Changes in thyroid hormones in patients undergoing liver transplantation

Department of Anesthesiology and Pain Medicine, Ajou University School of Medicine, Suwon, Korea

Sung-Yong Park, Jong-Yeop Kim, Jin-Soo Kim, Hae-won Joung, Yun-yong Jeong, Gyu-hyun Park, and Sook Young Lee

Background: Critical illness that requires major surgery is often associated with non-thyroidal illness syndrome (NTIS). The characteristic feature of NTIS is low serum triiodothyronine (T3) levels, and in severe illness, the levels of serum thyroxine (T4) are also low in the absence of a rise in thyroid stimulating hormone (TSH). However, little is known about the changes in thyroid hormones during and after liver transplantation (LT). This study was conducted in order to evaluate the intra- or postoperative changes in thyroid hormones.

Methods: Twenty-two patients who underwent LT were enrolled. Serum levels of triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), free T3 (FT3) and free T4 (FT4) were measured immediately after the induction of anesthesia (T1), at the end of the anhepatic period (T2), at the end of the surgical procedure (T3), and at 24 hours (T4) and 120 hours postoperatively (T5).

Results: The mean levels of T3, T4, FT3, FT4 and TSH were significantly decreased throughout the study when compared with the T1 value. The mean levels of T3, T4, FT3 and TSH were below the normal range from T2, T4 and T5.

Conclusions: We suggest that LT may induce NTIS by at least postoperative day 5. In the future, longer follow-up studies, and the effects of thyroid hormones on the prognosis and determination of the advantages and disadvantages of T3 replacement therapy to these patients will be required. (Anesth Pain Med 2015; 10: 214-218)

Key Words: Liver transplantation, Non-thyroidal illness syndrome, Thyroid hormones.

INTRODUCTION

Non-thyroidal illness syndrome (NTIS) is an abnormality of thyroid hormone concentrations without any evidence of coexisting thyroid or pituitary gland disease. NTIS is seen following major surgery and in a variety of illnesses including severe infections, myocardial infarction, starvation and acute liver failure [1-6]. The characteristic feature of this syndrome is a low serum triiodothyronine (T3) level, with the magnitude of these changes being related to the severity and prognosis of disease [4,6]. In severe illness, a low serum thyroxine (T4) level and an inappropriately low normal to subnormal thyroid stimulating hormone (TSH) level may also occur [7-11]. Although the pathogenesis of the NTIS is not fully understood, both central (pituitary and hypothalamic) and peripheral defects have been proposed [7,10], and the most commonly described defect being decreased activity of 5'-deiodination.

Little is known about the changes in thyroid hormones during and after liver transplantation (LT). This study was conducted in order to evaluate the changes in thyroid hormones in patients undergoing LT, during and after the operation up to postoperative day 5.

MATERIALS AND METHODS

Twenty-two patients scheduled for LT between 2009 and 2011 were serially enrolled in the study following approval by the Institutional Review Board of our Hospital. Written informed consent was obtained from the patients or care. Exclusion criteria included a history of hormonal disease, except for diabetes mellitus and reoperation.

Upon arrival in the operating theatre, standard monitoring was applied including 5-lead electrocardiography, pulse oxime-
try and invasive blood pressure monitoring by radial artery cannulation. Patients were anesthetized with intravenous thiopental sodium (4–5 mg/kg) and vecuronium (0.6 mg/kg). After the induction of anesthesia, radial artery (for sampling for the coagulation test) and femoral artery catheterization were carried out. Two introducer catheters (MAC™ Two-lumen Central Venous Access Set; Arrow International, Inc. Reading, PA, USA) and one 7.0 Fr. or 8.5 Fr. peripheral intravenous catheter (Rapid Infusion Catheter, Arrow International Inc., Reading, PA, USA) were inserted for pulmonary artery catheterization (SwanGanz CCOmbo CCO/SvO₂™; Edwards Lifesciences LLC, Irvine, CA, USA), veno-veno bypass (VVB) drain, volume infusion and administration of drugs. Anesthesia was maintained with desflurane (6–7 vol%) and neuromuscular blockade was achieved with continuous infusion of vecuronium (1–2 μg/kg/min).

