UDC: 616.441-008.441-097(497.751)"2020/2023"
Professional paper

PREVALENCE OF HYPERTHYROIDISM IN THE TETOVO REGION, NORTH MACEDONIA

Jehona IBRAHIMI[1], Mije REÇI[1*], Sheval F MEMISHI[1]

[1]Department of Biology, Faculty of Natural Sciences and Mathematics, University of Tetova-Tetovo, RNM*
[1]Department of of Biology, Faculty of Natural Sciences and Mathematics, University of Tetova-Tetovo, RNM
[*]Corresponding author e-mail: mije.reci@unite.edu.mk

Abstract

Hyperthyroidism is a pathological disorder characterized by increased thyroid hormone synthesis and secretion from the thyroid gland, whereas thyrotoxicosis refers to the clinical syndrome of excess circulating thyroid hormones, irrespective of the source. The most common cause of hyperthyroidism is Graves' disease, followed by toxic nodular goiter. Other important causes of thyrotoxicosis include thyroiditis, iodine-induced and drug-induced thyroid dysfunction, and factitious ingestion of excess thyroid hormones. Unrecognized and untreated hyperthyroidism leads to serious clinical complications with adverse outcomes for patients. Hence, adequate knowledge of the epidemiological features of such conditions is desirable to plan effective interventions. Our study aimed to estimate the prevalence of hyperthyroidism in the region of Tetovo, to have an overview of the frequency of hyperthyroidism. A retrospective cohort study was conducted using the data of individuals of the Tetovo region during the period 2020-2023. The tests were performed with the ECLIA method, while the patient samples were analyzed using the electrochemiluminescent immunoassay (ECLIA). Out of a total of 860 individuals checked, 173 of them were positive, so the overall prevalence was 20.1%. The prevalence increased with age and for men was 19.54%, but for women 20.36% (for 0.85% higher among women than men). This study can serve to monitor the patterns of hyperthyroidism in the researched region.

Keywords: Hyperthyroidism, prevalence, thyroid hormone, Graves' disease, ECLIA.

1. Introduction

Hyperthyroidism is a pathological disorder in which excess thyroid hormone is synthesized and secreted by the thyroid gland. It is characterized by normal or high thyroid radioactive iodine uptake (thyrotoxicosis with hyperthyroidism or true hyperthyroidism). Thyrotoxicosis without hyperthyroidism is caused by extrathyroidal sources of thyroid hormone or by a release of preformed thyroid hormones into the circulation with a low thyroid radioactive iodine uptake (Hedberg *et al*, 1987). Hyperthyroidism can be overt or subclinical. Overt hyperthyroidism is characterized by low serum thyroid-stimulating hormone (TSH) concentrations and raised serum concentrations of thyroid hormones: thyroxine (T4), tri-iodothyronine (T3), or both. Subclinical hyperthyroidism is characterized by low serum TSH, but normal serum T4 and T3 concentrations (Cooper *and* Biondi, 2012).

The prevalence of hyperthyroidism is 0·8% in Europe (Garmendia Madariaga *et al*, 2014) and 1·3% in the USA (Hollowell et al, 2002). Hyperthyroidism increases with age and is more frequent in women. Data for ethnic differences are scarce, but hyperthyroidism seems to be slightly more frequent in white people than in other races (Garmendia Madariaga *et al*, 2014). The incidence of mild hyperthyroidism is also reported to be higher in iodine-deficient areas than in iodine-sufficient areas, and to decrease after the introduction of universal salt iodization programs (Vejbjerg *et al*, 2009).

