THYROID STATUS AND TNF-ALPHA IN POST-REPRODUCTIVE WOMEN WITH COVID-19 AND 12 MONTHS AFTER THE DISEASE

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ABSTRACT

The aim. *To assess the thyroid status and its relationship with tumor necrosis factor alpha (TNF-alpha) in post-reproductive women in the acute phase of the COVID-19 of moderate course and 12 months after the disease.*

Materials and methods. *85 women aged 45 to 69 years were divided into groups: women without COVID-19, not vaccinated, with no antibodies to COVID-19 (IgG) – control group (n = 15); women in the acute phase of COVID-19 of a moderate course, accompanied by pneumonia – main group (n = 57); patients from the main group who agreed to be examined 12 months after having COVID-19 (n = 14); women with IgG in blood who deny any symptoms of COVID-19 in the last 12 months – asymptomatic COVID-19 (n = 13). Using hormone replacement therapy and the presence of thyroid disease in history were the exclusion criteria from the study.*

Results. *75.4 % of patients with COVID-19 had euthyroidism, 12.3 % had subclinical hyperthyroidism. An increase of free thyroxine (free T4) level in women with COVID-19 as compared to the control group (p = 0.004) and the group with asymptomatic COVID-19 (p = 0.054) was found. There was no statistically significant difference in the level of thyroid stimulating hormone between the groups. The level of C-reactive protein in women with COVID-19 was naturally higher as compared to the control group (p = 0.009) and the group of asymptomatic patients (p = 0.001). A lower TNF-alpha level was found in the group of patients without clinical signs of COVID-19 as compared to the control group (p = 0.007) and the group with COVID-19 (p = 0.00007). The analysis of correlation relationships revealed a positive correlation between of free T4 and TNF-alpha levels in women with COVID-19 (r = 0.38; p = 0.004).*

Conclusions. *The moderate course of COVID-19 in the post-reproductive women is associated with an increase of free T4 level, which positively correlates with TNF-alpha level. Twelve months after COVID-19, thyroid status in women remains at the level of the acute phase of the disease.*

Key words: *COVID-19, long-term consequences, thyroid status, tumor necrosis factor alpha, post-reproductive period*

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ТИРЕОИДНЫЙ СТАТУС И ФНО-АЛЬФА У ЖЕНЩИН В ПОСТРЕПРОДУКТИВНОМ ПЕРИОДЕ С COVID-19 И ЧЕРЕЗ 12 МЕСЯЦЕВ ПОСЛЕ ЗАБОЛЕВАНИЯ

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РЕЗЮМЕ

Цель исследования. *Оценка тиреоидного статуса и его взаимосвязь с фактором некроза опухоли альфа (ФНО-альфа) у женщин в пострепродуктивном периоде в острую фазу среднетяжёлого течения COVID-19 и через 12 месяцев после заболевания.*

Методы. *85 женщин в возрасте от 45 до 69 лет были разделены на группы: женщины, не болевшие COVID-19, не привитые, с отсутствием антител к COVID-19 (IgG) – контроль (n = 15); женщины в острой фазе COVID-19 со среднетяжёлым течением, сопровождающимся пневмонией – основная группа (n = 57); пациентки из основной группы, согласившиеся пройти обследование через 12 месяцев после COVID-19 (n = 14); женщины с наличием в крови IgG, отрицающие какие-либо симптомы COVID-19 за последние 12 месяцев – бессимптомное течение COVID-19 (n = 13). Женщины, принимающие заместительную гормональную терапию, имеющие в анамнезе заболевания щитовидной железы, были исключены из исследования.*

Результаты. *У 75,4 % пациенток с COVID-19 отмечен эутиреоз, в 12,3 % случаев – субклинический гипертиреоз. Выявлено повышение уровня свободного тироксина (Т4св.) в группе женщин с COVID-19 по сравнению с контролем (p = 0,004) и группой переболевших COVID-19 бессимптомно (p = 0,054). Не выявлено статистически значимой разницы по уровню тиреотропного гормона между исследуемыми группами. Уровень С-реактивного белка в группе женщин с COVID-19 был закономерно выше по сравнению с контролем (p = 0,009) и с группой переболевших бессимптомно (p = 0,001). Выявлен более низкий уровень ФНО-альфа в группе переболевших без клинических признаков по сравнению с контролем (p = 0,007) и с группой с COVID-19 (p = 0,00007). При анализе корреляционных взаимосвязей выявлена положительная корреляция между уровнем Т4св. и ФНО-альфа у женщин с COVID-19 (r = 0,38; p = 0,004).*

