interpretation would implicate that subtle hypothyroid status (FT3/FT4 ratio) should be considered as a marker of robustness, while either clinical or subclinical hyperthyroidism, which are known to exert a detrimental effect on survival, physical performance, cognitive status and bone mineral content¹⁰, should find a place among the markers of cancer frailty¹¹.

The high TSH level and low-limit range of FT3 detected in group B are known parameters in age-dependent literature, while the finest age-related TSH reference intervals¹² still have remained weakly defined. These TSH and FT3 levels fluctuations could be explained by decreasing of the de-iodination mechanism responsible for the conversion of T4 to T3, due to the age¹³.

Our data indicate the mean of TSH value at low limits and FT3 at the upper limits in group A. These conditions may be related to the peculiar eating habits based on the detox-diet, allowing efficacy elimination of various toxic substances that are presented at the environmental level¹⁴.

The diet of group A is predominantly made up of vegetables (often cultivated in personal and neighboring crops), which have probably developed antioxidant levels and protective molecules (fitochelatines). Conversely, group B, due to cognitive-related issues and disabilities, mainly feeds on refined industrial foods (data not shown)¹⁵. This particular hormonal relationship could, therefore, be predictive of longe-

vity, also by a lower incidence of severe chronic-degenerative pathologies in the elderly¹⁶. Furthermore, heavy limitations of this study should be considered.

- These results must be validated in a larger cohort study.
- The cross-sectional design of our study does not allow us to assess prospectively the impact of thyroid hormone status on survival. Although this issue needs further investigation, the results obtained in relatives of centenarians are suggestive of a thyroid resetting, which could promote longevity.
- As only patients with thyroid hormone values within the normal range were included in this analysis, the current study is unable to explain whether subclinical hypothyroidism could also be a marker of longevity or it rather would benefit from replacement therapy. However, there is no sufficient evidence to recommend routine treatment for patients with subclinical hypothyroidism, and this issue warrants further investigation. In addition, a previous study¹⁷ reports discordant results from ours: FT3 median value on control group (n=278 subjects aged from 60-85 years old) was 3.35 pg/mL and 2.85 pg/mL for >85 years.
- Finally, subjects carrying a catabolic state characterized by low FT3, which are known to be at risk of functional decline, cannot be identified in our study¹⁸.

CONCLUSIONS

Age-related subtle thyroid hypofunction (due to a reset of the thyroid function occurring between the sixth and the eighth decade of life) seems to be related to longevity in the subject aged >85 years. These parameters were measured in the frame of a comprehensive geriatric assessment by a FT3/FT4 ratio.

In addition, the next step of this study will focus on the evaluation of FT3/TSH ratio (needs more data), in order to check a possible correlation between longevity and cancer development. An additional aim will focus on the putative correlation between serological levels of thyroid hormones and the chronic disease frequency as well as psycho-motory capacity.



Promise in the next future, these preliminary results could be the related to longevity/environmental issue in order to plan a specific project of detox diet for people who lived in high environmental risk so called “Terra dei Fuochi”¹⁹.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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