REVIEW

Association between thyroid function tests at baseline and the outcome of patients with sepsis or septic shock: a systematic review

Anna G Angelousi¹, Drosos E Karageorgopoulos¹, Anastasios M Kapaskelis^{1,2} and Matthew E Falagas^{1,2,3}

¹Alfa Institute of Biomedical Sciences (AIBS), 9 Neapoleos Street, 151 23 Marousi, Athens, Greece, ²Department of Medicine, Henry Dunant Hospital, 11526 Athens, Greece and ³Department of Medicine, Tufts University School of Medicine, Boston 02153, Massachusetts, USA

(Correspondence should be addressed to M E Falagas at Alfa Institute of Biomedical Sciences (AIBS); Email: m.falagas@aibs.gr)

Abstract

Introduction: The severity of critical illness is associated with various patterns of thyroid hormone abnormalities. We sought to evaluate whether the outcome of patients with, specifically, sepsis or septic shock is associated with the thyroid function tests evaluated at diagnosis or admission in the intensive care unit (ICU).

Methods: We performed a systematic review of relevant studies by searching PubMed.

Results: We included nine studies that all had a prospective cohort design. Seven involved children or neonates, and two involved adults. Mortality was the outcome evaluated in eight studies, while the length of ICU stay was evaluated in the remaining study. In univariate analysis, six of the nine included studies showed that either, free or total, triiodothyronine or thyroxine was lower in the group of patients with sepsis or septic shock who had unfavorable outcome than in those who had favorable outcome. Two other studies showed higher TSH values in the group of patients with unfavorable outcome. No significant relevant findings were observed in the remaining study. Regarding the correlation of sepsis prognostic scoring systems with thyroid function tests, the three studies that provided specific relevant data showed variable findings.

Discussion: Most of the relevant studies identified favor the concept that decreased thyroid function at baseline might be associated with a worse outcome of patients with sepsis or septic shock. Although these findings are not consistent, the role of thyroid function in affecting or merely predicting the outcome of sepsis or septic shock merits further investigation.

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Introduction

Thyroid hormones play an important role in the adaptation of metabolic function to stress and critical illness (1). In hospitalized patients, thyroid hormone alterations are very common, particularly in those of increased age or in those with critical illness (2, 3). Low triiodothyronine (T₃) is commonly observed in the latter group of patients, which can be attributed to increased deiodination of thyroxine (T₄) to reverse T₃ (rT₃), rather than T₃, and increased catabolism of T₃ to 3,3-diiodothyronine (T₂) (4–6). With increasing severity of illness, low total and free T₄, and sometimes low TSH, can be observed (6). Decrease in plasma T₄-binding globulin (TBG) or transthyretin as well as accumulation of substances that lower the plasma thyroid hormone-binding capacity appear also to be important for the above-mentioned alterations in thyroid hormone levels during critical illness (4).

For the vast majority of patients, thyroid function abnormalities observed during critical illness are

transient and do not represent an underlying thyroid disease (7). Still, certain data suggest that the magnitude of thyroid hormone alterations in patients admitted to the intensive care unit (ICU) due to various causes is associated adversely with the patient outcome (8–11). In this review, we sought to evaluate systematically the association between baseline thyroid function and the outcome of patients with, specifically, sepsis or septic shock.

Methods

Data sources

To identify studies eligible for inclusion in this review, we searched PubMed, on February 1, 2009, applying the following combined search term: (thyroid disease OR thyroid OR hypothyroidism OR hyperthyroidism OR TSH OR T₄ OR T₃ OR thyroid hormones) AND (infection OR sepsis OR bacteremia OR pneumonia OR nosocomial

infection OR septic shock). The bibliographies of relevant articles were also hand searched. We performed an updated PubMed search on October 1, 2010.

Study selection criteria

We selected for inclusion in our review, case-control or cohort studies (either prospective or retrospective) or clinical trials that provided data on the association between thyroid hormones at baseline and the outcome of patients of any age with sepsis or septic shock. We considered baseline thyroid function tests as those referring to the time of diagnosis of sepsis or the time of admission in the ICU. We specifically evaluated English, French, German, Italian, and Spanish language articles.

Data extraction

Data extracted from each of the included studies were those referring to the study design, the characteristics of the study population and the subgroups of patients compared, the baseline values of thyroid hormones, and their statistical association with the patient outcome through univariate or multivariate analysis, where reported. We also extracted data on the correlation of the thyroid hormones at baseline with sepsis prognostic scores.

