

Characteristics of the Thyroid Profile in Various Clinical Forms of Glomerulonephritis and Correlations with the Cytokine System

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Abstract When the cytokine cascade reaction is stimulated and the factors of innate and adaptive immunity are activated under pathogenic conditions, the hypothalamic-pituitary-thyroid axis is activated simultaneously. The process of activation of this axis is a manifestation of the adaptive ability of the body, which is aimed at maintaining homeostasis in response to external stimuli, such as exposure to various microorganisms or psychological stress. *The purpose of our study* was to determine the pituitary-thyroid status in patients with various forms of glomerulonephritis and to study the relationship between indicators of thyroid status with indicators of cytokine, immune status, as well as other clinical and laboratory parameters in patients with glomerulonephritis. **Results and conclusions.** an analysis of the study of the state of thyroid status and the available correlations with the rest of the studied indicators of patients with various forms of GN revealed that 88.1% of patients with nephrotic form of GN and 56.3% with mixed form of GN revealed changes in the level of hormonal status of the pituitary-thyroid system characteristic of hypothyroidism. In the hypertensive form of GN, only 17.2% of patients were diagnosed with a hypothyroid condition. The indicators of thyroid status in the group of patients with latent GN did not differ from these indicators in the healthy group. After analyzing the correlations, it is possible to conclude about the negative effect of TSH hormone and autoantibodies to TPO on the functional state of the kidneys, while the positive effect of thyroid hormones – free T4 and free T3 on kidney function has been determined.

Keywords Glomerulonephritis, Thyroid hormones, Hypothyroidism, Cytokines, Interleukins

1. Introduction

The neuro-immune-endocrine system is a complex and multifunctional system with various regulatory mechanisms. It is believed that various diseases have common pathogenetic connections in this regulatory system, despite various clinical manifestations. It is known that many mediators produced by immunocompetent cells, such as lymphokines, interferons and interleukins, have hormonal properties [1,2,31,32,33,34,35]. The hypothalamic-pituitary-adrenal system controls the synthesis of antibodies and the release of mature B lymphocytes from the bone marrow. It should be noted that neuropeptide receptors have been found on cells of the immune system, through which the endocrine system can participate in regulating the body's immunoreactivity and vice versa, which shows how the immune and endocrine systems are interconnected with each other.

When the cytokine cascade reaction is stimulated and the

factors of innate and adaptive immunity are activated under pathogenic conditions, the hypothalamic-pituitary-thyroid axis is activated simultaneously. The process of activation of this axis is a manifestation of the adaptive ability of the body, which is aimed at maintaining homeostasis in response to external stimuli, such as exposure to various microorganisms or psychological stress [1,3,5,7,9,11,13,15,17,19,21,23,25,27,29].

Thanks to a number of studies, it is known about the mutual influence of the metabolism of thyroid, pituitary hormones and the functioning of the urinary system [2,4,6,8,10,12,14,16,18,20,22,24,26,28,30]. Considering the above, the study of thyroid status in patients with glomerulonephritis (GN) is of practical interest, especially depending on its forms and the level of pituitary-thyroid hormones.

Based on the above, the purpose of our study was to determine the pituitary-thyroid status in patients with various forms of GN and to study the relationship between indicators of thyroid status with indicators of cytokine, immune status, as well as other clinical and laboratory parameters in patients with glomerulonephritis.

2. Materials and Methods

Our study involved 103 patients with GN, aged 16 to 58 years (average age 35.6 ± 2.8). The average duration of GN in the examined patients was 3.8 ± 1.1 years. The diagnosis was established on the basis of the results of a clinical examination, data from laboratory and instrumental research methods. Depending on the clinical form of GN, patients were divided into four groups: group I (n=28) – patients with latent form of GN; group II (n=25) – patients with nephrotic form of GN; group III (n=25) – patients with hypertensive form of GN; Group IV (n = 25) – patients with a mixed form of GN.

To determine the cytokine content in the blood serum of the studied groups, a three-stage "sandwich" method was used - this is a type of three-phase ELISA. The concentration of interleukin-IL-1 β , IL-8, IL-10, IFN- γ was determined using a set of reagents from the company Vector-Best (Novosibirsk).

