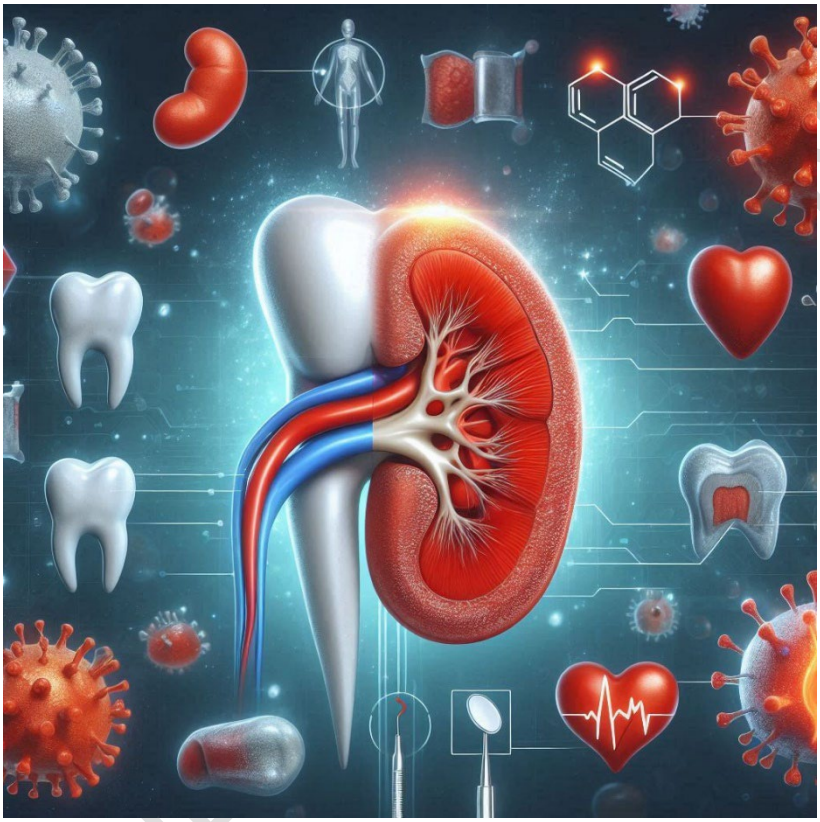
Linking Dental Services to Treatment Outcomes for Chronic Kidney Disease
A Rapid Response Review
July 2024



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Abbreviations

Abbreviation	Term	Abbreviation	Term
ACR	albumin-to-creatine ratio	**LDL**	low density lipoprotein
ACS	acute coronary syndrome	**MD**	mean difference
Alb	albumin	**nPCR**	normalized protein catabolism rate
ALC	absolute lymphocyte count	**NSPT**	non-surgical periodontal therapy
AMI	acute myocardial infarction	**PCS**	prospective cohort study
BUN	blood urea nitrogen	**PD**	peritoneal dialysis
CAD	coronary artery disease	**RCS**	retrospective cohort study
CHF	congestive heart failure	**SCD**	sudden cardiac death
CR	creatinine	**Serum Ca**	serum calcium
CV/CVD	cardiovascular disease	**Serum P**	serum phosphorus
eGFR	estimated glomerular filtration rate	**SMD**	standardized mean difference
ESRD	end stage renal disease	**SRP**	scaling and root planning
FPG	fasting plasma glucose	**TC**	Total cholesterol
eGFR	estimated glomerular filtration rate	**Tf**	Transferrin
Hb	hemoglobin	**TG**	Triglycerides
HD	hemodialysis	**TIBC**	Total iron binding capacity
HDL	high density lipoprotein	**TNF-α**	Tumor necrosis factor alpha
HR	hazard ratio	**TSAT**	Transferrin saturation
CRP	high sensitivity C-reactive protein	**UACR**	Urine albumin-to-creatinine ratio
IL	interleukin	**UPCR**	urine protein-to-creatinine ratio
IL6	interleukin	**WBC**	white blood cells

Background

In the past several years, there has been increasing appreciation for the interconnectedness of oral health and whole body wellness, highlighted by the US Surgeon General's report in 2000[1]. Many subsequent efforts have established a connection between oral diseases and impacts on a variety of systemic diseases[2]. The goal of this report is to review evidence on the efficacy of dental care/treatment in improving outcomes for patients with chronic kidney disease.

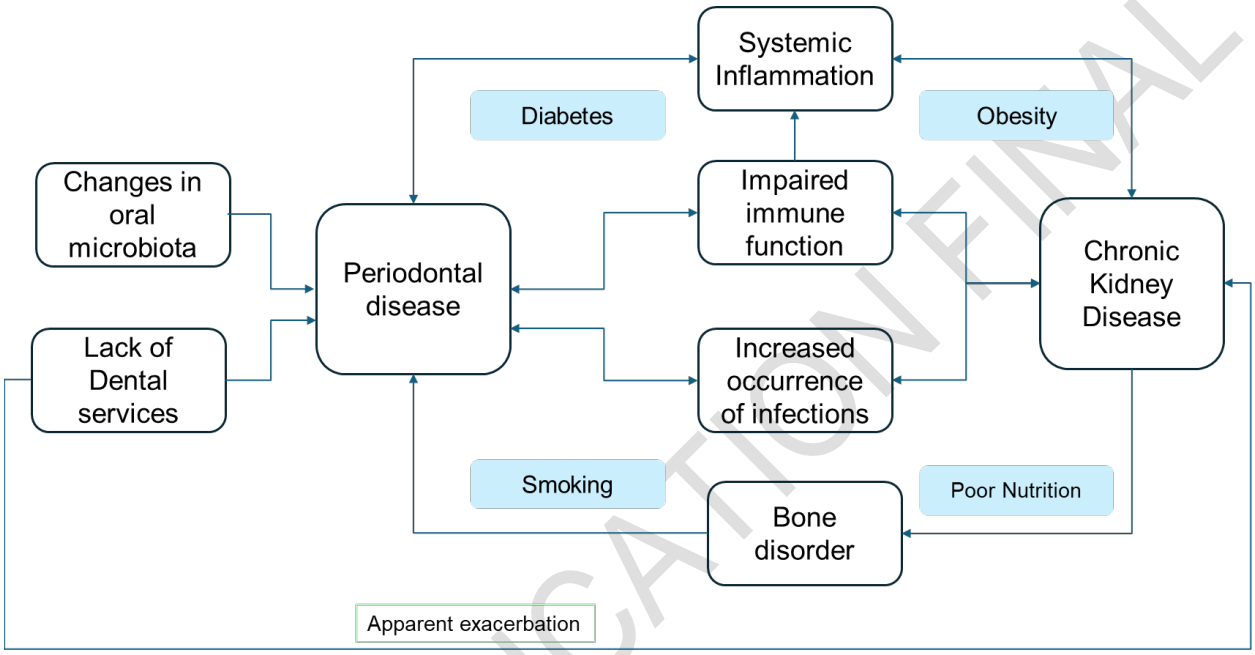
Chronic kidney disease (CKD) impacts a significant portion of the United States population, with approximately 35.5 million people affected, comprising ~14% of American adults[3], and 850 million globally[4]. CKD is multifactorial, with diabetes being the most common cause of kidney failure in the United States. Other causes of CKD include hypertension, heart disease, primary glomerular diseases, genetic diseases and risk factors, and systemic inflammatory diseases[5]. Often, multiple conditions in the setting of aging combine to predispose to CKD. Additionally, CKD is increasing in prevalence faster than diabetes, cardiovascular disease, stroke and cancer and is set to become the fifth leading cause of death worldwide[4].

CKD is a condition in which kidney function is impaired, leading to a buildup of excess fluid and toxic waste, which in turn causes other health complications such as high blood pressure, heart disease, and stroke. Kidney function and kidney damage are assessed by a number of biomarkers; serum creatinine and other serum biomarkers can be used to determine an estimated glomerular filtration rate (eGFR). CKD is classified into five stages[6] based on estimated glomerular filtration rate (eGFR) and evidence of kidney damage (typically assessed as protein or albumin in the urine).The stages in CKD are classified primarily based on the estimated glomerular filtration rate (eGFR). Stages 1, 2, 3 and 4 have eGFR values of >90, 60 – 89, 30 – 59 and 15 – 29 mL/min/1.73m^2 respectively. CKD stage 4 represents severe kidney damage. CKD stage 5, representing severe kidney damage or failing kidneys and also termed as end stage kidney disease (ESRD), is defined by eGFR below 15 mL/min/1.73m^2 and includes individuals with kidney failure treated with dialysis. Treatment for CKD stage 5 patients is dialysis or kidney replacement therapy. There are two types of dialysis: hemodialysis and peritoneal dialysis. Hemodialysis involves circulating blood through an external dialyzer (filtering machine) for filtration. Peritoneal dialysis is performed within a patient's body using the lining of the abdomen/peritoneum as a filter, and a dialysate or cleansing solution that is exchanged using a catheter.

Chronic oral diseases (COD) are a range of conditions that affect the mouth, including dental caries, gingival infection, periodontal disease, and tooth loss[4]. These are among the most common chronic diseases in the United States and can have a significant impact on overall health. CODs can have significant impact on other organ systems with perhaps the most notable albeit rare example being untreated *Streptococcus* infections resulting in an infection-associated glomerulonephritis that can result in kidney failure[7]. This connection extends beyond overt infectious pathology and far more often includes more commonplace factors that impact oral health including periodontitis, a polymicrobial inflammatory condition affecting 90% of adults worldwide to various degrees of severity. Severe periodontitis affects more than 15% of American adults[8], constituting a major cause of tooth loss and exacerbating various other conditions. Figure 1 shows a causal model schematically representing the relationship between CKD and COD.

Systemic inflammation is a known contributor to CKD disease progression[9], and periodontitis is a common cause of increased measures of a systemic inflammatory state[10]. It is notable that the

prevalence of periodontitis approaches 100% in patients on dialysis in some studies[11] suggesting that this is a near-ubiquitous comorbidity with severe CKD. Indeed, recent findings have identified that periodontitis is a risk factor for eGFR decline, and dental intervention may reduce total medical treatment for these patients by delaying or preventing disease progression[12]. Longitudinal studies suggest that these two diseases contribute to the progression of one another, so intervention at the level of the more readily treated disease (periodontitis) may offer significant advantages in total



reduction of health and financial burdens[13]. Some studies suggest that periodontitis may also significantly exacerbate cardiovascular risk and total mortality in patients with CKD at all severity levels[14].

Figure 1. Schematic representation of a causal model depicting the relationship between chronic kidney disease and periodontitis. Smoking, obesity, diabetes and poor nutrition are common risk factors for the two diseases. Single headed arrows represent the directionality of the specified outcome while double headed arrows signify the common causes and outcomes for both diseases.

The objective of this review is to synthesize the recently published evidence for the efficacy of dental services in improving health outcomes for patients with CKD by addressing the following five key questions:

KQ1: What is the effectiveness of dental services in improving health outcomes in persons with stage 4 CKD?

KQ 2: What is the effectiveness of dental services in improving treatment outcomes in people when provided prior to placement of hemodialysis access?

KQ 3: What is the effectiveness of dental services in improving treatment outcomes in people on hemodialysis for end-stage renal disease?

KQ 4: What is the effectiveness of dental services before and during peritoneal dialysis for end-stage renal disease?

KQ 5: Are there any dental services considered a standard of care for the management of persons with stage 4 and 5 CKD?

Methods

This rapid review used the following methods as part of the process:

- Literature search and screening of the resulting articles
- Selection of studies for inclusion in this rapid response
- Risk of bias (RoB) assessment for primary studies using the RoB 2[15], ROBINS[16] or NOS[17] tools
- Quality assessment for systematic reviews (AMSTAR2[18])
- Data extraction for primary studies and systematic reviews
- Assembling of the evidence tables mapped to each key question
- Qualitative synthesis of the findings

Literature Search

Using the framework shown in table 1, searches of the literature were conducted of the following biomedical databases: OVID MEDLINE (PubMed interface) and Embase. An experienced librarian conducted the searches. The search strategies used a combination of medical subject headings (i.e., controlled vocabularies) and keywords, and were written in the syntax of each database. The search strategies used terms for the intervention and condition as well as Boolean operators. All search results were limited to the English language and human species. Searches were initially restricted to the date range of May 2016 to May 2024 to ensure the literature was relevant to current trends. Due to the relatively low number of articles, the search was expanded to include articles from 2014 - May 2024. A detailed search strategy is included in Appendix A1. In addition to the article regarding practice guidelines captured in the literature search, we also conducted a hand search of the websites of the following organizations: Centers for Disease Control and Prevention[3], Kidney Disease: Improving Global Outcomes (KDIGO)[19] and, American Dental Association(ADA)[20]. We searched the practice guidelines for CKD and for dental treatment for patients with CKD and identified a total of 9 articles relevant to practice guidelines. A list of these articles relevant to practice guidelines is available in Table 5.

Table 1: PICOTS Table: Inclusion and exclusion criteria for studies in the review.

Study Parameter	Inclusion Criteria	Exclusion Criteria
Population	● Adults ● CKD stage 4 or 5 ● CKD 4 + hemodialysis ● End stage renal disease + hemodialysis ● End stage renal disease + peritoneal dialysis ● Dental conditions: periodontitis, gingivitis, endodontic abscess, caries	● Pregnant persons ● Persons with oral cancer
Intervention	● Dental services before or, r treatment for CKD: ○ Routine professional dental care (exam/cleaning) ○ Any dental treatment	● Home oral hygiene

Comparator	No dental services before, during, or after treatment for CKD	
Outcome(s)	Primary Outcomes ● Kidney function ○ eGFR ○ creatinine clearance ○ Albumin ○ Blood Urea Nitrogen (BUN) ● Increase time to dialysis ● Metabolic markers ● Acute Infection/Infection ● Mortality ● Other outcomes	● Only dental health outcomes relating to dental procedures are reported.
Timing	● Before or during treatment for CKD. ● Studies of minimum 3 months duration (it takes ~3 months for eGFR to stabilize)	None
Setting	● All countries	
Study Design	● Systematic literature reviews (SLRs)/meta-analyses (MA) ● Randomized controlled trials ● Non-controlled interventional trials ● Controlled and non-controlled observational studies ● Clinical practice guidelines	● Laboratory studies ● Animal studies ● Non-clinical studies
Language	● English language publications.	● Non-English language publications.
Publication dates	● 2014 – May 2024 for RCTs and controlled observational studies ● 2019 - 2024 for SLRs/MAs and clinical practice guidelines	● Articles published before 2014.

BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; RCT: randomized controlled trial; SLR: systematic literature review; MA: meta-analysis

We used Covidence[21] to manage the screening of the articles. All abstracts were reviewed by one reviewer, and a random selection of 10% of the abstracts were reviewed by a second reviewer. Consensus was reached for any conflicts by discussion. At this stage, we excluded abstracts that did not describe a dental treatment, or those that had healthy controls in one arm. Screening of the full text was done in duplicate to ensure capture of as many articles as possible. Data extraction was done by one reviewer and verified by another.

Risk of Bias assessments:

For primary randomized controlled trials (RCTs), the Cochrane Risk of Bias (RoB[15]) tool was used. Each RCT was classified as having low, moderate or high risk of bias. For single arm trials without a control group, the ROBINS[16] tool was used to determine low, moderate, serious or critical risk of bias. Cohort studies were assessed using the Newcastle Ottawa[17] tool. Systematic reviews and umbrella reviews or reviews of reviews were assessed for quality using the AMSTAR2[18] tool to assess if the

review was of high, moderate, low or critically low quality. To facilitate easier comprehension of the quality of the evidence across the different tools, we will employ the following terminology as shown in Table 2 below. The complete assessments of the studies and systematic reviews are available in Appendix A6.

Table 2: Mapping of quality terms from the three tools for assessing quality of the included studies.

Quality term used in this report	RoB Rating	ROBINS	NOS Rating	AMSTAR2 Rating
High	Low	Low	Good	High
Moderate	Some Concerns	Moderate	Fair	Moderate
Low	High	Serious	Poor	Low
Very low		Critical		Critically low

Data extraction:

Systematic reviews (SRs): Data were extracted into tables for the following fields: first author, year, number of systematic reviews (for URs), number of included studies, CKD stage, funding, study countries, period of study covered, intervention, main findings and strength of evidence (risk of bias of component studies, certainty of evidence, heterogeneity where reported).
Primary studies: Data were extracted into tables for the following fields: first author, year, study design, stage of CKD, funding, study country, number of subjects, follow-up time, intervention, outcome category, outcome in intervention group, outcome in control group, statistical significance of the outcomes post-dental therapy, and risk of bias assessment. Data tables were generated for articles which were relevant evidence for each key question.
Excluded studies: A list of excluded studies and reason for exclusion is provided in Appendix A3.

