TITLE OF THE STUDY: "ASSOCIATION OF SERUM VITAMIN D LEVELS IN AUTOIMMUNE THYROIDITIS"

Authors: Shah Manan BharatKumar[1], CSBR Prasad[2], Sumathi ME[3].

1- Post graduate, Department of Pathology, SDUMC, Kolar
2- Professor, Department of Pathology, SDUMC, Kolar
3- Professor and HOD, Department of Biochemistry, SDUMC, Kolar

Corresponding author: Shah Manan Bharatkumar

INTRODUCTION:

The thyroid gland is the body's largest endocrine gland. The follicular cells produces Thyroid hormone, which controls the rate of metabolism and parafollicular cells (C cells) produces calcitonin, which controls calcium metabolism. Thyroid disorders are a common clinical problem. Thyroid disorders both benign and malignant occur in men and women in all ages and more common in females, incidence being higher between puberty and menopause.

Thyroid diseases are now among the most common endocrine disorders throughout the world with no exception in India too. Few studies have projected that nearly 42 million people in India have thyroid disease and it's increasing day by day.[1] Abnormal thyroid function varies from 1–2% in males and 7-9% in females across different types of populations.[2]

The recent studies have shown that the human Autoimmune Thyroid Diseases (AITDs) affect up to 5% of the general population which includes Hashimoto's thyroiditis, Grave's disease and Gestational thyroiditis.[3] Among AITD, Hashimoto's thyroiditis (HT) and Grave's disease are more common. The incidence of Hashimoto's thyroiditis is 0.3 to 1.5 per 1000

persons per year, and it is more common in women than men by 4 to 10 times.[3] 7.5% of school going girls with goiter have Auto Immune Thyroid Disease (AITD).[4]

Like other autoimmune diseases, the etiopathogenesis of AITDs is multifactorial. A combination of genetic, immune, environmental factors and hormonal influences such as vitamin D play an important role. Like any other autoimmune diseases AITDs also are associated with production of antithyroid antibodies.[3]

Clinical presentations of Hashimoto's thyroiditis may vary from painless nodular thyroid enlargement to diffuse enlargement of thyroid gland associated with features of either hypothyroidism or hyperthyroidism.[5] Many investigations are done for diagnosis of Hashimoto thyroiditis including Ultra sonography (USG), FNAC, Thyroid hormones level, and thyroid auto antibody levels (antithyroglobulin and antithyroid peroxidaseantibodies). [5,6]

In recent years it has been shown that Vitamin D has immunomodulatory effect in addition to its well-recognized major role in calcium metabolism.[2,7,8,9] It is estimated that one billion people throughout the world suffer from vitamin D insufficiency or deficiency, thus making vitamin D a prime focus for current medical research.[10] It is also shown that low levels of vitamin D are observed in several autoimmune diseases including multiple sclerosis systemic lupus erythromatosus and type 1 diabetes[2,11,12] but there is paucity of literature about association of vitamin D in Autoimmune thyroiditis. Moreover though most of the studies have found association between these two, there are some studies shows no correlation or weak correlation.[2]

In view of these conflicting results in various studies, we have examined the levels of vitamin D in patient with thyroid disease and the correlation of vitamin D and Autoimmune

thyroiditis. In autoimmune disease of animal models, treatment with vitamin D shows reduction in severity of symptoms.[12]

OBJECTIVES OF THE STUDY:

1. To estimate serum vitamin D3 and Anti thyroperoxidase antibodies levels in patients with goiter.
2. To compare the serum vitamin D levels in AITD patients and controls.

REVIEW OF LITERATURE:

In general population, 79% of females and 1-2% of males show abnormal thyroid functions. A significant proportion of these patients with abnormal thyroid functions, lack anti thyroid antibodies and their abnormal thyroid functions may be due to other causes like nodular goiter, radiation exposure, iodine deficiency or idiopathic[13].

The pathogenesis of AITDs, like other autoimmune diseases, is multifactorial. A combination of genetic, immune, environmental factors and hormonal influences such as vitamin D play an important role. Like any other autoimmune diseases AITDs also are associated with production of antithyroid antibodies. Thyroid gland which is affected with AITD shows dominant T-cell infiltration[10].

