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Histopathological variation in thyroid dysfunction associated with musculoskeletal disorder patients

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Abstract---Thyroid dysfunction has been associated with musculoskeletal disorders and there is an increased number of evidences that proves their association. Thyroid dysfunction especially in the form of hypo and hyperthyroidism has been linked to several connective tissue conditions. The primary objective of this study is to establish the histopathological variations in individuals with thyroid dysfunction with a musculoskeletal disorder. In this study with 300 subjects with a diagnosis of thyroid dysfunction, the histopathology of the thyroid tissues was analysed along with their variations. As a part of the histological findings, the following were analysed and evaluated. The hyperplasia of the synovial lining, cellularity of synovial stroma, inflammatory infiltrate, lymphoid follicles and vascularity were noted in muscle tissues. It was found that the histopathological variants increased as the severity of the thyroid dysfunction here in the case of hypothyroidism.

Keywords---thyroid dysfunction, rheumatoid arthritis, hypothyroidism, hyperthyroidism, histopathology.

Introduction

Thyroid dysfunction occurs commonly in the form of hypothyroidism and thyrotoxicosis. (Cakir et al., 2003). Thyroid dysfunction has been associated with several conditions such as autoimmune conditions, connective tissue disorders and so on.(Arnaout et al., 1994). Drugs like Amiodarone which are used to treat arrhythmia is associated with thyroid dysfunction(Nakazawa et al., 2008)There has been increasing evidence that there is an association of thyroid dysfunction with common musculoskeletal disorders.

There is a higher number of thyroid abnormalities in connective tissue disorders.(Duncan Bassett & Williams, 2016). Pain, stiffness and weakness of the joints are some of the common complaints in individuals with hypothyroidism(Cakir et al., 2003).A cohort study done by Duyff et al concluded that there are muscle-related issues in most individuals with thyroid dysfunction (Duyff et al., 2000).Hypothyroidism is associated with increased bone density and bone fractures whereas hyperthyroidism is also linked with fracture along with osteoporosis. (Jacobs-kosmin & Dehoratius, 2005) The musculoskeletal disorders often manifest themselves as muscle weakness and wasting as commonly found in thyrotoxicosis. (Cakir et al., 2003)(Huang et al., 2014). Recent data suggests that there are genetic components and similar pathways that contribute to the association of Grave's disease and Rheumatoid Arthritis (Wu et al., 2021). Many functions of the body are regulated by the endocrine system especially the muscle tissues are also among them. Contractile function, metabolism and regeneration of the skeletal muscles are regulated by the thyroid hormone. Both an increased or decreased amount of thyroid hormones have been linked to muscle wasting.(Martin et al., 2018)

Hypothyroidism which is a form of thyroid dysfunction can be either a congenital or an acquired condition. It involves a number of complex hormones rather than one defective hormone. A histological study was done by Hayat et al where the tissues obtained from the parotid salivary gland and the thyroid gland were analyzed. The final results indicated that there are histological changes in the parotid salivary gland after induced hypothyroidism(Hayat et al., 2010). Another study by Taser et al compared the histology of subsynovial connective tissues of individuals with Carpal Tunnel Syndrome (CTS) and hypothyroidism. They found that there is a significant amount of edema in the tissues when the individuals had hypothyroidism along with CTS(Taser et al., 2017). Likewise,a mouse study on hyperthyroidism showed that it plays a role in fibrotic changes and how Vitamin D plays a protectant role in it by observing the histopathological changes in the tissues.(Kaplan et al., 2021) In this article, the histopathology of thyroid tissues along with the histopathology of the muscular tissues has been compared and reviewed on their associations with a musculoskeletal disorder.

Material Methods

Study Population

The study was done in the endocrinology and rheumatology OPD Clinic of IMS and SUM Hospital Bhubaneswar, Odisha, India where the patients were

diagnosed. About 300 patients with a mean age of 38.54 ± 8 years were included in this study. They were allocated into three categories based on the thyroid hormone levels. The categories were as follows: Hyperthyroidism, Hypothyroidism and rheumatoid arthritis. Individuals with rheumatoid diseases were considered for the study. However individuals with the following chronic conditions were excluded from the study: diabetes mellitus, alcoholism, liver disease, and kidney disease, drug use liable to cause musculoskeletal disease or neuropathy and other serious illnesses. From all the patients, their family history of thyroid diseases and smoking status were obtained. Blood pressure, weight, height and body mass index were measured. Before the blood samples were obtained, consent was obtained and all the subjects in this study participated voluntarily.