Results:

The literature search resulted in 515 records. After screening the abstracts, 62 articles were found eligible for full-text screening. Of these full-text articles, 23 articles fulfilled the inclusion/exclusion

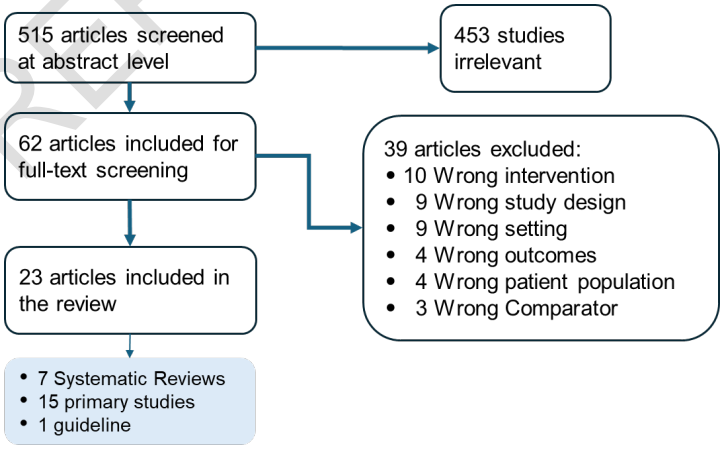


Figure 2: Flow diagram of literature search and triage process

criteria and were deemed relevant to the current review. A PRISMA flow diagram shown in Figure 2 summarizes the process of triaging the literature search results. Finally, of the 23 articles that were included for data extraction, 7 were systematic reviews and/or meta-analyses, and 15 articles were either randomized clinical trials, non-controlled clinical trials or observational studies, and one article related to practice guidelines. All of the systematic reviews were published in the time period 2019 - 2024. The primary studies were published in the time frame 2014 - 2023. Of the 15 primary studies, 6 were included in at least one of the SR/MAs. Some of the studies present in one or more of the SRs are also included separately as primary studies, because not all outcomes reported in the primary study were reported in the systematic review/s where they were included. All systematic reviews are in Appendix A2. All included primary studies are in Appendix A3. A list of all excluded studies along with the reason for exclusion is in Appendix A4. A list of all component studies in the included SRs are in Appendix A5. The studies that met inclusion criteria mostly included non-surgical periodontal treatment (NSPT) except in one study[22] where patients received endodontic (root canal) treatment.

Key Questions 1 and 2:

Key questions 1 and 2 are combined into one section since there were no studies relating specifically to patients prior to the placement of the arteriovenal fistula.
KQ1: What is the effectiveness of dental services in improving health outcomes in persons with stage 4 CKD?
KQ2: What is the effectiveness of dental services in improving treatment outcomes in people when provided prior to placement of hemodialysis access?

Key points:

See Table 2.1.

- There is no evidence available for the impact of dental services on health outcomes for persons specifically with stage 4 CKD alone.
- Kidney function: In patients with CKD (stages unknown) but not on dialysis, there is weak evidence of an improvement in eGFR (3 low quality SRs[23–25] and 1 high quality RCT[26]), but insufficient evidence for improved creatinine and UACR outcomes post-NSPT (1 low quality SR[25] and 1 high quality RCT[26]).
- Inflammation:
  - There is moderate evidence that NSPT results in lowering of CRP (4 low quality SRs, and 2 high quality primary studies). CRP was reported to be reduced in all reviews and primary studies where the outcome was reported.
  - There is weak evidence of lowering of IL6 after NSPT in all reviews/primary studies reporting on this outcome (3 low quality SRs[23,25,27]).
  - There is insufficient evidence for reduction of IL1β (1 high quality single-arm study[28]), and for TNFα outcomes post-NSPT (1 low quality SR[27]).

Table 2.1: KQ1/KQ2 (Stage 4 CKD) Summary of changes in outcomes in SRs and primary studies

SRs addressing KQ1 and KQ2						
Author Year; # of studies; CKD stage; Periodontal condition; Dialysis; Quality	**Kidney Function**	**Inflammatory & Metabolic**	**Iron**	**Lipids**	**Infection**	**Comorbidities & Mortality**
Delbove 2021[23]; 17; 2-5; Chronic; HD (n=10), PD (n=3), ND (n=6)[#] ; Low	↑ eGFR	↓ CRP ↓ IL6				
da Silva 2021[24]; 3; 3-5; Moderate – severe; None; Low	↑ eGFR					
Zhao 2020[25]; 5; 2–5D; Mild to chronic; HD (n=2), PD (n=1), ND (n=2); Low	eGFR: ns Cr: ns	↓ CRP				
Deschamps-Lenhardt 2019[27]; 6; 1-5; Moderate – chronic; NR; Low		↓ CRP ↓ IL6 ↓ TNFα				
Primary studies addressing KQ1 and KQ2						
Author Year; CKD Stage; Study design; Dialysis; Quality	**Kidney Function**	**Inflammatory & Metabolic**	**Iron**	**Lipids**	**Infection**	**Comorbidities & Mortality**
Vacchani 2021; CKD 3-4; RCT; ND; High	↑ eGFR ↓ UACR	↓ CRP				
Maheshwari 2023; CKD 3-4; non-controlled trial; ND; High		↓ CRP ↓ IL1β				

All changes shown are statistically significant ($p<0.05$).
CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; IL6: HD: hemodialysis; Interleukin 6; IL-1β: Interleukin-1 beta; ND: no dialysis; PD: peritoneal dialysis; TIBC: Total iron binding capacity; TNF-α: Tumor Necrosis Factor alpha; UACR: ; UACR: Urine albumin-to-creatinine ratio;

Detailed description of the evidence:

Four SRs[23–25,27] (all low quality) included a mixed population of stage 2-5, and with or without dialysis treatments. SRs that included patients with CKD but not on dialysis were not included for this KQ if they constituted less than 25% of the patient population[29,30]. Two SRs also included patients on HD/PD. Details of the characteristics of the SRs included for KQ1 and KQ2 are provided in Table 2.1 below. Table 2.3 contains the characteristics of the primary studies that map most closely to KQ1 and KQ2. All 4 included SRs for KQ1/KQ2 were of low quality. Certainty of evidence was not reported except in one SR where the quality of the evidence reported was low to very low.

There were no primary studies that evaluated the effectiveness of NSPT in an exclusively stage 4 CKD population. However, Vacchani et al.[26] and Maheshwari et al.[28] recruited individuals with CKD stage 3-5 (patients with CKD but not on dialysis). While the proportion of individuals with CKD 4 was not stated in either study, Vacchani et al. reported median baseline eGFR value of17.74 ±7.80 mL/min/1.73 m2 (note that the eGFR value range for CKD stage 4 is 15 – 29 mL/min/1.73 m2). Outcomes reported in the evidence for KQ1/KQ2 can be grouped into two broad categories: kidney function, and inflammatory

markers. Table 2.2 lists the SRs mapping to KQ1/KQ2, table 2.3 lists the characteristics of the included primary studies and table 2.4 contains the details for the primary studies.

Kidney Function:

- Three low quality SRs[23–25] reported on kidney function outcomes. Improvement in Glomerular Filtration Rate (GFR) in patients with CKD after periodontal treatment is a finding in two SRs[23,24]. The third SR[25] (low quality) showed no change. One SR[25] showed no change for creatinine. The heterogeneity was very low in one meta-analysis (I2 = 0%) and high in the other meta-analysis that was performed (I2 > 85%). Two of the SRs did not perform a meta-analysis. eGFR in 1 high quality RCT[26] had a significant increase and UACR was decreased at 6 months post-treatment.

Inflammatory Markers:

- CRP was reduced in all of the 3 systematic reviews[23,25,27] where it was reported (all low quality). However, meta-analysis for CRP outcomes was not performed in SRs that reported it. (Table 2.2). CRP was reduced in both of the high quality primary studies (1 RCT and 1 non-randomized controlled trial). Statistically significant reduction of systemic inflammation markers like CRP[23,25,27] and IL-6 levels[23,27] and TNFα[27] were reported across multiple SRs (all low quality). One high quality non-randomized controlled trial showed a significant reduction of IL1β[28].

Table 2.2: KQ1 and KQ2 Characteristics of included SRs (all low quality)

Author Year; # of studies; Total N; CKD stage; Periodontal condition; Dialysis; Baseline CRP	**Included locations; Quality; Certainty of Evidence; Quality of component studies**	**Dialysis**	**Outcome; follow-up duration**	**Results**	**Statistical heterogeneity**
Delbove 2021[23]; 17; 2-5; Chronic; HD (n=10), PD (n=3); ND (n=6)[#]; **CRP 3.0 – 6.2 mg/L**	Asia, South America, Europe, USA; Low; NR; Low - High	NR	● eGFR (n=3) ● CRP (n=11) ● IL6 (n=5) ● All-cause mortality (n=3)	● Increase in 2/3 studies ● Decrease in 9/11 studies ● Decrease in 4/5 studies ● Decrease in 1/3 studies	NR (no Meta-analysis)
da Silva 2021[24]; 3; 3-5; Moderate – severe; None; CRP NR	South America, Africa; Low; NR; High	None	● eGFR (n=3); 3 – 6months	MD: 7.01 [0.66, 13.36], p < 0.05	0%
Zhao 2020[25]; 5; 2–5; Mild to chronic; HD (n=2), PD (n=1), ND (n=2); **CRP 2.9 – 3.8**	Asia, South America; Low; Very Low for eGFR and Cr, NR for others; 3 moderate to high,	HD	● eGFR (n=2) ● BUN (n=3) ● Cr (n=1) ● CRP (n=3) ● IL6 (n=1) ● TNF-a (n=1);	● Increase in 2 studies ● Increase in 3 studies ● No difference ● Decrease in 3 studies ● Decrease ● No change	>85% for Cr, eGFR

mg/L	2 low.		● 8 weeks – 6 months		
Deschamps-Lenhardt 2019[27]; 6; 1-5; Moderate – chronic; NR; **CRP 3.0 – 6.2 mg/L**	Asia, Europe, South America Low; NR; NR	NR	● eGFR (n=2) ● Cr (n=1) ● CRP (n=2) ● IL6 (n=2) ● TNF-α, Ferritin (n=1) ● BUN, Tf (n=1) ● Metabolic markers; ● 6wks - 6 months	● Increased in 1/2 studies ● Decreased in 1/1 study ● Decreased 2/2 studies ● Decreased 2/2 studies ● Decreased in 1/1 study ● Decreased in 1/1 study ● No change in Lipids, inconsistent changes in Alb	NR (no meta-analysis)

#adds to more than 18 because some studies contain patients with HD and/or PD and/or non-dialysis.
Alb: Albumin; BUN: blood urea nitrogen; albumin-to-creatine ratio; Cr: Creatinine; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HD: hemodialysis; IL6: Interleukin 6; MD: mean difference; NR: Not reported; NSPT: Non-surgical periodontal treatment; OHI: Oral hygiene instruction; PD: peritoneal dialysis; RCT: randomized controlled trial; TNF-α: Tumor Necrosis Factor alpha; UACR: ; IL-1β: Interleukin-1 beta; UACR: Urine albumin-to-creatinine ratio; UPCR: urine-to-protein ratio.

Table 2.3 KQ1/KQ2 characteristics of the included primary studies.

Category	KQ1 & KQ2
Study design	Non-randomized/randomized controlled observational trial (0/2[26,28]) Observational study 0
Study countries	India
CKD stage	3 – 5 (non-dialysis)
Periodontitis severity	Moderate-severe
Dialysis type	None
Number of subjects (range)	130 (50, 80)
Follow-up time (range): Interventional studies Cohort studies	 6 months n/a
Intervention	NSPT with OHI (n=2)
Comparator	OHI (n=2)
Outcomes (broad categories)	Kidney function outcomes, inflammation-related outcomes

Table 2.4: Primary studies mapping to KQ1/KQ2 (all high quality)

Author Year; Country; Funding Source; CKD Stage Quality	Design; Total N; Time to follow-up;	Dental Service	Outcome	Outcome in Dental Care Group	Outcome in Control Group	Statistically Significant Findings for patients receiving periodontal therapy
Vachhani 2021[26]; India; None Reported; 3–5; High; **CRP: Treated: 6.6; Control: 4.8 mg/L**	RCT; 80; 6 months	*Treatment:* NSPT + OHI *Control*: OHI	*Average percent change relative to Baseline*			• CRP decreased ($p < 0.001$) • eGFR increased ($p < 0.001$) • UACR decreased ($p < 0.001$)
			CRP	-54.0**	41.5	
			eGFR	41.1**	-16.8	
			UACR	-25.1**	14.3	
Maheshwari 2023[28]; India; Federal; 3-4; High; **CRP: Treated: 5.1, Control: 3.7mg/L**	non-randomized controlled trial 50 6 months	*Treatment:* NSPT + OHI *Control*: none	*Average percent change relative to Baseline*			• CRP lower in treated group ($p < 0.001$) • IL-1β lower in treated group ($p = 0.03$) • No significant changes in creatinine, Alb, UPCR and ACR
			CRP	-39.0**	38.0	
			IL-1β	-15.6*	15.5	
			Cr	-2.7	-0.2	
			Alb	0.9	0.7	
			UPCR	-12.8	-0.5	
			UACR	2.2	0.1	

*p < 0.05, **p < 0.01, ***p < 0.001

Alb: Albumin; BUN: blood urea nitrogen; albumin-to-creatine ratio; Cr: Creatinine; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; IL-1β: Interleukin-1 beta; IL6: Interleukin 6; NR: Not reported; NSPT: Non-surgical periodontal treatment; nCT: non-randomized controlled trial; OHI: Oral hygiene instruction; RCT: randomized controlled trial; TNF-α: Tumor Necrosis Factor alpha; UACR: Urine albumin-to-creatinine ratio; UPCR: urine-to-protein ratio

Key Question 3:

KQ3: What is the effectiveness of dental services in improving treatment outcomes in people on hemodialysis for end-stage renal disease?

Key points:

See Table 3.1.

- Kidney Function: There is insufficient evidence for improved kidney function outcomes due to conflicting results across the literature where one SR[23] reported an increase in eGFR while the other[25] did not report a significant difference post-NSPT.
- There is insufficient evidence for no effect in serum creatinine due to inconsistent results from one low quality SR[25] and two moderate quality single arm studies[31,32] showing no change, and one high quality RCT[33] showing an increase.
- Inflammatory outcomes:

- There is moderate evidence that NSPT results in a reduction of CRP levels observed consistently across all included systematic reviews[23,25,27,29,30,34] (one high quality[29], one moderate[34] and four low quality) and 2[31,33] out of 3[31–33] primary studies of moderate to high quality.
- There is weak evidence that IL6 levels are reduced after NSPT (in 3 out of 4 low quality SRs[23,27,30] and one high quality RCT[33]) in patients receiving hemodialysis.
- There is insufficient evidence for no effect on TNF-α in 2 low quality SRs[27,34] and 1 high quality primary study[33].

- Lipid outcomes: There is insufficient evidence of no effect on lipid outcomes post-NSPT in patients on hemodialysis (1 high quality RCT).
- Cardiovascular Outcomes: There is insufficient evidence (2 prospective[35,36] and 2 retrospective[22,37] cohort studies, all high quality) that cardiovascular disease, cardiovascular events, strokes, congestive heart failure, sudden cardiac death and acute myocardial infarction are reduced post-NSPT.
- Mortality outcomes: There is weak evidence from 1 low quality SR and 6 high quality primary studies (1 RCT, 3 prospective and two retrospective cohort studies) that there is a favorable outcome for all-cause mortality after NSPT. There is insufficient evidence for cardiovascular (high quality cohort study[35]), malignancy-associated and other cause-mortality (high quality cohort study[22]).
- Infection outcomes: There is weak evidence[22,38–40] of no effect that infectious disease outcomes are lower in patients with CKD on hemodialysis post-NSPT or post-endodontic therapy (1 high quality RCT[38] and 3 high quality cohort studies[22,39,40]).
- Other outcomes: There is insufficient evidence for lower rates of bacteremia, pneumonia, osteomyelitis, brain abscess, renal and perinephric abscess outcomes in patients who underwent NSPT (1 high quality cohort study[39]).

