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Are Changes in Thyroid Hormones Associated with Mortality in Non-Thyroidal Illness Syndrome?

Emre Hoca, Hayriye Esra Ataoğlu, Süleyman Ahbab

ABSTRACT

Introduction: **Non-thyroidal illness syndrome (NTIS) can be defined as afunctional impairment of the hypothalamic-pituitary-thyroid axis accompanied by signs of non-thyroidal disease with changes in thyroid stimulating hormone (TSH), free T3 (fT3) and free T4 (fT4) levels. NTIS and thyroid hormone levels in this syndrome are thought to be related with mortality. This study was performed to evaluate the relationship between hormone levels and mortality in this syndrome.**

Methods: **The 5-year mortality data of patients who were hospitalized in the first 6 months of 2014 and whose thyroid hormone levels could be checked twice within 5 years were evaluated. In our study conducted with 405 patients whose thyroid function tests was repeated, the follow-up period was 5 years. Biochemical parameters including thyroid function tests were sent from all patients. NTIS was defined as a condition in patients with low fT3 levels (<2.5 pg/mL) and TSH levels within the normal range (0.38-5.33 mIU / L).**

Results: **128 patients died, and the number of surviving patients was 277 during the follow-up period. Positive acute phase reactants such as CRP, sedimentation, ferritin was high and albumin (negative acute phase reactant) and fT3 levels were low in patients who died. In addition, these changes in biochemical values were statistically significant. The mortality rate was increased in patients with low fT3 and high fT4 levels. In the follow-up period, changes in TSH levels were not significantly associated with mortality.**

Conclusion: **Both the decrease in fT3 levels and the increase in fT4 levels can be used as predictors and independent risk factors for long-term mortality risk in chronically ill and hospitalized patients with NTIS.**

Keywords: Mortality, non-thyroidal illness syndrome, serum free T3, serum free T4.

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I. Introduction

The evaluation of the varying thyroid functions in systemic diseases and stress is complex because changes in all levels of the hypothalamo-pituitary-thyroid (HPT) axis may occur. The non-thyroidal illness syndrome, first described in the 1970s and known as euthyroid sick syndrome or low T3 syndrome, is not considered a true syndrome, but reflects changes in thyroid function tests in various clinical situations. These changes are thought to result from adaptation of the body to inflammatory or catabolic conditions [1], [2]. Any acute, severe and/or critical illness can cause these measurements to be misleading, leading to changes in circulating thyroid hormone or TSH levels in the absence of underlying thyroid disease. The main reason of these hormonal alterations is thought to be the release of inflammatory cytokines such as IL-6 in the course of the diseases [3], [4]. Infectious diseases, traumas (especially surgical traumas), history of surgery and anesthesia, nutritional disorders (fasting, carbohydrate poor nutrition, anorexia nervosa), high dose corticosteroid administration, hospitalization in intensive care unit, severe stress, psychiatric diseases, chronic liver and kidney diseases, uncontrolled and/or complicated diabetes, myocardial infarction and respiratory failure are some of these conditions [5]–[7]. NTIS and thyroid hormone levels in this syndrome are also thought to be related with mortality [8], [9].

In this study, we aimed to evaluate the course of thyroid hormone levels during the follow-up of patients who were hospitalized in the Internal Medicine Clinic due to different acute or chronic diseases and have NTIS. Besides, it is aimed to evaluate the relationship between the course of these hormones' serum levels and mortality.

II. Material and Methods

A. Study Design

This retrospective cohort study used data from the University of Health Sciences, Haseki Training and Research

Hospital. The study was conducted in accordance with the declaration of Helsinki and scope of good clinical practice. Informed consent of all patients admitted to our clinic was obtained. The protocol of this study was approved by the Institutional Review Board of the University of Health Sciences, Haseki Training and Research Hospital (Ref. 540/04.10.2017). The current study was organized using a computerized database, established between January 1st and June 30th, 2014, in the University of Health Sciences, Haseki Training and Research Hospital, Internal Medicine Clinic. Data for the analysis were obtained from electronic hospital data processing system records and profile databases of University of Health Sciences, Haseki Training and Research Hospital. Standardized data collection includes patient demographic information, medical history, diagnostic testing and diagnoses of in-hospital. This data was obtained from the patients' electronic medical records. This study was consisted of 405 patients, 221 females and 184 males whose second thyroid function tests were in the first year after hospitalization and followed up for 5 years.