3. Results and Discussion

First, we decided to study the prevalence of thyroid pathology in GN, in which it was found that they did not have significant differences from the healthy group (Table 1). The unchanged euthyroid state of the thyroid gland was noted in most patients with GN and in the healthy group.

Table 1. The prevalence of thyroid diseases in patients with GH and healthy individuals (%)

Thyroid disease	Patients with GN n=103	A group of healthy people n=20
Euthyroidism	60,14 \pm 34,65	60,0 \pm 4,63
Nodular euthyroid goiter	10,51 \pm 4,15	15,0 \pm 3,72
Diffuse euthyroid goiter	25,22 \pm 3,61	25 \pm 4,84
Autoimmune thyroiditis	0	0

Subsequent ultrasound examination of the thyroid gland revealed no differences in different groups of patients with glomerulonephritis. (Table 2). As we can see, according to the results presented in the table 2. a greater number of patients with normal thyroid function were found in the group of patients with hypertensive GN, diffuse goiter in patients with latent GN, and nodular euthyroid goiter was more often detected in patients with nephrotic and hypertensive forms of GN.

The results of studies conducted by many scientists confirm the impossibility of accurately reflecting the functional state of the thyroid gland and the general metabolic status of the body with the level of hormone T4. Therefore, it cannot be used as a criterion for determining the presence of dysthyroidism. However, information about the content of TSH hormone and free fractions of thyroid hormones in the blood is a

significant indicator of the state of the pituitary-thyroid axis. [6,8].

Table 2. The prevalence of thyroid diseases in patients with GH, depending on the clinical form of the disease

	Clinical forms of GN			
	Latent n=28	Nephrotic n=25	Hypertensive n=25	Mixed n=25
Standard	59,03 \pm 7,84 (16)	60,0 \pm 7,9 (15)	64,0 \pm 8,23 (16)	60,0 \pm 7,9 (15)
Nodular euthyroid goiter	17,27 \pm 5,9 (5)	20,0 \pm 6,9 (5)	20,0 \pm 6,9 (5)	16,0 \pm 7,75 (4)
Diffuse goiter	24,33 \pm 6,72 (7)	20,0 \pm 6,9 (5)	16,0 \pm 7,75 (4)	20,0 \pm 6,9 (5)

The study was conducted among patients with GN in order to study the initial values of TSH, free T4, free T3 and the level of antibodies to TPO. Analysis of the results revealed that the levels of TSH hormone and autoantibodies to TPO in patients with GN were higher than those in the control group, with the exception of the latent form of the disease (Fig. 1.). At the same time, patients with nephrotic and hypertensive forms of glomerulonephritis had the highest average values of these indicators. In the group of patients with latent GN, there was a statistically significant decrease in the hormone TSH and anti-TPO compared with other forms of GN. The index of free T4 in patients with nephrotic and mixed forms of GN was lower than in the control group (Fig. 1.).

Further, the pituitary-thyroid status was considered depending on the clinical form of GN, and according to Fig. 1. and Fig. 2. The most pronounced changes in this status were observed in patients with nephrotic GN: in 14 (51%) patients with this form of GN, the blood content of free T4 was lower than the value of this indicator in healthy people, and the level of TSH was higher than the value corresponding to this indicator in healthy people. Thus, 51% of patients with nephrotic GN had laboratory signs of hypothyroidism.

By the end of the inpatient treatment period, TSH hormone levels remained high in patients with hypertension. The lowest knowledge of this hormone was observed in patients with a latent form of GN, who also had a low anti-TPO level by the end of treatment, but the level of free T4 was maximum compared with those with other forms of GN. In patients with nephrotic and mixed forms of GN, the level of free T4 was lower than in the healthy group, and this indicator was lowest in patients with latent form of GN, while the content of free T4 was highest relative to the levels of patients with other forms of the disease (Fig. 2).

Further, for a more complete comprehensive assessment of the thyroid system, some integral indicators were used:

1) ITI (T3fr.+T4fr.) / TTG; 2) T4sv./T3sv; 3) T4sv./TSH, which allowed for a more complete interpretation of the existing condition (Fig. 3.).

