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Effects of sex steroid hormones, thyroid hormone levels, and insulin regulation on thyrotoxic periodic paralysis in Chinese men

Wang Li,
Department of Endocrinology and Metabolism, Xijing Hospital, The Fourth Military Medical University, Xi'an Shaanxi 710032, China

Chen Changsheng,
Department of Health Statistics, The Fourth Military Medical University, Xi'an Shaanxi 710032, China

Fu Jiangfang,
Department of Endocrinology and Metabolism, Xijing Hospital, The Fourth Military Medical University, Xi'an Shaanxi 710032, China

Gao Bin,
Department of Endocrinology and Metabolism, Xijing Hospital, The Fourth Military Medical University, Xi'an Shaanxi 710032, China

Zhang Nanyan,
Department of Endocrinology and Metabolism, Xijing Hospital, The Fourth Military Medical University, Xi'an Shaanxi 710032, China

Li Xiaomiao,
Department of Endocrinology and Metabolism, Xijing Hospital, The Fourth Military Medical University, Xi'an Shaanxi 710032, China

Li Deqiang,
Department of Endocrinology and Metabolism, Xijing Hospital, The Fourth Military Medical University, Xi'an Shaanxi 710032, China

Xing Ying,
Department of Endocrinology and Metabolism, Xijing Hospital, The Fourth Military Medical University, Xi'an Shaanxi 710032, China

Zai Wensong, and
Department of Endocrinology and Metabolism, Xijing Hospital, The Fourth Military Medical University, Xi'an Shaanxi 710032, China

Ji Qiuhe
Department of Endocrinology and Metabolism, Xijing Hospital, The Fourth Military Medical University, Xi'an Shaanxi 710032, China

Correspondence to: Ji Qiuhe.

Conflict of interest We declare that we have no competing financial interests.

Abstract

Our study is to determine the expression of thyroid hormone, sex hormone, insulin, and C-peptide in Chinese male patients with thyrotoxic periodic paralysis (TPP). This study covered 102 patients with hyperthyroidism from Xijing Hospital. According to whether occurrence of TPP or not, patients were divided into two groups (those that were hyperthyroid with and without TPP) that were, matched with age, blood pressure, urea, and creatinine. We found the body mass index (BMI) in patients with TPP was higher than that in pure hyperthyroidism patients. The levels of the total thyroxine (T4), free triiodothyronine (FT3), and free thyroxine (FT4) were significantly lower in patients with TPP compared with pure hyperthyroidism patients, while serum testosterone levels were higher compared with pure hyperthyroidism patients. Moreover, after glucose administration, the concentration of insulin at 60, 120, and 180 min were significantly higher in patients with TPP than those in pure hyperthyroidism patients. The insulin area under the curve (AUC) was significantly increased in patients with TPP compared with pure hyperthyroidism patients. The levels of thyroid hormone, sex hormone, and insulin were different in Chinese male patients with TPP compared to those with only hyperthyroidism.

Keywords

Thyrotoxic periodic paralysis; Thyroid hormones; Chinese men; Hyperthyroidism insulin; Tesosterone

Introduction

Thyrotoxic periodic paralysis (TPP) is a serious complication of hyperthyroidism. TPP was once rare in Caucasians [1, 2] but is becoming more common with Asians such as Chinese, Japanese, Vietnamese, Filipinos, and Koreans. Thyrotoxic paralysis is 10 times more likely to occur in Asian populations than in non-Asians. An early study reported that the rate of hyperthyroidism associated with periodic paralysis in Chinese and Japanese was about 2% [3]. In Chinese, TPP occurs in 13–14% of hyperthyroid patients [4]. Although hyperthyroidism occurs mainly in the women, TPP has a predilection for males (the ratio between male and female from 20:1 to 70:1) [4–6], and usually occurs in patients between 20 and 30 years of age [7]. At present, it is not known why TPP shows these race and sex differences. One possible reason for racial distribution is related to the different subtypes of HLA antigens. HLA-DRw85 in Japanese, A2BW22/AWI9B 17 in Singapore Chinese, and HLA-B5/Bw46 in Chinese people of Hong Kong are the susceptibility genes [8]. HLA-B51 is the susceptibility gene in Chinese population [9].

