ORIGINAL ARTICLE

Associations like study of the Frequency Distribution of Positive Thyroid Peroxidase Antibody in Patients with Clinical and Subclinical Hypothyroidism and Related Factors in Semnan

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ABSTRACT

Introduction and aim: Considering thehigh relative frequency of hypothyroidism in the community and the importance of proper diagnosis and treatment of this disease in the regions, the present study aimed to investigate the frequency distribution of positive thyroid peroxidase antibody (TPOAb) in patients with clinical and subclinical hypothyroidism and related factors.

Materials and methods: In this cross-sectional study, 283 patients with hypothyroidism, who referred to the endocrinology clinic of Kowsar Hospital in Semnan during 6 months of 2019, were selected by simple random sampling method and after extracting the patients' information, the data were compared between the two groups of clinical and subclinical hypothyroidism. Data analysis was performed using statistical software.

Results: 94.3% of patients were diagnosed with clinical hypothyroidism and 5.7% were diagnosed with subclinical hypothyroidism. 51.9% had positive thyroid peroxidase antibody (TPOAb) TSH levels in patients with positive thyroid peroxidase antibody were significantly higher than patients with negative TPOAb (P = 0.003). The relative frequency of positive thyroid peroxidase antibodies in the group with clinical hypothyroidism was significantly higher than in patients with subclinical hypothyroidism (P = 0.018).

Conclusion: More than half of patients with hypothyroidism had positive thyroid peroxidase antibodies.high serum TSH level, and anti-thyroid peroxidase antibody titer are effective factors in the diagnosis of hypothyroidism and especially its clinical type.

Keywords: Anti-thyroid peroxidase antibody, Clinical hypothyroidism, Subclinical hypothyroidism

INTRODUCTION

The thyroid gland generally regulates the body's metabolism and energy[1]. By absorbing iodine, this gland produces thyroid hormones including thyroxine (T4) and triiodothyronine (T3), which are derivatives of the amino acid tyrosine[1,2]. Hypothyroidism or lack of thyroid gland decelerates the brain and physical functions, reduces cold resistance, and causes cardiovascular diseases such as the increased risk of myocardial infarction and aortic atherosclerosis, and also in infants causes hypoplasia of cortical neurons and mental retardation[3-7]. Muscle weakness, cold sensation, constipation, dry skin, depression, mental disorders, hoarseness, mucosal skin lesions, tongue enlargement, general body developmental delays, hearing impairment, learning disabilities, speech and language retardation, are considered as symptoms of hypothyroidism[8]. Hypothyroidism could also cause problems such as mood instability, depression, dementia, memory impairment, and mental health problems[9] .

Various studies have shown that the incidence of hypothyroidism is increasing in Europe. It is also reported that 4.3% of the US population has subclinical hypothyroidism and 0.3% has a clinical or overt type. Other studies have suggested that up to 15% of older women may have a subclinical form of hypothyroidism[10,11]. Hypothyroidism is more common in women, the elderly, and white people. It is also more common in people with autoimmune diseases[12-15]. Iodine deficiency is the most common cause of hypothyroidism worldwide; Thus, in the United States and other areas with adequate iodine intake, autoimmune thyroid disease (Hashimoto's thyroiditis) is the most common cause of hypothyroidism[16].

Hashimoto's thyroiditis is one of the autoimmune diseases of the thyroid gland and is currently the most common inflammatory thyroid disease and the most common cause of hypothyroidism in children and adults[3,4,17-20]. The annual global incidence of this disease is estimated[21,22] to be 0.3 to 1.5 cases per 1000 people and is generally more common in women[23,24]. This disease affects up to 2% of the general population and is generally more common in older women[25,26]. In the acute type of the disease, it is accompanied by loss of thyroid follicular cells, goiter, hypothyroidism, and decreased levels of T3 and T4 hormones, as well as autoantibody circulation against two specific thyroid antigens, namely thyroglobulin and thyroid peroxidase[27]. The main symptom of Hashimoto's thyroiditis is the presence of anti-thyroid peroxidase antibody[28]. However, 10 to 15% of people with Hashimoto's thyroiditis may be negative for the presence of antibodies[29]. Thyroid peroxidase is a specific enzyme in the membrane of thyroid cells that plays an important role in the production of thyroid hormones. This enzyme uses H_2O_2 from various activities to oxidize iodine so that iodine binds to the amino acid tyrosine, which is the starting point for the production of thyroid hormones[30-40].