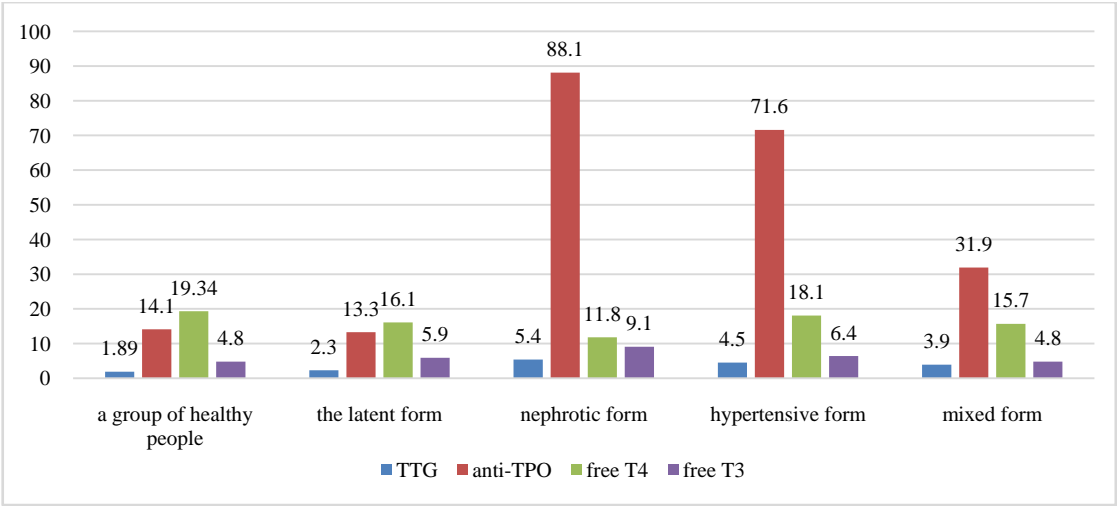


Figure 1. Thyroid hormone levels in various forms of GN before inpatient treatment

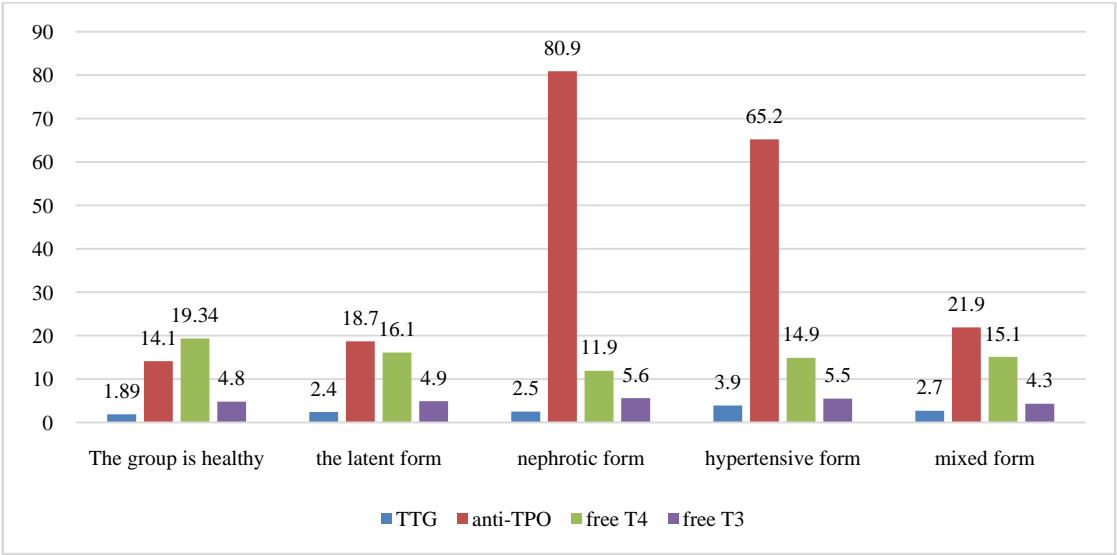


Figure 2. Thyroid hormone levels in various forms of GH after inpatient treatment

