Beyond the limitations of conventional periodontal care: multidisciplinary approach and novel methods

Ph.D. Thesis Booklet

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Budapest

2025

1. INTRODUCTION

1.1. What is the topic?

The primary focus of our studies is to explore innovative methods to improve the diagnotics of periodontal diseases and to identify a potential risk population in periodontics.

1.2. What is the problem to solve?

Periodontitis is not solely an oral condition. The pathogenesis is characterized by altered immune-inflammatory responses, dysbiosis and it can also contribute to systemic inflammation. Also, it is associated with several systemic diseases. Even though, the prevalence of inflammatory bowel diseases (IBDs) are growing, and their pathogenesis is characterized by similar alterations to the immune-inflammatory response, and microbiome, the association between IBDs and periodontitis has not yet gained enough interest.

Even though periodontitis affects 50 to 90% of adult population and causes irreversible tissue loss, the development of periodontitis can be prevented, and with adequate treatment, it’s progression and future

destruction can be decelerated and halted. Therefore, the primary focus of studies should be on establishing reliable and straightforward screening methods.

1.3. What is the importance of the topic?

In periodontitis the immune-inflammatory process results in the loss of periodontal tissues, which can lead to tooth loss or even edentulism, which contributes to additional health issues and have also significant psychological consequences. The keystone of periodontitis therapy is prevention; if prevention is already not possible, regular screening and follow-up are essential. It is of the utmost priority to develop easy and accessible methods that can be utilized by both periodontists and general dentists. The feasibility of various salivary biomarkers for detecting periodontal pathology is being extensively investigated, with matrix metalloproteinase-8 (MMP-8) emerging as the most promising candidate.

Furthermore, periodontitis may adversely impact the progression and clinical outcomes of pre-existing systemic diseases or conditions.

The prevalence of IBDs are increasing and despite advances in understanding, the current level of knowledge indicates that IBDs remain incurable. It is of main priority that patients with a life-long diseases are informed about the associated risk factors. Therefore, through increased awareness and interdisciplinary collaboration between gastroenterologists and dentists, the quality of life for IBD patients can be significantly improved.

1.4. What would be the impact of our research results?

Periodontitis treatment is administered by dentists, whereas IBD treatment falls under the care of gastroenterologists. However, the bidirectional association between these conditions necessitates a multidisciplinary approach in managing IBD. Furthermore, future studies aiming to explore the reasons for this association may contribute to a deeper understanding of the still incompletely understood pathogenesis of these diseases individually.

Conventional methods for diagnosing and monitoring periodontal disease are time-consuming

and may be inconvenient for the patient. Moreover, despite the availability of clinical and radiological diagnostic tools, diagnosing early-stage periodontal disease and monitoring its progression remains challenging. Salivary MMP-8 represents a straightforward and rapid diagnostic approach that has the potential to complement or replace conventional diagnostic methods, pending systematic evaluations confirming its reliability.

2. OBJECTIVES

2.1. Study I

The objective of our study was to explore the bidirectional relationship between two multifactorial diseases, periodontitis and IBDs through a systematic review and meta-analysis. Our goal was to enhance the accuracy of the meta-analysis, surpassing the significance of previous findings. Accordingly, we investigated whether patients with IBD are at increased risk of developing periodontitis, and conversely, whether individuals with periodontitis are at increased risk of developing IBD.

2.2. Study II

The objective of our systematic review and meta-analysis was to evaluate whether MMP-8 can differentiate between periodontitis, gingivitis, and periodontal health. To address this question, we conducted an analysis to determine whether significant differences exist in salivary MMP-8 levels among individuals with periodontitis, gingivitis, and those with healthy periodontium.

3. METHODS

3.1. Protocol an registration

The systematic reviews and meta-analyses were reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guideline. The recommendation of the Cochrane Handbook's for Systematic Reviews of Interventions Version 6.3. were followed. The protocols were registered on PROSPERO (International Prospective Register of Systematic Reviews) in advance (Study I.: CRD42021286161; Study II CRD42022362761).

