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Serum IGF-1 and IGFBP-3 levels in subclinical hypothyroid women

Research Article

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Abstract: Thyroid status is known to influence growth in mammals. The aim of this study is to investigate the possible relationship between autoimmune subclinical hypothyroidism and growth hormone (GH), insulin-like growth factor-1(IGF-1) and insulin-like growth factor binding protein-3(IGFBP-3) levels. Thirty-five women with autoimmune subclinical hypothyroidism, 33 years of age, were used as controls and enrolled in the study. Free triiodothyronin (FT3), free thyroxin(FT4), thyrotropin(TSH), anti-thyroid peroxidase(Anti-TPO), anti-thyroglobuline(Anti-Tg), GH, IGF-1 and IGFBP-3 levels were measured in blood samples and correlations among these parameters were evaluated. We found no significant differences in GH, IGF-1 or IGFBP-3 between patients and controls. In patients and controls, there were no correlations among thyroid hormones and IGF-1 or IGFBP-3 levels, but GH levels were correlated with FT3, FT4 and TSH only in patients' group. In controls, only IGF-1 and IGFBP-3 levels were correlated. The present study suggests that subclinical hypothyroidism with high TSH and antibody status does not affect IGF-1 and IGFBP-3 levels in adult women. To our knowledge, this is the first study concerning the relationship between autoimmune subclinical hypothyroidism and IGF-1 and IGFBP-3 levels.

Keywords: *IGF-1 • IGFBP-3 • Autoimmune subclinical hypothyroidism*

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1. Introduction

Thyroid hormones are known to influence somatic growth in mammalian species. Evidence has been found that thyroid hormones are important in the regulation of several growth factors, including nerve growth factor, epidermal growth factor, and eythropoietic growth factor [1-3]. A number of studies have shown that insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-3 levels in serum are dependent on thyroid hormone status [4,5]. This may be secondary to the effects of thyroid hormones on the pituitary-GH secretion; however, there is data, which supports that some of the effects are direct [6,7]. In vitro, thyroid hormones play a role in the regulation of IGF-1 and IGFBP-3 expression, and conversely, the growth hormone (GH) and IGF axis may affect thyroid function receptors expressed in thyroid tissue [8,9] In animal and human models, low levels of IGF-1 and IGFBP-3 were found in untreated hypothyroidism [10-12]. Clinical hypothyroidism has been found to be associated with decreases in serum levels of IGF-1 and treatment with L-thyroxine alone

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Table 1. Thyroid hormones, IGF-1 and IGFBP-3 levels in subclinical hypothyroid group and healthy controls. Values (means ± SEM) and statistical significance of the analyzed parameters.

	Patients Group (n=35)	Controls Group (n=33)	P
Age (years)	33.80±7.12	34.94±5.84	0.475
FREET3 (pg/ml)	2.72±0.46	2.96±0.77	0.129
FREET4 (ng/dl)	1.25±0.23	1.41±0.37	<0.05
TSH (μIU/ml)	9.26±4.01	1.42±0.90	<0.001
IGF-1 (ng/ml)	327.20±106.29	368.64±132.46	0.158
IGFBP-3 (μg/ml)	3.36±1.24	3.06±1.10	0.295
GH (ng/ml)	1,96±2,4	2,1±3.7	0.572
Anti-TPO (IU/ml)	468,69±420,20	23,17±59,70	<0.001
Anti-Tg (IU/ml)	219,69±527,96	40,93±86,15	<0.001

stimulates IGF-1 activity [11]. Clinical hypothyroidism is defined as low levels of thyroid hormones in the presence of high thyrotropin (TSH) levels. TSH is shown to stimulate differentiated function and growth in thyroid cells synergistically with IGF-1 in human thyroid cells [13]. There are data concerning the inhibitory effect of TSH on IGFBP-3 levels in functional human thyroid cell cultures in vitro [14]. Autoimmune thyroiditis, an important cause of hypothyroidism is characterized by the presence of thyroid auto antibodies, mainly anti-thyroid peroxidase (Anti-TPO) and anti-thyroglobuline (Anti-Tg). These antibodies are shown to alter proinflammatory cytokine levels [15]. Also in hypothyroid patients, IGF-1 and IGFBP-3 levels significantly decreased [16]. There are no data concerning the interaction of thyroid antibodies with IGF-1 and IGFBP-3 levels in patients with subclinical hypothyroidism. In this study, we investigated Anti-TPO, Anti-Tg, GH, IGF-1 and IGFBP-3 levels in female patients with subclinical hypothyroidism.

