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The immune modulatory effects of prolactin and cortisol in Hashimotos thyroiditis - A case control study

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Abstract

The immune modulatory effect of serum prolactin (PRL) and cortisol were studied in Hashimoto's thyroiditis (HT). The present case control study was conducted at the Department of Endocrinology, Institute of nuclear medicine and radiotherapy, Peshawar, Khyber-Pakhtunkhwa, Pakistan, from January 2017 to December 2017. Forty eight HT patients including (29 females) (34.97±1.454 years) and (19 males) (38.42±1.805 years) were selected. The thirty six control subjects included 21 females (31.43±1.698 years) and 15 males (37.93±2.561 years). HT females showed significantly higher (p = 0.0396) PRL values (631.8±119.7 mIU/L) than the control (322.7±44.84 mIU/L). Similarly HT males showed increased PRL values (p= 0.0215) (466.3±120.6 mIU/L) than control (134.4±19.59 mIU/L). In contrast, cortisol level was low in all HT patients (female= 101.9±20.37 ng/ml) and (male=106.8±21.77 ng/ml). Cortisol level in control females and males were (123±15.45 ng/ml.) and (163.9±23.25ng/ml) respectively. The TSH level was high in both males (16.24±1.135µIU/L) and females (5.793±1.395 µIU/L) patients while in control it was between the normal ranges (05-5µIU/L). The TT4 values in HT females (16.45±0.848 nmol/L) and males (6.956±2.667 nmol/L) were significantly lower than control. In conclusion, our results provide evidence for an altered prolactin-cortisol status in Hashimoto's thyroiditis patients.

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Introduction

Prolactin (PRL) is a neuroendocrine hormone secreted mainly from lactotroph cells of anterior pituitary gland. It is also produced to some extent from extra pituitary cells including some of the immune cells such as lymphocytes (Lajevardi *et al.,* 2016). It is structurally similar to cytokine having exquisite role in immune regulation such as the lymphocyte maturation and immunoglobulin production. The receptors for PRL are present at various immune cell surfaces such as macrophages, Natural killer cells, T and B lymphocytes (Shelly *et al.*, 2012).

Cortisol hormone is known for its anti-inflammatory and immunosuppressive properties. It brings change in immune regulatory process by inducing Th2-type immune response (da Rosa *et al.*, 2018). Autoimmune diseases (AID) arises due to the complex neuroendocrine-immune interactions triggered by environmental factors (Klecha *et al.*, 2008). In Cushing's syndrome and stress high thyroid stimulating hormone (TSH) levels were found to be associated with lower cortisol values (Walter *et al.*, 2012).

It is reported that there is association between PRL and AID (systemic and organ specific) such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis, Sjogren's syndrome, diabetes mellitus (type 1), autoimmune thyroid diseases (AITDs), Addison's diseases and multiple sclerosis (MS) (Savino, 2017). Thyroid gland is highly susceptible to autoimmune diseases. Among the most common AITDs are Hashimoto's thyroiditis (HT) and Graves' disease (GD). In Hashimoto's thyroiditis, the imbalance between Th1-Th2 immune response is caused by the neuroendocrine interactions resulting in Th1-cell-mediated reaction destructing the thyrocytes and causing hypothyroidism (Weetman and DeGroot, 2016).

Hyperprolactinemia mainly occurs due to hypothyroidism, pituitary disorders and use of antipsychotic drugs (Poyraz *et al.,* 2008). It also favors the production of various autoantibodies (especially thyroid autoantibodies) which result in autoimmune disorders (Sayki *et al.,* 2013). PRL classified as pro-inflammatory hormone, is known to break immune tolerance leading to autoimmune reaction (Costanza *et al.*, 2014). Studies in primates and humans reported the reduced level of serum glucocorticoids and increased level of serum PRL in autoimmune diseases such as systemic lupus erythematosus and others (Legakis *et al.*, 2001; Neidhart, 1996). The low level of cortisol may play an important role in the development of autoimmune disease. In various autoimmune diseases the cortisol level is abnormal suggesting its effect in immune regulatory process. Moreover low cortisol concentration are reported with high prolactin concentrations in autoimmune diseases. Thus corticosteroids provoke the immune regulatory effects of PRL (Orbach and Shoenfeld, 2007).

