EFFECT OF GRAVES' OPHTHALMOPATHY'S TREATMENT ON LEVELS OF INSULIN-LIKE GROWTH FACTOR-1

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Insulin-like growth factor 1 (IGF-1) is mainly produced by the liver as well as by target tissues in a paracrine/autocrine fashion. Clinical and experimental evidence suggests that the expression and synthesis of IGF-1 can be suppressed by glucocorticoids. The aim of this study was to assess the circulating IGF-1 concentrations in correlation with the glucocorticoid treatment in patients with autoimmune diseases. We evaluated 43 patients, 23 women and 20 men with Graves' ophthalmopathy. The subjects were between 27 and 39 years. 11 patients present mild ophthalmopathy, and 32 moderate-to-severe Graves' ophthalmopathy. All study participants were treated with antithyroid drugs and patients with moderate-to-severe Graves' ophthalmopathy recived glucocorticoids. Blood samples were drawn before the glucocorticoids therapy was initiated and after 2-month of the steroid treatment. IGF-1, free thyroxine (free T4) and thyroid-stimulating hormone (TSH) were assayed. Results were compared with values obtained for 34 control subjects without Graves' disease. The average value of IGF-1 and free T4 decrease significantly after treatment and TSH level increased at 2-month after the initiation of the therapy. The levels of the IGF-1 are within the normal range, but there were significant differences between levels of Graves' ophthalmopathy group compared to the control group (463.65±21.48 ng/dl vs 329.15±51.28 ng/dl, $p < 0.05$). In both groups IGF-1 correlated significantly with free T4 level ($r=0.994$, $p<0.001$ for Graves' ophthalmopathy group and $r=0.704$, $p<0.001$ for control group). The result and previously studies suggest an interrelation between the thyroid function, corticosteroid treatment and GH/serum IGF axis.

Key words: Insulin-like growth factor 1; glucocorticoids treatment; Graves' ophthalmopathy.

INTRODUCTION

The Insulin-like growth factor (IGF) system is comprised of the IGF ligands (IGF-1 and IGF-2), cell-surface receptors including the IGF-1 receptor (IGF-1R), the IGF-2 receptor (IGF-2R), and the insulin receptor, as well as a family of IGF-binding proteins (7 characterized IGFBP1-7)[1]. The actions of growth factors, include increases of cell division rate, cell size, protein synthesis, cell migration, as well as inhibition of apoptosis, secondary activation of receptor and its intrinsic tyrosine kinase activity initiating a signaling cascade that involves multiple intracellular signaling pathways, such as the phosphatidylinositol3-kinase (PI3K) and mitogen activated protein kinase (MAPK) pathways[2].

IGF-1 is produced primarily by the liver as well as by target tissues in a paracrine/autocrine fashion. Production is modulated by various hormones (insulin, growth hormone) and nutritional conditions. Clinical and experimental evidence suggests that the expression and synthesis of IGF-1 can be suppressed by glucocorticoids. Exogenous administration of by glucocorticoids suppresses the expression of IGF-1 messenger ribonucleic acid (mRNA) and IGF-1R mRNA as well as the IGF-1 bioavailability[3].

Graves' ophthalmopathy is an autoimmune disorder representing the most important extrathyroidal manifestation of Graves' disease, but it may occur in patients without current or prior hyperthyroidism or in patients who are hypothyroid due to chronic autoimmune Hashimoto's thyroiditis. According European Group on Graves' ophthalmopathy (EUGOGO) glucocorticoids therapy has been used in the management of moderate-to-severe Graves' ophthalmopathy through oral, local or intravenous therapy routes. Oral glucocorticoids therapy requires high doses of hormones for long periods of time. Local (retrobulbar or subconjuctival) glucocorticoids therapy is less effective than oral therapy and evidence for the superiority of intravenous glucocorticoid therapy is lacking but intravenous glucocorticoids are tolerated better than oral treatment. The expert of EUGOGO do not recommend glucocorticoid therapy in mild disease as the risks outweigh the benefits. Simple measures (euthyroidism should restored in all patients with Graves' ophthalmopathy) are usually sufficient[4].

The aim of this study was to assess the circulating IGF-I, concentrations related to glucocorticoid treatment in patients with Graves' ophthalmopathy.

MATERIALS AND METHODS

We evaluated 43 patients, 23 women (53.48%) and 20 men (46.51%), with Graves' ophthalmopathy. Subjects were between 27 and 39 years. 11 patients (25.58%) present mild ophthalmopathy, and 32 (74.41%) moderate-to-severe Graves' ophthalmopathy. All study participants were treated with antithyroid drugs and patients with moderate-to-severe Graves' ophthalmopathy received glucocorticoids. Blood samples were drawn before the glucocorticoids therapy was initiated respectively 2-month after the steroid treatment. IGF-1, free thyroxine (free T4) and thyroid-stimulating hormone (TSH) were assayed. TSH was measured using a chemiluminescent immunometric assay (normal range 0.10–4.50 mU/l), freeT4 with a direct, monoclonal antibody assay (normal range of 0.7 to 1.7 ng/dl) and serum levels of IGF-1 were determined by radio-immunoassay, (normal range between 25–39 years 114 to 492 ng/dl). Treatment was initiated with 1mg/kg prednisone or equivalent for patients with moderate-to-severe Graves' ophthalmopathy. Clinical response to glucocorticoids therapy and the development of steroid adverse events were followed. Results were compared with levels obtained in 34 healthy subjects.