2. Material and Methods

In this study, 35 females were admitted to the Department of Endocrinology, Cerrahpasa Medical Faculty as outpatients and 33 healthy age-matched females were included as the control group. The study group consisted of women with subclinical hypothyroidism. The mean age for the study group is 33,80±7,12 years and for the control group 34,94±5,84. Blood samples were withdrawn from both groups after overnight fasting for the determination of serum, FT3, FT4, TSH, Anti-TPO, Anti-Tg, GH, IGF-1 and IGFBP-3. The blood samples were centrifuged at 4000g for 5 minutes. For the IGFBP-3 measurement, serum samples were stored at –20ºC.

Serum FT3 and FT4 levels were measured by competitive analog-based immunoassay; TSH,GH and IGFBP-3 levels were measured by chemiluminescent immunometric assay on the Immulite 2000 (DPC; Los Angeles, USA). Serum Anti-TPO and Anti-Tg levels were determined with chemiluminescent microparticle immunoassay by Architech i2000 (Abbott,USA) automatic analyzer. Serum IGF-1 levels were measured by immunoradiometric assay (DSL-5600;Texas,USA).

The data were analyzed using Student's t test for FT3, FT4, Anti-TPO, Anti-Tg, GH, IGF-1 and IGFBP-3 levels and Mann-Whitney U test for TSH levels in both groups. Correlation between paired data sets were assessed using Pearson's Correlations, $p< 0.005$ was found to be as significant.

3. Results

Thyroid function levels of FT3, FT4 and TSH confirmed subclinical hypothyroidism at diagnosis in our patient group. FT3 and FT4 levels were similar in patients as well as the healthy controls (Table 1). TSH levels were significantly higher in patients than in healthy controls (Table 1). No significant changes were found between patients and controls for IGF-1 or IGFBP-3 (Table 1). No significant changes were found between patients and controls for GH (Table 1). Anti-TPO and Anti-Tg levels were significantly higher in patients group compared to control group.

In healthy controls, only IGFBP-3 and IGF-1 were correlated significantly. GH levels were correlated with FT3, FT4 and TSH levels only in patients' group. The correlations among parameters were shown in Tables 2 and 3.

4. Discussion

Clinical hypothyroidism has been demonstrated to be a low IGFBP-3 state, which can be reversed by LT4 replacement therapy [10,17,18]. Aydin et al. suggested

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Table 2. The correlations among GH, IGF-1, IGFBP3 and thyroid hormones and antibodies in patients with subclinical hypothyroidism.

	IGF-1		IGFBP-3		GH	
	R	p	r	p	r	p
IGF-1			0.298	0.082	-0.12	0.944
IGFBP-3	0.585	0.001***			0.33	0.846
GH	-0.12	0.944	0.33	0.846		
FT3	0.097	0.581	0.297	0.084	0.549	0.01
FT4	-0,228	0,188	-0.038	0.830	0.460	0.005
TSH	0.280	0.103	-0.255	0.140	0.424	0.01
Anti-TPO	-.0.48	0.780	-0.234	0.169	-0.033	0.848
Anti-Tg	0.256	0.133	0.79	0.646	0.146	0.397

Table 3. The correlations among GH, IGF-1, IGFBP3 and thyroid hormones and antibodies in control group.

	IGF-1		IGFBP-3		GH	
	r	p	r	p	r	p
IGF-1			0.585	0,001***	0.043	0.815
IGFBP-3	0.585	0,001***			-.0.113	0.538
GH	0.043	0.815	-.0.113	0.538		
FT3	-0,09	0,616	-0.181	0.313	0.098	0.587
FT4	0,173	0,336	-0.042	0,729	0.023	0.900
TSH	0,059	0,742	0.072	0.690	0.040	0.828
Anti-TPO	-0.160	0.382	0.051	0.783	-0.098	0.592
Anti-Tg	-0.070	0.704	0.060	0.746	0.157	0.391

