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Prevalence of Thyroiditis Following Either COVID -19 Infection or Vaccination in a Group of Egyptian (Hashimoto and Normal) Cases

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ABSTRACT

Background: Hashimoto's thyroiditis (HT), one of the most common autoimmune thyroid diseases (AITDs), is the major cause of hypothyroidism in the world's iodine-sufficient regions. The Severe Acute Respiratory Syndrome Virus 2 (SARS-CoV-2) causes COVID-19 illness, belong to the family of beta-coronaviruses which rapidly spread leading to COVID-19 pandemic on March 11, 2020. Since follicular thyroid cells express the angiotensin converting enzyme 2 (ACE2), the virus's receptor for cellular entry, they may serve as a direct target for SARS-CoV-2 infection.

Objective: The aim of the current work was to evaluate the thyroid function consequences following either (COVID-19) infection or vaccination in group of Hashimoto thyroiditis and normal subjects in relation to their clinical features, biochemical, immunological, and inflammatory markers.

Patients and Methods: This study was conducted on 80 subjects attending the COVID Vaccination Center and Emergency Isolation at Ain Shams University Hospital during the period from August to October 2022, 14 males, and 66 females, their age ranged from 18 to 70 years. They were divided according to thyroid Abs into Hashimoto's thyroiditis group and normal group, each of them divided into 2 subgroups (exposed to COVID 19 infection & got COVID 19 vaccine).

Results: This study showed significant increase in the level of TSH and decrease in the level of free T3, Free T4 in Hashimoto's patients who exposed to COVID19 infection (P-value <0,01). Significant decrease in the level of TSH and increase in the level of free T3, Free T4 in Hashimoto's subjects' group after their exposure to COVID19 vaccine (AstraZeneca) (P-value <0,01), normal subjects group after exposure to COVID19 infection (P-value .02 and <0,01) and normal subjects group after being exposed to COVID19 vaccine (AstraZeneca) (P-value .02 and .04).

Conclusion: COVID19 infection and vaccination against COVID might be followed by an attack of thyroiditis in Hashimoto patients and even in normal persons.

Keywords: Thyroiditis, COVID-19, Egyptian Hashimoto Cases.

INTRODUCTION

In regions of the world where iodine is abundant, Hashimoto's thyroiditis (HT), the most common autoimmune thyroid disease (AITD), is the main cause of hypothyroidism. Approximately 20–30% of patients have HT, which is thought to be caused by a confluence of genetic predisposition and environmental factors that results in the loss of immunological tolerance, an autoimmune attack on the thyroid tissue, and the development of the disease [(1)].

The global COVID-19 pandemic, which was brought on by the brand-new SARS-CoV-2 coronavirus, first appeared in Wuhan in December 2019. As a result of direct or indirect consequences of SARS-CoV-2 infection, thyroid gland dysfunction was a very prevalent endocrine complication during the COVID-19 pandemic [(2)].

The original SARS-CoV and the novel SARS-CoV-2 both enter target cells through the ACE2 receptor, which causes these receptors to be downregulated. The luminal surface of alveolar epithelial type II cells expresses over 83% of the ACE2 receptors, making these cells the main sites of viral invasion. Additionally, the widespread distribution of ACE2 receptors in extra-pulmonary tissues can be linked to the multi-organ dysfunction seen in these patients [(3)].

As follicular thyroid cells express the angiotensin converting enzyme 2 (ACE2), the virus's receptor for cellular entry, they may in fact be a direct target for SARS-CoV-2 infection. Additionally, thyroid peroxidase has been shown to cross-react with antibodies against the SARS-CoV-2 spike protein, indicating that molecular mimicry mechanisms may be to blame for thyroid auto-inflammatory damage [(4)]. Furthermore, COVID-19 is linked to a widespread inflammatory response that includes innate immune cells, T helper (h)1/17, and Th2 lymphocytes and may affect the thyroid. As a result, a broad range of thyroid illnesses caused by SARS-CoV-2 have been identified, from subacute thyroiditis to autoimmune thyroid diseases with accompanying symptoms of thyrotoxicosis and/or hypothyroidism [(4)].