More details for SRs and primary studies are in Tables 3.2 and 3.4.

Table 3.1 KQ3: Summary of changes in outcomes in SRs & primary studies (Stage 5 CKD/HD)

SRs addressing KQ3						
Author Year; # of studies; CKD stage; Periodontal condition; Dialysis; Quality;Certainty of Evidence	**Kidney Function**	**Inflammatory & Metabolic**	**Iron**	**Lipids**	**Infection**	**Comorbidities & Mortality**
Bezerra 2024[29]; 7; 5D; Mild – Severe; HD; High; Low		↓CRP				
Delbove 2021[23]; 17; 2-5; Chronic; HD (n=10); PD (n=3); none (n=4); Low; NR	↑ eGFR	↓ CRP ↓ IL6				All-cause Mortality: ns

Zhao 2020[25]; 5; 2–5; HD (n=2), PD (n=1), none (n=2); Mild to chronic; Low; Very Low for eGFR, Cr	eGFR: ns Cr: ns	↓ CRP				
Lai@ 2020[30]; 6; 3-5D; HD (n=3), PD (n=2), ND (n=1); NR; Low; NR		↓ CRP ↓ IL6				
Deschamps-Lenhardt 2019[27]; 6; 3-5 (n=4); HD (n=1); Moderate – chronic; Low; NR		↓ CRP ↓ IL6 ↓ TNF-a				
Yue 2020[34]; 5; 5; HD (n=3), PD (n=2); NR; Moderate; NR		↓ CRP IL6: ns TNF-a: ns Alb: ns				
Primary studies addressing KQ3						
Author Year; CKD Stage; Study design; Follow-up time; Quality	**Kidney Function**	**Inflammatory & Metabolic**	**Iron**	**Lipids**	**Infection**	**Comorbidities & Mortality**
Fang, 2015[33]; ESRD; HD; RCT; 6 months; High	↑ Cr	↓ CRP ↓ IL-6 ns: TNF-α ↑ Alb ↑ BUN ns: ALC ns: nPCR	↓ Ferritin ↑ Tf	ns: TC ns: TG ns: LDL ns: HDL		
Chung, 2022[38]; ESRD; HD; RCT; 3 months; High					ns: Infection event	ns: CV event ns: all-cause mortality
Vrinda, 2021[31]; ESRD; HD; non-controlled trial; 3 months; Moderate	ns: Cr	↓CRP ns: Alb	↑ Ferritin ↑ Iron ↑ TIBC ↑ TSAT			
	ns: Cr	ns: CRP ns: Alb	↑ Ferritin ns: Iron ↓ TIBC ↑: TSAT			
Rapone, 2019[32]; ESRD; HD; Uncontrolled trial; 6 months; Moderate	↓ Cr	ns: CRP ↓ Alb				
Santos-Paul 2019[36]; ESRD; HD; Prospective cohort study, historical						↓ CV event ↓ Coronary event ↓ CVD ns: All-cause mortality

control; 2 years; High						
de Souza, 2014[41]; ESRD; HD; Prospective cohort study; 5-6 years; High						ns: All-cause mortality
Palmer, 2015[35]; ESRD; HD; Prospective cohort study; 3 years; High						↓ All-cause mortality ↓ CVD mortality
Huang, 2018[37]; ESRD; HD; Retrospective Cohort Study; 5 – 7 years; High						↓ CVD ↓ ACS ↓ AMI ↓ Stroke ↓ Ischemic stroke ↓ Hemorrhagic stroke ↓ CHF ↓ SCD ↓ All-cause mortality
Huang, 2015[39]; ESRD; HD; Retrospective Cohort Study; 13 years; High					↓ infectious diseases ↓ acute/subacute infective endocarditis ns: bacteremia ↓ pneumonia ns: brain abscess ↓: osteomyelitis ns: renal and perinephric abscess	
Chiu 2021[22]; ESRD; PD/HD; Retrospective Cohort Study; 16 years; High					↓ Infectious diseases	↓ All-cause mortality ns: CAD, Cerebrovascular disease, malignancy-associated mortality ↑ other cause mortality
Yu, 2023[40]; ESRD; HD; Cohort case-control study; 3 months; High					ns: infective endocarditis	

All changes shown are statistically significant ($p<0.05$)

Alb: Albumin; BUN: blood urea nitrogen; albumin-to-creatine ratio; Cr: Creatinine; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HD: hemodialysis; IL6: Interleukin 6; ND: no dialysis; NR: Not reported; NSPT: Non-surgical periodontal treatment; OHI: Oral hygiene instruction; PD: peritoneal dialysis; RCT: randomized controlled trial; TIBC: Total iron binding capacity; TNF-α: Tumor Necrosis Factor alpha; TSAT: Transferrin

saturation; UACR: ; IL-1β: Interleukin-1 beta; UACR: Urine albumin-to-creatinine ratio; UPCR: urine-to-protein ratio.

Detailed description of the evidence:

For KQ3, 6 SRs[23,25,27,29,30,34] were included, of which one[29] was of high quality, one[34] of moderate quality and the others were of low quality (Table 3.2). The certainty of evidence was very low, low or not reported in the SRs. One SR[29] consisted of a purely HD population. All the other SRs were a mix of HD, PD and/or non-dialysis patients with CKD. The heterogeneous composition of the patient population makes it challenging to determine the level of relevance of the available evidence for any of the outcomes. Of the 11 primary studies that were included, 9 were high quality[22,33,35–41] and the remaining two[31,32] were of moderate quality. Of the primary studies, two were RCTs,[33,38] two were uncontrolled trials[31,32], 3 each of prospective[35,36,41] and retrospective[22,37,39] cohort studies and one observational case control study[40]. Outcomes that were reported fell into the following broad categories: kidney function, inflammatory, nutritional and lipid markers, cardiovascular-related outcomes, mortality outcomes and infection outcomes. Table 3.2 lists the SRs mapping to KQ3, table 3.3 lists the characteristics of the included primary studies and table 3.4 contains the details for the primary studies.

Kidney Function:

Serum creatinine was measured in 3 primary studies[31–33]: one high quality RCT[33] and two moderate quality single-arm studies[31,32]. The change in serum creatinine was statistically significant in two of the studies[32,33] with 14.9% and 50% increase at 6 months post-NSPT.

Inflammatory markers:

Six SRs and two primary studies[20,21] measured inflammatory markers like CRP, Ferritin, IL-6, IL-1b, TNF-a, serum Albumin, Hb and Erythrocyte sedimentation rates. All the SRs as well as the two primary studies showed a consistent and statistically significant reduction of CRP 3-6 months post-NSPT. In one of the studies[31], a significant reduction of CRP from baseline) was seen in patients who had been on hemodialysis for less than one year. In patients who had been on HD for more than one year, there was a reduction in CRP relative to baseline but the effect was not significant. Another inflammatory marker, IL-6, was reported as reduced post-NSPT in 3[23,27,30] out of 4 SRs and in one primary study[33] with a significant decrease at 6 months post-periodontal therapy.

There is inconsistent evidence for ferritin. In one study[31], serum ferritin showed a significant increase of ~9% at 6 months in patients on HD and in another[33], a reduction by ~20 %.

Nutrition-related markers:

Serum albumin is a key nutritional marker followed by blood urea nitrogen (BUN), There is inconsistent evidence for Albumin outcomes, One low quality SR, 1 high quality RCT and 2 moderate quality single arm studies report Alb outcomes. In two studies[32,33], the serum Alb levels were significantly different post-NSPT – an increase of ~3.7% at 6 months in one[33] and a reduction of 6% in another[32] post-NSPT while it was not significantly different in the third study[31]. No change post-NSPT of serum albumin in the SR[25]. BUN was significantly increased in one high quality RCT[33].

One or more Iron indices were measured in two studies - transferrin saturation (TSAT), serum iron and TIBC (Total iron binding capacity). Transferrin or transferrin saturation was reported in two studies[31,33]

(1 high quality RCT and one moderate quality single-arm study) showing a significant increase in both. TIBC showed a significant increase (~11.5%) in patients receiving hemodialysis for less than one year, but in patients receiving hemodialysis for more than one year, it showed a decrease (-1.4%) in one moderate quality single-arm study[31].

Lipid markers:

One high quality RCT[33] reported on lipid outcomes which were not significant.

Cardiovascular events:

Outcomes reported in the cohort studies relating to cardiovascular (CV) events include time to major CV event, time to a coronary event, time to CVD, coronary artery disease, cerebrovascular disease, CV disease, ACS, AMI, stroke (ischemic, hemorrhagic), CHF, SCD and all-cause mortality. Four cohort studies[22,35–37] assessed the incidence of cardiovascular mortality in patients with CKD receiving dental treatment. Three[22,36,37] of these four studies showed a significantly lower number of CV events for patients with CKD where the intervention arm was periodontal treatment (NSPT with or without flap surgery) or endodontal treatment . In these studies, patients were followed for a time period ranging from 2 to 16 years.

Mortality-related outcomes:

One high quality RCT[38] and five high quality cohort studies[22,35–37,41] reported on all-cause mortality (ACM). ACM was significantly lower in three cohort studies[22,35,37] involving ~3200 - 12400[22,35,37] patients followed for 3 – 16 years. The other two cohort studies with non-significant ACM outcomes were prospective cohort studies with 73[41] and 409[36] patients followed for 2 – 6 years. In the RCT[38], 11 patients were followed for only 3 months post-NSPT, which could be considered an inadequately powered study and/or inadequate follow-up time for a mortality outcome.

Infectious Disease:

The following conditions relating to infectious diseases were assessed in 3 cohort studies: infective endocarditis[39,40] all infectious disease[22,39], bacteremia, pneumonia[39], brain abscess[39], osteomyelitis[39], and renal and perinephric abscess[39]. Studies followed the patients for a period up to 16 years. Cohort sizes ranged from ~9,000 - 19,600.

One study[40] evaluated the rates of infective endocarditis on patients with CKD who receive periodontal treatment. The hazard ratio of 1.04 (95% CI: 0.71, 1.53) at 3 months post-periodontal therapy suggests that patients with CKD are *not* at a higher risk of developing infective endocarditis following periodontal treatment. Huang et al. reported on acute infective endocarditis and showed that the patients with CKD receiving dental treatment had a 0.54-fold lower incidence of infective endocarditis, suggesting infective endocarditis may not have arisen as a result of NSPT for patients with CKD. The Huang et al. and Chiu et al.[22,39] studies showed a lower risk (0.72-fold and a 12% reduction in incidence, respectively) of overall infectious disease burden as well as acute and subacute infective endocarditis, pneumonia, and osteomyelitis. Additionally, the Chiu study showed that infectious diseases had a significant role in mortality in patients with CKD who did not undergo endodontic therapy. No significant difference was reported in renal, and development of perinephric abscesses, bacteremia or brain abscesses post-periodontal therapy.

Two high quality cohort studies[22,39] show consistent evidence of a lower risk of of infectious disease incidence in patients with CKD who are undergoing treatment for periodontitis or root canal treatments.

Table 3.2 Details of SRs mapping to KQ3

Author Year; # of studies; CKD stage; Dialysis; Periodontal condition; baseline CRP	**Included locations; Quality of SR; Certainty of Evidence; Quality of primary studies**	**Outcome; follow-up duration**	**Results**	**Statistical heterogeneity**
Bezerra 2024[29]; 7; 5D; HD (n=7); Mild – severe; **CRP: 2.6 – 9.4mg/L**	Asia, South America, USA; High; Low; Moderate-high	CRP (6wks – 6 months)	SMD: 0.45 (95%CI [-0.25, -0.65], p 0.001)	0.0%
Delbove 2021[23]; 18; 2-5; HD (n=9), PD (n=3), ND (n=4); Chronic; **CRP: 0.4 – 9.4 mg/L & 30.5 mg/L**	Asia, South America, Europe, USA; Low; NR; Low - high	● eGFR (n=3)	● ↑ in 2/3 studies	NR (No meta-analysis)
		● CRP (n=11)	● ↓ in 9/11 studies	
		● IL6 (n=5)	● ↓ in 4/5 studies	
		● All-cause mortality (n=3)	● ↓ in 1/3 studies	
Zhao 2020[25]; 5; 2–5D; HD (n=2), PD (n=1), ND (n=2); Mild to chronic; **CRP: 2.9 – 3.8 mg/L**	Asia, South America; Low; Very Low for eGFR, Cr; 3 moderate – high, 2 low	● eGFR (3 – 6 months)	● No change	>85% for Cr, eGFR. No meta analysis performed for the other outcomes.
		● Cr (4 – 6 months)	● No change	
		● BUN (n=3) (2 – 4 months)	● ↑	
		● CRP (n=3)	● ↓ in all studies	
		● IL6 (n=1)	● ↓	
		● TNF-a (n=1);	● No change	
Yue 2020[34]; 5; 5D; HD, PD; NR; **CRP: 3.0 mg/L and NR**	Asia, USA; Moderate; NR; Moderate	● CRP (1 – 2 months)	● SMD: − 1.53, 95% CI [− 2.95 to − 0.11], p < 0.05	>90%
		● IL6, TNF-a (3 – 6 months)	● insufficient evidence	
		● Alb (3 – 6 months)	● insufficient evidence	
		● Lipids (3 – 6 months)	● insufficient evidence	
Lai@ 2020[30]; 6; 3-5D; HD (n=3), PD (n=2), none (n=1); NR;	Asia, USA; Low; NR; 2 high, 4	● CRP (1 – 3 months)	● MD=-0.58, 95% CI [-1.13, -0.02] , p = 0.04	> 90%
		● IL-6 (1 – 3 months)	● MD=-2.76, 95%CI [-5.15, -0.37], p = 0.02	

CRP: 3.0 – 4.7 mg/L	unknown	● TNF-a (1 – 3 months)	● No significant change	
Deschamps-Lenhardt 2019[27]; 6; 1-5; HD; none Moderate – chronic; **CRP: 3.0 – 6.2 mg/L**	Asia, Europe, South America; Low; NR; NR	● eGFR ● 6wks - 6 months	● insufficient evidence	NR (no meta-analysis)
		● Alb, Cr	● insufficient evidence	
		● CRP (n=3)	● ↓	
		● IL6	● insufficient evidence	

Alb: Albumin; BUN: blood urea nitrogen; albumin-to-creatine ratio; Cr: Creatinine; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; IL-1β: Interleukin-1 beta; IL6: Interleukin 6; NR: Not reported; NSPT: Non-surgical periodontal treatment; OHI: Oral hygiene instruction; RCT: randomized controlled trial; TNF-α: Tumor Necrosis Factor alpha; UACR:; UACR: Urine albumin-to-creatinine ratio; UPCR: urine-to-protein ratio

Table 3.3: Characteristics of primary studies mapping to KQ3

Category	KQ3
Study design	Non-randomized/randomized controlled observational trial (1/3) Observational study (7)
Study countries	India, China, Taiwan, Italy, Brazil, Taiwan, France, Hungary, Poland, Portugal, Spain, Argentina
CKD stage	ESRD
Periodontitis severity	NR (n=4), moderate severe (n=2), chronic (n=3)
Dialysis type	HD: 10; HD/PD: 1
Number of subjects (range)	217 (40 - 97) 52126 (40 – 19602)
	51909(73 - 19602)
Follow-up time (range): Interventional studies Cohort studies	 3 – 6 months 2 – 16 years
Intervention	Interventional studies: • SRP (n=1) • SRP + prophylaxis(n=1) • Antibiotic prophylaxis + standard NSPT + OHI (n = 1) • NSPT (n=1) Cohort studies: • Thorough debridement of the affected root surfaces or tooth extraction, and any other type of treatment considered suitable (plaque control, caries, endodontic intervention) (n=1) • SRP + flap surgery (n=2) • SRP, OHI, antibiotic prophylaxis, rubber cup prophylaxis (n=1) • Time since last dental visit (n=1) • Root canal therapy (n=1)
Comparator	No treatment or OHI (n=1)
Outcomes (broad categories)	Kidney function, inflammatory markers, metabolic markers, infections and infections, cardiovascular disease and/or events, mortality and other outcomes