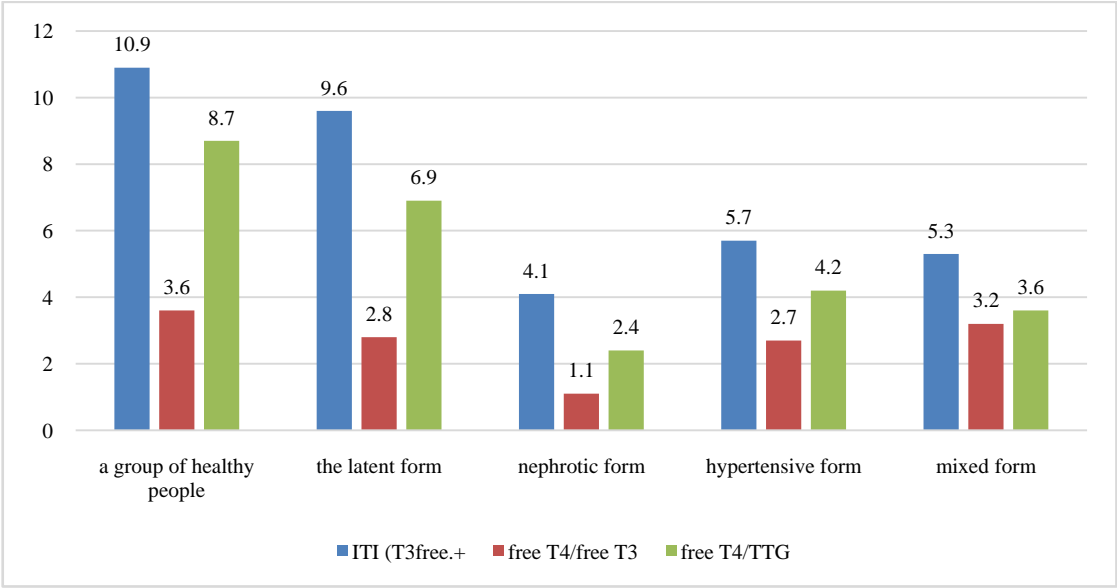


Figure 3. Integral indicators of thyroid status in various forms of GN before inpatient treatment

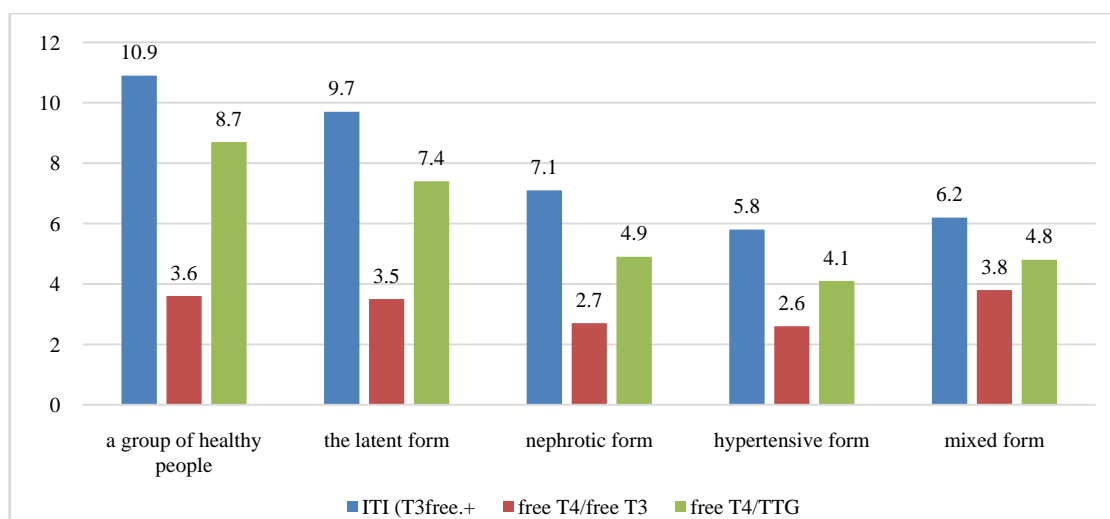


Figure 4. Integral indicators of thyroid status in various forms of GN after inpatient treatment

Table 3. Correlations of indicators of functioning of the pituitary-thyroid system in patients with GN

