CURRENT VIEWS IN DENTISTRY

INAUGURAL ISSUE

VOLUME 1 • ISSUE 1 • JUNE 2026

ONLINE ONLY

Paradigm Shift in Dental Scientific Publishing

Editor-in-Chief: **Young-Seok Park**
Seoul National University School of Dentistry

Independent not-for-profit open access journal | CONNECTING EVIDENCE. ADVANCING CARE. SHAPING THE FUTURE.

Current Views in Dentistry

Inaugural Issue

Volume 1, Issue 1, June 2026

Publication Information

Journal	Current Views in Dentistry
Publisher	SOGA Publishing
Format	Independent, not-for-profit, open-access, online-only journal
Editor-in-Chief	Prof. Young Seok Park, Seoul National University School of Dentistry
Website	https://sogapub.com/journals/current-views-in-dentistry/
Submission	submit_cvd@sogapub.com
ISSN	to be assigned
DOI	to be assigned

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Inaugural issue compilation. This file brings together the cover, issue information, contents, published articles, and abbreviated journal information for *Current Views in Dentistry*, Volume 1, Issue 1.

간행물 정보

제호	Current Views in Dentistry
권호	제1권 제1호 창간호
발행일	2026년 6월 1일
발행처	SOGA Publishing
발행지	서울특별시 강남구 논현로 209
발행 형태	독립 비영리 오픈액세스 온라인 전용 학술지
간행 주기	비정기 간행
편집장	Prof. Young Seok Park
ISSN	신청 예정
DOI	부여 예정
비고	본 간행물은 온라인 전용 전자간행물이며 비매품입니다.

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Article page numbers are retained as printed in the individual article PDFs.

EDITORIAL

Amid the Proliferation of Scholarly Journals

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Published: June 1, 2026 | DOI: to be assigned | Open Access

There has been a growing interest in what may be called the democratization of information: making access to scholarly articles easier, broader, and, in some cases, free. In institutions with sufficient financial resources, libraries have subscribed to academic journals on behalf of their members, enabling faculty, students, and researchers to download the articles they need at the moment they need them. Yet this convenience, which we now so easily take for granted, is in fact a relatively recent innovation.

It was not so long ago that we visited the library in person, searched through printed volumes of journals by hand, photocopied the articles we needed, and read them on paper. When a library did not hold a particular issue, we requested it through interlibrary loan. Waiting more than a week was nothing unusual, and the call from the librarian announcing the arrival of the requested material felt almost like the delivery of a Christmas gift. Today, unless one belongs to an older generation like myself, even printing out PDF articles has become increasingly uncommon. If saving paper may contribute to environmental preservation, we can only hope that the environmental burden caused by the ever-growing number of tablet PCs accumulating in our offices will prove to be smaller.

The movement known as Open Access has undoubtedly contributed to science, particularly for researchers and institutions in financially constrained environments. Yet Open Access has now become a preferred business model not only for predatory publishers, but also for traditional legacy publishers. Even in subscription-based journals, researchers may purchase Open Access options. But among those who pay for such options, how many do so primarily for the sake of colleagues in low-resource settings? In reality, many researchers are likely driven by a very human and understandable desire: to increase the visibility of their own work. Built upon this desire - in other words, upon this demand - a flood of publishers and journals has entered the academic marketplace.

And yet, one must still ask whether our scholarly community, and particularly the field of dentistry, truly has sufficient opportunities for the presentation of ideas, perspectives, and research outcomes. Business models may have changed, but the forms and culture of academic publishing have not evolved to the same degree. To take but one example, we continue to rely heavily on the conventional formats of the Original Article and the Review Article. These forms remain valuable, and their contributions to scholarship are unquestionable. However, in an era when scientific papers are being published in overwhelming volume, it has become increasingly difficult to gain a broader view of the intellectual landscape. We need not only to examine individual trees, but also to see the forest as a whole.

Current Views in Dentistry was founded with this purpose in mind.

Although its scope is confined to the discipline of dentistry, this journal seeks to move beyond rigid formal constraints and to welcome manuscripts of diverse types. A contribution may take the form of an unproven but thought-provoking hypothesis. It may be a personal reflection shaped by experience. It may be a historical overview, a conceptual essay, a critical interpretation of emerging trends, or a proposal for the future direction of dental science, education, policy, or practice. Yet even as we embrace this breadth of form, we shall not abandon the fundamental discipline of evidence-based thinking.

Whether this endeavor will ultimately contribute to the advancement of science and dentistry will be revealed only with time - through the life of this journal, and through the wisdom that this new experience may teach us.

May this inaugural issue be blessed with purpose, integrity, and enduring value.

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The Use of Polydeoxyribonucleotide in Dentistry: A Scoping Review

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Manuscript type: Scoping Review	Published: June 1, 2026 | DOI: to be assigned	Open Access

Abstract

Objectives

This scoping review aimed to map the current evidence on polydeoxyribonucleotide (PDRN) and related polynucleotide-based materials in dentistry, oral medicine, periodontology, implant dentistry, oral and maxillofacial surgery, temporomandibular disorders, and oral tissue regeneration.

Methods

A scoping review was conducted following established methodological frameworks and PRISMA-ScR principles. PubMed/MEDLINE and Embase were searched for studies evaluating PDRN, polynucleotides, PN-HA formulations, sodium-DNA preparations, salmon DNA-derived materials, or related nucleotide-based biomaterials in dental and oral-maxillofacial contexts. Clinical, preclinical, nonclinical, and supportive review-level evidence were mapped according to study type, indication, material formulation, delivery method, and outcome domain.

Results

The final evidence map included 49 articles: 13 clinical studies, 30 preclinical or nonclinical studies, and 6 supportive review or commentary articles. PDRN and related materials were investigated across bone regeneration, alveolar ridge preservation, sinus augmentation, implant-related hard- and soft-tissue regeneration, periodontal and mucogingival therapy, oral mucosal repair, MRONJ/BRONJ-related models, temporomandibular disorders, and postoperative morbidity after third molar surgery. Preclinical studies provided biological plausibility through anti-inflammatory, pro-angiogenic, pro-healing, and osteogenic effects. Clinical evidence was most consistent for short-term reduction of postoperative inflammatory morbidity, whereas evidence for periodontal, bone-regenerative, TMJ, and mucosal applications remained limited or heterogeneous.

Conclusions

PDRN and related polynucleotide-based materials show promise as locally delivered adjunctive agents in dental and oral-maxillofacial applications. However, current evidence remains heterogeneous and insufficient to establish them as stand-alone dental therapeutics. Future studies should adopt standardized material reporting, appropriate comparator groups, longer follow-up, and indication-specific controlled clinical trial designs.

Keywords: Polydeoxyribonucleotide; Polynucleotide; Dentistry; Regeneration; Scoping review

INTRODUCTION

Polydeoxyribonucleotide (PDRN) is a biologically active, DNA-derived compound consisting of short-chain deoxyribonucleotide polymers typically isolated and refined from salmonid species (Ku et al., 2026; Oh et al., 2025). Over the past decade, PDRN and structurally related polynucleotide-based materials have garnered considerable scientific interest in the field of regenerative medicine, principally owing to their documented capacity to attenuate inflammation, promote angiogenesis, confer cytoprotection, and facilitate tissue repair (Ku et al., 2026; Oh et al., 2025). At the molecular level, these biological effects are thought to be mediated through two principal mechanisms: stimulation of adenosine A2A receptors and supplementation of intracellular nucleotide pools via the salvage biosynthetic pathway (Ku et al., 2026). Through these pathways, PDRN supports cellular proliferation, extracellular matrix remodeling, neovascularization, and the restoration of damaged or inflamed tissue (Jeon et al., 2026; Ku et al., 2026).

The relevance of these properties to dentistry is considerable. Favorable clinical outcomes in the oral and maxillofacial region depend critically on the coordinated, sequential healing of both mineralized and non-mineralized tissues within an environment characterized by a resident microbial flora and a persistently active inflammatory milieu. Pathological conditions and therapeutic interventions such as periodontal regeneration, alveolar bone repair following tooth loss, implant osseointegration, oral mucosal wound healing, post-extraction socket recovery, medic-

ation-related osteonecrosis of the jaw (MRONJ), and temporomandibular joint (TMJ) disorders all share overlapping biological demands, including timely resolution of inflammation, sustained angiogenesis, fibroblast recruitment and activation, osteogenic differentiation, collagen synthesis, and tissue remodeling (Han et al., 2025; Ko et al., 2024; Lee et al., 2023; Mladenova et al., 2025). It is within this context that PDRN and related polynucleotide-based formulations have begun to be investigated as adjunctive therapeutic agents across a spectrum of dental, oral, and maxillofacial applications (Ku et al., 2026; Mari et al., 2025).

The emerging body of dental literature on this topic is, however, marked by considerable heterogeneity. At the clinical level, PDRN or polynucleotide-based preparations have been explored for their potential to reduce postoperative morbidity following impacted mandibular third molar surgery (Kim et al., 2026; Ronsivalle et al., 2025), to support regeneration of periodontal intrabony defects (Cairo et al., 2025), to augment outcomes in gingival recession management (Cardaropoli et al., 2025), to address residual periodontal pocketing (Pilloni et al., 2023), to treat oral mucosal lesions (Jara, 2025), to mitigate radiation-induced oral mucositis (Podlesko et al., 2018), and to alleviate symptoms associated with temporomandibular joint disorders (Cenzato et al., 2024; Choi et al., 2026). In the preclinical and in vitro domains, these materials have been examined with respect to osteoblast differentiation and mineralization (Jeon et al., 2026), gingival fibroblast behavior (Han et al., 2025; Pachhapure et al., 2025), oral epithelial cell migration (Mladenova et al., 2025), modulation of periodontal inflammatory cascades (Han et al., 2025), bone defect regeneration (Ko et al., 2024; Lee et al., 2023), maxillary sinus floor augmentation (Lee et al., 2023; Omori et al., 2025), peri-implant soft tissue augmentation (C. H. Kim et al., 2025), alveolar ridge dimensional preservation (Ko et al., 2024), and cytoprotection against bisphosphonate- or zoledronic acid-mediated cellular injury (D. W. Lee et al., 2019; Pachhapure et al., 2025). Beyond primary research, the retrieved literature further encompasses narrative reviews, systematic reviews, scoping reviews, and clinical commentaries addressing PDRN and polynucleotide-based biomaterials in the contexts of dentistry, tissue engineering, periodontal regeneration, bone healing, and TMJ prolotherapy (Ku et al., 2026; Y. Kim et al., 2025; Manfredini et al., 2023; Mari et al., 2025; Oh et al., 2025). Taken collectively, this distribution of evidence suggests that the field is expanding at a rapid pace yet remains fragmented across disciplines, clinical indications, study designs, and material formulations.