Table 3.4: Details of primary studies mapping to KQ3

Author Year; Country; Funding Source; CKD Stage; Dialysis; Periodontitis severity; Quality; baseline CRP	Design; Total N; Time to follow-up	Dental Service	Outcome	Outcome in Dental Care Group	Outcome in Control Group	Key Significant Findings for patients receiving periodontal therapy
Fang, 2015[33]; China; Province; 5; HD; Chronic; High; **CRP 3.0 mg/L**	RCT; 97; 6 months	*Treatment:* NSPT+OHI + supragingival prophylaxis at 3m post-treatment *Control:* no treatment	*Average percent change relative to Baseline*			• CRP lower (p < 0.001) • IL6 lower (p = 0.001) • Ferritin lower (p = 0.002) • Alb higher (p = 0.002) • Creatinine higher (p = 0.002) • BUN higher (p = 0.001) • Tf higher (p < 0.001) • No changes in lipids in either group
			CRP	-23.8***	6.6	
			TNF-α	-4.9	3.1	
			IL-6	-21.4**	5.1	
			Ferritin	-20.8**	-1.8	
			Alb	3.7**	0.3	
			Cr	14.9**	0.4	
			BUN	7.1**	1.7	
			ALC	2.4	-0.6	
			Tf	7.7***	1.2	
			nPCR	1.9	1.9	
			TC	-1.1	-1.5	
			TG	-3.7	-3.7	
			HDL	1.5	-2.9	
			LDL	-4.8	-3.9	
Chung, 2022[38]; Taiwan; Academic; 5; HD; Moderate-Severe; High; **CRP NR**	RCT; 14; 3 months	*Treatment:* NSPT; ABX prophylaxis; OHI *Control:* OHI	ACM; n (%)	0 (0%)	2 (29%)	• No differences observed in primary outcomes.
			CV events; n (%)	0 (0%)	1 (14%)	
			Infections; n (%)	3 (43%)	2 (29%)	
			HbA1c	no change	no change	
Vrinda, 2021[31]; India; None Reported; 5; HD;	Single arm Trial ; 20 ; (HD < 1 year); 3 months	*Treatment*: NSPT *Control*: pre-treatment	*Average %change relative to baseline*		*No control group*	• CRP lower in patients on <1y HD at 3m after NSPT (P = 0.04) • Improvement in several iron indices (Ferritin, TIBC,
			CRP	-12.2*		
			Ferritin	9.1***		
			Alb	1.5		
			Iron	21.5*		

Chronic; Moderate; **CRP: 8.06mg/L** **CRP: 8.37 mg/L**	20; (HD > 1 year); 3 months		TIBC	11.5***	*No control group*	TSAT) in patients in both groups • No changes in eGFR in either group
			TSAT	9.2*		
			Cr	-2.9		
			CRP	-8.8		
			Ferritin	9.8**		
			Alb	-1.7		
			Iron	0.6		
			TIBC	-1.4*		
			TSAT	2.0*		
			Cr	22.1		
Rapone 2019[32]; Italy; None Reported; 5/HD; NR; Moderate; **CRP: 1.28 mg/L**	Single Arm Trial; 66; 6 months	*Treatment:* NSPT *Control:* pre-treatment	*Average percent change relative to Baseline*			• ALB decreased (p < 0.001) • Serum creatinine increased (p = 0.002) • No significant changes in CRP
			Serum Alb	-6.0***	No control group	
			Serum Cr	50.0**		
			CRP	3.1		
Santos-Paul, 2019[36]; Brazil; None Reported; 5/ HD; Moderate-Severe; High; **CRP: NR**	PCS with historical control; 409; 2 years	*Treatment:* NSPT; OHI *Control:* no treatment	*Survival Log-rank Test*			• Lower rates of CV events • Lower rates of CV-related mortality in patients receiving NSPT
			Survival free of major CV event	94% (0.009)**	83%	
			Survival free of coronary event	97% (0.009)**	89%	
			Survival free of CVD	96% (0.037)*	87%	
			ACM	No difference		
de Souza, 2014[41]; Brazil; None Reported; 5/HD; Chronic; High; **CRP: 10.7 ± 15.4mg/L**	PCS; 73; 5 - 6 years	*Treatment:* NSPT; OHI; antibiotic and rubber cup prophylaxis *Control*: no trtmt, no CP	*Adjusted Hazard Ratio compared to no CP patients (95% CI); adjusted for age, gender, comorbidities, oral health, and CP status)*			No difference in survival between treated and untreated patients with CP on HD (P=0.774)
			Risk of Mortality	1.79 (0.71, 4.51)*	1.49 (0.54, 4.09)	
Palmer, 2015[35]; Europe (France, Hungary, Italy, Poland, Portugal, Spain), Argentina;	PCS; 3243; 1, 2, 3 years (data shown for 3 years)	*Treatment:* Last dental visit ≤6m	*Adjusted Hazard Ratio (95% CI); stratified by country and adjusted for age, sex, race, smoking history, income, medical history, dialysis vintage, mean arterial blood pressure, serum phosphorus, and hemoglobin levels.*			• Longer survival in treated patients on HD.
			All-cause mortality	0.79 (0.65, 0.96)*		

Hospital; Italy; 5/HD; NA; High; **CRP: NR**		*Control:* Last dental visit >6m	CVD mortality	0.73 (0.55, 0.97)*	
Huang, 2018[37]; Taiwan; Federal, Academia, Foundation, Consortia; 5/HD; NR; High; **CRP: NR**	RCS; 7226; 5 – 7 years	*Treatment*: SRP; flap surgery *Control*: no treatment	*Adjusted Hazard Ratio (95% CI); adjusted for age, gender, urbanization level, monthly income, Charlson comorbidity index, comorbidities, and medications*		• Lower risk of mortality • Lower risk of development of CVD and CVD-related events
			CVD	0.75 (0.69, 0.81)***	
			ACS	0.85 (0.74, 0.99)*	
			AMI	0.72 (0.58, 0.89)**	
			Stroke	0.67 (0.60, 0.76)***	
			Ischemic stroke	0.78 (0.68, 0.90)***	
			Hemorrhagic stroke	0.47 (0.37, 0.59)***	
			CHF	0.83 (0.73, 0.93)**	
			SCD	0.68 (0.48, 0.95)*	
			All-cause mortality	0.49 (0.45, 0.54)***	
Huang, 2015[39]; Taiwan; Federal, Academia, Foundation, Consortia; 5/HD; NR; High; **CRP: NR**	RCS; 8902; 13 years	*Treatment*: SRP; flap surgery *Control*: no treatment	*Hazard Ratio (95% CI)* *Only treatment group had patients with periodontitis*		• A lower risk (0.72-fold) of overall infectious disease burden • Lower risk of acute and subacute infective endocarditis, pneumonia, and osteomyelitis . • No difference in renal and perinephric abscesses, bacteremia or brain abscesses
			Overall infectious diseases	0.72 (0.66, 0.78)***	
			Acute and subacute infective endocarditis	0.54 (0.35, 0.84)**	
			Bacteremia	0.83 (0.68, 1.03)	
			Pneumonia	0.71 (0.65, 0.78)***	
			Brain abscess	0.68 (0.31, 1.50)	
			Osteomyelitis	0.77 (0.62, 0.96)*	
			Renal and perinephric abscess	0.53 (0.24, 1.17)	
Chiu, 2021[22]; Taiwan; Federal; 5/HD & PD; NA; High; **CRP: NR**	RCS; 12454; 2633 received treatment; 16 years	*Treatment:* Root canal therapy *Control:* no treatment	*% patients with event (age, sex, monthly income, and dialysis type and comorbidities)*		• Better overall survival in patients receiving endodontic therapy
			Cause of death	Root Canal treatment	Control
			ACM	22.79%**	34.93%
			CAD	13.83%	17.46%

			CHF	4.75%***	5.69%	
			ID	34.83%**	45.54%	
			CbVD	16.17%	11.28%	
			Malignancy	12.00%	9.65%	
			Other	23.17%*	16.06%	
Yu 2023[40]; Taiwan; Federal; 5/HD; High; **CRP: NR**	Case-control study; 19602; 3 months	*Treatment:* SRP *Control*: no treatment	*Adjusted Hazard Ratio (age, sex, monthly income, and dialysis type and comorbidities)*			• No greater risk of developing infective endocarditis for patients on HD
			Infective endocarditis	1.04 (0.71, 1.53)		

*p < 0.05, **p < 0.01, ***p < 0.001

ABX: antibiotics; ACM: all-cause mortality; Alb: Albumin; BUN: blood urea nitrogen; albumin-to-creatine ratio; CbVD: Cerebrovascular disease; CAD: Coronary artery disease; CHF: congestive heart failure; Cr: Creatinine; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; ID: Infectious Disease; IL-1β: Interleukin-1 beta; IL6: Interleukin 6; NR: Not reported; NSPT: Non-surgical periodontal treatment; OHI: Oral hygiene instruction; RCT: randomized controlled trial; TNF-α: Tumor Necrosis Factor alpha; UACR: Urine albumin-to-creatinine ratio; UPCR: urine-to-protein ratio

Key Question 4:

What is the effectiveness of dental services before and during peritoneal dialysis for end-stage renal disease?

Key points:

See Table 4.1.

Kidney Function: There is insufficient evidence for kidney function outcomes post NSPT (2 SRs[23,25] of low or very low quality, 2 primary studies[42,43] of moderate quality). There is insufficient evidence for no effect for serum calcium and serum phosphorus (1 moderate quality[43] single arm trial)

Inflammatory markers: There is moderate evidence that CRP is reduced post-NSPT consistently and statistically significantly in all of the systematic reviews[23,25,30,34] (low to very low quality) as well as in the two moderate quality primary studies[42,43] where it was measured. There is weak evidence for a reduction in IL6 levels (in 2 low quality SRs[23,30] out of the 3 SRs[23,30,34]) post-NSPT. We find insufficient evidence for no change in TNFα (one moderate quality[34] SR) post-NSPT.

Nutrition-related markers: There is weak evidence of no effect for serum albumin outcomes (1 moderate quality SR[34], 2 moderate quality[42,43] single arm trials).

Lipid markers: There is weak evidence for no effect after NSPT (2 moderate quality[42,43] single arm trials)

Cardiovascular Outcomes: There is insufficient evidence for benefit to patients regarding cardiovascular outcomes including coronary artery disease, congestive heart failure, peripheral arterial disease and malignancies(one high quality retrospective cohort study[22]).

All-cause mortality: Insufficient and inconsistent evidence is available for this outcome drawn from one low quality SR[23] and one high quality primary study (retrospective cohort study[22]). Both these articles include a mix of patients receiving HD and PD.

Infections: There is insufficient evidence for a reduction in infectious diseases (one high quality retrospective cohort study[22])

Table 4.1: KQ4: Summary of changes in outcomes in SRs & primary studies (Stage 5 CKD/PD)

SRs addressing KQ4						
Author Year; # of studies; CKD stage; Number of HD, PD and ND studies; Periodontal condition; Quality; Certainty of Evidence	**Kidney Function**	**Inflammatory & Metabolic**	**Iron**	**Lipids**	**Infection**	**Comorbidities & Mortality**
Lai 2020; 6; 3 – 5D; PD (n=2), HD (n= 3); none (n=1); NR; Low;		↓ CRP ↓ IL6				

NR						
Delbove 2021[23]; 18; CKD 2-5; HD (n=9), PD (n=3), ND (n=4); Chronic; Low; NR	↑ eGFR*	↓ CRP* ↓ IL6*				ns: ACM
Zhao 2020[25]; 5; 2–5D; HD (n=2), PD (n=1), ND (n=2); Mild to chronic; Low; Very Low for eGFR, Cr	ns: eGFR ns: Cr	↓ CRP*				
Yue 2020[34]; 5; 5D; HD (n=3), PD (n=2); NR; Moderate; NR		↓ CRP ns: IL6 ns: TNF-α ns: Alb				
Primary studies mapping to KQ4						
Author Year; CKD stage; Dialysis Type; Study design; Quality	**Kidney Function**	**Inflammatory & Metabolic**	**Iron**	**Lipids**	**Infection**	**Comorbidities & Mortality**
Siribamrungwong 2014[42]; ESRD/PD; Uncontrolled trial; Moderate	ns: Kt/V urea	↓ CRP ns: nPCR ↑ BUN ns: Alb	ns: Ferritin ns: TSAT	ns: TC		
Kocyigit 2014[43]; ESRD/PD; Uncontrolled trial; Moderate		↓ CRP ns: WBC, FPG, Serum Ca, Serum P, Alb	ns: TSAT ns: Hb	ns: TC ns: TG ns: LDL ns: HDL		
Chiu 2021[22]; ESRD/PD/HD; Retrospective cohort study; High					↓ ID	↓ ACM ↓ CAD ↓ CHF ↓ CbVD ↓ PAD ↓ Malignancy

All changes shown are statistically significant ($p<0.05$); BUN: blood urea nitrogen; CAD: coronary artery disease; CbVD: Cerebrovascular disease; CHF: Congestive heart failure; FPG: fasting plasma glucose; HD: hemodialysis; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; ID: Infectious disease; IL-1β: Interleukin-1 beta; IL6: Interleukin 6; NR: Not reported. PAD: Peripheral artery disease; TC: total cholesterol; TG: triglycerides; TNF-α: Tumor Necrosis Factor alpha; UACR: Urine albumin-to-creatinine ratio; PD: peritoneal dialysis; TSAT: transferrin saturation; Serum Ca: Serum Calcium; WBC: white blood cell count.

Detailed description of the evidence:

All of the SRs included for this KQ are of patients on ESRD which includes both HD and PD dialysis options (Table 4.2). One of the SRs[34] is of moderate quality and the others were of low quality[23,25,30]. None of the studies reported a subgroup analysis based on dialysis type. Therefore, there is no evidence from the SRs of an effect of NSPT on patients directly attributable to PD. In addition, the certainty of evidence was either very low/low for eGFR and creatinine outcomes[25], or not reported. The characteristics of the primary studies is given in Table 4.2. Three primary studies[22,42,43] were included for KQ4 (Table 4.4). Of these, one was a study[22] that includes both HD and PD, hence maps to both KQ3 and KQ4, and two uncontrolled trials of moderate quality recruited patients on PD and outcomes in those two studies can be ascribed to the CKD population undergoing PD. Specifically in this population,

Kidney Function:

Two of the SRs report on eGFR[23,25]. One of them show an increase[23] while the other shows no change[25]. Thus, the evidence available so far is insufficient for the eGFR outcome.

There is insufficient evidence for serum creatinine, which was reported only in one SR[25]. Weak evidence is seen for Alb outcomes, showing no change in both primary studies[42,43] with only patients receiving PD. No change was seen in Kt/v urea in one study[42].

Inflammatory markers, Nutritional and Lipid markers:

Similar to the other populations in KQ1-3, there is moderate evidence for a reduction in inflammation post-NSPT at 3 – 4 months in the primary studies[42,43]. All the four of the SRs[23,25,30,34] show a decrease in CRP as do two of the primary studies[42,43]. In both studies, CRP levels showed a significant decrease ranging between 32 - 42% at 3 - 4 months post-periodontal therapy. Two SRs[23,30] also show a decrease in IL-6 while the third[34] does not show a change. TNFα measured as an outcome in Yue et al.[34] does not show a difference between NSPT and control. Two studies[42,43] measured other inflammatory and iron markers like Ferritin, serum Albumin, Hb and Erythrocyte sedimentation rates. There is insufficient evidence for these markers. IN addition, we note insufficient evidence for serum albumin , serum calcium and serum phosphorous outcomes. Two studies[42,43]reported on serum albumin outcomes. Serum calcium and serum phosphorous measurements in one study[43] did not change post treatment. One or more Iron indices were measured in 4 studies - transferrin saturation (TSAT), serum iron and TIBC. Transferrin or transferrin saturation was reported in two studies[26,28,31,33,42–44]. Lipids tracked in 2 studies[33,42,43] showed no changes post-periodontal therapy.

Cardiovascular events:

Outcomes reported in the cohort study[22] relating to coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral artery disease and malignancy-related mortality are all evaluated in only one cohort study with a mix of patients on HD as well as PD.

Infectious Disease:

The cohort studies show consistent evidence of a lower risk of cardiovascular mortality and lower risk of infectious disease incidence in patients with CKD who are undergoing treatment for periodontitis or root canal treatments.

Table 4.2 Characteristics of SRs mapping to KQ4.