The activity of Na^+–K^+-ATPase pumps is significantly increased in patients with TPP relative to that in the euthyroid population or of simple hyperthyroidism patients [10]. The thyroid hormones can activate the Na^+/K^+-ATPase directly. The Na^+/K^+-ATPase showed an exaggerated responsiveness to stimulation with adrenaline in patients with TPP, which elevated entry of K^+ and might be responsible for hypokalemia. Episodes of TPP usually begin after the intake of a high-sugar diet, so most studies had hypothesized that the intake of high-sugar diet contributed to the etiology. In these patients after glucose loading, islet β-cell function was enhanced and insulin level was increased, this is accompanied by an

increase in catecholamine-mediated K^+ influx and a decrease in extracellular levels of K^+ [10–12]. In TPP patients, the gender difference was obvious, and it cannot be explained by the difference in insulin levels.

Increased entry of potassium could result in clinical muscle weakness and hypokalemia. The distal muscles are more commonly involved than the proximal muscle. The involvement may be from mild muscle weakness to complete paralysis, but the sensory function in patients is not affected. Involvement may be asymmetrical. The respiratory muscle and bulbar controlled muscle involved in severe attack may result in breathing difficulty or even be life-threatening. Therefore, early diagnosis and effective treatment is very necessary.

In the present study, we determined the body mass index (BMI), and levels of serum thyroid hormones, sex hormones, and insulin levels at different points during a glucose tolerance test, as well as C-peptide levels in 51 Chinese male patients with TPP. Controls included 51 hyperthyroid patients without TPP.

Results

General information

There were no significant differences of age, systolic blood pressure (SBP), diastolic blood pressure (DBP), blood urea nitrogen (BUN), and creatinine (Cr) between the two groups. The BMI in patients with TPP was higher than that in hyperthyroid patients without TPP (Table 1).

Thyroid function

There was no significant difference of serum total triiodothyronine (T3), reverse triiodothyronine (rT3), thyroglobulin antibody (Tg), and thyromicrosome antibodies (Tm) between the two groups. While the total thyroxine (T4), free triiodothyronine (FT3), and free thyroxine (FT4) levels in group 2 were lower than those in group 1 (Table 2).

Expression of sex hormones

There was no significant difference of follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol (E2), and progesterone (P) between the two groups. The testosterone (T) level in group 2 was higher than that in group 1 (Table 3).

Expression of glucose, insulin, and C-peptide

No significant differences were apparent in the blood glucose levels at different time points between the two groups. The serum insulin levels were significantly higher at 60, 120, and 180 min in group 2 relative to those of group 1. There was no significant difference in C-peptide between the two groups (Table 4).

The homeostasis model assessment for insulin resistance (HOMA-IR) and insulin area under the curve (AUC)

The insulin area under the curve (AUC) was significantly higher in group 2 than that of group 1, while no significant differences were apparent in the homeostasis model assessment for insulin resistance (HOMA-IR) between the two groups (Fig. 1).

Discussion

Many causes resulting in hyperthyroidism could lead to TPP, including Graves's disease, nodular goiter with hyperthyroidism, iodine-induced hyperthyroidism, excessive thyroxine supplements, or a single thyroid adenoma [13, 14]. The most common cause of TPP is Graves's disease. One hundred and two Chinese male patients with hyperthyroidism were selected in this study. According to whether occurrence of TPP or not, patients were divided into two groups, matched for age, blood pressure, urea, and creatinine. Our results indicated that levels of T4, FT3, and FT4 in male patients with TPP were significantly lower than those in hyperthyroidism patients without TPP. A clinical study had revealed that the symptoms of TPP would be relieved after control of hyperthyroidism [15]. Thyroid hormone can stimulate Na^+/K^+-ATPase expression in skeletal muscle [16]. Moreover, excessive thyroxine supplement in a hypopituitarism patient after surgical treatment of craniopharyngioma could lead to periodic paralysis [17], indicating that high thyroid hormone levels can lead to TPP.