A very few number of studies reviewed the relationship between hyperproctinemia and HT. The PRL response to thyrotropin releasing hormone (TRH) and its secretion is modulated by thyroid hormones. This suggest that hyperprolactinemia may be caused by low levels of thyroid hormones in blood serum (Coronel-Restrepo *et al.,* 2014). Similarly HT is reported to be more common in prolactinoma disease (33%) as compared to acromegaly disease (17%) (Dogansen *et al.*, 2016). Similar reports were given by Elenkova *et al.* (2016) that AITD is common in prolactinoma patients.

AITD was found to be more common in hyperprolactinaemic females. These females also showed high titers of antithyroid antibodies. It is reported that 25% of menstrual disorders in women is related to hyperprolactinemia. PRL is considered to be one of the factor that favors certain types of cancer such as breast and prostate cancer. Thus the relationship between PRL and specific thyroid diseases needs further investigation (Onal *et al.*, 2014). HPRL is also associated with high level of TSH which usually occurs in hypothyroidism (Khan *et al.,* 2018). The present study was designed to assess the prolactin and cortisol levels in Hashimotos thyroiditis patients and healthy controls in Khyber-Pakhtunkhwa, Pakistan.

Material and methods

Study area

The present case control study was conducted at the Department of Endocrinology, Institute of nuclear medicine and radiotherapy, Peshawar, Khyber-Pakhtunkhwa, Pakistan, from January 2017 to December 2017. The committee for advanced study and research board approved the study, and informed consent was taken from all the patients and control individuals included in the study.

Study participants

A total number of 48 Hashimoto's thyroiditis patients including 29 females (mean age with SD = 34.97±1.454 years) and 19 males (mean age with SD =38.42±1.805 years) were recruited for the study at the department of endocrinology, IRNUM hospital Peshawar. The healthy samples consisted of 21 female (mean age with SD= 31.43±1.698 years) and 15 males (mean age with SD= 37.93±2.561) were taken randomly from the students and university employees at the Islamia college Peshawar as control cases. Venous blood samples were taken from all the patients and control subjects.

Exclusion criterion

Patients undergoing steroids therapy (including oral contraceptives), using psychiatric drug; pregnant or breastfeeding; patients with any other systemic disease; and patients reluctant to participate were excluded from the study.

Procedure

The diagnosis of HT were based on the clinical findings and hormonal evaluation of total thyroxine (TT4), TSH (Thyroid stimulating hormone) and ATPO (thyroid peroxidase antibodies) using Elisa assays with the normal range 62-165nmol/L, 0.5-5.0μIU/L and 40-60 IU/mL respectively. Results higher than these cut off values were considered positive. The biochemical analysis were performed using Elisa Anti-TPO (AESKU, GERMANY), Elisa Anti TSHR (Diametra, Italy) kits. TSH was determined by immunoradiometric assay kit (Immunotech-Beckman Coulter Company, Czech Republic) and TT4 was determined by radioimmunoassay kit (Immunotech Beckman Coulter Company, Czech Republic). Serum PRL and cortisol (at evening 4.00pm) was measured in HT patients and control subjects by Elisa assay (PISHTAZTEB, DIAGNOSTICS Tehran, Iran and Cortisol–Elisa Diametra-Italy respectively). The normal range for prolactin are: Males: 425 mIU/L, Non pregnant females: 118-555mIU/L. The normal cortisol range for cortisol at 4: pm is 30-150ng/ml.

Statistical analysis

Statistical analysis was done using Graph pad prism software version 7. Descriptive statistics was utilized for results, and mean expressed as mean ± SD. Unpaired T-test was used for comparison and control. Statistical significance values were set as $P < 0.05$.

Results

Forty-eight HT patients and thirty six control individuals were selected. Out of forty eight HT patients, twenty nine were female with mean age 34.97±1.454 years and nineteen males with the mean age 38.42±1.805. The thirty six control individuals were having twenty one females, with mean age and SD (31.43±1.698 years) and fifteen males, with mean age 37.93±2.561 years. The ATPO concentration for the HT female and control was quite significant ($p = 0.0012$) with mean values 510.5±57.9 IU/mL and 24.54±1.969 IU/mL respectively. The TSH concentration for HT females and control also showed significantly higher values ($p=0.0348$) having mean values as 5.793±1.395μIU/L and 2.16±0.3585 μIU/L respectively. The high TSH and the presence of ATPO antibodies values confirmed HT. The Serum TT4 concentration for HT females and control were 16.45±0.8485 nmol/L and 95.63±6.684 nmol/L respectively ($p = <0.0001$). Serum level of Cortisol in female HT and control was (101.9 ± 20.37ng/ml) and (123±15.45ng/ml) respectively having no significant difference ($p=0.4458$). Serum level of prolactin in HT females and control was 631.8±119.7mIU/L and 322.7±44.84 mIU/L respectively ($p=0.0396$). These results shows high prolactin while low cortisol level in HT patients as compared to the control. The demographic and hormonal data of the HT and control is given the table 3.1 (female).