In all patients, VVB was used during the anhepatic stage. The cannulas were inserted into the femoral and portal vein, diverting their blood flow away from the liver and back to the right side of the heart via 2 large-bore catheters inserted during the induction of anesthesia.

Blood samples were collected for the measurement of serum concentrations of T₃, T₄, TSH, FT₃ and FT₄ immediately after the induction of anesthesia (baseline value, T₁), at the end of the anhepatic periods (T₂), at the end of the surgical procedure (T₃), at 24 hours (T₄) and 120 hours postoperatively (T₅). Serum was separated from the blood by centrifugation and stored at −70°C until assayed. Serum concentrations of hormones were measured using a chemiluminescent immunoassay (ADVIA Centaur, Simens, New York, NY, USA). The reference values were 60–181 ng/dl for total T₃, 4.5–10.9 μg/dl for total T₄, 2.3–4.2 pg/ml for FT₃, 0.8–1.5 μg/dl for FT₄ and 0.35–5.0 μIU/ml for TSH.

Statistical analyses were conducted using PASS 2005 (NCSS, Kaysville, Utah, USA) and SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Sample-size calculation was performed based on the results of a preliminary study under the following assumption: 80% power to detect a 25 ng/dl difference in serum T₃ concentrations at each time when compared with the baseline value, with a standard deviation of 15 ng/dl and an alpha level of 0.05 using a one sample t-test. This generates an estimate of 20 patients and with the assumption of loss, 22 patients were enrolled.

After testing normal distribution, repeated measure analysis of variance (RMANOVA) with Bonferroni’s correction was conducted to compare the thyroid hormone concentrations with each baseline value. Contrast comparisons were performed at each time point. All data are expressed as the number of patients or the mean ± standard deviation. A P value of < 0.05 is considered statistically significant.

RESULTS

Of the 22 patients assessed, 20 patients were enrolled in this present study. Two patients were excluded from the study for loss of data. The demographic characteristics and perioperative data of the patients are shown in Table 1.

All the mean thyroid hormone profiles (T₃, T₄, FT₃, FT₄, TSH) were within the normal range immediately following the induction of anesthesia (baseline value, T₁) (Table 2).

The mean level of T₁ decreased significantly throughout the study when compared with the baseline value (P < 0.05), and was below the normal range at 24 hours (T₄) and 120 hours after the surgery (T₅) (Table 2). The mean level of T₄ decreased significantly throughout the study when compared with the baseline value (P < 0.05), and was below the normal range from the end of the anhepatic phase (T₂, T₃, T₄, T₅) (Table 2). The mean level of FT₃ decreased significantly throughout the study when compared with the baseline value (P < 0.05), and was below the normal range at T₅ (Table 2). The mean level of FT₄ decreased significantly

Table 1. Demographic Characteristics and Perioperative Data

| Age (yr) | 46.0 ± 9.2 |
| Gender (M/F) | 15/5 |
| Height (cm) | 164.9 ± 7.6 |
| Weight (kg) | 63.5 ± 11.4 |
| Diagnosis | |
| Hepatitis B/C cirrhosis | 15/4 |
| Alcoholic cirrhosis | 1 |
| Child class A/B/C | 4/6/10 |
| Cadaveric/LRLT | 4/16 |
| Anesthesia time/Operation time (min) | 835.3 ± 92.4/751.7 ± 109.0 |
| Duration of venovenous bypass (min) | 121.0 ± 24.8 |
| Blood component infused during operation | |
| Packed red blood cell/Fresh frozen plasma (units) | 7.1 ± 5.7/4.2 ± 3.0 |
| Platelet concentration/Cryoprecipitate (units) | 5.7 ± 5.3/1.9 ± 1.9 |
| Exubation time in ICU (h) | 28.6 ± 31.1 |
| ICU days/Hospital days (d) | 7.0 ± 4.8/50.3 ± 30.5 |

