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Impact of non-severe infections on cortisol and thyroid stimulating hormone baseline levels in hospitalized patients: A monocentric cross-sectional study

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Objective. The hormonal balance is dependent on the internal and external stimuli. The baseline cortisol (BC) and thyroid stimulating hormone (TSH) levels have been observed to vary and have a predictive value in critical illness settings. Few reports have studied their variation in non-severe acute illness. The present study aims to describe the variation of BC and TSH levels and to determine the factors influencing BC and TSH levels in patients admitted with non-severe acute illness.

Patients and Methods. This is a cross-sectional study of patients admitted to Infectious Diseases and Endocrinology units at the Department of Endocrinology-Diabetology and Internal Medicine at Tahar Sfar University Hospital between March 15th and September 15th, 2020. BC and TSH levels were obtained during the hospitalization.

Results. A total of 143 patients were included in this study with 75 presenting with infection. All infections were community-acquired and predominantly non-severe. The BC levels were higher in patients with infection (p=0.004), especially those admitted via the emergency department (p=0.009) with a fever (p=0.015). The BC positively correlated with the temperature (p=0.002, r'=0.350), CRP levels (p=0.002, r'=0.355), neutrophil to lymphocyte ratio (p=0.045, r'=0.235), and SOFA score (p=0.023, r'=0.262). On the other hand, TSH levels were comparable in the presence of infection (p=0.400). TSH levels did not correlate with the fever, the severity of infection, or inflammation biomarkers. Both BC and TSH did not predict unfavorable outcomes in non-severe infected patients.

Conclusion. In patients admitted with critical acute infections, the BC levels seem to indicate a relatively more severe infectious state. On the other hand, TSH levels did not show significant variations in these patients.

Keywords: acute disease, hydrocortisone, infections, inpatients, thyrotropin

The hormonal environment is a hallmark of internal homeostasis. It allows a delicate yet continuous balance of metabolism and energy expenditure. Both cortisol and thyroid stimulating hormone (TSH) secretions have circadian fluctuations and are subjects for internal and external stimuli (Nicolaides et al. 2017; Thau et al. 2021; Hong and Lee 2022). Many studies conducted in the intensive care units have concluded that the cortisol baseline (BC) increases remarkably during severe acute stress, sepsis, and septic shock (Zhang et al. 2014). Similarly, a host of studies examined the variation and the prognostic value of thyroid hormones and TSH levels in patients in the intensive care units and those with

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sepsis or septic shocks (Hosny et al. 2015; Benea et al. 2019). However, little feedback is available regarding patients admitted to medical departments with stable conditions or non-severe infections. On the other hand, accounting for these influencing factors is essential for accurate interpretation of BC and TSH values in hospitalized patients, which may lead to management difficulties in some patients.

Therefore, this study was conducted to describe the variation of BC and TSH levels in admitted patients with acute, no critical illness and infection and to determine the factors associated with the variation of BC and TSH in a medical department, especially when presenting with an infection.

Materials and Methods

Subjects. This is a cross-sectional study of patients admitted to Infectious Diseases and Endocrinology units at the Department of Endocrinology-Diabetology and Internal Medicine at Tahar Sfar University Hospital between March 15th and September 15th, 2020. All patients were orally informed by the study in a Tunisian dialect. Written consent of the patients or the legal guardian was obtained on a consent sheet, when possible, while oral consent was obtained for illiterate patients.

Inclusion criteria. Patients included were those aged 15 or more and consenting to their inclusion.

Non-inclusion criteria. We did not include patients treated with supra-substitutive corticosteroids at the moment of hospitalization or less than 15 days before hospitalization, those with chronic kidney failure under dialysis or those who underwent dialysis before admission, those with known primary or secondary adrenal insufficiency, hypothyroidism or hyperthyroidism, and pregnant women.

Exclusion criteria. We excluded patients who refused further treatment and/or hospitalization, those treated with corticosteroids during the hospitalization and those whose BC and TSH levels were not obtained during hospitalization.