A further complexity is introduced by inconsistent nomenclature across the literature. Whereas many publications employ the term PDRN, others investigate broader or related constructs, including polynucleotides, polynucleotide–hyaluronic acid (PN-HA) complexes, sodium-DNA preparations, salmon DNA-based scaffolds, and DNA-containing biomaterial composites (Han et al., 2025; Mladenova et al., 2025; Oh et al., 2025). Although these materials may share conceptual or mechanistic similarities with PDRN, they differ meaningfully in molecular weight distribution, chemical composition, carrier system, mode of delivery, concentration, degradation kinetics, and intended clinical application. Indiscriminate aggregation of such diverse materials under a single label risks obscuring clinically and scientifically important distinctions. A comprehensive evidence map of this field should therefore systematically differentiate among PDRN, polynucleotide-based hydrogels, PN-HA formulations, DNA-containing three-dimensional scaffolds, injectable preparations, topical delivery agents, and scaffold-integrated release systems.

Prior reviews have contributed valuable but necessarily partial perspectives. Several have summarized the general biological mechanisms of PDRN and its potential dental applications (Ku et al., 2026), while others have concentrated on discrete topics such as periodontal regeneration (Mari et al., 2025), TMJ prolotherapy (Y. Kim et al., 2025), or tissue-engineering applications more broadly (Oh et al., 2025). Nevertheless, the dental literature as a whole has yet to be comprehensively and systematically mapped across the full spectrum of clinical, preclinical, mechanistic, and biomaterial-science evidence. In particular, it remains unclear which dental subspecialties have achieved early clinical translation of PDRN-based therapies, which fields remain confined to preclinical investigation, what delivery systems and formulations have been evaluated, and where the most consequential evidence gaps persist.

In light of this situation, a scoping review constitutes the most appropriate methodological approach. The objective of a scoping review is not to synthesize evidence toward a single aggregate treatment effect estimate, but rather to delineate the extent, nature, and distribution of the available literature (Peters et al., 2020; Tricco et al., 2018). In contrast to a narrowly defined systematic review, a scoping review is well suited to incorporate clinical studies, animal experiments, in vitro investigations, biomaterial characterization studies, case reports, and review articles within a unified framework, thereby enabling a holistic mapping of the evidence base before more focused systematic reviews or meta-analyses are warranted (Peters et al., 2020). This is especially fitting for a rapidly evolving area in which the terminology, interventions, target tissues, outcome domains, and levels of evidence remain diverse and incompletely characterized.

Accordingly, the aim of this scoping review is to systematically map the applications of PDRN and related polynucleotide-based materials across the fields of dentistry, oral medicine, periodontology, implant dentistry, oral and maxillofacial surgery, temporomandibular disorders, oral mucosal disease, and dental tissue engineering and regeneration. The specific objectives are fourfold: (1) to classify the available literature into clinical, nonclinical or preclinical, and other evidence categories; (2) to identify the dental and oral-maxillofacial indications in which PDRN or related materials have been investigated; (3) to summarize the material formulations, delivery methods, and outcome domains reported across the literature; and (4) to delineate the knowledge gaps that necessitate further mechanistic investigation, development of standardized preclinical models, and execution of rigorously designed clinical trials.

MATERIALS AND METHODS

Study design

This scoping review was designed to map the available evidence on the use of polydeoxyribonucleotide (PDRN) and related polynucleotide-based materials in dental, oral, craniofacial, and maxillofacial applications. A scoping review approach was selected because the literature was expected to be heterogeneous in terms of terminology, material formulation, study design, target tissue, delivery method, and outcome domain. The review was conducted to identify the extent, nature, and distribution of the available evidence rather than to estimate a pooled treatment effect. The methodological approach was guided by established scoping review methodology and reported with reference to the PRISMA extension for Scoping Reviews where applicable (Peters et al., 2020; Tricco et al., 2018).

Eligibility criteria

Studies were considered eligible if they investigated PDRN, polydeoxyribonucleotide, polydeoxyribonucleic acid, polynucleotide, polynucleotide–hyaluronic acid formulations, sodium-DNA preparations, salmon DNA-derived materials, DNA-containing scaffolds, or closely related nucleotide-based biomaterials in a dental, oral, craniofacial, or maxillofacial context.

Eligible clinical studies included randomized clinical trials, split-mouth studies, retrospective clinical studies, prospective clinical studies, pilot clinical studies, case series, and case reports involving human participants or patient-level clinical observations. Eligible preclinical or nonclinical studies included in vitro studies, animal studies, ex vivo studies, biomaterial scaffold studies, and mechanistic experimental studies involving oral, periodontal, mucosal, dental, bone, implant-related, temporomandibular, or jaw-related models. Records were excluded if they were unrelated to dentistry, oral medicine, oral and maxillofacial surgery, craniofacial tissue repair, dental tissue engineering, or relevant oral-maxillofacial biomaterial applications. Studies in which “polynucleotide” was used in an unrelated molecular biology, microbiology, oncology, or genetic context were also excluded. Non-English full-text articles were excluded at the full-text review stage.

Information sources and search strategy

The literature search was performed in PubMed/MEDLINE and Embase. The search strategy combined terms related to the intervention, including “polydeoxyribonucleotide,” “PDRN,” “poly-

deoxyribonucleic acid," "polynucleotide," "polynucleotides," "PN-HA," "salmon DNA," and related terms, with dental and oral-maxillofacial terms such as "dentistry," "dental," "oral," "periodontal," "implant," "maxillofacial," "oral surgery," "third molar," "alveolar ridge," "bone regeneration," "sinus floor elevation," "oral mucositis," "osteonecrosis of the jaw," "MRONJ," "BRONJ," "temporomandibular," "TMJ," "pulp," "endodontic," "periodontal ligament," and "tooth avulsion."

The search was intentionally broad because terminology in this field is inconsistent and relevant studies were expected to be distributed across periodontology, oral and maxillofacial surgery, implant dentistry, oral medicine, biomaterials, and regenerative medicine. Outcome-specific search terms were not added at the initial stage to avoid excluding studies that used different outcome terminology.

Study selection

The PubMed/MEDLINE and Embase searches retrieved a total of 110 records. These records were screened sequentially at the title, abstract, and full-text levels. Title screening was used to remove clearly irrelevant records, including studies unrelated to dentistry, oral medicine, oral and maxillofacial surgery, craniofacial tissue repair, or dental tissue engineering. Abstract screening was then performed to determine whether the study involved PDRN, polynucleotide-based materials, or related DNA-derived biomaterials in a relevant dental or oral-maxillofacial context.

Following title and abstract screening, 51 articles were selected for full-text assessment. At this stage, the 51 articles consisted of 32 preclinical or nonclinical evidence articles, 13 clinical evidence articles, and 6 other evidence articles, including narrative reviews, systematic reviews, scoping reviews, or clinical commentaries.

Full-text review was then performed to confirm language, intervention material, target tissue, study design, dental or oral-maxillofacial relevance, and suitability for the evidence map. During full-text review, two preclinical articles were excluded: one because it was not published in English and one because the full-text content was judged not to be sufficiently relevant to the scope of the present review. In addition, the 6 other evidence articles were excluded from the final primary evidence set because they did not provide original clinical or preclinical application-level data. These 6 articles were retained only as supportive contextual literature for the Introduction and Discussion, including background on mechanisms, prior reviews, biomaterial development, terminology, and translational interpretation. Therefore, the final primary evidence set comprised 43 articles: 13 clinical studies and 30 preclinical or nonclinical studies.

Evidence classification

The final primary evidence set was classified into two major evidence types: clinical evidence and preclinical or nonclinical evidence.

Clinical evidence was defined as human participant research or patient-level clinical observation. This category included randomized clinical trials, split-mouth studies, retrospective clinical studies, prospective clinical studies, pilot clinical studies, case series, and case reports. Preclinical or nonclinical evidence was defined as experimental evidence not involving direct clinical patient-level evaluation. This category included in vitro investigations, animal experiments, ex vivo studies, biomaterial scaffold studies, combined in vitro–in vivo studies, and mechanistic studies involving oral, periodontal, mucosal, dental stem cell, bone, implant-related, temporomandibular, or jaw-related models.

The 6 other evidence articles were not included in the final primary evidence set and were not used for application-level evidence charting. However, they were used as supportive literature to contextualize biological mechanisms, prior review findings, biomaterial heterogeneity, clinical translation, and methodological gaps. This distinction was made to preserve a clear separation between original evidence and review-level or commentary-based interpretation.

Data charting

Data were extracted using structured evidence charts developed specifically for this review. Because the included studies were heterogeneous in study design, material formulation, delivery method, target tissue, and outcome domain, separate evidence charts were prepared for clinical and preclinical/nonclinical evidence.

For clinical studies, the evidence chart included author, year of publication, country or region, study design, sample size, clinical condition or indication, intervention material, material class, dose or concentration when available, delivery method, comparator or control group, follow-up period, primary outcomes, secondary outcomes, key findings, adverse events, and major limitations. When applicable, additional information was charted regarding randomization, split-mouth design, blinding, patient-reported outcomes, radiographic assessment, volumetric analysis, periodontal parameters, pain scores, mouth opening, swelling, and functional outcomes.

For preclinical and nonclinical studies, the evidence chart included author, year, study type, experimental model, animal species or cell type, defect or disease model, target tissue, material class, formulation, scaffold or carrier system, dose or concentration, exposure condition, delivery method, comparator or control group, observation period, outcome domain, histological outcomes, histomorphometric outcomes, cellular outcomes, inflammatory markers, osteogenic markers, angiogenic markers, molecular pathways, and key findings. This chart was used to identify which applications remained at the mechanistic, in vitro, animal, or biomaterial-development stage.

For the 6 supportive other evidence articles, a separate contextual chart was prepared. This chart included author, year, article type, scope of review or commentary, material classes discussed, dental or regenerative relevance, principal conclusions, and role in the present review. These articles were used to contextualize the primary evidence but were not counted as part of the final primary evidence set.

Material and delivery classification

Because the retrieved literature used heterogeneous terminology, the materials were not treated as a single uniform intervention. Each study was coded according to material class, including PDRN, polynucleotide, PN-HA formulation, sodium-DNA preparation, salmon DNA-derived scaffold, DNA/protamine complex, PDRN-loaded scaffold, or other nucleotide-based biomaterial system.

Delivery methods were also coded separately. Categories included soluble cell-culture exposure, topical application, gel placement, submucosal injection, intrasocket placement, intra-articular or periarticular injection, graft soaking, collagen-matrix soaking, scaffold loading, bone graft combination, and other local delivery systems. This classification was used to avoid inappropriate aggregation of biologically and clinically distinct materials under a single PDRN label.

Synthesis of evidence

The evidence was synthesized descriptively. No meta-analysis was attempted because of the heterogeneity of the included studies in terms of material type, delivery route, study design, target tissue, comparator, and outcome measure. Instead, the synthesis focused on mapping the distribution of evidence across evidence type, dental application domain, material class, delivery method, exposure condition, and outcome domain.

The synthesis was organized around four major questions: first, which dental and oral-maxillofacial fields have investigated PDRN or related polynucleotide-based materials; second, which applications have reached clinical evaluation and which remain preclinical or nonclinical; third, what formulations, delivery systems, exposure conditions, and outcome domains have been used; and fourth, what knowledge gaps remain for future mechanistic studies, standardized preclinical models, and rigorously designed clinical trials.