STATISTICAL ANALYSES

Data are presented as mean ± SD. Clinical characteristics were compared using the t Student Test. Pearson's moment-product correlation coefficients were calculated to evaluate relationships between variables. Significance was defined at the 0.05 level of confidence. All calculations were performed using the Statistical Package for Social Sciences Softwaew (SPSS) version 15.

RESULTS

All study participants are diagnosed with hyperthyroidism based on their thyroid function tests. The baseline evaluated parameters are presented in Table 1.

The groups were similar in terms of age and sex but there were statistically significant differences for the recorded parameters in patients with Graves' ophthalmopathy compared with healthy subjects.

The mean value of IGF-1 and free T4 decreases significantly after treatment and mean value of TSH increase at 2-month after the initiation of the treatment.

Table 1

The baseline participants characteristic

	The study group	**The control group**	**p**
Age (years)	35.07±4.15	34.85±3.85	NS
TSH (mU/l)	0.02±0.01	1.92±0.42	$p < 0.05$
Free T4 (ng/dl)	4.72±1.04	1.16±0.19	$p < 0.05$
IGF-1 (ng/dl)	463.65±21.48	329.15±51.28	$p < 0.05$

Table 2

The baseline and after 2 month of treatment with antithyroid drugs of participants characteristic

	The baseline characteristic	**The characteristic after 2 month of treatment**	**p**
TSH (mU/l)	0.02±0.01	0.36±0.14	$p < 0.05$
Free T4(ng/dl)	4.48±1.61	1.11±0.14	$p < 0.05$
IGF-1 (ng/dl)	453.09±32.59	403.09±32.59	$p < 0.05$

Table 3

The baseline and after 2 month of treatment with antithyroid and glucocorticoids drugs of participants characteristic

	The baseline characteristic	**The characteristic after 2 month of treatment**	**p**
TSH (mU/l)	0.02±0.00	0.34±0.12	$p < 0.05$
Free T4(ng/dl)	4.82±0.77	1.16±0.87	$p < 0.05$
IGF-1 (ng/dl)	467.28±15.13	367.28±15.13	$p < 0.05$

DISCUSSION

The levels of the IGF-1 are within the normal range, but there were significant differences between mean levels of Graves' ophthalmopathy group compared to control group (463.65±21.48 ng/dl *vs* 329.15±51.28 ng/dl, $p < 0.05$). In both groups the IGF-1 level was significantly correlated with free the T4 level ($r=0.994$, $p<0.001$ for the Graves' ophthalmopathy group and $r=0.704$, $p<0.001$ for the control group).

The relationships between the thyroid function and pituitary growth hormone (GH) / serum IGF axis are complex. The pituitary secretion of GH are regulated by thyroid hormones at transcriptional level. Previous studies reported that hypothyroid patients are characterized by decreased plasma levels of IGF-I and reduced IGF bioactivity, whereas hyperthyroid patients have high plasma IGF-I levels. The regulation of the IGF system is dependent of the nutritional status; hyperthyroidism increases lipid and carbohydrate oxidation and modifies the actions of other regulatory hormones (insulin, glucagon, catecholamines)[5–11].

Treatment of Graves' ophthalmopathy improves thyroid function tests and decreases the level of IGF-1.Our results show that, at baseline, free T4, TSH and IGF-1 levels were similar in the studied groups. After 2 month of treatment, patients treated with antithyroid and glucocorticoids drugs are characterized by a significant decrease of the IGF-1 level compared to patients treated only with antithyroid drugs (367.28±15.13 ng/dl *vs.* 403.09±32.59 ng/dl, $p=0.002$).

Glucocorticoids modulate GH synthesis and secretion by influencing hypothalamic and pituitary function. Decreases in IGF-1 serum levels have been previously reported after corticosteroid administration in patients with various diseases; the decrease in IGF-1 serum levels particularly resulted from a decrease in the IGF-1 liver expression[12–14].

In research published in the Journal of Immunology, Dr. Smith. and his colleagues have identified the interaction between immunoglobulins and IGF-1R as a cause of inflammation and lymphocyte infiltration in Graves' disease and rheumatoid arthritis. In the previously mentioned article Dr. Smith reported that a disproportionately large fraction of peripheral blood T cells express IGF-1R in patients with Graves disease and the results support a potential role for IGF-1R as a determinant of immune responses through fibroblast and lymphocyte activation and expansion. The data implicates IGF-1R in the pathogenesis of Graves disease[15].

CONCLUSION

In this study we found significant differences for the recorded IGF-1 between patients with hyperthyroidism and subjects without hyperthyroidism.

The levels of the IGF-1 are within the normal range, but they were significantly increased in patients with hyperthyroidism, compared to a control group. In both groups, IGF-1 were significantly correlated with free T4 level.

The result are correlated with previous studies and suggest a relationships between the thyroid function, corticosteroid treatment and GH/serum IGF axis.

Treatment of Graves' ophthalmopathy with antithyroid and glucocorticoids drugs improves thyroid function tests and decreases the level of IGF-1. After 2 month of treatment patients treated with antithyroid and glucocorticoids drugs are characterized by significantly decreased levels of IGF-1, compared with patients treated only with antithyroid drugs.

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