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Original Article

Levothyroxine treatment restored the decreased circulating fibroblast growth factor 21 levels in patients with hypothyroidism

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ABSTRACT

Background and aims: Fibroblast growth factor 21 (FGF21) is an important endogenous regulator of energy metabolism. Thyroid hormone has been shown to regulate hepatic FGF21 expression in rodents. The goal of this study was to evaluate the plasma FGF21 levels in participants with normal thyroid function, subclinical hypothyroidism, or overt hypothyroidism and to investigate the change of plasma FGF21 levels in patients with overt hypothyroidism after levothyroxine treatment.

Methods: A total of 473 drug-naive participants were recruited, including 250 healthy control subjects, 116 patients with subclinical hypothyroidism, and 107 patients with overt hypothyroidism. Thirty-eight patients with overt hypothyroidism were assigned to receive levothyroxine treatment.

Results: The overt hypothyroidism group had decreased FGF21 levels compared with the control and subclinical hypothyroidism groups ($P < 0.01$). Levothyroxine treatment markedly attenuated the increased circulating levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), high-sensitivity C-reactive protein (hsCRP), and homeostasis model assessment index of insulin resistance (HOMA-IR) in patients with overt hypothyroidism. A significant increase in plasma FGF21 levels was observed after levothyroxine treatment ($P < 0.01$). The change in FGF21 levels was correlated with the increase of FT3 and FT4 after levothyroxine treatment (FT3: $r = 0.44$; FT4: $r = 0.53$; all $P < 0.05$).

Conclusions: Levothyroxine treatment ameliorated metabolic disorders and restored the decreased circulating FGF21 levels in patients with overt hypothyroidism. The increase in FGF21 levels after levothyroxine treatment might be partly associated with the amelioration of metabolic disorders in patients with hypothyroidism.

1. Introduction

Thyroid hormone is a pivotal regulator of glucose-lipid metabolism and energy homeostasis by interacting with the nuclear receptors in various tissues [1,2]. Our previous study was consistent with others and showed that hypothyroid patients had obvious insulin resistance and abnormal blood lipid profiles [3–5]. Fibroblast growth factor 21 (FGF21) is a member of the FGF super family, and endogenic FGF21 is predominantly released from hepatocytes [6]. FGF21 has been considered as an important endogenous regulator for glucose-lipid metabolism [6–8]. Both administration and transgenic overexpression of FGF21 protect animal models from diet-induced obesity and metabolic disorders [7,8]. Recently, some rodent studies have shown that thyroid hormone regulates FGF21 expression in the liver and adipose tissue; however, until now, few reports regarding the correlation of thyroid function and FGF21 levels in humans have been generated [9]. Our present study aimed to evaluate the plasma FGF21 levels in participants with normal thyroid function, subclinical hypothyroidism, or overt hypothyroidism and to investigate the change of plasma FGF21 levels in patients with overt hypothyroidism after levothyroxine treatment.

2. Materials and methods

2.1. Study design and participants

Between January 2013 and March 2014, a total of 223 drug-naïve patients, including 107 patients with overt hypothyroidism and 116 patients with subclinical hypothyroidism, were recruited from outpatients attending the Endocrinology Department of Beijing Chao-yang Hospital affiliated with Capital Medical University. Additionally, 250 healthy individuals who had undergone a routine physical examination were enrolled as the healthy control group. Free T3 (FT3), free T4 (FT4), TSH, anti-peroxidase, and anti-thyroglobulin antibody levels were measured in all participants. Meanwhile, all participants received a thyroid-echographic examination. We defined the healthy control subjects through the following criteria: the serum levels of TSH, FT4, and FT3 were in the normal ranges (TSH: 0.350–4.940 mIU/L; FT4: 9.10–19.24 pmol/L; FT3: 2.63–5.71 pmol/L) ; both anti-peroxidase and anti-thyroglobulin antibodies were negative; and the thyroid-echographic examination was normal. Overt hypothyroidism was

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diagnosed as increased serum TSH level with decreased FT4 level, and subclinical hypothyroidism was diagnosed as increased serum TSH level with normal FT4 level. The etiology of all patients was Hashimoto's thyroiditis diagnosed by diffuse hypoechogenicity and elevated plasma anti-peroxidase and/or anti-thyroglobulin antibodies. Subjects had a negative history of cardiovascular disease, hypertension, diabetes or pre-diabetes, liver and renal function impairment, systemic inflammatory disease, or cancer. Subjects were not taking lipid-lowering agents. The protocol was approved by the Ethics Committee of Beijing Chao-yang Hospital affiliated with Capital Medical University. Prior to the study, a written informed consent was obtained from all participants.

2.2. Interventional studies

In the overt hypothyroidism group, all patients received levothyroxine treatments starting with 50 μg/d. For better compliance and a higher follow-up rate, 38 patients who were long-term residents in the Beijing Chaoyang district were chosen to join the follow-up study. The serum levels of FT4, FT3, and TSH were measured every 4 weeks for dose adjustment. The euthyroid state was defined as the serum FT4, FT3, and TSH levels within their respective normal ranges (TSH: 0.350–4.940 mIU/L; FT4: 9.10–19.24 pmol/L; FT3: 2.63–5.71 pmol/L). An increment of 25 ug was made until the euthyroid state was achieved. These 38 patients with overt hypothyroidism were followed for 3 months after the euthyroid state was achieved (Fig. 1). No dietary recommendations were given. All participants gave the informed written consent about the side effects of levothyroxine replacement treatment at the onset of interventional studies.

