Circulating 3-T_1AM and 3,5-T_2 in critically ill patients a cross-sectional observational study

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Background

Critical illness hallmarks
- low circulating T_4 and T_3 concentrations
- elevated rT_3 , normal 3,3`-T_2, low-normal TSH

➢ referred to as non-thyroidal illness (NTI)
- Thyroid hormone (TH) metabolism substantially increased
  - enhanced deiodinase 3 (D3) / suppressed D1 activity
  - unaltered sulfotransferase activity (T_4- and T_3-sulfate elevated)

Hypothesis

During critical illness T_4 is not only metabolized to rT_3. Increased deiodination of T_4 and/or T_3 to 3,5-T_2 and/or 3-T_1AM contributes to high TH turnover.

Methods

- TSH, TT_4, TT_3 (Beckman Coulter, Immunotech, Czech Republic),
- rT_3 (ZenTech, Angleur, Belgium)
- TBG (LifeSpan Bioscience, Seattle, WA),
- ApoB100 (RnDSystems, Minneapolis, MN)
- 3,5-T_2 (Lehmphul I *et al.* 2014 Thyroid),
- 3-T_1AM (Hoefig CS *et al.* 2011 JCEM)

Characteristics of study population

Baseline characteristics and ICU outcome

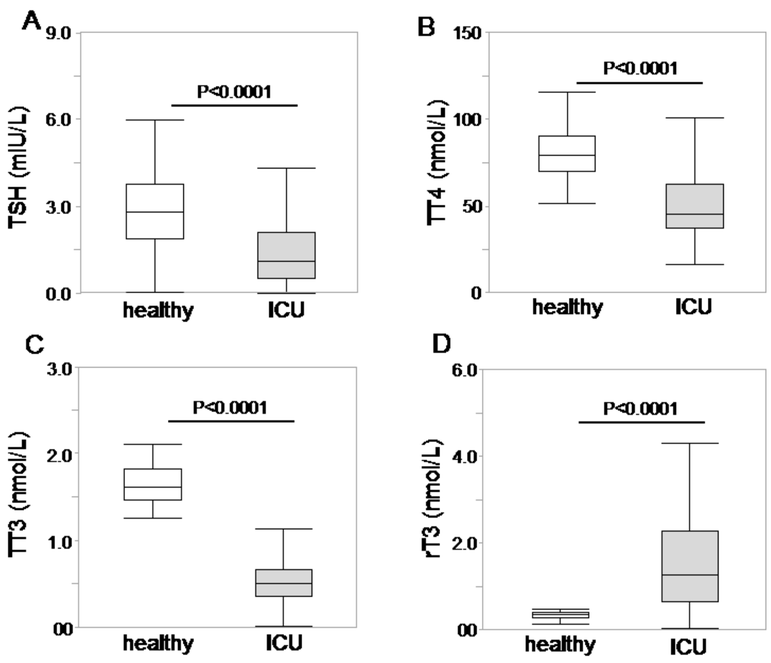
Morning blood samples were collected cross-sectionally from 83 surgical patients under intensive care unit (ICU) on a University Hospital ICU and from 38 demographically matched healthy volunteers.

	Healthy Controls (n=38)	ICU Patients (n=83)
Age, yr. - mean±SE	63.5±1.0	64.7±1.5
Gender, - n. (%) male	20 (53)	54 (65)
BMI, kg/m² - mean±SE	25.5±0.6	26.4±0.5
Days in ICU at day of sample - median [IQR]		3 [1-6]
Diagnostic category at ICU admission, n (%)		
Cardiac surgery	-	44 (53)
Complicated surgery		16 (19)
Transplantation		8 (10)
Trauma, burns or reconstructive surgery		8 (10)
Other		7 (8)
APACHE II score - mean±SE	-	26±1
Diagnosis of sepsis on admission, n (%)	-	25 (30)
Total ICU stay - median [IQR]		10 [4-20]
ICU nonsurvivor, n (%)	-	10 (12)

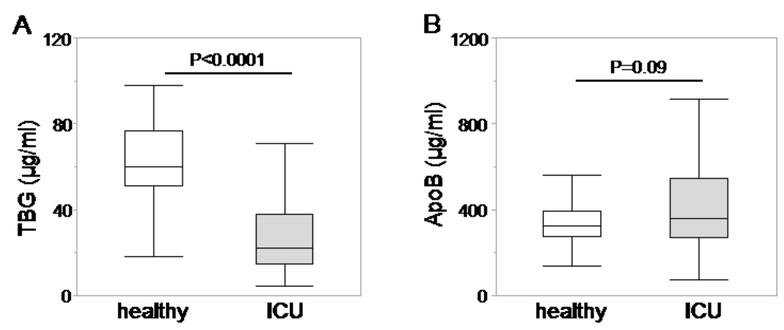
The Acute Physiology and Chronic Health Evaluation II (APACHE II) score reflects severity of illness, with higher values indicating more severe illness, and can range from 0 to 71. **SE** denotes standard error and **IQR** denotes interquartile range.