There are only a few studies correlating serum Vitamin D levels with serum anti TPO antibody and serum TSH levels. These studies have examined the impact of serum vitamin D deficiency on the incidence of AITDs in human, and yielding contrasting results. Most of the studies have shown that AITD especially HT is associated with lower level of serum vitamin D levels when compared with Non-AITD.[7,10,13,14] But a few studies failed to show a strong association with the titers of thyroid antibodies or the levels of thyroid hormones.[8,15]

NEED OF THE STUDY:

Contradictory results in the published literature on serum vitamin D levels and its association with AITD, necessitates further studies.

OBJECTIVES OF THE STUDY:

1. To estimate serum vitamin D and Anti thyroperoxidase antibody levels in patients with goiter.
2. To compare the serum vitamin D levels in AITD patient and control.

MATERIAL AND METHODS:

All patients with goiter referred to the cytology section for FNAC from various clinical departments of R. L. Jalappa Hospital and Research Centre, kolar included in the study during July 2017 to July 2018.

Written informed consent was taken from the all patients. After explaining the procedure, FNAC was done in cytology section of department of pathology.

After explaining the procedure and under aseptic precaution 2 ml of blood was collected from all patients who were cytologically diagnosed as Hashimoto's thyroiditis in a plain tube. Blood is allowed to clot for 30 minutes and serum was separated after centrifugation at 3000 rpm for 10 minutes. Serum used for estimation of Serum TSH, Serum Anti TPO antibodies and serum vitamin D levels by Chemiluminescent microparticle immunoassay (CMIA). Cytological Grading of lymphocytic thyroiditis was done by applying the criteria suggested by Bhatia et al.[16]

Table 1: Cytological grading system of inflammation in a case if auto immune thyroiditis suggested by Bhatia et al.[16]

GRADES	DESCRIPTION
I (Mild)	Few lymphoid cells infiltrating the follicles/increased number of lymphocytes in the background
II (Moderate)	Moderate lymphocytic infiltration or mild lymphocytic infiltration with Hurthle cell change/ giant cells/anisonucleosis
III (Severe)	Florid lymphocytic inflammation with germinal center formation, very few follicular cells left

Vitamin D status of cases and controls were categorized according to Endocrine society guidelines[17] as shown in table 2.

Table 2: Categorization of serum vitamin D status.[17]

Serum Vitamin D levels	Category
Less than 20 ng/dl	Deficient
21-30 ng/dl	Insufficient
30-100 ng/dl	Sufficient

Chi-square test was used as test of significance. Continuous data represented as mean and standard deviation. Independent t test/Mannwhiteney U test (Normality of date tested using

Shapiro test) was used as test of significance to identify the mean difference between two groups. P value <0.05 is considered as statistically significant.

RESULTS:

A total of 87 patient were taken in the study out of which 44 were cases and 43 were controls. All cases were confirmed with anti TPO antibodies. Mean age of 33 years among cases and mean age of 34 years among controls. Male: Female ratio was 1:21among cases and 1:10 among controls. Most commonly (88.64%, 39/44 cases) Hashimoto's thyroiditis was presented as diffuse swelling. 52.63% of cases (20/38 cases) were showing hypothyroidism and 52.27% of cases were showing grade 2 inflammation compare to only 7.89% of controls (3/38 controls) were showing hypothyroidism. (p value < 0.001) 88.63% of cases (39/44 cases) were showing significant low levels of vitamin D compare to only 4.38% (2/43 controls) of controls were showing low levels of vitamin D (p <0.001)

Present study also found that low levels of vitamin D and hypothyroidism were associated with higher grade (Grade 2 and Grade 3) of inflammation.

