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Thyroid hormones as potential prognostic factors in sepsis

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Abstract

Background: Sepsis is a life-threatening organ dysfunction caused by a dysregulated host reaction to infection. There is an upward trend in sepsis prevalence and mortality worldwide. Sepsis causes hypoxia, which reduces the ability of cells to produce ATP. This process is also influenced by thyroid hormones. Some of the previous studies revealed association between the mortality rate in sepsis and thyroid hormone levels. We aimed to evaluate thyroid hormones' predictive value in septic patients.

Methods: Forty-nine adult patients with sepsis admitted to the Intensive Care Unit of Allergy and Immunology Department at the University Hospital in Krakow, Poland, between 2015 and 2017 were enrolled in the study. Blood samples were obtained from septic patients immediately after establishing the diagnosis, in order to measure free triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) levels. The primary endpoint was 30-day survival rate. The secondary endpoint was death anytime during intensive care unit (ICU) stay.

Results: Patients who died within 30 days had significantly lower level of fT4 than survivors (9.8 vs. 12.7 pmol L^{-1}; $P = 0.033$). There was no statistically significant difference between the groups in TSH and fT3 levels. As for the secondary endpoint, both fT3 (1.6 vs. 1.8 pmol L^{-1}; $P = 0.021$) and fT4 (9.8 vs. 12.7 µIU mL^{-1}; $P = 0.019$) levels were significantly lower among non-survivors compared to survivors, which was not the case for TSH.

Conclusions: Thyroid hormone levels were significantly lower among patients who died during ICU stay. The results of the presented study suggest that fT3 and fT4 levels may be taken into consideration as potential new prognostic factors in sepsis.

Key words: sepsis, mortality rate, thyroid hormones.

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Despite recent developments in intensive care, sepsis remains one of the leading problems faced by clinicians involved in the field. Sepsis is the cause of approximately 34.0% and 37.4% admissions to Polish and European intensive care units (ICU), respectively, and it is associated with very high mortality, reaching 32.2% among patients with severe sepsis [1, 2]. Alarmingly, there is an upward trend in its prevalence and mortality rate worldwide [3]. Furthermore, sepsis is a crucial issue for the policymakers, due to the high cost of ICU treatment, estimated to be $27,461 per case, and the significant re-hospitalisation rate among sepsis survivors, reaching 63% [4, 5]. Considering the aforementioned data, precise and reliable predictive factors in sepsis are needed. However, the search for further prognostic biomarkers is ongoing.

Sepsis is associated with dysfunction of multiple organs. Respiratory failure, hypotension, and/or shock contribute to hypoxia, thus reducing the ability of cells to produce ATP (Figure 1). The impact of severe systemic diseases on thyroid metabolism is increasingly emphasised by researchers. The phenomenon is described as non-thyroidal illness syndrome. The hypothesis about the origin of the syndrome claims that it is a combination of physiological adaptation and pathological response to systemic lesions. According to current knowledge, the mechanism of developing a non-thyroidal disease syndrome is associated with a reduced signalling of thyroid-stimulating hormone (TSH) production by the hypothalamus. However, the basic reason for these changes has not been clearly explained [6].

Based on the available knowledge we hypothesise that thyroid function may be associated with outcomes in patients with sepsis and therefore its markers could be useful clinical risk predictors. Our aim was to evaluate the value of free triiodothyronine (fT3) and free thyroxine (fT4) as predictors of survival among patients with sepsis.

