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Clinical, Metabolic, Immunological and Estrogen Axis Features in Different Phenotypes of Autoimmune Thyroiditis

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Abstract Autoimmune thyroiditis (AIT) is a heterogeneous endocrine disorder characterized by diverse clinical phenotypes and complex interactions between hormonal, immunological, and genetic factors. This study aimed to evaluate the clinical, metabolic, immunological, and estrogen-related characteristics of different AIT phenotypes and to assess the role of estrogen receptor gene (ESR1) polymorphism in disease expression. A total of 122 patients with confirmed AIT were included and stratified into hypothyroid (n=43), euthyroid (n=66), and thyrotoxic (n=13) forms, alongside a control group of 100 healthy individuals. Comprehensive assessment involved clinical and anthropometric evaluation, thyroid function testing (TSH, free T3, free T4), immunological markers (anti-TPO, anti-thyroglobulin, TRAb), ultrasound parameters, and estrogen axis indicators (estradiol, sex hormone-binding globulin [SHBG], and free estradiol index). ESR1 genotyping was performed to explore genetic associations. Significant intergroup differences were observed. The hypothyroid phenotype was associated with higher body mass index, increased prevalence of arterial hypertension, type 2 diabetes, and dyslipidemia. Hormonal profiles differed markedly across phenotypes, with elevated TSH and reduced thyroid hormones in hypothyroid patients and inverse patterns in thyrotoxicosis. Immunological markers were significantly elevated in all AIT groups compared to controls. Estrogen axis analysis revealed reduced estradiol levels and free estradiol index in hypothyroid patients, whereas thyrotoxic patients demonstrated increased estrogen bioavailability and lower SHBG levels. ESR1 polymorphism was significantly associated with variations in SHBG and free estradiol index, indicating its role in regulating estrogen bioavailability. These findings underscore the importance of endocrine-genetic interactions in AIT pathogenesis and support the potential for personalized approaches in disease management.

Keywords Autoimmune thyroiditis, ESR1 polymorphism, Estrogen axis, Thyroid hormones, Immunogenetics

1. Introduction

One of the most widespread organ-specific autoimmune disorders is autoimmune thyroiditis (AIT) which is a major problem in contemporary endocrinology because of its heterogeneous clinical symptoms and complicated pathogenesis [1,2]. The disease has a range of functional phenotypes; hypothyroid, euthyroid, and thyrotoxic with different hormonal, immunological, and metabolic profiles [3]. According to epidemiological research, the prevalence of AIT is about 510% of the population with a clear female bias, pointing to the possible involvement of sex гормonal factors in the predisposition and development of the disease [4,5].

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The current ideas of the AIT pathogenesis are based on the multifactorial model of genetic predisposition, immune dysregulation, and environmental triggers [6]. One of the central processes is the breakdown of immune tolerance to thyroid-specific antigens that causes lymphocytic infiltration of the gland and the formation of autoantibodies, especially against thyroid peroxidase (TPO) and thyroglobulin [7,8]. These immunological mechanisms result in gradual tissue and functional damage to the thyroid. Moreover, the importance of endocrineimmune interactions, especially the effects of estrogen signaling on immune modulation and autoimmunity, are growingly emphasized [9,10].

Estrogens have their biological activity mainly on estrogen receptors such as estrogen receptor alpha encoded by the ESR1 gene. It has been demonstrated that genetic polymorphisms of ESR1 can affect receptor activity and can potentially modify estrogen bioavailability and immune responses [11,12]. It has been proposed by several studies that ESR1 variants can be a cause of susceptibility to

autoimmune diseases through their influence on the production of cytokine and activation of immune cells [13]. Nevertheless, the interaction of polymorphic ESR1 with estrogen metabolism and the clinical phenotypes of AIT is not well studied.

In addition, metabolic disruptions including obesity, dyslipidemia, and insulin resistance are a common occurrence in patients with AIT, especially in hypothyroid forms, and are linked to a higher risk of cardiovascular risk [14,15]. These results reveal that thyroid dysfunction, metabolic regulation, and systemic inflammation interact in a complex manner.