Заключение. *Среднетяжёлое течение COVID-19 у женщин в пострепродуктивном периоде ассоциировано с повышением Т4св., который положительно коррелирует с уровнем ФНО-альфа. Через 12 месяцев после COVID-19 тиреоидный статус у женщин сохраняется на уровне острой фазы заболевания.*

Ключевые слова: *COVID-19, отдалённые последствия, тиреоидный статус, фактор некроза опухоли альфа, пострепродуктивный период*

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OBJECTIVES

The COVID-19 pandemic caused by the SARS-CoV-2 virus has left its mark in history as a public health emergency of international concern. Although it is predominantly a respiratory disease, evidence suggests that it is characterized by multi-organ system damage [1, 2]. With increasing age, the vulnerability to moderate and severe COVID-19 and subsequent complications is known to be higher [3], with men having a more severe course of the disease [4], but in old age, sex differences in the course of COVID-19 are leveled off, which may be associated with a decrease in estrogen levels in women in the post-reproductive period [5].

Age-related estrogen deficiency in women is considered to be one of the principal causes of the various organs disorders development, including Thyroid disease [6–10]. The incidence of most Thyroid disorders is known to be high in postmenopausal and elderly women, which may lead to increased cardiovascular risk, bone fractures, cognitive impairment, depression and mortality [10].

Some studies have shown that the thyroid gland may be a target organ for SARS-CoV-2 with the development of its dysfunction during and after COVID-19 [11–13]. Thyroid status evaluation after prolonged time from recovery after COVID-19 has been performed in few studies [14, 15], and there are no studies in the available literature evaluating thyroid status 12 months after COVID-19. This may be due to the assumption of a duration of up to 6 months for the Post-COVID-19 syndrome, which is why most studies are limited to this time frame [16–18]. In addition, studies do not indicate the effect of age on changes in thyroid status in COVID-19, which may play a role in analyzing the findings [19]. Equally, it is of interest to evaluate the correlations of thyroid hormones with tumor necrosis factor alpha (TNF-alpha) in COVID-19. This cytokine plays a significant role in the pathogenesis of thyroid cancer [20], and in COVID-19 there is a statistically significant increase in its level, and TNF-alpha is considered a risk factor for death in patients with severe or critical COVID-19 [21].

THE AIM OF THE STUDY

Thyroid status evaluation in post-reproductive women with COVID-19 of a moderate course during the acute phase and 12 months after the disease, as well as correlations of thyroid hormones with tumor necrosis factor alpha in the acute phase of COVID-19.

MATERIALS AND METHODS

A short-term longitudinal case-control study was conducted.

The study included 94 women aged 45 to 69 years. In order to be selected into the main cohort, 64 women hospitalized in the Irkutsk Regional Infectious Clinical Hospital in the period from June 2020 to March 2021 with laboratory-confirmed PCR test for the presence of SARS-CoV-2 virus and moderate course of COVID-19 accompanied by pneumonia were examined. Upon admission of the patients to the hospital, questionnaires and analysis of medical records, general clinical examination, and computed tomography were performed. After clinical and anamnestic examination, 7 women with a history of thyroid disorder (manifest forms of the disease: autoimmune thyroiditis – 3; thyrotoxicosis – 1; hypothyroidism – 1; Graves' disease – 1; nontoxic goiter – 1) were excluded. Thus, the main cohort included 57 women (mean age 58 ± 6.33 years). Fourteen women who were called for a clinical and anamnestic examination agreed to be examined after 12 months from those who had survived COVID-19.

Thirty women who denied any symptoms of COVID-19 and had not been vaccinated in the past 12 months were examined to form a control group. The presence of COVID-19 IgG antibodies in blood was determined in all women, after which two groups were formed: without IgG (n = 17) and with IgG (n = 13). Two women with thyroid dysfunction were excluded from the group without IgG; thus, 15 women (mean age, 56 ± 6.52 years) formed the control group for comparison with the main cohort and the group of women who agreed to be examined 12 months after COVID-19. 13 women with IgG in their blood formed a separate group with asymptomatic COVID-19 (mean age, 54 ± 7.59 years).

