INTRODUCTION

“Peri-implant diseases” describe plaque-associated pathological conditions that develop inflammatory lesions in tissues around implants. A continuum exists between health and peri-implant diseases, categorized into peri-implant mucositis (MI) and peri-implantitis (PI). Concentrations of biomarkers in Peri-implant crevicular fluid (PICF), could determine disease and its severity. Clinical parameters alone do not assess the risk rate, onset, activity and progression of peri-implant destructive changes. IL-1β, TNF-α, IL-6 and MMP-8 are the most investigated biomarkers used in conjunction with clinical indices to prevent and comprehend pathogenesis of peri-implant diseases. Their concentrations vary in normal biologic, pathogenic conditions as well as after therapeutic interventions. Cytokines play an important role in modulating cellular and vascular inflammatory responses, which lead to release of collagenase MMP-8, that in turn is responsible for connective tissue destruction and is pertinent to early detection of PI.

MATERIALS & METHODS

A PICO question was defined. Manual as well as electronic screenings on MEDLINE/PubMed and EMBASE were performed from March 1995 to March 2018. The difference in IL-1β, IL-6, TNF-α and MMP-8 levels between implants in H, MI and PI and developing a recognizable pattern of the biomarkers releases were defined as primary outcomes; identifying factors that would minimize discrepancies in future investigations was a secondary outcome.

Inclusion Criteria:
1) original cross-sectional and longitudinal prospective clinical studies with the collection of pro-inflammatory cytokines in PICF from individuals with PI or MI; 2) Studies analyzed protein expression by enzyme-linked immunosorbent assay (ELISA) or flow cytometry using a cyometric bead array system

Exclusion Criteria:
1)Animal, in vitro studies, case reports, and reviews; 2) Studies with the collection of pro-inflammatory cytokines in tissue biopsies or saliva; 3) only analysis of osteogenic markers; 4) unreported exact numbers of cytokines levels; 5) fluid collection during early osteo-synthesis; 6) unclear peri-implant disease criteria, and 7) unreported anti-inflammatory and antibiotic medication in studies’ inclusion criteria.8)Therapeutic intervention.

Statistical Analysis:
Standardized mean difference (SMD) between two groups was analyzed with a random effects model to compare IL-1β, IL-6, TNF-α and MMP-8 levels between MI and PI. H, MI and PI. Heterogeneity was estimated by Q statistic significant at P<0.1 and quantified with the I² test.

RESULTS

1. In MI sites, the release of IL-6 and TNF-α was increased (SMD=1.17; 95% CI: 0.16; 3.19; p=0.031 and SMD= 3.91; 95% CI: 1.13; 6.70; p=0.006 respectively) MI group showed significantly higher IL-6 than H group (SMD = 1.94; 95% CI: 0.87; 3.35; p<0.001).

2. PI group showed higher release levels of both IL-6 (SMD=1.72; 95% CI: 0.50; 2.97; p=0.04) and TNF-α (SMD: 3.78; 95% CI: 1.67; 5.89; p=0.001). IL-8 release was much higher in PI compared to H sites (SMD: 2.21; 95% CI: 1.32; 3.11; p<0.001).

3. IL-1β in PI sites was similar to that in MI sites (SMD= 1.52; 95% CI: -0.03;3.07; p=0.055), with significant heterogeneity among these studies (I²=91.5%, I²=0.001). The heterogeneity difference was detected (I²=0.0%, p=0.734) upon removal of the study by Liu et al. (2017), and the result became significant (SMD= 0.60; 95% CI: 0.12; 1.08; p=0.015). PI group showed significantly higher release levels of IL-6 than that in MI group (SMD = 1.46; 95% CI: 0.36; 2.55; p=0.009).

4. Meta-analyses revealed high heterogeneity between these studies, with I² ranging from 30.3% to 98.1%.

5. Publication bias was assessed by Egger’s test; values for the 3 comparisons were respectively: IL-1β (p=0.159, 0.013/0.08), IL-6 (p=0.234; 0.641;0.08) and TNF-α (p=0.087;0.082).

MMP-8

Only 5 articles were included in this review investigating MMP-8 in healthy conditions vs peri-implant diseases. MMP-8 increased significantly between H and MI in one. Three other articles compared H to PI. MMP-8 was found in elevated amounts in PICF collected from a total of 65 implants; those were diagnosed with peri-implant diseases. Fifteen implants had MI and 70 had PI. Arakawa et al. only found MMP-8 in PICF (Arakawa et al. 2012). The sensitivity and specificity of peri-implant disease criteria were marked both high and significant (Janska et al. 2016). Further, a combination of microbiological profiling and MMP-8 found to have increased the accuracy of results previously obtained (Wang et al. 2016).

CONCLUSION

Within the limitations of this study, pro-inflammatory cytokines and metalloproteinases in PICF, such as IL-1β, IL-6, TNF-α and MMP-8, can be used as adjunct tools to clinical parameters (GI and IBo% p<0.05) to differentiate H from MI and PI.

Future research should focus more on longitudinal monitoring of biomarkers in order to derive a suitable range in health and disease conditions.

Use of IL-1 β, IL-6, TNF-α, MMP-8 biomarkers to distinguish peri-implant diseases: A systematic review and Meta-analysis


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