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The Grinspan Syndrome: "Fact" or "fiction" – A Meta Analysis research

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ABSTRACT

Grinspan Syndrome since its inception has been an arena of interest that has appeared very lucrative to numerous researchers due to its lack of clarity and enhanced ambiguity. This syndrome, which is a triad of Oral Lichen Planus (OLP), Diabetes Mellitus (DM) and Hypertension (HTN) as reported in the early 1963 by Grinspan has not found much appreciation in the literature thereafter.[1] There are few studies however which are affirmative towards the association but simultaneously there are more studies which deny it. In our present study therefore, which was based on the case control trials, we aimed at systematically reviewing various literatures available so far using network Meta Analysis in order to establish the exact association between the three entities. Meta Analysis was performed and odds ratios and 95% confidence intervals (CI) calculated. From a total of 45 identified records, 24 case control studies were included in the study. Meta Analysis projected the association between OLP and DM to be 0.1 (no association), between OLP and HTN to be 0.5 (no association) and between OLP, DM and HTN to be 0.5 (no association). Although the results of the intended study do not go in favour of the association between the three entities, further researches need to be carried out in order to make the scenario clearer because the association among the three entities raises a ambiguity or a doubt.

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1. Introduction

The Grinspan Syndrome is a "triad" of Oral Lichen Planus (OLP), Diabetes Mellitus (DM) and Hypertension (HTN), 1st coined by Grinspan in the year 1963 after he observed an interesting association between the three systemic disorders.[1] Although there were several questions raised by various researchers over this association who could not simulate similar association in their studies, it was in the year 1965 that the two eminent researchers, Grupper and Avril, confirmed the existence of this symptomatological triad.[1–3] DM and HTN are chronic diseases involving multiple systems of the body with cutaneous manifestations being quite common. However even after the descriptive and elaborate explanation given by the duo described above, the exact level at which Grinspan would have noticed the association amongst the 3 disorders was not clear. LP (1st coined by Erasmus Wilson in the year 1869) is a mucocutaneous disorder, with intraoral manifestations being a regular feature.[4,5] The aetiology of OLP in the eyes of evidence

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based dentistry largely suggests that it is an inflammatory T cell mediated immune response.[6] DM on the other hand is characterized by elevated levels of glucose in the blood.[4] This elevation is the result of a deficiency in insulin secretion or an increased cellular resistance to the actions of insulin, leading to a variety of metabolic abnormalities involving carbohydrates, fats and proteins.[6–8] The most common types of diabetes are type 1 (also known as insulin dependent) and type 2 (also known as non-insulin-dependent) of which Type 2 is the more prevalent type.[9,10]

The prevalence of OLP as an oral disease is 1–2% however in association with DM is 0.55–5.76%, the association of the triad has been reported to be 0.4–0.23%.[11,12] With so much of ambiguity in the literature related to the association among the three entities, it definitely brings an onus upon the modern day researchers to investigate into the basics of the studies and carry out further researches in order to clarify the same.[13,14,5,15,16] With this regard, the present study in the form of Meta Analysis, aims to establish the association between OLP, DM and HTN thus heralding a new era in terms of the clarity of the syndrome and also determining to a greater extent whether the three entities actually lie in a close relationship with each other based on the numerous research literature available so far.[17,8,12]

2. Aims and objectives

To statistically establish the association between Oral Lichen Planus (OLP), Diabetes Mellitus (DM) and Hypertension (HTN) using Meta Analysis. The objectives of the study included:

1. To establish the association between OLP and DM.
2. To establish the association between OLP and HTN.
3. To establish the association between OLP, HTN and DM.

3. Materials and methods

This study follows international guidelines for performing and reporting systematic reviews and Meta Analysis (Moher et al., 2009; Hoaglin et al., 2011; Jansen et al., 2011). We aimed at answering the following question: Since a long time, the concept of Grinspan Syndrome has been in literatures but its incidence and prevalence has always lacked enough evidence. In such a scenario, is there a definite relationship or association between the three entities that it comprises of or if it is just on the basis of chance factors.

