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SHORT COMMUNICATION

Association between oral lichen planus and Hashimoto thyroiditis: A systematic review

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1 | INTRODUCTION

During the last decade, several studies investigated the possible relationship between oral and systemic diseases (Serni et al., 2023). A correlation between oral lichen planus (OLP) and other autoimmune pathologies, like diabetes mellitus and thyroid diseases, was highlighted by recent metanalyses (De Porras-Carrique et al., 2022; Li et al., 2017). OLP and Hashimoto thyroiditis (HT), affecting predominantly middle-age women, seem to share many pathogenetic features, involving T lymphocytes, chemokines, and, probably, human thyroid autoantibodies (Wu et al., 2020).

This systematic review (SR) was designed to answer the following focused questions (FQs):

a. Are OLP patients more likely to be affected also by HT, compared to healthy individuals?
b. Are HT patients more likely to be affected also by OLP, compared to healthy individuals?

2 | METHODS

A protocol was designed according to the PRISMA checklist guidelines (Liberati et al., 2009) and registered on PROSPERO (ID Code: CRD42022332491).

Eligibility criteria were organized, according to PECO method, as follows. P (Population): general population, related to both *FQa* and *FQb*; E (Exposure): diagnosis of OLP (*FQa*), according to van der Meij-van der Wall criteria (van der Meij & van der Waal, 2003) and subsequent amendments (Warnakulasuriya et al., 2021), or obtained by medical records review or questionnaires; diagnosis of HT (*FQb*), assessed through thyroid peroxidase antibodies (TPOAb) and/or thyroglobulin antibodies (TgAb) and thyroid stimulating hormone (TSH) and/or free triiodothyronine (fT3), free thyroxine (fT4) titers (Ralli et al., 2020), or detected by medical records review or questionnaires; C (Comparison): controls not affected by OLP or other oral autoimmune diseases (*FQa*); controls not affected by HT or by other autoimmune thyroid diseases (ATDs) (*FQb*); O (Outcome): prevalence of HT (*FQa*); prevalence of OLP (*FQb*).

MEDLINE (PubMed), Cochrane Library, EMBASE, Google Scholar, and Web of Science, up to December 1st, 2022, were searched. The JBI's Critical Appraisal Tool for observational studies was used to determine risk of bias (JBI). The certainty of evidence was evaluated using the GRADE items.

To estimate the association between OLP and HT, meta-analyses were performed using Mantel–Haenszel odds ratio, with random effect models and 95% confidence intervals. The I^2 index was used to quantify heterogeneity. Subgroup meta-analyses were planned, based on different diagnostic methods to assess OLP and HT.

3 | RESULTS

Five studies were included (Brzak et al., 2020; Cankovic et al., 2016; Dave et al., 2021; Karimi et al., 2017; Zhou et al., 2018) (Figure 1),