Author Year; # of studies; CKD stage; Dialysis; Periodontal condition;	**Locations; Quality of SR; Certainty of Evidence; Quality of primary studies**	**Outcome; follow-up duration**	**Results**	**Statistical heterogeneity**
Delbove 2021[23]; 18; 2-5; HD (n=9), PD (n=3), ND (n=4); Chronic; **CRP 3.2 – 49.3 mg/L**	Asia, South America, Europe, USA; Low; NR; Low - high	● eGFR (n=3)	● ↑ in 2/3 studies	NR (No meta-analysis)
		● CRP (n=11)	● ↓ in 9/11 studies	
		● IL6 (n=5)	● ↓ in 4/5 studies	
		● ACM (n=3)	● ↓ in 1/3 studies	
Zhao 2020[25]; 5; 2–5D; HD (n=2), PD (n=1), ND (n=2); Mild to chronic; **CRP 2.9 – 3.8 mg/L**	Asia, South America; Low; Very Low for eGFR, Cr; 3 moderate – high, 2 low	● eGFR (3–6 months)	● No change	>85% for Cr, eGFR. No meta-analysis performed for the other outcomes.
		● Cr (4 – 6 months)	● No change	
		● BUN (n=3) (2–4 months)	● ↑	
		● CRP (n=3)	● ↓ in all studies	
		● IL6 (n=1)	● ↓	
		● TNF-α (n=1);	● No change	
Yue 2020[34]; 5; 5D; HD, PD; NR; **CRP 3.0 mg/L** & **NR**	Asia, USA; Moderate; NR; Moderate	● CRP (1 – 2 months)	● SMD: − 1.53, 95% CI [− 2.95 to − 0.11], p < 0.05	>90%
		● IL6, TNF-α, Alb, Lipids (3 – 6 months)	● insufficient evidence	
Lai@ 2020[30]; 6; 3-5D; HD (n=3), PD (n=2), ND (n=1); NR; **CRP 3.0 – 4.7 mg/L**	Asia, USA; Low; NR; 2 high, 4 unknown	● CRP (1–3 months)	● MD=-0.58, 95% CI [-1.13, -0.02] , p = 0.04	> 90%
		● IL-6 (1 – 3 months)	● MD=-2.76, 95%CI [-5.15, -0.37], p = 0.02	
		● TNF-α (1 – 3 months)	● No significant change	
		● Alb, Cr, IL6	● insufficient evidence	

ACM: all-cause mortality; Alb: Albumin; BUN: blood urea nitrogen; CAD: coronary artery disease; CbVD: Cerebrovascular disease; CHF: Congestive heart failure; Cr: Creatinine; FPG: fasting plasma glucose; HD: hemodialysis; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; ID: Infectious disease; IL-1β: Interleukin-1 beta; IL6: Interleukin 6; MD: mean difference; NR: Not reported. PAD: Peripheral artery disease; TC: total cholesterol; TG: triglycerides; SMD: standardized mean difference; TNF-α: Tumor Necrosis Factor

alpha; UACR: Urine albumin-to-creatinine ratio; PD: peritoneal dialysis; TSAT: transferrin saturation; Serum Ca: Serum Calcium; WBC: white blood cell count.

Table 4.3: Characteristics of primary studies mapping to KQ4

Category	KQ4
Study design	Non-randomized/randomized controlled observational trial (1/1) Observational study (1)
Study countries	Thailand, Turkey, Taiwan
CKD stage	ESRD
Periodontitis severity	Moderate severe (n=1), not applicable (n=1)
Dialysis type	PD:2; HD/PD: 1
Number of subjects (per study)	75 (32, 43) 12454
Follow-up time (range): Interventional studies Cohort studies	 16 weeks – 3 months 16 years
Intervention	Root canal therapy (n=1), NSPT (n=1)
Comparator	No treatment
Outcomes (broad categories)	Inflammatory factors, lipids, iron indices, metabolites, cardiovascular outcomes, Infectious diseases, Cerebrovascular disease, Malignancy, Other outcomes

Table 4.4: Details of primary studies mapping to KQ4

Author, Year; Country Funding; Source; CKD Stage; Dialysis; Quality	Design; Total N; Time to follow-up	Dental Service	Outcome	Outcome		Statistically Significant Findings for patients receiving periodontal therapy
				Treatment Group	Control Group	
Siribamrungwong, 2014[42]; Thailand; None Reported; 5/PD; Moderate; **CRP: 2.93mg/L**	Single Arm; 32; 4 months	*Treatment:* SRP; OHI *Control:* pre-treatment	*Average percent change relative to Baseline*			• CRP lower (P = 0.02) • BUN higher (P = 0.001) • Risk of Bias: Medium
			CRP	-32.6*	No control group	
			Ferritin	-24.1		
			BUN	8.6		
			Alb	1.8		
			TC	-3.4		
			TSAT	6.7		
			Kt/V urea	1.1		
			nPCR	-18.7		
Kocyigit 2014[43]; Turkey; None Reported; 5; PD; Moderate; **CRP: 10.2 (3.2–49.3) mg/L**	Single Arm; 43 (data shown for the 9 severe	*Treatment:* SRP; OHI; antibacterial rinse; necessary tooth extractions;	*Average percent change relative to Baseline*			• CRP decreased in patients with either slightly-to-moderate (n = 12, p = 0.014) or severe periodontitis (n = 9, p = 0.001) and receiving periodontal therapy.
			CRP	-41.6*		
			WBC count (mm^3)	-17.3	No control group	
			Hb	-1.6		
			FPG	18.6		

	periodontitis cases); 3 months	referrals for other treatments *Control:* pre-treatment	TC	0.0		
			TG	-14.7		
			LDL	10.1		
			HDL	-13.5		
			Serum Ca	-3.3		
			Serum P	-18.4		
			Serum Alb	-3.0		
			TSAT	0.0		
Chiu 2021[22]; Taiwan; Federal; CKD stage 5/HD & PD; NA; High; **CRP: NR**	RCS 12454; 2633 received treatment 16 years	*Treatment: R*oot canal therapy *Control:* no treatment	*% patients with event (age, sex, monthly income, and dialysis type and comorbidities)*			• No greater risk of developing infective endocarditis for patients on HD
			Cause of death	Root Canal treatment	No root canal treatment	
			ACM	22.79%	34.93%	
			CAD	13.83%	17.46%	
			ID	34.83%	45.54%	
			CbVD	16.17%	11.28%	
			Malignancy	12.00%	9.65%	
			Other	23.17%	16.06%	

*p<0.05; **p < 0.01; ***p < 0.001

ACM: all-cause mortality; Alb: Albumin; BUN: blood urea nitrogen; CAD: coronary artery disease; CbVD: Cerebrovascular disease; CHF: Congestive heart failure; Cr: Creatinine; FPG: fasting plasma glucose; HD: hemodialysis; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; Hb: Hemoglobin; HDL: High density lipoprotein; ID: Infectious disease; IL-1β: Interleukin-1 beta; IL6: Interleukin 6; Kt/V urea: measure of dialysis treatment; LDL: Low density lipoprotein; MD: mean difference; NR: Not reported. PAD: Peripheral artery disease; SMD: standardized mean difference; TC: total cholesterol; TG: triglycerides; TNF-α: Tumor Necrosis Factor alpha; TSAT: Transferrin saturation; UACR: Urine albumin-to-creatinine ratio; PD: peritoneal dialysis; TSAT: transferrin saturation; Serum Ca: Serum Calcium; WBC: white blood cell count:

Key Question 5:

Are there any dental services considered a standard of care for the management of persons with stage 4 and 5 CKD?

Key points:

There is little mention of guidelines for dental services for patients with CKD (any stage).

Practice Guidelines (KQ5):

We conducted a search of articles relevant to clinical practice guidelines for dental services for patients with CKD in response to KQ5.

Our searches yielded 6 articles of which 3 contained recommendations for clinical practice guidelines for dental services for patients with CKD or articles pertinent to this topic (Appendix A2). The other three articles describe a survey administered to heads of dental programs across the USA, querying them on the protocols defined in their institutions for dental treatment of patients with CKD.

Importantly, the practice guidelines from KDIGO for CKD, the NICE guideline for CKD and the European Renal Best Practice Group make no mention of dental care guidelines for patients with CKD of any stage[19,45,46].

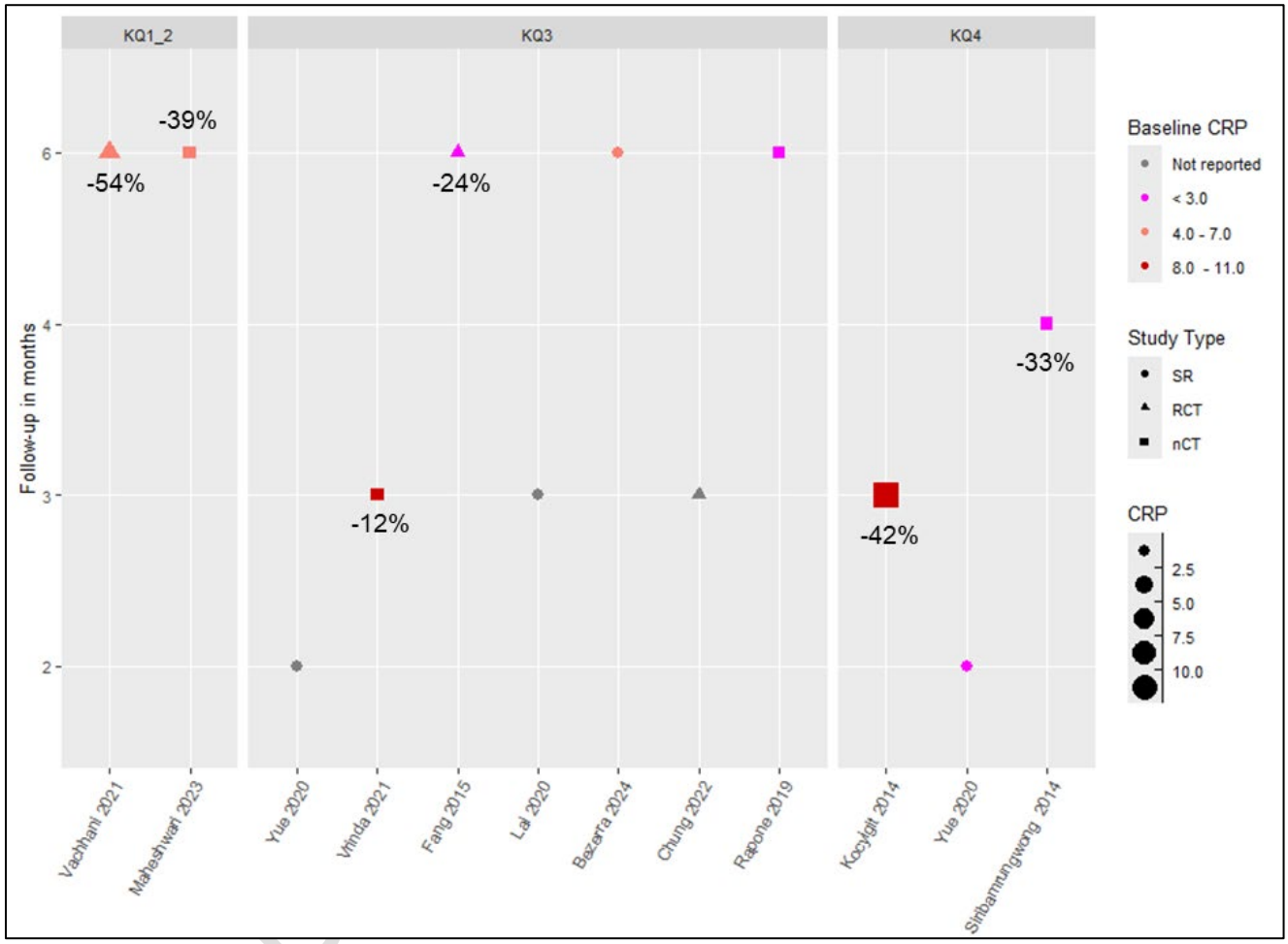
Howell et al conducted a series of surveys to collect information from directors of Advanced Education in General Dentistry (AEGD)[47], directors of nephrology fellowships[48] as well as deans of undergraduate dental programs[49] to determine the current protocol for renal patients in dental schools, specifically in the use of antibiotic prophylactics. Among AEGD directors and directors of nephrology fellowships, only 34% reported having an established protocol for treating ESRD, of which 65-70% of the programs reported following guidelines recommended by the AHA (American Heart Association). And among deans of dental programs, ~52% reported to not have an established protocol, and 54 - 62% of the programs that did have a protocol followed the AHA protocol or a modified protocol for prophylactic antibiotics. There is thus a lack of consistent, established protocols for prophylactic antibiotics during the treatment of dental conditions in patients with CKD.

Table 5: Clinical practice guidelines for patients with CKD

Year of publication	Title	Type of article	Recommendations regarding dental care strategy
2024	KDIGO (Kidney Disease: Improving Global Outcomes) 2024 Clinical practice guideline for the evaluation and management of CKD[19]	Guideline	None mentioned
2021	CKD: assessment and management[45]	NICE guideline	None mentioned
2017	Clinical Practice Guideline on management of older patients with CKD stage 3b or higher (eGFR<45 mL/min/1.73 m2): a summary document from the European Renal Best Practice Group[46]	Guideline	No recommendations regarding dental care.
Howell S, 2016	Protocols for treating patients with end-stage renal disease: a survey of AEGD/GPR dental residencies[47].	Survey	Consistent established protocols need to be developed for the safe treatment of dental conditions in patients with CKD.
Howell 2017	Protocols for treating patients with end-stage renal disease: a survey of nephrology fellowships[48].	Survey	Updated and evidence-based guidelines should be developed for the safe treatment of dental conditions in patients with ESRD.
Howell 2016	Protocols for treating patients with end-stage renal disease: a survey of dental programs[49].	Survey	Updated and evidence-based guidelines should be developed for the use of antibiotic prophylaxis treatment of dental conditions in patients with ESRD.

Summary of Outcomes:

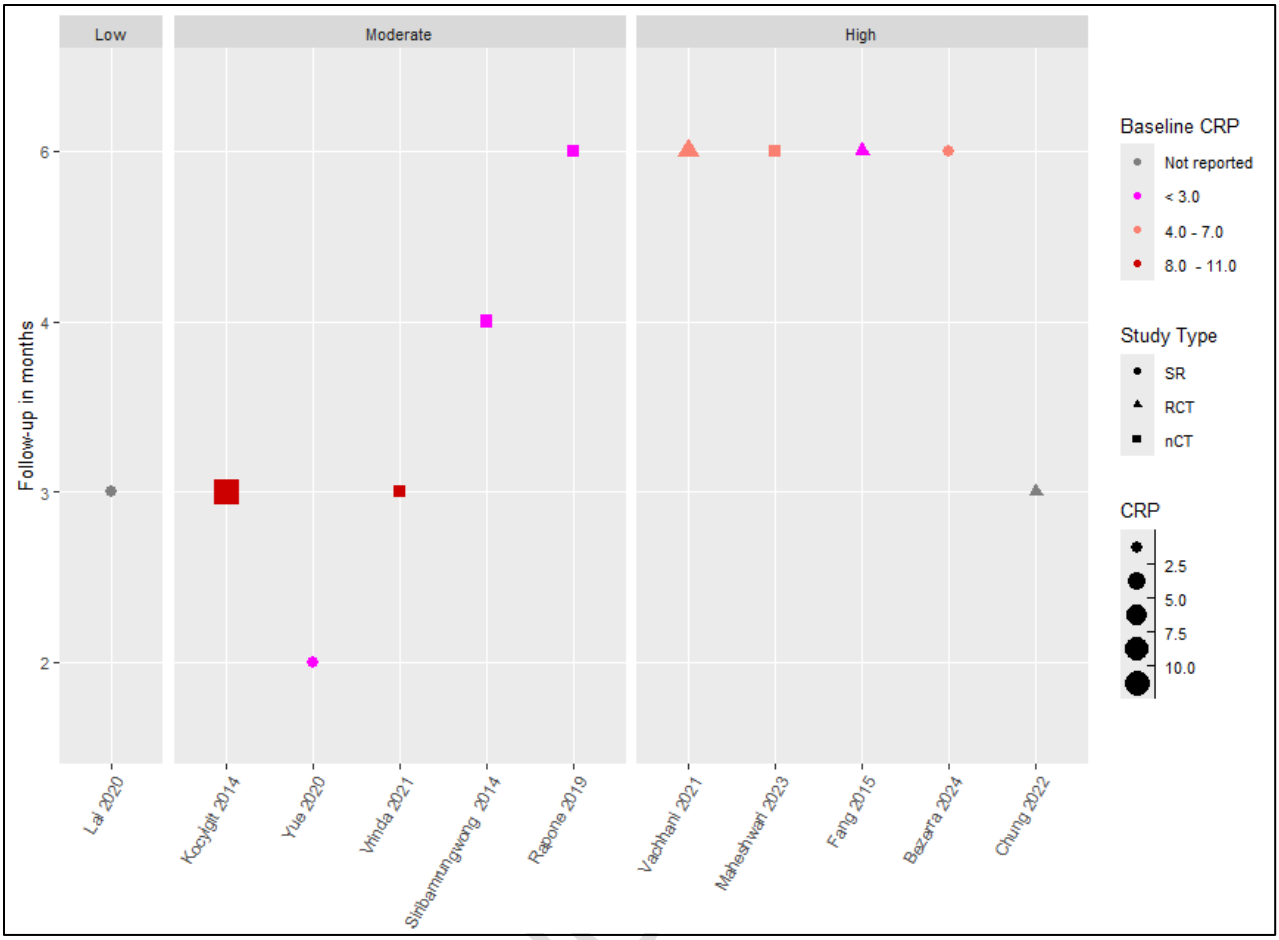
Given below is a summary of outcomes in table format and separated by the key questions. Overall, most of the studies/meta-analyses show statistically significant reductions in CRP in as little as 2 months (Figure 6.1), and that most of the studies show a follow-up time of 6 months. There is no



CRP: c-reactive protein: SR: systematic reviews; RCT: randomized clinical trial; nCT: non-controlled clinical trial;

Figures 6.1: Improvement in HbA1c characterized by study type. Each data point is sized according to the magnitude of the reduction in CRP. The shapes of each data point indicates whether it is an SR, RCT or nCT and the color indicates the range of the baseline CRP value in mg/dL.

evidence available for longer follow-up times. The SRs have a combination of non-dialysis (KQ2), hemodialysis (KQ3) and peritoneal dialysis (KQ4). Sub-study meta-analyses have not been reported in any of the SRs for dialysis status. The reduction in CRP varies between 0.5 – 10.9 mg/L across SRs and primary studies, amounting to a percent reduction of 12% – 54% in the primary studies. Figure 6.2 shows the evidence from RCTs as well as nCTs showing similar behavior of CRP across differing study qualities.



