

# Serum levels of thyroid hormones and thyroid stimulating hormone in patients with biliogenic and hyperlipidaemic acute pancreatitis: Difference and value in predicting disease severity

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## Abstract

**Objectives:** To compare retrospectively serum levels of thyroid hormones (THs) and thyroid stimulating hormone (TSH) between patients with biliogenic acute pancreatitis (BAP) and those with hyperlipidaemic acute pancreatitis (HLAP), in order to assess their value for predicting the severity of acute pancreatitis (AP).

**Methods:** Patients with AP were divided into BAP and HLAP groups, then further divided into either a mild AP (MAP) group or a moderately severe AP (MSAP) group. Routine blood parameters were measured. Free tri-iodothyronine (FT3), free thyroxine (FT4) and TSH levels were measured.

**Results:** Seventy-six patients with AP were enrolled in the study. FT3 and TSH levels were significantly higher in patients with MAP than in patients with MSAP. FT4 and TSH levels were significantly lower in the HLAP group than in the BAP group. TSH levels in both MAP and MSAP patients were significantly lower in the HLAP group than in the BAP group. TSH was inversely correlated with triglyceride levels in patients with HLAP. FT3 was a risk factor for MSAP in patients with AP and also demonstrated moderate accuracy in predicting AP severity.

**Conclusions:** THs and TSH decrease with the severity of AP, especially in patients with HLAP. FT3 may be a useful biomarker for the early assessment of the severity of AP.

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**Keywords**

Hyperlipidaemic acute pancreatitis, biliogenic acute pancreatitis, acute pancreatitis, thyroid hormones, thyroid stimulating hormone, severity

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**Introduction**

Acute pancreatitis (AP) is a common serious disorder characterized by the presence of necroinflammatory changes in the pancreas that can extend to extrapancreatic tissues, with or without functional changes in other organs.<sup>1</sup> Severe AP cases are often associated with severe complications and high mortality, although mild AP cases can be successfully managed by conservative measures.<sup>2</sup> AP has diverse aetiologies, with bile duct disease, alcohol and metabolic abnormalities (e.g. hyperlipidaemia [HL]) being the more common causes.<sup>3</sup> Currently, biliogenic AP (BAP) is the most common form of AP,<sup>4</sup> while hyperlipidaemic AP (HLAP) represents a form of AP with a rising incidence due to improvements in living standards and changes in dietary habits.<sup>3–6</sup> The underlying causes of BAP may include sphincter of Oddi dysfunction, inflammation, oedema and obstruction of the periampullary duodenum caused by common bile duct stones or a periampullary diverticulum, which can cause reverse flow of bile into the pancreas.<sup>3</sup> In addition, biliary tract infection and the spread of inflammatory exudates into the pancreas via lymphatic vessels may result.<sup>7</sup> HLAP may be related to injury to pancreatic acinar cells and capillary endothelial cells induced by free fatty acids (FFAs), which are the product of triglycerides (TG), abnormal trypsinogen activation and microcirculatory dysfunction.<sup>8–10</sup> Since AP of different aetiologies and severity may have different clinical outcomes and require different treatment, assessing disease severity is essential for selection of the most appropriate initial treatment.<sup>11</sup>

The thyroid gland is an important part of the endocrine system. Thyroid hormones

(THs) secreted by the thyroid gland, principally thyroxine (T4) and tri-iodothyronine (T3), play important roles in regulating the body's energy metabolism, promoting growth, development and tissue differentiation, and modulating islet function and sugar, fat and protein metabolism.<sup>12</sup> The majority of circulating T4 and T3 is bound to serum proteins and is largely biologically inert; determination of the levels of biologically active free T3 and T4 can more accurately assess the status of the thyroid gland.<sup>13</sup> Since the secretion of THs by the thyroid gland is regulated by many things, such as the hypothalamic–pituitary–thyroid axis and some pathological factors, serum TH levels may be altered in many disorders.<sup>14</sup> Nonthyroidal illness syndrome (NTIS) is a state of adaptation or dysregulation of thyrotrophic feedback control characterized by unusual levels of THs (typically decreased serum total T3 and FT3, increased reverse T3, normal or reduced serum total T4 and FT4, and normal or reduced serum thyroid stimulating hormone [TSH]); this condition is often seen in starvation, malnutrition, trauma, critical illness or in patients admitted to intensive care units.<sup>15</sup> NTIS has been associated with adverse clinical outcomes and is one of the most sensitive independent predictors of short-term survival in hospitalized elderly patients.<sup>16</sup>

Studies have shown that serum TH levels undergo significant changes in AP patients and return to normal as the condition improves.<sup>17–20</sup> In addition, serum TH levels have been demonstrated to be able to assess AP severity.<sup>17</sup> However, it remains unclear whether serum TH and TSH levels differ between patients with AP of different

aetiologies, and whether serum TH and TSH levels can be used to assess the severity of AP in such patients. The present study aimed to investigate possible differences in serum TH and TSH levels between patients with BAP and those with HLAP. The study also assessed the value of serum TH and TSH levels in predicting AP severity in patients with BAP and HLAP.