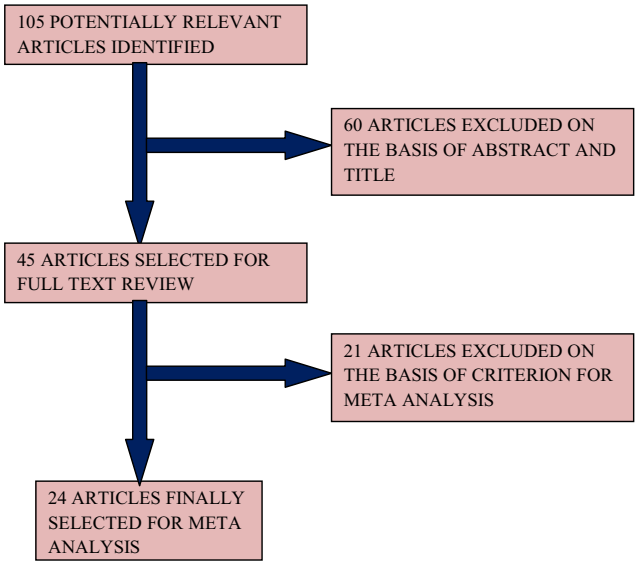
3.1. *Selection (inclusion and exclusion) criteria*

With the Cochrane collaboration taken as source for authenticated scientific research data, 45 case control articles were selected having undergone a randomized control trial. Out of these, the articles were screened and finally 24 articles (Table 1) were selected which met the criterion for Meta Analysis. Articles which were not published in English and where the full text could not be obtained were excluded. Case reports, reviews, non-RCTs and non-case control articles were also not included in the study. All the articles were checked for validity, eligibility and design of the study. There were 3 groups which were included in our study, viz.:

Table 1 – List of articles selected for the study based on Meta Analysis criterion.

Sn.	Researches conducted by	Case	Controls
1	Musa Sahin et al.	95	101
2	Gabriel Antonio et al.	1275	1275
3	Talamini R et al.	79	79
4	Franceschi S et al.	800	800
5	Ainamo J et al.	1000	1000
6	Salma Abdel Zaher et al.	980	900
7	Belmiro Cavalcanti et al.	465	335
8	Del Maso et al.	1000	1000
9	Seppala B et al.	150	75
10	Kaaks R et al.	145	88
11	Yang CS et al.	76	50
12	Mc Intyre G et al.	94	50
13	D'Ambrossio JA et al.	185	56
14	Chavez EM et al.	155	105
15	Anjana Bagewadi et al.	95	88
16	Pihlstorm et al.	485	340
17	Wilson TC et al.	150	90
18	Ara SA et al.	88	88
19	Bokharaei MM et al.	95	50
20	Al-Maweri SA et al.	150	90
21	Truelove EL et al.	1000	550
22	Hamilton BC et al.	1500	500
23	Macfarlane TW et al.	500	500
24	Morgan R et al.	264	150

Group 1: Diabetes Mellitus vs Oral Lichen Planus.
Group 2: Hypertension vs Oral Lichen Planus.
Group 3: Diabetes Mellitus vs Oral Lichen Planus vs Hypertension.



4. Results

Meta Analysis is a technique of combining the results of many studies in a rigorous and systemic manner to allow us to better

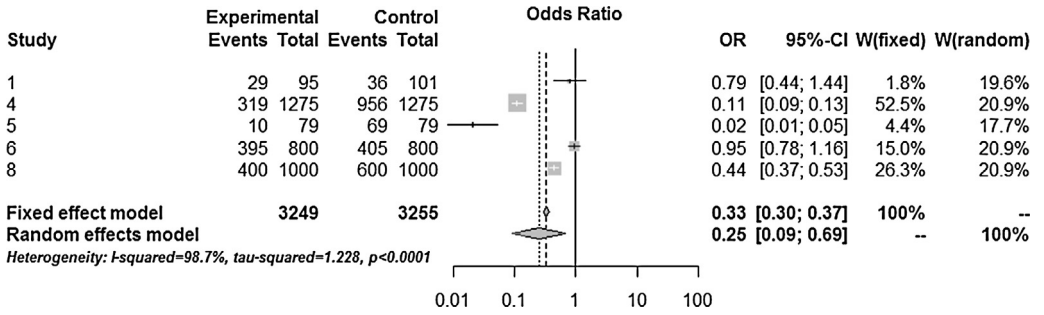


Fig. 1 – Meta Analysis graph of Group 1 showing no association between LP and DM.