	TTG (1)	TTG (2)	free T4 (1)	free T4 (2)	free T4 (1)	free T4	anti-TPO (1)	anti-TPO (2)
TTG (1)		0,39		-0,28				0,34
TTG (2)	0,41						0,26	0,36
free T4 (1)				0,21			-0,42	-0,30
free T4 (2)			0,24					
free T3 (1)						0,45	-0,21	
free T3 (2)					0,46		-0,19	
anti-TPO (1)		0,26	-0,39		-0,20	-0,21		0,41
anti-TPO (2)	0,33	0,34	-0,31				0,40	

Note:

(1) and (2) are the values of indicators on the 1st–2nd and 14th–15th day of inpatient treatment, respectively.

Assessment of the functioning of the pituitary-thyroid system using integral indicators showed their change in all forms of GN, the smallest changes were observed in the latent form, the most pronounced – in the nephrotic form of GN.

One of the integral indicators, ITI– was reduced in all groups, except for the group of patients with latent form of GN. When comparing the values of integral indicators between groups of patients, it was revealed that the group of patients with nephrotic GN differed most markedly from others, this group was characterized by the lowest values of integral indicators ($P < 0.01$). And for patients with latent GN, the integral indices of ITI and free T4/TSH had the highest readings (Fig. 4.).

It is important to point out that due to the fact that there is a negative logarithmic relationship between the levels of T4 and the hormone TSH, even a slight decrease in the level of free T4 leads to a fairly significant increase in the concentration of TSH.

It is known that subclinical hypothyroidism is characterized by a moderate increase in the concentration of the hormone TSH in the blood at normal levels of free T4 and free T3. Among the examined patients, 10 (35.7%) patients showed an increase in TSH levels at the concentration of free T4 at

the levels of the control group, that is, it can be stated that these patients have subclinical hypothyroidism, moreover, the largest number of these changes was revealed among 88.2% of patients with nephrotic GN, in whom laboratory signs of varying severity were revealed hypothyroidism.

Next in the incidence of thyroid disorders is a mixed clinical form of GN, in which 10 (35.7%) patients had free T4 levels below the control values, and the level of the hormone TSH was higher than the control group. In 4 (17.2%) patients with this form, the levels of free T4 had normal values together with high levels of the hormone TSH. Thus, 56.3% of patients with mixed GN had signs of hypothyroidism. Among the examined 25 patients with hypertension, only 1 patient had a complete picture of hypothyroidism (decrease in free T4 and increase in TSH hormone), 4 patients had an isolated increase in TSH (subclinical hypothyroidism). In total, we can say that with the hypertensive form of the disease, 17.2% of patients had a hypothyroid condition. In patients with latent form of GN, the thyroid status practically did not differ from this status in the control group.

Correlation analysis of thyroid status indicators in the examined patients with GN revealed an inverse relationship between the concentration of anti-TPO and the levels of thyroid hormones – free T4 and free T3 (Table 3). In contrast

to these relationships, the levels of anti-TPO and TSH had a positive correlation relationship.

Table 4. The relationship between all studied indicators and indicators of thyroid status in patients with GN