The most common causes of hyperthyroidism are Graves' disease (GD), followed by toxic multinodular goiters (TMNG) and toxic adenomas (TA). GD is an autoimmune condition that occurs with the loss of immunotolerance causing thyrotropin receptor antibodies (TRAb) to

https://doi.org/10.62792/ut.jnsm.v9.i17-18.p2792

form, bind, and subsequently stimulate the thyroid-stimulating hormone (TSH) receptors. This causes increased thyroid hormone synthesis and secretion (De Leo *et al*, 2016). Non-toxic nodular goiters can sporadically develop and become autonomous over time causing hyperthyroidism (Berghout *et al*, 1990). These conditions demonstrate autonomous hormone production, which can be from mutations of genes that regulate thyroid hormone synthesis or the TSH receptor causing familial and sporadic non-autoimmune hyperthyroidism (Gozu *et al*, 2010). The prevalence of TAs and TMNGs increases with age and iodine deficiency (Ross *et al*, 2016).

Other causes of hyperthyroidism include iodine-induced, TSH-producing pituitary tumors, trophoblastic and germ cell tumors, struma ovarii, thyroid cancer, silent or painless thyroiditis from pregnancy or medications such as lithium or tyrosine kinase inhibitors, painful thyroiditis from infections, amiodarone-induced thyroiditis, and exogenous thyroid hormone intake [(Ross *et al*, 2016) (De Leo *et al*, 2016) (Sippel *and* Chen, 2010) (Berta *et al*, 2019)]. Hyperthyroidism in pregnancy can be overt hyperthyroidism, most commonly from GD (De Leo *et al*, 2016), or subacute thyroiditis in the post-partum period. This type of thyrotoxicosis is usually self-limited followed by a period of hypothyroidism and then recovery of thyroid function (Pearce *et al*, 2003). Therefore, anti-thyroid medications and radioactive iodine (RAI) treatment are not recommended.

Amiodarone-induced thyroiditis can present as either type I or type II (De Leo *et al*, 2016). Type I occurs from underlying TMNG or GD that are exposed to high iodine content from amiodarone causing excess thyroid hormone production. Type II is a destructive thyroiditis from the toxicity of amiodarone on thyroid cells. It is usually self-limited, and may not require discontinuation of amiodarone.

The clinical manifestations of hyperthyroidism can be diverse as thyroid hormones can have an impact on a variety of systemic symptoms. The cellular effects of T3 binding to alpha and beta receptors increase thermogenesis and basal metabolic rates. This can result in constitutional symptoms of weight loss, fatigue, and heat intolerance. Skin changes can occur including warm, moist skin with thinning of hair and pretibial myxedema in GD. Musculoskeletal manifestations include weakness, increased bone resorption, osteoporosis, and increased risk of fracture. Patients can develop lymphadenopathy, gynecomastia in men, or oligomenorrhea in women. Gastrointestinal (GI) manifestations include dysphagia, hyper defecation, and hunger (Sippel *and* Chen, 2010.). Ophthalmologic findings include lid retraction and infiltrative GO can be seen in patients with GD [(Ross *et al*, 2016) (Bahn, 2010)]. Older age, smoking, longer duration of symptoms, and female gender are risk factors associated with GO (Boelaert et al, 2010). Significant cardiovascular manifestations are common in hyperthyroidism (Sippel *and* Chen, 2010). The most common cardiovascular manifestations of hyperthyroidism are hypertension and tachycardia (Berta *et al*, 2019).

For the diagnosis of hyperthyroidism, serum TSH should be measured first, because it has the highest sensitivity and specificity in the diagnosis of thyroid disorders (de los Santos *et al*, 1989). If low, serum free T4 or free T4 index, and free or total T3 concentrations should be measured to distinguish between subclinical hyperthyroidism (with normal circulating hormones) and overt hyperthyroidism (with increased thyroid hormones). It also identifies disorders with increased thyroid hormone concentrations and normal or only slightly raised TSH concentrations, as in patients with TSH-secreting pituitary adenomas or peripheral resistance to thyroid hormone (Vaidya *and* Pearce, 2014). The modalities preferred for assessing the cause of thyrotoxicosis vary widely. Different population characteristics, cultural backgrounds, and socioeconomic reasons partly explain these differences.