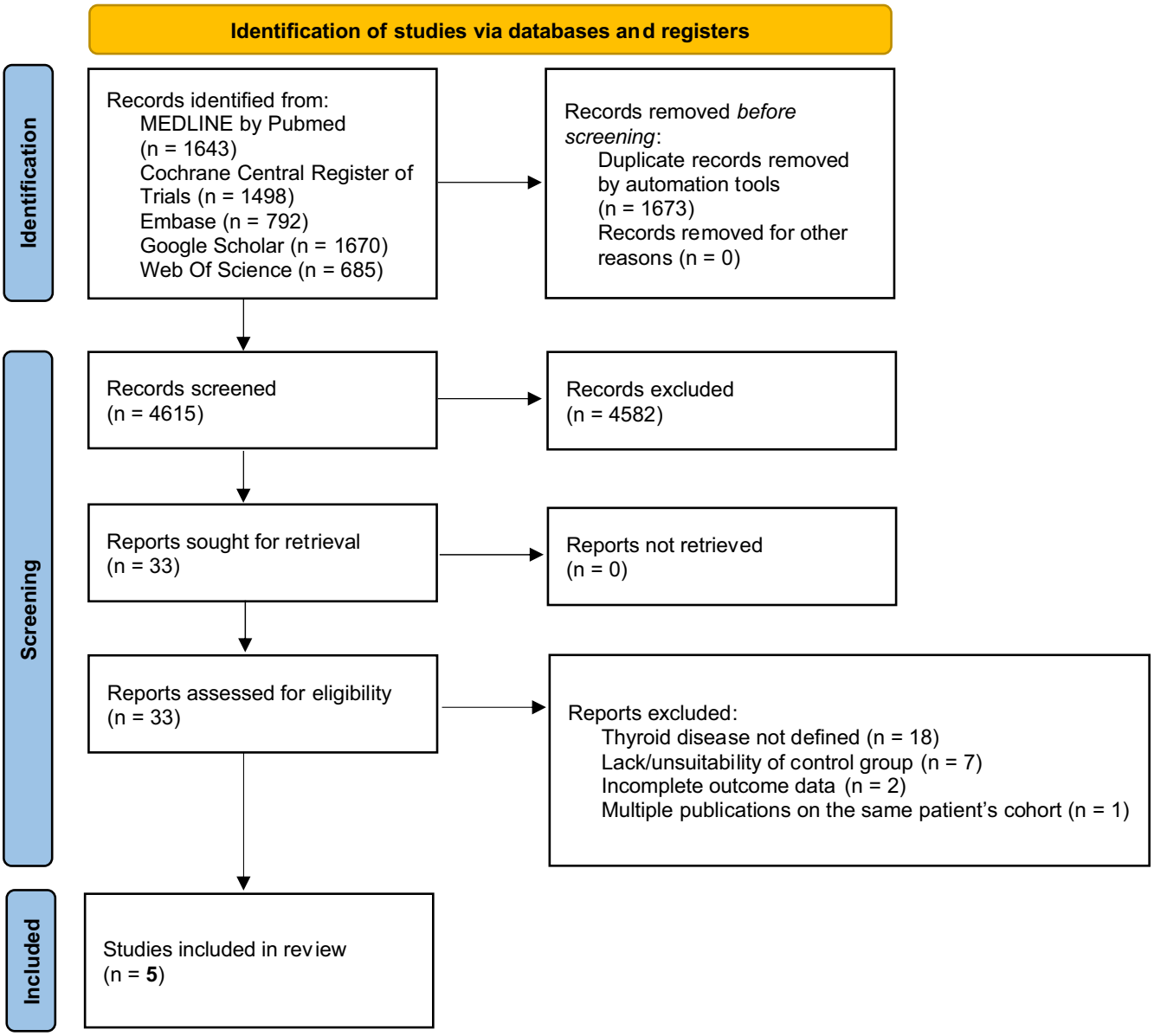

FIGURE 1 PRISMA 2020 flow diagram. Flow diagram showing the identification and selection process of the included studies.

all considering OLP as "exposure" and HT as "outcome" (*FQa*). No studies were retrieved to answer *FQb*. The diagnosis of OLP was always based on both clinical and histopathological criteria. Three studies were rated at high risk and two at unclear risk of bias.

A total of 1384 individuals were enrolled, 728 patients affected by OLP and 656 non-OLP controls. In four studies, a higher prevalence of HT in OLP patients was found, ranging from 1.28% to 20.83% (Table 1).

Higher odds of HT in OLP patients, compared with non-OLP controls, were detected (MH-OR = 2.29 [95% C.I. 1.43, 3.67]; $p = 0.0006$), with low heterogeneity ($I^2 = 11\%$). The certainty of evidence was low.

In studies where a diagnosis of HT was obtained by the evaluation of both thyroid autoantibodies titers and thyroid function tests ("Laboratory analyses"), similar results (MH-OR = 2.35 [95% C.I. 1.47, 3.75]; $p = 0.004$) were found, with low heterogeneity ($I^2 = 0\%$).

In studies where a diagnosis of HT was retrieved from medical records or questionnaires ("Medical records/self-reported"), a not statistically significant association between OLP and HT was detected (MH-OR = 1.73 [95% C.I. 0.15, 19.70]; $p = 0.66$), with substantial heterogeneity ($I^2 = 77\%$) (Figure 2).

4 | DISCUSSION

The possible relationship between Lichen Planus (LP), as a dermatosis, and autoimmune pathologies, specifically ATDs, has been poorly investigated (Guarnieri et al., 2017). Conversely, a correlation between HT and autoimmune dermatologic diseases, especially Psoriasis, has been reported, considering shared autoimmune processes, genetic susceptibility, and oxidative stress-mediated toxicity (Zhang, Zhang, et al., 2022).

TABLE 1 Characteristics of the included studies.

