Investigation of the Relationship between Thyroid Hormone Levels and Mortality in Old Patients Hospitalized in an Internal Medicine Intensive Care Unit from the Emergency Service

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Abstract

Objective: In our study, the purpose was to determine the relationship between thyroid hormones and mortality of patients over the age of 55 who were hospitalized in an intensive care unit from the emergency service.

Material and Methods: This study was planned as a prospective, randomized study, and patients hospitalized in an intensive care unit from the emergency medicine department were enrolled in this study following ethics committee approval. A standard data collection form was used to collect the data. After confirmation from the patients and their relatives, we included 73 patients in our study: 48 (65.8%) males and 25 (34.2%) females. Blood samples were taken from each patient, and thyroid hormone levels were studied in our laboratory. The "SPSS for Windows version 18" program was used for statistical analysis of the data. Chi-square test was used to compare categorical measures between the groups. Mann-Whitney U-test and t-test were used to compare quantitative measurements between the groups. The log-rank test was performed under Kaplan-Meier survival analysis to determine the relationship between the estimated lifetime and free T3 (fT3), free T4 (fT4), and thyroid-stimulating hormone (TSH).

Results: There was no statistically significant difference in mean ages and genders of patients who died and survived. The mean duration of hospitalization in the deceased patient group was lower than in the surviving patient group, but there was no statistically significant difference between the groups. According to the Kaplan-Meier survival analysis, the patients with low or high levels of fT3 were found to have a shorter median life expectancy. No significant relationship was found between mortality and fT4 TSH.

Conclusion: According to our study, increased or decreased levels of fT3 in patients over the age of 55 without known thyroid disease, hospitalized in an intensive care unit from the emergency department, showed increased mortality. This study will be useful for emergency medicine physicians to be able to predict the mortality of patients and contribute to more clinical experience. FT3 levels can be used as a prognostic indicator after more detailed studies are completed.

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Key words: Mortality, thyroid hormones, emergency

Introduction

The patients who apply to emergency services and need to be hospitalized carry high mortality risk due to several factors, such as multiple organ failure, a severe disease involving partial or complete dysfunction of organ systems, intoxication, trauma, or previous operation. The patients hospitalized in the intensive care unit may reveal various endocrine disorders because of either high stress levels due to their existing disease or ongoing medications. The most common endocrine change in those patients is euthyroid sick syndrome. Underlying diseases, stress, ongoing medications of the patient, and impaired nutritional status may lead to primarily low free T_3 (fT_3) and also suppressed free T_4 (fT_4) and thyroid-stimulating hormone (TSH) (1). Patients hospitalized for clinical conditions, such as sepsis, malignancy, trauma, burns, myocardial infarction, and cerebrovascular events or for prolonged hunger status more than 24-36 hours, demonstrate remarkable changes in their hypothalamic-pituitary-thyroid axis and thyroid hormone levels (2-5). The degree in the level of thyroid hormone is associated with the severity of the disease (6).

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The purpose of our study was to determine the relationship between thyroid hormone levels and mortality in the patients aged over 55 years without a known thyroid disease who were hospitalized in an intensive care unit from the emergency service.

Material and Methods

Our study, a prospective study design to include the patients over 55 years of age due to their consent without a known thyroid disease hospitalized in the internal medicine intensive care unit from the emergency service, was initiated after gaining ethical approval from the ethics committee of Medical Faculty of Cukurova University in the 4th Meeting Session, dated April 14,2009. A standard data collection form was used to collect the data. The data collection form included age, gender, application date to emergency service, diagnosis, protocol ID in the hospital records, test results during the study, duration from hospitalization in the internal medicine intensive care unit until final status (exit or discharge), and final status of the patient, and these data were recorded in detail for each patient. Blood samples were obtained from all of the patients after application to the emergency service, establishment of diagnosis, and hospitalization in the internal medicine intensive care unit to evaluate for the study. The obtained blood samples were tested for fT_3, fT_4, and TSH levels. The obtained blood samples were analyzed in the central laboratory of Balcali Hospital, Medical Faculty of Çukurova University.

Statistical Analysis

Statistical Package for Social Sciences 18.0 (SPSS Inc., Chicago, IL, USA) software was used for the statistical analysis of the data. The categorical measurements were expressed in numerical and percentile form, while numerical measurements were given in mean and standard deviation (as median and minimum-maximum when required). Chi-square test was used to compare categorical measurements between the groups. Mann-Whitney U-test and t-test were used to compare quantitative measurements between the groups. The log-rank test was performed under Kaplan-Meier survival analysis to determine the relationship between the estimated lifetime and fT_3, fT_4, and TSH. The statistical significance level was accepted as 0.05.

Findings

The study involved 73 patients, composed of 48 males (65.8%) and 25 females (34.2%), that were hospitalized to the internal medicine intensive care unit from the emergency service. Of these patients hospitalized to the internal medicine intensive care unit, 33 (45.2%) became exitus, while 40 (54.8%) were discharged. The mean age of the patients who became exitus after hospitalization to the intensive care unit and inclusion to our study was 67±10 years, while the mean age of the discharged patients was 65±8 years; no statistically significant difference was found between the groups.

