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What's new for the clinician – summaries of recently published papers (June 2026)

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1. DOES ENDODONTIC TREATMENT MODIFY SERUM INFLAMMATORY MARKERS OF CARDIOVASCULAR RISK IN INDIVIDUALS WITH ASYMPTOMATIC APICAL PERIODONTITIS? A SYSTEMATIC REVIEW AND META-ANALYSIS

Cardiovascular disease (CVD) remains the leading cause of mortality globally, responsible for approximately 32% of all annual deaths1. The pathogenesis of atherosclerosis and subsequent cardiovascular events is increasingly understood as driven not only by traditional risk factors – smoking, hypertension, dyslipidemia, and diabetesbut also by chronic low-grade systemic inflammation. Inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) have emerged as independent predictors of cardiovascular risk, with elevated levels correlating strongly with endothelial dysfunction, plaque instability, and adverse cardiac outcomes.[1]

Over the past two decades, the oral-systemic health paradigm has gained substantial traction, with particular attention devoted to the contribution of chronic oral infections to systemic inflammatory burden. While periodontal disease has been the most extensively studied oral condition in this context, asymptomatic apical periodontitis (AAP – a chronic inflammatory lesion of the periapical tissues resulting from pulpal necrosis – has recently attracted growing scientific interest. AAP is highly prevalent; epidemiological data suggest that at least one tooth with periapical radiolucency is present in approximately half of the global adult population1. Crucially, AAP is frequently undiagnosed and untreated because it often progresses without clinical symptoms, representing a persistent, subclinical inflammatory nidus.

The biological plausibility linking AAP to systemic inflammation rests on three principal pathways: (i) transient bacteremia arising from the infected root canal system, permitting hematogenous dissemination of endodontic pathogens; (ii) systemic absorption of bacterial toxins and byproducts (e.g., lipopolysaccharides); and (iii) the sustained release of pro-inflammatory cytokines and mediators from the periapical lesion into the systemic circulation. Studies have documented elevated serum levels of IL-1β, IL-6, IL-18, TNF-α, and CRP in individuals with AAP compared with healthy controls [8,9], suggesting that this "silent" infection may contribute to the maintenance of a chronic low-grade inflammatory state implicated in atherogenesis.

Whether endodontic treatment – root canal therapy or apical surgery – can reverse these systemic inflammatory perturbations remains a critical, clinically relevant question. Given the inconclusive nature of the evidence and the substantial public health implications, Silva Araújo and colleagues (2026)1 conducted this updated systematic review and meta-analysis to evaluate whether endodontic treatment modulates serum inflammatory markers associated with cardiovascular risk in individuals with AAP.

METHODOLOGY

This systematic review and meta-analysis was conducted according to PRISMA 2020 guidelines and prospectively registered with PROSPERO. The authors employed a comprehensive PICO-driven search strategy across multiple electronic databases – PubMed/MEDLINE, Embase, Web of Science, Scopus, and the Virtual Health Library (VHL) – supplemented by grey literature sources (CAPES, ProQuest, Google Scholar) and manual screening of reference lists. The search was initially performed between October and November 2022, with an update in September 2025, imposing no language or date restrictions.

Eligibility criteria were deliberately broad to capture the limited available evidence: observational studies (cohort, case-control) and experimental designs (randomised and non-randomised clinical trials, including before-and-after studies) were included if they evaluated endodontic treatment effects on serum inflammatory markers in participants with AAP. Exclusion criteria appropriately eliminated cross-sectional studies, case reports, reviews, and studies involving acute endodontic conditions, systemic comorbidities, or uncontrolled behavioral risk factors that could confound inflammatory marker measurements.

Two independent reviewers conducted all screening, data extraction, and risk-of-bias assessments, with discrepancies resolved by a third reviewer. Risk of bias was evaluated using the Newcastle–Ottawa Scale (NOS) adapted for intervention studies, with studies scoring 7–9 stars classified as low risk, 4–6 as moderate risk, and 0–3 as high risk. The certainty of evidence was appraised using the GRADE approach. Statistical analysis employed a random-effects model with Mantel–Haenszel estimation to calculate pooled mean differences (MD) and 95% confidence intervals (95% CI). Heterogeneity was quantified using Cochran's Q-test and I^2 statistics.