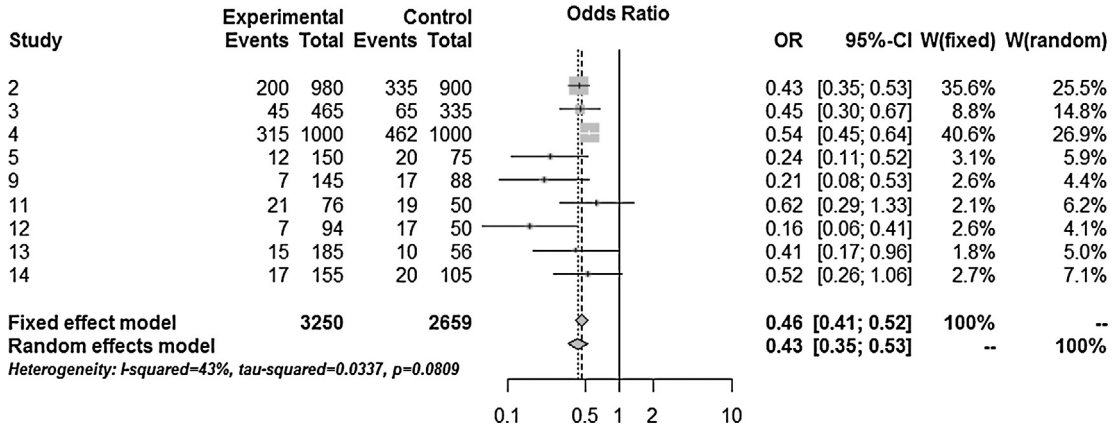


Fig. 2 – Meta Analysis graph of Group 2 showing no association between LP and HTN.

assess the prevalence rates of different types of interventions and determine which intervention has the best evidence regarding its effectiveness. A Meta Analysis of all the modalities including the above-mentioned parameters was carried out and the association of the 3 entities of Grinspan Syndrome was carried out in 3 different groups in order to demonstrate the title of the study. Odds ratios and 95% confidence intervals (CI) were calculated. From a total of 24 case control studies which were finally included in the study, the association (Fig. 1) in Group 1 was found to be almost negative (0.1) exemplifying that there is no association between Diabetes Mellitus and Lichen Planus. The second group (Fig. 2) too showed similar features indicating a negative or rather no association (0.5) between the 2 entities, i.e. Hypertension and Lichen Planus. Finally when all the 3 entities, i.e. DM, LP and HTN (Fig. 3) were taken into consideration together, there was no difference between the result from the other 2 groups which meant that none of the 3

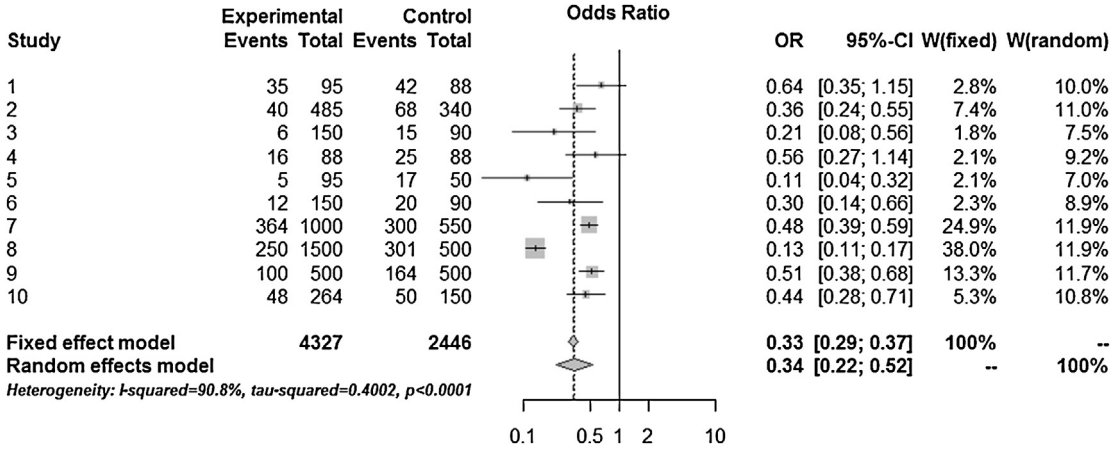


Fig. 3 – Meta Analysis graph of Group 3 showing no association among LP, HTN and DM.

entities of Grinspan Syndrome are associated with each other with an association of 0.5. However their associations in few of the published research literatures have been merely by chance.