B. Laboratory Measurements

Routine blood samples for all laboratory tests was drawn between 6 am and 7 am, in the morning and after a 12-hour fasting. Plasma biomarkers including complete blood count, kidney and liver functions, blood glucose, serum lipids and inflammatory markers including sedimentation and CRP were analyzed in the department of medical laboratory, University of Health Sciences, Haseki Training and Research Hospital. Laboratory findings were obtained from the patients' electronic medical records. Biochemical parameters were performed for all participants. The first blood samples levels measured at the time of the patients' first referral to the hospital. Second sample: 405 patients whose second thyroid function tests were accomplished in the first year after hospitalization. NTIS was defined as the condition found in patients with low fT3 (<2.5 pg/mL) and normal TSH levels (0.38-5.33 mIU/L).

C. Follow-up and end points

The follow-up period ended on 30th June 2019. All data were supported with the hospital records. Follow-up information was gathered through data processing system of University of Health Sciences, Haseki Training and Research Hospital. The primary endpoints of this study were composite outcome, including all-cause mortality, as documented in the database. The main outcome measure (dependent variable) in this study was all-cause-mortality. The Turkey National Death Registry System was used to verify mortality reports of the follow-up clinic. During the follow-up, a total of 128 participants died. We conducted the retrospective cohort study which included 405 patients (221 women and 184 men) with a median follow-up of 37 months (min: 1 - max: 41).

D. Statistical Analysis

Statistical analyzes were performed using the 17th version of SPSS (Statistical Package for Social Sciences) software (SPSS Inc., Chicago, Ill., USA). Whether the variables were suitable for normal distribution was examined using visual (histogram and probability charts) and analytical methods (Kolmogorov-Simirnov test). Descriptive statistics were made by giving mean ± standard deviation for normally distributed variables. Comparisons with normal distribution among the initial and control tests were compared with Student's t test, and comparisons with non-normally distributed tests were compared with the Wilcoxon rank sum test. Rates were compared with Fisher's exact test or chi-square test. Results with a p value of less than 0.05 were considered statistically significant.

III. Results

In the study conducted with 405 patients, the mean age was 62.67±16.90 (60.87±17.16 for men and 64.17±16.58 for women). During the follow-up period, 128 patients were died, and the number of surviving patients was 277. In the mortality developed patients' group the mean age, positive acute phase reactants such as CRP, sedimentation, ferritin and fT4 levels were higher, albumin (negative acute phase reactant), initial/follow up fT3 levels and fT3/fT4 ratio were lower than survivors as shown in the Table I. In the study, it was found that mortality was increased in patients who's initial fT3 levels were found to be low and who had low levels at the follow-up (<0.001), in Fig. 1. 43 of the 85 patients who's initial fT3 levels were found to be low and 18 of the 29 patients whose initial fT3 levels were normal but who had low fT3 levels during follow-up were died. It was also observed that the mortality was increased in patients who's initial and follow-up fT4 levels were found to be elevated (p <0.001), in Fig. 2. Of the 49 patients with elevated initial and follow-up fT4 levels, 29 were died. If the cutoff value of fT3 / fT4 ratio was taken as 2.27 (median value of the ratio in all patients) in patients with NTIS, it was shown that the mortality rate was higher in patients with a ratio below this value (p <0.007 and p <0.006, respectively), in Fig. 3. When the follow-up fT3 levels subtracted from the initial fT3 levels, the increase in the difference was also found to be associated with mortality (p: 0.005). In 405 patients with NTIS, there was no statistically significant relationship between mortality and TSH levels (p: 0.612).

TABLE I: The Relationship between Demographic/Laboratory Findings and Mortality during Hospitalization (N: 405)

	Survivor	Non-Survived	p
Gender (F/M)	164/113	57/71	0.006
Age (≥65) N (%)	112(40.4 %)	90(70.3%)	<0.001
CRP (mg/L)	47.2 ± 71.6	63.4 ± 71.5	0.035
Sedimentation (mm/h)	40.0 ± 30.2	48.4 ± 30.7	0.012
Ferritin (ng/mL)	148.7 ± 224.4	299.2 ± 408.7	<0.001
Albumin (g/dL)	3.5 ± 0.5	3.1 ± 0.6	<0.001
Creatinine (mg/dl)	1.2 ± 1.3	1.7 ± 1.9	0.012
Hemoglobin (g/dl)	10.7 ± 2.6	10.4 ± 2.1	0.166
Leukocyte (mm^3/uL)	8316 ± 4564	9291 ± 4608	0.048
fT3 (pg/mL) ($^*1^{st}$)	2.6 ± 0.5	2.4 ± 0.6	<0.001
fT4 (ng/dL) (1^{st})	1.0 ± 0.3	1.1 ± 0.3	0.011
TSH (mIU/L) (1^{st})	1.6 ± 1.3	1.7 ± 1.6	0.585
fT3/fT4 ratio (1^{st})	2.7 ± 1.0	2.3 ± 0.7	<0.001
fT3 (pg/mL) (2^{nd})	2.8 ± 0.6	2.3 ± 0.6	< 0.001
fT4 (ng/dL) (2^{nd})	1.0 ± 0.2	1.1 ± 0.3	0.005
TSH (mIU/L) (2^{nd})	1.9 ± 1.4	1.9 ± 1.5	0.890
fT3/fT4 ratio (2^{nd})	3.0 ± 0.8	2.3 ± 0.9	< 0.001