Sample Collection

Prior to the blood collection, 12 hours of fasting was requested from the subjects who participated in the study. In a freezer at -20°C until analysis, the samples were stored. The diagnostic division of endocrinology and rheumatology OPD Clinic of IMS and SUM Hospital Bhubaneswar, Odisha, India performed all the biochemical assays. The patients were selected for the study based on the abnormal hormonal levels

Histopathology

To indicate the need for a thyroid biopsy, at the Radiology Unit thyroid ultrasound was performed routinely. Indications such as cold nodules were in the ultrasound and hence biopsy was performed. For patients who had indications of subclinical hyperthyroidism (two patients and one control), using $^{99\text{m}}\text{Tc}$ radionuclide (g-rays emitters) and a gamma camera a thyroid scan was performed. Following a standard protocol, sections were stained with Haematoxylin and eosin for histological analysis

Haematoxylin-Eosin Staining

The synovial specimens were obtained from the knee (5), wrist (5), hip (2), elbow (1), shoulder (1), and thumb (1) which summed up to 15.12 was the median synovitis score for the 15 specimens. For analysing histopathology and for light microscopic study of tissues were administered for paraffin sectioning. The tissues were hydrated and then dehydrated in sorted alcohol series. Using xylene and chloroform, it was then cleared and then it was fixed in paraffin wax using a rotary microtome. After which the tissues sections were taken ($10\mu\text{m}$) out and kept overnight at room temperature. With descending alcohol concentrations followed by dist. H_2O , it was then deparaffinized and moistened. The sections were stained and then administered for ascending alcohol concentrations using Haematoxylin and Eosin stain. Using a DPX mount, the permanent slide was prepared. Under a light microscope (20x)(Olympus microscope) the slides were observed and using a Sony digital camera photomicrographs were took

Histomorphometry of thyroid cells

Using ocular micrometry, the diameter of cells present in the thyroid cells region were measured for H and E stained slides. Cells darkly stained, shrunken cells and with fragmented nuclei were excluded. Cells that were round, medium or large and clear were measured. Using the random selection technique, the cells for measurements were selected from the serial sections made for each group. The examination included every 6th section was included and a total of 7 sections randomly. The same neuron will not be present in two sections which are ensured by using this technique. On each brain randomly, a total of 7 sections were examined. Using ocular micrometry (using Image J) under $100 \times$ magnifications in a light microscope, the cell diameter was measured

Statistical analysis

By using SPSS statistical software (Windows version 12.0), the statistical analysis was done. The mean + SD were used to express the data. To assess the significance among the groups and between groups respectively, Analysis of variance (ANOVA) and Independent Student's t-test was used. It was considered to be significant if the 'p' values were <0.05

Results and Discussion

In this study, the samples from 300 thyroid biopsy materials were examined and evaluated. Among them, there were 58% of females and 42% of males, with the mean age of the patients as 38.54 ± 8 years. The thyroid hormone levels namely the T4, T4 and TSH were analysed and grouped into their respective categories. The analysis revealed that about 23% of the subjects had hypothyroidism; 46% of the subjects had hyperthyroidism and 31% of the subjects had rheumatoid arthritis.

The synovial tissues of the subjects were then examined by histopathology. The tissues analysed consisted of mild hypothyroidism disease associated with the musculoskeletal disorder (MHMD) (Figure 1(a)), less severe hypothyroidism disease associated with the musculoskeletal disorder (LSMD) (Figure 1(b)) and very severe hypothyroidism associated with the musculoskeletal disorder (VSHMD) (Figure 1(c)).

The histopathological findings included (HSL) hyperplasia of synovial lining; (SSC) cellularity of synovial stroma; (INF) inflammatory infiltrate; (LF) lymphoid follicles; (VAS) vascularity and the total histology score was obtained. For all the tissues, the results are integrated into a bar graph (Figure 2). From the graph, it can be seen that the HSL were the same in both MHMD and LSHMD whereas it was found to be increased in VSHMD. On the other hand, the SSC levels gradually increased in MHMD, LSHMD and VSHMD respectively. Finally, the total score of the histology was significantly higher in VSHMD when compared with MHMD and LSHMD.

