BIOMARKERS COMMON FOR INFLAMMATORY PERIODONTAL DISEASE AND DEPRESSION: A SYSTEMATIC REVIEW

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BACKGROUND

Although activated immune system can induce depressive symptoms, the source of immune activation relevant to depression remains unclear. Multiple lines of studies indicate that inflammatory oral pathology can be a potent inducer of chronic neuroimmune response which can contribute to the genesis of depressive symptoms.
The objective of this study was to summarize the evidence on the association between inflammatory periodontal diseases and depression mediated by or related to a broad range of biomarkers that are detectable in blood, cerebrospinal fluid, other circulatory fluid or local tissue exudate/secretion.

METHODOLOGY

Medline, Embase, PsycInfo, Cochrane Library, Web of Science and Scopus databases were searched from inception until November 25, 2020. Search terms included subject headings and synonyms for inflammatory periodontal disease and depression. Twenty-five studies that reported data on both depression and inflammatory periodontal disease as categories along with measurement of a biomarker were included. Data were extracted by two independent rates. Two reviewers independently selected the articles for inclusion and extracted information from each study. A third reviewer decided in case of discrepancy. We used the NIH 14-criteria quality assessment tool for evaluating each study quality. The protocol for this study is registered with PROSPERO, number CRD42021215524.

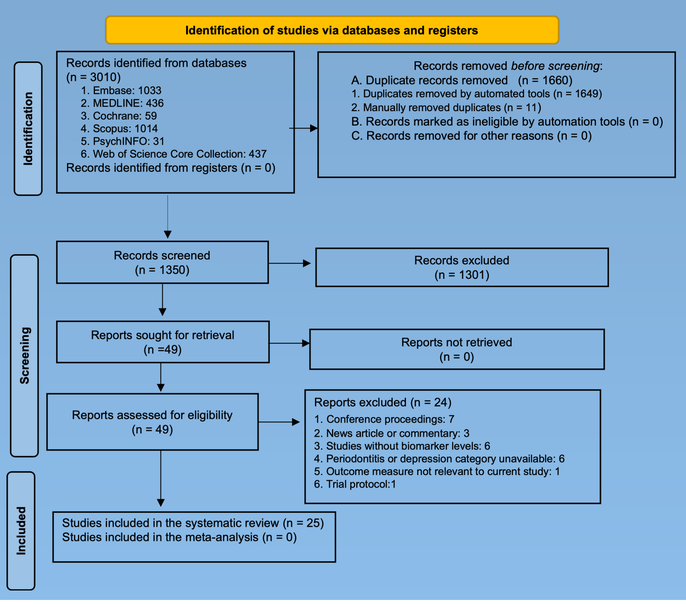

Figure 1: A PRISMA diagram illustrating the search strategy for the review

RESULTS

Twenty-five studies were included in the final review- eleven cross-sectional studies, ten case-control studies, four prospective cohort studies including three animal studies. Seven studies reported a positive association between depression and periodontal disease; one study reported a negative association and another seven studies found no such associations. The remaining studies did not report on the associations specifically, or assessments for the diseases were unstandardized. An association between a biomarker and IPD was reported by 17 studies of which 14 found an association; for MD the study numbers were 10 and 6, respectively. The biomarkers included blood, salivary, urinary and gingival crevicular fluid levels of CRP, Cortisol and other hormones, inflammatory cytokines (interleukin (IL)-1B, 6, 10, tumor growth factor, interferon-gamma) and brain derived neurotrophic factor. In most studies there were risks of bias due to the sample selection and assessment protocol. Limited number of studies for shared biomarkers using the same biological sample, and a wide heterogeneity of included samples precluded any possibilities of calculating pooled effects.

Table 1. Individual study details along with associations between depression and inflammatory periodontal disease. Also presented are the biomarkers reported in each study by depression and inflammatory periodontal disease, and the role of biomarker in the relationship between the two conditions.