Serum TSH levels and anti-thyroid peroxidase antibody titers are the most important factors in the development in which there was an abnormal increase in TSH, especially over the age of 50[35]. One of the proposed associations of autoimmune thyroid disorders are insulin resistances or evident diabetes that makes some need to

examine any suspected evidences of these associations like probable acanthosis nigricans of the patients may refer to treat them[36-38].

Due to the high relative frequency of hypothyroidism in the community and the importance of proper diagnosis and treatment of this disease and also due to the lack of appropriate and sufficient epidemiological information in the city of Semnan in relation to the cause of this disease, and also considering that Autoimmune thyroid diseases are the most common cause of hypothyroidism in areas with adequate iodine intake, We decided to design a study to investigate the frequency distribution of individuals with positive antithyroid peroxidase antibodies among patients with clinical and subclinical hypothyroidism.

MATERIALS AND METHODS

Study design: In this cross-sectional study, 283 patients with hypothyroidism who referred to the endocrinology clinic of Kowsar Hospital in Semnan during 6 months of 2019 and had a clinical follow-up file, were selected by simple random sampling method. Patients who met the inclusion criteria were evaluated for variables. The above research was carried out after registering the plan in the ethics council of the University of Medical Sciences and receiving the code of ethics.

Inclusion and exclusion criteria: Inclusion criteria included complete patient satisfaction, the patient's registered clinical file in the subspecialty clinic of Kowsar Hospital, which contained thyroid function tests (T4 Total, TSH,T3RU and Anti TPO), and the certain diagnosis of hypothyroidism for the patient. Exclusion criteria included patient dissatisfaction, pituitary disorders, use of thyroid dysfunction drugs (such as glucocorticoids, amiodarone, lithium, beta-blockers, interferon, and phenytoin) during the last 3 months before the study.

Data collection: In this study, the data collection tool was a researcher-made checklist. Demographic information and history of the patient such as age and sex, type of hypothyroidism, underlying disease and duration of hypothyroidism, laboratory findings including anti-thyroid peroxidase antibody titers, TSH and T4 total, and medical examination findings including thyromegaly and thyroid nodules, were gathered.T4 and TSH levels of all patients were measured and recorded at the time of admission. T4 levelswere measured by immunoassay method (Budapest Isotope kit, Hungary) and TSH levels were measured by IRMA method (Turku kit, Finland).

Procedure: After approval of the plan in the Research Council of Kowsar Educational, Research and Treatment Center of Semnan and obtaining approval from the Ethics Council of Semnan University of Medical Sciences, Initially, with the coordination of the head of the subspecialty clinic of Kowsar Hospital and obtaining written consent from patients, access to the registered clinical file of patients with hypothyroidism became possible. Then, among the recorded files and documents, a number of patients' clinical records that met the inclusion criteria were included in the study and were excluded if they met any of the exclusion criteria. Amongst the files included in the study, the required sample size of the study was selected by random sampling to collect the information needed to complete the designed checklist. In cases where complete information was not available or distorted in the patients' clinical file, the required information was completed by calling the telephone number mentioned in the file. Anti-thyroid peroxidase antibody levels above 80 units were considered as positive anti-thyroid peroxidase antibodies. Lastly, the results were evaluated and compared by type of hypothyroidism (clinical and subclinical) and positive anti-thyroid peroxidase antibody.

Data analysis: After data collection, in order to analyze data and compare the studied groups, Spss software version 25 was used, for statistical description, the mean and standard deviation and percentage were used. In the descriptive goals section, descriptive indicators, central indicators, and dispersion were used and in order to achieve analytical goals, the T-test was used. A significant level was considered 0.05.