It can be concluded that the severity of the total histopathology score increased as the level of hypothyroidism increased. It is evident that though there is a strong

association of thyroid dysfunction with musculoskeletal disorders, the effect of it in cellular differs strongly based on the level of thyroid dysfunction. Since there are changes in the total score of the histopathology, there are increased chances where there are also overlapping features in the musculoskeletal disorder. This can be further confirmed by doing an additional study on the subjects to draw further conclusions. Though some evidences suggest the association of thyroid dysfunction with musculoskeletal disorders. In this study, we found that there are histopathological variations when the tissues were examined. There was a significant increase in the size of the follicles in the VSHMD group (Table 1). The follicular colloid showed no vacuolation, and the amount of colloid appeared to have increased and reached the luminal surface of the lining cells. The stroma was found to be thinned out with no change in the vascularity of the gland. A significant decrease in the height and breadth of the follicular lining cells in the VSHMD group was observed as compared to MHMD and LHSMD groups

Other studies of similar nature establish the association of thyroid dysfunction with other disorders. The clinical research and clinicians should not only focus on thyroid dysfunction but on other conditions that might be associated with it for effective management and treatment. However, there might be limitations to this in terms of overlapping symptoms of different conditions in which case the management would not be easy. There are evidences that hyperthyroidism leads to wastage of skeletal muscles. This is due to the fact to the increased muscle protein degradation triggered by hyperthyroidism. (Ahmad et al., 2005). Patients with hyperthyroidism have shown increased recycling of calcium ions and are also a risk factor for myasthenia gravis. Hypothyroidism on the other has been associated with muscle energy metabolism. There are cellular mechanisms that relate the thyroid hormone with muscle tissues (Bloise et al., 2018). The thyroid hormones also play a vital role in skeletal maturation (Duncan Bassett & Williams, 2016). There are factors that enhance the thyroid hormones to act as a negative or a positive transcriptional factor for the muscle cells (Dentice et al., 2014). Apart from all these thyroid dysfunctions has been linked to Duchenne muscular dystrophy and there are mouse model studies that further confirms it (Bloise et al., 2018)

Conclusion

To conclude, there are well established histopathological changes in thyroid dysfunction when it is associated with musculoskeletal disorders. These are further backed up by cellular mechanisms and genetic factors that suggest the association of thyroid dysfunction with musculoskeletal disorders.