Considering the clinical heterogeneity of AIT and the possibility of genetic and hormonal influences, it is necessary to thoroughly characterize phenotypes. Clinical, immunological, hormonal, and genetic information can be integrated to enhance an insight into the disease mechanisms and assist in the personalized approaches to management.

Thus, the objective of the current research was to examine the clinical, metabolic, immunologic, and estrogen-dependent features of various phenotypes of autoimmune thyroiditis and to determine the contribution of ESR1 gene polymorphism in regulating hormonal homeostasis and clinical manifestations.

2. Materials and Methods

Population and study design. The study was a prospective observational study carried out at Samarkand city endocrinology dispensary between 2023 to 2025. First, 194 suspected patients of autoimmune thyroid pathology were screened. The enrolled patients were 122 individuals who had known autoimmune thyroiditis (AIT). A control group comprised 100 age- and sex-matched seemingly healthy persons without a history of thyroid or autoimmune disease.

Inclusion and exclusion criteria. The inclusion criteria included clinically and laboratory-confirmed AIT of thyroid function tests and positive thyroid autoantibodies in adults. The exclusion criteria were pregnancy or lactation, taking of medications that influence thyroid functioning (e.g., amiodarone, lithium), recent exposure to iodinated contrast agents (within 3 months), thyroid surgery or radioiodine therapy, other autoimmune diseases, non-autoimmune thyroiditis.

Anthropometric and clinical evaluation. Each participant was thoroughly clinically assessed, with medical history, duration of the disease, and comorbidities. Body mass index (BMI) was measured. Blood pressure and metabolic parameters (type 2 diabetes and dyslipidemia) were also measured.

Phenotype classification. Thyroid functional status was used to stratify patients with AIT into three phenotypes; hypothyroid (n=43), euthyroid (n=66), and thyrotoxic (n=13), based on the levels of serum thyroid-stimulating hormone (TSH) and free thyroid hormone.

Lab and immunologic testing. Venous blood samples were taken under the standard conditions. Thyroid performance was determined through tests of serum TSH, free triiodothyronine (fT3) and free thyroxine (fT4). The immunological parameters were anti-TPO antibodies, anti-Tg antibodies and TSH receptor antibodies (TRAb). Evaluation of estrogen axis involved serum estradiol, sex hormone-binding globulin (SHBG) and calculated free estradiol index.

Ultrasound examination. Thyroid ultrasonography was done to all patients to evaluate the volume, echogenicity, and vascularization of the glands. Hypoechogenicity and increased vascular patterns were identified by standardized criteria.

Genetic analysis. The genetic analysis focused on the ESR1 gene polymorphism related to estrogen receptor α signaling. Genotyping was performed using PCR-based methods. ESR1 genotypes were classified as AA, AG, and GG, and genotype/allele frequencies were compared between hypothyroid, euthyroid, thyrotoxic AIT groups and healthy controls. Associations between ESR1 genotype and estrogen-axis parameters, including estradiol, SHBG, and free estradiol index, were assessed using appropriate comparative and regression analyses. Where applicable, age, sex, BMI, and thyroid functional status were considered as potential confounding factors.

Statistical analysis. Statistical analysis was done using standard software packages. Quantitative variables were given in terms of mean and standard deviation or median (interquartile range), depending on distribution. ANOVA or Kruskal-Wallis test was used to carry out intergroup comparisons. The chi-square (X^2) test or the Fisher exact test was used to compare categorical variables. A $p<0.05$ was taken as significant.

3. Results

Basic demographic and anthropometric data.

The patients (n=122) and the healthy controls (n=100) were analyzed. Table 1 illustrates that the study groups were similar in terms of age (p=0.214) and sex distribution (p=0.392) hence sufficient matching and reduction of confounding effects of these factors on future comparisons.

Nevertheless, there were also considerable disparities in anthropometric parameters. Body mass index (BMI) was highest in the patients with hypothyroid AIT (28.6±4.9 kg/m²) than in those with euthyroid (26.9±4.2 kg/m²) and those with thyrotoxic (24.7±3.8 kg/m 2) (Table 1, p=0.018). The same case was noticed with overweight and obesity prevalence, which was significantly greater in the hypothyroid group (67.4%), compared to other groups (Table 1, p=0.006).