Numerous vaccines, including mRNA-based vaccines, viral vector vaccines, and inactivated viruses, have been developed to combat the pandemic. An increasing number of case reports have suggested a potential link between SARS-CoV-2 vaccines and thyroid disorders in the past year, replicating the range of thyroid dysfunction that has already been described to occur during SARS-CoV-2 infection. This is due to the widespread administration of SARS-CoV-2 vaccines [(5)].

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This study was aimed to evaluate the thyroid function consequences following either (COVID-19) infection or vaccination in group of Hashimoto thyroiditis and normal subjects in relation to their clinical features, biochemical, immunological, and inflammatory markers.

PATIENTS AND METHODS

This pilot study included a total of 40 Hashimoto thyroiditis and 40 age and gender matched controls who exposed to COVID 19 infection or who got COVID 19 vaccine, attending at the COVID Vaccination Center and Emergency Isolation at Ain Shams University Hospital, during the period from August to October 2022.

Participants were selected randomly and then divided into 4 groups according to the presence of thyroid Abs into Hashimoto's thyroiditis groups and normal groups.

They were instructed to revisit again within 3-6 wks. from either (COVID19) vaccination or infection which was confirmed by basic labs (lymphopenia, CRP, ESR, PCR for COVID 19) and by imaging high resolution CT chest (HRCT).

G**roup (1):** 20 Patients with Hashimoto's thyroiditis exposed to COVID 19 infection (3-6-weeks post covid), **Group (2):** 20 Patients with Hashimoto's thyroiditis who got COVID 19 vaccine (AstraZeneca) (3-6-weeks postvaccine), **Group (3):** 20 Normal subjects exposed to COVID 19 infection. (3-6-weeks post COVID), and **Group (4):** 20 Normal subjects who got COVID 19 vaccine (3 - 6 weeks post vaccine) (AstraZeneca).

Exclusion criteria included patients who were using drugs including systemic steroids, amiodarone, heparin, and dopamine that might affect their thyroid function.
Full medical history was taken from all subjects, emphasizing on personal data (age, gender, occupation, marital status, and smoking), history of pulmonary disease, history of Diabetes mellitus type 2, hypertension, coronary artery disease or heart failure, history of drug intake. Thorough clinical examination including blood pressure, pulse, respiratory rate, temperature, neck (thyroid) examination.

Laboratory studies: including CBC, Erythrocyte sedimentation rate [ESR], Thyroid profile (free T3, free T4, TSH), Antithyroid antibodies [Antithyroglobulin antibody (anti-Tg), Antithyroid peroxidase antibody (anti-TPO), PCR for covid19. CBC was done by automated cell counter (Mindray BC-215s. Antithyroid antibodies titer was measured with T enzyme-linked immunosorbent assay (ELISA).

Imaging:
- High resolution computed tomography (HRCT) chest.
- Neck ultrasound (U/S).

***Ethical Consideration*:**

This study was ethically approved by the Ethics Committee of Ain Shams University. Written informed consent of all the participants was obtained after being informed of the study's objectives and methodology. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical analysis

Data were gathered, edited, coded, and put into IBM SPSS version 23's statistical package for social science. In the case of parametric quantitative data, means, standard deviations, and ranges were displayed; in the case of non-parametric quantitative data, medians and interquartile ranges (IQR) were displayed. Quantitative and percentage representations of qualitative characteristics were also used. P value < 0.05 was considered significant.

RESULTS

This study was conducted on 80 subjects (40 Hashimoto thyroiditis, 40 normal subjects), aged 18-70 years attending at the COVID Vaccination Center and Emergency Isolation, Ain Shams University Hospital.
It showed significant increase in the level of TSH and decrease in the level of free T3, Free T4 in Hashimoto's patients who exposed to COVID19 infection (P-value <0,01). Significant decrease in the level of TSH and increase in the level of free T3, Free T4 in Hashimoto's subjects group after their exposure to COVID19 vaccine (AstraZeneca) (P-value <0,01), normal subjects group after exposure to COVID19 infection (P-value .02 and <0,01) and normal subjects group after being exposed to COVID19 vaccine (AstraZeneca) (P-value .02 and .04) . Furthermore, we found non-significant difference regarding –anti- TPO, Antithyroglobulin. In any group (P-value >0,05) (tables 1, 2).