Study	Population (country, type, mean age +- SD/range, female %)	Sample size, n	Association between IPD and MD	Biomarker	Sample source and assay method	Results: Biomarker by depression	Results: Biomarker by IPD	Role of biomarker in the relationship between IPD and MD
Bawankar (2018)	India, dental outpatients, 30-65 yrs, 70% women	N = 75 (control:25; patients with IPD: 50)	Mean depression score significantly higher in IPD than HC.	Cortisol, IL-1B	Serum, saliva/ELISA	ND	Salivary cortisol significantly higher in IPD group compared to non-smoking healthy patient controls (417.2±99.7 vs 19.5± 4.0 pg/ml). Higher serum (19.4±6.2 vs. 11.4±3.1 and salivary 251.4±81.2 pg/mlIL-B levels in IPD patients compared to healthy patient group.Serum cortisol levels not significantly different between IPD and no IPD. Smoking IPD group showed changes in the same direction.	
Beydoun (2020)	USA, Population-based, 52.7 (30-) yrs, 50% women	11813	Not reported	Complete blood count	whole blood/Beckman Coulter method for counting cells, 5-part differential		IPD was directly related to WBC count and %neutrophils and inversely related to %lymphocytes, especially among men. B (95% CI) in fully adjusted models for IPD predicting WBC count 0.2 (0.1,0.3), neutrophils % 0.7 (0.2,1.0), lymphocytes % -0.6 (-1.0, -0.2).	
Breivik (2015)	Norway, rats, 13 weeks, 56% female	43 (controls n=12; subjects: 31)	Significantly more severe periodontitis in depressed rats.	Cortisol, TGF-1B, GR (glucocorticoid receptor) expression	Serum, hippocampal tissue/RIA (Radioimmunoassay) for cortisol; ELISA for TGF-B; qRT-PCR for GR mRNA			Depression models of rat on top of ligature induced IPD had higher hippocampal GR Expression, and lower serum TGF-1B levels after LPS stimulation. TGF-B levels (pg/ml) in depression group (male 56.3±3.3; female 51.0±5.2) vs. healthy control group (male: 63.2±7.0, female 57.9±7.1); However, cortisol, IL-10 and TNF-a levels did not differ by depression status.
Breivik (2006)	Norway, rats, 13 weeks, 0% female	40	Periodontal bone loss was elevated (1.06 ± 0.25mm) in depressed rats vs (0.90 ± 0.13mm) sham-operated control rats (p<0.01), and were reversed with tianeptine.	Cortisol, TNF-a, TGF-1B, IL-10, GR expression	Serum , hippocampal tissue/RIA (Radioimmunoassay) for cortisol; ELISA for TGF-B; qRT-PCR for GR mRNA			Decreased GR expression in hippocampus of depression model rats. IPD+MD rats had significantly higher (1140.4 ± 387.5 ng/ml) serum cortisol levels compared with IPD only rats (756.0 ±422.7 ng/ml; p<0.05). IPD+MD rats also had higher TGF-1B (15.9 ±4.4 vs. 12.3 ±3.2) and decreased TNFa (561.6 ±643.6 vs. 2449.9 ±2506.3) levels. Upon LPS stimulation, compared with controls (627 ±569.4 ng/ml), significantly higher serum cortisol levels were found in the depression model rats (1017.3 ±606.4 nm/L p<0.05), demonstrating that the bulbectomy induced a stronger HPA axis responsiveness to the inflammatory LPS. Depression induced hyperresponsiveness of HPA axis (indicated by cortisol level) was not amenable to antidepressant treatment although TGF-1B and TNF-a changes were reversed.
Cakmak (2014)	Turkey, dental outpatients, 38.3 (24-63) yrs, 51% women	120 (n=40 with no periodontitis; n=41 with localized periodontitis; n=39 with generalized periodontitis)	No difference in depression scores between IPD groups	Cortisol, DHEA	GCF/ELISA		Higher DHEA (pg/ml) levels in local (64.07±30.87) as well as generalized chronic periodontitis (78.17±38.66) compared to patient controls without IPD (59.2 ±22.57). Cortisol levels did not differ across IPD groups.	
Cakmak (2019)	Turkey, dental outpatients, 40.4 (26-63) yrs, 40% women	55 (n=15 healthy controls; n=40 subjects with periodontitis)	No difference in depression scores after IPD treatment.	Cortisol, DHEA	GCF/ELISA		Higher cortisol (pg/ml) levels in localized (338.2± 309) and generalized (388.0± 368) chronic periodontitis compared to patient controls (81.4±27) p<0.001. No difference across groups at 6-month follow up, but levels decreased. DHEA levels were not different between the groups at baseline and at follow up.	