Data collection. The data were collected on a dedicated form. It included demographic data, patients' medical history, physical examination findings, and laboratory workup such as blood cell count (BCC), creatinine, glycated hemoglobin (HbA1c), fasting blood glucose (FBG), albumin, and C-reactive protein (CRP) levels. Glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD) formula: GFR (mL/min) = 186 × (creatinine (µmol/L) × 0.0113) – 1.154 × age – 0.203 × 1.21 (for patients with African origins) × 0.742 (for women). Neutrophil-lymphocyte count ratio (NLR) was calculated by the formula: NLR = neutrophil count/lymphocyte count. BC and TSH levels were obtained at 8:00 a.m. on the second or the third day of admission to account for hospitalization-induced stress. Normal BC and TSH ranges are defined as 62–194 ng/ml and 0.3–5.6 mIU/L, respectively. Possible drugs interfering with cortisol assay such as biotin supplements were accounted for (Kabiri et al. 2021).

Study groups. Patients included were divided into patients with and without infection. For patients with infection, we specified the site of infection, the delay between the onset of symptoms and admission, the severity of the infection, estimated by the Sequential Organ Failure Assessment (SOFA) score (Lambden et al. 2019), the number and duration of antibiotics used and the length of in-hospital stay. Severe infection was defined by a SOFA score ≥2.

Statistical analysis. Data entry and analysis were carried out with the Statistical Package for Social Sciences (SPSS) Statistics, version 23. The results were expressed as numerical values (percentages) for categorical variables, medians (interquartile range) for continuous variables when Kolmogorov-Smirnov p-value was inferior to 0.05 and means ±

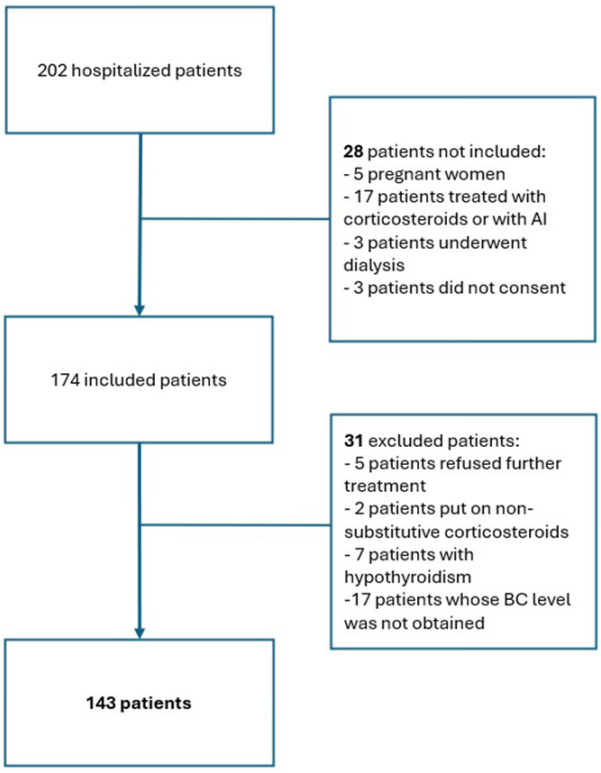

Figure 1. Flow-chart describing the study population.

standard deviation (SD) when Kolmogorov-Smirnov p-value was superior to 0.05. Univariate analysis was performed using the chi-square tests for categorical variables and the non-parametric Mann-Whitney test for continuous variables. The correlations were studied using the Spearman test, and the Spearman correlation coefficient was expressed as r', with positive r' value showing a positive correlation and vice-versa. The threshold for significance for all statistical analysis was defined as 0.05.

Results

Study population. During the study duration, a total of 202 patients were admitted to the units of Endocrinology and Infectious Diseases. Twenty-eight patients were not included, while 31 patients were excluded. Thus, a total of 143 patients were included (Figure 1).

Epidemiological characteristics, medical history, and physical examination findings. The median age of patients was 55 (3–67) years. The sex ratio was 1.1 with 75 male patients. Seventy-five patients were admitted with an infection. Fever was found in 30% of all admitted patients and 52% of those presenting with an infection. Table 1 summarizes the epidemiological characteristics, personal medical history, and physical examination features of all included patients as well as those with and without infection.

Laboratory work-up, BC, and TSH levels. The basal cortisol levels were significantly higher in patients with infection ($p<10^{-4}$), while both TSH and free thyroxine (FT4) levels were comparable in patients with and without infection, as shown in Table 2.

Characteristics and outcomes of patients with infection**.** The infection was community-acquired in all cases and was predominantly not severe with a SOFA score <2 in 64 cases (85.3%). Infection was documented in 28 cases (37%). The most common site of infection was urinary tract infection in 26 cases (34.3%) (Table 3).

