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A Systematic Review With An Insight To Discover The Association Between Oral Lichen Planus And Thyroid Diseases

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ABSTRACT

BACKGROUND

Oral Lichen Planus is an immune mediated disease which affects cutaneous tissue and oral mucosa. Thyroid disease is a common endocrine disorder which is prevalent world wide and approximately 42 million individuals in India suffer from Thyroid disorders. The objective of this systematic review is to evaluate the association between Oral Lichen Planus and Thyroid diseases.

METHODS

Articles were searched from databases such as PUBMED, Science Direct, ProQuest, Ingenta Connect and hand searched. We found 892 articles from primary databases and 2 from hand search after meeting the inclusion and exclusion criteria and six articles were assessed and included in our review, encompassing a wide geographic area.

RESULTS

Six studies were assessed with the common age group ranging between 40-70years and Oral Lichen Planus was confirmed by clinical and histopathological diagnosis. Investigations for Thyroid diseases included evaluation of T3,T4,TSH. This Systematic review found a positive correlation between OLP and Thyroid disease from the included studies.

CONCLUSION

A routine screening for Thyroid disease particularly, Hashimoto Thyroiditis is recommended upon the initial diagnosis of OLP. This procedure will facilitate early Thyroid disease diagnosis and also aid in the management of OLP.

INTRODUCTION

Oral Lichen Planus is a T-Cell mediated chronic inflammatory disorder affecting oral mucosa[1], with an incidence that is higher in women[2,3,4,5] than in men and age distribution varies around the world, but the disease is rare in children[6]. Etiology is not completely understood, however environmental variables like hepatitis virus infection, mechanical trauma, psychological stress, or changes in the microbiome can cause the disease in genetically vulnerable individuals and also immune-mediated mechanisms have been identified as a strong reason[7]. It is a challenge to diagnose OLP particularly in the absence of classic reticular pattern[8]. Thyroid Disease is a commmon endocrine disorder which is prevalent worldwide, it has been estimated that about 42 million people in India suffer from Thyroid diseases[9]. Etiology of Thyroid disease is multifactorial like genetic, congential, iodine defiency[10]. Thyroid hormone plays a very significant role in growth and development, regeneration, and metabolism[11]. Regulation of Thyroid level starts at the level of hypothalamus and any decrease in level of Thyroid hormone will be unpleasant for the quality of life[12].

An Association between Thyroid disease and OLP was identified in 1994 by Kurgansky et al[13], however it was not until the year 2009 that a positive significant correlation was found by Taiwan by Sun et al., who stated that 21.3 and 24.4% OLP patients had significantly higher levels of serum antithyroglobulin autoantibodies and antiThyroid microsomal autoantibodies respectively[14]. Later in 2018, Ting Ting Zhou found out that OLP was more frequently associated with Hashimoto's Thyroiditis[15].

METHODS

CRITERIA FOR SELECTION

We registered this systematic review in PROSPERO(CRD42023409020) International Prospective Register Of Systematic Review

INCLUSION:

1. Patients over 18 years of age were included
2. Patients diagnosed both clinically and histologically with oral lichen planus and with underlying Thyroid disease
3. Studies in english language alone were included
4. Only Case control studies published between the years 2014 to 2024 were included in the systematic review

EXCLUSION :

1. Pregnant subjects with OLP or existing Thyroid disease were excluded
2. Case reports, case series, scoping reviews, systematic reviews were excluded.

3. Vesiculobullous diseases/ autoimmune disorders other than OLP affecting the oral cavity were also excluded.
4. Oral lichenoid reactions were not included.

SEARCH STRATEGY

Our systematic review was performed following PRISMA Guidelines, 2021

Our Primary search engine was from PUBMED, Science Direct, ProQuest, Ingenta Connect, journals 2 articles found during hand search. The Mesh terms (oral lichen planus or lichen planus") and (Thyroid Disease or "HypoThyroidism" or "Thyroid nodule" or" hyperThyroidism" or "hashimoto disease" or "Graves' diseases" or "autoimmune Thyroiditis " or "Thyroid cancer" or "Thyroid carcinoma") were searched.