A thyroid radioactive iodine uptake test in patients with Graves' disease would show diffusely increased uptake. However, radioactive iodine uptake would be normal or high with an asymmetrical and irregular pattern in a toxic multinodular goiter, and a localized and focal

pattern in a toxic adenoma, with suppressed uptake in the remaining thyroid tissue. Radioactive iodine uptake in patients with thyrotoxicosis from extrathyroidal sources of thyroid hormone or the release of preformed thyroid hormones, as in silent or painful thyroiditis, will be very low (Cappelli *et al*, 2008).

The three options for treating patients with hyperthyroidism are antithyroid drugs (ATDs), radioactive iodine ablation, and surgery [(van Soestbergen, van der Vijver, *and* Graafland, 1992).

Unrecognized and untreated hyperthyroidism leads to serious clinical complications with adverse outcomes for patients. Hence, adequate knowledge of the epidemiological features of such conditions is desirable to plan effective interventions. Our study aimed to estimate the prevalence of hyperthyroidism in the region of Tetovo, to have an overview of the frequency of hyperthyroidism. A retrospective cohort study was conducted using the data of individuals of the Tetovo region during the period 2020-2023. And considering that hyperthyroidism is a chronic condition that occurs mostly in women between the ages of 30-50 years than in men, the purpose of this research was also to understand the eventual differences between genders and the most affected age groups.

2. Methodology

Thyroid disease is one of the most common endocrine disorders (Roberts *et al*, 2007). The laboratory diagnosis and monitoring of thyroid diseases such as hypo and hyperthyroidism are based on serum TSH measurement along with serum T4 and T3 (both free and total) (Sanchez-CarbayoM *et al*, 1994). The National Academy of Clinical Biochemistry (NACB) has recommended that the functional sensitivity of TSH assay be less or equal to 0.02 mIU/L. This permits patients with nonthyroid illness to be distinguished from those with primary hyperthyroidism. This is particularly important in patients hospitalized with nonthyroid illness where TSH concentration as low as 0.02 mIU/L may be encountered (Rawlins *and* Roberts, 2004).

The analytical sensitivity of TSH assay and its ability to reliably distinguish between euthyroid and hyperthyroid patients, especially in subclinical stages, where T4 and T3 levels are in the normal range makes it a very sensitive marker of primary thyroid function abnormalities (Col *et al*, 2004). Several years ago, the most commonly used assay for the measurement of TSH was radioimmunoassay which was considered the first-generation method with a functional sensitivity of 1 mIU/L, IRMA was the second-generation method with a functional sensitivity of 0.1 mIU/L from the 1990s to date, and the third-generation method was electrochemiluminescence assay that had been introduced with improved functional sensitivity (Rasmussen *et al*, 1997).

To define the best sensitive assay with good reliability, we performed an analytical evaluation of the new electrochemiluminescent immunoassay (ECLIA) for serum TSH, FT4, and T3 in the Elecsys 2010 immunoassay system. Elecsys 2010 is an automated reliable, efficient, and technically excellent instrument to use in the measurement of serum TSH, T4, and T3.

The study was carried out in the molecular laboratory "Laor" in Tetovo, using the SNIBE MAGLUM X apparatus for this method. The cases of the period 2020-2023 were taken as basic material for the realization of this study, to have an overview of the frequency of hyperthyroidism. Blood was collected from 860 individuals after 12 hours of fasting and was taken from people of different ages and physiological conditions from the region of Tetovo, out of which, 133 were males and 722 females. Serum specimens were used to evaluate the minimum detectable concentration and precisions for the three analytes (i.e.TSH, FT4, T3). After the blood was drawn from the patients, it was expected to coagulate. After coagulation, they were centrifuged for 10 minutes and then pipetted and inserted into the apparatus called

SNIBE MAGLUM X. After 18-20 minutes, the reading of the results was done. So, serum from 860 patients was used to evaluate the minimum detectable concentration, intra- and inter-assay precisions for TSH, FT4, T3, linearity for TSH assay, and method comparison study.