CRP: c-reactive protein: SR: systematic reviews; RCT: randomized clinical trial; nCT: non-controlled clinical trial;

Figures 6.2: Improvement in HbA1c characterized by study type. Each data point is sized according to the magnitude of the reduction in CRP. The shapes of each data point indicates whether it is an SR, RCT or nCT and the color indicates the range of the baseline CRP value in mg/dL.

Table 6. Summary of outcomes in the evidence base mapped to the key questions

Key Question	Overall Evidence
KQ1: What is the effectiveness of dental services in improving health outcomes in persons with stage 4 CKD? KQ2: What is the effectiveness of dental services in improving treatment outcomes in people when provided prior to	<u>Evidence from 4 systematic reviews (all low quality) and 2 high quality primary studies (1 RCT and 1 non-controlled trial) including all CKD stages 1-5.</u> • There is no evidence available for the impact of dental services on health outcomes for persons specifically with stage 4 CKD alone. • Kidney function: In patients with CKD (stages unknown) but not on dialysis, there is weak evidence of an improvement in eGFR (3 low quality SRs[23–25] and 1 high quality RCT[26]), but insufficient evidence for improved creatinine and UACR

placement of hemodialysis access? More details are in Table 2.1 – 2.4. Note: all described changes are statistically significant ($p < 0.05$) post-dental treatment relative to controls or to baseline status (in the case of studies with no control group).	outcomes post-NSPT (1 low quality SR[25] and 1 high quality RCT[26]). • Inflammation: o There is moderate evidence that NSPT results in lowering of CRP (4 low quality SRs, and 2 high quality primary studies). CRP was reported to be reduced in all reviews and primary studies where the outcome was reported. o There is weak evidence of lowering of IL6 after NSPT in all reviews/primary studies reporting on this outcome (3 low quality SRs[23,25,27]). o There is insufficient evidence for reduction of IL1β (1 high quality single-arm study[28]), and for TNFα outcomes post-NSPT (1 low quality SR[27]).
KQ 3: What is the effectiveness of dental services in improving treatment outcomes in people on hemodialysis for end-stage renal disease? More details in Table 3.1 – 3.4. Note: all described changes are statistically significant ($p < 0.05$)	<u>Evidence from 6 SRs (1 of high quality, 1 of moderate quality and 4 of low quality) and 11 primary studies (9 high quality, 2 moderate quality)</u> • <u>Kidney Function:</u> There is insufficient evidence for improved kidney function outcomes due to conflicting results across the literature where one SR[23] reported an increase in eGFR while the other[25] did not report a significant difference post-NSPT. • There is insufficient evidence for no effect in serum creatinine due to inconsistent results from one low quality SR[25] and two moderate quality single arm studies[31,32] showing no change, and one high quality RCT[33] showing an increase. • <u>Inflammatory outcomes</u>: o There is moderate evidence that NSPT results in a reduction of CRP levels observed consistently across all included systematic reviews[23,25,27,29,30,34] (one high quality[29], one moderate[34] and four low quality) and 2[31,33] out of 3[31–33] primary studies of moderate to high quality. o There is weak evidence that IL6 levels are reduced after NSPT (in 3 out of 4 low quality SRs[23,27,30] and one high quality RCT[33]) in patients receiving hemodialysis. o There is insufficient evidence for no effect on TNF-α in 2 low quality SRs[27,34] and 1 high quality primary study[33]. • <u>Lipid outcomes</u>: There is insufficient evidence of no effect on lipid outcomes post-NSPT in patients on hemodialysis (1 high quality RCT).

	• Cardiovascular Outcomes: There is insufficient evidence (2 prospective[35,36] and 2 retrospective[22,37] cohort studies, all high quality) that cardiovascular disease, cardiovascular events, strokes, congestive heart failure, sudden cardiac death and acute myocardial infarction are reduced post-NSPT. • Mortality outcomes: There is weak evidence from 1 low quality SR and 6 high quality primary studies (1 RCT, 3 prospective and two retrospective cohort studies) that there is a favorable outcome for all-cause mortality after NSPT. There is insufficient evidence for cardiovascular (high quality cohort study[35]), malignancy-associated and other cause-mortality (high quality cohort study[22]). • Infection outcomes: There is weak evidence[22,38–40] of no effect that infectious disease outcomes are lower in patients with CKD on hemodialysis post-NSPT or post-endodontic therapy (1 high quality RCT[38] and 3 high quality cohort studies[22,39,40]). • Other outcomes: There is insufficient evidence for lower rates of bacteremia, pneumonia, osteomyelitis, brain abscess, renal and perinephric abscess outcomes in patients who underwent NSPT (1 high quality cohort study[39]).
KQ 4: What is the effectiveness of dental services before and during peritoneal dialysis for end-stage renal disease? Details in Table 6C. Note: all described changes are statistically significant ($p < 0.05$)	Evidence for this key question was drawn from 4 SRs (1 moderate and 3 low quality) and 3 primary studies (2 high quality, one moderate quality). **Kidney Function**: There is insufficient evidence for kidney function outcomes post NSPT (2 SRs[23,25] of low or very low quality, 2 primary studies[42,43] of moderate quality). There is insufficient evidence for no effect for serum calcium and serum phosphorus (1 moderate quality[43] single arm trial) **Inflammatory markers**: There is moderate evidence that CRP is reduced post-NSPT consistently and statistically significantly in all of the systematic reviews[23,25,30,34] (low to very low quality) as well as in the two moderate quality primary studies[42,43] where it was measured. There is weak evidence for a reduction in IL6 levels (in 2 low quality SRs[23,30] out of the 3 SRs[23,30,34]) post-NSPT. We find insufficient evidence for no change in TNFα (one moderate quality[34] SR) post-NSPT.

	Nutrition-related markers: There is weak evidence of no effect for serum albumin outcomes (1 moderate quality SR[34], 2 moderate quality[42,43] single arm trials). **Lipid markers**: There is weak evidence for no effect after NSPT (2 moderate quality[42,43] single arm trials) **Cardiovascular Outcomes:** There is insufficient evidence for benefit to patients regarding cardiovascular outcomes including coronary artery disease, congestive heart failure, peripheral arterial disease and malignancies(one high quality retrospective cohort study[22]). **All-cause mortality**: Insufficient and inconsistent evidence is available for this outcome drawn from one low quality SR[23] and one high quality primary study (retrospective cohort study[22]). Both these articles include a mix of patients receiving HD and PD. **Infections**: There is insufficient evidence for a reduction in infectious diseases (one high quality retrospective cohort study[22])
Are there any dental services considered a standard of care for the management of persons with stage 4 and 5 CKD?	There is little mention of guidelines for dental services for patients with CKD (any stage). • KDIGO 2024 Clinical practice guideline for the evaluation and management of CKD makes no mention of dental care guidelines for patients with CKD. • The European Renal Best Practice group does not make a mention of dental care guidelines for patients with CKD. • The NICE guideline for CKD assessment and management does not make a mention of dental care guidelines for patients with CKD. • Similarly, there are no guidelines from dental organizations like the ADA about treatment for patients with CKD.

Discussion:

The evidence base used in this rapid review reported on kidney function, inflammatory, nutritional and lipid markers, mortality outcomes, cardiovascular-related outcomes and other outcomes. The clinical trials reported on molecular outcomes while the cohort studies reported on mortality, co-morbidity-related and infection-related outcomes. The systematic reviews frequently reported on kidney function, inflammation and related outcomes and less frequently on mortality-related outcomes.

Regarding evaluation of the effect of periodontal treatment on kidney function in patients with CKD, there is insufficient evidence to make a definitive conclusion about the impact of dental treatment. Evidence was sparse for eGFR, with only a handful of studies and/or SRs reporting them. The outcomes relating to kidney function like eGFR may be mainly relevant in the non-dialysis population (KQ1,2) where is weak evidence of improvement of eGFR. Other outcomes relating to kidney function

had insufficient evidence regarding the impact of NSPT in the 3 – 6 month time frame. Randomized clinical trials are few and far between and their design does not include patient population by stage or periodontitis severity. Subgroup analyses are lacking as well, precluding the ability to definitively reach conclusions about the evidence.

From the outcomes reported in the studies as well as in the meta-analyses, CRP was the outcome most commonly reported, showing a consistent decrease at 3-6 months after periodontal therapy regardless of study design or patient population (non-dialysis or dialysis, a range of periodontitis severity). This is a finding that is relevant to CKD since CRP is an established marker for inflammation and systemic inflammation has a deleterious effect on CKD, and. The association between CKD and periodontal disease has been reported in several studies and it has been hypothesized that the advent of periodontitis releases numerous inflammatory cytokines resulting in elevation of C-reactive protein systemically[25,50] Three other inflammatory markers that were also reported in one or more of the included studies were IL6, IL1β and TNFα. Of these, IL6 showed statistically significant reductions in a majority of the studies where it was reported. Less often, TNFα and IL1β outcomes were reported. TNFα levels did not change after the intervention of periodontal treatment in two of the three SRs where it was reported. In the SR where TNFa did show a reduction, four of the five component studies were of pre-dialysis patients, whereas in the two SRs that did not show an effect, a majority of the studies were of patients receiving HD or PD. There is weak evidence, therefore that TNFa levels may be impacted in pre-dialysis patients. These data point to a set of inflammatory markers, the chief among them being CRP, that show reduced levels up to 6 months after periodontal treatment. This reduction could signify an improvement in inflammatory status in the patients, most of whom are on dialysis treatment. In the primary studies, median reductions in CRP was ~33.5%. While there is no defined minimally important difference for CRP in CKD, the reductions reported in these studies are substantial.

Evidence regarding mortality, other co-morbidity outcomes and infection outcomes was also available in one SR and 6 retrospective or prospective cohort studies[22,35–37,39–41] with follow up times more than one year. The cardiovascular-related outcomes show a reduction for the NSPT group overall, as do many of the infection-related outcomes. The cohort studies are all high quality with thousands of patients followed for 2 – 16 years and conducted in Asia, Europe and South America. Additional cohort studies of the US population may strengthen the evidence directly applicable to the US population. One important safety outcome to note is that two cohort studies[37,40] reporting on infective endocarditis showed either a statistically lower[37] or similar[40] risk of infective endocarditis post-periodontal treatment for patients receiving dialysis, addressing concerns that periodontal treatment could make patients with CKD stage 5D vulnerable to the infection.

Strengths of the Studies: The strength of these studies lies in the consistent finding across multiple SRs, RCTs, and observational studies that dental treatment can significantly lower inflammation, a key indicator of CKD status. The inclusion of diverse populations from different countries also adds to the generalizability of the findings, suggesting that the benefits of periodontal or endodontic therapy for may apply broadly across various demographic groups.

Limitations in the Evidence Base: The evidence base has a few limitations. The studies in the systematic reviews are a mix of patients in various stages of CKD including non-dialysis, HD and PD. As a result, the outcomes reported represent a heterogeneous patient population. Similarly, the patients

in the studies have varying degrees of periodontitis severity, ranging from low to moderate to severe to chronic periodontitis. It should also be noted that the meta-analyses that were performed in 1 SR[24] had 0% heterogeneity, while for the other 3 SRs[25,30,34], >85% was reported. The other 2 SRs[23,27] did not perform a meta-analysis. Similarly, among the 15 primary studies, there are 3 RCTs[26,33,38] of high quality, 1[28] high quality non-randomized controlled trial, 4[31,32,42,43] moderate quality single arm trials, 3[35,36,41] high quality prospective cohort studies, 3[22,37,39] high quality retrospective cohort studies and 1[40] high quality cohort case-control study. As a result, the quality of the evidence may likely be influenced by the heterogeneity in the population, the severity of the dental condition and the study design. Patients who develop ESRD and undergo HD are also prone to a decline in nutritional parameters[51]. However, in the studies included, nutritional outcomes were rarely reported.

Another limitation is regarding the follow-up time in the included studies - none of the clinical trials included in this review followed the patients for more than 6 months, which may not be sufficient to see a lasting change in kidney function. Another gap worth pointing out is that none of the recent trials have been conducted in the USA, and none of the cohort studies were conducted in the USA. While the studies were conducted in different countries and reflect overall generalizability, it is not clear to what extent these evidences are generalizable to the US population.

Sub-group analysis of patients with CKD with risk factors like smoking status, obesity, diabetes and poor nutrition (see Figure 1), and other factors like age, gender and types of oral disease might offer more evidence on the magnitude of impact on outcomes after periodontal and other dental treatments.

Summary: Notwithstanding the gaps noted above or the heterogeneity in the studies, the patient population or periodontitis severity, there is consistent evidence showing a reduction in inflammation post-periodontal treatment in patients with CKD. The evidence for mortality and cardiovascular outcomes also offer evidence (although weak) that these outcomes may be favorable to patients with CKD in the medium term.
The Centers for Disease Control recommends oral health maintenance for patients with diabetes[52]. CKD is common in people with type 1 and type 2 diabetes. Approximately 1 in 2 adults with CKD has Diabetes[53]. Persons with CKD are also more susceptible to infections[54]. Therefore, the impact of dental treatment on diabetes outcomes for patients with diabetes may also apply to a large section of patients with CKD. We refer the reader to our rapid review on similar questions regarding persons with Diabetes.
Most of the evidence base has been from studies conducted outside of the United States in the last ten years, and the number of new studies globally each year is less than a handful as seen in the clinical trials database maintained at the National Library of Medicine[55]. It is therefore unlikely that the evidence base will change substantially over the next few years.

This rapid response has presented the available evidence regarding the impact of periodontal or other dental services to patients with CKD. The current evidence base has some limitations but points to the fact that periodontal service to patients with CKD and particularly those on dialysis may be beneficial for some clinically relevant outcomes.