The median delay between the onset of symptoms and the admission was 5 (3–7.75) days. The median duration of intravenous treatment with antibiotics was 7 (5–11) days, while the median duration of total antibiotic treatment was 12 (9.5–14) days. Association of antibiotics was needed in 32 patients (43.8%).

Table 1
Demographic characteristics, medical history, and physical examination findings of the study population, infected, and non-infected patients

Characteristics	Study population (n=143)	Infection group (n= 75)	Non-infection group (n=68)	p-value
Age				
<65 years	101 (71%)	54 (72%)	47 (69%)	0.705
≥65 years	42 (29%)	21 (28%)	21 (30%)	
Gender				
Men	75 (52%)	42 (56%)	33 (49%)	0.372
Women	68 (48%)	33 (44%)	35 (51%)	
Provenance of patients				
Emergency department	100 (69%)	65 (86%)	35 (51%)	$<10^{-4}$
Out-patient clinic/other departments	43 (31%)	10 (14%)	33 (49%)	
Medical history				
DM	75 (52%)	30 (40%)	45 (66%)	0.002
Hypertension	31 (21%)	12 (16%)	19 (27%)	0.084
Auto-immune disease	9 (6%)	3 (4%)	6 (8%)	0.200
CKD	17 (11%)	9 (2%)	8 (11%)	0.965
CVD	22 (15%)	10 (13%)	12 (17%)	0.475
Weight (kg)	70 [60–82]	68 [57–86]	73 [62–81]	0.600
Fever	44 (30%)	39 (52%)	5 (7%)	$<10^{-4}$
BMI (kg/m²)	26 [22–31]	25.5[2.6–32.3]	27.1 [23.4–31.0]	0.425

Abbreviations: BMI – body mass index; CKD – chronic kidney disease, CVD – cardiovascular disease; DM – diabetes mellitus.

Table 2
Results of laboratory work-up, basal cortisol and thyroid stimulating hormone levels in the study population patients with infection and those without infection

Feature	Study population	Patients with infection (n=75)	Patients without infection (n=68)	p-value
WBC (elements/mm^3)	7790 [6065–11505]	9260 [6440–13730]	6760 [5620–8780]	$<10^{-4}$
Neutrophils (elements/mm^3)	4640 [3320–7920]	6315 [4256–13730]	4030 [2847–5902]	$<10^{-4}$
Eosinophils (elements/mm^3)	90 [30.0–202.5]	70 [20–145]	130 [77–222]	0.001
Lymphocytes (elements/mm^3)	1960 [1247.5–2702.5]	1570 [955–2555]	2335 [1717–2812]	$<10^{-4}$
Haemoglobin (g/dL)	12.5 [10.6–13.6]	12 [9–13]	12 [11–13]	0.02
Platelets (10^3 elements/mm^3)	243 [176–315]	232 [157–322]	240 [190–299]	0.39
HbA1c (%)	11.4 [6.67–13.07]	7 [5–11]	12 [11–14]	$<10^{-4}$
Fasting glucose (mmol/L)	10 [5.43–14.00]	6 [4–11]	12 [9–16]	$<10^{-4}$
TC (mmol/L)	4 [3.1–5.0]	3 [2–4]	4 [3–5]	$<10^{-4}$
HDL-C (mmol/L)	0.83 [0.60–1.06]	0.6 [0.5–0.9]	1 [0.8–1.2]	$<10^{-4}$
LDL-C (mmol/L)	2.3 [1.6–3.0]	1 [1–2]	2.1 [2–3]	0.002
TG (mmol/L)	1.5 [1.15–2.13]	1 [1–1]	1 [1.0–2.1]	0.080
Creatinine (µmol/L)	69 [56.0–104.5]	72 [59–113]	66 [51–104]	0.131
eGFR (ml.min^{-1})	100 [62–136]	99 [57–11]	102 [66–149]	0.284
Albumin (g/L)	33.7 [30.0–36.7]	31 [28–35]	34 [32–37]	0.001
CRP (mg/L)	10.5 [2–107]	89 [17–175]	2 [0–6]	$<10^{-4}$
BC (ng/ml)	130 [9–173]	144 [106–189]	113 [94–145]	0.004
TSH (mIU/L)	1 [1–2]	1 [0–2]	1 [1–2]	0.545

Abbreviations: BC – basal cortisol; CRP – C-reactive protein; eGFR – estimated glomerular filtration rate; HbA1c – glycated hemoglobin; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TC – total cholesterol; TG – triglycerides; TSH – thyroid stimulating hormone; WBC – white blood cells.