3. Results and Discussion

Preliminary processing of the data obtained from the work sample for the period 2020/23 which consisted of 860 persons, the results showed that the average hyperthyroidism, in the sample of people in the region of Tetovo, which has undergone serological testing, is close to 20.1%. Serological examination confirmed the presence of the disease in both sexes and all age groups, but with a different level in different sexes and in different age groups. To assess the level of the disease, we made a rough Professional paper in terms of gender (male and female) and age group: 0-25, 26-50, and over 50. Hence, 860 samples of persons were tested, of which 178 of them tested positive and are presented in the following tables according to gender and age group.

Table 1. General data of the work sample for hyperthyroidism, for the period 2022/2023 in the region of Tetovo

Years	Tested	Positive	%
2020	202	36	17.8
2021	260	52	20
2022	332	67	20.1
2023	66	18	27.2
Total	860	173	20.1

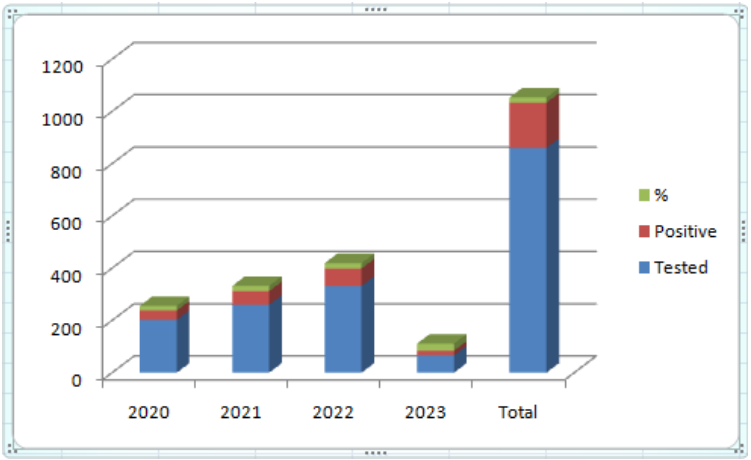

Figure 1. Data presentation from table 1

The results presented in Table 1 show that for 4 years (2020-2023), from the total number of 860 individuals tested, 173 individuals were detected with hyperthyroidism, or with a prevalence of about 20.1%.

Regarding the prevalence of hyperthyroidism over the years, the data reflect that the lowest prevalence was in 2020, with about 17.8%, however, in the following years the prevalence has an increasing tendency. This growth trend is evidenced by the highest prevalence recorded in 2023 for only 3 months (January, February, and March), with about 27.2%.

Table 2. Prevalence of hyperthyroidism by sex

Years	Tested women	Positive women	%	Tested men	Positive men	%
2020	161	32	19.8	41	4	9.7
2021	224	45	20	36	7	19.4
2022	279	53	18.9	53	14	26.4
2023	58	17	29.3	3	1	33.3
Total	722	147	20.3	133	26	19.5