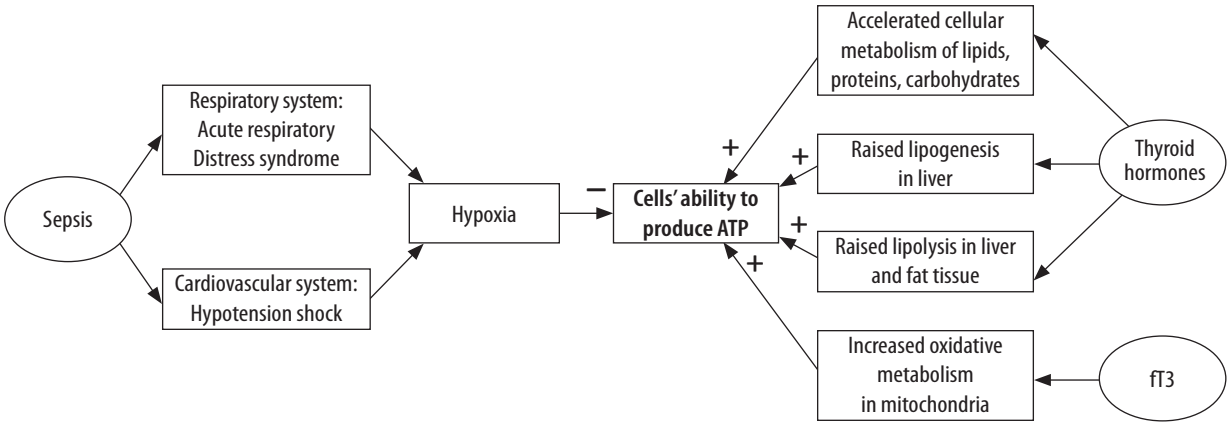

FIGURE 1. Opposite influence of sepsis and thyroid hormones on intracellular ATP production (based on [7])

METHODS

The study was initiated in 2015, when sepsis was being diagnosed according to the 2nd Sepsis Consensus, based on systemic inflammatory response syndrome (SIRS) criteria, determined by a coincidence of two out of the four factors mentioned below:

- heart rate > 90 beats min^{-1},
- body temperature > 38°C or < 36°C,
- WBC count > 12 G L^{-1} or < 4 G L^{-1},
- respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mm Hg [8].

This prospective study includes patients admitted to the Intensive Care Unit of Allergy and Immunology Department at the University Hospital in Krakow, Poland between 2015 and 2017. The inclusion criteria were: age ≥ 18 years and sepsis diagnosed according to the 2nd International Definition [8]. The exclusion criteria included: pregnancy, history of thyroid disease, and lack of patient's consent. Acute Physiology and Chronic Health Evaluation III (APACHE III), Acute Physiology and Chronic Health Evaluation IV (APACHE IV), Sepsis-related Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS), and Multiple Organ Dysfunction Score (MODS) scales were calculated for each patient. Clinical data were collected during hospitalisation.

Blood samples for TSH, fT3, and fT4 level measurements were obtained from septic patients immediately after establishing the diagnosis. The measurements were performed using an ECLIA electro-chemiluminescence immunoassay analyser (Cobas 6000, Roche, Switzerland).

The primary endpoint was 30-day mortality rate. The secondary endpoint was ICU mortality. The design of the study is presented in Figure 2.

The results were interpreted statistically using *U* Mann-Whitney test, Student's *t*-test, and ROC curve analysis by means of Statistica 12 software (Statsoft, version 12.5.192.0, Tulsa, USA). Continuous variables were compared using *U* Mann Whitney test or Student's *t*-test as appropriate and presented as median (interquartile range) and mean (standard deviation), respectively. Discrete variables were presented as *n* (%). *P* values < 0.05 were considered statistically significant.

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the

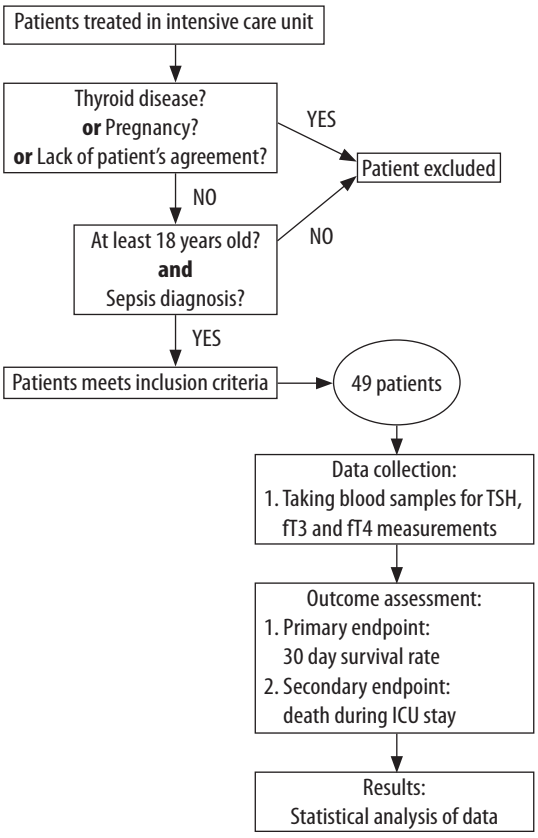

FIGURE 2. Study flowchart including detailed inclusion and exclusion criteria

Bioethics Committee of the Jagiellonian University (approval number: 122.6120.231.2015).