RESULTS

Overview of the Mapped Evidence

Following sequential title, abstract, and full-text screening, 49 articles were included in the final evidence map. These comprised 13 clinical studies, 30 nonclinical or preclinical studies, and 6 other articles, including narrative reviews, systematic re-

views, scoping reviews, and clinical commentaries. Of the 49 included articles, 41 were classified as Core evidence and 8 as Supportive evidence. Core articles were defined as those directly examining PDRN or related polynucleotide-based materials within dental, oral, periodontal, implant-related, temporomandibular, mucosal, craniofacial, or jaw-related contexts (Cenzato et al., 2024; Choi et al., 2026; Kim et al., 2026; Ko et al., 2024; Lee et al., 2023a; Mladenova et al., 2025; Pilloni et al., 2023).

The included evidence spanned several application domains: osteogenesis and bone regeneration, alveolar ridge preservation, maxillary sinus augmentation, implant-related hard- and soft-tissue regeneration, periodontal inflammation and regeneration, oral mucosal repair, medication-related or bisphosphonate-related osteonecrosis of the jaw (MRONJ/BRONJ), temporomandibular joint (TMJ) disorders, and postoperative morbidity following mandibular third molar surgery (Bitto et al., 2013; Kim et al., 2026; Ko et al., 2024; Lee et al., 2019; Omori et al., 2025; Ronsivalle et al., 2025).

Substantial heterogeneity was observed across both material class and delivery method. The reviewed studies employed soluble PDRN, injectable PDRN, polynucleotide–hyaluronic acid (PN-HA) gels, polynucleotide hydrogels, sodium-DNA preparations, salmon DNA scaffolds, DNA/protamine complexes, and PDRN-loaded scaffold systems (Buffoli et al., 2017; Colangelo et al., 2025; Han et al., 2025; Katsumata et al., 2015; Sato et al., 2020). Delivery methods included soluble cell-culture exposure, topical gel application, submucosal injection, intrasocket placement, pericapsular or periarticular TMJ injection, graft soaking, collagen-matrix soaking, scaffold loading, and bone-graft combination protocols (Cenzato et al., 2024; Kim et al., 2026; Lim et al., 2023; Mladenova et al., 2025; Omori et al., 2025). Across all domains, these materials were employed primarily as local adjunctive agents rather than as stand-alone therapeutics (Ko et al., 2024; Lee et al., 2023b; Pilloni et al., 2023).

Nonclinical and Preclinical Evidence

General Characteristics of the Preclinical Evidence

The preclinical evidence comprised 30 articles, encompassing in vitro studies, animal studies, combined in vitro–in vivo investigations, and scaffold-based biomaterial studies. These studies addressed osteoblast differentiation, mineralized tissue formation, angiogenesis, fibroblast migration, collagen synthesis, inflammatory modulation, mucosal healing, cytoprotection under bisphosphonate or zoledronic acid challenge, and scaffold-supported tissue repair (Han et al., 2025; Jeon et al., 2026; Mladenova et al., 2025; Pachhapure et al., 2025; Picciolo et al., 2021).

Preclinical findings were not uniform across material types. PDRN, PN-HA, sodium-DNA, salmon DNA scaffolds, and DNA/protamine complexes differed in formulation, carrier, exposure concentration, degradation behavior, and intended application (Buffoli et al., 2017; Katsumata et al., 2015; Mladenova et al., 2025; Sato et al., 2017; Sato et al., 2020). Accordingly, preclinical studies were mapped by target tissue, delivery route, exposure condition, outcome domain, and biological markers, rather than being interpreted as a single homogeneous intervention class.

Bone Regeneration, Osteogenesis, and Scaffold-Based Models

Bone regeneration constituted the largest preclinical evidence cluster. In an osteoblast–osteoclast differentiation model, PDRN enhanced osteoblast differentiation, as evidenced by increased alkaline phosphatase (ALP) activity, elevated mineralized matrix deposition, and upregulation of Runx2 and osteocalcin expression, while exerting no direct effect on osteoclast precursor viability, TRAP-positive osteoclast formation, or resorptive pit formation (Jeon et al., 2026). These findings suggest a predominantly osteoblast-oriented anabolic effect, without direct suppression of osteoclastogenesis (Jeon et al., 2026).

DNA-based scaffold studies demonstrated that salmon DNA promoted osteoblast migration and osteogenic differentiation in osteoblast-lineage models, with increases in ALP activity and upregulation of Runx2, Osterix, and mineralization-related markers (Katsumata et al., 2015; Sato et al., 2017). These effects were attributed not only to intrinsic DNA-derived bioactivity but also to scaffold-derived phosphate release and subsequent activation of sodium-dependent phosphate cotransporters, indicating that DNA-containing scaffolds may act through mechanisms distinct from those of soluble PDRN or injectable PN-HA formulations (Katsumata et al., 2015; Sato et al., 2017).

Animal defect studies provided supportive but heterogeneous evidence. In a nude mouse subcutaneous implantation model, PDRN combined with demineralized dentin matrix induced bone-like tissue formation with osteoblasts and fibroblasts, with the highest new bone formation ratio observed at the 2-week time point (Kim et al., 2016). Sodium-DNA promoted bone healing in rat calvarial defects and was associated with expression of osteogenic markers including RUNX2, osteocalcin, and osteopontin (Buffoli et al., 2017). A DNA/protamine complex paste enhanced regeneration in mandibular vertical or saddle-type alveolar ridge defects in dogs relative to blank controls and β-tricalcium phosphate (β-TCP; Sato et al., 2020). Conversely, a rabbit calvarial scaffold study using hydroxyapatite/TCP blocks loaded with PDRN demonstrated radiographic improvement at higher PDRN concentrations without a corresponding increase in histomorphometric bone formation (Lim et al., 2021). Collectively, these findings indicate that carrier system, concentration, defect type, and outcome modality substantially influence the apparent bone-regenerative effect of nucleotide-derived materials.

Alveolar Ridge Preservation, Implant-Related Bone Regeneration, and Sinus Augmentation

Several preclinical studies addressed clinically relevant dental bone-regeneration models. In a beagle dog alveolar ridge preservation model, an alloplastic graft soaked in 1.875 mg/mL PDRN and covered with a barrier membrane produced significantly greater early new bone formation, increased neovascularization, higher early micro-CT new bone volume/total volume ratio, and reduced buccal ridge-volume loss compared with graft and membrane alone (Ko et al., 2024). This model provided one of the most directly translational preclinical signals for PDRN as an adjunct in post-extraction socket healing and ridge dimensional maintenance (Ko et al., 2024).

In implant-related hard-tissue augmentation, PDRN was evaluated in buccal dehiscence and sinus floor elevation models with simultaneous implant placement. In a beagle dog buccal dehiscence model, collagenated biphasic calcium phosphate combined with PDRN tended to enhance early bone formation around augmented immediate implant sites, although the magnitude and consistency of the effect varied across outcome measures and healing intervals (Lee et al., 2023a). In a lateral-window sinus floor elevation model, PDRN combined with collagenated synthetic bone substitute did not substantially alter total augmented height or overall bone-to-implant contact; however, more favorable new bone formation and bone-to-implant contact were observed in apical regions and in areas adjacent to the Schneiderian membrane (Lee et al., 2023b).

The sinus augmentation evidence was inconsistent across studies. A rabbit sinus floor elevation pilot study suggested that PDRN increased newly formed bone area at selected healing intervals, although statistical significance was limited to specific time points (Lim et al., 2025). In a sequential rabbit sinus lift model, the addition of PN-HA gel to deproteinized bovine bone mineral (DBBM) did not improve new bone formation at 2 or 10 weeks and did not prevent sinus mucosa thinning or perforation (Maniwa et al., 2024). In contrast, a subsequent rabbit sinus augmentation study with simultaneous implant placement reported significantly higher new bone formation at 10 weeks and fewer sinus mucosa perforations when DBBM was combined with PN-HA gel (Omori et al., 2025). These discrepant outcomes suggest that implant placement, healing duration, graft–membrane interaction, sinus mucosal response, and histological endpoint selection may substantially influence the observed effect of PN-HA in sinus augmentation models (Maniwa et al., 2024; Omori et al., 2025).

Peri-Implant and Gingival Soft-Tissue Augmentation

Preclinical soft-tissue augmentation studies primarily investigated PDRN as an adjunct to xenogeneic collagen matrices or volume-stable collagen matrices. In a gingival phenotype modification model, a xenogeneic collagen matrix soaked in PDRN increased gingival thickness and yielded outcomes comparable to subepithelial connective tissue grafting for selected parameters

(Lim et al., 2023). In a buccally positioned implant model, collagen matrix combined with PDRN produced keratinized tissue height and tissue thickness gains approaching free gingival graft outcomes under certain conditions, although higher PDRN concentration did not consistently improve results (Kim et al., 2025a). In an immediate implant soft-tissue augmentation model, a volume-stable collagen matrix soaked in PDRN did not clearly enhance soft-tissue volume gain beyond the collagen matrix alone, and subepithelial connective tissue grafting generally remained superior at and above the implant platform level (Lee et al., 2024a).

Collectively, these findings indicate that collagen-matrix-based PDRN delivery is technically feasible for peri-implant and gingival soft-tissue augmentation, but its incremental benefit over collagen matrices alone remains inconsistent (Kim et al., 2025a; Lee et al., 2024a; Lim et al., 2023). Wound dehiscence and secondary healing were reported in several animal experiments, suggesting that matrix stability, surgical environment, PDRN concentration, and tissue exposure duration may be critical determinants of soft-tissue outcomes (Kim et al., 2025a; Lee et al., 2024a).

Oral Soft-Tissue Repair and Mucosal Healing Models

In vitro oral soft-tissue studies demonstrated that PN-HA and PN-based materials can modulate fibroblast and epithelial cell behavior. PN-HA enhanced migration of human palatal fibroblasts and oral epithelial cells, stimulated fibroblast proliferation, induced epithelial differentiation markers, and promoted epithelial proliferation in coculture, potentially through fibroblast-derived fibroblast growth factor 7 (FGF7) and hepatocyte growth factor (HGF; Mladenova et al., 2025). In a combined 2D and 3D gingival fibroblast model, two commercially available PN-based formulations (Odonto-PN and Regenfast) supported spheroid disassembly and closure of wound-like defects, with the PN-HA formulation demonstrating more sustained migration and scratch-closure activity even under mitomycin C-mediated inhibition of proliferation (Colangelo et al., 2025). These findings suggest that PN-based hydrogels may facilitate oral soft-tissue repair primarily through enhancement of cell migration, viability maintenance, and fibroblast–epithelial crosstalk, rather than through proliferative mechanisms alone (Colangelo et al., 2025; Mladenova et al., 2025).

An in vitro oral mucositis model using human gingival fibroblasts and oral mucosal epithelial cells demonstrated that PDRN attenuated lipopolysaccharide (LPS)-induced inflammatory signaling, including suppression of NF-κB activation and reduction of TNF-α and IL-6 expression, while increasing IL-10 and restoring Wnt/β-catenin, VEGF, and EGF-related healing pathways (Picciolo et al., 2021). Abrogation of these effects by an adenosine A2A receptor antagonist supported a central role for A2A receptor signaling in PDRN-mediated anti-inflammatory and pro-healing responses (Picciolo et al., 2021). Although this model did not fully replicate radiation- or chemotherapy-induced oral mucositis, it provided mechanistic rationale for the clinical exploration of topical or locally delivered PDRN in oral mucosal inflammation.