Cakmak (2016)	Turkey, dental outpatients, 24-60 yrs, 49% women	92 (n=31 controls; 61 with periodontitis)	Depression scores significantly elevated in the aggressive periodontitis group, but not in the chronic periodontitis group.	Cortisol, DHEA, Salivery flow rate	GCF, Saliva/ELISA		GCF cortisol, saliva cortisol, GCF DHEA and saliva DHEA are elevatad, both in generalized and localized chronic periodontitis groups compared to periodontally healthy patients.	
Cohen-Cole (1983)	USA, dental outpatients ≈24.3 (14-33) yrs, 60% women	70 (n=35 healthy controls; n=35 patients with ANUG)	Elevated depression score in acute necrotizing ulcerative gingivitis patients. OR (MD in IPD)= 4.24	Cortisol	Serum, urine/not reported		Elevated urine and serum cortisol and depression score in IPD patients compared to healthy controls. No significant differences between IPD patients and controls on measures of growth hormone, prolactin, or spot urine catecholamines. Lymphocyte function as well as polymorphonuclear leukocyte phagocytosis and chemotaxis were significantly depressed in IPD group compared to controls.	Elevated urine and serum cortisol and depression score in IPD patients, but no analysis of the three factors together.
da Silva (2015)	Brazil, school students, 11.4 (11-12) yrs, 67% women	64 (n=21 healthy controls; n=43 patients with gingivitis)	No correlation between MD and IPD. Mean depression score in gingivitis 12.3 (SD 9.1) vs no gingivitis 10.0 (SD 8.6) OR for gingivitis (with depression score as predictor): 1.01 (0.96-1.08; P=0.585) Coef. 0.01).	Cortisol	Saliva/Enzyme immunoassay		No significant differences in the diurnal decline of salivary cortisol between patients with IPD and contorls (0.17±0.09 vs. 0.24±0.21 ug/dl).	There was a strong correlation between MD and biomarker (diurnal decline in salivary cortisol) r in IPD group (r= -0.64; p<0.01), but NOT in control group (r=0.07, NS).
Fenol (2017)	India, prison inmates, 38.6±10.9 (25-60) yrs, only men	70	Significant associations between high stress levels (with stress measure incorporating depression symptom load along with anxiety and general stress) and clinical attachment level/probing pocket depth. However, data on depression is not explicitly presented.	Cortisol	Saliva/RP Elecsys kit		Higher salivary cortisol (26.08±4.14 (severe IPD), 18.72±2.47 (moderate IPD) vs. control group 9.01±2.67 units; P=0.001). Salivary cortisol correlated positively and significantly with clinical attachment level and probing pocket depth.	
Gomes (2018)	Brazil, dental outpatients, ≈43.5 (18+) yrs, 60% women	47	Higher depression scores in chronic apical periodontitis group (BDI 13.5±1.9 vs. 2.3±3.1; HDRS 11.5±1.0 vs. 3.6±1.7). BDI and CAP: F=10.08 df 1/43. P=0.003 partial eta sq. 0.190) HDRS and CAP (F=17.03, df 1/43, P<0.001, partial eta sq. 0.284)	LPS (lipopolysaccharide), LOOH (hydroperoxide), Nox (nitric oxide metabolites), TRAP (total radical trapping antioxidant parameter), AOPP (advanced oxidation protein products), PON1 (paraoxonase total activity)	root canal tissue (LPS), plasma/ELISA	There were significant correlations between root canal LPS and depression measured with the HDRS (r = 0.799, p < 0.001, n = 47) as well as the BDI scale (r = 0.759, p < 0.001, n = 47).	Clinical depression was significantly associ ated with increased root canal LPS, plasma AOPP, NOx, LOOH, and TRAP values, while there were no significant effects of –SH groups and PON1 activity. Note: AOPP = advanced oxidation protein products, NOx = nitric oxide metabolites, LOOH = lipid peroxides (LOOH), -SH = -sulfhydryl (SH) groups, TRAP = total radical trapping antioxidant parameter, and PON1 = paraoxonase.	Patients with IPD+MD had greatly increased root canal LPS level as compared to IPD-MD group. In subjects with IPD, there were significant correlations between root canal LPS and HDRS (r = 0.734, p < 0.001, n = 34) and the BDI (r = 0.704, p < 0.001, n = 34). Association between depression and IPD was attributable , at least in part, to increased root canal LPS levels in IPD patients.