Studies reporting HT prevalence in OLP cases compared to non-OLP controls													
		Patient *N*		Patient age (SD)		OLP gender		Control gender		HT prevalence *N* (%)		Diagnostic methods	
Study	Design	OLP	Controls	OLP	Controls	M	F	M	F	OLP	Controls	OLP	HT
Cankovic 2016	Retrospective	48	71	59.8 (13)	64.1 (10.9)	15	33	15	56	7 (14.58)	2 (2.82)	vdM 2003	Questionnaire
Arduino 2017	Prospective	307	242	58.3 (13.5)	58.0 (10.5)	104	203	90	152	30 (9.77)	11 (4.54)	vdM 2003	fT4, TSH, TPOAb
Zhou 2018	Cross-sectional	192	162	49.53 (9.93)	50.96 (8.96)	47	145	32	130	40 (20.83)	16 (9.88)	vdM 2003	TPOAb, TgAb, fT3, fT4, tT3, tT4, TSH echography
Dave 2021	Retrospective	156	156	61 (13.8)	61 (13.8)	38	118	38	118	2 (1.28)	4 (2.56)	vdM 2003	Clinical records review
Brzak 2020	Cross-sectional	25	25	55.8 (10.26)	51.96 (11.13)	0	25	0	25	5 (20.0)	2 (8.0)	vdM 2003	fT3, fT4, TSH, TPOAb, TgAb

Abbreviations: F, Female; fT3, Free triiodothyronine; fT4, Free thyroxine; HT, Hashimoto thyroiditis; M, Male; *N*, Number; OLP, Oral lichen planus; SD, Standard deviation; TgAb, Thyroglobulin antibodies; TPOAb, Thyroid peroxidase antibodies; TSH, Thyroid stimulating hormone; tT3, Total triiodothyronine; tT4, Total thyroxine; vdM, van der Meij and van der Waal.

The present metanalysis showed a statistically significant association between OLP and HT. In OLP patients, a wide range of HT prevalence was reported, probably due to different methods used to diagnose HT. Nevertheless, in those studies where accurate diagnostic criteria for HT were applied, including both specific thyroid autoantibodies titers and thyroid function tests, this type of association was strengthened. Our data seem to support the hypothesis that some OLP patients could be affected by a wider, genetically determined, autoimmune condition that leads to self-aggression also against targets other than oral keratinocytes, including thyrocytes (Li et al., 2017).

Some researchers also hypothesized that, in HT patients, keratinocytes could express thyroid stimulating hormone receptor (TSHR) and thyroglobulin (TG), becoming targets of thyroid autoantibodies, such as thyrotropin receptor antibodies (TRAb) and TGAb (Cianfarini et al., 2010). Unfortunately, no case–control studies considering HT as "exposure" and OLP as "outcome" were retrieved; therefore, there is currently insufficient evidence supporting this hypothesis.

Moreover, circulating TPOAb may cross-react with unspecified keratinocytes proteins. Once bounded to the respective targets, they may activate CD95- (Fas/Apo-1) mediated apoptosis and subsequent T lymphocytes response, leading to the occurrence of OLP lesions. Thus, it could be hypothesized that the severity of OLP lesions could be linked to the serum levels of TPOAb (Alikhani et al., 2017). Nevertheless, it seems there is no "dose response effect" between HT and OLP prognosis (Zhang, Hou, et al., 2022). In fact, some studies reported that in patients affected by both OLP and ATDs, OLP lesions were less severe compared to individuals affected only by OLP (Robledo-Sierra et al., 2018). At the present, however, there is no evidence in specific clinical features of OLP lesions in HT patients.

The limits of this SR should be underlined. Only five, mainly retrospective and cross-sectional studies, with quite high risk of bias and, in two cases, no strict diagnostic criteria for HT were included. The latter aspect, in particular, may have increased the number of HT false positives. Therefore, it is not possible to confirm the existence of a direct correlation or a cause–effect relationship between these two diseases and to assess whether OLP precedes HT or vice versa, or if the co-occurrence of both diseases could be due to a common genetic susceptibility.

5 | CONCLUSIONS

A statistically significant association between OLP and HT was found. OLP patients should be carefully evaluated for signs and symptoms of HT and referred to an endocrinologist to detect subclinical, undiagnosed forms of HT. Further laboratory analyses and well-designed case–control prospective studies are needed to better investigate the possible cause–effect relationship between OLP and HT and, altogether, between LP and other autoimmune diseases, particularly ATDs.