(CRP: C-reactive protein, fT3: Free T3, fT4: Free T4, TSH: Thyroid Stimulating Hormone).

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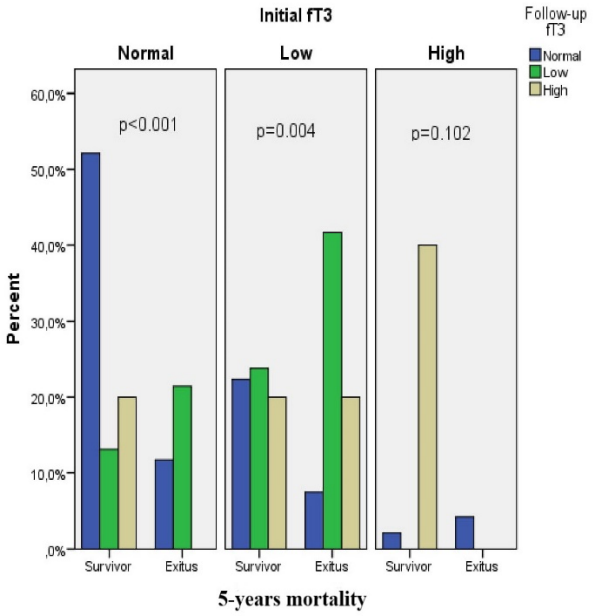

Fig. 1. Relationship between changes in fT3 levels and mortality.

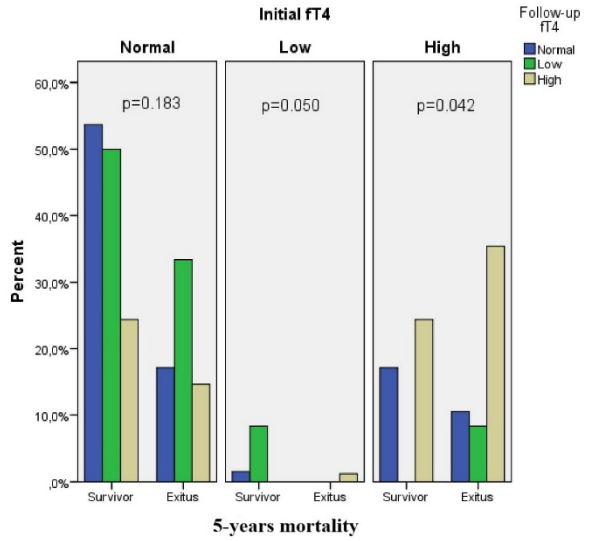

Fig. 2. Relationship between changes in fT3 levels and mortality.

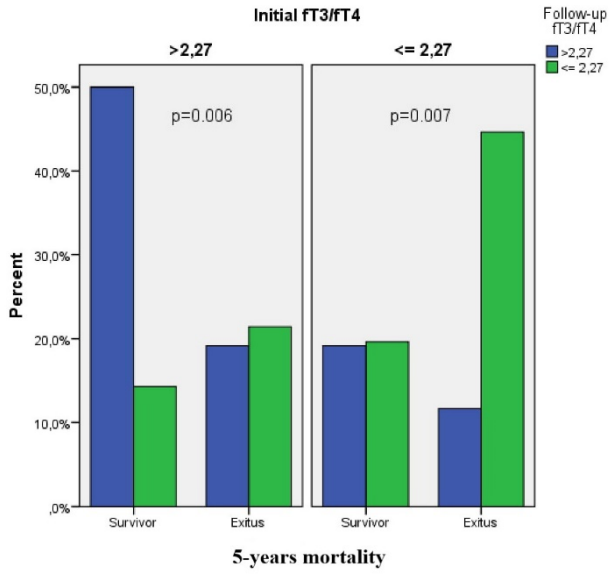

Fig. 3. Relationship between changes in fT3/fT4 ratio and mortality.