Results

Characteristics of the included studies

From the literature searches that we performed in PubMed, we retrieved a total of 3633 articles. After first screening, based on the title and the abstract, we selected 202 articles for further detailed evaluation, after which, we identified nine studies as eligible for inclusion in this review (12–19). The process of selecting articles for inclusion in this review is depicted graphically in Fig. 1.

All of the nine included studies had a prospective cohort design. Five of the studies involved children (1, 13–15, 17), two additional studies involved exclusively neonates (12, 16), and the remaining two studies involved adults (18, 19). Mortality was the outcome evaluated in eight of the studies (1, 12–19), while in the remaining study, the outcome evaluated was the length of stay in the pediatric ICU (PICU) (13). In six of the included studies, it was specifically reported that the blood samples for thyroid hormone measurements were taken before administration of dopamine (1, 12–16, 19).

Association of thyroid hormones at baseline with outcome

In Table 1, we present data on the association between serum thyroid hormone levels at baseline and the outcome of patients with sepsis or septic shock.

Figure 1 Flow diagram of the detailed process of the selection of articles for inclusion in our review.

Specifically, six of the nine studies included in this review showed, by univariate analysis, that among patients with sepsis or septic shock those with an unfavorable outcome had lower baseline serum levels of, either total or free, T_3 or T_4 , than those with a favorable outcome (12–16, 19). In two other studies that involved children and adults, who in both studies were admitted in the ICU due to septic shock, there was no difference in baseline T_3 or T_4 between non-survivors and survivors

Table 1 Association between baseline thyroid hormones and outcome of patients with sepsis or septic shock in different studies.

Study	Study design	Characteristics of whole study population	Comparison of patient groups (unfavorable versus favorable outcome), n	Age in years, median (range) or mean $\pm$ s.d.	Sex (males/total)	Values of thyroid hormones in the compared groups			Comparison in univariate analysis		Comparison in multivariate analysis		
						Thyroid hormone levels, units	Unfavorable outcome	Favorable outcome	Significance	Significance	Variables entered in the model	Significance	Independent predictor variables
(12)	Prospective case-control study	Cases: 143 newborns admitted in PICU with sepsis due to <i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Klebsiella oxytoca</i>	Sepsis non-survivors versus sepsis survivors, 20 vs 123	All were term- or preterm neonates	72/143	T ₃ , ng/dl (mean $\pm$ s.d.)	112.8 $\pm$ 51.0	172.2 $\pm$ 61.5	P < 0.001	P < 0.001 ^a	NA	P < 0.001	Euthyroid sick syndrome
		Controls: 149 healthy newborns				T ₄ , ng/dl (mean $\pm$ s.d.)	5.9 $\pm$ 1.5	7.1 $\pm$ 2.3	P < 0.01				
		Controls: 149 healthy newborns				TSH, mIU/l (mean $\pm$ s.d.)	2.2 $\pm$ 1.4	4.1 $\pm$ 2.1	P < 0.01				
(1)	Prospective cohort study	Twenty-four children admitted in PICU with septic shock due to pulmonary, CNS, or GI infections due to bacteremia by <i>Escherichia coli</i> or <i>Streptococcus pneumoniae</i> or <i>Staphylococcus aureus</i>	Non-survivors versus survivors, 12 vs 12		13/24	T ₃ , ng/dl (median (95% CI))	40 (40.00–40.23) ^b		NS	NA	NA	NS	NA
						T ₄ , μ g/dl (median (95% CI))	4.45 (1.9–6.0) ^b		NS				
						fT ₃ , pg/ml (median (95% CI))	1.85 (0.57–0.95) ^b		NS				
(13)	Prospective cohort study	Forty-four children in PICU who survived from meningococcal septic shock (31 had meningococemia)	Patients with long versus short PICU stay ^c , 11 vs 33	2.5 (0.1–15.7) vs 5 (0.3–16.1)	6/11 vs 21/33	fT ₄ , pmol/l (geometric mean $\pm$ s.e.m.)	1.21 (0.27–2.96)	0.26 (0.22–0.88)	P = 0.04				
						T ₃ , nmol/l (geometric mean $\pm$ s.e.m.)	0.24 (0.20–0.28) ^d	0.38 (0.36–0.40) ^d	P = 0.022 (r = –0.35) ^e	NS	Dopamine administration, IL6, T ₄	P < 0.05	IL6, T ₄
						T ₄ , nmol/l (geometric mean $\pm$ s.e.m.)	Low in 50%, normal in 50%	High in 50%, normal in 50%	NS	NS	on admission, IL6 on admission, age, gender, time to first petechia	P < 0.05	
						rT ₃ , nmol/l (geometric mean $\pm$ s.e.m.)	High		NS				
						T ₃ /rT ₃ (geometric mean $\pm$ s.e.m.)	Low		NS				
						TSH, mIU/l (geometric mean $\pm$ s.e.m.)	Normal		NS	NS			

