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Non-Thyroidal Illness Syndrome in Primary Hyperparathyroidism

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Abstract

Introduction: Primary Hyperparathyroidism (PHPT) is associated with chronic inflammation and metabolic disorders. Although NTIS is associated with critical illness disorders, the association between NTIS and PHPT has not been investigated. We aimed to investigate the presence of NTIS in PHPT patients.

Methods: The cross-sectional study included thirty-four patients with PHPT and 58 age- and gender-matched controls. Serum free triiodothyronine (T3), free thyroxine (T4), Thyroid-Stimulating Hormone (TSH), high sensitivity C-reactive protein (hs-CRP) was compared between groups.

Results: Serum glucose, insulin, HOMA-IR and lipids were higher in PHPT than in controls ($p<0.05$). Serum TSH value did not differ between PHPT group and control (1.74 ± 0.21 *vs.* 1.89 ± 0.19 μ IU/mL, $p>0.05$). Serum sT3 (2.91± 0.07 *vs.* 2.95 ± 0.08 pg/mL, $p>0.05$) and sT4 (1.0 ± 0.02 *vs.* 1.13 ± 0.02 ng/dL, $p>0.05$) value did not differ between PHPT group and control. NTIS did not observe in both patients with PHPT and controls. hs- CRP was higher in PHPT group than in controls (2.33 ± 037 *vs.* 1.54 ± 0.35 mg/L, $p=0.034$). hs- CRP was positively correlated with iPTH value ($r=0.35$, $p=0.02$).

Conclusion: NTIS response did not represent in PHPT, independent of chronic inflammation (hs-CRP) and metabolic disorders. Although chronic inflammatory state and metabolic disorders is observed in patients with PHPT, NTIS is not associated with PHPT.

Keywords: Hyperparathyroidism; Non-Thyroidal Illness Syndrome; Metabolic Disorders; Inflammation

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Introduction

Primary Hyperparathyroidism (PHPT) is one of the most common endocrine disorders. PHPT is associated with low grade chronic inflammation and cardio metabolic disorders [1]. The changes in metabolism of thyroid hormones apart from the diseases that affect thyroid are known as the Non-Thyroidal Illness Syndrome (NTIS) [2]. NTIS is characterized by low plasma triiodothyronine (T3) and/or low plasma thyroxine (T4), and increased plasma reverse T3 (rT3) concentration with normal range or slightly decreased Thyroid-Stimulating Hormone (TSH) concentration. NTIS represents absence of elevation in TSH despite decreased in plasma thyroid hormone [2-3]. NTIS has been observed in acute and chronic illness such as cardiovascular and gastrointestinal disease, renal insufficiency, infectious disease, cancer, trauma, burns, fasting, bone marrow transplantation and myocardial infarction [4-5]. NTIS occurs in acute phase of disease has been mediated by cytokines. Proinflammatory cytokines such as IL-1β, IL-6, TNF-α and interferon γ inhibit genes involved in thyroid hormone metabolism [6,7]. CRP is regarded as an inflammatory indicator. IL-6 and hs-CRP level was reported to increase in patients with asymptomatic PHPT [1]. Grey et al. [7] found high serum IL-6 level in patients with untreated PHPT compared to controls [8]. Increased in CRP was associated with NTIS, cardiovascular complications, metabolic syndrome and atherosclerosis [9].

Although chronic inflammatory state and cardio metabolic disorder is observed in patients with PHPT, the association between NTIS and Primary Hyperparathyroidism (PHPT) has not been investigated. We aimed to investigate the existence of NTIS in PHPT patients with chronic inflammation and metabolic disorders.