RESULTS

We enrolled 49 patients with a mean age of 59.4 (± 14.1) years, diagnosed with sepsis, 31 (63.3%) of whom were males. The 30-day and ICU mortality in the study group amounted to 40.8% (20/49) and 42.9% (21/49), respectively. In our study group sepsis was caused by bacterial (38.8%, 19/49) and viral/fungal (24.5%, 12/49) infection or the pathogen remained unknown (36.7%, 18/49). The most common sites of infection were the following: respiratory tract (65.3%, 32/49), blood (8.2%, 4/49), urinary tract (4.1%, 2/49), and leg ulcer (2%, 1/49). In seven cases (14.3%) multiple sites of infection were observed. The origin of infection remained unknown in three patients. Median predicted mortality rate in the study population based on APACHE IV score on the first day of hospitalisation amounted to 79.1%. Detailed demographic, clinical data as well as APACHE scores are shown in Table 1.

Patients who died had significantly lower fT3 and fT4 levels in comparison with survivors. This was not observed in the case of TSH (Table 2, Figure 3). All patients who died during the hospitalisation had fT3 values below the lower reference range, and we did not observe such a relationship regarding fT4 and TSH. Figure 3 shows the differences in fT3, fT4, and TSH depending on survival status in two endpoints.

ROC curves for fT3 and fT4 as predictors of survival revealed that AUC values were moderately high and slightly better for the secondary endpoint – death anytime during ICU stay (fT3 [AUC = 0.7; $P = 0.009$]; fT4 [AUC = 0.7; $P = 0.014$]) than for the primary endpoint – 30-day survival rate (fT3 [AUC = 0.66; $P = 0.04$]; fT4 [AUC = 0.68; $P = 0.028$]). Figure 4 and 5 present ROC curves for the primary and the secondary endpoint, respectively.

TABLE 1. Comparison of demography data, comorbidities and APACHE scores between survivors and non-survivors (during the whole ICU stay)

Factor	All , $n = 49$	ICU stay		
		Survivors, $n = 28$	Non-survivors, $n = 21$	P
Demography				
Age (years)	59.4 ± 14.1	55.3 ± 14.8	64.9 ± 10.9	0.017
Male	31 (63)	17 (55)	14 (45)	
Female	18 (37)	11 (61)	7 (39)	
Length of the ICU stay (days)	13.5 (9–20)	14 (10–23)	13 (5–20)	0.216
Comorbidities				
Arterial hypertension	16 (33)	12 (43)	4 (19)	
Diabetes mellitus	11 (22)	4 (14)	7 (33)	
Heart failure	6 (12)	4 (14)	2 (10)	
Atrial fibrillation	5 (10)	3 (11)	2 (10)	
Hematological diseases	5 (10)	3 (11)	2 (10)	
Oncological diseases	4 (8)	3 (11)	1 (5)	
APACHE IV				
Value	114.5 (105.3–125.3)	108 (89–113)	125 (117–149)	0.0003
Predicted mortality rate	79.1% (65.3–87.4)	72.7% (58.1–79.4)	84.2% (79.7–93.1)	0.0008

Values are presented as n (%) or median (IQR) or mean (SD).

TABLE 2. Thyroid hormone levels by mortality rate

Hormone	Range	All , $n = 49$	30th day			ICU stay		
			Survivors $n = 29$	Non-survivors $n = 20$	P	Survivors $n = 28$	Non-survivors $n = 21$	P
fT3 (pmol L^{-1})	3.1–6.8	1.7 (1.4–2.1)	1.8 (1.5–2.4)	1.6 (1.3–1.9)	0.059	1.8 (1.6–2.4)	1.6 (1.3–1.9)	0.021
fT4 (pmol L^{-1})	12.0–22.0	11.8 (9.2–15.1)	12.7 (10.6–16.1)	9.8 (8.2–13.6)	0.033	12.7 (10.8–16.1)	9.8 (8.4–13.6)	0.019
TSH (μIU mL^{-1})	0.3–4.2	0.5 (0.3–1.7)	0.5 (0.3–1.7)	0.4 (0.2–1.7)	0.970	0.5 (0.3–1.5)	0.5 (0.3–2.1)	0.600

Values are presented as median (IQR).