Our data showed that the thyroid hormone levels were lower in patients with TPP than those in the simple hyperthyroidism patients. According to the phenomenon we presume that periodic paralysis may occur in the early stage of hyperthyroidism, even before hyperthyroidism appearance. Therefore, the patients with TPP would see a doctor in early stage, while the patient without periodic paralysis would be diagnosed after the hyperthyroidism symptoms was serious. Our data also showed that after hyperthyroidism appeared, the higher thyroid hormone level is not necessary for high incidence of periodic paralysis.

Thyroid function is regulated by hypothalamus–pituitary-thyroid axis. In hyperthyroidism, the excessive amount of thyroid hormones acted on tissue, causing a range of pathological and physiological changes, and then feedback inhibition of pituitary gonadotropin secretion, affecting the function of pituitary–gonadal axis. The study reported that the serum testosterone levels in hyperthyroid patients were significantly higher compared with normal controls, the increase of testosterone was considered to be beneficial to compensation and recovery of heart function for men with hyperthyroidism [18].

Our study found that serum testosterone levels in patients with TPP were higher than that in pure hyperthyroidism patients. The further increase in androgen levels increased Na^+/K^+-ATPase activity, resulting in an intracellular accumulation of K^+ [19]. This may be one of the reasons leading to TPP. Further study is necessary to explore whether the increase in androgen levels result the incidence differences between men and women.

Our results also showed that BMI in patients with TPP was higher than that in pure hyperthyroidism patients, the average BMI >24. This suggested most of the patients with TPP were not thin people. Previous study had pointed out that the excessive thyroid hormone can enhance the sensitivity of muscle cells to insulin and increase synthesis and activity of cell membrane Na^+/K^+-ATPase. Hyperinsulinemia can become increasingly dangerous as serum potassium levels continue to decrease due to intracellular sequestration, leading to paralysis [15]. Many studies have confirmed that in patients with hyperthyroidism, there was insulin resistance [20] and glucose-stimulated insulin secretion deficiency [21]. We observed serum insulin and C-peptide levels in two groups after glucose administration. The results showed that the insulin secretion in both two groups reached the peak at 120 min after glucose administration. However, the peak in normal people was at 60 min. The results indicated insulin secretion could be delayed in hyperthyroidism patients. No significant differences were apparent in fasting concentration of insulin between the two groups, while the concentration of insulin at 60, 120, and 180 min were significantly higher in patients with TPP than those in pure hyperthyroidism patients. The insulin AUC was significantly increased in patients with TPP compared with pure hyperthyroidism patients, which noted there were hyperinsulinemia and insulin resistance in patients with TPP.

Our results also showed that there were no differences in serum C-peptide levels in the two groups. The serum insulin we measured included proinsulin (PI) and true insulin (TI). Proinsulin was metabolized in the body, resolving into insulin and C-peptide. In our results, insulin levels were increased, while no significant change in the level of C peptide in the patients with TPP. It’s mechanism in periodic paralysis need to be further clarified.

In summary, the clinical features of TPP in Chinese men included more severe insulin resistance and increased levels of testosterone compared with pure hyperthyroidism patients. The thyroid hormone levels were lower in patients with TPP than those in the simple hyperthyroidism patients. The results showed that there were differences of BMI, insulin levels, and sex hormone levels in patients with TPP compared with pure hyperthyroidism patients. Further studies will determine the mechanism responsible for these differences.