Data are the mean ± SD or the number of patients (n = 20). LRLT: living donor related liver transplantation, ICU: intensive care unit.
Table 2. Changes in Serum Thyroid Hormone Concentration

|        | T1       | T2       | T3       | T4       | T5       |
|--------|----------|----------|----------|----------|----------|
| T3 (ng/dl) | 88.8 ± 19.3 | 65.5 ± 17.5* | 62.5 ± 18.8* | 50.5 ± 18.6* | 46.8 ± 13.0* |
| T4 (μg/dl) | 5.9 ± 2.3 | 3.3 ± 1.0* | 2.8 ± 0.8* | 2.6 ± 0.7* | 2.8 ± 0.9* |
| FT3 (pg/ml) | 2.7 ± 0.7 | 2.4 ± 0.6* | 2.4 ± 0.7* | 2.4 ± 0.6* | 2.0 ± 0.5* |
| FT4 (ng/dl) | 1.1 ± 0.2 | 1.0 ± 0.2* | 1.1 ± 0.2 | 0.9 ± 0.2* | 0.8 ± 0.2* |
| TSH (μIU/ml) | 3.7 ± 2.7 | 1.5 ± 1.1* | 1.3 ± 1.0* | 1.1 ± 1.0* | 1.2 ± 1.5* |

Data are the mean ± SD (n = 20). T1: at the time after the induction of anaesthesia, T2: anhepatic phase during the surgery, T3: the time at the end of the surgical procedure, T4: 24 hours after the surgery, T5: 120 hours after the surgery, T3: triiodothyronine (normal range 60–181 ng/dl), T4: thyroxine (normal range 4.5–10.9 ng/dl), FT3: free triiodothyronine (normal range 2.3–4.2 pg/ml), FT4: free thyroxine (normal range 0.8–1.5 ng/dl), TSH: thyroid stimulating hormone (normal range 0.35–5.50 μIU/ml). *P < 0.05 vs T1 value in each variable.

Throughout the study when compared with the baseline value (P < 0.05), except the level of T3 (Table 2). The mean level of TSH decreased significantly throughout the study when compared with the baseline value (P < 0.05) (Table 2).

**DISCUSSION**

Our results show that LT induces NTIS with a decrease in T3, T4, and TSH levels by at least postoperative day 5.

'NTIS' is commonly used to describe the typical changes in thyroid-related hormone concentrations that can arise in the serum following any acute or chronic illness without primary thyroid diseases [8]. The syndrome is characterized by a low serum triiodothyronine (T3) level. In severe and prolonged illness, the level of TSH is low in the presence of a low T3 and T4 [7-10,12]. In our present study, a decline in T3, T4, FT3, FT4 and TSH levels were observed when compared with each baseline value. The mean levels of T3 and T4 show a subnormal range from T3 and T2, with inappropriately low TSH. These findings are compatible to NTIS that have been shown in severe illness.

The mechanism of NTIS is not yet fully understood. However, a wide range of central and peripheral mechanisms are suggested: modifications to the hypothalamic-pituitary axis [5,9,10], altered binding of thyroid hormone to circulating binding proteins [13,14], decreased transport of thyroid hormone across the plasma membrane [15], decrease in peripheral conversion of T4 into T3 by 5’-deiodinases [11,12,16], and changes in thyroid hormone receptor expression or function [7,17].

The thyroid produces T4 and T3 in a ratio of approximately 17 : 1, and the circulating levels of each hormone are also determined by extra-thyroidal conversion of T4 to T3 [11]. In humans, peripheral thyroid hormone metabolism is mediated by the three iodothyronine deiodinases D1, D2, and D3 [8,16]. D1 and D2 (5’-deiodinase) play a key role in the production of serum T3 from T4. D1 also contributes to the breakdown of the metabolite rT3 [8,16]. Conversely, D3 (5'-deiodinase) inactivates both T3 and T4 generating T2 and rT3 respectively [8,16]. The generally accepted main pathophysiology of NTIS is a decreased activity of 5’-deiodinase (hepatic/renal D1 and skeletal muscle D2) and an increased activity of 5-deiodinase (hepatic and skeletal muscle D3) [11,12,16]. As a consequence, plasma T3 decreases and plasma rT3 increases. In our study, the levels of T3 decreased.