MRONJ/BRONJ-Related Models and Inflammatory Cytoprotection

Three preclinical studies examined bisphosphonate- or zoledronic acid-associated jaw complications and related cytotoxic or inflammatory pathways. In a rat BRONJ model involving ovariectomy, molar extraction, and systemic zoledronic acid administration, local PDRN treatment reduced necrotic bone percentage and increased vascularity and osteoclast counts, with the 8 mg/kg local dose producing the most pronounced improvement (Lee et al., 2019). In RAW 264.7 macrophages preconditioned with zoledronic acid and subsequently stimulated with LPS, PDRN attenuated pro-inflammatory responses and modulated key inflammatory mediators, including IL-1β, IL-6, TNF-α, inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and vascular endothelial growth factor (VEGF; Han et al., 2018). In human gingival fibroblasts, PDRN mitigated zoledronic acid-induced growth suppression by reducing intracellular reactive oxygen species, suppressing TANK-binding kinase 1 (TBK1) activation, and partially restoring protein kinase B (PKB/Akt) phosphorylation (Pachhapure et al., 2025).

These findings collectively suggest that PDRN may modulate both inflammatory and cytoprotective pathways relevant to MRONJ/BRONJ pathophysiology (Han et al., 2018; Lee et al., 2019; Pachhapure et al., 2025). However, the existing models do not fully recapitulate the polymicrobial, vascular, immunological, pharmacological, and surgical complexity of human MRONJ, and the evidence therefore remains at the preclinical stage.

Experimental Periodontitis and Periodontal Inflammatory Models

Periodontal inflammatory models supported a potential anti-inflammatory and matrix-modulating role for PDRN and PN-HA. In a rat ligature-induced periodontitis model, local application of 0.75% PDRN gel restored more normal histological architecture, reduced inflammatory and apoptotic protein expression, and preserved Bcl-2 expression compared with vehicle controls (Bitto et al., 2013). Inhibition of these effects by the selective A2A receptor antagonist 3,7-dimethyl-1-propargylxanthine (DMPX) supported the involvement of adenosine A2A receptor signaling in PDRN-mediated periodontal anti-inflammatory activity (Bitto et al., 2013). In HGF-1 human gingival fibroblasts stimulated with Porphyromonas gingivalis LPS, a cross-linked PN-HA formulation reduced IL-6 production and phospho-NF-κB p65 activation while promoting collagen type I and proteoglycan deposition (Han et al., 2025). Although these findings support anti-inflammatory and matrix-modulating effects in periodontal soft tissues, they do not establish true periodontal regeneration in defect-based preclinical models (Bitto et al., 2013; Han et al., 2025).

Dental and Gingival Stem Cell Models

PDRN was additionally evaluated in dental and gingival mesenchymal stem cell systems. In stem cells from human exfoliated deciduous teeth (SHED), PDRN enhanced cellular proliferation, migration, resistance to oxidative stress, and mitochondrial function, with these effects associated with activation of the Akt signaling pathway (Yun et al., 2024). In gingiva-derived mesenchymal stem cell spheroids, PDRN did not substantially alter spheroid morphology or cellular viability, but modulated osteogenic differentiation in a concentration-dependent manner: 75 μg/mL PDRN significantly enhanced calcium deposition, whereas RUNX2 and COL1A1 mRNA expression profiles varied across the tested concentration range (Lee et al., 2024b). These findings indicate that PDRN may prime oral and dental progenitor cells toward regenerative behavior; however, translation to pulp regeneration, periodontal regeneration, or bone defect repair requires validation in integrated in vivo models (Lee et al., 2024b; Yun et al., 2024).

Clinical Evidence

General Characteristics of the Clinical Evidence

The clinical evidence comprised 13 studies addressing postoperative mandibular third molar morbidity, TMJ disorders, periodontal and mucogingival regeneration, alveolar bone regeneration, and oral or perioral mucosal conditions (Cardaropoli et al., 2025; Choi et al., 2026; Kim et al., 2026; Pilloni et al., 2023). Study designs included randomized clinical trials, split-mouth comparative studies, retrospective cohort studies, prospective case series, pilot studies, and case reports, with sample sizes ranging from single-patient case reports to a retrospective cohort of 66 patients (Choi et al., 2026; Jara, 2025; Kim et al., 2026; Rho et al., 2025). Follow-up periods ranged from 7-day postoperative assessments in third molar surgery studies to 12-month evaluations in periodontal and mucogingival applications (Cardaropoli et al., 2025; Pilloni et al., 2023; Ronsivalle et al., 2025).

PN-HA formulations were most frequently employed in periodontal, bone-regenerative, and TMJ applications, whereas PDRN preparations were primarily used as injectable or topical adjuncts in third molar surgery, TMJ prolotherapy, actinic cheilitis, and radiation-induced oral mucositis (Cenzato et al., 2024; Choi et al., 2026; Jara, 2025; Podlesko et al., 2018). Delivery methods included submucosal injection, intrasocket gel placement, pericapsular TMJ injection, periodontal defect gel application, graft combination with DBBM or collagen membranes, collagen matrix soaking, and topical spray application (Beretta et al., 2025; Kim et al., 2026; Ronsivalle et al., 2025; Severi et al., 2026).

Postoperative Morbidity Following Mandibular Third Molar Surgery

Two clinical studies evaluated PDRN or PN-HA formulations in the context of mandibular third molar extraction. In a prospective randomized double-blind split-mouth trial of 30 patients undergoing bilateral impacted mandibular third molar extraction, submucosal injection of 1.875 mg PDRN per 1.0 mL significantly reduced pain scores and facial swelling on postoperative days 3 and 7 compared with saline injection (Kim et al., 2026). Three-dimensional facial scan superimposition confirmed lower swelling volumetrics on the PDRN-treated side, whereas pain duration and probing depth distal to the second molar at 60 days did not differ significantly between sides (Kim et al., 2026). In a retrospective split-mouth study of 18 patients undergoing bilateral partially impacted mandibular third molar removal, intrasocket PN-HA gel placement reduced early pain scores, attenuated swelling increases, and accelerated recovery of maximum interincisal distance, with the greatest intergroup differences observed at approximately 48 to 72 hours postoperatively (Ronsivalle et al., 2025). Across both studies, findings suggest a consistent short-term clinical signal that local PDRN or PN-HA may reduce early inflammatory morbidity following mandibular third molar surgery, although longer-term socket healing and distal second molar periodontal outcomes remain insufficiently characterized (Kim et al., 2026; Ronsivalle et al., 2025).

Temporomandibular Joint Disorders

Three clinical studies evaluated PDRN or PN-HA injections in patients with temporomandibular disorders or TMJ osteoarthrosis. In a retrospective chart review of 66 patients with TMD refractory to conventional treatment, prolotherapy with either hypertonic dextrose or PDRN significantly reduced pain scores and improved maximum mouth opening after a mean of approximately 2.3 treatment sessions per patient (Choi et al., 2026). Both groups demonstrated significant within-group improvement; however, no statistically significant between-group difference was identified when comparing PDRN and dextrose as proliferant agents (Choi et al., 2026). In a single-blind randomized clinical trial, repeated pericapsular PN-HA injection produced significantly greater pain reduction than physiotherapy at 12 weeks in patients with TMJ osteoarthrosis, although maximum mouth opening did not demonstrate a statistically significant between-group difference (Cenzato et al., 2024). In a pilot study evaluating visual-inertial odometry-assisted TMJ injection guidance, both augmented-reality-guided and manual palpation-guided groups received PN-HA; accordingly, this study addressed injection guidance technology rather than the independent efficacy of the polynucleotide component itself (Farronato et al., 2025). The available TMJ evidence suggests potential benefit of PDRN or PN-HA injection for pain reduction and improvement in mandibular function, but the independent contribution of polynucleotides relative to injection effects, hyaluronic acid, dextrose, physiotherapy, or guidance methodology remains unresolved (Cenzato et al., 2024; Choi et al., 2026; Farronato et al., 2025).

Periodontal, Mucogingival, and Alveolar Bone Regenerative Applications

Five clinical studies addressed periodontal, mucogingival, or alveolar bone regenerative applications of PN-HA formulations. In a randomized split-mouth single-blind clinical trial of 50 patients with residual periodontal pockets, adjunctive subgingival PN-HA gel following re-instrumentation did not confer statistically significant additional reductions in probing depth, clinical attachment gain, or pocket closure compared with re-instrumentation alone at 48 weeks (Pilloni et al., 2023). Pocket closure was achieved at 76% of PN-HA test sites and 70% of control sites, and the material was well tolerated without reported adverse events (Pilloni et al., 2023).

In a retrospective multicenter case series of 43 patients with 55 infrabony defects, treatment with PN-HA gel, with or without DBBM, was associated with probing depth reduction, clinical attachment gain, pocket closure, and radiographic bone fill at one year (Cairo et al., 2025). In a single-patient case report involving a molar intrabony defect, DBBM combined with PN-HA gel was used in conjunction with a single flap approach and periosteal pedicle flap, yielding pocket closure and substantial radiographic remineralization at 12 months (Severi et al., 2026). In a prospective case series of 16 patients with 67 multiple adjacent type 1 gingival recessions, coronally advanced flap combined with a volume-stable collagen matrix soaked in PN-HA produced high mean root coverage, frequent complete root coverage, increased gingival thickness, low postoperative pain scores, and favorable esthetic outcomes at 12 months (Cardaropoli et al., 2025). In a proof-of-concept clinical and histological case series of six patients undergoing staged horizontal alveolar bone regeneration, DBBM mixed with PN-HA and covered by a collagen membrane yielded uneventful postoperative healing, clinically stable augmentation, histological evidence of lamellar new bone formation, and a mean horizontal bone gain of approximately 4.9 mm (Beretta et al., 2025).

Across periodontal and regenerative clinical applications, PN-HA was used broadly as an adjunct to established surgical and regenerative procedures; however, controlled evidence remains limited and inconsistent. The only adequately controlled trial of residual pocket management failed to demonstrate consistent superiority of PN-HA over re-instrumentation alone, whereas uncontrolled case series and case reports reported favorable healing when PN-HA was used in combination with bone grafts, collagen matrices, barrier membranes, or specific flap designs (Beretta et al., 2025; Cairo et al., 2025; Cardaropoli et al., 2025; Pilloni et al., 2023; Severi et al., 2026).

Oral Mucosal and Lip Applications

Three clinical studies evaluated PDRN or polynucleotide-based therapy for oral or perioral mucosal conditions. In a single case report of actinic cheilitis, one session of subdermal PDRN infiltration was associated with improvements in epithelial integrity, lip texture, pain, and oral function over a short observation period (Jara, 2025). In a prospective multicenter open-label study of 30 participants with dry and chapped lips, three sessions of highly purified polynucleotide injection into the vermilion zone significantly improved lip wrinkle and roughness scores through week 9; transient injection-site swelling, pain, and erythema were reported as common mild adverse reactions (Rho et al., 2025). In a case series of three patients with grade 3 radiation-induced oral mucositis occurring during head-and-neck cancer treatment, topical PDRN spray was well tolerated and did not interrupt oncological therapy; pain relief and mucositis improvement were observed in two patients, whereas one patient experienced only transient analgesia (Podlesko et al., 2018). Evidence in this domain remains exploratory, as it is derived exclusively from uncontrolled prospective studies, case reports, or small case series (Jara, 2025; Podlesko et al., 2018; Rho et al., 2025).