Results

The systematic search yielded 6,295 records. Following duplicate removal, title/abstract screening, and full-text evaluation, 16 studies were assessed for eligibility and eight were included in the qualitative and quantitative synthesis. Two additional studies were identified through manual reference screening.

The included studies exhibited considerable methodological diversity: four employed a hybrid before-and-after design with cross-sectional healthy controls; two were before-and-after studies without internal controls; and two were preliminary intervention studies without controls. Sample sizes ranged from 11 to 115 participants (ages 18–75 years). Endodontic

protocols varied: six studies used conventional nonsurgical root canal treatment, one combined nonsurgical and surgical approaches, and one compared nonsurgical retreatment with apical microsurgery. Follow-up periods ranged from 7 days to 12 months. Twenty-three distinct inflammatory markers were evaluated, with CRP (7 studies), IL-1 (2), IL-6 (2), TNF-α (2), ICAM-1 (2), VCAM-1 (2), and complement C3 (2) being most frequently assessed.

All eight included studies were rated as having moderate risk of bias (NOS scores 4–6). According to GRADE, the certainty of evidence for all meta-analysed outcomes was rated as very low primarily due to non-randomized designs, lack of random allocation, and substantial heterogeneity and imprecision.

For studies incorporating control groups (n=4), all used healthy external controls. For the four studies lacking controls, the authors employed two strategies: (1) values from control groups of other included studies, and (2) established reference values for healthy populations. This methodological approach enabled inclusion of all studies in quantitative syntheses.

The pooled analyses suggested potential reductions in key inflammatory markers following endodontic treatment:
C-reactive protein (CRP): pooled Mean Difference (MD) = 0.05 (95% CI: –0.01, 0.10) for self-controlled designs; pooled MD = 0.76 (95% CI: –0.15, 1.67) for external control designs. The confidence intervals included values approaching control group levels.

Interleukin-6 (IL-6): pooled Mean Difference (MD) = 0.81 (95% CI: –0.27, 1.90) for self-controlled designs, with post-treatment levels trending toward healthy control values.

Tumor necrosis factor-alpha (TNF-α):pooled Mean Difference (MD) = 1.04 (95% CI: –0.38, 2.46) for self-controlled designs, similarly approaching control levels post-intervention.

No significant differences were observed for the adhesion molecules ICAM-1; [MD = 32.15 (95% CI: 9.32, 54.99), self-control] or VCAM-1 [MD = 0.00 (95% CI: –0.00, 0.01), self-control] between groups before or after intervention.

Heterogeneity was substantial across all analyses ($I^2 > 50\%$, $p < 0.05$) and persisted despite subgroup analyses stratifying by control type (self-controlled vs. external control).

Conclusion

Silva Araújo and colleagues concluded that, despite limited and very low-certainty evidence, endodontic treatment appears to reduce serum levels of CRP, IL-6, and TNF-α in individuals with asymptomatic apical periodontitis, with post-treatment values approaching those of healthy controls. The authors appropriately temper this conclusion, emphasising that the high heterogeneity, moderate risk of bias across all included studies, and very low GRADE ratings preclude definitive causal inference. No effect was demonstrated for the endothelial adhesion molecules ICAM-1 and VCAM-1.

Implications for Practice

The findings provide modest support for the proposition that root canal treatment may confer benefits beyond local infection control and tooth preservation. Clinicians should recognise that untreated AAP represents not merely a localised dental pathology but potentially a contributor to systemic inflammatory burden. However, the very low certainty of evidence means that endodontic treatment should not be promoted primarily as a cardiovascular risk reduction strategy; rather, the possible systemic benefits should be considered an ancillary advantage of appropriate local therapy.

In summary, while this systematic review offers a tentatively encouraging signal that endodontic treatment may attenuate systemic inflammatory markers associated with cardiovascular risk, the evidence remains insufficient to alter clinical guidelines or justify treatment decisions on systemic grounds alone. It does, however, reinforce the broader principle that oral health is inseparable from systemic health and provides a compelling rationale for continued research investment in this domain.