Table 1. Demographic and hormonal data of control and HT female patients (± standard error of the mean).

Parameters (Normal Range)	Control (n=21) Mean±SD	HT (n=29) Mean±SD	t- value, (P value)
ATPO (40-60 IU/mL)	24.54±1.969	510.5±57.9	3.437(0.0012)
TSH (0.5-5.0 µIU/L)	2.16 ± 0.3585	5.793 ± 1.395	2.173 (0.0348)
TT4 (62-165nmol/L)	95.63 ± 6.684	16.45 ± 0.8485	13.76(<0.0001)
Cortisol (30-150 ng/ml)	123 ± 15.45	101.9 ± 20.37	t= 0.7687(0.4458)
Prolactin (118-555 mIU/L)	322.7 ± 44.84	631.8 ± 119.7	2.116 (0.0396)

P < 0.05, statistically significant. Significant *p* values are shown in bold.

The demographic details of male HT patients and control were given in the table 3.2. Nineteen HT males with mean age 38.42 ±1.805 years and fifteen control with the mean age 37.93±2.561 years were selected. The serum TSH for HT male patients showed the mean value of 16.24±1.135 µIU/L and for control it was 3.407±0.2672µIU/L with a *p value (<0.0001)* as significant association. The serum ATPO value of the HT male subjects was 537±71.14 IU/mL, while for healthy controls it is equal to 50.07±1.594 IU/mL with the *p* value as significant *(<0.0001)*. Serum TT4 values for HT males is 6.956±2.667 nmol/L) and control is (108.3±7.1063nmol/L) with *p* value *(<0.0001)* showing significant difference. The cortisol concentration in HT males was lower (106.8±21.77ng/ml) than the control subjects (163.9 ± 23.25 ng/ml) with *p* value *(0.0845)*. The value of prolactin in HT patients confirmed hyperprolactinemia showing the mean value higher than the normal (466.3±120.6mIU/L), while in control patients it is (134.4±19.59mIU/L) showing a significant difference (*p= 0.0215)*.

Table 2. Demographic and hormonal data of control and HT male patients (± standard error of the mean).

Parameters Normal values	Control (n=15) (Mean ± SD)	HT (n=19) (Mean ± SD)	t- value, (P value)
ATPO (40-60 IU/mL)	50.07 ± 1.594	537 ± 71.14	6.06 (<0.0001)
TSH (0.5-5.0 µIU/L)	3.407 ± 0.2672	16.24 ± 1.135	9.851 (<0.0001)
TT4 (62-165nmol/L)	108.3 ± 7.106	6.956 ± 2.667	14.54 (<0.0001)
Cortisol (at 4:00 pm) (30-150 ng/ml)	163.9 ± 23.25	106.8 ± 21.77	t=1.781 (0.0845)
Prolactin (425 mIU/L)	134.4 ± 19.59	466.3 ± 120.6	2.418 (0.0215)

P < 0.05, statistically significant. Significant *p* values are shown in bold.

Discussion

In the present study, Hashimoto's thyroiditis patients showed relatively lower cortisol (18/48, 37.5%) and higher PRL values (13/48, 27.08%) than the healthy controls. The HPRL in females was 26.68% while in males it was 36.84%. The deviation of HPRL value from the normal value (555mIU/L) is 631.8±119.7mIU/L in females while in male the deviation from normal (425mIU/L) is 466.3±120.6 mIU/L. These results showed that the female HT patients showed more deviation in prolactin concentration as compared to the male HT patients. The cortisol values for HT patients was with in the normal range but comparatively lower than the normal control subjects. In the control subjects the cortisol level in males were slightly greater than the normal values.