Table (1): Comparison between specific laboratory tests in group 1 before and 3-to-6-week after exposure to COVID19, and in group 2 before and 3-to-6-week after exposure to COVID19 vaccine:

		Group (1) **Hashimoto** exposed to COVID 19 infection		**Test value**	**P-value**	**Sig.**
		1st visit	**2nd visit**			
Free T3	Mean ± SD	2.86 ± 0.43	2.21 ± 0.38	6.098•	**0.001**	HS
Free T4	Mean ± SD	1.37 ± 0.15	0.87 ± 0.29	5.958•	**0.001**	HS
TSH (mIU/L)	Median (IQR)	2.85 (2.23 – 3.25)	3.55 (2.95 – 65)	-3.922≠	**0.001**	HS
	Range	1.9 – 4.04	2.2 – 100			
Anti TPO	Negative	0 (0.0%)	0 (0.0%)	–	–	–
	Positive	20 (100.0%)	20 (100.0%)			
Anti thyroglobulin	Negative	8 (40.0%)	8 (40.0%)	0.000*	1.000	NS
	Positive	12 (60.0%)	12 (60.0%)			
		Group (2) **Hashimoto** who got COVID 19 vaccine		**Test value**	**P-value**	**Sig.**
		1st visit	**2nd visit**			
Free T3	**Mean ± SD**	2.79 ± 0.44	3.10 ± 0.47	-5.397•	**0.001**	HS
Free T4	**Mean ± SD**	1.03 ± 0.28	1.29 ± 0.31	-4.796•	**0.001**	HS
TSH	**Median (IQR)**	2.95 (2.2 – 3.55)	3.2 (2.9 – 3.8)	-2.582≠	**0.010**	HS
	Range	1.4 – 4	2 – 4.2			
Anti TPO	**Negative**	0 (0.0%)	0 (0.0%)			
	Positive	20 (100.0%)	20 (100.0%)			
Anti thyroglobulin	**Negative**	10 (50.0%)	10 (50.0%)	0.000*	1.000	NS
	Positive	10 (50.0%)	10 (50.0%)			

Median, IQR and Range: non-parametric test.

Table (2): Comparison between specific laboratory tests in group 3 before and 3-to-6-week after exposure to COVID19, and in group 4 before and 3-to-6-week after exposure to COVID19 vaccine:

		Group (3) **Normal** exposed to COVID 19 infection		**Test value**	**P-value**	**Sig.**
		1st visit	**2nd visit**			
Free T3	Mean ± SD	2.72 ± 0.38	3.26 ± 0.51	-8.860•	**0.001**	HS
Free T4	Mean ± SD	0.97 ± 0.26	1.35 ± 0.23	-9.965•	**0.001**	HS
TSH	Median (IQR)	2.35 (2 – 2.8)	2 (1.3 – 2.4)	-2.301≠	**0.021**	S
	Range	1.1 – 3.2	1 – 2.8			
Anti TPO	Negative	20 (100.0%)	20 (100.0%)	–	–	–
	Positive	0 (0.0%)	0 (0.0%)			
Anti thyroglobulin	Negative	20 (100.0%)	20 (100.0%)	–	–	–
	Positive	0 (0.0%)	0 (0.0%)			
		Group (4) **Normal** who got COVID 19 vaccine		**Test value**	**P-value**	**Sig.**
		1st visit	**2nd visit**			
Free T3	Mean ± SD	2.98 ± 0.65	3.19 ± 0.59	-2.210•	**0.040**	S
Free T4	Mean ± SD	1.24 ± 0.28	1.43 ± 0.43	-2.170•	**0.043**	S
TSH	Median (IQR)	2.45 (2 – 2.75)	2 (1.5 – 2.55)	-2.229≠	**0.026**	S
	Range	1.1 – 3.7	0.7 – 4.1			
Anti TPO	Negative	20 (100.0%)	20 (100.0%)	–	–	–
	Positive	0 (0.0%)	0 (0.0%)			
Anti thyroglobulin	Negative	20 (100.0%)	20 (100.0%)	–	–	–
	Positive	0 (0.0%)	0 (0.0%)			

Median, IQR and Range: non-parametric test.