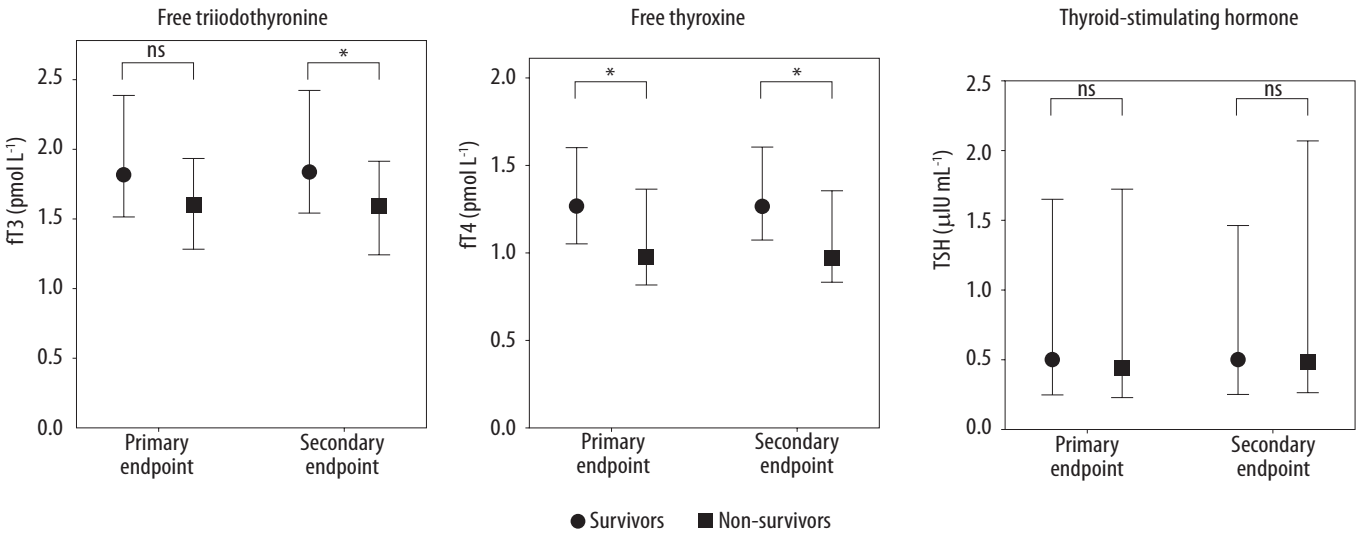

FIGURE 3. The differences in fT3, fT4, and TSH depending on survival status in two endpoints

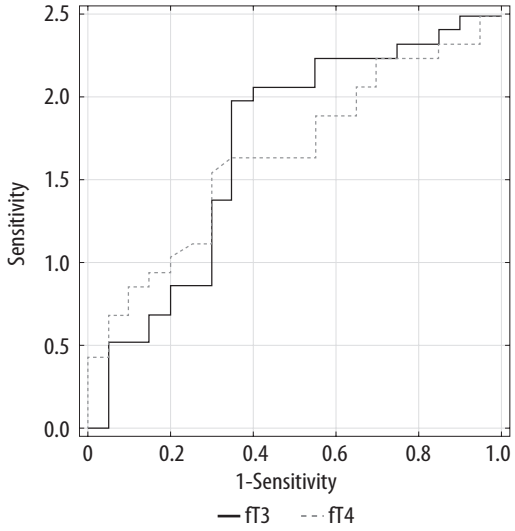

FIGURE 4. ROC curves for fT3 and fT4. 30-day survival rate. Suggested cut-off points: 1.4 and 10.5 for fT3 and fT4, respectively