STUDY SELECTION

Two of the reviewers independantly assessed the titles, and abstracts and full texts of all identified studies. Third reviewer was consulted when disagreements occured between first and second reviewers. The fourth reviewer helped the first two reviewers in article search and selection. In the initial computerised search, 892 from databases and 2 hand search, and 88 duplicates were removed on comparing database searches, 806 were included for screening title and abstract screening. On evaluation 765 were found to have irrelevant titles and abstracts and were excluded as it were books, NEWS paper publications, meta-analyses, reviews and the remaining 41 were assessed for full text screening. Further more on excluding full text articles with irrelevant information, 6 studies were included in our review to be analyzed.(Figure 1)

RESULTS

A total of six studies from all over the world including study population from Israel, Italy, Spain, Sweden, China were analyzed.(Table 1) In all the six studies age groups ranged between 40-70years. The criteria for oral lichen planus were confirmed by clinical and histopathological diagnosis and the investigation for Thyroid diseases included evaluation of T3,T4,TSH. The most common type of lichen planus was reticular type followed by erosive form and most common Thyroid disease was Hasimoto Thyroiditis followed by hypoThyroidism and in some articles Thyroid nodules were also seen .

QUALITY ASSESSMENT

The methodological quality of included studies was assessed using Joanna Briggs Institute critical appraisal tool to evaluate underlying publication bias.(Table 2)

DISCUSSION

Oral Lichen Planus (OLP) chronic mucocutaneous condition, the exact origin of which yet remains unexplained is a disease commonly affecting females[2,3,4,5]. Since OLP and Thyroid disease have known to be caused by immune-modulated processes and still under debate, and corticosteriods are the mainstay of treatment for oral lichen planus[16], a systematic review was conducted to deduce an association between the two diseases, which have a common autoimmune origin.

Six publications in total that satisfied the inclusion criteria were included, and the information from the articles were merged for our systematic review. The included articles suggested a strong association between OLP and Thyroid disease with mean age in and around the 5th decade of life with a high prevalance was in women, because most of the population included given studies were women, implying the fact that OLP is common among women [2,3,4,5]. Of the Thyroid diseases identified to be associated with OLP, Hashimoto Thyroiditis was more commonly associated with oral lichen planus[5,15], reticular lichen planus was the most common type and erosive lichen planus being the second most common type [15,17,18] . Four out of six articles revealed a strong association between the two diseases and the possible pathogenesis stated that basal keratinocyte can express TSHr(Thyroid stimulating hormone receptor) and TG(thyroglobulin), which can be recognised by TRAb(thyrotropin receptor antibodies) and

TGAb(thyroglobulin antibody) circulatingTPO Ab(anti Thyroid peroxidase antibody) in Hashimoto Thyroiditis(HT) and may cross react with unknown protein on keratinocyte membrane which induces apoptosis. This basal keratinocyte initiated T lymphocyte reaction which in turn leads to release of chemokines that attract additional lymphocytes and other immune cells will lead to development of OLP[19].
Ujjawal Khurana et al., in 2015 reported that a predisposing role of HT to OLP may be suggested in the fact that circulating antiThyroid antibodies may trigger an autoimmune response in the mucosa and skin, leading to the development of lichenoid lesions in skin, as skin is a target tissue for Thyroid hormone action which helps in epidermal proliferaton and differentiation[20].

Pathologies of the Thyroid gland can induce the production of cytokines TNF- α, INF-γ from the Thyroid follicular cells[21]. The blood samples of oral lichen planus patient showed marked increase in the cytokines, TNF- α, INF-γ, and this can prove the immune-mediated pathology between Thyroid diseases and oral lichen planus[7].

Hawkins et al., in 1993 identified a strong correlation between HLA-DRw9 and a number of autoimmune disorders, such as Graves' disease and HT in chinese population[22], Similarly Lin and Sun's et al., in his 1990 study revealed that Chinese OLP patients had noticeably greater rates of HLA-DRw9 occurrences. This common finding can suggest a predisposition in the co- occurences of Thyroid disease and OLP[23].

Environmental triggering factors stated structural similarity between microbial antigens and human autoantigens can turn a defensive immune reaction into an autoimmune reaction in genetically predisposed subjects mainly because of specific HLA alleles where Borrelia infection has been found as a predisposing factor in both Thyroid disease and lichen planus. The other infectious agents that has been linked to AITD(Auto immune Thyroid disease) are Epstein–Barr virus, hepatitis C virus, parvovirus B19, human herpesvirus-6, and Helicobacter pylori and lichen planus was found to be associated with Epstein–Barr virus (HHV4), Herpesvirus-7, Hepatitis C virus, Human papillomavirus[24].

Milad alikhani et al., in 2016 suggested that a rise in Serum IL-8 is a sensitive marker and is used to assess the disease activity of oral lichen planus[25]. The level of IL-8 is also raised in patients with increased TPOAb indicating that these patients tend to develop erosive lichen planus[26].