3.2. Literature search

Our systematic searches were conducted in three electronic databases: MEDLINE (via PubMed), EMBASE, and the Central Cochrane Register of Controlled Trials (CENTRAL). The exact dates of the searches, the detailed search key and methods are specified in the original publications.

3.3. Eligibility criteria

3.3.1. Study I

All studies investigating the association between IBD and periodontitis, were considered eligible. In order to investigate the association between the aforementioned diseases, two questions were defined, and two different PECO frameworks were formed, therefore including studies using different exposed and control groups. The prevalence of periodontitis was retrieved from studies which compared the prevalence of periodontitis in patients with IBD diagnosis compared to non-IBD patients. Furthermore, the reversed association was also investigated.

3.3.2. Study II

In eligible studies, the salivary MMP-8 levels of

patients with gingivitis, periodontitis and patients with healthy periodontium were compared.

3.4. Study selection and data collection

Endnote X9 was used for the selection process (Clarivate Analytics, Philadelphia, PA, USA). Duplicates were removed both automatically and manually. Then, the articles were selected manually by two independent investigators in a stepwise manner based on their title, abstract, and full-text contents. Cohen's kappa coefficient was calculated to measure interrater reliability during the selection process.

3.5. Data collection

Data was extracted independently in a pre-defined Excel data sheet by two review authors. Disagreements were solved by consensus. In the case of missing data, we contacted the corresponding author. In the case of overlapping populations, the studies with more participants were included.

3.6. Quality assessment

The Newcastle-Ottawa Scale was used to assess the quality of the studies included in the meta-analyses.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was used to evaluate the level of certainty of evidence for the outcomes examined in the meta-analyses.

3.7. Data synthesis and analysis

3.7.1. Study I

All statistical analyses were made with R [v4.1.1] using the meta [5.0.0] package. For categorical outcomes, the odds ratio (OR) with a 95% confidence interval (CI) was used for the effect size measure. To calculate the OR, the total number of patients and those with the event of interest was extracted from each study. If available, the OR values were used if the patient quantity with the event of interest could not be extricated.

To estimate the heterogeneity, the variance measure $\tau 2$ was used. Forest plots were used to graphically summarize the results. For analysis with at least 10 studies, funnel plots and Egger's test with a 10% significance level were used to check for potential publication bias.

3.7.2. Study II

All statistical analyses were performed with open-source R software, supplemented with the packages meta, dmetar and metafor. Forest plots were used as well to summarize the results graphically.

Mean differences (MD) were calculated with 95% CIs to compare MMP-8 levels among patient groups using a random effect model with inverse variance weighting. The sample size, mean, and standard deviation (SD) were used for the pooled effect calculation. Subgroup analyses were performed using mixed-effects models to compare the different salivary MMP-8 measurement methods.

4. RESULTS

4.1. Study I - Investigating the association between IBD and periodontitis

Data from six articles encompassing a total of 1,605 patients—898 diagnosed with IBD (either CD or UC) and 707 healthy controls—were analyzed to evaluate the association between IBD and periodontitis (PD). On average, the odds ratio (OR) (pooled effect size) of having PD was 2.65 (95% CI:

2.09-3.36), indicating a statistically significant difference between the investigated groups. The odds of having PD are higher in the population with IBD compared to the healthy population, which indicates that patients with IBD have a higher chance of developing periodontitis compared to individuals without IBD.

Through subgroup analysis, both IBD types – CD and UC patients – were evaluated separately.

From the six studies, covering 1,605 patients, 514 were classified CD. On average, the OR for the presence of PD was 2.22 (95% CI: 1.49-3.31).

From the investigated exposed population, 384 participants had UC diagnosis. On average, the OR of having PD was 3.52 (CI: 2.56-4.83). It can be concluded that the odds of having PD in both CD and UC population are higher than those in the healthy population. Notably, the OR is highest in the UC population compared to the controls.

Two studies met our defined PECO 2 framework. These studies utilized the databases of insurance companies and identified 6,646 CD and 6,108 UC patients. The control population comprises

10,085,738 healthy controls. Despite the enormous database, the results are derived only from two studies, therefore yet only tendencies could be examined from the statistical evaluation.