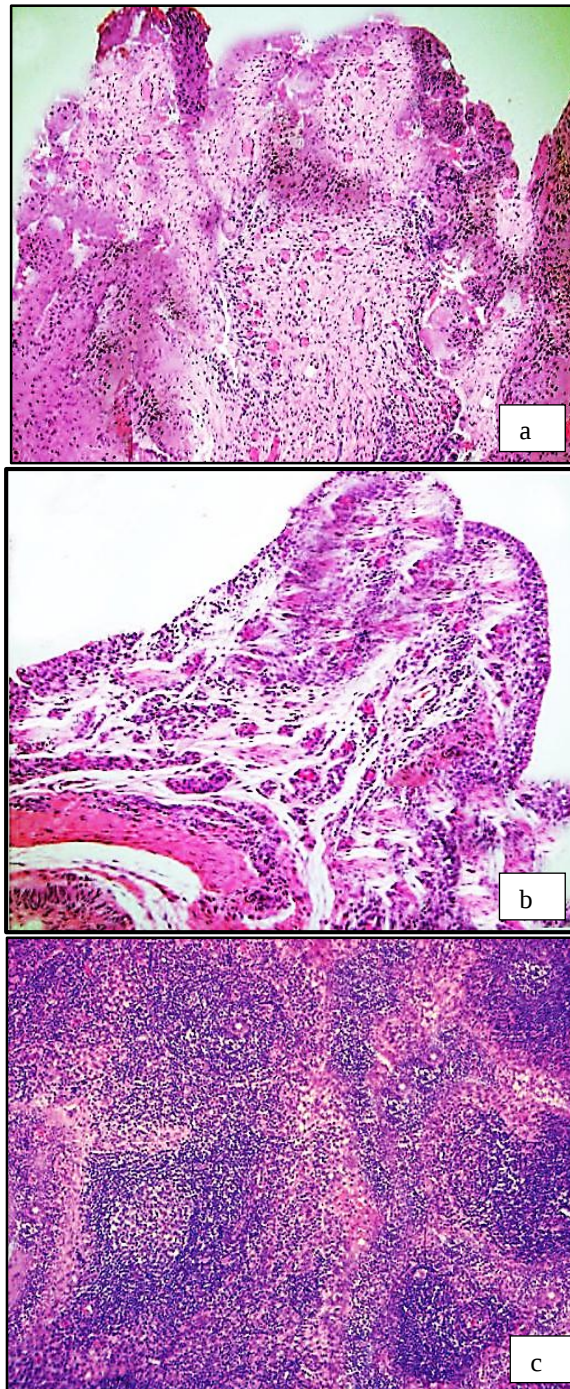


Figure 1(a) The synovial tissues showed mild hypothyroidism disease associated with the musculoskeletal disorder (MHMD); **Figure 1(b)** showed less severe hypothyroidism disease associated with the musculoskeletal disorder (LSMD); **Figure 1(c)** showed very severe hypothyroidism associated with the musculoskeletal disorder (VSHMD).

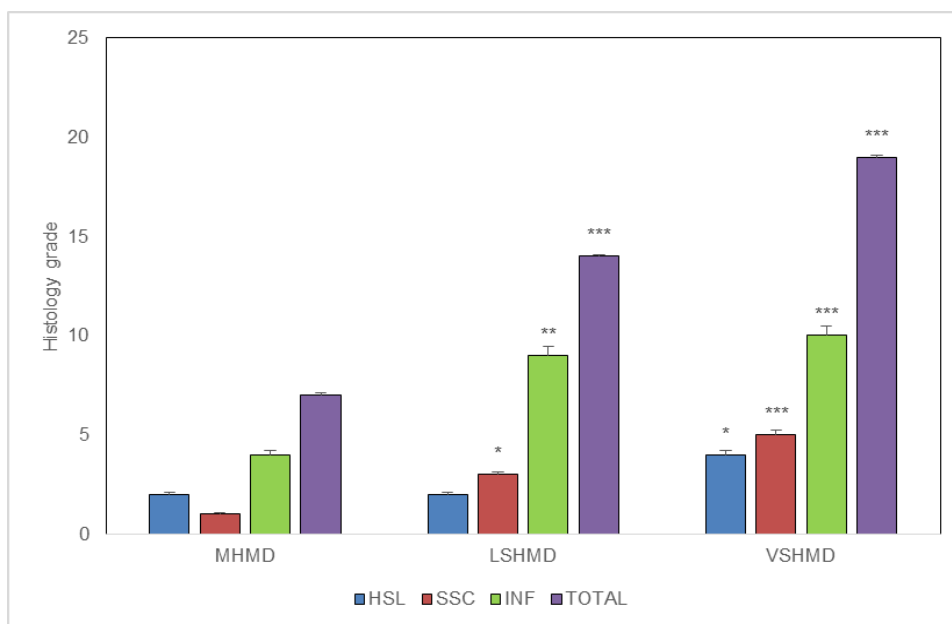


Fig 2: Histological appearance was scored for the presence of HSL: hyperplasia of synovial lining; SSC: cellularity of synovial stroma; INF: inflammatory infiltrate; LF: lymphoid follicles; VAS: vascularity; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared with the control group [n = 10, mean $\pm$ S.D.].

	Epithelial cell (μ)		Follicle (μ)	
	Height	Breadth	Long dm	Short dm
MHMD	5.99 $\pm$ 0.99	5.13 $\pm$ 0.45	79.45 $\pm$ 4.2	68.76 $\pm$ 6.5
LSHMD	6.21 $\pm$ 0.38*	5.85 $\pm$ 0.32*	82.11 $\pm$ 3.6*	70.45 $\pm$ 5.1
VSHMD	7.09 $\pm$ 0.51*	6.45 $\pm$ 0.21*	89.43 $\pm$ 2.7*	90.87 $\pm$ 6.8*

Table 1: Histomorphometry of epithelial cells and follicles in thyroid tissue

* $p < 0.05$, compared with the MHMD group [n = 10, mean $\pm$ S.D.].