The use of hormone replacement therapy (HRT) was a criterion for not including women in the study.

All study participants were examined by a general practitioner-cardiologist with calculation of body mass index (BMI), measurement of blood pressure, body temperature, and electrocardiogram. To exclude the presence of COVID-19 at the time of the study, an appropriate rapid test (RAPID BIO, Russia) was performed.

Venous blood was used for laboratory tests, which was collected from 8.00 to 9.00 AM on an empty stomach in accordance with generally accepted requirements. Blood was centrifuged for 10 min at 1,500 rpm, serum was separated and stored at –40 °C until assayed.

Thyroid status indicators were determined: free thyroxine (free T4), thyroid stimulating hormone (TSH)), IgG, C-reactive protein (CRP) and TNF-alpha levels. IgG level was determined on Multiscan Go analyzer (Thermo Scientific, Finland) using Vector-Best commercial kits (Russia). The concentration of free T4 (pmol/l) and TSH (mmol/l) was determined by enzyme immunoassay on Microplate reader ELx808 analyzer (USA) using Alkor Bio commercial kits (Russia); CRP (pg/ml) and TNF-alpha (pg/ml) – using Vector-Best commercial kits (Russia).

Informed consent to participate in the study was signed by each woman. The study protocol was reviewed and approved by the Biomedical Ethics Committee of Scientific Centre for Family Health and Human Reproduction Problems (excerpt from the minutes of the meeting No. 6.1 of June 19, 2020).

Statistical analysis

No pre-calculation of sample size was made. The data obtained were processed in Statistica 10 program (StatSoft Inc., USA). The proximity to the normal law of distribution of quantitative signs was evaluated by visu-

al-graphical method, as well as Kolmogorov – Smirnov (K-S) test (with Lilliefors correction) and Shapiro – Wilk (S-W) test. Data for age and BMI are presented as arithmetic mean ± standard deviation (m ± σ); for laboratory parameters, as median and interquartile range (Me [Q1; Q3]). Intergroup differences for independent samples were analyzed using the Kruskal – Wallis test (ANOVA) and the median test followed by post hoc comparisons using the Mann – Whitney U test. Intragroup differences were analyzed using the Wilcoxon test. Pearson correlation analysis with determination of correlation coefficient (*r*) was used to analyze the relationships between the indicators. The significance level was taken as 5 % (0.05).

RESULTS

In the first step, we analyzed the distribution of COVID-19 patients according to specified free T4 and TSH intervals. In most cases, euthyroidism was noted in the patients, and subclinical hyperthyroidism was registered in 12.3 % of cases (Table 1).

TABLE 1

DISTRIBUTION OF PATIENTS WITH COVID-19 DEPENDING ON THYROID STATUS

Free T4 10.0-23.2 pmol/l	TSH 0.23–3.4 mmol/l	Patients with COVID-19
↔	↔	43 (75.4 %)
↔	↑	3 (5.3 %)
↔	↓	7 (12.3 %)
↑	↔	2 (3.5 %)
↓	↔	1 (1.75 %)
↓	↑	1 (1.75 %)

Note. ↔ – within reference values; ↓ – below reference values; ↑ – above reference values