## Patients and methods

### *Patient population*

This retrospective study enrolled sequential patients with AP who were sequentially admitted to the Department of Gastroenterology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China between January 2012 and January 2013. The diagnosis of AP was made when at least two of the following three criteria were met: (i) classic abdominal pain; (ii) elevation of amylase and/or lipase three-times above the upper limit of normal; (iii) evidence of acute pancreatitis revealed by contrast-enhanced computed tomography (CT)/magnetic resonance imaging or abdominal ultrasound. HLAP was diagnosed in patients with AP when TG levels exceeded 11.3 mmol/l or when TG levels were 5.65–11.30 mmol/l, chylous serum was observed, and other causes such as biliary obstruction were excluded. BAP was diagnosed in patients with AP when biliary obstruction was suspected according to biochemical parameters or imaging findings and confirmed by endoscopic retrograde cholangiopancreatography (ERCP). AP was classified by severity as mild acute pancreatitis (MAP) or moderately severe acute pancreatitis (MSAP), based on the 2012 Atlanta classification.<sup>20</sup> MAP was defined by the presence of clinical features and biochemical changes typical of AP, without organ failure, local or systemic complications. MSAP was defined by the presence of clinical features and biochemical

changes typical of AP, with transient organ failure (spontaneously resolved in 48 h), local complications or exacerbation of comorbid disease (not spontaneously resolved in 48 h). A diagnosis of fatty liver was made when ultrasonography revealed a 'bright' liver with increased echogenicity, or CT showed a lower density in the liver than in the spleen. Patients with AP due to other causes, such as ERCP or surgery, use of anticoagulant drugs and chronic pancreatitis, and those with a previous history of thyroid disease or diseases that could cause abnormal TH were excluded. Patients who were taking medications that may affect thyroid hormone secretion and metabolism (e.g. amiodarone) before enrolment were also excluded.

This study was conducted according to the principles of the Declaration of Helsinki and the guidelines of the Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University, Beijing, China. The study was approved by the Ethics Committee of Beijing Chaoyang Hospital (no. 2012-ke-9) and written informed consent was obtained from all patients.

### *Biochemical measurements*

Venous blood samples (15 ml) were collected from the cubital vein into VACUETTE<sup>®</sup> Z Serum Clot Activator tubes (Greiner Bio-One, Kremsmünster, Austria) within 48 h of hospital admission. The blood samples were sent immediately to the hospital laboratory for testing. Haematological parameters including white blood cell count (normal range,  $3.97\text{--}9.15 \times 10^9/\text{l}$ ), haemoglobin (Hb; normal range, 131–172 g/l), haematocrit (HCT; normal range, 38.0–50.8%) and platelet count (PLT; normal range,  $85\text{--}303 \times 10^9/\text{l}$ ) were measured using a Sysmex XS-800i Automated Haematology Analyser (Sysmex, Kobe, Japan). Liver and kidney function, and lipid parameters, were assessed using a Dimension<sup>®</sup> RxL Max<sup>®</sup>

integrated chemistry system (Dade-Behring Diagnostics, Marburg, Germany). Measured parameters included albumin (normal range, 32–55 g/l), alanine aminotransferase (ALT; normal range, 10–40 U/l), aspartate transaminase (AST; normal range, 10–42 U/l),  $\gamma$ -glutamyltransferase (GGT; normal range, 5–85 U/l), alkaline phosphatase (ALP; normal range, 50–136 U/l), total bilirubin (normal range, 3.4–20.5  $\mu$ mol/l), direct bilirubin (Dbil; normal range, 0.0–6.8  $\mu$ mol/l), glucose (Glu; normal range, 3.3–6.1 mmol/l), calcium (Ca; normal range, 2.1–2.6 mmol/l), creatinine (Cr; normal range, 53–115  $\mu$ mol/l), cholesterol (CHOL; normal range, 3.62–5.70 mmol/l), high-density lipoprotein cholesterol (HDL-C; normal range, 1.03–1.55 mmol/l), low-density lipoprotein cholesterol (LDL-C; normal range, 1.81–3.36 mmol/l) and TG (normal range, 0.56–2.26 mmol/l). Thyroid function parameters including free T3 (FT3; normal range, 1.71–3.71 pg/ml), free T4 (FT4; normal range, 0.70–1.48 ng/dl) and TSH (normal range, 0.35–4.94  $\mu$ IU/ml) were measured using an ARCHITECT i2000SR Immunoassay Analyser (Abbott Laboratories, Abbott Park, IL, USA).