that IGF-1 and IGFBP-3 levels were affected by thyroid hormones in selenium- and iodine deficient children [19]. Alikasifoglu et al. also showed that hypothyroidism due to iodine deficiency had a negative impact on growth, as well as IGF-I and IGFBP-3 levels in pediatric group [20]. Nanto-Salonen et al. demonstrated that the effect of thyroid hormones on IGF-1 and IGFBP-3 was age-dependent in rat models [21]. In the mentioned study, IGFBP-3 and -4 levels were decreased in adult rats, whereas no induction of IGFBP-2 expression was found, which was present in congenital hypothyroid rats. The authors concluded that there was a critical period during the perinatal development of the rat, during which thyroid hormones were essential for normal IGFBP levels. Adult animals showed a completely different IGFBP response to hypothyroidism, with a decrease in IGFBP-3 and -4 levels. However, Ramos et al. suggested that IGFBP-2 was up regulated by T4 deprivation in both groups of neonatal and adult thyroidectomized rats [22]. They found a good correlation as well as a partial correlation between IGFs and thyroid hormones in both neonatal and adult thyroidectomized populations, suggesting a direct effect in vivo of T4 on the hepatic secretion of IGFs, as previously suggested in vitro [23]. In human model,Cassio et al. suggested that intrauterine production of IGF-1 was affected partially by fetal thyroid function [24]. In the mentioned study, infants with congenital hypothyroidism had lower GHBP levels than control group, and intrauterine IGF-1 production seemed independent of the levels of GHBP. Bona et al. demonstrated a linear correlation between IGF-1 and IGFBP-3 in congenital hypothyroid children, who were euthyroid under LT4 replacement therapy and age-matched controls, but not in patients with hypothyroidism, which began in postpubertal age [18]. In this group, the correlation between IGF-1 and IGFBP-3 tended to be negative but was statistically insignificant. Recently, Akin et al.reported that patients with untreated subclinical hypothyroidism had similar IGF-1 and significantly lower IGFBP-3 and levels compared to control subjects. They also found a significant correlation between IGF-1 and IGFBP-3 levels [25]. In our study, we also found a significant correlation between IGF-1 and IGFBP-3 in control group, but not in patients with subclinical hypothyroidism. Inukai et al. found a significant positive correlation between IGFBP-3 levels and FT3 and FT4 levels in hyper-, hypo- and euthyroid subjects [26]. They also found a significant negative correlation between TSH and IGFBP-3 levels. In the mentioned study, IGF-1 was not correlated with FT3, FT4 and TSH. Iglesias et al. demonstrated low levels of circulating IGF-1 and IGFBP-3 in adult patients with untreated hypothyroidism

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[10]. In the mentioned study, there was no correlation between serum levels of IGF-1 and IGFBP-3 and the serum levels of TSH, FT4 and T3. Also in our study group with subclinical hypothyroidism, we did not find any correlation between IGF-1 and IGFBP-3. Our study group consisted of adult women with high TSH levels, but we did not find any correlation between TSH and IGF-1 and between TSH and IGFBP-3 either. GH levels were significantly correlated both with FT4 and TSH levels. IGF-1 and IGFBP-3 levels of our study group were similar to those of control group. This finding was inconsistent with Akin's data [25]. Our findings suggest that in adult population with normal thyroid hormone levels and high TSH, IGF-1 and IGFBP-3 axis seem to be unaffected, and this finding is similar to that of Bona et al., who worked with treated patients with normalized TSH levels; but larger studies are needed to elucidate the interaction between thyroid and IGF and IGFBP systems [18]. Nielsen et al. demonstrated that following challenge with TPO, the mononuclear cells' production of the pro-inflammatory cytokines TNF-α, IL-6 and IFN-γ, and the anti-inflammatory cytokine IL-10, correlated with the Anti-TPO content of the serum present in the culture [15]. Interferon treatment is shown to be associated with an increase in IGF-1 levels in patients with chronic hepatitis C and direct stimulatory effect of interferon on IGF-I secretion could not be excluded [27]. Our results might be at least partially explained with high titers of thyroid autoantibodies, which might increase IGF-1 levels, which were expected to be lower and contribute to the similarity between IGF-1 and IGFBP-3 levels in patients and controls.

To our knowledge, this is the first study concerning the relationship between hormone and antibody levels in subclinical hypothyroidism and IGF-1 and IGFBP-3 levels.

5. Conclusion

The present study suggests that subclinical hypothyroidism as a high TSH- and high antibody status does not affect IGF-1 and IGFBP-3 levels in adult women. To our knowledge, this is the first study concerning the relationship between thyroid hormone and antibody levels in subclinical hypothyroidism and IGF-1 and IGFBP-3 levels.

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