Material and Methods

Thirty four patients with PHPT and 58 age- and sex-matched healthy subjects as a control were included in study. Patients with PHPT treated in Diskapi Training and Research Hospital, Endocrinology and Metabolism, between December 2011 and May 2012. Patients with any chronic diseases such as rheumatoid arthritis, diabetes mellitus, systemic lupus erythematous, hypertension, thyroid diseases, infective diseases, liver or renal diseases were not included in study. The study was approved by the Ethics Committee of our hospital and an informed consent was obtained from all participants prior to the study. Fasting serum glucose, insulin, High-Density Lipoprotein-Cholesterol (HDL-cholesterol), Low-Density Lipoprotein-Cholesterol (LDL-cholesterol), total cholesterol, triglyceride, creatinine, phosphorus, intact Parathyroid Hormone (iPTH), Alkaline Phosphatase (ALP) and high sensitivity C - reactive protein (hs-CRP) were measured. Serum TSH, sT3 and sT4 were measured by using chemiluminescence micro particle immunochemistry (Abbott, Architect i2000, Abbott Laboratories Diagnostic Unit IL, ABD). Anti-thyroid peroxidase antibodies (anti-TPO), anti-thyroglobulin antibodies (anti-TG) were measured by using a competitive chemiluminescent immunoassay (Siemens, Advia centaur XP). Reference limits: sT4 (0.7-1.48 ng/dl), sT3 (1.71-3.71 pg/ml), TSH (0.35-4.94 micro IU/ml), anti-TG (0-60 U/ml), anti-TPO (0-57 U/ml). Anti-TPO and anti-TG concentrations were accepted as positive if they were above 57 IU/ml and 60 IU/ml, respectively. The estimation of insulin resistance was calculated with homeostasis model assessment (HOMA-IR) index (fasting glucose X fasting insulin/405). Serum 25-hydroxy vitamin D (25-OH-VitD, NA >30 ng/ml) was measured by using chemiluminescent immunoassay method (Advia Centaur XP, Siemens Healthcare Diagnostics Inc, Tarrytown ABD).

Statistical Analysis

Statistical analysis was performed using SPSS 18.0 (SPSS, Inc) software. Variables are presented as mean ± Standard Deviation (SD) or median (with inter quartile range), percentages (%). Normality was tested using the Kolmogorov-Smirnov and Shapiro-Wilk W test. The categorical variables were analyzed with the Chi-square test. Mann-Whitney U test was used for continuous variables which were not normally distributed. Student's t test was used for normally distributed continuous variables between two groups. The associations were tested by Pearson and Spearman's correlation coefficients. Statistical significance was defined as a $p<0.05$.

Results

Baseline characteristics of PHPT groups and controls are shown in Table 1. Mean age (51.7 ± 9.1 *vs.* 48.5 ± 6.5 years, $p>0.05$) and female (85 *vs.* 73%, $p>0.05$) did not differ between groups. Serum glucose, insulin and HOMA-IR, lipids, calcium, ALP and iPTH value were higher in PHPT group than in controls ($p<0.05$). Serum phosphorus and 25-OH-vitamin D was lower in PHPT group than in controls ($p<0.05$). Serum TSH value did not differ between PHPT group and control (1.74 ± 0.21 *vs.* 1.89 ± 0.19 μ IU/mL, $p>0.05$). Serum sT3 (2.91 ± 0.07 *vs.* 2.95 ± 0.08 pg/mL, $p>0.05$) and sT4 (1.0 ± 0.02 *vs.* 1.13 ± 0.02 ng/dL, $p>0.05$) value did not differ between PHPT group and control. Percentage of patients with positive anti-TPO and anti-TG did not differ between groups ($p>0.05$). NTIS did not observe in both patients with PHPT and controls. hs- CRP was higher in PHPT group than in controls (2.33 ± 037 *vs.* 1.54 ± 0.35 mg/L, $p=0.034$). hs- CRP was positively correlated with iPTH value ($r=0.35$, $p=0.02$).

Table 1: Characteristics of the patients with PHPT and control.

	PHPT (n=34)	Control (n=58)	P
sT4 (ng/dL)	1.13 ± 0.02	1.0 ± 0.02	0.072
sT3 (pg/mL)	2.95 ± 0.08	2.91 ± 0.07	0.705
TSH (micro IU / ml)	1.74 ± 0.21	1.89 ± 0.19	0.638
Glucose (mg/dl)	92.84 ± 2.47	86.13 ± 2.31	0.061
Creatinine (mg/dl)	0.76 ± 0.03	0.77 ± 0.03	0.825
Calcium (mg/dl)	11.01 ± 0.14	9.37 ± 0.13	<0.001
Phosphorus (mg/dl)	2.71 ± 0.09	3.39 ± 0.08	<0.001
Alkaline phosphatase (mg/dl)	108.66 ± 8.15	74.31 ± 7.87	0.006
Total cholesterol (mg/dl)	295.46 ± 5.66	191.83 ± 4.98	0.038
TG (mg/dl)	241.06 ± 13.89	157.76 ± 12.23	0.024
LDL (mg/dl)	189.52 ± 5.52	116.25 ± 4.79	0.032
HDL (mg/dl)	35.94 ± 2.28	47.04 ± 1.98	0.035
İPTH (pg/ml)	245.58 ± 16.53	60.85 ± 15.46	<0.001
25-OH-vitD (ng/ml)	10.96 ± 3.58	26.21 ± 3.46	0.027
hs-CRP (mg/L)	2.33 ± 0.37	1.54 ± 0.35	0.034
HOMA-IR	3.71 ± 0.39	2.13 ± 0.33	0.017
Anti-TG positive (%)	24	28	0.247
Anti-TPO positive (%)	31	34	0.325