Table 1. Baseline demographic and anthropometric characteristics

Parameter	Hypothyroid (n=43)	Euthyroid (n=66)	Thyrotoxic (n=13)	Control (n=100)	p-value
Age (years)	45.6 ±12.1	42.3 ±11.4	39.8 ±10.7	41.9 ±11.9	0.214
Female (%)	83.7	78.8	84.6	68.0	0.392
BMI (kg/m²)	28.6 ±4.9	26.9 ±4.2	24.7 ±3.8	25.6 ±3.9	0.018
Overweight/Obesity (%)	67.4	54.5	38.5	34.0	0.006
Smoking (%)	9.3	16.7	15.4	14.0	0.281
Family history of AID (%)	39.5	31.8	46.2	12.0	<0.001

Note: *Intergroup comparisons were performed using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test for non-normally distributed variables. Categorical variables were compared using Pearson's chi-square (χ^2) test or Fisher's exact test where appropriate. A p-value <0.05 was considered statistically significant. AID - autoimmune diseases.*

Table 2. Clinical characteristics and comorbidities

Parameter	*Hypothyroid*	*Euthyroid*	*Thyrotoxic*	*Control*	*p-value*
Disease duration (years)	6.1 (3.2-9.4)	4.3 (2.1-7.6)	2.4 (1.1-4.0)	—	<0.001
Hypertension (%)	41.9	28.8	23.1	21.0	0.046
Type 2 diabetes (%)	20.9	12.1	7.7	6.0	0.031
Dyslipidemia (%)	48.8	36.4	23.1	2.0	0.012
Goiter (%)	72.1	59.1	46.2	0	<0.001
Thyroid volume (cm³)	18.6 ±6.3	16.9 ±5.8	13.2 ±4.9	11.8 ±3.7	<0.001

Note: *Intergroup comparisons were performed using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test for non-normally distributed variables. Categorical variables were compared using Pearson's chi-square (χ^2) test or Fisher's exact test where appropriate. A p-value <0.05 was considered statistically significant.*

Table 3. Thyroid function and immunological parameters

Parameter	Hypothyroid	Euthyroid	Thyrotoxic	Control	p-value
TSH (mIU/L)	9.8 ±3.6	2.2 ±0.7	0.06 ±0.04	2.3 ±0.8	<0.001
Free T4 (pmol/L)	9.6 ±2.1	15.1 ±2.8	21.4 ±6.3	15.4 ±2.6	<0.001
Free T3 (pmol/L)	3.1 ±0.6	4.6 ±0.7	8.2 ±1.9	4.7 ±0.6	<0.001
Anti-TPO (+, %)	100	92.4	92.3	0	<0.001
Anti-Tg (+, %)	72.1	59.1	46.2	0	<0.001
TRAb (+, %)	0	0	69.2	0	<0.001

Note: *Intergroup comparisons were performed using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test for non-normally distributed variables. Categorical variables were compared using Pearson's chi-square (χ^2) test or Fisher's exact test where appropriate. A p-value <0.05 was considered statistically significant.*

Table 4. Estrogen axis parameters

Parameter	Hypothyroid	Euthyroid	Thyrotoxic	Control	p-value
Estradiol (pmol/L)	148 ±66	170 ±72	214 ±88	186 ±80	0.012
SHBG (nmol/L)	58.9 ±22.1	53.1 ±20.4	41.6 ±16.9	61.8 ±23.4	<0.001
Free estradiol index	2.76 ±1.18	3.34 ±1.42	4.62 ±1.71	3.65 ±1.58	<0.001

These results indicate that there is a close relationship between impaired thyroid functioning and metabolic imbalance which could be mediated by a slowing down of basal metabolism and lipid metabolism. Moreover, autoimmune diseases in the family history were more prevalent in AIT patients (Table 1, p<0.001), which confirms the importance of genetic predisposition in the formation of diseases. Conversely, there was no significant difference in smoking prevalence between groups (p=0.281), which means that the role of the given behavioral factor in the cohort under study was not significant.