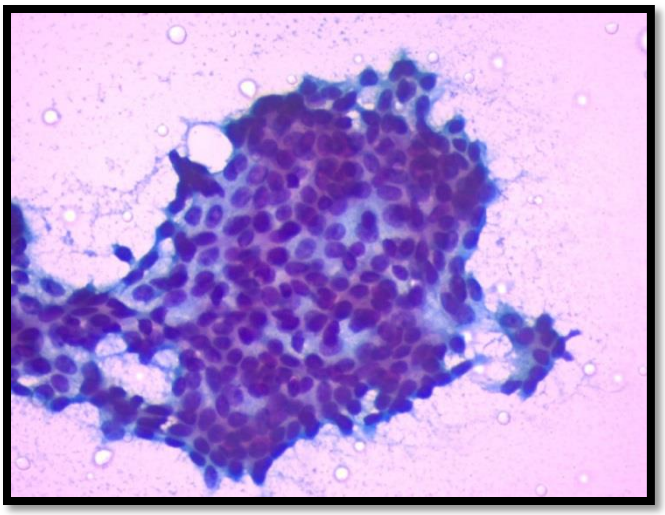

Figure 28: Grade 1 Hashimoto's thyroiditis showing occasional lymphocytes (arrows) infiltrating in to the follicles. (Rapid PAP, HP) (Case no. C/2141/18)

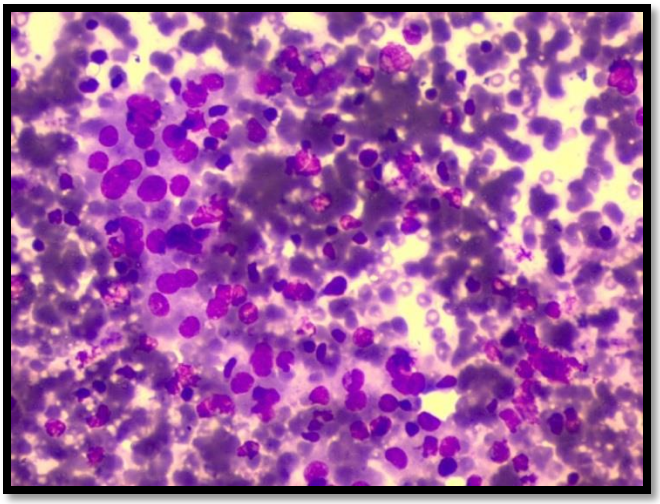

Figure 29: Grade 2 Hashimoto's thyroiditis showing moderate lymphocytic infiltration (White Arrow) with Hurthle cell change (Black Arrow). (H&E, HP) (Case no. C/1194/17)

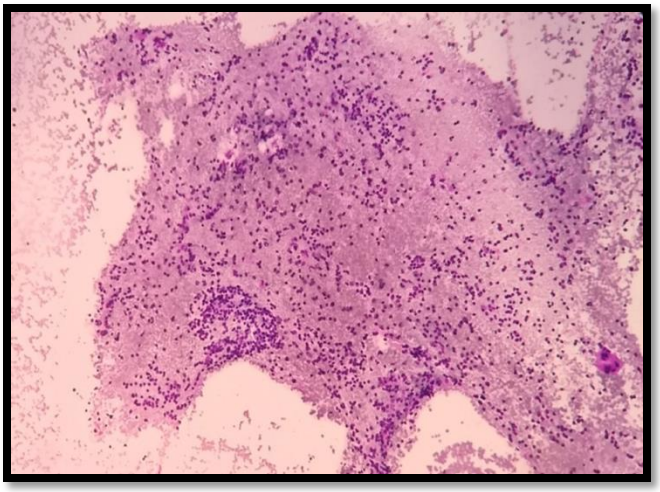

Figure 30: Grade 3 Hashimoto's thyroiditis showing florid lymphocytic inflammation with germinal center formation. (H&E. LP) (Case no. C/2657/17)