On comparing the 4 groups regarding the laboratory tests at first visit: there was a statistically highly significant difference regarding presence of lymphopenia and ESR and CRP being higher in group 1 and 3 than group 2 and 4, HRCT showing ground glass opacities in group 1 nd 3 with (P-value <0.001) (table 3 and Figures 1,2,3).

Table (3): Comparison between groups as regard laboratory tests at first visit:

		Group 1 Hashimoto Exposed to infection	Group 2 Hashimoto exposed to vaccine	Group 3 euthyroid exposed to infection	Group 4 euthyroid exposed to vaccine	Test value	P-value	Sig.
		No. = 20	No. = 20	No. = 20	No. = 20			
TLC	Normal Lymphopenic	0(0.0%) 20 (100.0%)	20 (100.0%) 0 (0.0%)	0 (0.0%) 20 (100.0%)	20 (100.0%) 0 (0.0%)	80.000*	0.001	HS
ESR mm/hr	Median (IQR) Range	37 (34.5 – 40) 30 – 50	10 (6 – 12) 2 – 15	50 (42.5 – 60) 30 – 79	8 (5 – 11) 2 – 15	63.321≠	0.001	HS
CRP mg/l	Negative Positive	0 (0.0%) 20 (100.0%)	20 (100.0%) 0 (0.0%)	0 (0.0%) 20 (100.0%)	20 (100.0%) 0 (0.0%)	80.000*	0.001	HS
ABG	Normal	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)	–	–	–
PCR	Negative Positive	0 (0.0%) 20 (100.0%)	20 (100.0%) 0 (0.0%)	0 (0.0%) 20 (100.0%)	20 (100.0%) 0 (0.0%)	80.000*	0.001	HS
HRCT	Normal Peripheral ground glass opacities	9 (45.0%) 11 (55.0%)	20 (100.0%) 0 (0.0%)	6 (30.0%) 14 (70.0%)	20 (100.0%) 0 (0.0%)	37.411*	0.001	HS

Post Hoc analysis						
	Group 1Vs group 2	Group 1 Vs group 3	Group 1 Vs group 4	Group 2Vs group 3	Group 2Vs group 4	Group 3Vs group 4
CBC	0.000	-	0.000	0.000	-	0.000
ESR	0.000	0.000	0.000	0.000	0.425	0.000
CRP	0.000	-	0.000	0.000	-	0.000
PCR	0.000	-	0.000	0.000	-	0.000
HRCT	0.000	0.327	0.000	0.000	-	0.000

Median, IQR and Range: non-parametric test.

