

Effect of steroid replacement on thyroid function and thyroid autoimmunity in Addison's disease with primary hypothyroidism

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ABSTRACT

Background: Steroid replacement without thyroxine supplementation normalizes thyroid function test (TFT) in some but not all Addison's disease patients with primary hypothyroidism. Both autoimmune and nonautoimmune mechanisms contribute to this improvement in TFT. However, the documentation of the change in thyroid autoimmunity after cortisol replacement is very limited in the literature. The aim of this study was to determine the effect of steroid replacement on TFT and anti-thyroid peroxidase antibody (anti-TPO-Ab) titer in Addison's disease with primary hypothyroidism. **Materials and Methods:** This observational study was conducted in a tertiary care center in South India. Six Addison's disease patients with primary hypothyroidism, who were only on steroid replacement, were included in the study. Low serum cortisol (<83 nmol/L) with high plasma adrenocorticotrophic hormone (>22 pmol/L) and/or hyperpigmentation of skin/mucous membranes was considered as the diagnostic criteria for Addison's disease. Primary hypothyroidism (both overt and subclinical) was defined as high thyroid stimulating hormone (TSH) with/without low free thyroxine (fT4). TFT and anti-TPO-Ab were performed before and after steroid replacement in all of them. **Results:** Poststeroid replacement, there was a normalization of TSH in all but one subjects. In overt hypothyroidism patients, fT4 also normalized. The improvement in TFT was not associated with decreasing titer of the anti-TPO-Ab in all six patients. However, there was a significant difference in TSH after steroid replacement compared to the baseline status. **Conclusions:** The concept of normalization of primary hypothyroidism with cortisol replacement in patients with Addison's disease should be recognized to avoid iatrogenic thyrotoxicosis caused by thyroxine replacement. Both autoimmune and nonautoimmune mechanisms contribute to these alterations.

Key words: Addison's disease, anti-thyroid peroxidase antibody, autoimmunity, cortisol, hypothyroidism

INTRODUCTION

Primary hypothyroidism is present in up to 50% of cases with autoimmune primary adrenal insufficiency.^[1] Cortisol deficiency *per se* is responsible for primary hypothyroidism in a section of these patients.

Failure to recognize this fact may cause mislabeling of them as autoimmune polyendocrine syndromes (APSs), and they might receive unnecessary lifelong thyroxine supplementation. It can lead to iatrogenic thyrotoxicosis that necessitates the increase in steroid replacement to prevent adrenal crisis. There are several explanations for the coexistence of primary hypothyroidism with chronic cortisol deficiency. Though few authors have

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proposed the autoimmune theory, the documentation of the change in thyroid antibody titer after cortisol replacement among patients with primary adrenal insufficiency is very limited in the literature.^[2,3] Here, we present the data of the thyroid function test (TFT) and anti-thyroid peroxidase antibody (anti-TPO-Ab) titer in six patients with primary adrenal insufficiency with primary hypothyroidism before and after cortisol replacement.

MATERIALS AND METHODS

This observational study was conducted in a tertiary care center in South India over 5 years (2010–2014). Thirty-one patients with Addison's disease were managed in the Endocrinology Department of this institute during this duration. Low serum cortisol (<83 nmol/L) with high plasma adrenocorticotropic hormone (ACTH) (>22 pmol/L) and/or hyperpigmentation of the skin/mucous membranes was considered as the diagnostic criteria for Addison's disease.^[4] Anti-adrenal antibody against 21-hydroxylase, human immunodeficiency virus (HIV) serology, Mantoux test, chest X-ray, and computerized tomography (CT) of adrenals were done in all patients. Twenty-nine of 31 Addison's disease patients had TFT. Among them, 15 were hypothyroid, 12 were euthyroid, and 2 were thyrotoxic [Figure 1]. Primary hypothyroidism (both overt and subclinical) was defined as high thyroid stimulating hormone (TSH) with/without low free thyroxine (fT4) while thyrotoxicosis was defined as low TSH with/without elevated fT4. Nine primary hypothyroidism patients were already on thyroxine supplementation. Remaining six Addison's disease patients with primary hypothyroidism, who were only on steroid replacement, were included in this study. TFT and anti-TPO-Ab were performed before and after steroid replacement in them.