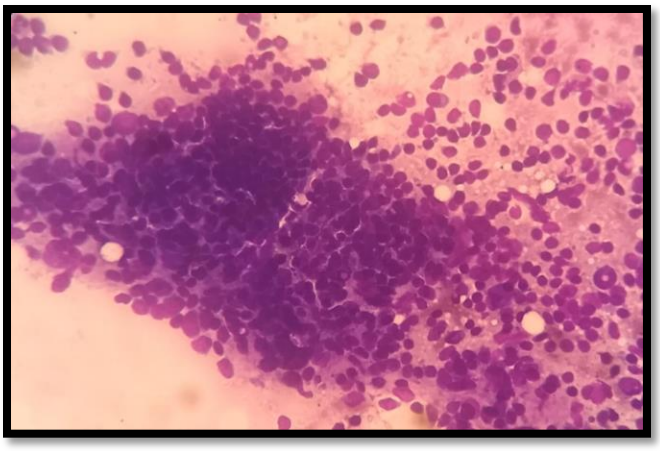

Figure 31: Grade 3 Hshimoto's thyroiditis showing florid lymphocytic infiltration with lymphoid follicle formation. (H&E, HP) (Case no. C/451/18)

Table 3: Age distribution of cases and controls

Age	Cases (44)	Control (43)
10-19	8	6
20-29	8	9
30-39	12	12
40-49	12	12
50-59	4	4
Total	44	43

Table 4: Male: Female ratio

M:F	Male (6)	Female (81)
Cases (44)	2	42
Controls (43)	4	39

Table: 5 clinical thyroid swelling of cases at presentation.

Thyroid swelling	cases
Diffuse swelling	39 (88.64%)
Nodular swelling	5 (11.36)
Total number of cases	44

Table 6: Serum Vitamin D levels in Cases and Control (ng/dL)

Sr. Vitamin D levels	Cases (44)	Controls (43)	P value*
Less than 20 ng/dL	39	2	Less than 0.01
21-30 ng/dL	5	36	
30-100 ng/dL	0	5	

Table 7: Thyroid profile of Cases (38/44) and Control (31/43)

	Cases (38)	Controls (31)	P value
Hypothyroidism	20	3	Less than 0.01
Hyperthyroidism	3	10	
Euthyroid	15	18	

Table 8: Cytological Inflammation grade of cases

Grade	Cases (44)
1	5
2	23
3	16

Table 9: Serum vitamin D levels and degree of inflammation of cases

Sr. Vitamin D levels	Sufficient levels	Insufficient levels	Deficient	P Value
Grading	**30-100 ng/dL (0)**	**21-30 ng/dL (5)**	**Less than 20 ng/dL (39)**	
Grade 1	0	0	5	Less than 0.01
Grade 2	0	3	20	
Grade 3	0	2	14	

Table 10: Thyroid profile and Degree Inflammation of cases (38/44)

	Grade 1 (5)	Grade 2 (22)	Grade 3 (11)	P Value
Hypothyroidism (20)	0	10	10	Less than 0.01
Hyperthyroidism (3)	0	2	1	
Euthyroid (15)	5	10	0	

DISCUSSION:

Thyroid disorders are among the most common clinical problem and endocrine disorders including benign and malignant both throughout the world. Though it occurs more commonly in females it also has become a major health problem in male population too. The incidence of thyroid diseases in female seen more commonly during reproductive age group this is because female are more susceptible to the goitrogenic effect of iodine deficiency during this period.

Autoimmune thyroid are also on a rising trend affecting approximately 5% of general population overall. This includes most common Hashimoto's thyroiditis followed by Graves's disease and Gestational thyroiditis. The incidence of Hashimoto's thyroiditis is 0.3 to 1.5 per 1000 persons per year, and it is more common in women than men by 4 to 10 times.[3] 7.5% of school going girls with goiter have Autoimmune thyroid disease (AITD).[4]

Like other autoimmune diseases, the etiopathogenesis of AITDs is multifactorial. A combination of genetic, immune, environmental factors and hormonal influences such as vitamin D play an important role and are associated with production of antithyroid antibodies.[3]

Although distinct in manner, Hashimoto's thyroiditis and Grave's disease shows similar pathophysiology and antibodies. Both are characterized by inflammatory infiltrate in form of lymphocytes in thyroid gland.[4]

AGE AND GENDER DIATRIBUTION:

Bhatia et al (2007)[16] noted in their study that are among the AITD patients were ranging from 6 to 60 and most common occurrence in 3rd and 4th decade.