Clinical Safety and Tolerability

Across the 13 clinical studies, PDRN and polynucleotide-based materials were generally well tolerated, and no serious treatment-related adverse events were reported (Beretta et al., 2025; Kim et al., 2026; Pilloni et al., 2023; Podlesko et al., 2018). Periodontal, bone-regenerative, and third molar studies consistently reported uneventful postoperative healing without material-related infection, allergic reaction, or graft-related complication (Beretta et al., 2025; Kim et al., 2026; Pilloni et al., 2023; Ronsivalle et al., 2025). TMJ studies reported no major adverse effects following PDRN or PN-HA injection, although safety interpretation was constrained by short follow-up durations and modest sample sizes (Cenzato et al., 2024; Choi et al., 2026; Farronato et al., 2025). Injection-site reactions were most prominent in the prospective lip study, in which swelling, pain, and erythema occurred frequently in the immediate post-injection period but were predominantly mild and transient in nature (Rho et al., 2025). In aggregate, the short-term tolerability profile of PDRN and PN-HA appears favorable across the evaluated dental and oral-maxillofacial applications; however, long-term and repeated-use safety data remain insufficient.

Cross-Domain Synthesis of Preclinical and Clinical Evidence

The preclinical evidence provides biological plausibility for PDRN and related polynucleotide-based materials through demonstrated effects on osteoblast differentiation, angiogenic signaling, fibroblast migration, collagen synthesis, inflammatory resolution, epithelial repair, and cytoprotection under bisphosphonate or zoledronic acid challenge (Han et al., 2018; Jeon et al., 2026; Mladenova et al., 2025; Pachhapure et al., 2025; Picciolo et al., 2021). The most directly translational preclinical domains were

alveolar ridge preservation, sinus augmentation, implant-related bone regeneration, gingival phenotype modification, oral mucosal repair, and BRONJ/MRONJ-related models (Ko et al., 2024; Lee et al., 2019; Lim et al., 2023; Omori et al., 2025).

The strongest alignment between preclinical and clinical evidence was identified for short-term inflammatory modulation and soft-tissue healing. Preclinical studies consistently demonstrated anti-inflammatory, pro-migratory, and pro-healing effects, while clinical studies reported reductions in postoperative pain, swelling, or mucosal symptoms at early time points (Kim et al., 2026; Mladenova et al., 2025; Picciolo et al., 2021; Ronsivalle et al., 2025). Translational alignment was comparatively weaker for true periodontal or osseous regeneration, as preclinical models frequently yielded favorable histological or early bone-healing signals, whereas clinical regenerative studies were often uncontrolled or confounded by concurrent interventions including bone grafts, barrier membranes, collagen matrices, and surgical flap designs (Beretta et al., 2025; Cairo et al., 2025; Ko et al., 2024; Lee et al., 2023a; Pilloni et al., 2023). Evidence was particularly inconsistent in sinus augmentation and peri-implant soft-tissue augmentation, where conceptually similar material approaches produced divergent outcomes depending on the experimental model, material concentration, carrier system, and selected endpoint (Kim et al., 2025a; Lee et al., 2024a; Maniwa et al., 2024; Omori et al., 2025).

Overall, PDRN and related polynucleotide-based materials are most appropriately characterized at present as locally delivered regenerative or anti-inflammatory adjuncts, rather than as established stand-alone dental therapeutics. The current body of evidence supports clinical feasibility and short-term tolerability; however, definitive efficacy for most indications remains unproven, owing to small sample sizes, heterogeneous material formulations, a paucity of adequately powered controlled trials, limited follow-up durations, and the inherent difficulty of isolating the active polynucleotide component from carrier materials or co-administered interventions (Beretta et al., 2025; Cenzato et al., 2024; Cardaropoli et al., 2025; Choi et al., 2026; Pilloni et al., 2023). Future studies should report material composition, molecular weight distribution, concentration, carrier system, release profile, delivery route, and exposure duration in standardized detail to facilitate meaningful cross-study comparisons. Future clinical trials should also incorporate comparator arms that allow the independent contribution of PDRN or polynucleotides to be distinguished from hyaluronic acid vehicles, collagen matrices, bone grafts, barrier membranes, injection procedure effects, and surgical flap designs (Han et al., 2025; Mladenova et al., 2025; Omori et al., 2025).

DISCUSSION

Principal Findings

This scoping review systematically mapped the available evidence on PDRN and related polynucleotide-based materials across dental, oral, periodontal, implant-related, temporomandibular, mucosal, and craniofacial applications. The final evidence map demonstrated that this field is expanding rapidly yet remains heterogeneous with respect to study design, material terminology, delivery method, target tissue, and translational maturity. The 49 included articles comprised 13 clinical studies, 30 nonclinical or preclinical studies, and 6 other articles including reviews and commentaries. Across all domains, PDRN and related polynucleotide-based materials were most consistently employed as locally delivered adjunctive agents rather than as stand-alone therapeutics.

The overarching finding was that the preclinical literature provides biologically plausible support for PDRN and polynucleotide-based therapies through several converging mechanisms, including osteoblast differentiation, angiogenic signaling, fibroblast migration, collagen synthesis, inflammatory modulation, epithelial repair, and cytoprotection under inflammatory or bisphosphonate-related challenge (Bitto et al., 2013; Han et al., 2025; Jeon et al., 2026; Mladenova et al., 2025; Pachhapure et al., 2025; Picciolo et al., 2021). These mechanisms are consistent with the broader regenerative medicine literature, in which PDRN is described as acting principally through adenosine A2A receptor stimulation, salvage pathway-mediated nucleotide provision, angiogenic modulation, and tissue repair-associated cellular activation (Ku et al., 2026; Oh et al., 2025). The clinical evidence, however, remains early and uneven. The most consistent short-term signals were observed in the context of postoperative morbidity following mandibular third molar extraction, whereas evidence for periodontal regeneration, mucogingival augmentation, alveolar bone repair, TMJ disorders, and oral mucosal conditions was more limited or inconsistent (Cenzato et al., 2024; Choi et al., 2026; Kim et al., 2026; Pilloni et al., 2023; Ronsivalle et al., 2025).

Biological Plausibility and Translational Rationale

The biological rationale for PDRN in dentistry is conceptually compelling. Favorable clinical outcomes in the oral and craniofacial environment depend on the coordinated resolution of inflammation, sustained angiogenesis, fibroblast recruitment and activation, epithelial migration, osteogenic differentiation, and extracellular matrix remodeling — all processes in which PDRN and polynucleotide-based materials have demonstrated activity in preclinical models. Notably, PDRN enhanced osteoblast differentiation markers without directly suppressing osteoclastogenesis, suggesting a primarily anabolic effect on the osteoblastic lineage in mineralized tissue repair rather than a global suppressor of bone remodeling (Jeon et al., 2026). In oral soft-tissue models, PDRN and PN-HA formulations modulated gingival fibroblast behavior, attenuated inflammatory signaling, and promoted collagen and proteoglycan deposition (Han et al., 2025; Mladenova et al., 2025). These findings are consistent with the mechanistic framework described in general regenerative medicine reviews, where PDRN is positioned as a pleiotropic tissue repair agent acting through A2A receptor activation, extracellular matrix remodeling, angiogenesis, and nucleotide salvage pathway support (Ku et al., 2026; Oh et al., 2025).

Nevertheless, biological plausibility should not be conflated with clinical efficacy. The majority of preclinical outcomes were derived from surrogate markers — including ALP activity, Runx2 and osteocalcin expression, VEGF-related signaling, NF-κB modulation, histomorphometric new bone formation, or fibroblast scratch-assay migration (Bitto et al., 2013; Jeon et al., 2026; Picciolo et al., 2021; Sato et al., 2017). Although these markers are valuable for mechanistic interpretation, they do not necessarily predict durable clinical outcomes such as long-term implant survival, stable marginal bone levels, sustained pocket closure, complete periodontal regeneration, predictable keratinized tissue gain, or prolonged pain relief. The current literature therefore supports PDRN and related materials as promising biologically active adjuncts, but not yet as validated dental therapeutics with established clinical efficacy.

Material Heterogeneity as a Central Challenge

One of the most consequential challenges identified in this review was the profound inconsistency in material terminology and characterization across the included literature. Although many studies employed the term PDRN, others investigated polynucleotides, PN-HA complexes, sodium-DNA, salmon DNA scaffolds, DNA/protamine complexes, or PDRN-loaded biomaterial scaffolds (Buffoli et al., 2017; Colangelo et al., 2025; Katsumata et al., 2015; Sato et al., 2020). While these materials may share nucleotide-derived origins or conceptual similarity, they differ substantially in molecular weight distribution, chemical composition, carrier system, degradation profile, release kinetics, and intended delivery route. The distinction between PDRN and polynucleotides (PN) is particularly important: PDRN conventionally refers to shorter, low-molecular-weight DNA fragments (typically below 1,500 kDa), whereas PN formulations may include longer deoxyribonucleotide chains with potentially different receptor binding profiles and biological activities (Ku et al., 2026).

This material heterogeneity fundamentally complicates cross-study interpretation. Soluble PDRN exposure in cell culture cannot be directly equated with a PN-HA hydrogel placed into a periodontal pocket, a PDRN-soaked collagen matrix used for peri-implant soft-tissue augmentation, or a salmon DNA scaffold implanted into a calvarial bone defect (Colangelo et al., 2025; Lim et al., 2023; Mladenova et al., 2025; Sato et al., 2017). Furthermore, when PDRN is incorporated into complex multicomponent scaffolds containing bone morphogenetic protein-2 (BMP-2), magnesium hydroxide, bone extracellular matrix, or ceramic components, the independent biological contribution of the polynucleotide fraction becomes particularly difficult to isolate (Lim

et al., 2021; Oh et al., 2025). To enable meaningful comparison across future studies, investigators should report material composition, molecular weight distribution, nominal concentration, carrier system, degradation profile, release kinetics, delivery route, exposure duration, and timing of application according to standardized reporting criteria.

Bone Regeneration and Implant-Related Applications

Bone regeneration constituted the largest preclinical evidence cluster in this review. Multiple studies suggested that PDRN or DNA-derived scaffold materials may augment osteogenesis, early bone formation, angiogenesis, and bone defect repair (Buffoli et al., 2017; Jeon et al., 2026; Kim et al., 2016; Ko et al., 2024; Lee et al., 2023a). These findings are consistent with the conclusions of a prior scoping review of PDRN in bone healing, which identified an enhancing effect on new bone formation when PDRN was combined with grafting materials, while emphasizing the need for future controlled clinical studies (Manfredini et al., 2023). In the present review, the most clinically relevant preclinical signals for bone-regenerative applications arose from alveolar ridge preservation, lateral bone augmentation, sinus floor elevation, and peri-implant bone regeneration models (Ko et al., 2024; Lee et al., 2023a; Lee et al., 2023b; Lim et al., 2025; Omori et al., 2025).