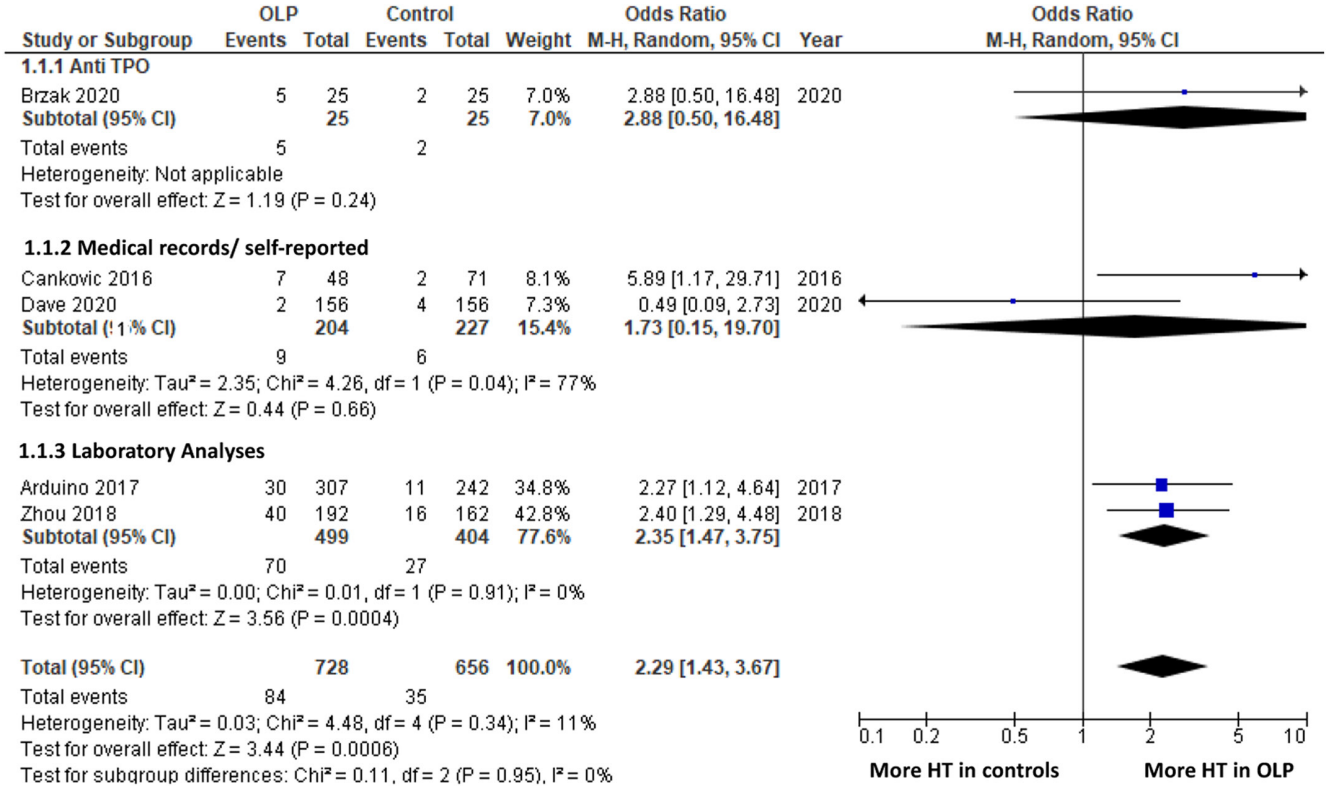

FIGURE 2 Risk of HT in OLP patients compared with non-OLP subjects. Anti TPO, thyroid peroxidase antibodies; CI, confidence interval; HT, Hashimoto thyroiditis; M-H, Mantel–Haenszel; OLP, oral lichen planus.

AUTHOR CONTRIBUTIONS

Lapo Serni: Writing – original draft; conceptualization; methodology; supervision. **Luigi Barbato:** Supervision; writing – original draft; formal analysis. **Michele Nieri:** Formal analysis; supervision. **Mattia Mallardi:** Data curation; investigation. **Désirée Noce:** Investigation; data curation. **Francesco Cairo:** Supervision; validation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Regarding the present manuscript, there are no conflicts of interest to be disclosed by the authors.

DATA AVAILABILITY STATEMENT

Data from this study are available by the corresponding author upon pertinent request.

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