Clinical features and comorbidities.

Clinical characteristics analysis showed a high level of heterogeneity among AIT phenotypes (Table 2). The duration of the disease was the longest in the hypothyroid group (6.1 [3.299.4] years), then the euthyroid and thyrotoxic ones (Table 2, p<0.001), which indicates the progressive course of the autoimmune destruction of the functioning.

Hypothyroid patients had a significant higher prevalence of cardiometabolic comorbidities. This group had the highest rate of arterial hypertension (41.9%), type 2 diabetes (20.9%), and dyslipidemia (48.8%), all p<0.05 (Table 2).

The results suggest that hypothyroid AIT has a clustering of metabolic risk factors that can lead to a higher cardiovascular morbidity.

Moreover, hypothyroid patients had more structural thyroid changes. Goiter was widespread (72.1%), and the volume of thyroid was greatly enlarged (18.6±6.3 cm 3) in comparison with other groups (Table 2, p<0.001). It indicates chronic inflammatory remodeling and fibrosis of thyroid tissue.

Thyroid status and immunological test.

The parameters of thyroid functioning varied significantly among phenotypes as shown in Table 3. Hypothyroid AIT patients had a very high TSH level (9.8±3.6 mIU/L) compared to thyrotoxic AIT patients (0.06±0.04 mIU/L) (p<0.001).

On the other hand, the levels of free T3 and free T4 were lowest in hypothyroid patients and highest in thyrotoxic patients (Table 3, p<0.001), which is indicative of different functional conditions of thyroid hormone synthesis and regulation.

The immunological analysis showed that all AIT groups had high levels of thyroid-specific autoantibodies. High levels of autoimmune activity were observed with 100% positive anti-TPO in patients with hypothyroidism and over 90% in other phenotypes (Table 3, p<0.001). Interestingly, TSH receptor antibodies (TRAb) were only present in the thyrotoxic group (69.2%), which is an indication of a congruence with the Graves-like immunopathological processes.

These results corroborate that although all AIT phenotypes have an autoimmune basis, the immunological profile is different according to the functional status, with more complicated antibody patterns in thyrotoxicosis.

Polymorphism of estrogen axis and ESR1. Considerable variations in estrogen related parameters were observed between groups (Table 4). The lowest level of estradiol was in the patients having hypothyroidism (148±66 pmol/L) and the highest in the thyrotoxic patients (214±88 pmol/L) (Table 4, p=0.012).

Compared to the control group (76.0467 nmol/L), there was a significant decrease in the SHBG levels in the thyrotoxic group (41.6±16.9 nmol/L), and a maximum value of the free estradiol index was observed in the thyrotoxic group (4.62±1.71) (Table 4, p<0.00 This trend indicates that there is augmented bioavailability of estrogen in hyperthyroid conditions, probably because of modified synthesis of binding proteins in the liver.

The results showed that ESR1 genotype was significantly associated with SHBG and free estradiol index, but not with total estradiol level. This suggests that ESR1-related variation may be linked more closely to estrogen bioavailability than to absolute estradiol concentration. However, because the study was observational, these associations should not be interpreted as causal. They indicate a possible relationship between estrogen receptor genetic variability and hormonal regulation in different AIT phenotypes.

Notably, gene polymorphism analysis of ESR1 showed significant correlations with SHBG (p=0.003) and free estradiol index (p=0.001), but not with total estradiol concentration (p=0.421). These results suggest that ESR1 polymorphism is a major determinant of the estrogen bioavailability instead of the absolute levels of the hormone.

Pathophysiologically, this indicates that endocrine-immune interactions can be altered by genetic variation in the estrogen receptor signaling pathway, and it is involved in phenotypic variability in AIT. This process might be one of the reasons of the female predominance and heterogeneity of the disease manifestation.

4. Conclusions

Autoimmune thyroiditis demonstrates marked clinical, metabolic, immunological, and endocrine heterogeneity. ESR1 polymorphism was associated with SHBG and free estradiol index, suggesting a possible role in estrogen bioavailability. Nevertheless, these findings are associative and require confirmation in larger studies with detailed hormonal stratification and functional genetic analysis.

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