Nevertheless, both studies concluded that periodontitis was significantly associated with the risk of subsequent UC, but not with subsequent CD**)**.

4.2. Study II – Investigating the role of MMP-8 in periodontal diseases

20 studies, encompassing 1,725 participants, were selected for the statistical analysis. The level of MMP-8 was specified in ng/ml. The different laboratory methods (IFMA, ELISA, LUMINEX) were handled separately as subgroups.

Salivary MMP-8 levels were significantly higher in patients with periodontitis. (MD=273.26, CI: 194.42;352.10). Among the different measurement methods, MMP-8 level measures with ELISA showed the greatest difference, (MD=318.92, CI: 205.48;432.37) which utilizes tMMP-8 levels. This was followed by IFMA, which measures aMMP-8 levels (MD=239.02, CI: 62.20;415.83), then by LUMINEX (MD=183.38, CI: 178.92;187.84).

Our comparison of gingivitis versus healthy populations is derived from data encompassing 704 patients originating from 10 studies. Patients diagnosed with gingivitis presented elevated salivary MMP-8 levels compared to those in healthy individuals (MD=122.82, CI: 64.19;181.45). The highest mean difference was measured with ELISA (tMMP-8) (MD=191.85, CI: 174.56; 209.15), followed by IFMA (aMMP-8) (MD=91.96, CI: -63.99;247.91) and Luminex (MD=68.30, CI: 58.92;77.68).

In addition, the salivary MMP-8 levels of the two exposed groups, gingivitis and periodontitis was compared. MMP-8 level is significantly higher in the saliva of patients with periodontitis compared to gingivitis. (MD=112.04, CI: 56.15;167.92). The highest difference was observed by ELISA (tMMP-8) (MD=196.39, CI: -24.33;417.10). By IFMA (aMMP-8) the results were (MD=86.18, CI: 0.10;172.27) and by Luminex one study found (MD=115.10 CI:105.08;125.12)

5. CONCLUSIONS

Our first systematic review and meta-analysis confirmed that patients with IBD have an increased risk of developing periodontitis. Although the findings suggest a tendency for periodontitis to be associated with an increased risk of UC, but not CD, more studies are needed to establish a definitive bidirectional association. Nevertheless, patients with IBD should be regarded as a risk population in dental care. Therefore, a multidisciplinary approach should be adopted in their treatment, involving both gastroenterologists and dentists, with a particular focus on the prevention of periodontitis.

According to our second statistical evaluation, patients with periodontitis or gingivitis exhibited significantly higher salivary MMP-8 levels compared to those with a healthy periodontium. Additionally, there was a significant difference between the two affected groups, with the periodontitis group showing higher MMP-8 levels than the gingivitis group. Consequently, measuring salivary MMP-8 levels may serve as a reliable method for distinguishing between periodontal

health and periodontal disease, as well as for differentiating between gingivitis and periodontitis. However, the statistical analysis could evaluate solely laboratory-based techniques, even though more easily applicable chair-side methods are also available and gaining attention. Measuring MMP-8 levels holds significant potential for revolutionizing the diagnosis of periodontitis. Nonetheless, further studies are necessary to verify its reliability, particularly concerning chair-side methods.

5.1. Publications related to thesis

Domokos Z, Uhrin E, Szabó B, Czumbel ML, Dembrovszky F, Kerémi B, Varga G, Hegyi P, Hermann P and Németh O (2022) Patients with inflammatory bowel disease have a higher chance of developing periodontitis: A systematic review and meta-analysis. **Front. Med.** 9:1020126.

doi: 10.3389/fmed.2022.1020126

Q1, IF: 3.9

Domokos Z, Simon F, Uhrin E, Szabó B, Váncsa S, Varga G, Hegyi P, Kerémi B, Németh O. Evaluating salivary MMP-8 as a biomarker for periodontal diseases: A systematic review and meta-analysis. Heliyon. 2024 Nov 14;10(22):e40402.

doi: 10.1016/j.heliyon.2024.e40402

Q1, IF: 3.4