References

- Ahmad, K. R., Saleem, S., Raees, K., & Mufti, S. A. (2005). *Histology, histochemistry and morphometry of overloaded skeletal muscles under normal, hypo and hyper-thyroid status n pigeon*. Pun Univ J Zool 2005; 20(2), 189–199.
- Arnaout, M. A., Nasrallah, N. S., & Ei-Khateeb, M. S. (1994). Prevalence of abnormal thyroid function tests in connective tissue disease. *Scandinavian Journal of Rheumatology*, 23(3), 128–132. <https://doi.org/10.3109/03009749409103044>
- Bloise, F. F., Oliveira, T. S., Cordeiro, A., & Ortiga-Carvalho, T. M. (2018). Thyroid hormones play role in sarcopenia and myopathies. *Frontiers in Physiology*, 9(MAY), 1–7. <https://doi.org/10.3389/fphys.2018.00560>
- Cakir, M., Samanci, N., Balci, N., & Balci, M. K. (2003). Musculoskeletal manifestations in patients with thyroid disease. *Clinical Endocrinology*, 59(2), 162–167. <https://doi.org/10.1046/j.1365-2265.2003.01786.x>

5. Dentice, M., Ambrosio, R., Damiano, V., Sibilio, A., Luongo, C., Guardiola, O., Yennek, S., Zordan, P., Minchiotti, G., Colao, A., Marsili, A., Brunelli, S., Del Vecchio, L., Larsen, P. R., Tajbakhsh, S., & Salvatore, D. (2014). Intracellular inactivation of thyroid hormone is a survival mechanism for muscle stem cell proliferation and lineage progression. *Cell Metabolism*, 20(6), 1038–1048. <https://doi.org/10.1016/j.cmet.2014.10.009>
6. Duncan Bassett, J. H., & Williams, G. R. (2016). Role of thyroid hormones in skeletal development and bone maintenance. *Endocrine Reviews*, 37(2), 135–187. <https://doi.org/10.1210/er.2015-1106>
7. Duyff, R. F., Van Den Bosch, J., Laman, D. M., Potter Van Loon, B. J., & Linssen, W. H. J. P. (2000). Neuromuscular findings in thyroid dysfunction: A prospective clinical and electrodiagnostic study. *Journal of Neurology Neurosurgery and Psychiatry*, 68(6), 750–755. <https://doi.org/10.1136/jnnp.68.6.750>
8. Hayat, N. Q., Tahir, M., Munir, B., & Sami, W. (2010). Effect of methimazole-induced hypothyroidism on histological characteristics of parotid gland of albino rat. *Journal of Ayub Medical College, Abbottabad : JAMC*, 22(3), 22–27.
9. Huang, S. W., Lin, J. W., Wang, W. Te, Wu, C. W., Liou, T. H., & Lin, H. W. (2014). Hyperthyroidism is a risk factor for developing adhesive capsulitis of the shoulder: A nationwide longitudinal population-based study. *Scientific Reports*, 4, 4–7. <https://doi.org/10.1038/srep04183>
10. Jacobs-kosmin, D., & Dehoratius, R. J. (2005). *Musculoskeletal manifestations of endocrine disorders*. Current opinion in Rheumatology 17(1); 64–69.
11. Kaplan, S., Türk, A., Aydın, H., Erten, M., & Kırıcı, P. (2021). Vitamin D improves oxidative stress and histopathological damage in rat ovaries caused by hyperthyroidism. *Journal of Obstetrics and Gynaecology Research*, 47(10), 3551–3560. <https://doi.org/10.1111/jog.14948>
12. Martin, A. I., Priego, T., & López-Calderón, A. (2018). Hormones and muscle atrophy. *Advances in Experimental Medicine and Biology*, 1088, 207–233. https://doi.org/10.1007/978-981-13-1435-3_9
13. Nakazawa, T., Murata, S., Kondo, T., Nakamura, N., Yamane, T., Iwasa, S., & Katoh, R. (2008). *Histopathology of the thyroid in amiodarone-induced hypothyroidism*. *Pathology International*, 55–58. <https://doi.org/10.1111/j.1440-1827.2007.02189.x>
14. Taser, F., Deger, A. N., & Deger, H. (2017). Comparative histopathological evaluation of patients with diabetes, hypothyroidism and idiopathic carpal tunnel syndrome. *Turkish Neurosurgery*, 27(6), 991–997. <https://doi.org/10.5137/1019-5149.JTN.17618-16.1>
15. Wu, D., Xian, W., Hong, S., Liu, B., Xiao, H., & Li, Y. (2021). Graves' Disease and Rheumatoid Arthritis: A Bidirectional Mendelian Randomization Study. *Frontiers in Endocrinology*, 12(August), 1–9. <https://doi.org/10.3389/fendo.2021.702482>