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Appendix A1: Literature Search Strategy

	Source:	Ovid MEDLINE® ALL 1946 to June 04, 2024	
	#	search string	# results
CKD terms	1	exp *renal insufficiency, chronic/ or *diabetic nephropathies/ or *kidney transplantation/ or exp *renal dialysis/	266155
	2	((chronic kidney or chronic renal) adj3 (disease* or fail* or replace* or end stage or dysfunction* or insufficien*)).ti,ab.	109054
	3	(end stage renal or end stage kidney or kidney failure or renal failure or ESRD or diabetic nephropath* or diabetic kidney or kidney dysfunction* or renal dysfunction*).ti,ab.	192059
	4	(h?emodialysis or h?emodiafiltration or ((kidney or renal or peritoneal) adj3 dialysis)).ti,ab.	119669
	5	kidney transplant*.ti,ab.	52268
	6	**1 or 2 or 3 or 4 or 5**	**449854**
Dental terms	7	exp *dental health services/ or *oral health/ or *preventive dentistry/ or exp *oral hygiene/ or exp *dental prophylaxis/ or exp *periodontics/ or *pulpitis/ or *candidiasis, oral/ or exp *stomatitis/ or exp *xerostomia/ or exp *periodontal diseases/ or exp *dental caries/ or exp *mouth, edentulous/	197420
	8	(dental or dentistry or periodont* or gingivitis or (gum adj3 disease*) or tooth loss or number of teeth or shortened dental arch or functional dentition or edentul* or missing teeth or missing tooth or prosthodonti* or ((dental or tooth or teeth or root or periapical) adj3 (cavit* or caries or carious or decay* or lesion*)) or oral health or oral disease* or DMF index or DMFT or DMFS).ti,ab.	406317
	9	(((endodontic or periapical or periodontal or gingival or tooth or teeth or mouth or oral or pulpal) adj3 (abscess* or infection*)) or pulpitis or oral candidiasis or stomatitis or xerostomia).ti,ab.	39435
	10	**7 or 8 or 9**	**507012**
Various exclusion filters	11	6 and 10	1891
	12	limit 11 to yr="2016 -Current"	725
	13	12 and (Dental Care for Children/ or exp Pregnancy/ or Pregnant Women/ or exp Child/ or exp Infant/ or Adolescent/)	72

	14	12 not 13	653
	15	limit 14 to (address or autobiography or bibliography or biography or case reports or classical article or clinical trial, veterinary or comment or congress or dataset or dictionary or directory or duplicate publication or editorial or electronic supplementary materials or "expression of concern" or festschrift or historical article or interactive tutorial or interview or introductory journal article or lecture or legal case or legislation or letter or news or newspaper article or observational study, veterinary or periodical index or personal narrative or portrait or randomized controlled trial, veterinary or retracted publication or "retraction of publication" or technical report or video-audio media or webcast)	97
	16	14 not 15	556
	17	limit 16 to animals	29
	18	16 and (exp in vitro techniques/ or exp drug evaluation, preclinical/ or exp models, animal/ or veterinary medicine/ or Clinical Trials, Veterinary as Topic/ or Observational Studies, Veterinary as Topic/ or exp animal experimentation/)	13
	19	16 and (animal model* or companion animal* or service animal* or disease model* or veterinar* or mouse or mice or rat or rats or rodent or rodents or swine or pig or pigs or rabbit or rabbits or murine or porcine or cat or cats or dog or dogs or feline or canine or monkey or monkeys or primate or primates or cow or cows or cattle or bovine or veterinar* or animal stud*).ti,ab.	27
	20	17 or 18 or 19	**41**
	21	**16 not 20**	**515**

Appendix A2: Systematic Reviews

Author; Year; # of studies; CKD stage; Periodontal condition	**Included locations; Quality of SR; Certainty of Evidence; Quality of primary studies**	**Outcome; follow-up duration**	**Results**	**Statistical heterogeneity**
Bezerra 2024[29]; 7; 5D; HD (n=7); Mild – severe;	Asia, South America, USA; High; Low; Moderate-high	CRP (n=5); 6wks – 6 months	SMD: 0.45 (95%CI [-0.25, -0.65], p 0.001)	0.0%
Delbove 2021[23]; 18; 2-5; HD (n=9), PD (n=3), none (n=4); Chronic;	South America, Africa; Low; NR; High	● eGFR (n=3) ● CRP (n=11) ● IL6 (n=5) ● All-cause mortality (n=3)	● Increase in 2/3 studies ● Decrease in 9/11 studies ● Decrease in 4/5 studies ● Decrease in 1/3 studies	Not reported
da Silva 2021[24]; 3; 3-5; Moderate - severe	South America, Africa	● eGFR (n=3); 3 – 6months	MD: 7.01	0%
Zhao 2020[25]; 5; 2–5D; Mild to chronic; Low	Asia, South America	● eGFR (n=2) ● BUN (n=3) ● Cr (n=1) ● CRP (n=3) ● IL6 (n=1) ● TNF-a (n=1); 8 weeks – 6 months	● Increase in 2 studies ● Increase in 3 studies ● No difference ● Decrease in 3 studies ● Decrease No change	>85% for Cr, eGFR
Deschamps-Lenhardt 2019[27]; 6; 1-5;	Asia, Europe, South America	● eGFR (n=2) ● Cr (n=1) ● CRP (n=2) ● IL6 (n=2) ● TNF-a, Ferritin	● Increased in 1/2 studies ● Decreased in 1/1 study ● Decreased 2/2 studies ● Decreased 2/2 studies ● Decreased in 1/1 study	NR (no meta-analysis)

Moderate – chronic; Low		(n=1) ● BUN, Tf (n=1) ● Metabolic markers; ● 6wks - 6 months	● Decreased in 1/1 study No change in Lipids, inconsistent changes in Alb	
Yue 2020[34]; 5; 5D	Asia, USA	● Inflammatory markers ● metabolic markers; ● 6 wks – 6 months	● CRP decreased ● IL6: No change ● TNF-a: No change ● Alb: No change	>90%
Lai@ 2020[30]; 6; 3-5D	Asia, USA	● CRP ● IL-6 ● TNF-a; ● 1 – 3 months	● Decreased ● Decreased ● No change	> 90%

Appendix A3: Primary Studies

Author Year; Country; Funding Source; CKD Stage; Periodontitis severity; RoB/NOS/ROBINS	Design Total N Time to follow-up	Dental Service	Outcome	Outcome in Dental Care Group	Outcome in Control Group	Key Significant Findings for patients receiving periodontal therapy
Vachhani 2021[26] India None Reported 3–5 (non-dialysis) Low (RoB)	RCT 80 6 months	*Treatment:* NSPT + OHI *Control*: OHI	*Average percent change relative to Baseline*			• CRP decreased (p < 0.001) • eGFR increased (p < 0.001) • UACR increased (p < 0.001) Risk of Bias: Low
			CRP	-54.0	41.5	
			eGFR	41.1	-16.8	
			UACR	-25.1	14.3	
Maheshwari 2023[28] India Federal 3-4 Low (RoB)	non-randomized controlled trial 50 6 months	*Treatment:* NSPT + OHI *Control*: none	*Average percent change relative to Baseline*			• CRP lower in treated group (p < 0.001) • IL-1b lower in treated group (p = 0.03) • No significant changes in creatinine, Alb, UPCR and ACR Risk of Bias: Low
			CRP	-39.0	38.0	
			IL-1β	-15.6	15.5	
			Cr	-2.7	-0.2	
			Alb	0.9	0.7	
			UPCR	-12.8	-0.5	
			UACR	2.2	0.1	
Vrinda, 2021[31]; India;	Comparative Trial	*Treatment*: SRP	*Average %change relative to baseline*		*No control group*	• CRP lower in patients on <1y HD at 3m after NSPT (P = 0.04)

None Reported; CKD stage 5/HD; Chronic; Medium (ROBINS)	20 (HD < 1 year) 3 months	*Control*: pre-treatment	CRP	-12.2		● Improvement in several iron indices (Ferritin, TIBC, TSAT) in patients in both groups ● No changes in eGFR in either group ● Risk of Bias: Medium
			Ferritin	9.1		
			Alb	1.5		
			Iron	21.5		
			TIBC	11.5		
			TSAT	9.2		
			Cr	-2.9		
	20 (HD > 1 year) 3 months		CRP	-8.8	*No control group*	
			Ferritin	9.8		
			Alb	-1.7		
			Iron	0.6		
			TIBC	-1.4		
			TSAT	2.0		
			Cr	22.1		
Fang, 2015[33]; China; Province; CKD stage 5/HD; Chronic; Low (RoB)	Randomized Parallel Control Trial 97 6 months	*Treatment:* SRP; OHI; supragingival prophylaxis at 3m post-treatment *Control:* no treatment	*Average percent change relative to Baseline*			● CRP lower (p < 0.001) ● IL6 lower (p = 0.001) ● Ferritin lower (p = 0.002) ● Alb higher (p = 0.002) ● Creatinine higher (p = 0.002) ● BUN higher (p = 0.001) ● Tf higher (p < 0.001) ● No changes in lipids in either group ● Overall Risk of Bias: Low
			CRP	-23.8	6.6	
			TNF-α	-4.9	3.1	
			IL-6	-21.4	5.1	
			Ferritin	-20.8	-1.8	
			Alb	3.7	0.3	
			Cr	14.9	0.4	
			BUN	7.1	1.7	

			ALC	2.4	-0.6	
			Tf	7.7	1.2	
			nPCR	1.9	1.9	
			TC	-1.1	-1.5	
			TG	-3.7	-3.7	
			HDL	1.5	-2.9	
			LDL	-4.8	-3.9	
Chung, 2022[38]; Taiwan; Academic; CKD stage 5/HD; Moderate-Severe; Low (RoB)	Randomized controlled trial 14 3 months	*Treatment:* NSPT; Amoxicillin prophylaxis ; OHI *Control:* OHI	All-cause mortality; n (%)	0 (0%)	2 (29%)	• No differences observed in primary outcomes. • Overall Risk of Bias: Low
			CV events; n (%)	0 (0%)	1 (14%)	
			Infections; n (%)	3 (43%)	2 (29%)	
			HbA1c	no change	no change	
Rapone 2019[32]; Italy; None Reported; CKD stage 5/HD; NR; Medium (ROBINS)	Single Arm Trial 66 6 months	*Treatment:* SRP *Control: pre-treatment*	*Average percent change relative to Baseline*			• ALB decreased ($p < 0.001$) • Serum creatinine increased ($p = 0.002$) • No significant changes in CRP • Risk of Bias: Medium
			Serum Alb	-6.0	No control group	
			Serum Cr	50.0		
			CRP	3.1		
Santos-Paul, 2019[36]; Brazil; None Reported; CKD stage 5/ HD; Moderate-Severe; Good (NOS)	PCS with historical control 409 2 years	*Treatment:* NSPT; OHI *Control:* no treatment	*Survival Log-rank Test*			• Lower rates of CV events • Lower rates of CV-related mortality in patients receiving NSPT
			Survival free of major CV event	94% (0.009)	83%	
			Survival free of coronary event	97% (0.009)	89%	
			Survival free of CVD	96% (0.037)	87%	
			All-cause mortality	No difference		
Huang, 2018[37]; Taiwan; Federal, Academia, Foundation, Consortia;	RCS 7226 5 – 7 years	*Treatment*: SRP; flap surgery	*Adjusted Hazard Ratio (95% CI); adjusted for age, gender, urbanization level, monthly income, Charlson comorbidity index, comorbidities, and medications*			• Lower risk of mortality Lower risk of development of CVD and CVD-related events
			CVD	0.75 (0.69, 0.81)		

CKD stage 5/HD; NR; Good (NOS)		*Control*: no treatment	ACS	0.85 (0.74, 0.99)	
			AMI	0.72 (0.58, 0.89)	
			Stroke	0.67 (0.60, 0.76)	
			Ischemic stroke	0.78 (0.68, 0.90)	
			Hemorrhagic stroke	0.47 (0.37, 0.59)	
			CHF	0.83 (0.73, 0.93)	
			SCD	0.68 (0.48, 0.95)	
			All-cause mortality	0.49 (0.45, 0.54)	
de Souza, 2014[41]; Brazil; None Reported; CKD stage 5/HD; Chronic; Good (NOS)	PCS 73 5 - 6 years	*Treatment:* SRP; OHI; antibiotic and rubber cup prophylaxis *Control*: no treatment and no CP	*Adjusted Hazard Ratio compared to no CP patients (95% CI); adjusted for age, gender, comorbidities, oral health, and CP status)*		No difference in survival between treated and untreated patients with CP on HD (P=0.774)
			Risk of Mortality	1.79 (0.71, 4.51)	1.49 (0.54, 4.09)
Palmer, 2015[35]; Europe (France, Hungary, Italy, Poland, Portugal, Spain), Argentina; Diaverum and LCO (hospital), Italy; CKD stage 5/HD; NA; Good (NOS)	PCS 3243 1, 2, 3 years (data shown for 3 years)	*Treatment:* Last dental visit ≤6m *Control:* Last dental visit >6m	*Adjusted Hazard Ratio (95% CI); stratified by country and adjusted for age, sex, race, smoking history, income, medical history, dialysis vintage, mean arterial blood pressure, serum phosphorus, and hemoglobin levels.*		Longer survival in treated patients on HD.
			All-cause mortality	0.79 (0.65, 0.96)	
			CVD mortality	0.73 (0.55, 0.97)	
Huang, 2015[39]; Taiwan; Federal, Academia, Foundation, Consortia;	RCS 8902 13 years	*Treatment*: SRP; flap surgery	*Hazard Ratio (95% CI)* *Only treatment group had patients with periodontitis*		• A lower risk (0.72-fold) of overall infectious disease burden • Lower risk of acute and subacute infective endocarditis, pneumonia, and osteomyelitis .
			Overall infectious diseases	0.72 (0.66, 0.78)	

CKD stage 5/HD; NR; Good (NOS)		*Control*: no treatment	Acute and subacute infective endocarditis	0.54 (0.35, 0.84)	• No difference in renal and perinephric abscesses, bacteremia or brain abscesses
			Bacteremia	0.83 (0.68, 1.03)	
			Pneumonia	0.71 (0.65, 0.78)	
			Brain abscess	0.68 (0.31, 1.50)	
			Osteomyelitis	0.77 (0.62, 0.96)	
			Renal and perinephric abscess	0.53 (0.24, 1.17)	
Chiu, 2021[22]; Taiwan; Federal; CKD stage 5/HD & PD; NA; Good (NOS)	RCS 12454; 2633 received treatment 16 years	*Treatment:* Root canal therapy *Control:* no treatment	*% patients with event (age, sex, monthly income, and dialysis type and comorbidities)*		• Better survival in patients receiving endodontic therapy
			Cause of death	Root Canal treatment	No root canal treatment
			All-cause Mortality	22.79%	34.93%
			CAD	13.83%	17.46%
			Infectious Disease	34.83%	45.54%
			Cerebrovascular Disease	16.17%	11.28%
			Malignancy	12.00%	9.65%
			Other	23.17%	16.06%
Siribamrungwong, 2014[42]; Thailand; None Reported; CKD stage 5/PD; Medium (ROBINS)	Single Arm 32 16 weeks	*Treatment:* SRP; OHI *Control:* pre-treatment	*Average percent change relative to Baseline*		• CRP lower (P = 0.02) • BUN higher (P = 0.001) Risk of Bias: Medium
			CRP	-32.6	No control group
			Ferritin	-24.1	
			BUN	8.6	
			Alb	1.8	
			Total cholesterol	-3.4	
			TSAT	6.7	
			Kt/V urea	1.1	
			nPCR	-18.7	

<table>
<tr>
<td>Kocyigit, 2014[43]

Turkey

None Reported

CKD stage 5/PD;
Fair (NOS)</td>
<td>Single Arm

43 (data shown for the 9 severe periodontitis cases)

3 months</td>
<td>Treatment:
SRP; OHI; antibacterial rinse; necessary tooth extractions; referrals for other treatments

Control:
pre-treatment</td>
<td colspan="3">Average percent change relative to Baseline
<table>
<tr><td>WBC count (mm^3)</td><td>-17.3</td><td rowspan="11">No control group</td></tr>
<tr><td>Hb</td><td>-1.6</td></tr>
<tr><td>FPG</td><td>18.6</td></tr>
<tr><td>TC</td><td>0.0</td></tr>
<tr><td>TG</td><td>-14.7</td></tr>
<tr><td>LDL</td><td>10.1</td></tr>
<tr><td>HDL</td><td>-13.5</td></tr>
<tr><td>Serum Ca</td><td>-3.3</td></tr>
<tr><td>Serum P</td><td>-18.4</td></tr>
<tr><td>Serum Alb</td><td>-3.0</td></tr>
<tr><td>TSAT</td><td>0.0</td></tr>
<tr><td>CRP</td><td>-41.6</td></tr>
</table></td>
<td>CRP decreased in patients with either slightly-to-moderate (n = 12, p = 0.014) or severe periodontitis (n = 9, p = 0.001) and receiving periodontal therapy.
Risk of Bias: Medium</td>
</tr>
<tr>
<td>Yu 2023[40];
Taiwan;
Federal;
CKD stage 5/HD;
Good (NOS)</td>
<td>Cohort Case-control study