As described previously, our findings are compatible with NTIS that have been shown in severe illness. These may be caused by alterations in the set point of the HPT axis [8]. Fliers et al. [10] reported a decrease in thyrotrophin releasing hormone gene expression in the neurons of the hypothalamus, which are required to promote TSH synthesis and are responsible for the set point of the HPS axis in patients with NTIS. In addition, multiple causes such as fasting and cytokines are suggested as possible causes for this change [5,8].

Whether alterations of the central part of the HPT axis precede changes in peripheral thyroid hormone metabolism instead of *vice versa*, or occur simultaneously, is presently unknown. Recently, Boelen et al. [9] reported almost simultaneous involvement of the whole HPT axis in the downregulation of thyroid metabolism during acute illness. In our present study, all of the thyroid hormones significantly decreased from the anhepatic period, which could mean involvement of the central part of HPT axis from the early phase.

In NTIS with severe illness, the concentration of the thyroid hormone-binding proteins often decreases as a consequence of the 'acute phase response', which arises from impaired
synthesis, rapid breakdown, and movement out of the plasma space [13]. Following cardiac bypass surgery, thyroid hormone-binding globulin (TBG) levels may fall as much as 60% in 12 hours [14]. In our current study, all the operations were performed under VVB with a mean operation time of 14 hours. Although, we did not measure the TBG concentration, all of these could be possible players in the induction of NTIS during LT.

Cerillo et al. [1], evaluated the thyroid function at 0, 12, 48, 120 hours and 6 months postoperatively following uncomplicated coronary artery bypass grafting (CABG). They showed that FT3 remained reduced to postoperative day 5, and normalized by 6 months in 87.5% of patients. We evaluated the thyroid function profile in patients undergoing LT and all the thyroid hormonal profiles including FT3 still remained low normal or subnormal by postoperative day 5. In the future, more long-term follow-up studies in patients undergoing LT may be required.

Controversy continues as to whether NTIS requires T3 replacement therapy [18]. Recently, Choi et al. [19] reported a reduction in the number of patients requiring vasopressors with perioperative oral T3 replacement therapy in those that underwent CABG. In the future, prospective trials should be conducted in order to identify whether patients undergoing LT may actually benefit from replacement therapy.

Due to the fact that LT requires a large volume infusion, it is likely that hemodilution was responsible for these observed hormonal changes. However, it has been proven that the measurement of FT3, and FT4 concentrations is not affected by hemodilution [20]. In our current study, the mean levels of FT3 and FT4 decreased during the perioperative period. In addition, the mean levels of thyroid hormones still decreased during postoperative periods, while only a little blood loss and body fluid shift were noted. These findings could indicate that hemodilution is not a major factor affecting thyroid hormone levels.

The two major limitations of our study are: 1) we did not consider many factors in the inclusion criteria of the patients such as the Child class and the kinds of LT (cadaveric or living-related LT) that could affect the levels of thyroid hormones, and 2) the baseline concentrations of thyroid hormones did not reach preoperative levels, therefore the anesthesia itself could induce the decrease of thyroid hormones.

In conclusion, we suggest that LT may induce NTIS, with a decrease in the mean levels of T3, T4, and TSH, by at least postoperative day 5. In the future, longer follow-up studies, and the determination of the advantages and disadvantages of T3 replacement therapy in these patients will be required.

REFERENCES

1. Cerillo AG, Storti S, Mariani M, Kallushi E, Bevilacqua S, Parri MS, et al. The non-thyroidal illness syndrome after coronary artery bypass grafting: a 6-month follow-up study. Clin Chem Lab Med 2005; 43: 289-93.

2. Velissaris T, Tang AT, Wood PJ, Hett DA, Ohi SK. Thyroid function during coronary surgery with and without cardiopulmonary bypass. Eur J Cardiothorac Surg 2009; 36: 148-54.