Reference

1. Silva Araújo, R., Abreu Fonseca Thomaz, E.B., da Silva Magalhães, E.I. *et al*. Does endodontic treatment modify serum inflammatory markers of cardiovascular risk in individuals with asymptomatic apical periodontitis? a systematic review and meta-analysis. Clin Oral Invest 30, 214 (2026)

2. COMPARATIVE EVALUATION OF THE CYTOTOXIC EFFECTS OF FLUORIDATED AND NON-FLUORIDATED TOOTHPASTE ON THE BUCCAL MUCOSA: A 12 WEEK FOLLOW UP – A RANDOMISED CONTROLLED STUDY

Fluoride remains the cornerstone of modern caries prevention, with its incorporation into toothpastes, mouthwashes, varnishes, and professional gels representing one of public health dentistry's most successful interventions. The World Health Organisation, dental associations worldwide, and extensive systematic evidence consistently support the use of fluoride dentifrices for reducing dental caries incidence across all age groups 1. Standard fluoride concentrations in over-the-counter toothpastes typically range from 1,000 – 1,500 ppm, while prescription formulations may exceed 5,000 ppm. Despite decades of proven efficacy, fluoride safety—particularly at higher concentrations and with chronic exposure– continues to generate scientific debate and public concern.

The oral mucosa serves as the primary interface between the external environment and systemic circulation, functioning as both a protective barrier and a site of active absorption. Buccal epithelial cells, in particular, are exposed to topical agents during oral hygiene procedures and can accumulate fluoride, potentially serving as a long-term reservoir1. This biological reality raises legitimate questions about whether routine, twice-daily exposure to fluoridated toothpaste over years or decades may exert subtle cellular effects that remain undetected by conventional clinical examination.

Micronucleus formation in exfoliated buccal cells has emerged as a validated, minimally invasive biomarker for genotoxicity and chromosomal instability. Micronuclei originate from acentric chromosome fragments or whole chromosomes that fail to segregate during mitosis, reflecting DNA damage, impaired DNA repair, or mitotic spindle dysfunction1. The buccal micronucleus cytome assay, typically employing Papanicolaou or Giemsa staining, offers a practical method

for monitoring environmental and occupational genotoxic exposures in human populations. Beyond micronuclei, nuclear abnormalities – including binucleation, nuclear buds, karyorrhexis, and pyknosis – provide complementary information about cytotoxicity, chromosomal loss, and apoptotic processes.

Previous investigations into fluoride genotoxicity have yielded inconsistent findings. In vitro studies and animal models have reported DNA strand breaks, chromosomal aberrations, and micronucleus induction at various fluoride concentrations. However, human in vivo evidence remains limited and contradictory. Some researchers have identified increased micronuclei frequencies in populations consuming high-fluoride drinking water, while others found no genotoxic effect from fluoride varnish applications or standard toothpaste use This inconsistency likely reflects variations in fluoride formulation, concentration, exposure duration, tissue type examined, and methodological rigor.

Compounding the complexity, commercial toothpastes contain numerous excipients beyond fluoride—abrasives (silica, calcium carbonate), surfactants (sodium lauryl sulfate), humectants, binders, flavoring agents, and preservatives – that may independently or synergistically influence mucosal cell integrity. Sodium lauryl sulfate, in particular, has been associated with mucosal irritation, desquamation, and nuclear morphological changes in prior studies [8]. Disentangling fluoride-specific effects from formulation-dependent effects represents a significant methodological challenge.

The growing consumer interest in "natural," fluoride-free oral care products has intensified the need for robust comparative safety data. While non-fluoridated alternatives containing hydroxyapatite, essential oils, or herbal extracts have gained market share, their relative biological safety profiles remain inadequately characterised. Clinicians require evidence-based guidance to counsel patients – particularly those with mucosal sensitivity, existing oral pathologies, or heightened concern about chemical exposure – on dentifrice selection without compromising caries prevention.

Against this backdrop, Ravindran and colleagues conducted a 12-week randomised controlled trial comparing the cytotoxic effects of a fluoridated toothpaste (1,400 ppm sodium fluoride) versus a non-fluoridated alternative on buccal mucosal cells. This study addresses an important gap by providing prospective, parallel-group human data on a clinically relevant exposure scenario.

Methodology: This prospective, double-blind, parallel-group randomised controlled trial enrolled 40 systemically healthy adults aged 18–50 years from a single dental institution in India. Participants were randomly allocated via envelope method to either a fluoridated toothpaste group (Parodontax, 1,400 ppm fluoride as sodium fluoride 0.31% w/w; n=20) or a non-fluoridated group (n=20). Exclusion criteria appropriately eliminated smokers, alcohol consumers, pan masala users, pregnant or lactating women, patients undergoing radiotherapy, those with systemic illness, and individuals using additional fluoride products or undergoing dental treatment that could confound mucosal status.