5. Discussion

The Meta Analysis based on the results from numerous research literatures from the Cochrane collaboration, showed almost no association between DM, OLP and HTN.[13,18–20] For the first time, the prevalence of DM among patients with oral LP was announced 40% by Grinspan et al. amongst the other studies done so far, some of them revealed that the prevalence of DM among patients with LP is more than normal population.[21–23] The prevalence of DM among patients with LP was 42% in 1976, 28% in1984 and 3% in 1993.[24,25] In last decade, in 2000, Guggenheimer et al. reported the incidence rate of 0.5% of oral LP among patients with insulin dependent DM.[26–31]

In our study, out of 15 researches which were obtained from the Cochrane review conducted in order to establish the association between DM and LP, 5 could meet the criterion for Meta Analysis research. In these 5 researches although few authors like Musa Sahin et al. and Gabriel Antonio et al. have documented in affirmation regarding the association but majority of them contradictorily hypothesized that there can be instances where DM could be associated with LP but it is just a chance factor which cannot be relied upon as according to their research results approximately 90% of the subjects did not show any association between the two entities.[32,33] In our study too, based on the odds ratios, no association was established between DM and LP.

Similarly, out of 15 research articles based on association between LP and HTN, 9 of them could meet the Meta Analysis criterion for systematic review. There was a similar thought process in the literatures in this section as well where in the basis of the association was laid down on chance factors rather than any concrete evidence based link between the underlying pathologies of the 2 entities. The studies conducted by Salma Abdel Zaher et al. and Belmiro Cavalcanti et al. do agree over the debate on association between the two entities on a positive note, the remaining authors post the association as a mere chance factor having no concrete basis of association.[34–36] A similar conclusion was drawn from our study as well where no association could be established between LP and HTN.

In the third group where all the 3 entities (DM, LP, HTN) were compared together for their association, 10 research articles from the Cochrane collaboration were included in the study and all of them met the criterion for Meta Analysis. From these mentioned literatures extracts, it is quite agreeable that DM and HTN do not play a direct role in the aetiology of LP as none of the study results agree in favour of the association between the three entities. Anjana Bagewadi et al., Pihlstrom BL et al. and the other authors in this section of selected articles very clearly documented about the negative association between the three entities of Grinspan. However, few studies post a slight ambiguity towards the outcome of their results based on the confounding factors.[37,38] A similar result was highlighted in our study as well where the Meta Analysis results highlighted no association between LP, DM and HTN. The occurrence of LP in the oral cavity could be due to the drugs given to the patients suffering from these systemic ailments. Such oral lesions may also be dependent on the type of drug and its duration.

Shortcoming is, the fact that the clinicopathological diagnosis of Oral Lichen Planus in all the studies wasn't based on a similar standard criteria, given that patients may develop hypersensitivity to drugs used for treating these systemic diseases, i.e. Diabetes Mellitus and Hypertension causing Lichenoid reactions. There is no enough evidence of detailed recording of drug history in the study samples.

5.1. *Future recommendations*

There is a further need to investigate the confounding factors that may affect the patient's immunity like duration and status of systemic disease. A multi centric study with a standard protocol is required to evaluate the association between Lichen Planus, Diabetes Mellitus and Hypertension.

6. Conclusion

OLP, DM and HTN are 3 systemic disorders with varying aetiologies and different underlying pathophysiologies. Since the inception of the term called ''Grinspan Syndrome'', a lot of discussions and doubts have been the limelight of various studies carried out in this regard till date. Thus it can be concluded that OLP may not be directly associated with DM and HTN but could be attributing to LP like lesions in the oral cavity as a result of various medications these patients are on. However, with the Meta Analysis result proving negative with respect to the association in all the 3 groups mentioned in the study, it clearly elucidates the ambiguity which has till date remained a dilemma in our minds regarding the same.

Conflicts of interest

The authors have none to declare.

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