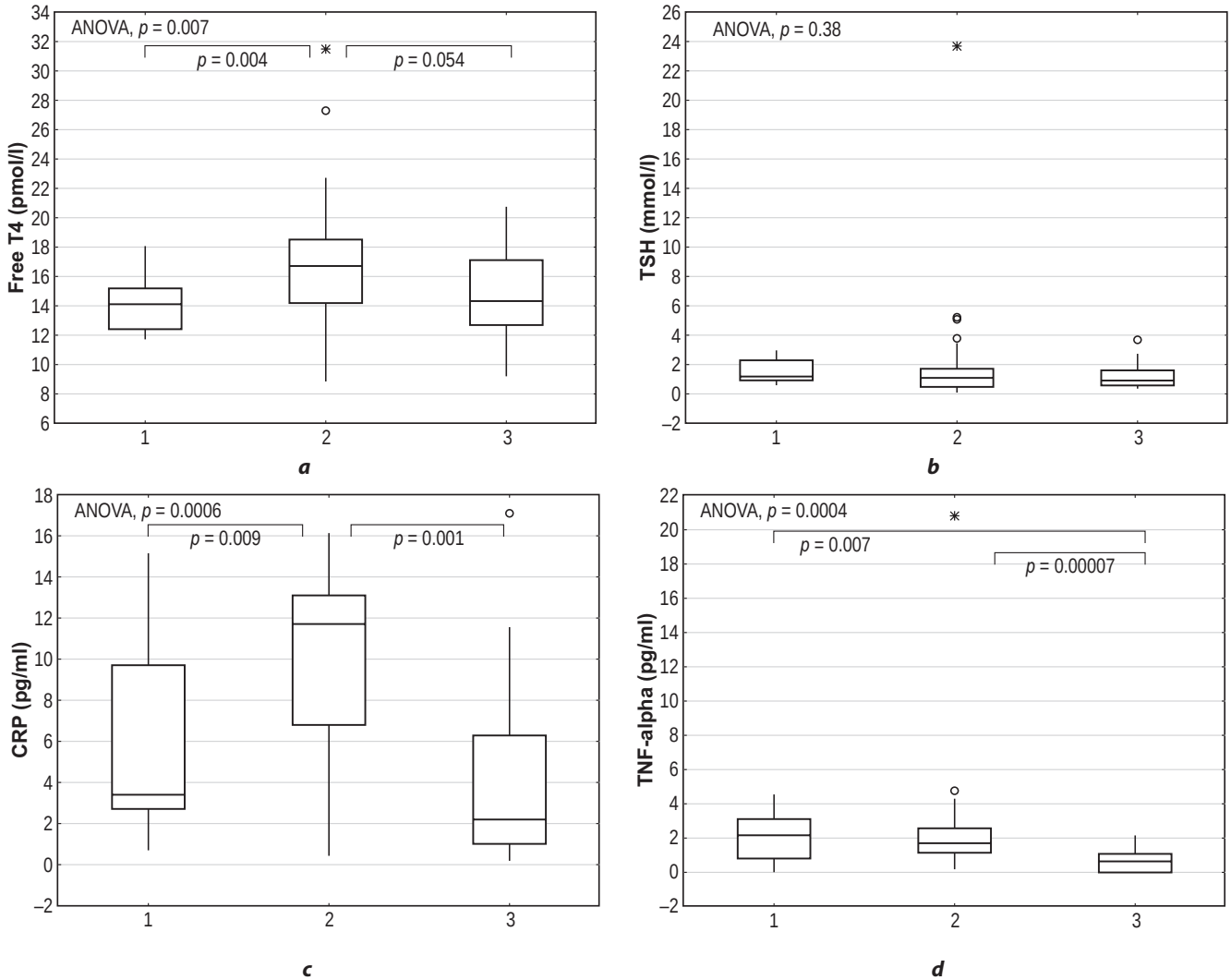

FIG. 1.

*Levels of free thyroxine (**a**), thyroid-stimulating hormone (**b**), C-reactive protein (**s**) and tumor necrosis factor alpha (**d**) in women of post-reproductive age in control group (1; n = 15), group with COVID-19 (2; n = 57) and group with asymptomatic course of the disease (3; n = 13)*

Then we performed an intergroup comparative analysis of the levels of the hormones studied, the results of which indicate an increased free T4 level in the group of women with COVID-19 (16.7 [14.2; 18.5] pmol/l) compared with controls (14.1 [12.4; 15.2] pmol/l) and the group of COVID-19 asymptomatic survivors (14.3 [12.7; 17.1] pmol/l) (Fig. 1a). No statistically significant difference in TSH level was found between the studied groups (Fig. 1b).

Moreover, the level of CRP in the group of women with COVID-19 (11.7 [6.8; 13.1] pg/ml) was consistently higher compared with the control (3.4 [2.7; 9.7] pg/ml) and the group with asymptomatic course of the disease (2.2 [1; 6.3] pg/ml) (Fig. 1c).