Apyrexia was obtained after a median of 1 (0–3) days. The median duration of in-hospital stay was 8 (6–12) days. Six patients (8%) had a worsening of their clinical picture and two of them died.

Variation of BC and TSH levels, demographic characteristics, and physical examination findings in patients with infection. The BC and TSH did not correlate with age (p=0.967 and p=0.434, respectively). The BC levels were higher in patients admitted via the emergency department (p=0.009) and those without chronic kidney disease (CKD) (p=0.040). The BC levels were significantly higher in patients who presented fever upon admission, 160.0 (120.0–192.2) ng/mL vs. 133.0 (93.2–169.0) ng/mL (p=0.015) with a positive correlation between BC and temperature (p=0.002, r'=0.35). The BC also inversely correlated with DBP (p=0.008, r'=–0.3). There was no significant correlation between BC and weight (p=0.237) or body mass index (BMI) (p=0.100). TSH levels were comparable in the presence of fever (p=0.060) and were not correlated to weight (p=0.230), BMI (p=0.840) systolic blood pressure (SBP) (p=0.824) or diastolic blood pressure (DBP) (p=0.360) (Table 4).

Variation of BC and TSH levels with laboratory work-up findings in patients with infection. The BC levels were positively correlated with CRP (p=0.002, r'=0.355) and NLR (p=0.045, r'=0.235) and negatively with albumin (p=0.003, r'=–0.353) and high-density lipoprotein (HDL) cholesterol (p=0.014, r'=–0.307) levels. There was no correlation between BC and BCC features, creatinine (p=0.260), eGFR (p=0.547), HbA1c (p=0.15), FBG (p=0.485), and low-density lipoprotein (LDL) cholesterol levels. On the other hand, TSH levels only tended to negatively correlate with albumin levels (p=0.580 r'=–0.58) and did not correlate with CRP (p=0.290, creatinine (p=0.264), eGFR (p=0.540), and lipid levels.

Additionally, there was no correlation between BC and TSH levels (p=0.598) in patients with infection.

Variation of BC and TSH levels with characteristics of infection. The BC levels were positively correlated with SOFA score (p=0.023, r'=0.262). However, there was no significant difference in BC levels in patients with severe or non-severe infections (p=0.060) (Table 5).

The BC and TSH did not significantly vary with the infection site (p=0.062 and p=0.780, respectively). Neither TSH nor BC levels were impacted by the delay between the onset of the symptoms and the admission (p=0.940 and p=0.910, respectively) (Table 5).

Association of BC and TSH to the outcome in patients with infection. There was no significant difference in BC (p=0.072) and TSH (p=0.823) levels in patients whose clinical states worsened. The BC was positively correlated with the duration before obtaining apyrexia (p=0.040, r'=0.278) and the duration of dual antibiotic therapy (p=0.042, r'=0.36). The BC was more elevated in patients who needed to be put on multiple antibiotics (p=0.020), while it only tended to correlate with the total duration of antibiotic treatment (p=0.051). TSH was not correlated to the duration of intravenous (p=0.913) or total (p=0.536) treatment.

Neither BC nor TSH were correlated with the length of in-hospital stay (p=0.064 and p=0.628, respectively).

Table 3
Characteristics of the infection among infected patients

Feature	Number (%)
Prior antibiotic treatment	
Yes	16 (22)
No	59 (78)
Causative agent	
Bacteria	58 (75.3)
Virus	5 (6.5)
Parasite	3 (3.9)
Not specified	11 (14.3)
SOFA	
<2	64 (85.3)
≥2	11 (14.7)
CRP (mg/L)	
<12	15 (20.3)
>12	59 (79.7)
Infection site	
Urinary	26 (34.6)
Skin	13 (17.3)
Central nervous system	12 (16)
Pulmonary	4 (5.3)
Intracellular infections	8 (10.6)
Other	12 (15.9)

Abbreviations: CRP – C-reactive protein; SOFA – Sequential Organ Failure Assessment.