Materials and methods

Subjects

The study was performed in Chinese male patients with hyperthyroidism, the ages between 21 and 50, who had been consented to participate in the study. Outpatients and inpatients with diagnosed hyperthyroidism in Xijing Hospital were examined between January 2003 and June 2008. The ethics committee of the Xijing Hospital of the Fourth Military Medical University approved the study protocol. The patients were divided into two groups according to whether occurrence of periodic paralysis or not, matching with age, blood pressure, urea, and creatinine (Table 1). Group 1 is 51 patients with simple hyperthyroidism. Group 2 consisted of 51 patients with TPP. Inclusion criteria were: (1) the diagnosis of hyperthyroidism was based on nuclear medicine diagnostic criteria of Xijing Hospital; (2) the blood was taken before using any anti-thyroxine therapy for newly diagnosed patients; (3) for relapsed patients, without taking any anti-thyroid drugs 1 year. The exclusion criteria were: (1) the patients with history of heart failure and myocardial infarction, fever, or

nephropathy and other complications, serum creatinine level <133 μmol/l; (2) using lipid-lowering drug, antidiabetic drug, diuretic, or ACEI antihypertensive drug in 3 days before taking blood; (3) potassium supplement in 1 day before taking blood; (4) age above 50 years. Before examination, the patients with TPP received intravenous or oral potassium supplement, and serum potassium reached normal levels in stable condition, and the symptoms of periodic paralysis had disappeared.

Methods

Blood was drawn after 10 h fasting. The sex hormone levels were detected by radioimmunoassay, using RIA kit (Tianjin Concord Biotechnology Company) and γ-counter with 16 detectors (U.S. Capintec Company). The blood urea nitrogen (BUN), creatinine (Cr), and serum potassium (Potassium) were determined by the Hitachi 7600 automatic biochemical analyzer. Oral glucose tolerance test (OGTT) was performed at the same time. The patients were administered with a glucose solution (75 g/200 ml), and blood samples were collected at 0 and 60, 120 and 180 min, respectively, after glucose administration for glucose and insulin determination. Blood glucose concentrations were evaluated by the Hitachi 7600 automatic biochemical analyzer. The insulin levels were measured by Insulin RIA kit (Tianjin Concord Biotechnology Company).

Statistical analysis

All statistical analysis was performed using SPSS 11.0 software. Each value is presented as the mean ± SE. A probability value of <0.05 was considered to be statistically significant. The general information, thyroid function and sex hormone index of two groups were evaluated using *t*-test. The changes of glucose, insulin, and C-peptide were assessed by Repeated Measure ANOVA.

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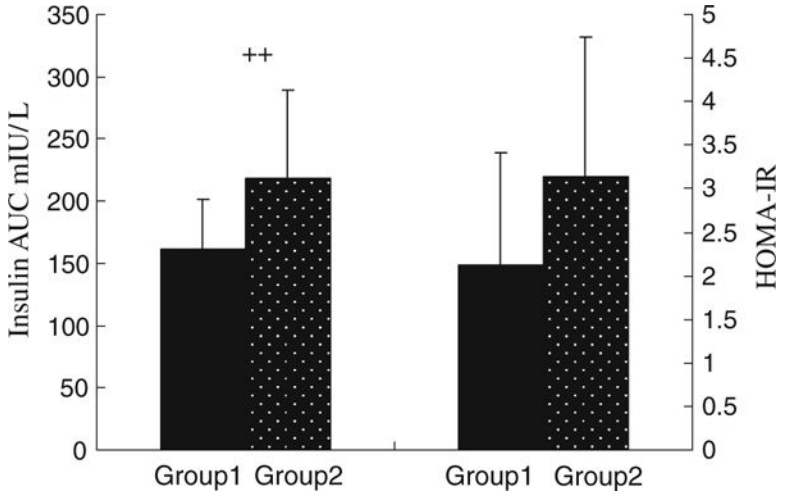

Fig. 1.