IV. Discussion

NTIS is an important clinical condition that occurs during the course of critical diseases, and it may be difficult to recognize and diagnose this syndrome during follow-up. The reason for this syndrome being an important condition is that, if diagnosed, it allows the physician to predict mortality by considering thyroid hormone levels and changes of these hormones after the patient's recovery from the actual disease. According to some studies, the incidence of NTIS in hospitalized critically ill patients with different diagnoses has been shown to be between 60% and 70% [10]–[12]. Plikat *et al.* [11] observed that approximately 44% of patients hospitalized in the intensive care unit have NTIS. Explaining the relationship between changes in thyroid hormone profile and mortality/survival is another important issue in the follow-up of patients with NTIS. In this way, it will be more clearly understood which examinations should be performed while monitoring patients with NTIS, how the results of the examinations can be interpreted, and the course of the disease will be. The results of studies evaluating the relationship between mortality and changes in thyroid hormone levels in patients with NTIS are controversial and sometimes contradictory. Reference [12] demonstrated that the decrease in T3 hormone levels is associated with an increase in mortality, especially in elderly patients. Advanced age, low albumin, high creatinine, low hemoglobin levels are associated with increased mortality. There are different conclusions about the relationship between other thyroid hormone levels (fT4 and TSH) and mortality. In a study with the participation of 558 patients aged over 85 and conducted by [13], it was shown that the decrease in fT3 levels was associated with an increase in mortality rate in patients with NTIS. However, the relationship between fT4 hormone levels and mortality could not be clearly explained.

In a study designed by [14], with the data of 301 patients (156 females, 145 males, 65-101 years of age and hospitalized for acute illness), it was found that increased mortality was associated with a decrease in T3 hormone levels. When the data in the same study are evaluated, it was recommended that T3 hormone levels should be considered in addition to TSH, since TSH levels may not have a diagnostic value in patients with critical disease. Levels of inflammatory cytokines such as IL-6 and glucocorticoids are increasing in the course of diseases [15], [16]. These changes are effective in the development of non-thyroidal illness syndrome by causing decrease in the activity of type-1 and type-2 deiodinase enzymes with an increase in type-3 deiodinase enzyme activity. Reference [17] indicated that decreased T3, increased T4 and decreased TSH levels were found to be associated with increased mortality. In our study, although similar results were found for T3 and T4, changes in TSH levels were not found to have a significant relationship with mortality. In a study conducted by [18] with Caucasian angiography patients, low fT3 and high fT4 levels increased mortality for all causes and cardiovascular causes, regardless of age and sex. In two different studies were shown that non-thyroidal illness syndrome was found to be common in acute or chronic liver diseases (hepatitis, cirrhosis, etc.) and the decrease in T3 level was associated with worsening in prognosis [19], [20]. In a study performed in China in 2014 with patients diagnosed with chronic renal failure, it was

found that the risk of mortality increased due to cardiovascular events in patients with NTIS (low T3, high IL-6 levels) [21]. When the findings of our study are examined, it could be seen that the increase in fT4 levels and the decrease in fT3 levels have a significant relationship with mortality. Also, it was observed that further decrease in fT3 levels in follow-up period was associated with mortality. Changes in TSH levels were not found to be significantly correlated with mortality.

V. Conclusion

Close follow-up is important during and after hospitalization in cases with non-thyroidal illness syndrome. TSH levels solely are not sufficient to evaluate the thyroid functions. To gain an idea about prognosis and to evaluate the course of the disease, it would be appropriate to monitor the levels of fT3 and fT4 together with TSH (even more than TSH levels). In NTIS, low fT3, low fT3/fT4 ratio and high fT4 levels can be used as independent risk factors for increased mortality and predictors for increased mortality.

Recommendation

TSH levels solely are not sufficient to evaluate the thyroid functions in non-thyroidal illness syndrome. To gain an idea about prognosis and to evaluate the course of the disease, it would be appropriate to monitor the levels of fT3 and fT4 together with TSH.

Author Contributions

Prof. Dr. Esra Ataoğlu and Dr. Emre Hoca conceived and designed the study, collected data, and analyzed the data. Assoc. Prof. Dr. Süleyman Ahbab played a role in clinical help and reviewed the article with Dr. Emre Hoca.

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None.

Conflict of Interest

There was no conflict of interest.

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