Table 4
Variation of basal cortisol and thyroid stimulating hormone (TSH) according to demographic characteristics

Feature		Cortisol (ng/ml)	p-value	TSH (mIU/ml)	p-value
Age					
<65 years		130 [99–174]	0.480	1.6 [0.9–2.2]	0.380
>65 years		123.5 [98.41–168.00]		1.5 [1.3–3.4]	
Gender					
Male		131.5 [103.7–173.5]	0.760	1.5 [0.7–2.7]	0.630
Female		123 [89–173]		1.6 [1.2–2.5]	
Provenance of patients					
Emergency room		139.5 [104.5–185.5]	**0.009**	1.5 [0.9–2.1]	0.400
Outpatient setting		106 [77.67–137.00]		2.1 [1–3]	
Chronic diseases					
Diabetes	Yes	130.5 [100.7–173.7]	0.300	1.5 [1.0–2.6]	0.780
	No	128 [99–173]		1.5 [0.8–2.7]	
High blood pressure	Yes	121.5 [87.6–166.2]	0.490	1.9 [1.4–2.7]	0.290
	No	131 [101–174]		1.5 [0.9–2.7]	
Cardiovascular diseases	Yes	128 [88.5–171.0]	0.700	2.7 [1.2–3.5]	0.100
	No	130 [101.0–173.7]		1.5 [0.9–2.1]	
Chronic renal failure	Yes	107 [95.2–123.7]	**0.040**	1.9 [1.3–4.7]	0.280
	No	132 [100.4–177.5]		1.5 [0.9–2.6]	

Table 5
Variation of basal cortisol and thyroid stimulating hormone levels with the characteristics of infection

Feature	Cortisol (ng/ml)	p-value	TSH (mUI/l)	p-value
Prior antibiotic treatment				
Yes	129 [89.5–160]	0.234	1.6 [1.2–2.1]	0.489
No	150 [106–191]		1.5 [0.95–2.76]	
Causative agent				
Bacteria	145 [106–190]	0.500	1.5 [0.94–2.40]	0.170
Virus	189 [120–319]		1.27 [0.88–1.74]	
Parasite	132 [109–]		2.8 [1.9–]	
SOFA				
<2	141 [101–180]	0.060	1.5 [1.0–2.2]	0.780
≥2	160 [135–225]		1.8 [0.37–4.67]	
CRP (mg/ml)				
<12	101 [91–149]	**0.013**	1.53 [1.20–2.14	0.790
>12	152 [116–191]		1.58 [0.93–2.80]	

Abbreviations: CRP – C-reactive protein; SOFA – Sequential Organ Failure Assessment; TSH – thyroid stimulating hormone.

Discussion

Hormonal homeostasis is delicately affected by external and internal environments (Maxime and Annane 2005). Both adrenal and thyroid secretion may be influenced by external and internal stressors and it has been proven that fluctuate with external and internal factors (Thau et al. 2021; Hong and Lee 2022). It has been proven (Thau et al. 2021; Hong and Lee 2022) that both adrenal and thyroid secretions may be influenced by external and internal stressors. The interpretation of the BC and TSH values variations in patients should be taken into consideration.

This study aimed to describe and analyze the variation of BC and TSH levels in patients admitted to a medical department where patients are usually stable and do not present a severe illness or infection. Globally, demographic characteristics, medical history, and BMI did not impact the values of BC and TSH. Our results revealed that BC levels were higher in case of an infection, fever, and seemed to indicate a more severe clinical presentation and predict longer more intensive management. On the other hand, BC levels were poorly indicative of the outcome. On the other hand, TSH levels showed no significant variation or prognostic value in non-severe illness or infection.

The BC and TSH levels did not vary according to age, gender, and a medical history of diabetes, hypertension or cardiovascular disease. According to most studies, the BC levels did not vary between the different age groups (Wolf et al. 2002; Roelfsema et al. 2017). However, some studies have reported a positive correlation with age (Terzidis et al. 2011). Aging could be associated with an increased secretion of cortisol explained by the alteration of enzymes responsible for steroidogenesis and therefore, the loss of the feedback on cortisol secretion (Wolf et al. 2002; Yiallouris et al. 2019). The TSH levels have been shown to have a U-shaped relationship with age in both iodine-sufficient Caucasian (Taylor et al. 2023) and Korean populations (Park et al. 2018) as it tended to increase with age. Although some studies have shown that daily production of cortisol was higher in men, no difference in BC between men and women has been reported (Van Cauter et al. 1996; Roelfsema et al. 2017) although some studies have reported higher values of TSH in women (Park et al. 2018).