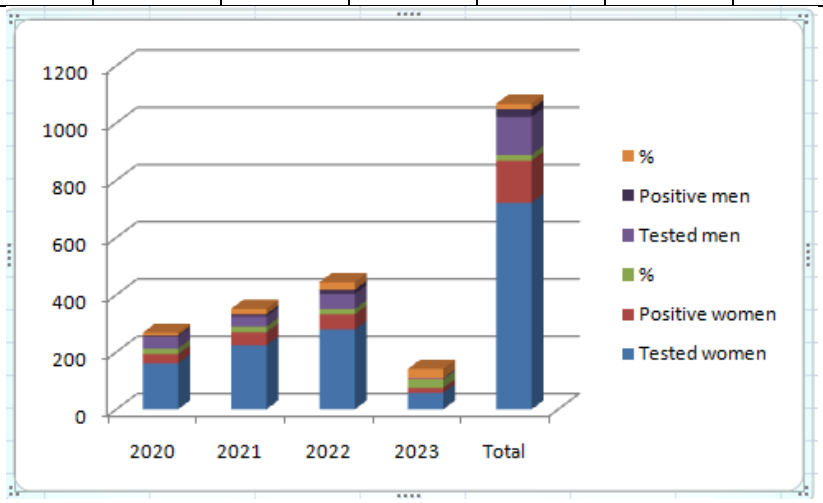

Figure 2. Data presentation from table 2.

The results of Table 2 show that out of 133 men tested, 26 (19.5%) of them were positive, while out of 722 women tested, 147 (20.3%) of them were diagnosed with hyperthyroidism. As can be seen, from the comparisons between the sexes, in the female gender the difference is slightly higher than in the male gender by 0.85%. So, hyperthyroidism is more frequent in women.

Table 3. Prevalence of hyperthyroidism by age group

Years	Age groups	Tested	Positive	(%)
2020	0-25	9	0	0
	26-50	108	18	16.6
	>50	86	18	20.9
2021	0-25	19	5	26.3
	26-50	137	28	20.4
	>50	104	19	18.2
2022	0-25	31	6	19.3
	26-50	164	26	15.8
	>50	138	35	25.3
2023	0-25	7	1	14.2
	26-50	33	5	15.1
	>50	26	12	46.1
Total	0-25	66	12	18.1
	26-50	442	78	17.6
	>50	354	83	23.4

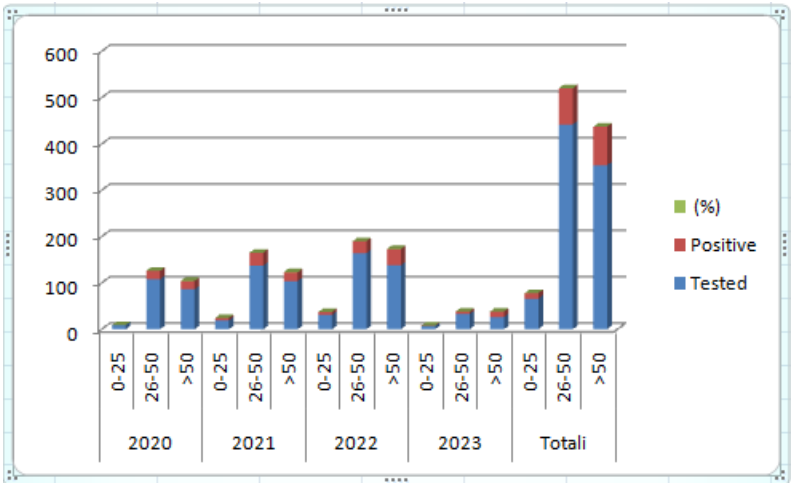

Figure 3. Data presentation from table 3

Based on the number of tested and positive for the 4 years (2020-2023) in total tested in the 0-25 age group, 66 people were tested and 12 or 18.1% were diagnosed, in the 26-50 age group 442 individuals were tested while 78 or 17.6% were diagnosed in the over 50 age group, 354 individuals were tested while 83 or 23.4% were diagnosed. So, hyperthyroidism increases with age.

4. Conclusions

From the analysis, comparison, and discussion of the data we can come to the following conclusions:

As for hyperthyroidism in the Tetovo region during the period 2020-2023, out of 860 individuals tested in total, 173 of them were positive, or 20.1%.

With hyperthyroidism according to gender, out of 133 men tested, 26 cases were positive (19.54%), and out of 722 women tested, 147 of them (20.36%). From the comparisons between the sexes, in the female sex, for about 0.85%, the difference is slightly higher than in the male sex.