### Statistical analyses

All statistical analyses were performed using the SPSS<sup>®</sup> statistical package, version 17.0

(SPSS Inc., Chicago, IL, USA) for Windows<sup>®</sup>. Numerical data were expressed as mean  $\pm$  SD and independent-samples *t*-test was used to compare the means between two groups. Categorical data were compared using  $\chi^2$ -test. The relationship between two variables was evaluated using Spearman's correlation coefficient analysis. Logistic regression analysis was used to assess the possibility of using THs and TSH as risk factors for AP severity, and their diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis, with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) being calculated. *P*-values < 0.05 were considered statistically significant.

### Results

Seventy-six patients with AP were included in the study (54 men and 22 women) with a mean  $\pm$  SD age of 49.5  $\pm$  16.4 years (range, 24–89 years). Patients' clinical characteristics are presented in Table 1. There were 31 patients with HLAP (age range, 24–51 years) and 45 patients with BAP (age range, 25–89 years). The mean age was significantly lower and the proportion of patients with fatty liver was significantly higher in the HLAP group than in the BAP

**Table 1.** Clinical and demographic characteristics of patients with acute pancreatitis, stratified into a hyperlipidaemic acute pancreatitis (HLAP) group and a biliogenic acute pancreatitis (BAP) group.

Characteristic	HLAP group <i>n</i> = 31	BAP group <i>n</i> = 45	Statistical significance <sup>a</sup>
Age, years	35.8 $\pm$ 17.4	58.8 $\pm$ 14.1	<i>P</i> < 0.001
Sex, male/female	25/6	29/16	NS
Concomitant type 2 diabetes mellitus	11	8	NS
Presence of fatty liver	29	13	<i>P</i> < 0.001
MAP/MSAP	20/11	20/25	NS

Data presented as mean  $\pm$  SD or *n* patients.

<sup>a</sup>HLAP group compared with BAP group; independent-samples *t*-test or  $\chi^2$ -test.

MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis, NS, no significant between-group difference (*P*  $\geq$  0.05).

**Table 2.** Routine blood parameters for patients with acute pancreatitis stratified into a hyperlipidaemic acute pancreatitis (HLAP) group and a biliogenic acute pancreatitis (BAP) group.

Parameter	HLAP group <i>n</i> = 31	BAP group <i>n</i> = 45	Statistical significance <sup>a</sup>
WBC, 10 <sup>9</sup> /l	13.90 ± 4.09	13.63 ± 4.62	NS
Hb, g/l	168.29 ± 17.22	139.04 ± 28.58	<i>P</i> < 0.001
HCT, %	0.45 ± 0.04	0.41 ± 0.05	<i>P</i> = 0.006
PLT, 10 <sup>9</sup> /l	222.45 ± 52.32	194.16 ± 56.71	<i>P</i> = 0.031
ALB, g/l	39.36 ± 3.13	39.00 ± 4.87	NS
ALT, U/l	52.87 ± 41.50	151.27 ± 153.19	<i>P</i> < 0.001
AST, U/l	68.65 ± 107.19	220.69 ± 254.36	<i>P</i> = 0.001
GGT, U/l	78.87 ± 59.30	296.51 ± 256.96	<i>P</i> < 0.001
ALP, U/l	92.76 ± 24.99	142.53 ± 87.68	<i>P</i> = 0.002
Tbil, μmol/l	22.26 ± 14.19	27.50 ± 30.76	NS
Dbil, μmol/l	4.14 ± 7.89	15.18 ± 23.65	<i>P</i> = 0.005
Glu, mmol/l	15.18 ± 8.19	9.68 ± 10.83	<i>P</i> = 0.019
Ca, mmol/l	1.93 ± 0.28	2.19 ± 0.17	<i>P</i> < 0.001
Cr, μmol/l	72.24 ± 16.45	83.51 ± 21.69	<i>P</i> = 0.017
CHOL, mmol/l	9.74 ± 11.74	4.43 ± 1.07	<i>P</i> = 0.018
HDL-C, mmol/l	1.49 ± 1.62	1.38 ± 0.54	NS
LDL-C, mmol/l	2.89 ± 1.47	2.17 ± 0.81	<i>P</i> = 0.007
TG, mmol/l	28.75 ± 17.05	1.38 ± 1.04	<i>P</i> < 0.001

Data presented as mean ± SD.

<sup>a</sup>HLAP group compared with BAP group; independent-samples *t*-test.