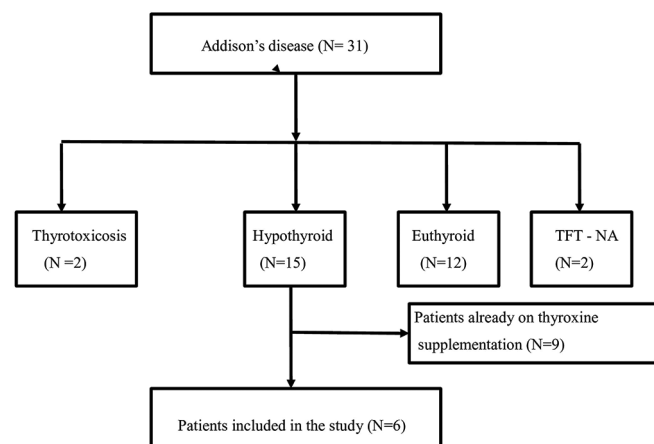


Figure 1: Flow chart of inclusion of patients in the study. TFT-Thyroid function test; NA-Not available

Hormone assays were performed in all patients using the chemiluminescence technique (ADVIA Centaur XP Immunoassay System, Siemens Healthcare Global, USA) with the following reference ranges: TSH, 0.35–5.50 mIU/L; free T4, 11.45–22.65 pmol/L; and cortisol (8 a.m.), 119–618 nmol/L. Plasma ACTH was measured using the chemiluminescence technique (IMMULITE 1000 Immunoassay System, Siemens Healthcare Global, USA) with the reference range from 1 to 10 pmol/L. Anti-TPO-Ab was measured by enzyme-linked immunosorbent assay (ELISA) using kits from Hycor Biomedical Inc., California, USA. The detection limit of this assay kit was 1810 U/L, and anti-TPO-Ab titer >50,000 U/L was considered as positive. The intra- and inter-assay coefficient of variation (CV) were 5% and 10%, respectively. Anti-adrenal antibody against 21 hydroxylase was estimated by qualitative ELISA using kits from Cusabio biotechnology company, Hubei, China. Both the intra- and inter-assay CV of this kit were <15%.

Statistical analysis was performed using SPSS software version 17 (IBM company, Chicago, IL, USA). Normality of data was checked with Shapiro–Wilk test. All continuous normally distributed data were summarized as mean with standard deviation except anti-TPO-Ab titer, which was expressed as median with interquartile range. The categorical data were expressed as frequency (as percentages). Paired Student's *t*-test and Wilcoxon signed-rank test were used to compare the parameters (TFT and anti-TPO-Ab titre) before and after steroid replacement. The value *P* < 0.05 was considered as significant.

RESULTS

There were four female and two male patients [Table 1]. Their mean age was 24.5 years. They were symptomatic for a period ranging from 2 to 12 months. None had a history of tuberculosis in the past. There was no history of intake of drugs known to affect the thyroid or adrenal function. They did not have any other comorbidity. All patients had hyperpigmentation of the skin and mucous membranes at the diagnosis. Clinical examination did not reveal thyromegaly in any of the patients. At baseline, all patients had primary hypothyroidism before steroid replacement. Two patients had overt hypothyroidism (TSH >5.5 mIU/L and fT4 < 11.45 pmol/L). All patients had low 8 a.m. serum cortisol (<83 nmol/L) with high plasma ACTH (>22 pmol/L). The anti-adrenal antibody was not detected in any of the subjects. Mantoux test, HIV serology and chest X-ray were normal in all of them. Adrenoleukodystrophy could not be ruled out in the case of patient 2 due to lack of facility for estimation of very