RESULTS

The mean age of patients with clinical hypothyroidism was 35.70 years and patients with subclinical hypothyroidism were 36.59 years. Among the patients studied, 260(91.9%) were female and 23 (8.1%) were male. There was no statistically significant difference between the age and gender of patients with clinical hypothyroidism and patients with subclinical hypothyroidism. Table 1 shows the age and gender distribution of people with positive thyroid peroxidase antibody and those without this antibody. 147 patients (68.8%) had positive thyroid peroxidase antibody

94.% of the studied patients had clinical hypothyroidism and 5.7% had subclinical hypothyroidism [2] . The distribution of positive thyroid peroxidase antibody showed that 68.8% of people with clinical hypothyroidism had positive thyroid peroxidase antibody and 51.9% of people had subclinical hypothyroidism. The frequency of positive thyroid peroxidase antibody was significantly different between the two groups of clinical and subclinical hypothyroidism (P = 0.018). Regarding diabetes, 3.7% of patients in the clinical group and 6.3% in the subclinical group had diabetes (Table 2). Among the patients, 259 were women of reproductive age, of which 9.8% had clinical hypothyroidism. None of the patients with subclinical hypothyroidism were pregnant. Also, 20.6% of patients with clinical hypothyroidism and 31.3% of patients with subclinical hypothyroidism, had thyromegaly. There was no significant difference in terms of family history, pregnancy, and thyromegaly between the patients with clinical hypothyroidism and subclinical hypothyroidism (p> 0.05).

There was no statistically significant difference between patients with clinical and subclinical hypothyroidism regarding TSH level (P = 0.924) and T4 level (P = 0.412). Also, according to Table 3, there was no statistically significant difference between the groups with positive and negative thyroid peroxidase antibody regarding T4 level (P = 0.369); However, TSH levels in patients with positive thyroid peroxidase antibody were significantly higher than those with negative thyroid peroxidase antibody (P = 0.003).

Table 1 Distribution of age and gender of patients with clinical and subclinical hypothyroidism by thyroid peroxidase antibody.

Thyroid peroxidase antibody	Age (years)					
	Mean			standard deviation		P value
Positive	35.37			10.99		0.228
Negative	36,69			21.94		
	Gender					
	female		male		total	
	Quantity	Percentage	Quantity	Percentage	Quantity (Percentage)	
Positive	137	93.2	10	6.8	147 (100)	0.397
Negative	123	90.4	13	9.6	136 (100)	

Table 2 Frequency distribution of variables in patients with clinical and subclinical hypothyroidism

Type hypothyroidism	Clinical		Subclinical		P value
	Frequency	Percentage	Frequency	Percentage	
Hypothyroidism	267	94.3	16	5.7	0.34
positive thyroid peroxidase antibody	136	68.8	11	51.9	0.018
Diabetes mellitus	10	3.7	1	6.3	0.615
Family history	91	34.1	5	31.3	0.818
Pregnancy	24	9.8	0	0	0.247
Thyromegaly	55	20.6	5	31.3	

Table 3: Distribution of TSH and T4 levels in patients with clinical and subclinical hypothyroidism by thyroid peroxidase antibody and type of hypothyroidism

characters		TSH		T4	
		with		without	
		Mean	Standard Deviation	Mean	Standard Deviation
Hypothyroidism	Clinical	8.00	11.45	7.38	5.64
	Subclinical	9.29	6.76	5.99	2.41
	P value	0.924		0.412	
Thyroid Peroxidase antibody	Positive	9.50	13.14	6.58	2.72
	Negative	6.51	8.46	8.07	7.38
	P value	0.003		0.369	

Table 4: Distribution of family history, pregnancy, thyromegaly, and thyroid nodule by thyroid peroxidase antibody

Thyroid peroxidase antibody	Family history of hypothyroidism					P value
	With		Without		Total	
	Quantity	Percentage	Quantity	Percentage	Quantity%	
Positive	50	34.0	97	66.0	147(100)	0.973
Negative	46	33.8	90	66.2	136(100)	
	Pregnancy					
	Yes		No		Total	
	Quantity	Percentage	Quantity	Percentage	Quantity%	
Positive	10	7.3	127	92.7	137(100)	0.173
Negative	14	11.5	108	88.5	122(100)	
Thyromegaly	With		Without		Total	
	Quantity	Percentage	Quantity	Percentage	Quantity%	
Positive	41	28.9	106	71.1	147(100)	0.004
Negative	19	14.0	117	86.0	136(100)	
Thyroid nodule	**With**		**Without**		**Total**	
	Quantity	Percentage	Quantity	Percentage	Quantity%	
Positive	18	15.2	129	87.8	147(100)	0.064
Negative	8	5.9	128	94.1	136(100)	