Johannsen (2007)	Sweden, ≈52.1±4.5 yrs, Women (100%) on long term sick leave drawn from an insurance provider´s list	49 (n=29 controls, n=20 patients)	MD patients had significanlty worse periodontal conditions, dental plaque, gingival inflammation, bleeding on probing, probing depth (PI, GI, BOP, PD), but not increased clinical attachment level.	Cortisol, IL-1Bb, IL-6, MMP (matrix metalloproteinase)-8, MMP-9	GCF, saliva/ELISA, RIA (Radioimmunoassay	Gingival crevicular fluid IL-6 level was significantly higher in the depression group compared to the controls (3.84 ± 1.58 pg per site and 0.79 ± 1.83 pg per site, respectively, p < 0.003), but no difference was observed for IL-1B, MMP8, MMP9 or salivary cortisol. Patients with depression also had lower mean level of cortisol in the gingival crevicular fluid than in the controls.		
Johannsen (2006)	Sweden, 42±9.3 (patients); 54.5 (2.9) yrs, Women (100%) on long term sick leave drawn from an insurance provider´s list	72 (n=43 patients and 29 controls)	MD patients had significantly higher amount of dental plaque (0.18±0.13 vs. 0.10±0.10 unit) and higher GI (1.53±0.26 vs. 0.89±0.35) than control subjects, even after correction for multiple comparison (p<0.001).	Cortisol, IL-1B, IL-6, MMP (matrix metalloproteinase)-8, MMP-9	GCF, saliva/ELISA, RIA (Radioimmunoassay	MD patients had higher GCF levels of cortisol (3.5 nmol/l ±3.3 SD) and 0.30 nmol/l ±0.3 SD) and IL-6 (2.03 ±1.6 vs 0.79 ±1.8 pg/site) compared to controls (p<0.05). MD patients had lower MMP-9 (19.4±12.1 vs 30.6±18.5 ng/site) but GCF IL-1B and salivary cortisol were not different betwen the two groups.		
Karimi (2017)	Iran, dental outpatients, 42.4±5.4 (cases); 44.5±8.4 yrs(controls), 40% women	30 (n=15 patients with periodontal disease and n=15 healthy controls)	87% with periodontal disease had depression compared with 60% without periodontal disease (test isignificant; too small sample size).	IgA	Saliva		Salivary IgA level was lower in patients with periodontal disease (207.95+57.21) compared to the controls (312.66+107.3 units) (P=0.001).	
Katuri (2016)	India, dental outpatients, 46.83 - 47.13 yrs, 53% women	70 (n=23 with depression, n=24 without depression and n=23 yoga-practicing)	No difference between the groups with regards to periodontal parameters	cortisol	serum	Serum cortisol levels and HAM-A scale and ZSDS scores showed highly significant value(P<0.001) in groupI subjects when compared with groupII and groupIII subjects		
Kurer (1995)	UK, dental outpatients, 20-50 (not specified), women% not reported	47	Depression was associated with plaque level (r=0.28; p<0.05), but not gingivitis.	Cortisol	saliva/radioimmunoassay	No associations between cortisol level and depression score	No associations between cortisol level and plaque or gingivitis.	
Leira (2019)	Spain, dental outpatients, 47 yrs, ≈97.7% women	179 (n=102 with migrane and n=77 healthy controls)	IPD-migrane higher prevalence	CGRP (Calcitonin gene-related peptide), IL-6, IL-10	serum/ELISA		IPD (with migraine) was associated with higher serum CGRP levels (19.7 ± 6.5 versus 15.3 ± 6.2 pg/mL, P < 0.0001) and IL-6 (15.1 ± 9.2 versus 9.6 ± 6.3 pg/mL, P < 0.0001), independent of depression. IL-10 did not show a difference.	IPD (with migraine) was associated with higher serum CGRP levels (19.7 ± 6.5 versus 15.3 ± 6.2 pg/mL, P < 0.0001) and IL-6 (15.1 ± 9.2 versus 9.6 ± 6.3 pg/mL, P < 0.0001), independent of depression. IL-10 did not show a difference.
Moss (1996)	USA, dental outpatients, 44.4 (8.6) case; 43.8 (9.3) yrs controls, women % not reported	148 (n=71 patients; n=77 controls)	Depression was associated with extensive periodontal disease. Higher OR for depression and Bf interaction and depression - Bf, Aa, Pg antibody interaction (1.28 ORH	Antibodies (igG) against Bf, Aa, Pg	blood/Antibody assay		IgG against Porphyromonas gingivalis and Actinobacillus actinomycetemcomitans) were strongly associated with Periodontitis (OR 4.54 (95% CI 2-10) and 5.3 (95%CI 2-12).	IgG against Bacterioides forsythus) was associated with periodontal disease only among individuals with higher depression scores (OR 6.75 (95% CI 1.3-36.5).
Nascimento (2018)	Brazil, population-based, 31 yrs, 49% women	539	Higher risk of periodontitis (RR 1.19) and more severe periodontitis in patients with depressive symptoms, but not as MD categories.	CRP	serum		No significant differences between CRP levels of periodontitis patients and healthy controls, as well as between CRP levels of patients with depression versus non-depressed subjects.	Association between depressive symptoms and periodontitis was not mediated by systemic inflammation.