Tingting zhou et al., in 2018 explained the possible association between hashimoto Thyroiditis and oral lichen planus, where lymphocytic infiltration and fibrosis of thyroid gland is a common feature of autoimmune Thyroiditis (Hashimoto Thyroiditis) which is also a finding
for lichen planus that shows necrosis of basal cell layer and dense lymphocytic infiltration in connective tissue[15].

Jairo robledo sierra et al., in 2015 stated that patients with oral lichen planus who were taking levothyroxine for thyroid diseases[18], showed less severity and milder symptoms of the lesion of the lesions when compared to patient who were not taking levothyroxine for thyroid diseases. However Lazar Kats et al., in 2019 reported that there were no significant associations between the co-existence of oral lichen planus and thyroid diseases as there were no significant coreleation found between case and control group and p-value was remarkably low[17].

Yunju et al., 2019 stated that prevalence of Thyroid nodule in OLP patients is low, and that thyroid nodules came in second after Hashimoto Thyroiditis in encountering common thyroid diseases. In his study 190 people were identified with Thyroid diseases and oral lichen planus of which 62 patients presented with Thyroid nodule and 11 patients went on to acquire Thyroid carcinoma as a result of their condition.The majority of Thyroid nodules are safe to treat with a surveillance program, if they are benign and clinically insignificant. Thyroid cancers were brought on by the malignant transformation of Thyroiditis or Thyroid nodules. We must give this phenomenon careful consideration. The economic cost of treatment of thyroid cancer is rising despite the disease's low death rate due to rising incidence rates, which include primary thyroid cancer and malignant transformation of diverse thyroid disorders. Then again, using OLP as a possible warning sign for thyroid cancer, cannot be validated yet, as the proof for co-relation is still rudimentary[27].

CONCLUSION

The etiology of OLP is unclear, however the studies included in our systematic review, found a positive and statistically significant correlation between OLP and thyroid disease. A routine screening for thyroid disease particularly Hashimoto Thyroiditis is recommended upon the initial diagnosis of OLP. This procedure will facilitate early thyroid disease diagnosis and also aid in the management of OLP. Oral Lichen Planus is a chronic disease and treating the underlying condition with a multi-disciplinary approach will prevent multiple drug interventions.

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Figure 1 - PRISMA FLOW CHART