Table 1 Continued

Values of thyroid hormones in the compared groups										Comparison in univariate analysis		Comparison in multivariate analysis		
Study	Study design	Characteristics of whole study population	Comparison of patient groups (unfavorable versus favorable outcome), n	Age in years, median (range) or mean $\pm$ s.d.	Sex (males/total)	Thyroid hormone levels, units	Unfavorable outcome	Favorable outcome	Significance	Significance	Variables entered in the model	Independent predictor variables		
(14)	Prospective cohort study	Forty-five children admitted in PICU with meningococcal sepsis or septic shock	Non-survivors versus septic shock survivors and sepsis survivors, 8 vs 30 and 7	1.1 (0.5–9.4) vs 4.3 (0.1–16.1) and 6.1 (2.3–12.2) ($P<0.05$)	7/8 vs 19/30 vs 4/7	T ₃ , nmol/l (median (IQR))	0.49 (0.34–0.61)	0.40 (0.30–0.52) and 0.45 (0.42–0.61)	NS and NS	NS	T ₄ , fT ₄ , T ₃ , fT ₃ , T ₃ /fT ₃ , TSH, TBG, age, gender, cotin, sol, NEFA/albu, min ratio, time to first petechia, IL6	IL6		
						T ₄ , nmol/l (median (IQR))	38 (25–46)	56 (49–73) and 86 (68–92)	$P<0.05$ and $P<0.05$	NS	H, TBG,			
						fT ₄ , pmol/l (median (IQR))	15 (13–21)	18 (15–20) and 19 (14–20)	NS and NS	NS	age, gender, cotin, sol,			
						rT ₃ , nmol/l (median (IQR))	0.75 (0.55–1.21)	1.40 (1.11–1.73) and 1.17 (1.00–1.28)	$P<0.05$ and $P<0.05$	NS	NEFA/albu, min ratio,			
						T ₃ /fT ₃ (median (IQR))	0.71 (0.33–0.80)	0.30 (0.20–0.44) and 0.41 (0.36–0.58)	$P<0.05$ and $P<0.05$	NS	time to first petechia,			
						TSH, mIU/l (median (IQR))	0.88 (0.52–1.14)	0.84 (0.59–1.18) and 0.80 (0.65–1.61)	NS	NS	IL6			
						TBG, mg/l (median (IQR))	9 (6–10)	12 (10–15), and 18 (14–19)	$P<0.05$ and $P<0.05$	NS				
(15)	Prospective cohort study	Seventy-two children admitted in the PICU with sepsis or septic shock due to bacteremia by <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i> , <i>Staphylococcus aureus</i> , or <i>Escherichia coli</i>	Non-survivors versus survivors, 26 vs 46	Sepsis cases: 2.5 $\pm$ 2.3, septic shock cases: 3.0 $\pm$ 2.3	35/72	T ₃ , nmol/l (mean $\pm$ s.d.)	0.58 $\pm$ 0.16	1.00 $\pm$ 0.16	$P<0.001$	NA	NA	NA		
						T ₄ , nmol/l (mean $\pm$ s.d.)	64.5 $\pm$ 15.8	105.78 $\pm$ 19.35	$P<0.001$	NA				
						fT ₃ , pmol/l (mean $\pm$ s.d.)	0.016 $\pm$ 0.004	0.030 $\pm$ 0.005	$P<0.001$	NA				
						fT ₄ , pmol/l (mean $\pm$ s.d.)	12.77 $\pm$ 3.22	20.64 $\pm$ 3.48	$P<0.001$	NA				
						TSH, mIU/l (mean $\pm$ s.d.)	4.2 $\pm$ 2.2	4.9 $\pm$ 2.1	NS	NA				
						T ₃ , ng/dl (mean $\pm$ s.d.)	57.7 $\pm$ 21.1	116.5 $\pm$ 50.6	$P<0.001$	NA	NA	NA		
						T ₄ , μ g/dl (mean $\pm$ s.d.)	4.6 $\pm$ 3.1	7.3 $\pm$ 4.0	$P<0.01$	NA				
(16)	Prospective cohort study	Forty-nine neonates with sepsis (documented bacteremia in 11 and meningitis in 8)	Non-survivors versus survivors, 16 vs 33	0.73 $\pm$ 0.03	ND	TSH, μ U/ml (mean $\pm$ s.d.)	9.0 $\pm$ 13.4	9.6 $\pm$ 10.5	NS	NA				
						T ₃ , nmol/l (median (IQR))	0.53 (0.43–0.76)	0.38 (0.26–0.42)	$P<0.05$	NA	NA	NA		
						T ₄ , nmol/l (median (IQR))	38 (25–46)	44 (39–56)	NS	NA				
						fT ₄ , pmol/l (median (IQR))	14 (13–21)	16 (15–19)	NS	NA				
						rT ₃ , nmol/l (median (IQR))	0.75 (0.55–0.97)	1.44 (0.99–1.85)	$P<0.01$	NA				
						T ₃ /fT ₃ (median (IQR))	0.76 (0.64–0.85)	0.43 (0.17–0.35)	$P<0.01$	NA				
						TSH, mIU/l (median (IQR))	0.97 (0.52–1.56)	0.29 (0.15–0.54)	$P<0.01$	NA				
(17)	Prospective cohort study	Twenty-six children admitted in PICU with sepsis due to bacteremia by <i>Neisseria meningitidis</i>	Non-survivors versus survivors, 8 vs 18	0.83 vs 2.4 ($P<0.05$)	16/26	T ₃ , ng/ml (mean $\pm$ s.d.)	0.038 $\pm$ 0.19	0.038 $\pm$ 0.16	NS	NA	NA	NA		
						T ₄ , ng/ml (mean $\pm$ s.d.)	46.1 $\pm$ 19.7	44.6 $\pm$ 9.7	NS	NA				
						TSH, μ U/ml (mean $\pm$ s.d.)	0.44 $\pm$ 0.61	0.79 $\pm$ 0.68	$P=0.18$ (NS)	NA				
						T ₃ , nmol/l (mean $\pm$ s.d.)								
						T ₄ , nmol/l (mean $\pm$ s.d.)								
						TSH, mIU/l (mean $\pm$ s.d.)								
						T ₃ , ng/dl (mean $\pm$ s.d.)								
(18)	Prospective cohort study	Twenty-seven adults admitted in the ICU with septic shock due to pneumonia, peritonitis, urinary tract infection, or bacteremia	Non-survivors versus survivors, 12 vs 15	50 $\pm$ 19	18/27	T ₃ , ng/ml (mean $\pm$ s.d.)	0.038 $\pm$ 0.19	0.038 $\pm$ 0.16	NS	NA	NA	NA		
						T ₄ , ng/ml (mean $\pm$ s.d.)	46.1 $\pm$ 19.7	44.6 $\pm$ 9.7	NS	NA				
						TSH, μ U/ml (mean $\pm$ s.d.)	0.44 $\pm$ 0.61	0.79 $\pm$ 0.68	$P=0.18$ (NS)	NA				
						T ₃ , nmol/l (mean $\pm$ s.d.)								
						T ₄ , nmol/l (mean $\pm$ s.d.)								
						TSH, mIU/l (mean $\pm$ s.d.)								
						T ₃ , ng/dl (mean $\pm$ s.d.)								