The evidence was encouraging but not uniform. In a beagle dog alveolar ridge preservation model, PDRN-soaked alloplastic grafting was associated with greater early new bone formation, increased neovascularization, and reduced buccal ridge-volume loss compared with graft and membrane alone (Ko et al., 2024). In sinus augmentation and implant-related bone models, PDRN or PN-HA occasionally improved region-specific or time-dependent outcomes — such as apical new bone formation, bone-to-implant contact near the Schneiderian membrane, or histomorphometric bone area at selected healing intervals — but these effects were not consistently reproduced across different models or material formulations (Lee et al., 2023b; Lim et al., 2025; Omori et al., 2025). Conversely, one sequential rabbit sinus lift study found no benefit of adding PN-HA to DBBM at either 2 or 10 weeks, and a rabbit calvarial scaffold study reported radiographic improvement without corresponding histomorphometric confirmation of enhanced bone formation (Lim et al., 2021; Maniwa et al., 2024).

These inconsistencies suggest that the apparent bone-regenerative effects of PDRN and related materials may be substantially influenced by defect morphology, carrier material, local vascularity, material concentration, healing interval, and the specific outcome modality evaluated. At the clinical level, translation remains limited. The only available clinical and histological case series reporting horizontal ridge augmentation with DBBM mixed with PN-HA showed favorable outcomes but lacked a control group, precluding any attribution of benefit to the PN-HA component specifically (Beretta et al., 2025). PDRN and PN-HA therefore appear biologically plausible as bone-regenerative adjuncts, but adequately controlled clinical studies are required before any definitive claim of clinical benefit beyond established grafting, membrane, or flap procedures can be made.

Periodontal and Mucogingival Applications

The periodontal evidence exhibited a pattern parallel to that observed in bone regeneration: strong biological plausibility, encouraging uncontrolled case-level clinical signals, but limited and inconsistent controlled evidence. In a rat ligature-induced periodontitis model, PDRN reduced inflammatory and apoptotic signaling through mechanisms dependent on adenosine A2A receptor activity (Bitto et al., 2013). In human gingival fibroblasts stimulated with Porphyromonas gingivalis LPS, a cross-linked PN-HA formulation reduced IL-6 production and NF-κB pathway activation while promoting collagen type I and proteoglycan deposition (Han et al., 2025). These findings provide mechanistic support for a role of PDRN or PN-HA in periodontal inflammatory modulation and soft-tissue matrix remodeling.

The available clinical evidence is, however, mixed. The randomized split-mouth trial by Pilloni et al. (2023) — the only adequately controlled periodontal clinical study identified in this review — found that adjunctive subgingival PN-HA gel following re-instrumentation did not produce statistically significant improvements in probing depth reduction, clinical attachment gain, or pocket closure at 48 weeks compared with re-instrumentation alone. This finding is clinically important because it suggests that the anti-inflammatory and matrix-modulating properties observed in preclinical models may not translate consistently into measurable therapeutic advantage under controlled conditions. In contrast, multiple uncontrolled periodontal and mucogingival case series reported favorable outcomes when PN-HA was combined with guided tissue regeneration, bone grafting, gingival recession coverage, or horizontal ridge augmentation procedures (Beretta et al., 2025; Cairo et al., 2025; Cardaropoli et al., 2025; Severi et al., 2026). A recent systematic review concluded that PDRN may offer clinical benefit in periodontal regeneration through anti-inflammatory, angiogenic, and tissue repair effects, while simultaneously acknowledging the need for additional well-designed clinical trials and standardized treatment protocols (Mari et al., 2025). The present review supports a cautious interpretation consistent with that conclusion: PN-HA appears clinically feasible and biologically attractive as an adjunct to established periodontal and regenerative procedures, but current controlled data do not yet support a reproducible incremental clinical benefit attributable to the polynucleotide component.

Peri-Implant and Gingival Soft-Tissue Augmentation

The peri-implant soft-tissue evidence is predominantly preclinical and centers on collagen matrix-based PDRN delivery systems. PDRN-soaked xenogeneic collagen matrices or volume-stable collagen matrices were evaluated in gingival phenotype modification, buccally positioned implant, and immediate implant soft-tissue augmentation models (Kim et al., 2025a; Lee et al., 2024a; Lim et al., 2023). These studies indicated that PDRN may support keratinized tissue height gain and gingival thickness increase when incorporated into collagen matrices; however, the incremental benefit relative to collagen matrices alone was not consistently demonstrated across different experimental conditions and outcome measures.

The observation that higher PDRN concentrations did not reliably produce superior soft-tissue outcomes carries important implications (Kim et al., 2025a). This finding suggests that PDRN may not follow a predictable linear dose-response relationship in vivo, and that factors such as excessive local concentration, insufficient matrix retention, rapid washout, compromised wound stability, or matrix-tissue interface dynamics may modify or attenuate the biological response. Wound dehiscence and secondary-intention healing were documented in several preclinical soft-tissue models, indicating that matrix design, surgical wound stability, local oral microbial environment, PDRN concentration, and tissue exposure duration may collectively determine clinical outcomes (Kim et al., 2025a; Lee et al., 2024a). Future preclinical and clinical studies should therefore characterize not only the active polynucleotide molecule, but also the delivery scaffold architecture, material retention kinetics, optimal concentration range, and surgical environment requirements.

Oral Mucosal and Perioral Applications

The oral mucosal and perioral evidence points to possible tissue-reparative and symptom-modulating properties but remains at an early exploratory stage. In an in vitro oral mucositis model, PDRN attenuated LPS-induced NF-κB activation, reduced TNF-α and IL-6 expression, increased IL-10, and restored Wnt/β-catenin, VEGF, and EGF-related healing pathways through adenosine A2A receptor-dependent mechanisms, thereby providing a mechanistic basis for local PDRN application in inflamed oral mucosa (Picciolo et al., 2021). In the clinical domain, topical PDRN spray was associated with pain relief and improvement in radiation-induced oral mucositis in a case series of three patients, although the absence of a concurrent control group and the use of adjunctive supportive care preclude any definitive conclusions regarding treatment efficacy (Podlesko et al., 2018). PDRN was additionally reported in a single case of actinic cheilitis, and a prospective multicenter study investigated highly purified polynucleotide injection for dry and chapped lips; however, these reports remain case-level or uncontrolled and are partly positioned within dermatological or aesthetic practice contexts rather than conventional dental therapeutics (Jara, 2025; Rho et al., 2025).

A published clinical commentary describing the use of PN-HPT in late facial polymethylmethacrylate (PMMA)-related soft-tissue

complications further illustrates the broader craniofacial and aesthetic interest in polynucleotide-based tissue remodeling (Palmieri & Raichi, 2022). Although contextually relevant for understanding soft-tissue remodeling and perioral applications, this report differs substantially from controlled dental studies in terms of indication, tissue environment, endpoint selection, and intervention design and should not be interpreted as dental regenerative evidence. Oral and perioral mucosal applications should therefore be considered exploratory at present, and future research priority should be directed toward adequately controlled studies in radiation-induced oral mucositis, post-surgical mucosal wound healing, and oral inflammatory disorders.

MRONJ/BRONJ-Related Implications

The MRONJ/BRONJ-related evidence is mechanistically informative but remains entirely preclinical. In a rat model of bisphosphonate-related osteonecrosis of the jaw, local PDRN administration reduced necrotic bone percentage and increased vascularity and osteoclast counts, suggesting a possible role in restoring bone remodeling capacity and vascular integrity in tissues suppressed by bisphosphonate exposure (Lee et al., 2019). In vitro, PDRN attenuated zoledronic acid- and LPS-induced inflammatory responses in RAW 264.7 macrophages, and separately mitigated zoledronic acid-induced growth suppression in human gingival fibroblasts through modulation of reactive oxygen species, TBK1 signaling, and PKB/Akt phosphorylation (Han et al., 2018; Pachhapure et al., 2025). Together, these studies suggest that PDRN may act on inflammatory, angiogenic, and cytoprotective pathways with direct relevance to MRONJ pathophysiology.

However, clinical MRONJ is a complex, multifactorial condition involving antiresorptive pharmacological exposure, oral microbial biofilm, impaired mucosal wound healing, vascular compromise, immune dysregulation, surgical trauma, and patient-level systemic risk factors including malignancy, corticosteroid use, and nutritional status (Khan et al., 2015; Ruggiero et al., 2014). Current preclinical models cannot adequately recapitulate this pathological complexity. PDRN should therefore be regarded as a candidate adjunctive agent warranting further investigation in MRONJ research, rather than as a clinically established therapeutic option. Clinical translation would require clearly defined patient populations, validated staging criteria such as those of the American Association of Oral and Maxillofacial Surgeons (AAOMS), standardized background surgical or pharmacological therapy, and clinically meaningful primary outcomes including mucosal closure, osseous exposure resolution, infection control, pain reduction, and freedom from recurrence.

Temporomandibular Joint Applications

The TMJ literature indicates a possible symptom-modulating role for PDRN or PN-HA injections, but the evidence base is methodologically limited and does not yet permit definitive efficacy conclusions. A retrospective prolotherapy study reported significant within-group improvements in pain scores and maximum mouth opening following either PDRN or dextrose injection, but identified no statistically significant between-group difference between the two proliferant agents (Choi et al., 2026). A randomized clinical trial demonstrated significantly greater pain reduction after repeated pericapsular PN-HA injection compared with a physiotherapy program at 12 weeks; however, between-group improvement in maximum mouth opening did not reach statistical significance (Cenzato et al., 2024). An augmented-reality-guided injection pilot study evaluated the feasibility of guided TMJ delivery, but as both guided and manually palpated groups received PN-HA, the study addressed injection guidance accuracy rather than the independent clinical efficacy of the polynucleotide formulation (Farronato et al., 2025). A supportive review of TMD prolotherapy concluded that prolotherapy may represent a conservative regenerative option for refractory temporomandibular disorders, while noting that hypertonic dextrose remains the more established and better-evidenced proliferant and that PDRN-specific TMD evidence is still preliminary (Kim et al., 2025b). The present review supports that assessment. Although PDRN or PN-HA injection may reduce pain and improve mandibular function in selected patients with TMD or TMJ osteoarthrosis, future studies must employ study designs capable of distinguishing the specific contribution of the polynucleotide component from hyaluronic acid vehicles, dextrose, needling effects, placebo injection, physiotherapy, arthrocentesis, and the natural fluctuation of TMD symptoms.

Postoperative Inflammatory Morbidity After Third Molar Surgery

The most clinically coherent and internally consistent signal in the present review was identified in the context of mandibular third molar surgery. Two studies — one prospective randomized double-blind split-mouth trial and one retrospective split-mouth study — reported reductions in early postoperative pain, facial swelling, or trismus following local PDRN or PN-HA application at the third molar site (Kim et al., 2026; Ronsivalle et al., 2025). These outcomes align well with preclinical evidence demonstrating anti-inflammatory and pro-healing effects of PDRN and polynucleotide-based materials in fibroblast, mucosal, and inflammatory cell models (Han et al., 2025; Picciolo et al., 2021). Relative to true bone or periodontal regeneration endpoints, postoperative inflammatory morbidity may constitute a more immediately testable clinical indication because relevant outcomes — including pain intensity scores, three-dimensional facial swelling volumetrics, maximum interincisal distance, analgesic consumption, and patient-reported discomfort — are short-term, objectively quantifiable, and biologically linked to the inflammatory resolution processes in which PDRN has demonstrated preclinical activity.