Table 1: Baseline parameters

Patient number	Age (year)	Gender	TSH (mIU/L)	ft4 (pmol/L)	Anti-TPO-Ab titre (U/L)	Anti-adrenal Ab	CT adrenals
1	36	Male	12.32	12.61	503,000	Not detected	Normal
2	1	Female	9.24	10.93	24,700	Not detected	Atrophy
3	29	Male	6.05	13.90	900,000	Not detected	Atrophy
4	37	Female	13.60	7.60	964,000	Not detected	Atrophy
5	24	Female	15.47	20	120,000	Not detected	Atrophy
6	20	Female	9.15	14.54	88,600	Not detected	Atrophy

TSH: Thyroid stimulating hormone, ft4: Free thyroxine, Anti-TPO-Ab: Anti-thyroid peroxidase antibody, CT: Computed tomography

long chain fatty acid in the blood in our center. However, she did not have any clinical features suggestive of central nervous system dysfunction, and her magnetic resonance imaging of the brain was normal. Five had adrenal atrophy, and one had normal sized adrenals without any calcification in CT scan. Hence, the etiology of Addison's disease was probably idiopathic in all of them.

Post replacement, there was normalization of TSH in all subjects except patient 1 [Table 2]. The mean time gap between baseline and repeat blood tests was 7 months. There was a significant difference in TSH after steroid replacement compared to baseline [Table 3]. In patients with overt hypothyroidism (patients 2 and 4), ft4 normalized poststeroid replacement. Anti-TPO-Ab titer was increased in patient 5 despite normalization of serum TSH.

DISCUSSION

High serum cortisol is associated with immunosuppression, and its resolution is associated with induction of autoimmune diseases. This fact is similar to exacerbation of autoimmunity during postpartum following immunosuppression associated with pregnancy. Takasu *et al.* described three cases of thyroiditis with increasing titer of thyroid autoantibodies following surgery of adrenocortical adenoma in patients with Cushing's syndrome.^[5] Similar findings were documented in 20 Cushing's syndrome patients in a study by Colao *et al.*^[6] Other autoimmune diseases such as psoriasis, celiac disease, sarcoidosis, and fulminant sclerosing pancreato-cholangitis were also reported after cure from Cushing's syndrome.^[7]

In contrast, low serum cortisol level is associated with autoimmunity like Hashimoto's thyroiditis with hypothyroidism.^[3,8] It is seen in any patient with hypocortisolemia irrespective of the etiology.^[8,9] Lymphocytic infiltration of thyroid was observed in 82% (53/65) patients with atrophic (presumed autoimmune) Addison's disease in contrast to 31% (19/62) with adrenocortical failure due to tuberculosis.^[10] This phenomenon may be due to exacerbation of underlying autoimmune disease or induction of *de novo* autoimmune disease. Treatment of

Table 2: Poststeroid replacement parameters

Patient number	TSH (mIU/L)	ft4 (pmol/L)	Anti-TPO-Ab titer (U/L)	Time gap between two blood tests (months)
1	10.23	16.86	1,300,000	12
2	0.85	19.04	28,300	6
3	1.49	13.64	2000	7
4	5.2	13.51	57,200	8
5	3.01	15.19	738,000	4
6	2.97	23.80	66,800	5

TSH: Thyroid stimulating hormone, ft4: Free thyroxine, Anti-TPO-Ab: Anti-thyroid peroxidase antibody

Table 3: Changes in thyroid function and thyroid autoimmunity following steroid replacement

Parameters	Before replacement	After replacement	P
TSH (mIU/L)	11±3.45	3.95±3.42	0.005
ft4 (pmol/L)	13.25±4.12	16.99±3.86	0.146
Anti-TPO-Ab titer* (U/L)	311,000 (843,000)	62,000 (856,000)	0.60

*Expressed as median with inter-quartile range. TSH: Thyroid stimulating hormone, ft4: Free thyroxine, Anti-TPO-Ab: Anti-thyroid peroxidase antibody

cortisol deficiency was also associated with resolution of autoimmune disease like stiff-man syndrome.^[11]

To conclude, normalization of hypercortisolism (resolution of Cushing's syndrome) is associated with induction of autoimmunity and normalization of hypocortisolism (treatment of adrenal insufficiency) is associated with resolution of autoimmunity. Recent studies indicate that physiological levels of glucocorticoids have an immune-modulatory action causing a shift in patterns of cytokine production from a TH1 to the TH2 type pattern.^[12] Hence, glucocorticoid level in physiological level is required for optimal function of the immunity system. Based on the above concept, autoimmune diseases like primary hypothyroidism associated with idiopathic Addison's disease may not always present as the components of APS. Rather, they may just reflect the state of underlying cortisol deficiency.

