Supplementary tables:

Table 1: Epidemiological studies of the periodontal disease and systemic disease connection

Table 2: Interventional studies

Table 3: Studies on bacteremia of periodontal pathogens and periodontal pathogens identified in CVD in Periodontitis.

Table 1: Epidemiological studies of the periodontal disease and systemic disease connection

Reference & year	Research focus	Sample size	Biomarkers	Parameters	Conclusion
Noack et al., 2001	To examine whether CRP plasma levels are increased in periodontitis and if there is a relation to severity of the periodontal disease and to periodontal micro flora.	174 subjects Serum levels were assessed.	Serum C- Reactive Protein	CAL, PPD, P.g , P.i, C.r, T.f, in subgingival plaque samples was measured by immunofluorescence microscopy.	There are elevated levels of CRP associated with infection with subgingival organisms associated with periodontal disease including P.g, T.f, P.i, C.r. the positive co relation between CRP and periodontal disease might be possible underlying pathway in association with periodontal disease. And they observed higher risk for CVD in the subjects.[10]
Nishi Singh et al., 2017	To analyze the levels of ALP in GCF and serum of patients with gingivitis, chronic & aggressive periodontitis before and after SRP & to compare the difference within the study groups.	24 subjects GCF and serum samples were obtained. 3 groups: Gingivitis, Aggressive Periodontitis and Chronic Periodontitis.	Serum and GCF Alkaline Phosphatase.	BOP, PI, GI, BI, PPD, CAL.	ALP levels in GCF increased significantly during active phase of disease followed by statistically significant reduction after phase I therapy. Baseline levels of ALP in GCF was CP > AP > G with maximum reduction in GCF ALP after SRP in G > CP > AP group.[11]
Delange et al., 2017	To compare levels of interleukin (IL)-6 and C-reactive protein (CRP) across increasing severity of periodontal disease status among younger adults between the ages of 21 and 43 years.	59 subjects Blood samples. 3 groups: Mild PPD, Moderate PPD, Severe PPD	IL-6 CRP	BOP, BOP, PPD, CAL.	In this otherwise healthy AI/AN adult sample, moderate periodontal disease compared with none or mild periodontal disease was associated with increased levels of IL-6. High levels of CRP found in this population warrant further research.[12]
Abdul karem et al., 2018	To evaluate the serum ceruloplasmin (CP) level after	80 subjects	Serum Ceruloplasmin	BOP, PPD, CAL	Non-surgical periodontal therapy has a reducing effect on the serum

	non-surgical periodontal therapy in chronic periodontitis patients.	Blood Samples 2 groups: Group1: Periodontitis Group2: Periodontally healthy			CP level in chronic periodontitis patients. Serum CP level represents a potential biomarker indicator of the chronic periodontitis disease.[13]
Aranka Ilea et al., 2019	To assess the prevalence of periodontal disease in a group of patients with cardiovascular disease and to establish the correlation between serum levels of inflammatory markers and periodontal status in these patients.	20 subjects Serum Samples Group1: Periodontitis Group2: Periodontally healthy	WBC, CRP, Plasma fibrinogen and ESR.	PI, GBI, OHI	Results indicated that the prevalence of periodontal disease in patients with cardiovascular disease was 55%, and higher in females than males.[14]
Y. Leira et al., 2019	To examine whether the levels of NT-proBNP in serum are increased in periodontal disease and if there is a relationship to severity of periodontitis.	40 subjects Serum Samples 2 groups Group1: Periodontitis Group2: Non-Periodontitis	Serum Brain natriuretic peptide	CAL, GR, PESA, PISA	In periodontitis, increased serum NT-proBNP levels are observed in comparison with individuals without periodontitis. Moreover, the greater the degree of periodontal destruction, the higher the levels of NT-proBNP in serum.[15]
Mazen Ameen et al., 2020	To assess the levels of the cardiac biomarkers in smokers versus non-smokers chronic periodontitis (CP) patients and periodontally healthy subjects, also to correlate cardiac biomarkers level with the severity of CP.	80 subjects Blood samples 3 groups: Group1: Smoker CP Group2: Non-Smoker CP Group3: Non-smoker healthy	ALT, AST, Tr-I, CK, and LDH	BOP, PPD, CAL, PI, GI	Cardiac biomarkers affected by CP and worse aggravated by the presence of smoking that could play a bidirectional effect on periodontitis and cardiovascular (CV) conditions. [16]
Mili Gupta et al., 2020	To correlate the levels of sCD40 L and MCP-1 in serum and gingival crevicular fluid (GCF) of patients with chronic periodontitis.	45 subjects Serum and GCF samples Group1: 15 healthy patients Group 2: 30 Chronic periodontitis patients.	sCD40 L and MCP-1	BOP, PPD, CAL, GI, PI	The positive correlation observed suggests this pathway as one of the mechanisms that may lead to increasing severity of periodontal disease and its systemic effects. [17]