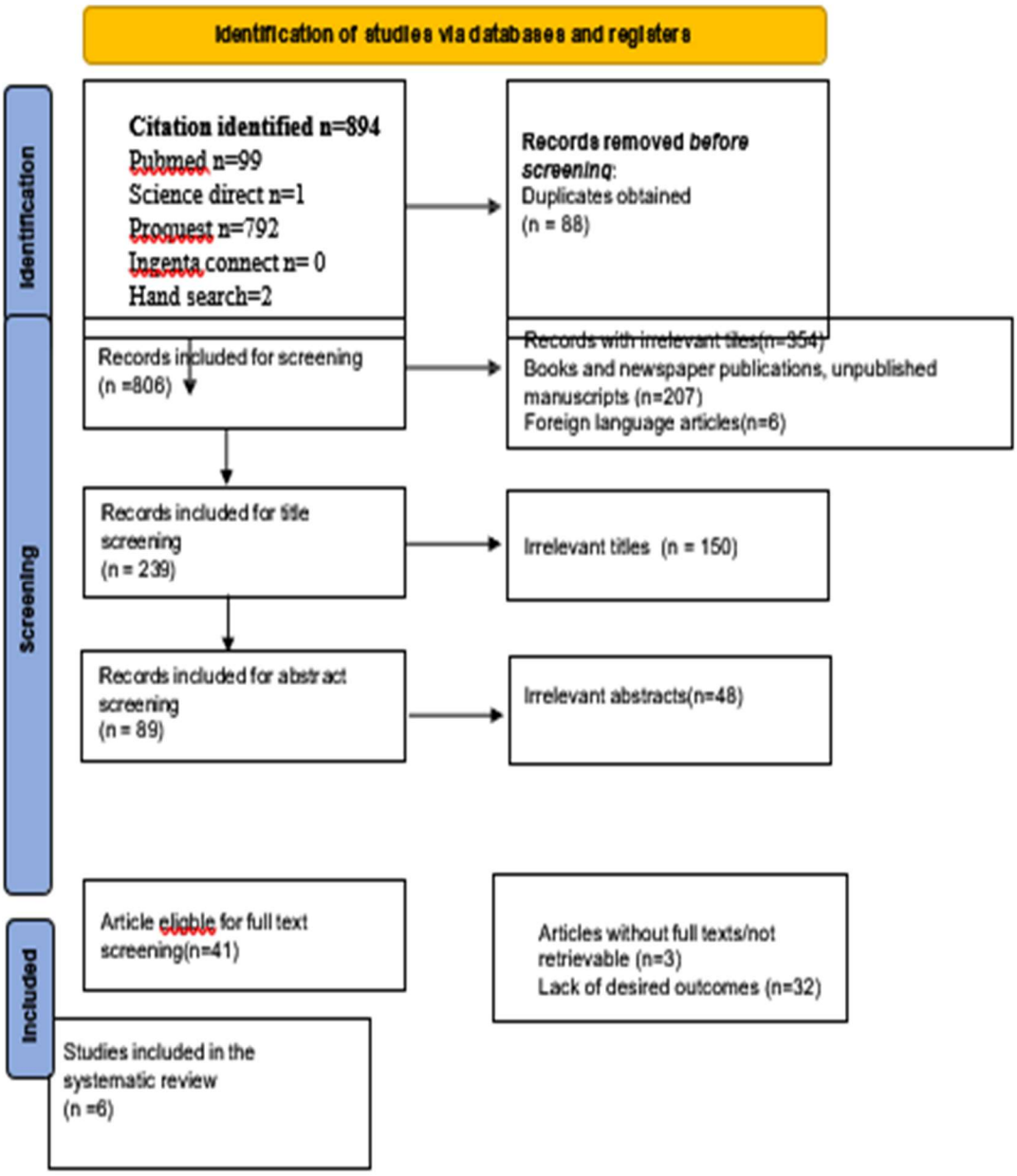

Table 1- DATA EXTRACTION

AUTHOR	YEAR	TOTALSAMPLE	AGE	MALE	FEMALE	TYPE OF LICHEN PLANUS	TYPE OF THYROID
JAIRORO BLE DOSIE RRA 2015	2015	1611	50-60	570	1041	RETICULAR FORM(74.1%), PLAQUE-LIKE(7.4%), ERYTHEMATOUS(12.0%), ULCERATIVE (1.9%)	Hashimoto Thyroiditis (22.1%), HypoThyroidism (58.1%), Non-toxic goitre (2.3%), Throid nodule (1.2%), Multinodular goitre (2.3%), Grave's disease

							(10.5%), Thyrotoxicosis (3.5%)
MARIA J OSEGARCIA - POLA 2016	2016	215	50-55	71	144	NON EROSIVE FORM(60.9%), ATROPHIC FORM(39.1%)	HypoyThyroidism (11.6%), EuThyroid goitre(2.8%), Goitre hyperThyroidism (0.5%), Cancer Thyroid(0.5%)
PAOLA GARDUINO ET AL 2017	2017	307	50-60	104	203	-	HypoyThyroidism (39.4%), Hashimoto Thyroiditis (42.3%), Nodular Thyroid disease(12.7%), Hyperthyrodism (5.6%)

TINGTING ZHOU ET AL 2018	2018	477	42-52	47	145	EROSIVE FORM (26%), NON EROSIVE (74%)	Hashimoto Thyroiditis (3.16 CI), Thyroid nodule(2.30 CI), HypoThyroidism (1.85 CI)
LAZARKATS 2019	2019	102	40-70	30	72	RETICULAR FORM(54.9%), EROSIVE FROM(27.5%), ATROPHIC FORM(17.6%)	HypoThyroidism (12.7%),Other Thyroid gland conditions (3.9%)
YUNJUTANG 2020	2020	190	40-70	23	167	EROSIVE FORM(13.7%), NON-EROSIVE FORM(86.3%)	Hashimoto Thyroiditis(37.4%),Throid nodule (32.6%), Hyperthroidism (3.2%), HypoThyroidism (3.7%),Thyroid cancer(5.8%), Multiple(17.4%)

Table 2- RISK OF BIAS

AUTHOR											% YES	RISK

JAIRO ROBLEDO SIERRA 2015											77.77	LCW
MARIA JOSE GARCIA-POLA 2016											77.77	LCW
PAOLA GARDUINO ET AL 2017											88.88	LCW
TINGTING ZHOU ET AL 2018											77.77	LCW
LAZARKATS 2019											77.77	LCW
YUNJUTANG											88.8	LCW

2020											8	