Uma P. et al (2013)[18] noted in their study that are among the AITD patients were ranging from 7 to 73 and most common occurrence in 3rd and 4th decade.

In current study age among the AITD patients were ranging from 13 to 59 years and most common occurrence is seen in 4rd and 5th decade of life

Table 11: Age of occurrence of AITD: Comparison with various studies

Age	Bhatia et al[16]	Uma P. et al[18]	Present Study
Year of study	2007	2013	2018
Total number of cases	76	309	44
Age range	6 to 60	7 to 73	13 to 59 years
Most common age group	3rd and 4th decade	3rd and 4th decade	4rd and 5th decade, followed by 3rd decade

Moreover in the present study the highest incidence of AITD was in the age group of 31-39 years which is similar to Bhatia et al but study done by Uma et al shows most common age group of 21-30 years followed by 31-40 years.

Above findings shows that AITD are more common in age group of 21 to 40 years.

Table 14: Gender distribution among AITD cases: Comparison with various studies

M:F	Bhatia et al[16]	Uma P. et al[18]	Unal AD et al[7]	Present Study
Year of study	2007	2013	2014	2018
Total No. of cases	76	309	405	44
Male	6 (7.89%)	12 (3.89%)	89.4%	2 (4.55%)
Female	70 (92.11%)	297 (96.11%)	10.6%	42 (95.45%)
M:F Ratio	1:11.66	1:24.75	1:8.43	1:21

Table 14 shows that AITD are more common in female than male worldwide in various studies.

In a study done by Uma et al (2013)[18], 96.22% of cases were females and rest were males out of 309 cases. Male female ration was 1:24.7.

In a study done by Bhatia et al (2007)[18], 92.11% of cases were females and rest were males out of 76 AITD cases. Male female ration was 1:11.6.

In a study done by Unal AD et al (2014)[7], 89.4% of cases were females and rest were males out of 405 AITD cases. Male female ratio was 1:8.4.

In present study, Male: Female ratio was 1:21 which in concordance with other studies.

Nego ST et al[19] (2014) stated that prevalence of autoimmune disorders including hashimoto's thyroiditis is more in female population is probably due to multiple environmental factors.

According to Fairweather D et al[20] (2008), high prevalence of autoimmune thyroiditis especially Hashimoto's thyroiditis is can be due to sex hormones. Furthermore estrogen increases and testosterone decreases the severity of disease.

TYPE OF SWELLING:

Table 15: Type of thyroid swelling at presentation of cases of Hashimoto's thyropiditis: comparison with various studies

	Bhatia et al[16]	Singh et al[21]	Anila et al[22]	Present study
Year of study	2007	2009	2016	2018
Diffuse swelling	68 (89.47%)	130 (86.7%)	46 (77%)	39 (88.64%)
Nodular swelling	2 (2.63%)	20 (13.3%)	14 (23%)	5 (11.36%)
No goitre	6 (7.9%)	-	-	-
Total number of cases	76	150	60	44

In a study done by Bhatia et al[16] (2007), 68/76 (89.47%) of cases presented with diffuse swelling, 2/76 (2.63%) cases presented with nodular and 6.76 (7.9%) cases presented with no thyromegaly

In a study done by Singh et al[21] (2009), 130/150 (86.7%) of cases presented with diffuse swelling whereas 20/150 (13.3%) cases presented with nodular swelling

In a study done by Anila et al[22] (2016), 46/60 (77%) of cases presented with diffuse swelling whereas 14/60 (23%) cases presented with nodular swelling

In present study, 39/44 (88.64%) cases presented with diffuse swelling whereas 5/44 (11.36%) cases presented with nodular swelling. which in concordance with other studies.

Above findings shows that the most common presentation of Hashimoto's thyroiditis is diffuse thyroid swelling in various studies worldwide.

According to Kumar V et al[5] (2015) in Hashimoto's thyroiditis there are antibodies against the thyroid antigen and diffuse involvement of thyroid by inflammatory infiltrate in form of lymphocytes and plasma cells which causes follicular cell destruction. This can be a reason of clinically diffuse goitre in a case of Hashimoto's thyroiditis. Moreover clinical state of hypothyroidism can also be a cause of thyroid enlargement.