Based on the age groups, considering the total number of checks and diagnoses for the 4 years (2020-2023), in the 0-25 age group the prevalence of hyperthyroidism was 18.1%. in the 26-50 age group, it was 17.6%, and 23.4% in the over 50 age group.

Hyperthyroidism increases with age and is more frequent in women.

In summary, since the prevalence of hyperthyroidism in our study-based result is 20.1%, we concluded from our study that hyperthyroidism is positively linked with family history and previous history, and due to this chance of developing hyperthyroidism increases in a person who has any family history/previous history. It also affects the quality of life and it is the leading cause of morbidity.

Our study also concluded that if once in a lifetime a person develops hyperthyroidism the chances of recurrence of the disease increased to 50%. The prevalence of hyperthyroidism is n=173 (20.1%) which shows that the prevalence of hyperthyroidism is significant. So, treatment options should be planned and educated the people to improve their quality of life with underlying disease I.e. regular checkups, observation of symptoms, and proper treatment as directed by the physician.

Hyperthyroidism is a complex pathology with many etiologies in which multiple diagnostic modalities can be utilized to identify the best treatment. The treatment of choice is preference-sensitive and should involve a shared decision-making process between the patient and provider. Thus, patient education is important so that each individual understands their options

and can choose the treatment that best addresses their concerns. Successful treatment of hyperthyroidism has been reported in many studies. Although future research could close some of the gaps that exist in terms of long-term outcomes, patients and providers should be optimistic for good outcomes with the treatment modalities currently available.

We recommend that the study be conducted at the standard level with an even larger sample number so that we can gain more knowledge about this disease and its prevalence. This way we can inform people more accurately about this disease. Also, a better medicinal system should be introduced for the treatment of hyperthyroidism and an alternative system of medicine i.e. homeopathic system of medicine should be introduced for the treatment of hyperthyroidism.

References

[1] Amanda R. and Rebecca S. Sippel, 2020 Feb. Hyperthyroidism. *Gland Surg*. 9(1): 124–135. doi: 10.21037/gs.2019.11.01. PMCID: PMC7082267. PMID: 32206604.

[2] Bahn R.S., 2010. Graves' ophthalmopathy. *N Engl J Med*; 362:726-38. 10.1056/NEJMra0905750.

[3] Berghout A., Wiersinga W.M., Smits N.J. and Touber J.L., 1990. Interrelationships between age, thyroid volume, thyroid nodularity, and thyroid function in patients with sporadic nontoxic goiter. *Am J Med*; 89:602-8. 10.1016/0002-9343(90)90178-G.

[4] Berta E., Lengyel I., Halmi S., Zrínyi M., Erdei A., Harangi M., Páll D., Nagy E.V. and Bodor M., 2019. Hypertension in Thyroid Disorders. *Front Endocrinol (Lausanne)*; 10:482. 10.3389/fendo.2019.00482.

[5] Boelaert K., Torlinska B., Holder R.L. and Franklyn J.A., 2010. Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. *J Clin Endocrinol Metab*; 95:2715-26. 10.1210/jc.2009-2495.

[6] Cappelli C., Pirola I., De Martino E., Agosti B., Delbarba A., Castellano M. and Agabiti Rosei E., 2008. The role of imaging in Graves' disease: a cost-effectiveness analysis. *Eur J Radiol*.; 65:99–103.

[7] Carlo Cappelli, Ilenia Pirola, De Martino E., Cooper D.S. and Biondi B. 2012. Subclinical thyroid disease. *Lancet*; 379:1142–54.

[8] Col N.F., Surks M.I. and Daniels G.H., 2004. Subclinical thyroid disease: clinical applications. *JAMA*; 291:239–43.

[9] De Leo S., Lee S.Y. and Braverman L.E., 2016. Hyperthyroidism. *Lancet*; 388:906-18. 10.1016/S0140-6736(16)00278-6.