Table 1 Continued

Study	Study design	Characteristics of whole study population	Comparison of patient groups (unfavorable versus favorable outcome), n	Age in years, median (range) or mean $\pm$ s.d.	Sex (males/total)	Values of thyroid hormones in the compared groups			Comparison in univariate analysis		Comparison in multivariate analysis		
(19)	Prospective cohort study	Thirty-seven adults with sepsis	Non-survivors versus survivors, 15 vs 22	57.6 $\pm$ 17.8	37/37	T ₃ , ng/dl (mean $\pm$ s.d.)	30.40 $\pm$ 13.40	52.5 $\pm$ 19.60	P < 0.001	NA	NA	NA	NA
						T ₄ , μ g/dl (mean $\pm$ s.d.)	5.50 $\pm$ 1.70	7.20 $\pm$ 2.80	P < 0.05	NA	NA	NA	NA
						fT ₄ l, (mean $\pm$ s.d.)	3.47 $\pm$ 0.89	4.53 $\pm$ 1.79	P < 0.05	NA	NA	NA	NA
						rT ₃ , ng/dl (mean $\pm$ s.d.)	41.20 $\pm$ 18.20	40.80 $\pm$ 12.90	NS	NA	NA	NA	NA
						TSH, μ U/ml (mean $\pm$ s.d.)	1.85 $\pm$ 0.81	1.86 $\pm$ 0.68	NS	NA	NA	NA	NA