WBC, white blood cell count; Hb, haemoglobin; HCT, haematocrit; PLT, platelet count; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT,  $\gamma$ -glutamyltransferase; ALP, alkaline phosphatase; Tbil, total bilirubin; Dbil, direct bilirubin; Glu, glucose; Ca, calcium; Cr, creatinine; CHOL, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; NS, no significant between-group difference (*P* ≥ 0.05).

group (*P* < 0.001 for both comparisons), but sex distribution, the proportion of patients with concomitant type 2 diabetes mellitus and the MAP/MSAP ratio were comparable between the two groups.

As shown in Table 2, Hb, HCT, PLT, Glu, CHOL, LDL-C and TG were significantly higher, and ALT, AST, GGT, ALP, Dbil, Ca and Cr were significantly lower, in the HLAP group than in the BAP group (*P* < 0.05 for all comparisons), while other parameters showed no significant between-group difference.

Serum levels of FT4 and TSH were significantly lower in the HLAP group than in the BAP group (*P* < 0.05 for both comparisons), although serum levels of FT3

showed no significant between-group difference (Table 3).

In the overall patient population, serum levels of FT3 and TSH were significantly higher in the MAP group than in the MSAP group (*P* < 0.05 for both comparisons) (Table 4). In both the HLAP and BAP groups, serum levels of FT3 (*P* = 0.027, *P* = 0.002, respectively) and TSH (*P* = 0.014, *P* = 0.049, respectively) were significantly higher in patients with MAP than in patients with MSAP (Table 5). Serum levels of FT4 and TSH in MAP patients were significantly lower in the HLAP group than in the BAP group (*P* = 0.047, *P* = 0.049, respectively), although serum levels of FT3 showed no significant difference between the

**Table 3.** Thyroid hormone and thyroid stimulating hormone (TSH) levels in patients with acute pancreatitis, stratified into a hyperlipidaemic acute pancreatitis (HLAP) group and a biliogenic acute pancreatitis (BAP) group.

Parameter	HLAP group n = 31	BAP group n = 45	Statistical significance <sup>a</sup>
FT3, pg/ml	1.72 ± 0.41	1.72 ± 0.47	NS
FT4, ng/dl	0.91 ± 0.12	0.99 ± 0.16	P = 0.016
TSH, µIU/ml	0.20 ± 0.15	0.36 ± 0.40	P = 0.023

Data presented as mean ± SD.

<sup>a</sup>HLAP group compared with BAP group; independent-samples t-test.

FT3, free tri-iodothyronine; FT4, free thyroxine; NS, no significant between-group difference ( $P \geq 0.05$ ).

**Table 4.** Relationship between thyroid hormone and thyroid stimulating hormone (TSH) levels and severity of acute pancreatitis in patients stratified into a mild acute pancreatitis (MAP) group and moderately severe acute pancreatitis (MSAP) group.

Parameter	MAP group n = 40	MSAP group n = 36	Statistical significance <sup>a</sup>
FT3, pg/ml	1.90 ± 0.45	1.51 ± 0.33	P < 0.001
FT4, ng/dl	0.96 ± 0.16	0.96 ± 0.14	NS
TSH, µIU/ml	0.37 ± 0.41	0.21 ± 0.19	P = 0.025

Data presented as mean ± SD.

<sup>a</sup>MAP group compared with MSAP group; independent-samples t-test.

FT3, free tri-iodothyronine; FT4, free thyroxine; NS, no significant between-group difference ( $P \geq 0.05$ ).

**Table 5.** Relationship between thyroid hormone and thyroid stimulating hormone (TSH) levels and severity of acute pancreatitis in patients with hyperlipidaemic acute pancreatitis (HLAP) or biliogenic acute pancreatitis (BAP), further stratified into a mild acute pancreatitis (MAP) group and moderately severe acute pancreatitis (MSAP) group.

Parameter	HLAP group n = 31		BAP group n = 45	
	MAP n = 20	MSAP n = 11	MAP n = 20	MSAP n = 25
FT3, pg/ml	1.84 ± 0.41	1.49 ± 0.34 <sup>a</sup>	1.97 ± 0.50	1.52 ± 0.34 <sup>d</sup>
FT4, ng/dl	0.91 ± 0.14	0.91 ± 0.08	1.02 ± 0.17 <sup>a</sup>	0.94 ± 0.10
TSH, µIU/ml	0.24 ± 0.17	0.13 ± 0.06 <sup>a</sup>	0.49 ± 0.53 <sup>a</sup>	0.24 ± 0.22 <sup>b,c</sup>

Data presented as mean ± SD.

<sup>a</sup>P < 0.05 compared with MAP patients in HLAP group; independent-samples t-test.

<sup>b</sup>P < 0.05 compared with MSAP patients in HLAP group; independent-samples t-test.

<sup>c</sup>P < 0.05 compared with MAP patients in BAP group; independent-samples t-test.