The study of the relationship between frequency and family history showed that 34.0% of patients had a family history of positive thyroid peroxidase antibody and 33.8% of patients had negative thyroid peroxidase antibody, which there was no statistically significant difference between them (P=0.973). 7.3% of patients with positive thyroid peroxidase antibody and 11.5% (14 people) of patients without positive thyroid peroxidase antibody were pregnant. There was no statistically significant difference in terms of pregnancy (P = 0.173). Regarding thyromegaly, 27.9% of patients with positive thyroid peroxidase antibody and 14 % of patients without positive thyroid peroxidase antibody were diagnosed with the disease. There was a significant difference in terms of the frequency of thyromegaly between the patients with and without positive thyroid peroxidase antibody (P=0.004). 15.2% of patients with positive thyroid peroxidase antibody and 5.9% of patients without positive thyroid peroxidase antibody had thyroid nodules and the rest did not show any sign this gland.

There was no significant difference between the relative frequency of thyroid nodules in the two groups (P = 0.064).

DISCUSSION

The results of the present study showed that 51.9% of the studied patients had positive thyroid peroxidase antibody. Asadikaram and Torkzadeh in a cross-sectional study in Rafsanjan concluded that the positive titer of the anti-TPO antibody was 58.6%[39], which has been close to our study. In another study, among those with thyroid dysfunction, 46.3% were positive for thyroid peroxidase antibodies[40]. However, in Iran, higher levels of positive thyroid peroxidase antibodies have been observed in about 88.9% and 61%[41,42], which indicates the different distribution of this defect in different populations. Shivaprasad et al. In a cross-sectional study in India in 2017 reported a positive thyroid peroxidase antibody titer in 16.7% of diabetic patients[43]; Also, in another study in Argentina, the relative frequency of positive thyroid peroxidase antibody titer was observed in 13% of the diabetic population[44]. This rate was lower than the results of the present study; The reason for this difference may be due to differences in the type of statistical population studied; Because in the present study, people with subclinical and clinical hypothyroidism were examined.

The results of the present study showed that 94.3% of the studied patients had clinical hypothyroidism and 5.7% had subclinical hypothyroidism. Hosseini et al. (2016) reported the incidence of subclinical and clinical hypothyroidism in individuals with normal thyroid function, 8.8 and 7.1 cases per 1000, respectively[42]. In a study by Robles-Osorio et al., 77.8% of the subjects had clinical hypothyroidism and 22.2% had subclinical hypothyroidism[18], which has been close to the results of the present study. According to a study by Usha et al. (2009) in India, thyroid dysfunction was present in 19.6% of the population, of which 19.4% had subclinical hypothyroidism[40] and this relative frequency has been higher than the present study. The reason for this difference may be due to differences in the type of statistical population studied.