The homeostasis model assessment for insulin resistance (HOMA-IR) and insulin area under the curve. ++ versus group 1, differences were considered significant for $P < 0.05$

Table 1

The general information of the patients

	Group1 (*N* = 51)	Group2 (*N* = 51)	Normal values
Age (year)	35.3 ± 12.5	34.1 ± 10.6	–
Systolic blood pressure (mmHg)	127 ± 5.7	126 ± 4.5	90–139
Diastolic blood pressure (mmHg)	75 ± 11	77 ± 12	60–89
BUN (mmmol/l)	3.93 ± 0.91	4.15 ± 1.06	2.8–7.2
Cr (μmmol/l)	82.1 ± 10.92	78.6 ± 12.01	53–125
Serum potassium (mmmol/l)	3.84 ± 0.28	3.81 ± 0.51	3.5–5.5
BMI (kg/m^2)	20.51 ± 3.9	24.25 ± 3.1 *	18.5–23.9

* Versus group 1. Differences were considered significant for $P < 0.01$. *BUN* blood urea nitrogen, *Cr* creatinine, *BMI* the body mass index

Table 2

The thyroid function index in two groups

	Group1 (*N* = 51)	Group2 (*N* = 51)	Normal values
T_3 (ng/ml)	4.07 ± 1.77	2.95 ± 1.25	0.8–2.0
T_4 (ug/dl)	218.7 ± 61.9	168.0 ± 59.0 $^{+}$	57–135
TSH (uIU/ml)	0.04 ± 0.037	0.31 ± 0.56 *	0.20–7.0
FT_3 (pmmol/l)	38.52 ± 18.10	19.74 ± 8.90 $^{+}$	2.8–10.4
FT_4 (pmmol/l)	100.44 ± 46.96	41.53 ± 27.26 *	9.9–24.2
rT_3 (nmol/l)	2.71 ± 1.45	1.95 ± 1.55	0.5–1.5
Tg (%)	21.58 ± 12.10	29.24 ± 16.58	<15
Tm (%)	25.75 ± 13.37	32.95 ± 16.79	<12

*Versus group 1, differences were considered significant for $P < 0.01$,

$^{+}$versus group 1, differences were considered significant for $P < 0.05$.

T3 total triiodothyronine, *rT3* reverse triiodothyronine, *Tg* thyroglobulin antibody, *Tm* thyromicrosome antibodies, *T4* the total thyroxine, *FT3* free triiodothyronine, *FT4* free thyroxine

Table 3

The sex hormones expression in two groups ($n = 51$, $\overline{x} \pm s$)

	Group1 (*N* = 51)	Group2 (*N* = 51)
FSH (mIU/ml)	9.97 ± 4.42	9.18 ± 3.46
LH (mIU/ml)	11.05 ± 5.49	9.60 ± 4.66
PRL (ng/ml)	13.18 ± 5.15	15.8 ± 5.48
E_2 (pg/ml)	44.43 ± 20.07	37.05 ± 15.16
P (ng/ml)	0.61 ± 0.23	0.75 ± 0.27
T (ng/dl)	509 ± 228	850 ± 263[+]

[+]Versus group 1, differences were considered significant for $P < 0.05$.

FSH follicle stimulating hormone, *LH* luteinizing hormone, *PRL* prolactin, *E2* estradiol, *P* progesterone, *T* the testosterone

Table 4

Expression of glucose, insulin and C-peptide in two groups ($n = 51$, $\overline{x} \pm s$)

	Time (min)			
	0	**60**	**120**	**180**
Glucose(mmol/l)				
Group1	4.12 ± 0.71	8.88 ± 2.02	8.69 ± 3.02	6.37 ± 1.43
Group2	4.73 ± 1.02	9.81 ± 3.75	9.43 ± 3.33	6.88 ± 1.82
Insulin (mIU/l)				
Group1	14.52 ± 6.99	67.57 ± 24.5	70.29 ± 18.7	32.83 ± 10.6
Group2	14.94 ± 7.56	89.31 ± 26.6 $^{+}$	93.17 ± 35.6 $^{+}$	57.42 ± 29.3 *
C-peptide (mIU/l)				
Group1	2.12 ± 0.73	7.23 ± 3.88	9.08 ± 2.75	6.39 ± 2.42
Group2	1.87 ± 0.79	6.43 ± 2.59	8.79 ± 1.85	6.71 ± 2.67

*Versus group 1, differences were considered significant for $P < 0.01$,

$^{+}$versus group 1, differences were considered significant for $P < 0.05$