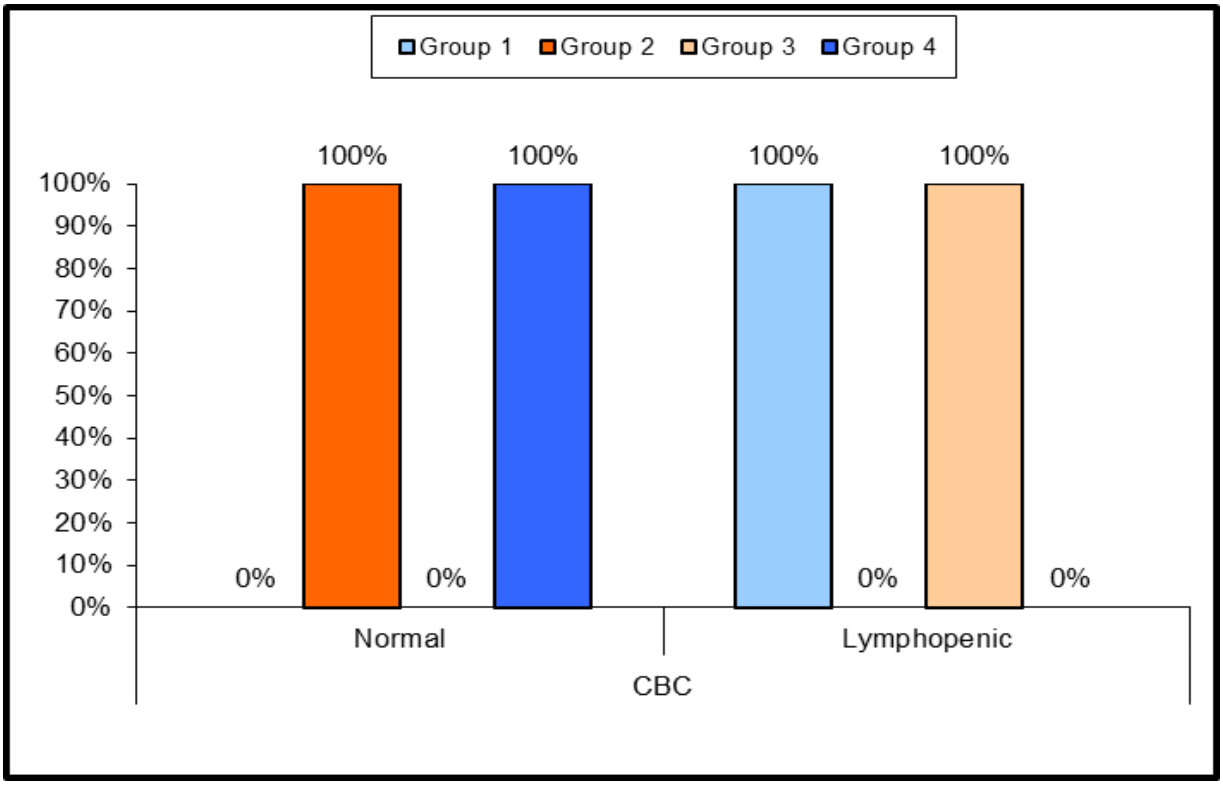

Figure (1): Comparison between groups regarding CBC.