AITD AND THYROID PROFILE:

Table 16: comparison of thyroid profile of Hashimoto's thyroiditis with various studies

Study	Year of study	%of hypothyroid cases
Bhatia et al[16]	2007	98.68%
Singh et al[21]	2009	58%
Uma et al[18]	2013	62.78%
Anila et al[22]	2016	30%
Present study	2018	52.63%

In a study done by Bhatia et al[16] (2007), Singh et al[21] (2009), Uma et al[18] (2013) and Anila et al[22] (2016) noted 98.68%, 58%, 62.78% and 30% of cases were in hypothyroid state at the time of presentation respectively.

In present study, 52.63% of cases were in hypothyroid state at the time of presentation which is in concordance with all other studies except anila et al[22] which showed only 30% of cases in hypothyroid state.

Above result shows that most common presentation of Hashimoto's thyroiditis is hypothyroid state.

According to Kumar V et al[5] (2015) in Hashimoto's thyroiditis there are antibodies against the thyroid antigen on thyroid follicular cells and causes destruction and apoptosis of cells and disruption of thyroid follicles. This causes transient hyperthyroid state due to release of thyroid hormones into the circulation (Also known as "Hashitoxicosis"). Later hypothyroid supervenes.

In present study, we found maximum cases in hypothyroid state probably due to late presentation of the cases. The explanation can be given for the late presentation is because Hashimoto's thyroiditis usually cases painless swelling.

GRADE OF INFLAMMATION OF HASHIMOTOS THYROIDITIS AND THYROID PROFILE:

Table: 17: Grade of inflammation of Hashimoto's thyroiditis and its comparison with thyroid profile

Grade	**Uma P et al[18]**			**Present study**		
Year of study	**2013**			**2018**		
Total number of cases	**309**			**44**		
	Hyperthyroidism	**Hypothyroidism**	**Euthyroid**	**Hyperthyroidism**	**Hypothyroidism**	**Euthyroid**
Grade 1	**13**	**58**	**57**	**0**	**0**	**5**
Grade 2	**9**	**128**	**34**	**2**	**10**	**10**
Grade 3	**0**	**8**	**2**	**1**	**10**	**0**

As shown in table 17, Uma et al[18] (2013) noted that maximum cases were of hypothyroidism and they were showing grade 2 inflammation.

As shown in table 17, there is no linear correlation with grading of inflammation and thyroid profile state of the patient.

Present study also noted the similar findings and did not find any linear correlation between thyroid profile of the Hashimoto's Thyroiditis patients and grading of inflammation which states that presence of antibody dictates inflammation rather than antibody levels.

CYTOLOGICAL GRADE OF HASHIMOTOS THYROIDITIS:

Table 18: Comparison of Cytological grading of Hashimoto's thyroiditis with various studies.

Grade	Bhatia et al[16]	Singh et al[21]	Uma P. et al[18]	Anila KR et al[22]	Present study
Year of study	2009	2009	2013	2016	2018
Total number of cases	76	150	309	60	44
Grade 1	38.67%	18%	41.41%	45%	5 (11.36%)
Grade 2	44%	26%	55.34%	36.67%	23 (52.28%)
Grade 3	17.33%	56%	3.24%	18.33%	16 (36.36%)

In a study done by Bhatia et al[16] (2007), maximum cases had Grade 2 (44%) inflammation followed by grade 1 (38.67%) and grade 3 (17.33%).

In a study done by Singh et al[21] (2009), maximum cases had Grade 3 (56%) inflammation followed by grade 2 (26%) and grade 1 (18%).

In a study done by Uma et al[18] (2013), maximum cases had Grade 2 (55.34%) inflammation followed by grade 1 (41.41%) and grade 3 (3.24%).

In a study done by Anila et al[22] (2016), maximum cases had Grade 1 (45%) inflammation followed by grade 2 (36.67%) and grade 3 (18.33%).