Many studies have reported higher blood cortisol in patients having diabetes or metabolic syndrome (Kluwe et al. 2021) or hypertension (Carroll et al. 2011). Higher TSH levels and frequency of subclinical hypothyroidism have been reported in Indian women with type 2 diabetes (Nair et al. 2018). Higher TSH levels are associated with increased leptin secretion, resistance to insulin and hyperinsulinism, and supplementation with thyroid hormones enhanced insulin sensitivity (Vemula et al. 2023). In our population, the included patients had many comorbidities that could influence both blood pressure and BC, which could explain the absence of an association between hypertension and the BC levels.

Many studies have established a correlation between BC and blood creatinine levels with an inverse correlation with eGFR. This elevated BC could be explained by a diminished activity of 11-beta-hydroxysteroid dehydrogenase leading to a decrease in the renal elimination of blood cortisol (Sagmeister et al. 2019). Additionally, Asvold et al. (2011) have reported a negative correlation between TSH levels in the normal range and eGFR. The small sample size of patients with CKD in our study could explain these discrepancies with data from the literature.

The patients admitted after consulting the emergency room had higher BC than those admitted via the outpatient' settings. This could be explained by the supplementary stress felt by patients when suddenly and urgently were admitted. In contrast, admission through the outpatients' settings is usually planned and the patient is aware of his pathology and prognosis and arrangement for the hospital stay.

Many studies have concluded that infected patients had higher BC than patients admitted for other diseases, especially when presenting with fever (Manary et al. 2006; Pinto et al. 2006; Lesur et al. 2010; Opolot et al. 2015). The cortisol secretion is the human body's response to limit the inflammation caused by the immune barrier's invasion by microorganisms. When the infectious agent is detected, pro-inflammatory cytokines are liberated such as tumor necrosis factor-alpha, interleukin 1, interleukin 2, and interleukin 6. These substances stimulate the hypothalamic-pituitary axis with an increased secretion of adrenocorticotropic hormone (ACTH) and cortisol (Nickler et al. 2017; Tan et al. 2020).

The other mechanism of BC elevation during infection is the secretion of neutrophil elastase, an enzyme that degrades the cortisol-biding globulin and therefore, increases the proportion of free cortisol (Baricevic et al. 2004). The cortisol metabolism has been found to decrease during septic states (Bone et al. 2002; Tan et al. 2020). Current understanding of the thyroid hormone during acute illness, especially infection, describes central and peripheral changes of thyroid hormone homeostasis as an adaptive mechanism in these states (Benea et al. 2019). Typical hormonal changes are low free triiodothyronine (FT3) levels and normal or modestly increased thyroxine (T4) levels with a decreased T3/T4 ratio (Li et al. 2022). TSH levels may also be lower in case of acute illness. These changes are grouped as the "euthyroid sick syndrome" or "nonthyroidal illness syndrome". Patients with euthyroid sick syndrome do not present signs of hypothyroidism and there is little evidence that thyroid hormone replacement may be beneficial (Li et al. 2022).

Although most of our patients did not have a severe infection and their SOFA score was <2, the BC was positively correlated to their SOFA score. This observation has been widely reported in the literature (Bone et al. 2002; Ho et al. 2006; Rotman-Pikielny et al. 2006; Christ-Crain et al. 2007; Lesur et al. 2010; Kolditz et al. 2012; Mueller et al. 2014; Zhang et al. 2014; Nickler et al. 2017; Menon et al. 2018; Tan et al. 2020). Zhang et al. (2014) have found that the BC increased gradually with the severity of the infection. Ho et al. (2006) have reported the same conclusions when compared healthy patients, infected patients, and those presenting a septic shock. The BC levels were found to be correlated to multiple scores used to appreciate the severity of infections such as the SOFA score (Zhang et al. 2014), the Glasgow Meningococcal Septicaemia Prognostic Score (GMSPS) (Bone et al. 2002), the Pneumonia Severity Index (PSI) or the CRB-65 score in cases of community-acquired pneumonia (Kolditz et al. 2012; Mueller et al. 2014), le Pediatric Risk of Mortality (PRISM) (Menon et al. 2018). On the other hand, a study analyzing TSH, FT4, and FT3 levels in patients admitted with sepsis to the intensive care units have found that the mean level of FT3 was lower in patients with septic shock (1.3±0.4 pg/ml) and severe sepsis (1.7±0.2 pg/ml) as compared to patients with sepsis (2.4±1.2 pg/ml) (Hosny et al. 2015).