Discussion

This cross-sectional study suggested that NTIS did not represent in PHPT patients, independent of chronic inflammation (hs-CRP) and metabolic disorders, compared to control. NTIS response did not exhibit in patients with PHPT, even in chronic inflammation and metabolic disorder. Chronic inflammatory state and metabolic disorders is observed in patients with PHPT but NTIS is not associated with PHPT.

Present study showed that PHPT was associated with chronic inflammation and cardio metabolic disorders. Hs-CRP was related with iPTH level. Cardio metabolic disorders such as serum glucose, insulin, HOMA-IR and lipids were higher in PHPT group compared to controls. Present study showed NTIS did not represent in PHPT patients, independent of chronic inflammation (hs-CRP) and cardio metabolic disorders. NTIS response did not exhibit in patients with PHPT, even in chronic inflammation and cardio metabolic disorders. Several studies reported that PHPT is associated with chronic inflammation [1,10]. Emam AA et al. [1] showed increased in hs-CRP and IL-6 level in patients with asymptomatic PHPT [1]. NTIS has been observed in acute and chronic illness such as cardiovascular and gastrointestinal disease, renal insufficiency, infectious disease, cancer, trauma, burns, fasting, bone marrow transplantation and myocardial infarction [4,5,11,12]. Decrease in serum T3 and T4 concentration as the severity of disorders and prognosis [3]. NTIS is mediated by cytokines [13]. Proinflammatory cytokines such as IL-1β, IL-6, TNF-α and interferon γ inhibit genes involved in thyroid hormone metabolism [9,11]. Experimental studies have shown that cytokines inhibit the conversion of T4-T3 during NTIS [14]. Proinflamatory cytokines effect on decreasing activity of D1 enzyme [13]. CRP shows systemic inflammation and atherosclerosis [14]. Increased in CRP was related with NTIS, cardiovascular complications, metabolic syndrome and atherosclerosis [9,14]. Martocchia et al. [9] reported

to increase in CRP resulting in impaired conversion of free T4 to T3 [9]. NTIS is acute phase response to systemic illness and calorie restriction. Absence of elevated TSH reflects a major change in negative feedback mechanism of Hypothalamic-Pituitary-Thyroid (HPT) axis. NTIS is associated with suppression of hypothalamic Thyrotropin-Releasing Hormone (TRH) and reducing secretion of TSH despite decreased in plasma thyroid hormone [3-4]. NTIS includes change in the central regulation of the thyroid axis such as decrease in TSH pulsatilite [3]. Central down regulation of the HPT axis at the hypothalamus and pituitary in NTIS correlates with TRH mRNA expression in the hypothalamic para ventricular nucleus [15]. Thyroid hormone Receptor (TR) β alters in thyroid hormone negative feedback at both hypothalamus and anterior pituitary [3]. NTIS represents alterations in thyroid hormone metabolism enzymes such as deiodinases type 1 (D1), type 2 (D2) and type 3 (D3) [12]. Furthermore, NTIS induces changes in thyroid hormone receptors (TRα and TRβ) and thyroid hormone transporters [3]. The reduction in conversion of extra thyroidal T4 to T3 is considered as main underlying mechanism [4-5]. Peripheral change in thyroid axis including change in concentrations of thyroid hormone binding proteins and transporters, thyroid hormone deiodinases activity and thyroid hormone receptor expression have been observed. D2 enzyme up regulation increases local conservation of T4 into T3 and decreases TRH mRNA expression at hypothalamus [3,4]. Inflammation during NTIS inhibits TRH neurons via hypothalamic down regulation of HPT axis [3]. NTIS occurs in acute phase of disease has been mediated by cytokines. Induction of cytokines, activation of inflammatory signaling pathways such as nuclear factor kappa-light-chain-enhancer of activated B cells (NFkβ) at acute phase of disease [16].