We found lower TNF-alpha levels in the group of survivors without clinical signs (0.6 [0.01; 1] pg/ml) compared with controls (2.11 [0.77; 3.08] pg/ml) and the group with COVID-19 (1.7 [1.1; 2.5] pg/ml) (Fig. 1d). When analyzing correlations, a significant positive correlation between free T4 and TNF-alpha levels was revealed (Fig. 2).

In the final phase of the study, we performed a comparative analysis of the investigated parameters in women in the acute phase of COVID-19 and in the same women 12 months after recovery. We did not find any differences in both thyroid hormone levels, CRP and TNF-alpha levels (Fig. 3).

DISCUSSION

This study demonstrates for the first time the results of thyroid status assessment in women of post-reproductive age in the long-term post-COVID-19 period. Previous studies of patients with COVID-19 have found a correlation of low free triiodothyronine (free T3), free T4, and TSH concentrations with COVID-19 severity and mortality [22–24]. However, the results of M. Chen et al. did not demonstrate any changes in free T4 content with decreased levels of free T3 and TSH; at the same time, thyroid hor-

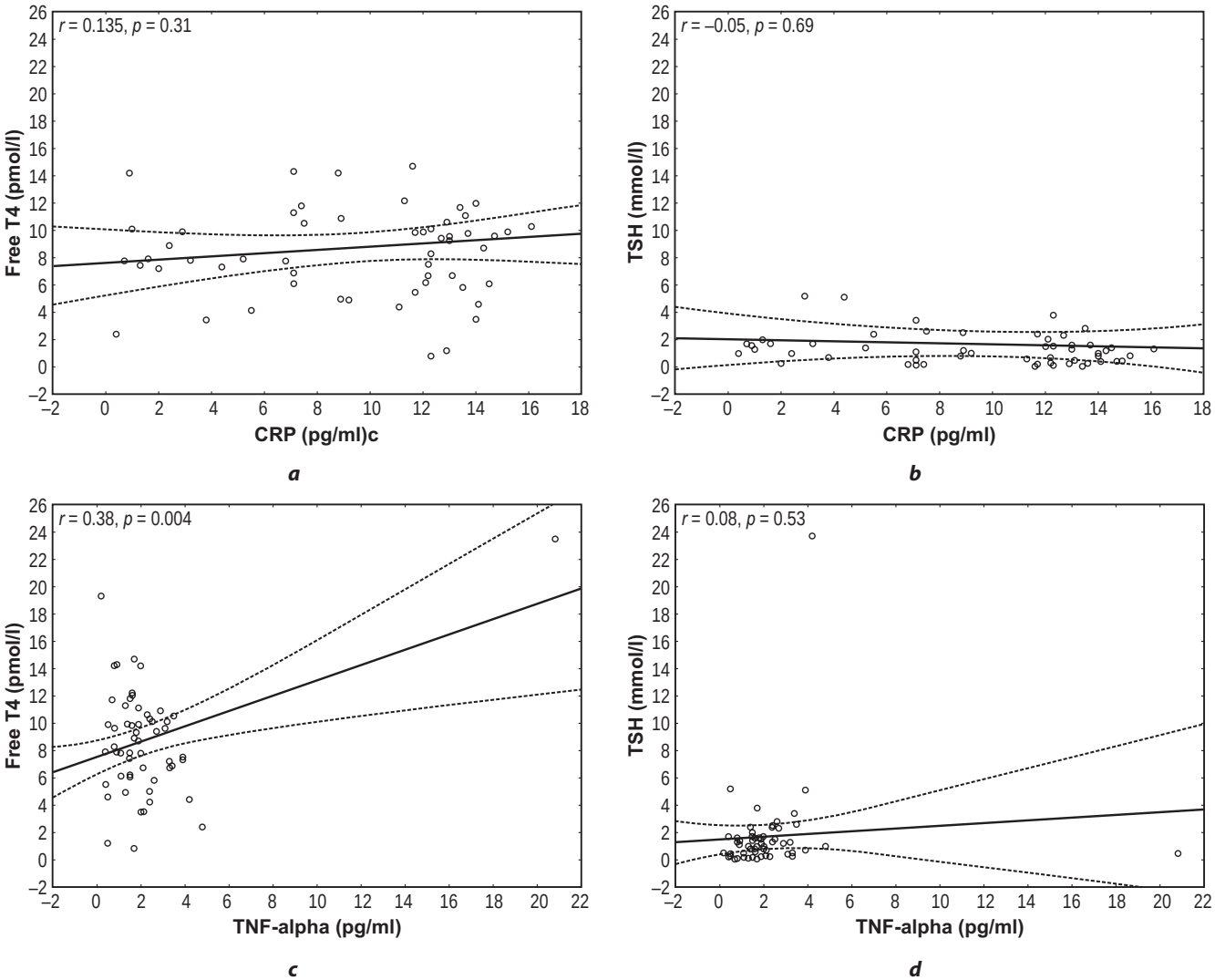

FIG. 2.

*Correlations between the levels of C-reactive protein (**a**, **b**), tumor necrosis factor alpha (**c**, **d**) and thyroid hormones in women of post-reproductive age in the acute phase of COVID-19*