The mean duration of hospitalizations were 13±14 days and 22±23 days in the exitus and discharged patients, respectively. Mean duration of hospitalization of the exitus patients was remarkably shorter, and there was a statistically significant difference between the groups (p=0.01).

The relationship between the fT_3, fT_4, and TSH levels and median life expectancy was analyzed by Kaplan-Meier survival analysis. Mean fT_3 levels of the exitus and discharged patients were 2.22±1.7 pg/mL and 1.88±0.8 pg/mL, respectively. As shown in the Table 1 and

Table 1. Results of the Kaplan-Meier survival analysis performed for fT_3

fT_3 pg/mL	Mean life expectancy (days)	Median life expectancy (days)	95% confidence interval	P value
st_3 <1.38	32.5±11.6	20	13.9-26	0.18
st_3: 1.39-2	43.7±4.9	56		
st_3>2	18.3±3.5	18	1.6-34.4	

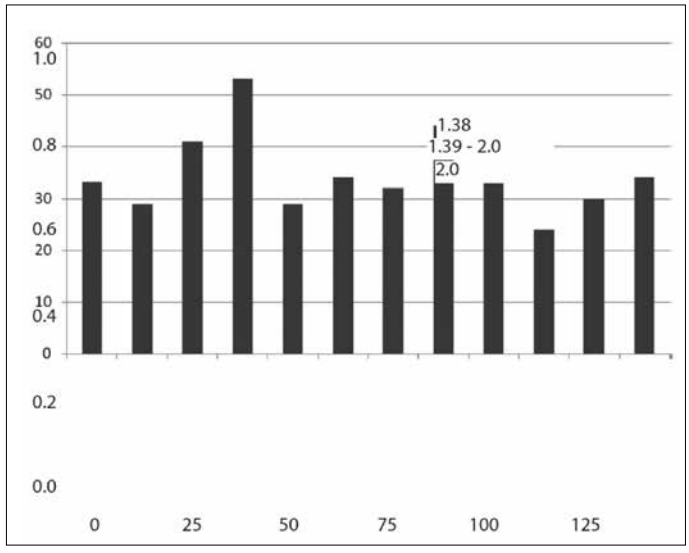

Figure 1. Kaplan-Meier survival analysis chart performed for fT_3

Figure 1, it has been determined that median lifetime expectancy of the patients with low or high fT_3 levels was statistically significantly shorter according to the results of the Kaplan-Meier survival analysis (p=0.018).

According to the results of the Kaplan-Meier survival analysis for thyroid-stimulating hormone and fT_4, no statistically significant relationship was found between levels of TSH and fT_4 and median life expectancy (TSH P=0.5) (fT_4 p=0.261).

Mean fT_4 levels of those who became exitus (1.26±0.6 ng/dL) and discharged (1.23±0.2 ng/dL) were similar (p=0.48). Mean TSH levels of the exitus patients (1.13±1.1 Mu/L) was lower than the mean TSH levels of the discharged patients (1.59±1.8 Mu/L); however, no statistically significant difference was found between the groups (p=0.23).

Discussion

The increased elderly population increases the incidence of old patients with major diseases. It has been reported in the literature that elderly patients make up 46% of the hospitalized patients in the intensive care units (7). Mortality rate increases significantly parallel with elderly age in hospitalized patients (8-11). However, no significant relationship was found between age and mortality rate in the patients included in our study. It has been concluded that age level over 55 of our patients provided these results.

Patients hospitalized in the intensive care units generally have diseases with high mortality rate. Although these patients frequently reveal changes in thyroid hormone levels, detection of their effect on mortality will be helpful for clinicians to determine the prognosis of the patients. Thyroid hormones have important tasks in metabolism.

Thyroid hormones stimulate all stages of carbohydrate metabolism; increase in glucose absorption through the gastrointestinal tract, glycolysis, glycogenolysis, and use of glucose by the cells; cause increased concentration of free fatty acids in the blood by mobilizing free fatty acids; facilitate their use by cells; reduce blood cholesterol level by increasing the number of LDL receptors in the liver; reduce levels of phospholipids and triglycerides; increase metabolic rates in a major part of the human body except brain, retina, spleen, testicles, lung, uterus, and adenohypophysis; increase oxygen consumption by increasing tissue metabolism and lead to increased final metabolic products; and cause increased rate and power of cardiac contractility by increasing the number of the beta receptors in the heart. Increased metabolic rate leads to consumption of oxygen and production of carbon dioxide, and consequently, the frequency and depth of respiration increase, causing increased secretion of other endocrine glands (12, 13).