All the HT confirmed positive for ATPO. Notably HT patients revealed higher TSH in 89.47% (17 /19) males and 44.82% (13/29) females. While the lower T4 levels were reported in all the HT patients. None of the control subjects were confirmed positive for anti-TPO anti bodies. Several studies suggested the impact of prolactin on immune regulation and its possible role in various autoimmune diseases such as systemic lupus erythematosus, multiple sclerosis, diabetes mellitus, autoimmune thyroid diseases, rheumatoid arthritis, celiac disease and Addison's disease. Similarly the altered cortisol level was revealed by number of studies which showed its permissive effect in the onset of AITD. The HPRL with low cortisol may stimulate the immune response. It was reported by Orbach and Shoenfeld, (2007) that nineteen percent of chronic thyroiditis patients had

HPRL which supports our results (27.083% HPRL). It is also confirmed that the prevalence of HPRL is much higher in primary hypothyroid patients (42.4%) while in normal population it is only 3%. Similarly the immune modulatory role of cortisol and prolactin is studied by Legakis *et al.* (2001) in thirty seven HT patients along with the normal controls. They also showed that HT patients had lower serum cortisol (13.5±3.2µg/dl) and higher HPRL (14.0±3.8ng/ml), consistent with our results suggesting their role in pathogenesis of Hashimoto's thyroiditis.

Shelly *et al.* (2012) evaluated the role of prolactin and reproductive hormone especially estrogen in immune regulation. PRL increases the production of cytokines, autoantibodies and immune globulins. It means that increase level of thyroid autoantibodies may be due to the increase level of prolactin hormone. Walter *et al.* (2012) reported the positive correlation of high serum cortisol and high TSH levels (range 0.5-10uIU/L) in young healthy individuals (mean 20.98+/−0.37 years). This result suggested that subclinical hypothyroidism may cause hypercortisolemia. Agha-Hosseini *et al.* (2016) reported the contradictory results about serum cortisol (morning) in HT females. They reported higher serum cortisol level. Cortisol was thought to have a protective role in certain types of autoimmunity.

Moreover the Hashimoto's thyroiditis (ATD) was also found to be more frequent in prolactinoma disease confirmed by Dogansen *et al.* (2016) and Elenkova *et al.* (2016). This suggests the increase level of prolactin to be involved in the pathogenesis of Hashimoto's thyroiditis. Onal *et al*, (2014) also studied hyperprolactinemia in patients with thyroid disorders and found that HPRL is more prevalent in autoimmune thyroid disorders. At the same time they also reported that thyroid auto antibodies (ATPO and anti-Tg) are high in those having HPRL. It means that hyperprolactinemia and hypothyroidism are interconnected as confirmed by our results.

Various animal model and human studies have also shown the correlation between increased levels of PRL and other autoimmune diseases. Orbach *et al.* (2012) reported that 18 % of the SLE patients showed HPRL but anemia and proteinuria were also reported. The association of prolactin and adrenocorticoid axis was studied in extensively in SLE.

It suggested the simultaneous activation of neurohormonal pathways. Shoenfeld *et al.* (2008) reported that hyperprolactinemia was found in 15-33% of SLE patients. But at the same time Karimifar *et al.* (2013) concluded that prolactin hormone might not have any a role in the SLE disease activity. Moszkorzova *et al.* (2002) reported that prolactin to be an essential factor in autoimmune disease activity.

The role of prolactin and glucocorticoids have also been studied in RS which provide the evidence about increased prolactin and low cortisol level (at different timings) showing a relationship between hormonal disequilibrium and diurnal disease activity (Zoli *et al.* 2002). Now recently Wei *et al.* (2017) reported hyperprolactinemia in multiple sclerosis (MS) patients. Similarly Khan *et al.* (2018) studied the serum prolactin, follicle stimulating hormone (FSH) and luteinizing (LH) hormones in the autoimmune thyroid patients (28 HT and 13 GD). Hyper prolactinemia ($p< 0.05$) was confirmed in hypothyroid females which is compatible with our results. More over increased serum FSH and LH hormones were also reported.

So the role of prolactin hormone along with cortisol is important aspect to be studied for understanding the pathology of autoimmune diseases. More research is needed to Fig. out the role of prolactin as well as cortisol in hashimoto's thyroiditis.

Conclusion

Our study demonstrate clearly depicts high prolactin and lower cortisol levels in HT patients which suggest the abnormal pituitary and adrenocorticoid axis. These findings suggest the role of these hormones in the HT disease activity. This information may help to elaborate the research of HT thyroiditis and to find out the mechanisms by which prolactin and cortisol effects the disease.

Abbreviations

Hashimoto's thyroiditis=HT, Prolactin=PRL, Anti thyroid peroxidase antibodies = ATPO, Tetra-iodothyroxine =TT4.

Conflict of interest

There is no conflict of interest among the authors

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