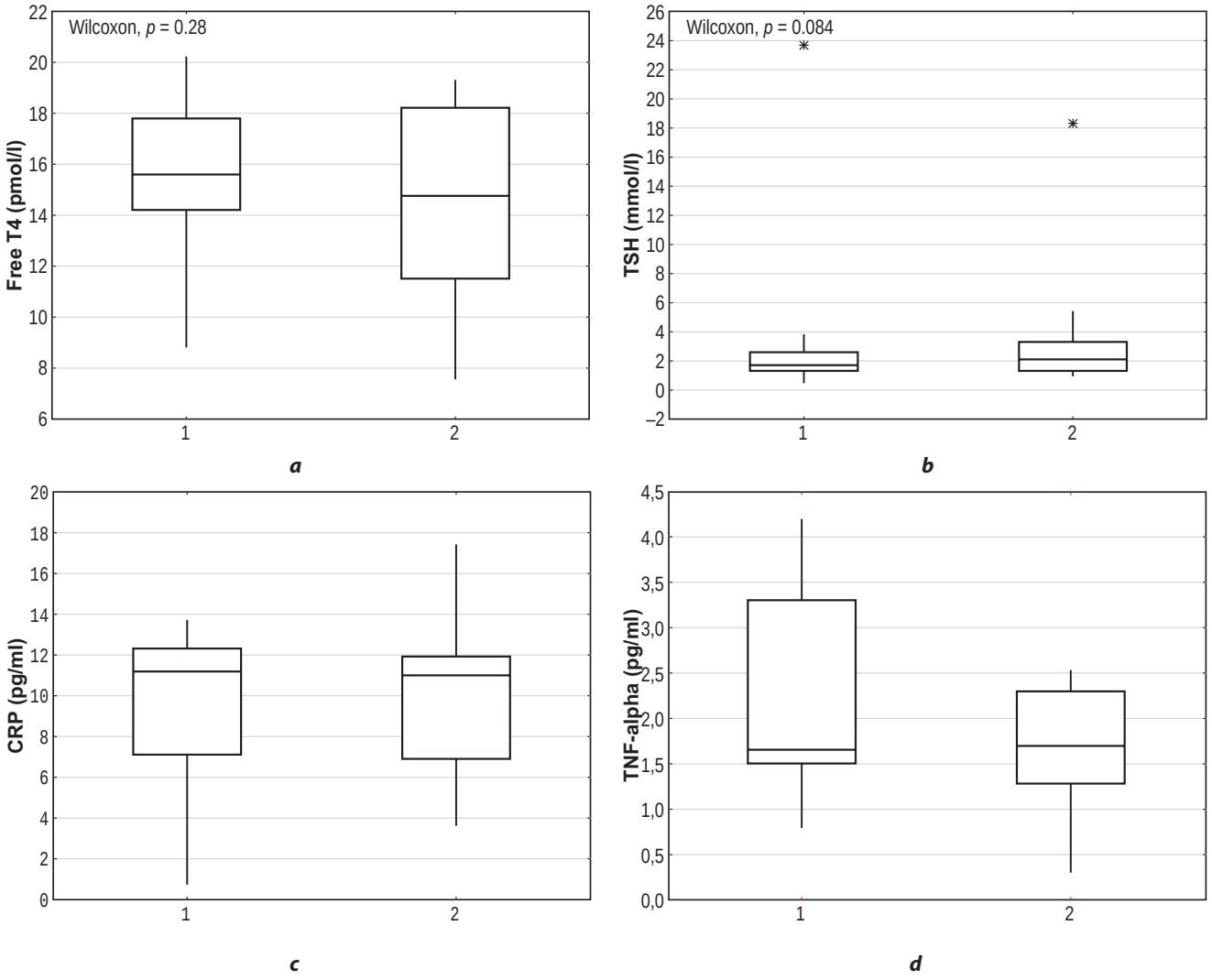

FIG. 3.

*Levels of free thyroxine (**a**), thyroid-stimulating hormone (**b**), C-reactive protein (**c**) and tumor necrosis factor alpha (**d**) in women of post-reproductive age in groups with COVID-19 (1; n = 14) and 12 months after COVID-19 (2; n = 14)*

mone levels in patients immediately after recovery corresponded to control values [25]. The results obtained in our study suggest an increase in free T4 in the acute phase of the disease, which is not consistent with the few studies presented above. As it is known, the main function of free T4 is the activation of metabolic processes, which is accompanied by an increase in cellular oxygen consumption [26]. This may be related to changes in free-radical homeostasis in the acute phase of COVID-19 [27–31], shown in a number of studies to be associated, in particular, with changes in thyroid function. Moreover, our study revealed a positive correlation between free T4 and one of the key mediators of immune response, inflammation and apoptosis – TNF-alpha, the level of which is increased in autoimmune thyreopathies [32]. When assessing TNF-alpha levels in hypo- and hyperthyroidism, an increase in its level was shown, while a decrease in the cytokine level was noted with normalization of thyroid function only in patients with hyperthyroidism after adequate treatment [33].

This study did not reveal a higher level of TNF-alpha in patients in the acute phase of the disease compared with controls, which may be related to the post-reproductive age of women in the compared groups, since it is known about the increased level and important role of this cytokine in aging processes [34]. In addition, the participants of this study were patients with moderately severe COVID-19, and significant elevation of TNF-alpha was observed in severe and critical disease [21]. It should be noted that TNF-alpha levels are lower in asymptomatic women of the same age, even compared to controls, which probably indicates better functioning of their organs and systems and a more adapted immune system. The results of an earlier study demonstrated higher physical and emotional health scores in this group [35].