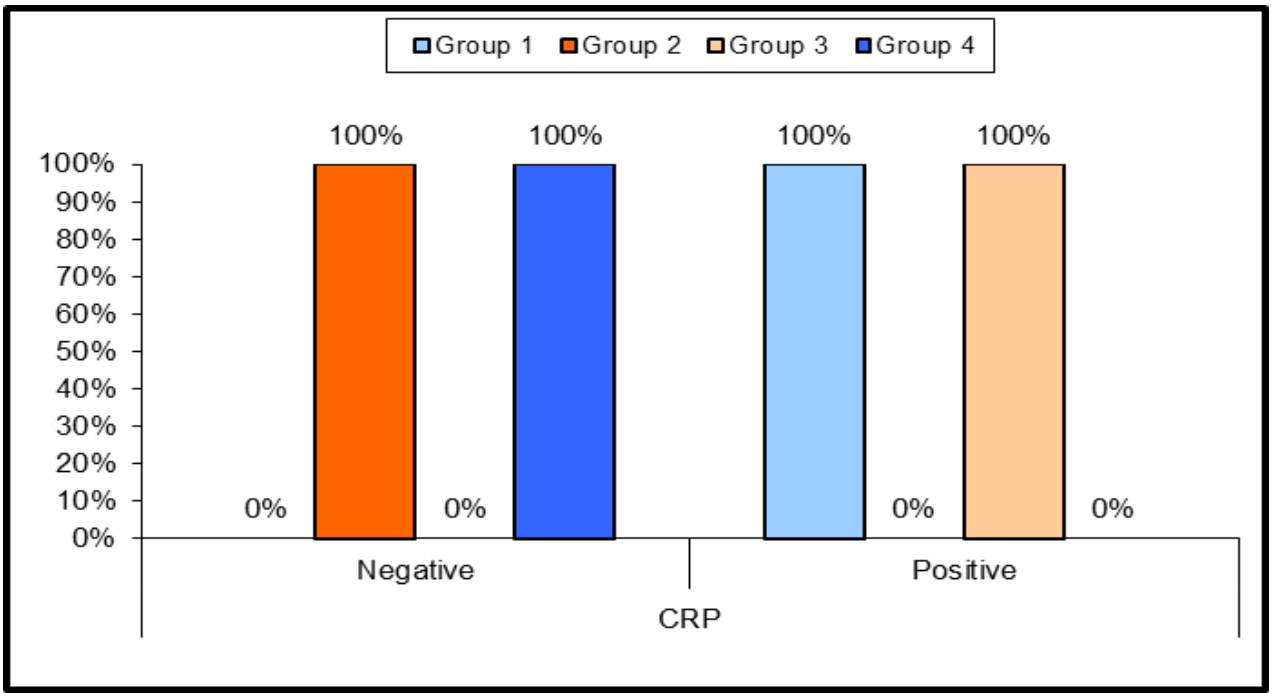

Figure (2): Comparison between groups regarding CRP

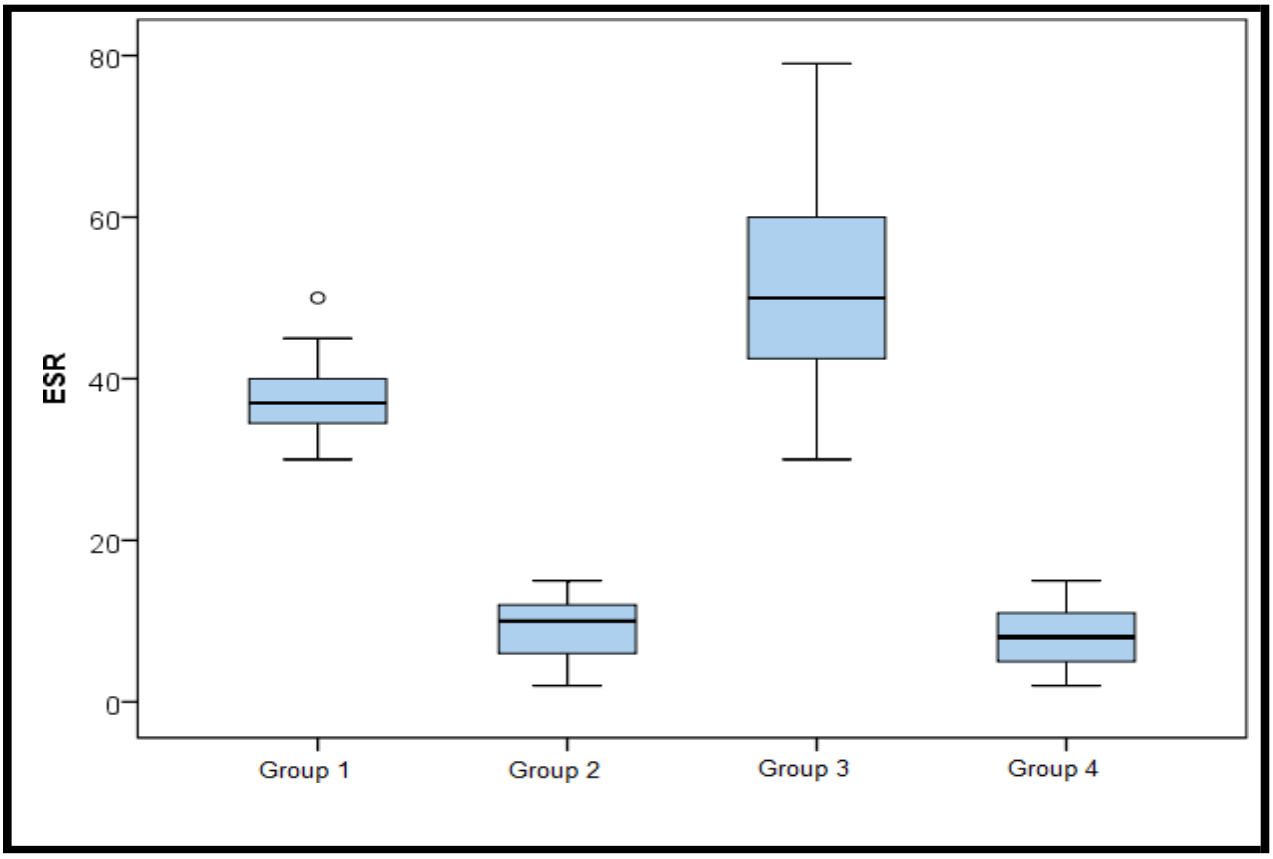

Figure (3): Comparison between groups regarding ESR

DISCUSSION

Our study demonstrated significant increase in the level of TSH and decrease in the level of free T3, Free T4 in Hashimoto's patients who exposed to COVID19 infection.