<sup>d</sup>P < 0.01 compared with MAP patients in BAP group; independent-samples t-test.

FT3, free tri-iodothyronine; FT4, free thyroxine; NS, no significant between-group difference ( $P \geq 0.05$ ).

**Table 6.** Logistic regression analyses to assess the possibility that free tri-iodothyronine was a risk factor for moderately severe acute pancreatitis in all patients with acute pancreatitis (AP), in patients with hyperlipidaemic acute pancreatitis (HLAP) and in patients with biliogenic acute pancreatitis (BAP).

Group	B	SE	P-value	OR	95% CI
AP	-2.492	0.724	0.001	0.083	0.020, 0.342
HLAP	-2.549	1.215	0.036	0.078	0.007, 0.845
BAP	-2.570	0.911	0.005	0.076	0.013, 0.453

SE, standard error; OR, odds ratio; CI, confidence interval.

**Table 7.** Value of free tri-iodothyronine in predicting AP severity in all patients with acute pancreatitis (AP), in patients with hyperlipidaemic acute pancreatitis (HLAP) and in patients with biliogenic acute pancreatitis (BAP).

Group	Cut-off, pg/ml	AUC (95% CI)	SE, %	SP, %	PPV, %	NPV, %
AP	1.615	0.748 (0.637, 0.859)	75.0	85.0	81.8	79.1
HLAP	1.655	0.757 (0.579, 0.935)	81.8	85.0	75.0	89.5
BAP	1.615	0.761 (0.613, 0.909)	76.0	85.0	86.4	73.9

AUC, area under curve; CI, confidence interval; SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value.

two groups (Table 5). Serum levels of TSH in MSAP patients were significantly lower in the HLAP group than in the BAP group ( $P=0.024$ ), while serum levels of FT3 and FT4 showed no significant between-group difference (Table 5).

Correlations between serum FT3, FT4 and TSH levels and CHOL, HDL-C, LDL-C and TG were analysed in all patients, in patients with HLAP and in patients with BAP. The results showed that serum TSH levels were significantly inversely correlated with TG in patients with HLAP ( $r=-0.414$ ,  $P=0.021$ ), but not in patients with BAP.

Logistic regression analysis was performed to assess the possibility of FT3, FT4 and TSH being risk factors for MSAP in all patients with AP, in patients with HLAP and in patients with BAP. Only FT3 was identified as a risk factor for MSAP. A reduction in FT3 by one increased the risk of MSAP by 12.05, 12.82 and 13.16 times in all

patients with AP, patients with HLAP and patients with BAP, respectively (Table 6).

The value of FT3 in predicting the severity of AP was assessed using a ROC curve analysis. The cut-off values, area under the ROC curve, sensitivity, specificity, PPV and NPV in all patients with AP, in patients with HLAP and in patients with BAP are shown in Table 7.

## Discussion

Serum levels of FT3 and FT4 have been found to be reduced in patients with AP in previous studies.<sup>17,18</sup> One possible explanation for this reduction in THs is cytokine elevations caused by the inflammatory response and endotoxins in AP. These can alter serum TH levels directly or indirectly, for example, by impairing the hypothalamic-pituitary-thyroid axis,<sup>21</sup> reducing the activity or release of TSH<sup>22-24</sup>, inhibiting the



synthesis or conversion of THs and regulating the protein binding of THs.<sup>22,25</sup> An increased level of tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) has been found in patients with AP and correlated with prognosis; TNF- $\alpha$  elevation inhibits the stimulatory effect of TSH on thyroglobulin production by thyroid cells, and activation of adenylyl cyclase and the cyclic adenosine monophosphate (cAMP) system.<sup>23,26,27</sup> Interleukin (IL)-1, IL-6 and interferon (IFN)- $\gamma$  levels are also elevated in AP.<sup>28</sup> IL-1 and IL-6 can inhibit the release of iodinated THs, generation of cAMP by thyroid cells, expression of deiodinase mRNA, and activity of deiodinase.<sup>29-32</sup> IFN- $\gamma$  inhibits thyrotropin-induced thyroglobulin gene transcription and generation of cAMP by thyroid cells.<sup>33,34</sup> In addition, this present study found that patients with HLAP and patients with BAP had significantly different serum levels of FT4 and TSH.