Indications	Anti-TPO (1)	TTG (1)	TTG (2)	Free T4 (1)	Free T4 (2)	Free T3 (1)	Free T3 (2)
IL-1 β (1)		0,38		-0,24	-0,38	0,35	
IL-1 β (2)			0,61				
RAIL-1 β (2)			0,57				
RAIL-1 β (1)			0,31				
IL-4 (1)				-0,37			
IFN- γ (1)				0,34			
CD3+-lymphocytes, % (1)	0,28						
CD8+-lymphocytes, abs (2)			0,26				
CD20+-lymphocytes, abs (1)							
CD20+-lymphocytes, % (2)			-0,24				
CD20+-lymphocytes, abs (2)		-0,19	-0,26				
CD25+-lymphocytes, % (1)		-0,33		0,28	0,15		
CD25+-lymphocytes, abs (1)		-0,38					
IgM (2)			0,18				
IgA (1)					-0,29		
IgA (2)			0,23				
Phagocytic index (2)							-0,28
Red blood cells (1)		-0,32		0,37		0,18	
Erythrocytes in the blood (2)	-0,19	-0,31			0,28	0,17	
ESR (1)		0,49		-0,39			
Creatinine in the blood (1)	0,19	0,35		-0,14			
Creatinine in the blood (2)	0,19			-0,21		-0,25	
Total protein in the blood (1)		-0,25					
Urea in the blood (2)				-0,14			
Albumin in the blood (1)			-0,37				
AsAT (2)	0,22						
CRP (2)	0,21					-0,22	-0,29
Specific gravity of urine (1)			-0,18	0,24			
Specific gravity of urine (2)	-0,23	-0,31	-0,27		0,38		
Daily diuresis (1)	-0,15						
Protein in urine (1)	0,28			-0,32		-0,18	
Protein in urine (2)				-0,26			
Hyaline cylinders in urine (1)		0,25		0,22			
Hyaline cylinders in urine (2)	-0,19	0,17			-0,19	-0,17	-0,41
Granular cylinders in urine (1)				-0,24			
Granular cylinders in urine (2)				-0,21			
Erythrocytes in urine (1)						-0,34	
Erythrocytes in urine (2)						-0,28	
Creatinine in urine (1)							
Daily diuresis (1)	-0,17					0,23	0,24
Daily diuresis (1)				0,19			
GFR (1)		-0,35					
Tubular reabsorption (1)		-0,37					

The most interesting and promising in practical terms were the results of a correlation analysis between indicators of thyroid status, cytokine and immune systems, with indicators reflecting the functional state of the kidneys, in the studied groups of patients (Table 4). According to the data obtained, the level of free T4 had correlations with a number of laboratory parameters of urine and blood, which showed the functional state of the kidneys: positive associations with the specific gravity of urine, the amount of urine excreted, creatinine in urine and negative – with the content of protein, hyaline cylinders in urine. The level of the same hormone had positive correlations with the content of erythrocytes, CD25+ lymphocytes and IFN- γ in the blood, and negatively with the levels of IL-1 β , IL-8, ESR, creatinine and urea in the blood serum. The correlations of free T3 largely reflected those of free T4.

The nature of the relationship between these indicators and the TSH level was completely different. The TSH content had a negative relationship with the expression level of CD25+ lymphocytes, total protein, blood albumin, GFR, tubular reabsorption, specific gravity of urine, as well as a positive relationship with the level of IL-1 β , blood creatinine, ESR, hyaline cylinders in urine.

The nature of the relationship between the level of autoantibodies to TPO and many of the considered indicators is similar to the relationship between the level of TSH and the same indicators. Special attention should be paid to the correlations found in the integral indicator – ITI. The ITI indicator had the same spectrum of connections as the free hormones T4 and T3, but unlike them, most correlations of values in the ITI indicator were moderate or strongly pronounced.

Thus, an analysis of the study of the state of thyroid status and the existing correlations with the rest of the studied indicators of patients with various forms of GN revealed that 88.1% of patients with nephrotic form of GN and 56.3% with mixed form of GN revealed changes in the level of hormonal status of the pituitary-thyroid system characteristic of hypothyroidism. In the hypertensive form of GN, only 17.2% of patients were diagnosed with a hypothyroid condition. The indicators of thyroid status in the group of patients with latent GN did not differ from these indicators in the healthy group. After analyzing the correlations, it is possible to conclude about the negative effect of TSH hormone and autoantibodies to TPO on the functional state of the kidneys, while the positive effect of thyroid hormones – free T4 and free T3 on kidney function has been determined.

4. Conclusions

1. Studying the state of thyroid status and the available correlations with the rest of the studied indicators of patients with various forms of GN, revealed that 88.1% of patients with nephrotic form of GN and 56.3% with mixed form of GN revealed changes in the level of hormonal status of the pituitary-thyroid

system, characteristic of hypothyroidism.

2. In the hypertensive form of GN, only 17.2% of patients were diagnosed with a hypothyroid condition. The indicators of thyroid status in the group of patients with latent GN did not differ from these indicators in the healthy group. After analyzing the correlations, it is possible to conclude about the negative effect of TSH hormone and autoantibodies to TPO on the functional state of the kidneys, while the positive effect of thyroid hormones – free T4 and free T3 on kidney function has been determined.

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