In present stdy, maximum cases had Grade 2 (52.28%) inflammation followed by grade 3 (36.36%) and grade 1 (11.36%). Which is in concordance with Bhatia et all and Anila et al.

Above findings shows that maximum cases had grade 2 inflammation at the time of presentation in various studies worldwide.

VITAMIN D AND AITD:

Table 19: Comparison of serum vitamin D levels of Hashimoto's thyroiditis patients with various studies

Study	Year of study	Total number of cases	Cases with Vitamin D deficiency
Kivity et al[2]	2011	50	36 (72%)
Unal et al[7]	2014	281	183 (65%)
Mazokopakis et al[9]	2015	218	186 (85.32%)
Jie Ma et al[11]	2015	140	131 (93.57%)
Bakr et al[24]	2017	60	43 (71.66%)
Present study	2018	44	39 (88.63%)

In a study done by Kivity et al[2] (2011), Unal et al[7] (2014), Mazokopakis et al[9] (2015), Jie Ma et al[11] (2015) and Bakr et al[23] (2017) noted 72%, 65%, 85.32%, 93.57%, and 71.66% cases of Hashimoto's thyroiditis with serum vitamin D deficiency at the time of presentation respectively.

In a present study, 88.63% of cases had Serum vitamin D deficiency which in concordance with other studies. This data suggest an association if vitamin deficiency and AITD. Though the explanation of the same is no clear, weather serum vitamin D deficiency is a primary phenomenon and involved in pathomechanism of AITDs or just a consequence.

According to kivity et al[2] low levels of vitamin D in other autoimmune disease is due to,

1. Malabsorption (Systemic sclerosis , Inflammatory bowel disease).
2. Skin involvement result in to reduction in sun exposure (Dermatomyositis, SLE)
3. Reduced outdoor activity due to disease disability (Multiple sclerosis, Rheumatoid arthritis)
4. Chronic corticosteroid treatment

However AITD patients do not suffer from any of the above.

It is also shown that patient with hyperthyroidism, increased bone turnover can lead to high serum calcium levels and negative feedback mechanism on vitamin D and parathyroid hormone.[24]

Thus, it seems that vitamin D has a primary role in pathogenesis of AITDs especially Hashimoto's thyroiditis.

CONCLUSION:

The result of this study found that the majority (i.e. 88.63%) of patients with Hashimoto's thyroiditis had significant low levels of vitamin D levels. Low levels of vitamin D were seen in higher grade (Grade 2 and Grade 3) of inflammation which shows that its association with severity of the disease. It also shows positive correlation with thyroid profile and shows that most of the Hashimoto's thyroiditis cases were in hypothyroid state and with higher grade of inflammation.

KEYWORDS:

Auto Immune Thyroiditis, Hashimoto's thyroiditis, Grave's disease, vitamin D

BIBLIOGRAPHY

1. Ambika GU, Usha VM. Thyroid disorders in India: An epidemiological perspective . Indian Journal of Endocrinology and Metabolism. 2011;15: 78-81.
2. Kivity S, Nancy AL, Michael Z, Yinon S, Endre VN, Katalin D et al. Vitamin D and autoimmune thyroid diseases. Cellular & Molecular Immunology. 2011;8:243-7.
3. Iddah MA, Macharia BN. Autoimmune Thyroid Disorders. ISRN Endocrinology. 2013; 2013:1-9.
4. Mathew john. Burden of Thyroid Diseases in India. Need for Aggressive Diagnosis. Medicine update. 2008;18:334-41
5. Kumar V, Abbas AK, Aster JC. Robbins and cotran Pathologic basis of disease. 9th ed. Canada: Elsevier; 2015.
6. Miguel AS, Rosalyn ES. The thyroid, parathyroid and neck masses other than lymphnode. In: Koss LG, Melamed MR. Koos‟ diagnostic cytology and its histopathologic bases. 5th Ed. United State of America. Lippincott Williams and Wilkins;2006.1148-85.