(P)ICU, (pediatric) intensive care unit; GI, gastrointestinal tract; f(t/r) T₃, (free/reverse) triiodothyronine; fT₄l, free thyroxine (index); TBG, thyroxine-binding globulin; IQR, interquartile range; CI, confidence interval; NS, non-significant; NA, non-available; NEFA, non-esterified fatty acid level in the albumin fraction of blood serum.

^aBy multivariate analysis euthyroid sick syndrome was related by augmented mortality' ($P < 0.001$).

^bValues for the whole study population.

^cShort PICU stay cases was defined as < 7 days and long stay as more than 7 days.

^dCI extracted from graphs.

^er, Spearman's correlation coefficient.

(1, 18). In the remaining study, which evaluated children with meningococcal sepsis admitted to the PICU, those who did not survive had higher baseline serum levels of T₃ than those who survived, while no difference was detected in the total and free T₄ levels (17). In this study, non-survivors also had higher baseline levels of TSH.

Higher baseline TSH values in non-survivors were also observed in another study that evaluated children with septic shock admitted to the PICU. This study did not demonstrate differences in the levels of T₃ or T₄ between non-survivors and survivors (1). On the contrary, lower baseline TSH was associated with higher mortality in a study that evaluated septic neonates admitted in the ICU (12); this was also accompanied with lower T₃ and T₄. The baseline TSH levels in the remaining six studies did not differ between patients with an unfavorable outcome compared with those with a favorable outcome. In addition, a lower rT₃ value and a higher T₃/rT₃ ratio were associated with an adverse outcome in two studies (14, 17), whereas non-significant findings were observed in the other two studies that assessed the same parameters (13, 19).

Three of the included studies further evaluated the above-described associations in multivariate analysis. One of these studies showed that in pediatric patients who survived meningococcal septic shock, lower baseline serum T₄ was an independent predictor of an unfavorable outcome, specifically prolonged ICU stay (13). The baseline interleukin 6 (IL6) level was also independently associated with this outcome. The length of ICU stay was estimated to increase by 15% for every doubling of the IL6 concentration and 16% for every 10 nmol/l decrease in the T₄ level (13). The second study that included pediatric ICU patients with meningococcal sepsis or septic shock showed that the effect of the thyroid function tests on mortality lost significance in the multivariate analysis, and that IL6 was the only independent predictor of this outcome (14). In the remaining study, which was performed on newborns admitted to the ICU with bacterial sepsis, the presence of euthyroid sick syndrome was independently associated with mortality (12).

In Table 2, we present data on the correlation of thyroid function tests at baseline with various sepsis prognostic scores. Such associations were reported in three of the nine included studies, which all evaluated children with meningococcal sepsis or septic shock admitted to the PICU (13, 14, 17). In one of these studies, both the pediatric risk of mortality (PRISM) score and the sequential organ failure assessment score had a moderate negative correlation with the baseline T₄ value (14). In another study, the PRISM score had a rather weak positive correlation with baseline TSH (17). In the remaining study, no significant relevant associations were observed (13).

Table 2 Correlation between baseline thyroid hormones and sepsis prognostic scores in patients with sepsis or septic shock included in different studies.