Although both FT3 and FT4 levels may decline in patients with AP,<sup>18</sup> only FT3 was found to be significantly lower in the MSAP group compared with the MAP group in the present study. This can be explained by the impaired activity of hepatic thyroxine 5'-deiodinase.<sup>17,35</sup> Although both T3 and T4 can be secreted by the thyroid gland, ~80% of circulating T3 is produced from T4 via deiodination (catalysed by 5'-deiodinase).<sup>36</sup> Patients with AP often have concomitant infections, and endotoxins produced by bacteria enter the liver via the portal vein, stimulate the activation of Kupffer cells, cause lysosomal rupture and result in liver necrosis.<sup>37</sup> Biliary obstruction in patients with BAP even aggravates liver necrosis.<sup>38</sup> Conversely, various cytokines released by inflammatory pancreatic tissue, such as TNF- $\alpha$ , can also cause hepatic injury.<sup>21,23,24</sup> As a result, activity of hepatic thyroxine 5'-deiodinase is impaired, and conversion from T4 to T3 is affected, which may result in the more significant decline of FT3 in AP patients.<sup>25</sup>

Circulating T3/T4 can feed back to the hypothalamus and anterior pituitary gland to negatively regulate thyrotropin releasing hormone (TRH) and TSH release.<sup>39</sup> However, serum levels of TSH were also significantly decreased in the MSAP group compared with MAP group in the present study, despite the decline in FT3 levels. Since TSH levels are regulated dually by THs and TRH, the decline of TSH may be caused by the impact of endotoxins and cytokines on the hypothalamus and pituitary gland or the altered response of the pituitary gland to THs.<sup>21</sup> The majority of critically ill patients with infection have substantially elevated catecholamine and glucocorticoid levels, and often develop hypofunction of the hypothalamus and pituitary gland, therefore having a reduced release of TRH and TSH.<sup>14,40</sup>

The present study found that serum levels of FT4 and TSH were significantly lower in the HLAP group than in the BAP group, although FT3 levels showed no significant between-group difference. In addition, serum levels of TSH were inversely correlated with TG in patients with HLAP, but not in patients with BAP. These findings suggest that HLAP and BAP may have a different pathogenesis and clinical course. HL can not only be the consequence of AP but also it can be an independent factor causing AP.<sup>5</sup> Approximately 12–50% of patients with AP had abnormal serum lipid levels, and 1–12% of AP cases are caused by HL.<sup>4,5</sup> THs have diverse effects on lipid metabolism, and hypothyroidism causes hypercholesterolaemia.<sup>41</sup> Previous studies demonstrated that HLAP patients had significantly elevated FFA levels and that FFA levels were associated with AP severity.<sup>42,43</sup> Interestingly, FFA levels are derived mainly from TG-rich lipoproteins by lipolysis catalysed by lipoprotein lipase.<sup>43</sup> FFAs can directly damage pancreatic acinar cells and significantly inhibit the protein binding, deiodination and conversion of THs.<sup>9,44</sup>



Therefore, the current study findings suggest that patients with HLAP more easily develop NTIS and have more significant changes in TH levels, compared with patients with BAP.

The present study demonstrated that serum levels of FT3 and TSH were significantly lower in patients with MSAP compared with patients with MAP, in the overall AP patient population and in the HLAP and BAP groups, suggesting that serum FT3 and TSH levels are associated with AP severity. Studies have demonstrated that NTIS is associated with nonthyroid disease severity.<sup>45,46</sup> This present study further demonstrated that the FT3 level was an independent risk factor for MSAP. Given that low FT3 and FT4 levels can reduce oxygen and energy consumption, we suggest that the decline of serum levels of FT3 and FT4 may be a self-protective physiological mechanism adopted by critically ill patients. Consistent with this suggestion, it has been observed that TH levels return to normal when patients with NTIS recover.<sup>19</sup> Currently, there is no evidence that hormone replacement therapy can help patients recover more rapidly.

The present study had several limitations. First, the sample size was relatively small, which might have resulted in insufficient statistical power. Secondly, the mean age was significantly lower in the HLAP group than in the BAP group, and the confounding effect of age could not be excluded. Thirdly, patients with severe AP were not included in this study as there were very few cases. Finally, the timing of TH and TSH detection may have an impact on the results. However, due to the fact that the patients were admitted at different times after the onset of abdominal pain, TH and TSH levels were measured as early as possible. In addition, TH and TSH levels were only measured once, and thus it was not possible to assess whether THs and TSH had different declining speeds between MAP and

MSAP patients. Future studies should carefully address these issues.

In conclusion, the present study demonstrated that decreased TH and TSH levels may be closely associated with AP severity. The TH abnormality appears to be more significant in patients with HLAP than in patients with BAP. Detection of THs levels in patients with early AP, especially HLAP patients, may help predict disease severity, select appropriate initial treatment and improve prognosis.

### Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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### References

1. Klöppel G. Acute pancreatitis. *Semin Diagn Pathol* 2004; 21: 221–226.
2. Wijffels NA, van Walraven LA, Ophof PJ, et al. Late development of pancreas necrosis during acute pancreatitis: an underestimated phenomenon associated with high morbidity and mortality. *Pancreas* 2007; 34: 215–219.
3. van Geenen EJ, van derPeet DL, Bhagirath P, et al. Etiology and diagnosis of acute biliary pancreatitis. *Nat Rev Gastroenterol Hepatol* 2010; 7: 495–502.
4. Sekimoto M, Takada T, Kawarada Y, et al. JPN Guidelines for the management of acute pancreatitis: epidemiology, etiology, natural history, and outcome predictors in acute pancreatitis. *J Hepatobiliary Pancreat Surg* 2006; 13: 10–24.
5. Athyros VG, Giouleme OI, Nikolaidis NL, et al. Long-term follow-up of patients with acute hypertriglyceridemia-induced pancreatitis. *J Clin Gastroenterol* 2002; 34: 472–475.

6. Chang MC, Su CH, Sun MS, et al. Etiology of acute pancreatitis—a multi-center study in Taiwan. *Hepatogastroenterology* 2003; 50: 1655–1657.
7. Weiner S, Gramatica L, Voegle LD, et al. Role of the lymphatic system in the pathogenesis of inflammatory disease in the biliary tract and pancreas. *Am J Surg* 1970; 119: 55–61.
8. Hackert T, Pfeil D, Hartwig W, et al. Platelet function in acute experimental pancreatitis induced by ischaemia-reperfusion. *Br J Surg* 2005; 92: 724–728.
9. Ewald N, Hardt PD and Kloer HU. Severe hypertriglyceridemia and pancreatitis: presentation and management. *Curr Opin Lipidol* 2009; 20: 497–504.
10. Waterford SD, Kolodecik TR, Thrower EC, et al. Vacuolar ATPase regulates zymogen activation in pancreatic acini. *J Biol Chem* 2005; 280: 5430–5434.
11. Brisinda G, Vanella S, Crocco A, et al. Severe acute pancreatitis: advances and insights in assessment of severity and management. *Eur J Gastroenterol Hepatol* 2011; 23: 541–551.
12. Sinha RA, Singh BK and Yen PM. Thyroid hormone regulation of hepatic lipid and carbohydrate metabolism. *Trends Endocrinol Metab* 2014; 25: 538–545.
13. Bartalena L, Bogazzi F, Brogioni S, et al. Measurement of serum free thyroid hormone concentrations: an essential tool for the diagnosis of thyroid dysfunction. *Horm Res* 1996; 45: 142–147.
14. Fliers E, Alkemade A and Wiersinga WM. The hypothalamic–pituitary–thyroid axis in critical illness. *Best Pract Res Clin Endocrinol Metab* 2001; 15: 453–464.
15. DeGroot LJ. Dangerous dogmas in medicine: the nonthyroidal illness syndrome. *J Clin Endocrinol Metab* 1999; 84: 151–164.
16. Tognini S, Marchini F, Dardano A, et al. Non-thyroidal illness syndrome and short-term survival in a hospitalised older population. *Age Ageing* 2010; 39: 46–50.
17. DeSola C, Redondo M, Pallarés F, et al. Thyroid function in acute pancreatitis. *Rev Esp Enferm Dig* 1998; 90: 15–22.
18. Medina-Santillán R, Vázquez-Savedra JA, Tanimoto M, et al. Decrease in the serum concentration of triiodothyronine in patients with acute edematous pancreatitis. *Arch Invest Med (Mex)* 1989; 20: 243–245. [Article in Spanish, English abstract].
19. Pappa TA, Vagenakis AG and Alevizaki M. The nonthyroidal illness syndrome in the non-critically ill patient. *Eur J Clin Invest* 2011; 41: 212–220.
20. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; 62: 102–111.
21. Imura H, Fukata J and Mori T. Cytokines and endocrine function: an interaction between the immune and neuroendocrine systems. *Clin Endocrinol (Oxf)* 1991; 35: 107–115.
22. Dubuis JM, Dayer JM, Siegrist-Kaiser CA, et al. Human recombinant interleukin-1 beta decreases plasma thyroid hormone and thyroid stimulating hormone levels in rats. *Endocrinology* 1988; 123: 2175–2181.
23. Malleo G, Mazzon E, Siriwardena AK, et al. Role of tumor necrosis factor-alpha in acute pancreatitis: from biological basis to clinical evidence. *Shock* 2007; 28: 130–140.
24. Poth M, Tseng YC and Wartofsky L. Inhibition of TSH activation of human cultured thyroid cells by tumor necrosis factor: an explanation for decreased thyroid function in systemic illness? *Thyroid* 1991; 1: 235–240.
25. Ongphiphadhanakul B, Fang SL, Tang KT, et al. Tumor necrosis factor-alpha decreases thyrotropin-induced 5'-deiodinase activity in FRTL-5 thyroid cells. *Eur J Endocrinol* 1994; 130: 502–507.
26. Norman JG, Fink GW and Franz MG. Acute pancreatitis induces intrapancreatic tumor necrosis factor gene expression. *Arch Surg* 1995; 130: 966–970.
27. Rasmussen AK, Kayser L, Feldt-Rasmussen U, et al. Influence of tumour necrosis factor-alpha, tumour necrosis factor-beta and interferon-gamma, separately and added together with interleukin-1 beta, on the function of cultured human thyroid cells. *J Endocrinol* 1994; 143: 359–365.
28. Wilson PG, Manji M and Neoptolemos JP. Acute pancreatitis as a model of sepsis.