In our infected patients, we found a correlation between BC and CRP. These findings have also been reported by Nickler et al. (2017) and Juutilainen et al. (2011). Although the CRP does not have a high diagnostic value in infections, since it lacks specificity, this marker is widely available and affordable (Castelli et al. 2004). A meta-analysis conducted by Tan et al. (2020) have shown that a cut-off of 12 mg/L is more suited to differentiate between an infection and an infection with the sepsis. Patients with a CRP higher than 12 mg/L had a higher BC in our study. Additionally, the BC levels were correlated with NLR, an increasingly studied biomarker of sepsis cancer as well as cardiovascular diseases (Buonacera et al. 2022). Erturk et al. (2023) have observed a similar moderate positive correlation between BC and NLR in patients with COVID-19 infection.

The infection site or the causative microorganism was not associated with a variation of BC in our patients. Rotman-Pikielny et al. (2006) have found that patients with a skin infection or pneumonia had higher BC than patients with a urinary tract infection. The nature of the germ did not influence

the BC in the literature that we reviewed. However, a few studies have compared heterogeneous infections although most of them has been focused on the infection site or a specific infectious agent (Bone et al. 2002; Kolditz et al. 2012; Mueller et al. 2014).

Neither BC nor TSH levels were significantly associated with an unfavorable outcome. The data concerning the prognostic value of BC are vast and sometimes contradictory. Most studies have shown that higher BC values are predictive of worse outcomes in patients with sepsis (Bone et al. 2002; Zhang et al. 2014; Nickler et al. 2017). Tan et al. (2020) have found that elevated BC levels are associated with higher mortality rates in patients with SARS-COV-2 infection. Similarly, Erturk et al. (2023) have observed that BC levels are a good predictive marker of the severity of COVID-19 infection, though it was inferior to CRP and ferritin levels. Additionally, Rothwell and Lawler (1995) have shown that an endocrine index combining BC, TSH, and thyroid hormone levels had a better predictive value of outcome in ICU patients than the APACHE II score. Since only a few patients had an unfavorable outcome in our study, it is difficult to assert to the prognostic value of TSH and BC levels in patients admitted with no critical illness.

To our knowledge, this study is the first to evaluate the variation of BC and TSH in infected patients with no severity criteria. The BC levels were higher in patients with infection and correlated positively with the temperature and the severity of the infectious state and were poorly indicative of the outcome.

The limited sample size in our study makes it hard to come to conclusions. The reduced population size is mainly due to the study being conducted in the context of the COVID-19 pandemic, as patients were more reluctant to consult the emergency department, and hospitalization rates for non-covid cases were reduced as part of the overall health strategy. The heterogeneous population makes it delicate to analyze the variation of BC and TSH levels in all morbid groups. Additional hormonal evaluation (ACTH, FT3) could shed more light on the hormonal imbalance in the study population. These dosages, however, are not routinely accessible in our context and their practical implication in our daily practice is limited. More enlarged studies should be conducted to be able to generalize our findings.

Conclusions

Basal cortisol levels were not influenced by demographic characteristics and medical history but rather by the burden of the acute noncritical illness presented in the patients. The basal cortisol seemed to reflect an initial, relatively more severe state of the infection, since it correlated with SOFA score and CRP levels and was associated with more intensive treatment. TSH levels, on the other hand, showed little variation and no discriminatory value in patients admitted with non-severe illnesses and infections. Thus, measuring TSH in patients with non-severe infection when suspecting hypo- or hyper-thyroidism shows no interpretation bias, while basal cortisol levels are tightly influenced by the septic state. Thus, defining the proper normal range for basal cortisol in the context of infection is essential and it requires more extensive studies. Our study also suggests that basal cortisol may be an interesting decision-making tool in borderline initial clinical presentations with infection, allowing for more precise and personalized management of patients.

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