Boyapathi et al., 2020	To compare and correlate the occurrences of periodontitis with serum levels of cardiac-biomarkers in patients with coronary heart-disorders	63 subjects Blood samples Group1: Periodontitis group Group2: Non-Periodontitis group	TP-1, LDL, VLDL, TC, hs-CRP	BOP, PPD, CAL, GI, PI	The study reveals, a strong association between periodontitis and diseases of cardiovascular nature, highlighting the need for awareness and timely medical interventions to prevent periodontitis from scaling up and interfering with the risk of cardiovascular problems.[18]
Ibrahim Fazal et al., 2022	To compare the levels of NT-proBNP in GCF and serum in patients with chronic generalized periodontitis.	19 subjects Serum and GCF samples collected before and 6 weeks after SRP	NTProBNP	BOP, PPD, CAL, GI, PI	NSPT has a reducing effect on the serum and GCF NT-proBNP levels in chronic periodontitis patients. In addition, serum and GCF BNP levels represent a potential biomarker of chronic periodontitis and may indicate NSPT may avoid the risk of CVD events by reducing systemic inflammation caused by local factors.[19]

CHD: Coronary heart disease. TP: Troponin, LDL: low density lipoprotein, CRP: C reactive Protein, BOP: bleeding on probing, PPD: probing pocket depth, CAL: clinical attachment loss, GI: Gingival index, PI: Plaque index, OHI: Oral health Index, GBI: Gingival bleeding Index, BNP: Brain natriuretic peptide, ALP: Alkaline phosphatase, RR: Relative risk. Statistically significant adjusted measure of association. SES: Socioeconomic status. BMI: Body mass index. HR: Hazard ratio. SBP: Systolic blood pressure. OR: Odds ratio.

Table 2: Interventional studies

REFERENCE	STUDY DESIGN	SAMPLE SIZE	BIOMARKER	INTERVENTION	DURATION	RESULT
Caúla et al.,[31]	RCT	66	CRP, ESR, TC, HDL, LDL and TGs	NSPT	2 months 6 months	All ↓ except HDL ↑
Vidal et al.,[32]	Cohort	26	CRP, FGN, IL6, SBP, DBP, LVM, and PWV	NSPT	3 months 6 months	All ↓ after 6 months
Bresolin et al.,[33]	Prospective Clinical	33	CRP, TC, VLDL, HDL, TGs, FGN, IL-6, and TNF-α	NSPT	180 days	All ↓ except TNF-α
López et al.,[34]	RCT	315	TC, HDL, and LDL and glucose, CRP, and FGN	NSPT+ amoxicillin and metronidazole	6 months	Only CRP and Fibrinogen ↓
Bokhari et al.,[35]	RCT	246	CRP, FGN and white blood cells.	NSPT	2 months	All ↓
Banthia et al.,[36]	Clinical Study	40	TLC, DLC and platelet count, BT and CT	NSPT	2 weeks	All ↓
Kiany and Hedayati[37]	RCT	25	IgM aCLA, IgG aCLA	NSPT	6 weeks	All ↓
Gupta et al.,[38]	Cross sectional	150	CRP	SPT	3 months	All ↓
Grazziani et al.,[39]	RCT	38	CRP, IL6 and TNF-α	NSPT	1 day 1 week 3 months	All ↑ after 24 hrs. but ↓ after 1week and 3 months
Houckenet al.,[40]	Case–control and pilot intervention	109	Pulse-wave velocity (PWV), SBP, DBP, TC, HDL, and LDL	NSPT	3 months 6 months	PWV not changed and the others ↓
Torumtay et al.,[41]	Case control	50	CRP, IL6, IL-10, TAC, TOS, FPG, HbA1c, TRG, TC, HDL, LDL, SBP and DBP	NSPT	3 months 6 months	All ↓ except HbA1c, SBP, DBP unchanged after 6 months
Sidheshappa et al.,[42]	Clinical trial	30	TLC, platelet count	NSPT	1 week and 2 weeks	All ↓
Arvanitidis et al.,[43]	Clinical trial	25	Binding of PAC-1, P-selectin and CD63, TLC and platelet count	NSPT	3 months	All ↓