During acute stress or critical illness-induced alterations within thyroid axis occur in the first days of critical illness. Acute change is characterized by alterations in peripheral thyroid hormone uptake, thyroid hormone binding and change in activity and expression of type-1 and type-3 deiodinases [4]. Acute alterations have observed in nutrient restriction and represents adaptive and beneficial. NTIS in prolonged phase of critical disease has observed in patients on intensive medical care for weeks or months that are fully fed. Hypothalamic TRH expression, TSH secretion, and thyroidal hormone release are decreased during prolonged critical illness [4]. Up regulation of type-2 deiodinase, increased in receptor sensitivity and increased in mono carboxylated transporters expression has observed in prolonged critical illness with adequate nutrition support [4]. This tissue response is suggested to a compensatory mechanism to low thyroid hormone availability [4].

Cross-sectional study showed that NTIS did not exhibit in PHPT patients, independent of chronic inflammation (hs-CRP) and cardio metabolic disorders. NTIS response did not represent in patients with PHPT, even in chronic inflammation and cardio metabolic disorders. Although chronic inflammatory state and metabolic disorders is observed in patients with PHPT, NTIS is not associated with PHPT. Randomized controlled trials should investigate the existence of NTIS in acute alterations and prolonged phase of critically ill patients.

References

1. Emam AA, Mousa SG, Ahmed KY, Al-Azab AA. Inflammatory biomarkers in patients with asymptomatic primary hyperparathyroidism. Med Princ Pract. 2012;21(3):249-53.
2. Docter R, Krenning EP, de Jong M, Hennemann G. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism. Clin Endocrinol (Oxf). 1993;39(5):499-518.
3. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. Lancet Diabetes Endocrinol. 2015;3(10):816-825.
4. Farwell AP. Nonthyroidal illness syndrome. Curr Opin Endocrinol Diabetes Obes. 2013;20(5):478-84.
5. Sato K, Satoh T, Shizume K, Ozawa M, Han DC, Imamura H, et al. Inhibition of 125I organification and thyroid hormone release by interleukin-1, tumor necrosis factor-alpha, and interferon-gamma in human thyrocytes in suspension culture. J Clin Endocrinol Metab. 1990;70(6):1735-43.
6. Tang KT, Braverman LE, DeVito WJ. Tumor necrosis factor-alpha and interferon-gamma modulate gene expression of type I 5'-deiodinase, thyroid peroxidase, and thyroglobulin in FRTL-5 rat thyroid cells. Endocrinology. 1995;136(3):881-8.
7. Grey A, Mitnick MA, Shapses S, Ellison A, Gundberg C, Insogna K. Circulating levels of interleukin-6 and tumor necrosis factor-alpha are elevated in primary hyperparathyroidism and correlate with markers of bone resorption--a clinical research center study. J Clin Endocrinol Metab. 1996;81(10):3450-4.
8. Martocchia A, Cola S, Frugoni P, Indiano I, D'Urso R, Falaschi P. The burden of comorbidity and the C-reactive protein levels in nonthyroidal illness syndrome with metabolic syndrome and atherosclerosis-related cardiovascular complications. Ann N Y Aca Sci. 2010;1193:164-6.
9. Bilezikian JP, Khan AA, Potts JT; Third International Workshop on the Management of Asymptomatic Primary Hyperthyroidism. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. J Clin Endocrinol Metab. 2009;94(2):335-9.
10. Golombek SG. Nonthyroidal illness syndrome and euthyroid sick syndrome in intensive care patients. Semin Perinatol. 2008;32(6):413-8.
11. Lechan RM. The dilemma of the nonthyroidal illness syndrome. Acta Bio-Medica Atenei Parm 2008;79(3):165-71.
12. Yu J, Ronald JK. Regulation of hepatocyte thyroxine 5′-deiodinase by T3 and nuclear receptor coactivators as a model of the sick euthyroid syndrome. J Biol Chema. 2000;275(49):38296-301.
13. Venugopal SK, Devaraj S, Yuhanna I, Shaul P, Jialal I. Demonstration that C-reactive protein decreases eNOS expression and bioactivity in human aortic endothelial cells. Circulation. 2002;106(12):1439-41.
14. 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(12):4032-6.
15. Nagaya T, Fujieda M, Otsuka G, Yang JP, Okamoto T, Seo H. A potential role of activated NF-κB in the pathogenesis of euthyroid sick syndrome. J Clin Invest. 2000;106(3):393-402.
16. Kwakkel J, Wiersinga WM, Boelen A. Differential involvement of nuclear factor-kappaB and activator protein-1 pathways in the interleukin-1beta-mediated decrease of deiodinase type 1 and thyroid hormone receptor beta1 mRNA. J Endocrinol. 2006;189*(1):37-44.