2.3. Clinical tests

A standard questionnaire was used to collect the information about health status and medications. Blood samples were obtained after an overnight fast and stored at −80°C. Fasting blood glucose (FBG), fasting insulin (FINS), FT3, FT4, TSH, and high-sensitivity C-reactive protein (hsCRP) were measured at the central chemistry laboratory in Beijing Chao-yang Hospital affiliated with Capital Medical University. Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglyceride (TG) levels were measured by colorimetric enzymatic assays with an autoanalyzer (Hitachi 7170). The plasma concentrations of FGF21 were determined using ELISA according to the manufacturer's protocols (Millipore, USA). The intra- and inter-assay variations were 3.9% and 10.9%, respectively. Homeostasis model assessment index of insulin resistance (HOMA-IR) and β cell function (HOMA-β) were calculated [10,11]. In the levothyroxine replacement treatment group, these measurements were repeated at 3 months after the euthyroid state was achieved.

2.4. Statistical analysis

Data were analyzed by SPSS 15.0 (SPSS, Inc, Chicago, IL). Continuous data were expressed as the means ± SD. Because TG, FINS, HOMA-IR, HOMA-β, hsCRP, TSH, and FGF21 did not have a normal distribution, they were expressed as medians with upper and lower quartiles. After log transformation, TG, FINS, HOMA-IR, HOMA-β, hsCRP, TSH, and FGF21 were fitted to a normal distribution. The differences between groups were analyzed using ANOVA or the chi-square test. Changes in parameters from baseline values within a group were evaluated using a two-tailed paired t-test. We also used Pearson, Spearman, and multivariate stepwise regression analysis. All statistical tests are two-tailed, with $P < 0.05$ considered significant.

3. Results

3.1. Baseline characteristics of control subjects and patients with subclinical and overt hypothyroidism

The baseline characteristics of all participants are listed in Table 1. The mean ages were 50.0 ± 12.8, 46.7 ± 15.3, and 44.8 ± 15.2 years in the control, subclinical, and overt hypothyroidism groups, respectively. There was no significant difference in gender, BMI, TG, FBG, and HOMA-β among the three groups. A significant trend was observed for TC, HDL-C, LDL-C, FINS, HOMA-IR, hsCRP, FT3, FT4, TSH, and FGF21 among all groups (TC, HDL-C, LDL-C, HOMA-IR, FT3, FT4, TSH, and FGF21: $P < 0.01$; FINS and hsCRP: $P < 0.05$; Fig. 2). We next performed post hoc analysis and found that, except for TSH and FGF21, these differences were significant only when comparing the overt hypothyroidism group with the control and subclinical hypothyroidism groups. Patients with overt hypothyroidism had significantly increased TC, LDL-C, HDL-C, hsCRP, and HOMA-IR levels than the control and subclinical hypothyroidism groups (TC, LDL-C, HDL-C, and HOMA-IR: $P < 0.01$; hsCRP: $P < 0.05$). The FGF21 levels were decreased in the overt hypothyroidism group compared with the control group and the subclinical hypothyroidism group (all $P < 0.01$).

3.2. The correlation between FGF21 and thyroid function

In addition, we investigated the correlation between circulating FGF21 levels and thyroid function in all participants. The circulating FGF21 levels were significantly and positively associated with FT3 and FT4 levels (FT3: $r = 0.205$, $P < 0.01$; FT4: $r = 0.161$, $P < 0.05$). A negative association of FGF21 and TSH levels was also observed ($r = -0.141$, $P < 0.05$). After adjusting for TG and HOMA-IR, a positive association of FGF21 and FT3, and a negative association of FGF21 and TSH were still observed (FT3: $r = 0.150$, $P < 0.05$;TSH: $r = -0.146$, $P < 0.05$; Fig. 3A and B).

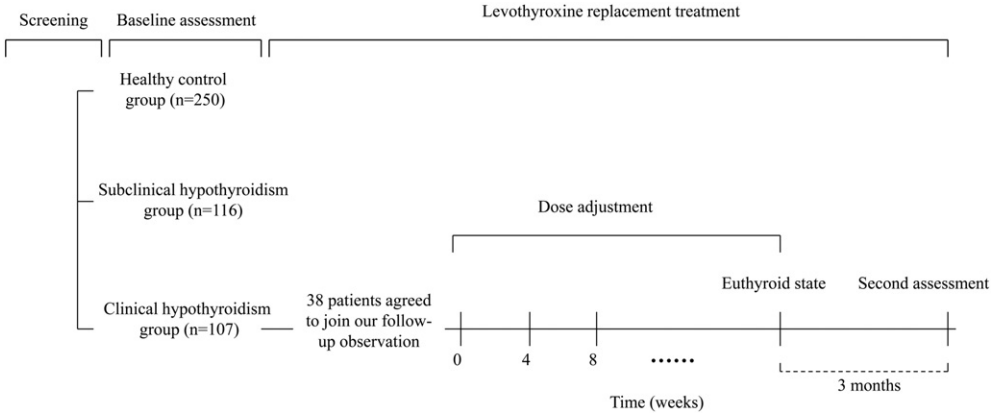

Fig. 1. Study design and timeline of testing procedures.