Petit (2020)	France, dental inpatients, 51.3 yrs, 30-40% women	71	Stress levels associated positively with worsened non-surgical periodontal treatment (SRP) outcomes (based on BOP and PD)	Cortisol, Chromogranin-A	serum, plasma/immunoassay	Cortisol not associated with Depression score on DASS42	Stable cortisol and chromogranin-A levels at baseline and 6 months of non-surgical perodontal treatment despite improvement in multiple measures of periodontal outcomes.	
Refulio (2013)	Peru, dental outpatients, 30-65 yrs, 64% women	70 (n=36 with periodontitis and n=34 without periodontitis)	All patients with chronic periodontitis received depression diagnosis.	Cortisol	saliva/SCL (high sensitivity electrochemiluminescence)		The more severe the Periodontitis, the higher the coritisol levels (OR for periodontitis as outcome by cortisol levels 4.14 (95% CI 1.43-12.01)	
Rodriguez Franco (2020)	Mexico, psychiatric inpatients, 46.4 years, 51% women	61 (n= 35 periodontitis patients; n=10 MD; n=16 with depressive symptoms)	Depression negatively predicted clinical attachment loss in their model	IL1b, IL6, MMP8	saliva/ELISA	Depressive symptoms unrelated to proinflammatory immune response	Clinical attachment loss in IPD was associated with proinflamatory immune response (a composite of IL-1B, IL-6, MMP-8)	The activation of proinflammatory immune parameters in periodontal damage was independent of depression in their predictive (hypothetical) models.
Rosania (2009)	USA, dental outpatients, 45-82 yrs, 69% women	45 recall patients with periodontitis	Positive correlations between missing teeth and depression (r=0.54, P<0.001)	CORT	saliva/RIA (Radioimmunoassay)	Cortisol levels not associated with depression score. However, in regression models involving stress as a predictor, stress and cortisol levels were predictors of attachment loss. Cortisol level negatively predicted depression (B=-032, t=-2.3, P=0.028).	Positive correlation between Cortisol and higher degrees of periodontal disease measures (probing depth, tooth loss, CAL)	Cortisol & depression were significant predictors for missing teeth
Solis (2016)	Brazil, psychiatric outpatients, 18-58 yrs, 82% women	72 (n=36 depression patients; n=36 healthy controls)	Healthy periodontal sites were indifferent between patients without and without depression. (Previous article: periodontal clinical parameters were not different between patients with MDD and control subjects.)	IL6, IL1b, INFg	GCF, whole blood, stimulated WBC/ELISA	Blood IL-6 and IL-1B and GCF IL-1B were modestly lower in MDD patients compared to controls. WBC upon LPS stimulation showed no differences in cytokine levels between MD and no MD group.		Cytokine differences in depression were independent of periodontal disease, no mediation analysis was available for IPD-MD associations
Wang (2019)	China, mice, 6 weeks, 100% female	18	Periodontal disease induced by Porphyromonas gingivalis or LPS caused depression-like behavior in mice.	cortisol, p75NTR, BDNF, TNFa, IL-6, IL1a	serum, hippocampus, astrocytes, blood,	Depression like behavior in animal models of P. gingivalis accompanied increased number of activated astrocyte and reduced levels of mature BDNF. These effects were reversed by TLR-4 inhibitor TAK242.	P. gingivalis inculation and LPS from P. gingivalis caused increased alveolar bone loss (mandible) in mice. The mice hid significantly elevated serum IL-1a and TNF-a and cortisol levels as well as PFC and hippocampal TNF-a, IL-6 and IL-1a expression compared with the control group.	Periodontal mouse model showed downregulated BDNF maturation through astrocytic p75NTR leading to depression like behavior.

CONCLUSION AND FUTURE DIRECTIONS

Immune-inflammatory contribution to depression was also evident in the context of inflammatory periodontal diseases, but whether biomarkers mediated associations between inflammatory periodontal disease and depression need to be tested through methodologically rigorous studies aiming specifically at this hypothesis.

Included studies

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