Nevertheless, even within this relatively promising domain, the current evidence remains insufficient to support a definitive clinical recommendation. The available studies focused exclusively on early postoperative endpoints and did not assess longer-term outcomes such as socket bone fill, distal second molar periodontal health, alveolar osteitis incidence, postoperative infection, or wound-healing complications (Kim et al., 2026; Ronsivalle et al., 2025). Future randomized controlled trials in third molar surgery should incorporate standardized surgical difficulty scoring, analgesic consumption monitoring, three-dimensional volumetric swelling analysis, trismus recovery indices, distal second molar periodontal parameter assessment, and systematic adverse event surveillance.

Clinical Safety and Tolerability

Across the clinical studies included in this review, PDRN and polynucleotide-based materials were consistently reported as well tolerated, and no serious treatment-related adverse events were documented (Beretta et al., 2025; Cenzato et al., 2024; Kim et al., 2026; Pilloni et al., 2023). Transient injection-site swelling, pain, and erythema were the most frequently reported reactions in the prospective lip study, and topical PDRN spray was well tolerated without interruption of oncological therapy in oral mucositis cases (Podlesko et al., 2018; Rho et al., 2025). Preclinical studies also generally supported biocompatibility; however, some outcomes indicated that material concentration, carrier design, wound stability, and scaffold properties may alter the local tissue response in ways that are not fully captured by cell viability assays alone (Kim et al., 2025a; Lim et al., 2021; Oh et al., 2025).

The apparent favorable safety profile requires cautious interpretation. Most clinical studies were small in sample size, short in follow-up duration, and uncontrolled in design. Critical safety questions remain inadequately characterized, including long-term and repeated-use safety for intra-articular TMJ injections, use in potentially malignant disorders such as actinic cheilitis, application in immunocompromised or oncology patients, behavior in combination with scaffold or graft systems, and safety under conditions of chronic inflammatory disease. Future clinical studies should incorporate systematic, pre-specified adverse event reporting that includes infection, persistent swelling, pain, allergic or hypersensitivity reactions, delayed wound healing, graft or scaffold exposure, foreign-body reactions, mucosal changes, and requirement for retreatment or surgical revision.

Clinical and Research Implications

The totality of the evidence presented in this review positions PDRN and related polynucleotide-based materials at a transitional point between experimentally promising regenerative biologics and incompletely validated clinical adjuncts. These materials appear most mechanistically relevant — and clinically testable — in settings where inflammation resolution, angiogenesis, fibroblast migration, and early tissue repair are primary determinants of outcome, which may account for the relatively coherent signals observed in postoperative inflammatory morbidity, oral mucosal inflammation, soft-tissue repair models, and early

bone-healing contexts (Kim et al., 2026; Ko et al., 2024; Mladenova et al., 2025; Picciolo et al., 2021; Ronsivalle et al., 2025).

For true regenerative endpoints — encompassing periodontal regeneration, alveolar ridge augmentation, sinus floor elevation, and peri-implant tissue augmentation — the required level of evidence is substantially higher. These indications demand demonstration of durable structural and functional benefits through adequately powered controlled clinical trials incorporating radiographic, histological, volumetric, patient-reported, and long-term stability outcomes. The currently available case reports and uncontrolled case series contribute valuable feasibility data but are inherently insufficient for isolating the effect of PN-HA or PDRN from concurrently employed procedures such as guided tissue regeneration, bone grafting, collagen membrane placement, connective tissue grafting, or coronally advanced flap design (Beretta et al., 2025; Cairo et al., 2025; Cardaropoli et al., 2025; Severi et al., 2026).

Future research should prioritize standardized material reporting and indication-specific study design. At minimum, clinical and preclinical studies should specify the exact material class, source species, molecular weight distribution, nominal concentration, carrier system, anticipated release profile, delivery route, exposure duration, timing of application relative to the surgical or therapeutic procedure, and the nature and composition of any co-administered materials or procedures. These recommendations align with proposals in broader tissue-engineering and biomaterial reviews emphasizing the need for standardization, quality control, regulatory clarity, and rigorous long-term safety evaluation for PDRN-based and polynucleotide-based biomaterials (Oh et al., 2025). Above all, study designs should include appropriate comparator arms that permit the independent contribution of the polynucleotide-derived component to be distinguished from hyaluronic acid vehicles, collagen matrices, bone graft materials, barrier membranes, injection procedure effects, and surgical flap designs.

Limitations of the Evidence Base

The primary limitation of the current evidence base is its substantial heterogeneity. Included studies varied widely in material class, carrier system, delivery method, dose and concentration, clinical or experimental indication, model type, comparator condition, observation period, and outcome domain. This heterogeneity precluded quantitative synthesis and renders broad generalizations about efficacy inappropriate. A second fundamental limitation is the pronounced imbalance between preclinical biological plausibility and clinical validation: a substantial body of mechanistic and animal data reported favorable cellular, histological, and inflammatory outcomes, while only a limited number of adequately designed controlled clinical studies were identified. Third, the frequent use of combination protocols — in which PDRN or PN-HA was administered alongside bone graft materials, collagen matrices, barrier membranes, hyaluronic acid, or established surgical techniques — fundamentally limited the ability to attribute observed outcomes to the nucleotide-derived material specifically.

A further limitation is that a portion of the supportive evidence was drawn from fields adjacent to dentistry, including tissue engineering, dermatological soft-tissue remodeling, and aesthetic medicine (Oh et al., 2025; Palmieri & Raichi, 2022). Such literature provides useful mechanistic and translational context but should not be interpreted as direct dental efficacy evidence. Finally, many studies were characterized by small sample sizes, pilot or retrospective designs, uncontrolled case-series structures, or short follow-up durations. These features are appropriate for the early-stage evidence mapping objectives of a scoping review but are insufficient to inform definitive clinical guidance.

Overall Interpretation

In summary, PDRN and related polynucleotide-based materials should currently be regarded as promising locally delivered adjuncts exhibiting anti-inflammatory, pro-angiogenic, pro-healing, and potentially osteogenic properties. The preclinical evidence is strongest for biological plausibility, particularly in osteogenesis, early bone healing, gingival fibroblast migration, inflammatory pathway modulation, oral mucosal repair, and MRONJ/BRONJ-relevant cytoprotection (Han et al., 2018; Jeon et al., 2026; Lee et al., 2019; Mladenova et al., 2025; Picciolo et al., 2021). The clinical evidence is most developed for short-term postoperative inflammatory morbidity following third molar surgery, TMJ symptom modulation, and exploratory periodontal and mucogingival adjunctive applications (Cenzato et al., 2024; Choi et al., 2026; Kim et al., 2026; Pilloni et al., 2023; Ronsivalle et al., 2025).

At present, the available evidence does not support the positioning of PDRN or polynucleotide-based materials as established stand-alone dental therapeutics. Their most defensible current role is as adjunctive biologic agents whose clinical value must be evaluated within well-defined indications, standardized material and delivery protocols, and appropriately controlled trial designs. The next phase of research in this field should transition from broad exploratory enthusiasm toward indication-specific, material-specific, and comparator-controlled investigation, with the ultimate objective of generating reproducible, clinically meaningful evidence capable of informing evidence-based dental practice.

CONCLUSIONS

This scoping review shows that PDRN and related polynucleotide-based materials have been explored across a broad range of dental, oral, and maxillofacial applications, including bone regeneration, periodontal and peri-implant tissue repair, oral mucosal healing, MRONJ/BRONJ-related models, temporomandibular disorders, and postoperative inflammatory morbidity. The preclinical evidence provides a biologically plausible basis for their use, particularly through anti-inflammatory, pro-angiogenic, fibroblast-modulating, epithelial-reparative, and osteogenic effects. However, the clinical evidence remains early, heterogeneous, and largely adjunctive in nature.

At present, PDRN and polynucleotide-based materials should be regarded not as established stand-alone therapeutics, but as promising local biologic adjuncts. The most coherent clinical signal was observed in short-term postoperative morbidity after mandibular third molar surgery, whereas evidence for periodontal regeneration, bone augmentation, mucogingival surgery, TMJ disorders, and oral mucosal disease remains preliminary or confounded by concomitant procedures and carrier materials.

Future research should move from broad exploratory application toward indication-specific and material-specific evaluation. Standardized reporting of material composition, molecular weight, concentration, carrier system, delivery route, exposure time, and release profile is essential. Well-designed controlled clinical trials are needed to determine whether PDRN or related polynucleotide-based formulations provide clinically meaningful benefits beyond established treatments such as hyaluronic acid, collagen matrices, bone grafts, membranes, flap designs, injections, or conventional supportive care. Only through such rigorously designed translational studies can their true role in dental regenerative therapy be defined.

ACKNOWLEDGEMENTS

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2021R1I1A2048516), Korea

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Table 1. Summary of clinical evidence on PDRN and polynucleotide-based materials in dentistry