19602

3 months</td>
<td>Treatment:
SRP

Control: no treatment</td>
<td colspan="3">Adjusted Hazard Ratio (age, sex, monthly income, and dialysis type and comorbidities)
<table>
<tr><td>Infective endocarditis</td><td>1.04 (0.71, 1.53)</td></tr>
</table></td>
<td>• No greater risk of developing infective endocarditis for patients on HD</td>
</tr>
</table>

5D: includes patients at CKD stage 5 receiving dialysis; @translated from Chinese using google translate

Appendix A4: Excluded studies with reason for exclusion

Study	DOI	Title	Exclusion Reason
Ferreira 2024	https://dx.doi.org/10.1111/odi.14981	Periodontitis and systemic parameters in chronic kidney disease: Systematic review and meta-analysis.	Wrong intervention
Oza 2024	https://doi.org/10.1590/pboci.2024.033	Effect of Non-Surgical Periodontal Therapy on Chronic Kidney Disease Patients: A Systematic Review	Wrong outcomes
Chen 2023	https://dx.doi.org/10.4317/medoral.26307	Association between periodontitis and its treatment on mortality rates of end-stage renal disease: A systematic review and meta-analysis.	Two studies in primary study list
Serni 2023	https://dx.doi.org/10.1111/odi.14062	Association between chronic kidney disease and periodontitis. A systematic review and metanalysis.	Wrong setting
He 2023	https://dx.doi.org/10.1111/jre.13161	Demystifying the connection between periodontal disease and chronic kidney disease - An umbrella review.	very little detail on treatment
Bunte 2023	https://doi.org/10.21203/rs.3.rs-3355849/v1	Patient-related factors that link chronic kidney disease and periodontitis: a meta-analysis and scoping review	Wrong intervention
Moest 2022	https://dx.doi.org/10.1007/s00784-021-04202-1	Frequency of the necessity of dentoalveolar surgery or conservative treatment in patients before kidney transplantation depending on the duration of dialysis and causative nephrological disease.	Wrong patient population
Hirano 2022	https://dx.doi.org/10.1007/s40620-021-00987-2	Frequency of tooth brushing as a predictive factor for future kidney function decline.	Wrong intervention
Souza 2022	https://dx.doi.org/10.1016/j.abd.2020.09.019	Uremic stomatitis.	Wrong study design
Mabrouk 2022	https://dx.doi.org/10.1111/ajt.17110	Gingival hypertrophy in a kidney transplant recipient.	Wrong study design
Taylor 2021	https://dx.doi.org/10.1177/0022034520965958	Does Nonsurgical Periodontal Treatment Improve Systemic Health?.	Wrong patient population
Sharma 2021	https://dx.doi.org/10.1111/jcpe.13414	Oxidative stress links periodontal inflammation and renal function.	Wrong study design

Chang 2021	https://dx.doi.org/10.1097/MD.0000000000027845	Improved oral hygiene care and chronic kidney disease occurrence: A nationwide population-based retrospective cohort study.	Wrong setting
Hirano 2021	10.21203/rs.3.rs-164266/v1	Frequency of Tooth Brushing as a Predictive Factor for Future Kidney Function Decline	Wrong intervention
Tabesh 2021	10.21203/rs.3.rs-985514/v1	Oral Health-related Quality of Life and Periodontal Status in Chronic Kidney Disease Patients: A Cross Sectional Study	Wrong setting
Grubbs 2020	https://dx.doi.org/10.1016/j.xkme.2019.09.005	Nonsurgical Periodontal Therapy in CKD: Findings of the Kidney and Periodontal Disease (KAPD) Pilot Randomized Controlled Trial.	Wrong study design
Kaneko 2020	https://dx.doi.org/10.14740/jocmr4085	Medical and Dental Visits of Chronic Kidney Disease-Diagnosed Participants Analyzed From the Specific Health Checkups Results in Japan: TAMA MED Project-CKD.	Wrong intervention
Assante 2020	https://dx.doi.org/10.23736/S0026-4970.19.04151-7	Correlations between dental assistance/oral health and clinical intercurrences in an end-stage kidney disease patients: a historical cohort study.	Wrong setting
Mizutani 2020	https://dx.doi.org/10.1038/s41598-020-78724-1	Poor oral hygiene and dental caries predict high mortality rate in hemodialysis: a 3-year cohort study.	Wrong intervention
Jamieson 2020	https://dx.doi.org/10.1186/s13104-020-05317-6	Lessons learned from a periodontal intervention to reduce progression of chronic kidney disease among Aboriginal Australians.	Wrong setting
Yoshioka 2020	https://dx.doi.org/10.1155/2020/4042129	Association between Oral Health Status and Diabetic Nephropathy-Related Indices in Japanese Middle-Aged Men.	Wrong setting
Chadban 2020	https://doi:10.1097/tp.0000000000003136	KDIGO clinical practice guideline on the evaluation and management of candidates for kidney transplantation	Wrong patient population
Wallace 2019	https://pubmed.ncbi.nlm.nih.gov/31490048/	The Relationship Between Oral Health and Hemodialysis Treatment Among Adults with Chronic Kidney Disease: A Systematic Review.	Wrong intervention
Iordanishvili 2019	https://dx.doi.org/10.17116/stomat20199803125	[Characteristics of dental hard tissues in chronic kidney disease: morphology, chemical composition, possibilities of remineralizing therapy].	Wrong comparator
Ruokonen 2019	https://dx.doi.org/10.1007/s00784-018-2647-z	Oral symptoms and oral health-related quality of life in patients with chronic kidney disease from predialysis to posttransplantation.	Wrong setting

Wangerin 2019	https://dx.doi.org/10.1053/j.ajkd.2018.10.013	Long-term Association of Periodontitis With Decreased Kidney Function.	Wrong patient population
Wright 2019	https://doi.org/10.1186/s12882-019-1530-8	Clinical practice guideline on undernutrition in chronic kidney disease	Wrong setting
Costantinides 2018	https://dx.doi.org/10.1155/2018/9610892	Dental Care for Patients with End-Stage Renal Disease and Undergoing Hemodialysis.	Narrative or Literature Review
Iwasaki 2017	https://dx.doi.org/10.1002/cre2.50	Periodontitis and health-related quality of life in hemodialysis patients.	Wrong intervention
Huang 2017	https://dx.doi.org/10.1016/j.jds.2016.12.006	Dental restorative treatment expenditure and resource utilization in patients with chronic kidney disease: A nationwide population-based study.	Wrong study design
Perozini 2017	https://dx.doi.org/10.1155/2017/9858073	Medical and Periodontal Clinical Parameters in Patients at Different Levels of Chronic Renal Failure.	Wrong setting
Lee 2017	https://dx.doi.org/10.1902/jop.2013.130015	Relationship between periodontal disease and chronic kidney disease: A systematic review of cohort studies	Wrong setting
Cao 2016	https://dx.doi.org/10.3760/cma.j.issn.0376-2491.2016.01.003	[The clinical study of IgA nephropathy with severe chronic periodontitis and aggressive periodontitis].	Wrong intervention
Yoshioka 2016	https://dx.doi.org/10.5527/wjn.v5.i5.455	Factors associated with regular dental visits among hemodialysis patients.	Wrong study design
Pieralisi 2015	https://dx.doi.org/10.1111/jop.12277	Oral lesions and colonization by yeasts in hemodialysis patients.	Wrong outcomes
Nylund 2015	https://dx.doi.org/10.3290/j.qi.a34698	Oral health in predialysis patients with emphasis on periodontal disease.	Wrong outcomes
Ruospo 2014	https://dx.doi.org/10.1093/ndt/gft401	Prevalence and severity of oral disease in adults with chronic kidney disease: a systematic review of observational studies.	Wrong intervention
Pejcic 2014	https://dx.doi.org/10.1159/000357274	Effect of periodontal treatment in renal transplant recipients.	Wrong outcomes
Lee 2014	https://dx.doi.org/10.1902/jop.2013.130015	Surgical treatment for patients with periodontal disease reduces risk of end-stage renal disease: a nationwide population-based retrospective cohort study.	Wrong setting

Appendix A5: List of studies in the systematic reviews and primary studies.

Study Name	Publication Year	Country	Present in which SR
Almeida	2017	Brazil	Zhao 2020, Deschamps-Lenhardt 2019, Delbove 2021, daSilva 2021
Artese	2010	Brazil	Zhao 2020, Deschamps-Lenhardt 2019, Delbove 2021, daSilva 2021
Ausavarungnirun	2016	Thailand	Deschamps-Lenhardt 2019
Bastos	2011	Brazil	Deschamps-Lenhardt 2019
Borawski	2007	Poland	Deschamps-Lenhardt 2019
Brito	2012	Brazil	Deschamps-Lenhardt 2019
Brotto	2011	Brazil	Deschamps-Lenhardt 2019
Chang	2017	Taiwan	Deschamps-Lenhardt 2019
Chen	2015	Taiwan	Deschamps-Lenhardt 2019
Chung	2022	Taiwan	Primary Study Table
Ebong	2018	Cameroon	daSilva 2021
Fang	2015	China	Delbove 2021, Lai 2020, Yue 2020, Deschamps-Lenhardt 2019, Bezerra 2024, Primary Study Table
Fisher	2011	USA	Deschamps-Lenhardt 2019
Fisher & Taylor	2009	USA	Deschamps-Lenhardt 2019
Fisher, Taylor	2008	USA	Deschamps-Lenhardt 2019
Fisher, Taylor, Shelton	2008	USA	Deschamps-Lenhardt 2019
Garcez	2009	Spain	Deschamps-Lenhardt 2019
Graziani	2010	Italy	Deschamps-Lenhardt 2019
Grubbs	2011	USA	Deschamps-Lenhardt 2019
Grubbs	2015	USA	Deschamps-Lenhardt 2019
Grubbs	2016	USA	Deschamps-Lenhardt 2019
Grubbs	2019	USA	Bezerra 2024
Guo	2017	China	Lai 2020, Deschamps-Lenhardt 2019, Delbove 2021, Bezerra 2024
Han	2013	Korea	Deschamps-Lenhardt 2019
Haoping	2018	Unknown (China)	Lai 2020

Huang	2015	Taiwan	Delbove 2021, Primary Study Table
Huang	2018	Taiwan	Delbove 2021, Primary Study Table
Ioannidou	2011	USA	Deschamps-Lenhardt 2019
Ioannidou	2013	USA	Deschamps-Lenhardt 2019
Ioannidou & Swede	2011	USA	Deschamps-Lenhardt 2019
Iwasaki	2012	Japan	Deschamps-Lenhardt 2019
Iwasaki	2016	Japan	Deschamps-Lenhardt 2019
Kadiroglu	2006	NA	Delbove 2021
Kocyigit	2014	Turkey	Primary Study Table
Kocyigit	2014	NA	Delbove 2021
Kshirsagar	2005	USA	Deschamps-Lenhardt 2019
Lee	2014	China	Deschamps-Lenhardt 2019, Delbove 2021
Li	2019	NA	Yue 2020
Liu	2013	China	Deschamps-Lenhardt 2019
Ma	2018	NA	Yue 2020
Messier	2012	USA	Deschamps-Lenhardt 2019
Mizutani	2020	Japan	Primary Study
Nylund	2015	Finland	Deschamps-Lenhardt 2019
Nylund	2017	Finland	Deschamps-Lenhardt 2019
Palmer	2015	Europe; SA	Primary Study Table
Perozini	2017	Brazil	Deschamps-Lenhardt 2019
Rapone	2019	NA	Delbove 2021
Salimi	2014	USA	Deschamps-Lenhardt 2019
Santos-Paul	2019	Brazil	Delbove 2021, Primary Study Table
Sharma	2014	UK	Deschamps-Lenhardt 2019
Shin	2017	Korea	Deschamps-Lenhardt 2019
Siribamrungwong	2012	Thailand	Zhao 2020, Delbove 2021, Bezerra 2024
Siribamrungwong	2013	Thailand	Delbove 2021
Siribamrungwong	2014	Thailand	Zhao 2020, Bezerra 2024, Primary Study Table
Sobrado	2007	Portugal	Deschamps-Lenhardt 2019
Tadakamadla	2014	India	Deschamps-Lenhardt 2019
Tasdemir	2018	NA	Delbove 2021

Thorman	2009	Spain	Deschamps-Lenhardt 2019
Vilela	2011	Brazil	Deschamps-Lenhardt 2019, Delbove 2021, Bezerra 2024
Vrinda	2021	India	Primary Study Table
Wehmeyer	2013	USA	Lai 2020, Delbove 2021
Wehmeyer	2014	USA	Yue 2020
Xin	2018	Unknown (China)	Lai 2020
Yazdi	2013	Iran	Delbove 2021, Bezerra 2024
Yoshihara	2007	Japan	Deschamps-Lenhardt 2019
Yoshihara	2016	Japan	Deschamps-Lenhardt 2019
Yoshihara	2017	Japan	Deschamps-Lenhardt 2019
Zhang	2017	China	Deschamps-Lenhardt 2019
Zhang	2017	Taiwan	Lai 2020
Zhang	2017	NA	Yue 2020
de Souza	2014	Brazil	Delbove 2021, Primary Study Table

Appendix A6: Risk of bias and Amstar2 assessments

AMSTAR2 rating of the systematic reviews:

Author, Year	1[a]	2[b]	3[c]	4[d]	5[e]	6[f]	7[g]	8[h]	9[i]	10[j]	11[k]	12[l]	13[m]	14[n]	15[o]	16[p]	Total Score
Chen 2023	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	Low
Deschamps-Lenhardt 2019	YES	YES	YES	YES	YES	YES	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low
Zhao 2020	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	Low
Yue 2020	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NA	YES	Moderate
Delbove 2021	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES	NO	YES	YES	Low
de Silva 2021	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	NO	NO	NO	Low
Bezerra 2024	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	High
Lai 2020	YES	NO	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	Low

The columns in blue are the critical domains.

a. Did the research questions and inclusion criteria for the review include the components of PICO?
b. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
c. Did the review authors explain their selection of the study designs for inclusion in the review?
d. Did the review authors use a comprehensive literature search strategy?
e. Did the review authors perform study selection in duplicate?
f. Did the review authors perform data extraction in duplicate?
g. Did the review authors provide a list of excluded studies and justify the exclusions?
h. Did the review authors describe the included studies in adequate detail?
i. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
j. Did the review authors report on the sources of funding for the studies included in the review?
k. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?
l. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
m. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
n. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
o. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
p. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Risk of bias rating (ROB) of the randomized clinical trials:

ROB	Risk of bias domains						Quality as mapped in the report
	D1	D2	D3	D4	D5	Overall	
Chung 2022	Low	Low	Low	Low	Low	Low	High
Fang 2015	Low	Low	Low	Low	Low	Low	High
Maheshwari 2023	Low	Low	Low	Low	Low	Low	High
Vacchani 2021	Low	Low	Low	Low	Low	Low	High

Risk of bias rating (ROBINS I) of the uncontrolled clinical trials:

ROBINS I	Risk of Bias domains								Quality as mapped in the report
	D1	D2	D3	D4	D5	D6	D7	Overall	
Siribamrungwong 2013	High	High	Low	Moderate	Low	Moderate	Low	Moderate	Moderate
Vrinda 2021	High	Low	Low	Low	Low	Moderate	Low	Moderate	Moderate
Rapon 2019	Moderate	Moderate	Low	Low	Low	High	Low	Moderate	Moderate

Newcastle-Ottawa Score for cohort studies:

NOS	Selection				Comparability	Outcome			
Author Year	Representativeness of Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Outcome of Interest Not Present at Study Start	Comparability of Cohorts	Assessment of Outcome	Follow-up Long Enough for Outcome	Adequacy of Follow-up of Cohorts	Quality as mapped in the report
Santos-Paul 2019	1	1	1	1	1	1	1	1	High
Huang 2015	1	1	1	1	1	1	1	1	High
Huang 2018	1	1	1	1	1	1	1	1	High
de Souza 2014	1	1	1	1	1	1	1	1	High
Kocyigit 2014	1	1	1	1	1	1	1	0	High

Chiu 2021	1	1	1	1	2	1	1	1	High
Palmer 2015	1	1	1	1	1	1	1	1	High
Yu 2022	1	1	1	1	1	1	1	2	High