The thyroid gland secretes whole amounts of thyroxine (T_4) and 10% of the T_3 of thyroid hormones. The rest of T3 is produced by deiodination of thyroxine by peripheral tissues (12, 13); 99.8% of the triiodothyronine is bound to proteins (46%, 53%, and 1% of T_3 is bound to TBG, albumin, and TBPA, respectively), and 99.98% of thyroxine is bound to proteins (67%, 20%, and 13% of T_4 is bound to TBG, TBPA, and albumin, respectively). Triiodothyronine has important characteristics, such as less binding to proteins, shorter half-life than T_4, and its rapid effect in tissue. Various factors affect the level of TBG. The factors that increase TBG level include pregnancy, estrogen, clofibrate, tranquilizers, and use of heroin. The factors that reduce TBG level include glucocorticoids, androgens, danazol, and use of L-asparaginase. Total thyroid hormone level increases and free thyroid hormone levels decrease as TBG increases. Consequently, the TSH (thyroid-stimulating hormone, thyrotropin) level increases by negative feed-back, and free thyroid hormone levels in the blood circulation reach normal levels. As a consequence, the patient remains euthyroid. Reverse physiological events occur in situations with reduced TBG levels (13).

Thyroid hormones are deiodinated in many tissues, such as primarily liver and kidneys. In adult persons, 33% and 45% of thyroxine is converted to triiodothyronine and rT_3 (reverse T_3), respectively. Of the triiodothyronine in the circulation, 13% is secreted by thyroid gland, whereas 87% is produced by thyroxine deiodination. Of the rT_3 in the circulation, 5% is secreted by thyroid gland, whereas 95% is produced by thyroxine deiodination. Deiodination is mediated by two different enzymes. The formation of T_3 is mediated by 5'-deiodinase, whereas formation of rT_3 is mediated by 5-deiodinase. The enzyme 5'-deiodinase also provides conversion of rT_3 to T_2 (diiodothyronine) (12, 13). The enzyme 5'-deiodinase is inhibited in many conditions. The inhibition of this enzyme increases the amount of T_3. The factors that decrease the amount of T_3 by inhibiting the enzyme 5'-deiodinase include burns, trauma, advanced stage of cancer, cirrhosis, renal failure, myocardial infarction, inflammatory diseases, and hunger. As T_3 decreases, basal metabolic rate is slowed down, and protein breakdown is maintained.

Euthyroid sick syndrome observed in intensive care unit patients is considered a body adaptation to maintain energy by reducing the metabolic rate (14-16). Cytokines increase, depending on severity of the disease, in intensive care unit patients. Due to the effect of cytokines, level of fT_3, tissue response to T3, and response of TRH to TSH decrease (17, 18). In hunger, thyroid hormone levels decrease due to suppressed TRH expression in the paraventricular nucleus of the hypothalamus (19). Also, 40%-70% of patients hospitalized for non-thyroidal diseases may reveal abnormalities in one or more thyroid functions tests. In such conditions, incidence of true hypothyroidism or hyperthyroidism is less than 1%, and transient central hypothyroidism has been reported in some those patients (20).

Many endocrine system changes may be encountered in intensive care patients due to rapid and transient or permanent changes that occur in the hypothalamic-pituitary-thyroid axis. Some studies have shown decreased T_3 levels in patients with surgery, burns, acute coronary syndrome, cancer, and renal and hepatic failure (21, 22). Many studies have shown that mortality rate increases or shows no change as suppression of thyroid hormone levels increases in intensive care unit patients. Some researchers found mortality associated with suppressed fT_3, while another researcher suggested that suppressed fT_4 was associated with mortality, whereas some researchers have stated that both of them are associated with mortality; furthermore, fT_3 and fT_4 were better prognostic indicators than the APACHE II Scoring System (1, 22-27). In contrast with those, it has been proposed that thyroid hormone levels are not indicators with respect to mortality (11). We have detected in our study that mortality increases in patients with low or high fT_3, while TSH and fT_4 are not associated with mortality. Similar to other previous studies, a gender difference did not change mortality (1, 28). It has been determined that fT_3 may be used in the estimation of mortality rate for patients over 55 years of age without a known thyroid disease hospitalized in the internal medicine intensive care unit from the emergency service. However, more comprehensive and detailed research is necessary to clarify the relationship completely between thyroid hormone levels and mortality.

Study Limitations

This study was done on 73 patients; it would be of beneficial to carry out a multi-center study on more patients.

Conclusion

We have detected in our study that low or high fT_3 levels increase mortality in patients over 55 years of age without a known thyroid disease hospitalized in the internal medicine intensive care unit from the emergency service. This study will be helpful for clinicians of emergency services to estimate the mortality of their patients and also their clinical experience. fT_3 may be used as a prognostic indicator in more comprehensive studies that will be conducted in the future.

Ethics Committee Approval: The ethical approval was obtained from the Ethics Committee of Medical Faculty of Çukurova University in the 4th Meeting Session dated April 14, 2009.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Y.T., M.O.A., M.K.; Analysis/ Interpretation - Y.T., M.T., M.G.; Literature Search - Y.T., M.O.A., M.T., M.G.; Writing - Y.T., M.O.A., A.A.; Critical Reviews - Y.T., A.S., M.O.A.

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