Results

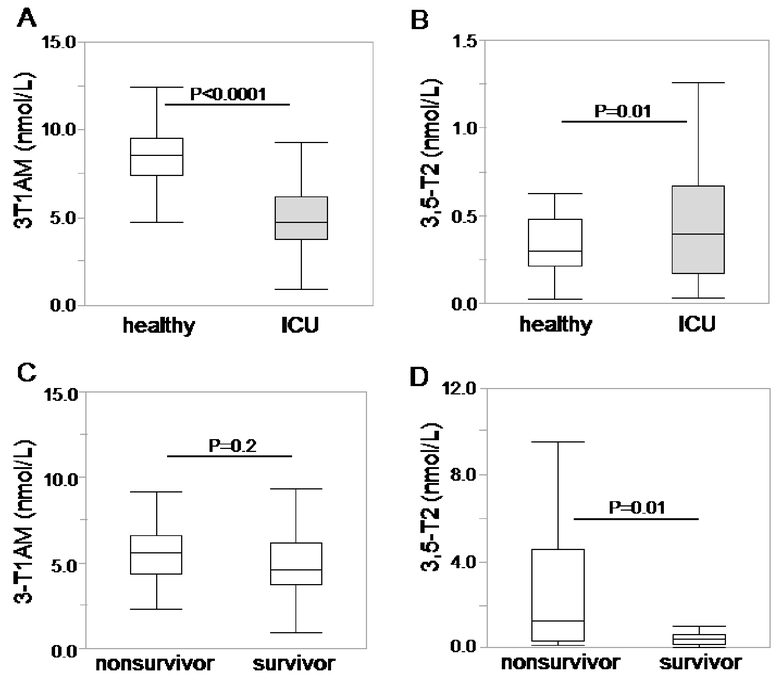
(1) Comparison of serum TH concentrations for healthy control subjects and ICU patients



(2) TH binding proteins



(3) Comparison of serum 3-T_1AM and 3,5-T_2 in healthy control subjects and ICU patients



(1) Serum TSH (A), total T_4 (B), total T_3 (C), rT_3 (D) of healthy (controls) (n=38) and ICU (intensive care unit patients) (n=83). **(2)** Serum TBG (A) and ApoB (B) of healthy controls (n= 38) and ICU patients (n=83). Data are presented as medians ± SE and IQR. **(3)** Serum 3-T_1AM (A) and 3,5-T_2 (B) of healthy (n= 38) and ICU (n=83) individuals. Serum 3-T_1AM (C) and 3,5-T_2 (D) of surviving (n=73) and nonsurviving (n=10) ICU patients.

Multivariable linear regression analysis determining significant and independent associations between serum 3-T_1AM / 3,5-T_2 and potential TH precursors

Univariable analysis	Estimated difference (95% CI) for 3-T_1AM (nmol/L)	R^2	P-value
TT_4 (nmol/L)	0.05 (0.02 – 0.07)	0.129	<0.0001
TT_3 (nmol/L)	2.50 (1.73 – 3.27)	0.262	<0.0001
rT_3 (nmol/L)	-0.45 (-0.73 – -0.17)	0.078	0.002
3,5-T_2 (nmol/L)	-0.39 (-0.69 – -0.09)	0.055	0.01
	Estimated difference (95% CI) for 3,5-T_2 (nmol/L)		
TT_4 (nmol/L)	-0.02 (-0.03 – -0.01)	0.062	0.006
TT_3 (nmol/L)	-0.72 (-1.23 – -0.22)	0.064	0.005
Multivariable analysis	**Estimated difference (95% CI) for 3-T_1AM (nmol/L)**	**R^2**	**P-value**
All		0.279	<0.0001
TT_4 (nmol/L)	0.01 (-0.03 – 0.04)		0.7
TT_3 (nmol/L)	2.22 (0.91 – 3.53)		0.001
rT_3 (nmol/L)	-0.03 (-0.37 – 0.30)		0.8
3,5-T_2 (nmol/L)	-0.17 (-0.47 – 0.14)		0.2
	Estimated difference (95% CI) for 3,5-T_2 (nmol/L)		
All		0.074	0.01
TT_4 (nmol/L)	-0.01 (-0.03 – 0.01)		0.2
TT_3 (nmol/L)	-0.44 (-1.14 – 0.24)		0.2

Critically ill patients revealed:
- **Median 44% lower serum 3-T_1AM**
- **Median 30% higher serum 3,5-T_2 compared to healthy volunteers**

Non-survivors and sepsis-patients:
- **Significantly higher 3,5-T_2**
- **Unchanged 3-T_1AM compared to other patients**

Reduced serum 3-T_1AM positively correlates with low serum T_3 (p<0.001)

Conclusion

We observed in critically ill patients:

- Increased circulating **3,5-T_2**, most so in patients with unfavorable outcome
- Possible explanations:
  - ➢ Increased conversion from its precursors
  - ➢ Decrease in 3,5-T_2 metabolism
  - ➢ Decrease in tissue uptake
- Circulating **3-T_1AM** was suppressed
- Independently correlated to low T_3 concentrations
- Possible explanations:
  - ➢ Decreased availability of T_3 as precursor
  - ➢ Decreased conversion of 3,5-T_2 to 3-T_1AM

Further investigation on function of 3-T_1AM or 3,5-T_2 during critical illness is needed

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