[10] de los Santos E.T., Starich G.H. and Mazzaferri E.L., 1989. Sensitivity, specificity, and cost-effectiveness of the sensitive thyrotropin assay in the diagnosis of thyroid disease in ambulatory patients. *Arch Intern Med*; 149:526–32.

[11] Garmendia Madariaga A., Santos Palacios S., Guillén-Grima F. and Galofré J.C., 2014. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *J Clin Endocrinol Metab*.; 99:923–31.

[12] Gozu H.I., Lublinghoff J., Bircan R. and Paschke R., 2010. Genetics and phenomics of inherited and sporadic non-autoimmune hyperthyroidism. *Mol Cell Endocrinol*; 322:125-34. 10.1016/j.mce.2010.02.001.

[13] Hedberg C.W, Fishbein D.B., Janssen R.S., Meyers B., McMillen J.M., MacDonald K.L., White K.E., Huss L.J., Hurwitz E.S. and Farhie J.R., 1987. An outbreak of thyrotoxicosis caused by the consumption of bovine thyroid gland in ground beef. *N Engl J Med*; 316:993–98.

[14] Hollowell J.G., Staehling N.W., Flanders W.D., Hannon W.H., Gunter E.W., Spencer C.A. and Braverman L.E., 2002. Serum TSH, T (4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*; 87:489–99.

[15] Pearce E.N., Farwell A.P. and Braverman L.E., 2003. Thyroiditis. *N Engl J Med*; 348:2646-55. 10.1056/NEJMra021194.

[16] Rasmussen A.K., Hilsted L., Perrild H., Christiansen E., Siersbaek-Nielsen K. and Feldt-Rasmussen U., 1997. Discrepancies between thyrotropin (TSH) measurement by four sensitive immunometric assay. *Clin Chim Acta*.;259:117–28.

[17] Rawlins M.L. and Roberts WL., 2004. Performance characteristics of six Third-generation Assay for thyroid-stimulating hormone. *Clin Chem*; 50:2338–44.

[18] Roberts R.F., Laulu S.L. and Roberts W.L., 2007. Performance characteristics of seven automated thyroxine and T-uptake method. *Clin Chim Acta*; 377:248–55.

[19] Ross D.S., Burch H.B., Cooper D.S., Greenlee M.C., Laurberg P., Luiza Maia A., Rivkees S.A., Samuels M., Sosa J.A., Stan M.N. and Walter M.A., 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid*; 26:1343-421. 10.1089/thy.2016.0229.

[20] Sanchez- Carbayo M., Mauri M., ALfayate R., Miralles C. and Soria F., 1994. Analythical evaluation of TSH & thyroid hormones by electrochemiluminescent immunoassay. *Clin Biochemistry*; 32:395–403.

[21] Simone De Leo, Sun Y. Lee and Lewis E. Braverman., 2016 Mar 30. Hyperthyroidism. doi: 10.1016/S0140-6736(16)00278-6. *PMCID*: PMC5014602. NIHMSID: NIHMS798460. PMID: 27038492.

[22] Sippel R.S. and Chen H., 2010. The Handbook of Endocrine Surgery Hyperthyroidism Hackensack, NY: *World Scientific Publishing Co. Pte. Ltd.*

[23] Vaidya B. and Pearce S.H., 2014. Diagnosis and management of thyrotoxicosis. *BMJ*; 349: g5128.

[24] van Soestbergen M.J., van der Vijver J.C. and Graafland A.D., 1992. Recurrence of hyperthyroidism in multinodular goiter after long-term drug therapy: a comparison with Graves' disease. *J Endocrinol Invest*.; 15:797–800.

[25] Vejbjerg P., Knudsen N., Perrild H., Laurberg P., Carlé A., Bülow Pedersen I., Rasmussen L.B., Ovesen L. and Jørgensen T., 2009. Lower prevalence of mild hyperthyroidism related to a higher iodine intake in the population: prospective study of a mandatory iodization programme. *Clin Endocrinol (Oxf)*; 71:440–45.