This result came in line with **Allam *et al.* [6],** who found a 42-year-old female patient was diagnosed with Hashimoto's thyroiditis (HT) for 10 years, 6-weeks after exposure to COVID19 infection, Laboratory investigations showed increase in the level of TSH, decrease in the level of both FT4, FT3**.**

The presence of mixed inflammatory cells and histiocytes, as well as granulomatous inflammation and scathed follicular cells, in the pathology report of the patients who had deep hypothyroidism suggested a pattern of destructive follicular thyroiditis [7].

Surprisingly, we found significant increase in the level of free T3, Free T4 and decrease in the level of TSH in normal subjects after exposure to COVID19 infection.

These results came in line with **Wang *et al.* [2],** who discovered the first case of postcovid subacute thyroiditis in an 18-year-old woman In March 2020. Laboratory investigations were done 5weeks after exposure to COVID19 infection, showed decrease level of TSH, increase level of both FT4, FT3**.**

This was also consistent with the findings of **Khatri *et al.* [8],** who stated that a Caucasian lady, 41, went to the emergency room 6 weeks after contracting the COVID 19 infection due to discomfort and swelling in her anterior neck. TSH levels were low and thyroid hormone levels were high according to thyroid function testing. Thyroid uptake and scan performed and was diagnostic of thyroiditis.

Similarly, **Barrera *et al.* [9],** documented a case of 37-year-old female presented with severe neck pain radiating to the right jaw one month after COVID 19 infection. Her lab tests showed an undetectable TSH, increase level of free T4, free T3. Tg and TPO antibodies were negative. A thyroid iodine scan revealed no absorption of radioactive iodine.

Additionally, our study showed significantly increase in the level of free T3, Free T4 in normal subjects after being exposed to COVID19 vaccine (AstraZeneca) in contrast to TSH being decreased in them.

This agreed with **Stasiak and Lewiński [10],** who disclosed a case of a 55-year-old female patient who complained of neck pain. Three weeks before these symptoms appeared, she had taken her first AstraZeneca dosage. The free T3 and free T4 levels in the blood were elevated. Tests for thyroid antibodies were negative for her. An ultrasound of the thyroid revealed a hypertrophic thyroid gland with mixed echotexture. Hypervascularity was absent. The symptoms were consistent with thyroiditis.

Moreover, **Franquemont and Galvez [11],** documented a case of 69-year-old male presented with pain in front of his neck 14 days following AstraZeneca vaccine. His investigations 4 weeks postimmunization revealed an elevated free T4 and free T3, with a suppressed TSH and negative thyroid antibodies with normal thyroid scan.

In addition, **Goindoo *et al.* [12],** documented a case report of 50 year old Asian female developed neck pain 10 day after first dose of AstraZeneca COVID-19 vaccination. Her investigations showed increase level of Free T4, free T3 and decrease level of TSH, with negative Thyroid antibodies. Thyroid uptake showed relatively reduced tracer uptake.

This might be a result of an adjuvant-induced autoimmune inflammatory syndrome. Due to the dysregulation of both the innate and adaptive immune systems, vaccination adjuvants have the potential to cause severe autoimmune responses in those who are susceptible to them. Additionally, the SARS CoV-2 spike glycoprotein is encoded by a recombinant replication-deficient chimpanzee adenovirus vector found in the AstraZeneca vaccine, which may play a role in vaccination-induced thyroiditis [13].

Postvaccination thyroiditis in Hashimoto's patients was reported with other type of vaccination like Moderna mRNA-1273 vaccine. It was documented by **Ruggeri *et al.* [14]**, a 55-year-old woman with HT was the subject of a case report research. She received the Moderna mRNA-1273 vaccine's first dose. She started experiencing tremors and palpitations after 10 days. TSH levels were repressed while FT4 and FT3 levels were increased during thyroid function testing.

Additionally, we found significant increase in the level of free T3, Free T4 in Hashimoto's subjects after their exposure to AstraZeneca vaccine, with non-significant difference regarding –anti- TPO, Antithyroglobuli TSH.

CONCLUSION

COVID19 infection and vaccination against COVID might be followed by an attack of thyroiditis in Hashimoto patients and even in normal persons.

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