Study	Baseline sepsis prognostic score, median (range) or mean $\pm$ s.d. (patients with unfavorable versus favorable outcome)	Correlation of thyroid hormones with sepsis prognostic score					
		T ₃	T ₄	fT ₃	fT ₄	TSH	TBG
(13)	PRISM: 24 (12–46) vs 20 (9–35)	NS	NS	NS	NS	NS	NS
(14)	PRISM: 32 (23–43) vs 21 (8–35) and 9 (5–13)) SOFA: 15 (13–19) vs 9 (3–17) and 2 (0–6))	NS	$r = -0.62$ ($P < 0.05$) $r = -0.69$ ($P < 0.05$)	NS	NS	NS	$r = -0.54$ ($P < 0.05$) $r = -0.57$ ($P < 0.05$)
(17)	PRISM: 31 (29–34) vs 17 (14–17)	$r = 0.29$ (NS)	$r = -0.34$ (NS)	ND	$r = -0.41$ (NS)	$r = 0.42$ ($P < 0.05$)	ND

fT₃, free triiodothyronine; fT₄, free thyroxine; TBG, thyroxine-binding globulin; PRISM, pediatric risk of mortality score; SOFA, sequential organ failure assessment score; APACHE, acute physiologic and chronic health evaluation score; NS, non-significant; ND, no data were reported; r , Spearman's correlation-coefficient.

Discussion

The majority (six out of nine) of the evaluated relevant studies showed that lower baseline thyroid hormone values, either T₃ or T₄, are associated with worse outcome for patients with sepsis or septic shock. The above observations apply mainly to children rather than to adults, as the latter group was evaluated in only two of the included studies. Still, definite conclusions on the above issue cannot be drawn on the basis of the data available herein, as the associations observed were not always consistent between the included studies, or within each study with regard to different thyroid function tests evaluated. Moreover, the association of thyroid hormones at baseline and the outcome of patients with sepsis or septic shock was not commonly evaluated in appropriate multivariate models to adjust for the effect of potential confounders.

It is interesting that one of the included studies showed that, among the 26 children with meningococcal sepsis studied, the 18 who survived had lower T₃ levels at PICU admission than the 8 who did not survive (17). This finding stands in contrast to the rest of the included studies, which either showed the opposite or no relevant association. One potential explanation for the discordant findings of the study in this regard is that ten of the survivors received treatment with dopamine, whereas the non-survivors received norepinephrine or dobutamine. Dopamine can suppress the pituitary release of TSH and thus potentially the production of T₃ (20), while norepinephrine is believed to stimulate the secretion of TSH (21). Notably, the non-survivors in this study also had higher TSH levels (17). Yet, it was not specifically stated whether dopamine administration preceded the collection of blood samples for the thyroid hormone measurements. However, in the great majority of the remaining studies, thyroid hormone measurements were performed prior to dopamine use (1, 12–15, 19).

In addition, in the study, in which higher T₃ levels were observed in non-survivors of meningococcal septic shock, the age of the non-survivors was significantly lower than that of the survivors (10 vs 29 months respectively) (17). The changes that occur in thyroid hormone levels during the first month of life could, at least in part, account for the differences in the T₃ levels observed in this study. Specifically in neonates, the plasma thyroid hormone levels are typically elevated compared with those in older children (22). This is related to the TSH surge that occurs in the immediate postnatal period and to the elevated TBG levels secondary to maternal estrogen (22). In normal term neonates, the total and free T₄ levels fall gradually over the next 4–6 weeks but remain higher than in older children and adults for a few months. The T₃ levels gradually reach those of infancy, between 2 and 12 weeks of life (22, 23). In early neonatal life, there has also been observed an increased activity of type III deiodinase (D3) enzyme with secondary increase in rT₃ levels and increase in the degradation of T₃ to T₂, which reaches the adult range during the fourth postnatal month (22, 23).

It is questionable whether the findings of our review can be applicable to adult patients with sepsis or septic shock, who were evaluated in only two of the included studies. Relevant data suggest that children have different hemodynamic responses to critical illness and septic shock. Children more commonly suffer from progressive cardiac failure than adults and can respond to inotropic therapy (24). Mortality in pediatric septic shock is usually lower than in adults (24).

It is generally accepted that the alterations in thyroid hormones observed during critical illness constitute part of an adaptive metabolic response. This is based on the finding that the great majority of patients recover normal thyroid function after the critical illness subsides (25). It has also been suggested that the decrease in metabolic function observed during the systemic inflammatory response syndrome and the accompanying multiorgan

dysfunction may help protect cell survival (26). Still, thyroid disorders are relatively common in the general population, with an estimated prevalence of 1–10% (27). The presence of even subclinical abnormalities might be important (28), as subclinical hypothyroidism has been linked to excess mortality in certain patient groups (28, 29). Some studies have also found that a subset of patients with critical illness can have true hypothyroidism (11). High TSH or reduced rT_3 can be suggestive of such a diagnosis (11, 30). Thus, the findings of some of the studies included in our review that higher TSH, lower rT_3 , or lower T_3 and T_4 are associated with an unfavorable outcome of patients with sepsis or septic shock could imply that, at least for a minority of these patients, thyroid hypofunction during sepsis or septic shock might influence *per se* the outcome of this condition. This hypothesis merits further evaluation in appropriately designed studies.