In the present study, the relative frequency of positive thyroid peroxidase antibodies in the group of patients with clinical hypothyroidism was significantly higher than in patients with subclinical hypothyroidism. Other similar studies have shown that a history of thyroid disorders is associated with a positive thyroid peroxidase antibody and this factor could be considered as a risk factor in the diagnosis of autoimmune thyroid disorders[42,45]. In the study by Robles-Osorio et al. a positive family history of thyroid disease and a positive titer of anti-TPO antibodies were identified as factors associated with hypothyroidism[18], while in our study, the only significant correlation was between hypothyroidism and the positive titers of anti-TPO antibodies. Another similar study showed that the percentage of people with positive thyroid peroxidase antibody in the hypothyroid group was higher than other groups and the difference between these 4 groups was significant in this regard; 64.5% of people with hypothyroidism had positive thyroid peroxidase antibodies; It was concluded that due to the significant increase of anti-TPO antibody in patients compared to healthy individuals, the pathological role of this autoantibody in autoimmune and non-autoimmune thyroid diseases has been identified and its role could not be ignored[4] In a study in line with the present study, it was shown that the cause of autoimmunity was an increase in the relative frequency of positive thyroid peroxidase antibodies[39]. In a study by Hosseini et al., it was shown that only a positive titer of anti-TPO antibody and TSH concentration above 1.88 million units per liter increased the risk of hypothyroidism in individuals with normal thyroid function. In addition, high serum TSH levels and positive anti-TPO antibody titers were the most important factors in the development of hypothyroidism in the elderly[42]. In the present study, the results also showed that TSH levels and, consequently, the relative frequency of thyroid diseases in patients with positive thyroid peroxidase antibody, were significantly higher than those without positive thyroid peroxidase antibody. In a descriptive-analytical study by Legakis et al. (2013) in Athens, it was shown that a positive anti-TPO antibody titer was associated with high levels of TSH in people over the age of 50 [35], and these findings were in line with the results of the present study. In a study conducted in 2016 in Tehran to examine the relative frequency of thyroid disorders in patients older than 55 years, the results showed that 61% of those with subclinical hypothyroidism and 84.2% of those with overt hypothyroidism had positive Anti-TPOAb titers, and thus it could be concluded that high serum TSH levels and anti-thyroid peroxidase antibody titers were the most important factors in the development of hypothyroidism in the elderly[42], which are consistent with the results of the present study.

Based on the findings of this study and comparison, with the results of similar studies, it could be concluded that the frequency of positive anti-thyroid peroxidase antibodies is high in the population with hypothyroidism. Due to the pathophysiological role of anti-thyroid peroxidase antibody[46] and its significant relationship with subclinical hypothyroidism[18,39,42,45] and due to the high relative frequency of hypothyroidism in the community and the importance of proper diagnosis and treatment of this disease and lack of facilities for the measurement of urinary iodine levels and considering that autoimmune thyroid diseases are the most common cause of hypothyroidism in areas with adequate iodine intake, it appears that high serum TSH levels and anti-thyroid peroxidase antibody titers have been the most important factors in the diagnosis of hypothyroidism, especially its clinical type. Therefore, it is suggested that in future studies, with specific interventions, it would be determined that whether the treatment of clinical hypothyroidism and, consequently, the reduction of thyroid hormone levels as one of the therapeutic cases, could reduce positive anti-thyroid peroxidase antibody in patients, and it is also suggested to examine the cause-and-effect relationship between these cases.

One of the limitations of our study was that it was not possible to assess urinary iodine levels in this study due to limited resources and costs. Another limitation of the study was the cross-sectional form of the study in which the simultaneous measurement of exposure and outcome, which is a feature of this type of study, weakened the

possibility of examining the causal relationship and therefore the analysis of the results must be done with more caution. In addition, there were certainly many known and unknown factors, particularly the type of nutrition, genetics, and the method of controlling metabolic disorders, that might have influenced the frequency distribution of positive thyroid peroxidase antibodies in patients with clinical and subclinical hypothyroidism and it was not possible to evaluate all of these factors in one study and would require further studies in a wider statistical community; However, in this study, the maximum possible effort was made to achieve accurate results and better generalization of the results by controlling the limitations that could be eliminated. Also, the Retrospective form of the study was another limitation of this research.

CONCLUSION

More than half of patients with hypothyroidism had positive thyroid peroxidase antibodies. TSH levels and, consequently, the relative frequency of thyroid diseases in patients with positive thyroid peroxidase antibody, were significantly higher than those without positive thyroid peroxidase antibody. Based on the findings of this study and comparison with the results of similar studies, it appears that high serum TSH levels and anti-thyroid peroxidase antibody titers have been effective factors in the diagnosis of hypothyroidism and especially its clinical type; However, due to the descriptive form of this study, it is necessary to conduct interventional studies as well as a more widespread systematic review, in order to remove the limitations of the present study and more effectively generalize the results to other statistical communities with more transparency. It is also recommended to implement appropriate strategies such as partial screening of thyroid disorders in different populations and to examine its relation with various variables such as anti-thyroid peroxidase antibodies and TSH for more efficacy and faster treatment.

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