The intervention required twice-daily brushing for two minutes using the modified Bass technique with a provided soft-bristled manual toothbrush and pea-sized toothpaste quantity over 12 weeks. Compliance was monitored through periodic follow-up visits and verbal confirmation, though objective measures (e.g., returned tube weighing) were not employed. No washout period preceded the intervention, and baseline cytological assessments were not performed—a significant methodological limitation. Post-intervention buccal mucosal cells were collected via Cytobrush, fixed in 95% alcohol, and stained using the Papanicolaou method. Micronuclei frequency, cellular changes (binucleation, nuclear buds), and nuclear alterations were quantified microscopically with ImageJ software analysis.

Results

The study achieved balanced baseline demographics with a mean participant age of 34.4 years and no significant between-group differences in age or gender distribution.
Intragroup analysis revealed no statistically significant increase in cellular changes for either the fluoridated (p=0.087) or non-fluoridated (p=0.370) groups over the 12-week period. However, intergroup comparison demonstrated a statistically significant increase in cells with cellular changes in the fluoridated group (p=0.048), suggesting a fluoride-associated effect.

Nuclear changes were not statistically significant within the fluoridated group (p=1.000) but reached significance within the non-fluoridated group (p=0.033)—a counterintuitive finding. The intergroup comparison showed no significant difference (p=1.000).

The most robust finding was a highly significant difference in micronuclei frequency between groups (p=0.0001), with the fluoridated group exhibiting elevated frequencies. A strong negative correlation existed between toothpaste type and micronuclei count (r=–0.853, p=0.000), indicating that non-fluoridated toothpaste use was associated with fewer micronuclei. A moderate negative correlation between toothpaste type and cellular changes (r=–0.361, p=0.022) further supported this pattern.

Neither gender nor age significantly influenced micronuclei or cellular changes. A weak negative correlation between gender and nuclear changes (r=–0.326, p=0.040) suggested minor sex-related differences in nuclear alterations, though this finding was isolated and of uncertain clinical relevance.
Conclusion: The authors conclude that fluoridated toothpaste use over 12 weeks is associated with significantly increased micronuclei frequency and cellular changes in buccal mucosal cells compared with non-fluoridated alternatives, implying cytogenetic damage. They acknowledge that nuclear changes were paradoxically significant only in the non-fluoridated group, and that intergroup differences in nuclear changes were absent. The study emphasises that while fluoride's caries-preventive benefits are well-established, its potential mucosal cytotoxicity warrants consideration, particularly with prolonged exposure to higher concentrations.

Implications for Practice

The statistically significant increase in micronuclei frequency in the fluoridated group represents the study's most compelling finding. Micronuclei are established biomarkers of chromosomal damage with recognised relevance to carcinogenesis risk assessment. However, the clinical significance of elevated buccal micronuclei from a 12-week toothpaste exposure remains uncertain. The buccal mucosa

is a rapidly renewing epithelium with substantial regenerative capacity, and transient cytogenetic changes may not translate to persistent pathology or systemic risk. Without long-term follow-up or outcome data, these findings should be regarded as hypothesis-generating rather than practice-changing.

Dental practitioners must weigh the substantial, evidence-based caries-preventive benefits of fluoride against the tentative safety signals identified in this study. Caries remains one of the most prevalent chronic diseases globally, and fluoride toothpaste is a primary prevention tool with proven population-level impact. Abandoning or broadly discouraging fluoride use based on a single small study with methodological limitations would be premature and potentially harmful. Instead, clinicians should engage in individualised risk assessment: patients with high caries risk, limited access to dental care, or established fluoride tolerance should continue standard fluoride regimens. Conversely, patients with documented mucosal sensitivity, recurrent aphthous stomatitis, or strong preference for fluoride-free products may be counseled about non-fluoridated alternatives, with the understanding that caries risk may increase and enhanced preventive monitoring may be warranted.

In summary, this study raises pertinent questions about the biological safety of chronic fluoride exposure at standard toothpaste concentrations but does not provide sufficient evidence to modify established clinical practice.

REFERENCE

1. Ravindran R, Elumalai A, Vijayarangan A, *et al*. Comparative evaluation of the cytotoxic effects of fluoridated and non-fluoridated toothpaste on the buccal mucosa: A 12-week follow-up—a randomized controlled study. Clin Oral Invest 2026;30:209.

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