- J Antimicrob Chemother* 1998; 41(Suppl A): 51–63.
29. Hermus RM, Sweep CG, van derMeer MJ, et al. Continuous infusion of interleukin-1 beta induces a nonthyroidal illness syndrome in the rat. *Endocrinology* 1992; 131: 2139–2146.
  30. Kung AW and Lau KS. Interferon-gamma inhibits thyrotropin-induced thyroglobulin gene transcription in cultured human thyrocytes. *J Clin Endocrinol Metab* 1990; 70: 1512–1517.
  31. Jakobs TC, Mentrup B, Schmutzler C, et al. Proinflammatory cytokines inhibit the expression and function of human type I 5'-deiodinase in HepG2 hepatocarcinoma cells. *Eur J Endocrinol* 2002; 146: 559–566.
  32. Wajner SM, Goemann IM, Bueno AL, et al. IL-6 promotes nonthyroidal illness syndrome by blocking thyroxine activation while promoting thyroid hormone inactivation in human cells. *J Clin Invest* 2011; 121: 1834–1845.
  33. Bianchi R, Mariani G, Molea N, et al. Peripheral metabolism of thyroid hormones in man. I. Direct measurement of the conversion rate of thyroxine to 3,5,3'-triiodothyronine (T3) and determination of the peripheral and thyroidal production of T3. *J Clin Endocrinol Metab* 1983; 56: 1152–1163.
  34. Boelen A, Schiphorst MC and Wiersinga WM. Relationship between serum 3,5,3'-triiodothyronine and serum interleukin-8, interleukin-10 or interferon gamma in patients with nonthyroidal illness. *J Endocrinol Invest* 1996; 19: 480–483.
  35. Zargar AH, Ganie MA, Masoodi SR, et al. Prevalence and pattern of sick euthyroid syndrome in acute and chronic non-thyroidal illness—its relationship with severity and outcome of the disorder. *J Assoc Physicians India* 2004; 52: 27–31.
  36. Lum SM, Nicoloff JT, Spencer CA, et al. Peripheral tissue mechanism for maintenance of serum triiodothyronine values in a thyroxine-deficient state in man. *J Clin Invest* 1984; 73: 570–575.
  37. Keller GA, West MA, Cerra FB, et al. Multiple systems organ failure. Modulation of hepatocyte protein synthesis by endotoxin activated Kupffer cells. *Ann Surg* 1985; 201: 87–95.
  38. Hou CT, Rees KR and Shotlander VL. A mechanism of liver necrosis after biliary obstruction in the rat. *J Pathol Bacteriol* 1962; 83: 469–473.
  39. Vigneri R, Papalia D, Pezzino V, et al. Triiodothyronine and thyrotropin-releasing hormone interaction on TSH release in man. *Hormones* 1972; 3: 250–256.
  40. Mebis L and van den Berghe G. The hypothalamus-pituitary-thyroid axis in critical illness. *Neth J Med* 2009; 67: 332–340.
  41. Sasaki S, Kawai K, Honjo Y, et al. Thyroid hormones and lipid metabolism. *Nihon Rinsho* 2006; 64: 2323–2329. [Article in Japanese, English abstract].
  42. Domschke S, Malfertheiner P, Uhl W, et al. Free fatty acids in serum of patients with acute necrotizing or edematous pancreatitis. *Int J Pancreatol* 1993; 13: 105–110.
  43. Sztefko K and Panek J. Serum free fatty acid concentration in patients with acute pancreatitis. *Pancreatology* 2001; 1: 230–236.
  44. Farwell AP. Nonthyroidal illness syndrome. *Curr Opin Endocrinol Diabetes Obes* 2013; 20: 478–484.
  45. Meyer S, Schuetz P, Wieland M, et al. Low triiodothyronine syndrome: a prognostic marker for outcome in sepsis? *Endocrine* 2011; 39: 167–174.
  46. Özcan KS, Osmonov D, Toprak E, et al. Sick euthyroid syndrome is associated with poor prognosis in patients with ST segment elevation myocardial infarction undergoing primary percutaneous intervention. *Cardiol J* 2014; 21: 238–244.