Some studies performed in animal models of sepsis or septic shock support the hypothesis that relative thyroid insufficiency is associated with a worse outcome. For example, lower baseline serum T_4 and free T_4 have been associated with decreased likelihood for survival in severely ill dogs (puppies) with parvoviral diarrhea (31). In an experimental sepsis model in rats, those that were previously thyroidectomized showed abolishment of the hyperdynamic response that physiologically accompanies early-stage sepsis. In the thyroidectomized animals (32), it was observed that the administration of T_4 reversed the decrease in survival.

Another experimental study in rats showed that thyroid hormone supplementation during sepsis can increase survival (33). A particular beneficial effect of thyroid hormone administration in rats with experimentally induced sepsis has been documented on lung mechanics and histology, which was mainly attributed to enhanced synthesis of surfactant (34, 35). Still, other studies on experimentally induced sepsis have failed to show a benefit of thyroid hormone replacement (7, 32, 36). In humans, there is little evidence regarding thyroid hormone substitution during critical illness. Of note, some relevant clinical studies have suggested that T_4 supplementation can lead to reduction in the needs for vasoactive drug administration in circulatory shock (37).

Thyroid hormone supplementation during sepsis or septic shock can lead to a reciprocal decrease in TSH. This issue needs particular attention, as there appears to be a rather complex pathophysiological interplay between TSH and the immune system. Specifically, TSH has been shown to affect the function of various types of hematopoietic and immune system cells that express the TSH receptor (38, 39). Such cells mainly include subsets of hematopoietic cells in the bone marrow, as well as peripheral monocytes, dendritic cells, and T-lymphocytes. Furthermore, some of the above cell types can produce biologically active TSH that can have autocrine and paracrine actions, which can influence the early stages of the immune response to an

antigen (38, 39). These actions can include the regulation of the synthesis and release of mediators of inflammation, such as IL6 and tumor necrosis factor- α (TNF- α). Various immune system cells have also been found to express T_3 , a process that is under the influence of TSH (40). It has thus been hypothesized that the immune system cells can affect the systemic thyroid hormone activity.

It is debatable whether the data included in our review regarding the association between thyroid function and sepsis or septic shock can be extrapolated to other types of critical illness. Several inflammatory cytokines, such as IL1 β , IL6, and TNF- α , can suppress, via direct or indirect pathways, the thyroid function at different levels (41, 42). In sepsis, the increase in the production of pro-inflammatory cytokines is more pronounced than that in other types of critical illness (43, 44). In this respect, baseline levels of thyroid hormones, including T_4 , T_3 , and TSH, can be substantially lower in septic patients than in non-septic patients with critical illness of similar severity (45). The degree of endothelial activation and dysfunction can also be greater in sepsis than in other types of critical illness, as reflected by higher levels of E-selectin, intercellular adhesion molecule-1, and von Willebrand factor activity that have been observed in some studies (43, 44, 46).

The findings of our review regarding the association between thyroid hormone abnormalities and the outcome of patients with sepsis or septic shock indicate that these abnormalities could be of prognostic value. In the studies included in our review, the association between established sepsis prognostic systems and baseline thyroid hormones was at the most moderate. Thus, the prognostic value of thyroid hormones may be independent of other prognostic markers. Likewise, other studies performed in critically ill patients have shown that taking into consideration the baseline thyroid function tests can add to the predictive capacity of the APACHE score (11, 47).

In conclusion, the majority of the identified studies that evaluated the baseline thyroid function tests in patients with sepsis or septic shock provide data that favor the existence of an association between lower T_3 or T_4 and worse outcome. Since thyroid hormone abnormalities are very common in septic patients, future studies should aim to more clearly establish the strength of the above-mentioned association or even examine whether a causal relationship between thyroid hypofunction and adverse outcome exists. The role of the thyroid hormone abnormalities as predictors of outcome of septic patients on top of the known risk prognostic scoring systems warrants also further evaluation.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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