Cortisol *per se* also controls the thyroid axis at the level of pituitary and hypothalamus both by direct and indirect mechanisms (through lipocortin 1 and somatostatin).^[13] In addition, glucocorticoid has the effect on diurnal variation

of thyroid hormones in the blood, i.e. the level of serum TSH decreases as cortisol in plasma increases during the daytime.^[13] Metyrapone administration leads to increase in serum TSH level by inducing hypocortisolemia.^[14] Similarly, glucocorticoids in physiological and pharmacological doses suppress the serum TSH level in euthyroid and hypothyroid subjects through an effect on the pituitary gland without alteration of serum thyroxine level.^[14] Hypercortisolism induces central hypothyroidism by lowering serum TSH and low cortisol increases serum TSH level leading to subclinical primary hypothyroidism.^[15,16] Hence, a physiological level of steroid is necessary for optimal thyroid function. There are also other proposed theories regarding the regulation of thyroid axis by cortisol. Hypothyroidism may be an adaptation of the body to hypocortisolism state, i.e., resistance to TSH at the level of thyroid and decrease in T3 and its nuclear receptors in the periphery.^[3,17] Thus, nonautoimmune mechanisms also contribute to hypothyroidism associated with Addison's disease.

In our case series, TSH normalized with decreasing titer of anti-TPO-Ab in patients 3, 4, and 6. This was caused by the resolution of thyroid autoimmunity with normalization of hypocortisolemia. However, the additional role of nonautoimmune mechanism could not be ruled out in them. But, this was the only mechanism in case of patients 2 and 5, where the resolution of hypothyroidism was not associated with decreasing titer of anti-TPO-Ab. Rather the antibody titer was increased significantly with normalization of TSH in patient 5. In the case of the first patient, TSH was decreased but not normalized with increasing titer of anti-TPO-Ab. Similar findings were found in a case report of Addison's disease with hypothyroidism by Petersen and Bergman.^[2] Thyroglobulin antibody was negative both at baseline and after steroid treatment. In addition, colloid antibody that was positive before treatment became negative after replacement. In contrast, the microsomal thyroid antibody titer increased despite improvement in TFT-like our patients 1 and 5. TSH was normalized within 2–6 weeks of steroid replacement in three pediatric subjects (2–14 years) in a case series by Abdullatif and Ashraf.^[16] All of their patients had low free T4 with high TSH level like our patients 2 and 4. However, they did not document the change in thyroid autoimmunity with the replacement of steroids.

It may take many months for normalization of TFT by steroid replacement alone in a subset of patients with Addison's disease like our first patient. One school of thought is to start thyroxine in all cases and then to taper cautiously later. However, there will be a risk of iatrogenic

thyrotoxicosis leading to the adrenal crisis. Therefore, European thyroid association guideline recommends considering thyroxine supplementation in case of persistent hypothyroidism after at least 4 weeks' of steroid replacement in these patients.^[1] The adrenal antibody was negative in all of our patients. However, neither adrenal antibodies nor baseline cortisol level was different in Addison's disease with/without hypothyroidism in a study by Barnett *et al.*^[18]

The major drawback of this study was limited sample size with variable duration of follow-up, maximum up to 12 months. Neither ultrasonography nor fine needle aspiration biopsy of thyroid was done in any of our patients.

CONCLUSIONS

It is important to recognize the concept of normalization of hypothyroidism with cortisol replacement in patients with Addison's disease and further study is required to look into the exact pathogenesis of this concept.

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Conflicts of interest

There are no conflicts of interest.

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