3. Rodriguez-Perez A, Palos-Paz F, Kaptein E, Visser TJ, Dominguez-Gerpe L, Alvarez-Escudero J, et al. Identification of molecular mechanisms related to nonthyroidal illness syndrome in skeletal muscle and adipose tissue from patients with septic shock. Clin Endocrinol (Oxf) 2008; 68: 821-7.

4. Karga H, Papioannou P, Venetsanou K, Papandroulaki F, Karaloizos L, Papioannou G, et al. The role of cytokines and cortisol in the non-thyroidal illness syndrome following acute myocardial infarction. Eur J Endocrinol 2000; 142: 236-42.

5. Boelen A, Wiersinga WM, Fliers E. Fasting-induced changes in the hypothalamus-pituitary-thyroid axis. Thyroid 2008; 18: 123-9.

6. Kostopanagiotou G, Kalimeris K, Mourouzis I, Costopanagiotou C, Arkadopoulos N, Panagopoulos D, et al. Thyroid hormones alterations during acute liver failure: possible underlying mechanisms and consequences. Endocrine 2009; 36: 198-204.

7. Beigneux AP, Moser AH, Shigenaga JK, Grunfeld C, Feingold KR. Sick euthyroid syndrome is associated with decreased TR expression and DNA binding in mouse liver. Am J Physiol Endocrinol Metab 2003; 284: E228-36.

8. Warner MH, Beckett GJ. Mechanisms behind the non-thyroidal illness syndrome: an update. J Endocrinol 2010; 205: 1-13.

9. Boelen A, Kwikkel J, Thijssen-Timmer DC, Alkemade A, Fliers E, Wiersinga WM. Simultaneous changes in central and peripheral components of the hypothalamus-pituitary-thyroid axis in lipopolysaccharide-induced acute illness in mice. J Endocrinol 2004; 182: 315-23.

10. Fliers E, Guldenaar SE, Wiersinga WM, Swaab DF. Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal illness. J Clin Endocrinol Metab 1997; 82: 4032-6.

11. Peeters RP, Wouters PJ, Kaptein E, van Toor H, Visser TJ, Van den Berghe G. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. J Clin Endocrinol Metab 2003; 88: 3202-11.

12. Peeters RP, van der Geyten S, Wouters PJ, Darras VM, van Toor H, Kaptein E, et al. Tissue thyroid hormone levels in critical illness. J Clin Endocrinol Metab 2005; 90: 6498-507.

13. Jirasakuldech B, Schussler GC, Yap MG, Drew H, Josephson A, Michl J. A characteristic serpin cleavage product of thyroxine-binding globulin appears in sepsis sera. J Clin Endocrinol Metab 2000; 85: 3996-9.
14. Afandi B, Schussler GC, Arafeh AH, Boutros A, Yap MG, Finkelstein A. Selective consumption of thyroxine-binding globulin during cardiac bypass surgery. Metabolism 2000; 49: 270-4.

15. Kaptein EM, Kaptein JS, Chang EI, Egodage PM, Nicoloff JT, Massry SG. Thyroxine transfer and distribution in critical nonthyroidal illnesses, chronic renal failure, and chronic ethanol abuse. J Clin Endocrinol Metab 1987; 65: 606-16.

16. Bianco AC, Kim BW. Deiodinases: implications of the local control of thyroid hormone action. J Clin Invest 2006; 116: 2571-9.

17. Yu J, Koenig RJ. Regulation of hepatocyte thyroxine 5'-deiodinase by T3 and nuclear receptor coactivators as a model of the sick euthyroid syndrome. J Biol Chem 2000; 275: 38296-301.

18. Kaptein EM, Sanchez A, Beale E, Chan LS. Clinical review: Thyroid hormone therapy for postoperative nonthyroidal illnesses: a systematic review and synthesis. J Clin Endocrinol Metab 2010; 95: 4526-34.

19. Choi YS, Kwak YL, Kim JC, Chun DH, Hong SW, Shim JK. Peri-operative oral triiodothyronine replacement therapy to prevent postoperative low triiodothyronine state following valvular heart surgery. Anaesthesia 2009; 64: 871-7.

20. Ekins R. Measurement of free hormones in blood. Endocr Rev 1990; 11: 5-46.