Zhou et al.,[44]	RCT	107	SBP, DBP, EM, CRP, IL-6	intensive periodontal treatment	1 months 3 months 6 months	SBP ↓ but DBP, EM, and CRP ↓ after 3 and 6 months but IL-6 ↓ only after 6 months
De Souza et al.,[45]	RCT	44	CRP	NSPT	60 days	All ↓
Jockel-Schneider et al.,[46]	RCT	55	PWV, PPao, RRsys, Aix, and MAP	NSPT + amoxicillin (500 mg) and metronidazole (400 mg),	12 months	PWV ↓, PPao ↑ RRsys and MAP not changed
Saffi et al.,[47]	RCT	69	FMD, sVCAM-1, sICAM-1, and P selectin	NSPT	3 months	All ↓ except FMD
Morozumi et al.,[48]	RCT	31	CRP, IFN-γ, IL-5, IL-6, IL-12, TNF-α	NSPT	1 day 6 weeks	All ↑ after 1 day After 6 weeks: CRP, IFN-γ and IL-6 ↓ IL-5, IL-12, TNF-α ↑
Moeintaghavi et al., [49]	RCT	30	TC, LDL, HDL, TGs, CRP), and FBS.	SPT and NSPT	3 months	All ↓ except HDL

RCT, randomized clinical trial NSPT, non-surgical periodontal therapy; SPT, surgical periodontal therapy; TC, total cholesterol; HDL, high-density lipoprotein; TGs, triglycerides; LDL, low-density lipoprotein; FGN, fibrinogen; CRP, C-reactive protein; IL, interleukin; TNF, tumor necrosis factor; ESR, erythrocyte sedimentation rate; LVM, left ventricular mass; TAC, total antioxidant capacity; TOS, Total oxidant status; TLC, Total leucocyte count; DLC, differential leucocyte count; BT, bleeding time; CT, clotting time; EM, Endothelial Microparticles; FMD, flow-mediated dilation; PWV, pulse wave velocity; Aix, augmentation index; PPao, central pulse pressure; RRsys, peripheral systolic pressure; MAP, Mean arterial pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; FBS, Fasting Blood sugar. ↓ mean decrease, ↑ mean increase

Table 3: Studies on bacteremia of periodontal pathogens and periodontal pathogens identified in CVD in Periodontitis.

REFERENCE	STUDY DESIGN	METHODOLOGY TECHNIQUE	TREATMENT	PERIODONTAL PATHOGENS
[7]Nakano et al., **	Cross sectional	Specific PCR	No treatment	Aa (35%), Pg (20%), Td (20%)
[62]Balejo et al., *	RCT	Culture, q PCR	SRP + CHX	Pg (Change in levels. By culture from 113.8 to 782.4, by qPCR from 0.5 to 512.5)
[79]Forner et al., *	Cross sectional	Lysis filtration	Chewing gum + SRP	Pg (10%), Pi (40%), Fn (40%)
[80]Lafaurie et al. *	Cross sectional	Culture	SRP	Pg (28.5%), Tf (7.1%), Fn (11.9%)
[81]Perez-Chaparro et al., *	Cross sectional	Culture	SRP	Pg (43.7%)
[82]Castillo et al., *	Cross sectional	Nested PCR	SRP	Pg (31%), Aa (21.4)
[83]Waghmare et al., *	Cross sectional	Culture	SRP	Pg (37.5%), Pi (15%), Tf (12.5%)
[84]Sharmann et al., *	RCT	Culture, Lysis centrifugation	SRP + Povidone Iodine	Pi (5.2%), Fn (5.2%)
[85]Marin et al., *	Cross sectional	Culture, qPCR, Lysis centrifugation	Toothbrushing	Fn (33%)
[86]Elkaim et al., **	Cross sectional	Hybridization	No treatment	Aa (54.4%), Pg (72.7%),
[87]Gaetti- Jardim et al., **	Cross sectional	RT-PCR	No treatment	Aa (46.2%), Pg (53.8%), Tf (25.6%), Pi (59%), Fn (0)
[65]Figuero et al., **	Cross sectional	Nested PCR	No treatment	Aa (66.7%), Pg (78.6%), Tf (61.9%), Fn (50%)

*(*Bacteremia after periodontal procedure. **Periodontal pathogen in atheromatous lesion. C-S, cross sectional; SRP, scaling and root planing; RCT, randomized clinical trial; Pg, Porphyromonas gingivalis; Tf, Tannerella forsythia; Td, Treponema denticola; Pi, Prevotella intermedia; Aa, Aggregatibacter actinomycetemcomitans; Fn, Fusobacterium nucleatum; FISH, florescence in situ hybridization; qPCR, quantitative polymerase chain reaction.)*