When thyroid status was assessed 12 months after the disease, the persistence of elevated free T4 levels was found, as well as control TSH levels in women. There are few studies on thyroid status in the post-COVID-19 period. Thus, E. Urban et al. showed that its volume 2–7 months after COVID-19

is smaller than in healthy people, without a significant difference in the content of thyroid hormones [14], and B. Khoo et al. found an increase in the level of TSH in COVID-19 survivors up to control values after 52–108 days from the moment of hospitalization [15].

In our opinion, the wide age range of the patient sample in previous studies may be one of the reasons for their inconsistency with the results of the present study of thyroid hormone levels in COVID-19. Meanwhile, there is increasing evidence that the reference range of TSH increases with age, which may be related to the impaired feedback of the pituitary gland to the target organ in the elderly [19]. The results of the study by N. Milinković et al. in which 22,860 age-differentiated serum samples were analyzed, showed an increase in TSH levels in men over 70 years of age, while in women no differences between age groups were found. In addition, sex differences in free T4 levels have been found in the 31–40 and 41–50 age groups, with lower values in women [36]. Based on the above, it seems essential to take into account age and gender aspects when assessing thyroid status.

Study limitations

Study limitations include the small number of patients who agreed to be evaluated 12 months after COVID-19 and the small number of women who were assigned to the control group due to the high prevalence of SARS-CoV-2.

CONCLUSION

The results of the study indicate long-term changes in thyroid status in women in the post-reproductive period who have survived COVID-19 and the need to monitor it in the long-term post-COVID-19 period in order to timely diagnose the development of pathologic conditions of the thyroid gland.

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Conflict of interest

The authors of this article confirm that there is no conflict of interest.

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