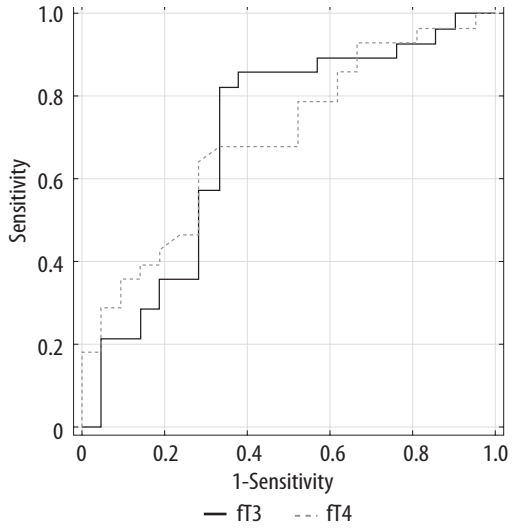

FIGURE 5. ROC curves for fT3 and fT4. ICU survival rate. Suggested cut-off points: 1.8 and 10.5 for fT3 and fT4, respectively

DISCUSSION

In this prospective study we sought potential differences in the thyroid hormone levels measured immediately after establishing the diagnosis of sepsis between survivors and non-survivors. The results showed that patients who died within 30 days of observation had lower levels of fT4. Analysis of the secondary endpoint – death anytime during ICU stay – indicated lower levels of both fT3 and fT4 among non-survivors. We did not find any significant differences in TSH levels between the groups.

Despite significant progress in sepsis diagnosis and management, there is still an upward trend in sepsis-associated mortality observed worldwide [9–11]. Due to the recent change in sepsis definition, current epidemiological data remains scarce. In the UK between the years 2011 and 2015 sepsis and septic shock led to death in 30–33% and 56–57% cases, respectively [12]. The mortality rate we observed in the current study was similar and equalled 43%. Its reduction is one of the most important goals of contemporary intensive care research. Prognostic factors reliably predicting sepsis outcome and improvement of the performance of commonly used clinical severity scores are needed.

Several publications bring up the topic of the role of thyroid hormones in the management of sepsis and their impact on the outcomes. In the retrospective review of 231 patients with surgical sepsis Todd *et al.* [13] showed results similar to those presented in the current study, i.e. decreased baseline T3 and fT4 levels were associated with mortality. There are also other reports that, similarly to ours, documented a correlation between hypothyroxinaemia and mortality in sepsis and/or ICU mortality [14–16].

Moreover, a study by Meyer *et al.* [17] suggested a relationship between T3 and fT4 serum level and mortality rate on the last day of hospitalisation; however, thyroid hormone levels measured on admission did not differ between survivors and non-survivors.

Interestingly, there are also several studies showing an opposite tendency. In the research by Ray *et al.* [18] TSH, T3, and fT4 levels were measured in 180 critically ill patients after three hours of ICU admission. It did not show any statistically significant differences in T3 and fT4 levels between patients who had died and those who had survived. Nevertheless, numerous factors may explain the contrasting results; for instance, the differences in timing of blood sample gathering, the fraction of thyroid hormones measured (free vs. total), and medical diagnosis. Furthermore, the research was performed more than 20 years ago, and there was a significant disproportion in the number of patients between the study groups.

Available literature suggests that not only thyroid hormone baseline levels, but also dynamics of their change throughout various stages of the disease are related to mortality rate. The explanation of the phenomena requires further prospective studies, performed on larger population with serial thyroid hormone measurements [18]. This will allow the precise evaluation of prognostic values of thyroid hormones in sepsis, and could also shed some light on the potential therapeutic value of thyroid hormone supplementation.

The current study has several limitations. The study group is rather small and consists of a specific population of patients with non-surgical sepsis. Due to the low number of events we were not able to perform adjusted analysis for the prognostic value of thyroid hormones in our cohort, and the group of survivors and non-survivors differed significantly in terms of age and APACHE IV severity. Moreover, we obtained only one blood sample from each patient at the very beginning of the disease course, and therefore we were unable to observe changing trends in thyroid hormone levels during the treatment. Finally, we included patients diagnosed with sepsis according to the 2nd definition whereas the 3rd is currently the binding one.

CONCLUSIONS

Current study shows that septic patients who do not survive tend to have lower thyroid hormones levels. Our results suggest that thyroid hormones can potentially be taken into consideration as new prognostic factors in sepsis. In the future their replacement may play some role in sepsis management. However, it would require further prospective or randomised controlled studies to understand the subject better.

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3. Conflict of interest: none.
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