7. Unal AD, Tarcin O, Parildar H, Cigerli O, Eroglu H, Demirag NG. Vitamin D deficiency is related to thyroid antibodies in autoimmune thyroiditis. Centr Eur J Immunol. 2014;39:493-7.
8. Muscogiuri G, Tirabassi G, Bizzaro G, Orio F, Paschou SA, Vryonidou A. Vitamin D and thyroid disease: to D or not to D? European Journal of Clinical Nutrition 2015; 69: 291-6
9. Elias EM, Maria GP, Konstantinos CT, Athanasios DE, Dimitrios AK, Anastasios AT. Is vitamin D related to pathogenesis and treatment of Hashimoto's thyroiditis? Hell J Nucl Med 2015; 18: 222-7
10. Jiying W, Shishi L, Guo C, Chenlin G, Jianhua H, Haihua Z et al. Meta-Analysis of the Association between Vitamin D and Autoimmune Thyroid Disease. Nutrients. 2015;7: 2485-98.
11. Jie M, Di W, Chenyang L, Chenling F, Nannan C, Jing L et al. Lower Serum 25-Hydroxyvitamin D Level is Associated With 3 Types of Autoimmune Thyroid Diseases. Medicine. 2015; 39; 1-7.
12. Giovanna M, Joanna M, Chantal M, Badenhoop K, Tamer G, Orio F et al. Vitamin D as a potential contributor in endocrine health and disease. European J of Endocr. 2014; 171: 101-110.
13. Mazokopakis EE, Papadomanolaki MG, Tsekouras KC, Evangelopoulos AD, Kotsiris DA, Tzortzinis AA. Is vitamin D related to pathogenesis and treatment of Hashimoto's thyroiditis? Hell J Nucl Med. 2015;18:222-7.
14. Tamer G, Arik S, Tamer I, Coksert D. Relative vitamin D insufficiency in Hashimoto's thyroiditis. Thyroid. 2011; 21: 891-6.
15. Muscogiuri G, Mitri J, Mathieu C, Badenhoop K, Tamer G, Orio F et al. Mechanisms in endocrinology: Vitamin D as a potential contributor in endocrine health and disease. Eur J Endocrinol. 2014;171:101-10.
16. Bhatia A, Rajwanshi A, Dash RJ, Mittal BR, Saxena AK. Lymphocytic thyroiditis - is cytological grading significant? A correlation of grades with clinical, biochemical, ultrasonographic and radionuclide parameters. Cyto Journal. 2007; 4: 1-6.
17. Sandhiya S, Vijneswaran G, Nishanthi A, Alphienes SX, Sureshkumar S, Sadishkumar K et al. Systemic review on vitamin D levels in apparently healthy Indian population and analysis of its association factors. Indian J Endocr Metab. 2017; 21: 765-75.
18. Uma P, Kartheek BVS, Himaja S, Chandra LJ, Kasi BA, Bhagya LA. Lymphocytic thyroiditis: a correlation of cytological grades with clinical, biochemical and ultrasound findings. Int Res Med Sci. 2013;1:523-31.
19. Nego ST, Steyn FJ, McCombe PA. Gender difference in autoimmune disease. Neuroendocrinology. 2014;35:347-69.
20. Fairweather D, Frisancho-Kiss S, Noel RR. Sex differences in autoimmune disease from pathological perspective. Am J Pathol. 2008;173:600-9.

21. Singh N, Surendra K, Negi VS, Siddaraju N. Cytomorphologic study of Hashimoto's Thyroiditis and its serologic correlation. Acta cytologica. 2009;53:507-516.
22. Anila KR, Nileena N, Jayasree K. Cytomorphologic spectrum of lymphocytic thyroiditis and correlation between cytological grading and biochemical parameters. J Cytol. 2016;33:145-9.
23. Bakr HG, Meawed TE. Relevance of 25 (OH) vitamin D deficiency on Hashimoto's Thyroiditis. Egypt J Immunol. 2017;24:53-62.
24. Iqbal AA, Burgess EH, Gallina DL, Nanes MS, Cook CB. Hypercalcemia in hyperthyroidism: patterns of serum calcium, parathyroid hormone, and 1,25-dihydroxyvitamin D3 levels during management of thyrotoxicosis. Endocr Pract 2003; 9:517–521.