Domain	Study	Design / sample	Material & delivery	Comparator / follow-up	Main outcomes	Key findings	Interpretation
Third molar surgery	Kim et al. (2026)	Prospective randomized double-blind split-mouth trial; 30 patients	PDRN 1.875 mg in 1.0 mL; submucosal injection at flap base	Saline; days 3, 7, 14, 60	Pain, swelling, PROs, distal second molar probing depth	Lower pain and facial swelling on days 3 and 7; better patient-centered score at day 14; no meaningful difference in pain duration or distal second molar probing depth at day 60	Strongest short-term clinical signal for PDRN; focused on early postoperative morbidity
Third molar surgery	Ronsivalle et al. (2025)	Retrospective split-mouth study; 18 patients	PN-HA gel; intrasocket placement before suturing	No adjunct; 7 days	Pain, swelling by 3D facial scan, mouth opening	Lower early pain, smaller swelling increase, faster mouth-opening recovery; greatest effect at 48–72 h; no complications	Supports short-term morbidity reduction, but retrospective and short follow-up
TMJ / TMD	Choi et al. (2026)	Retrospective chart review; 66 refractory TMD patients	PDRN prolotherapy; periarticular / ligamentous TMJ-region injection	Hypertonic dextrose; mean follow-up about 2.4 months	VAS pain, MMO, joint sounds, displacement, deflection	Both PDRN and dextrose groups improved; no significant difference between agents	PDRN appears feasible as proliferant, but effect cannot be separated from injection/prolotherapy effect
TMJ / osteoarthrosis	Cenzato et al. (2024)	Single-blind randomized clinical trial; 60 patients	PN-HA pericapsular injection	Physiotherapy; 12 weeks	Pain, MMO, lateral excursion	Greater VAS pain reduction in PN-HA group; lateral excursion improved; MMO not significantly different between groups	Best comparative TMJ evidence, but PN contribution cannot be separated from HA/injection effect
TMJ / osteoarthrosis	Farronato et al. (2025)	Pilot clinical study; 10 patients with bilateral TMJ osteoarthrosis	PN-HA injection with augmented/mixed-reality guidance	Manual palpation-guided PN-HA injection	Pain, mandibular movement, procedural feasibility	Guided group showed within-group improvement; between-group differences not significant; procedure required more time	Mainly evaluates guidance technology, not independent PN-HA efficacy
Residual periodontal pockets	Pilloni et al. (2023)	Randomized split-mouth single-blind trial; 50 patients	PN-HA gel after subgingival re-instrumentation	Re-instrumentation alone; 48 weeks	PD reduction, CAL gain, pocket closure, bleeding index	Both groups improved; no significant additional PD/CAL/pocket closure benefit; pocket closure 76% vs 70%; no adverse events	Important negative/neutral controlled trial; PN-HA did not consistently outperform conventional therapy
Periodontal infrabony defects	Cairo et al. (2025)	Retrospective multicenter case series; 43 patients / 55 defects	PN-HA gel ± DBBM depending on defect morphology	No control; 1 year	PD, CAL, pocket closure, radiographic bone fill	Marked PD reduction, CAL gain, pocket closure, radiographic bone fill; uneventful healing	Promising but uncontrolled; PN-HA effect confounded by graft use and defect selection
Periodontal intrabony defect	Severi et al. (2026)	Case report; 1 severe molar intrabony defect	DBBM mixed with PN-HA gel; single flap approach + periosteal pedicle flap	No control; 12 months	Pocket closure, radiographic remineralization	Pocket closure and substantial radiographic remineralization	Feasibility example only; effect inseparable from surgical design and xenograft
Gingival recession	Cardaropoli et al. (2025)	Prospective case series; 16 patients / 67 RT1 recessions	Volume-stable collagen matrix soaked in PN-HA; coronally advanced flap	No control; 12 months	Root coverage, gingival thickness, pain, esthetics	Mean root coverage about 96%; complete root coverage about 81%; increased thickness; low pain and high esthetic satisfaction	Clinically promising mucogingival application, but no comparator
Horizontal alveolar bone regeneration	Beretta et al. (2025)	Proof-of-concept clinical/histologic case series; 6 patients	DBBM mixed with PN-HA gel + collagen membrane	No control; implant placement / biopsy at 5 months	Horizontal bone gain, histologic new bone	Uneventful healing; about 4.9 mm horizontal gain; new bone about 41%	Direct clinical histologic evidence, but small uncontrolled case series
Actinic cheilitis	Jara (2025)	Case report; 1 patient	PDRN subdermal infiltration	No control; short-term follow-up	Epithelial integrity, pain, lip texture/function	Reported improvement in epithelial integrity, pain, texture, and function	Exploratory only; potentially malignant lesion requires caution and longer follow-up
Dry/chapped lips	Rho et al. (2025)	Prospective multicenter open-label study; 30 enrolled / 27 completed	Highly purified polynucleotide injection into vermilion zone; 3 sessions	No control; 9 weeks	Lip wrinkle, roughness, GAIS, adverse events	Improved wrinkle and roughness scores; transient swelling, pain, redness common but mild	Perioral soft-tissue evidence; primarily aesthetic/dermatologic, not conventional dental therapy
Radiation-induced oral mucositis	Podlesko et al. (2018)	Case series; 3 head and neck cancer patients	Topical PDRN spray	No control; during RT/CRT	Mucositis grade, pain, tolerability, treatment interruption	Well tolerated; two patients improved from grade 3 to grade 2 with pain relief; one had limited response	Preliminary supportive evidence for oral mucosal healing; very small uncontrolled series

Table 2. Summary of preclinical / nonclinical evidence on PDRN and polynucleotide-based materials in dentistry

Domain	Study	Model / design	Material & delivery / exposure	Main outcome domains / markers	Key findings	Interpretation
Bone biology / osteogenesis	Jeon et al. (2026)	MC3T3-E1 pre-osteoblasts; bone marrow macrophage osteoclast precursors	PDRN 0, 10, 20 μg/mL in osteogenic or osteoclastogenic culture	ALP, mineralization, Runx2, Osterix, osteocalcin, TRAP, resorption pits	Enhanced osteoblast differentiation and mineralized matrix formation; no direct effect on osteoclastogenesis	Mechanistic evidence for osteoblast-oriented anabolic activity
MRONJ-related cytoprotection	Pachhapure et al. (2025)	Human gingival fibroblast HGF-1 cells under zoledronic acid challenge	ZA 50 μM ± PDRN 100 μg/mL	Viability, ROS, p-TBK1, p-Akt/PKB, p-STAT3	PDRN mitigated ZA-induced growth suppression, reduced ROS, suppressed TBK1 activation, and partially restored Akt signaling	Relevant to soft-tissue cytoprotection in MRONJ-like conditions
Oral soft-tissue regeneration	Mladenova et al. (2025)	Primary human palatal fibroblasts; oral epithelial cells; coculture	PN-HA formulation at 2.5 mg/mL	Migration, proliferation, epithelial differentiation, FGF7, HGF, VEGF, inflammatory genes	PN-HA enhanced fibroblast and epithelial migration, supported epithelial proliferation, and modulated paracrine repair signals	Strong oral-cell mechanistic evidence for soft-tissue wound repair
Oral / periodontal soft-tissue repair	Colangelo et al. (2025)	Primary gingival fibroblasts; 2D scratch and 3D spheroid assays	Odonto-PN or Regenfast PN-HA; 100 μg/mL	Fibroblast viability, scratch closure, spheroid disassembly, outgrowth	Both materials supported viability and fibroblast outgrowth; PN-HA showed stronger sustained migration / closure	Supports PN and PN-HA as fibroblast-modulating wound-repair materials
Sinus augmentation / implant	Omori et al. (2025)	Rabbit bilateral maxillary sinus augmentation with simultaneous custom implants	Bio-Oss + PN-HA gel vs Bio-Oss alone	Histology, micro-CT, new bone, osseointegration, sinus mucosa integrity	PN-HA group showed higher new bone formation at 10 weeks and fewer sinus mucosa perforations	Positive rabbit sinus evidence when implant placement was included
Periodontal soft-tissue healing	Han et al. (2025)	HGF-1 gingival fibroblasts; P. gingivalis LPS inflammatory model	PN, HA, PN-HA; 0.5–2.5 mg/mL; PG-LPS 1 μg/mL	Proliferation, migration, collagen I, proteoglycan, IL-6, p-NF-κB p65	PN-HA promoted migration and matrix deposition while reducing IL-6 and NF-κB activation	Direct mechanistic support for periodontal wound-healing and anti-inflammatory effects
Sinus augmentation	Maniwa et al. (2024)	Rabbit bilateral sinus augmentation without implant-focused endpoint	Bio-Oss + PN-HA gel vs Bio-Oss alone	Histology, new bone fraction, residual biomaterial, sinus mucosa reaction	PN-HA did not improve new bone formation at 2 or 10 weeks and did not protect sinus mucosa	Important negative/mixed sinus evidence; effect appears model-dependent
Sinus augmentation	Lim et al. (2025)	Rabbit sinus floor elevation pilot study	PDRN 2 mg/mL with collagenated BCP graft	Micro-CT, histology, newly formed bone area	Test sites tended to show greater new bone area; significance limited to selected time points	Suggests possible time-dependent early bone-forming effect
Dental stem cells	Yun et al. (2024)	Stem cells from human exfoliated deciduous teeth, SHED	PDRN exposure; key assays around 50 μg/mL	Proliferation, migration, colony formation, oxidative stress resistance, mitochondrial function, Akt	PDRN enhanced SHED proliferation/migration and resistance to oxidative stress via Akt-associated pathways	Suggests dental stem-cell priming potential
Peri-implant soft tissue	Kim et al. (2025)	Dog buccally positioned implant model after keratinized tissue removal	Xenogeneic collagen matrix + PDRN; 2 or 4 mg/mL concepts	KT width, tissue thickness, STL scan, histomorphometry	XCM + PDRN produced KT/tissue gains approaching FGG-like outcomes in selected conditions; higher concentration was not necessarily better	PDRN-loaded collagen matrix may support KT augmentation, but dose/delivery matter
Gingival stem cells / osteogenesis	Lee H. et al. (2024)	3D gingiva-derived stem cell spheroids	PDRN 0–100 μg/mL in osteogenic culture	Viability, spheroid morphology, ALP, calcium deposition, RUNX2, COL1A1	PDRN did not alter viability markedly but modulated osteogenic differentiation; 75 μg/mL enhanced calcium deposition	Concentration-dependent osteogenic modulation in 3D oral stem-cell model
Immediate implant soft tissue	Lee H.K. et al. (2024)	Dog immediate implant placement model	Volume-stable collagen matrix soaked in PDRN 2 mg/mL	Soft-tissue volume, mucosal thickness, STL analysis, histomorphometry	VCMX + PDRN did not clearly outperform VCMX alone; SCTG generally remained superior near implant platform	Shows PDRN-loaded matrix does not consistently add benefit over matrix alone
Alveolar ridge preservation	Ko et al. (2024)	Beagle dog extraction socket preservation model	Alloplastic graft soaked in PDRN 1.875 mg/mL + collagen membrane	New bone, blood vessels, micro-CT NBV/TV, ridge-volume change	Greater early new bone formation, higher vascularity, and reduced buccal ridge-volume loss	One of the strongest translational preclinical signals for ARP
Lateral bone augmentation / implant	Lee D. et al. (2023a)	Beagle dog buccal dehiscence with immediate implant placement	Collagenated BCP graft + PDRN	Micro-CT, histology, new bone area, mineralized tissue, BIC	PDRN tended to improve early bone formation around augmented immediate implant sites	Supports early implant-related hard-tissue augmentation, but effect size was variable
Gingival phenotype modification	Lim et al. (2023)	Dog gingival defect / recession model	XCM soaked in PDRN 2 mg/mL for 5 min	Gingival thickness, STL analysis, histomorphometry	XCM/PDRN increased gingival thickness and showed outcomes comparable to SCTG in selected parameters	Preclinical support for PDRN-loaded collagen matrix in phenotype modification
Sinus augmentation / implant	Lee D. et al. (2023b)	Beagle lateral-window sinus floor elevation with simultaneous implant placement	Collagenated synthetic bone graft + PDRN	New bone, residual graft, augmented height, BIC	Overall augmented height and total BIC were not substantially different; apical / Schneiderian membrane-adjacent areas favored PDRN	Region-specific early osteogenic benefit rather than global improvement
Bone tissue engineering / scaffold	Kim D.S. et al. (2021a)	hMSCs, endothelial / immune assays, animal bone-defect models	PLGA + $Mg(OH)_2$ + bone ECM scaffold with PDRN/BMP2 nanocomplex	Osteogenesis, angiogenesis, anti-inflammation, bone regeneration	Scaffold showed synergistic pro-osteogenic, pro-angiogenic, and anti-inflammatory effects	Supportive platform evidence; PDRN effect cannot be isolated from BMP2/scaffold components
Bone tissue engineering / scaffold	Kim D.S. et al. (2021b)	hBMSCs, HUVECs, osteoclast-related assays, animal bone-defect model	PLGA/MH/ECM scaffold loaded with PDRN	ALP, Runx2, VEGF, tube formation, osteoclast markers, bone repair	PDRN-containing scaffold improved osteogenic and angiogenic behavior and reduced osteoclast-related activity	Supportive evidence for controlled PDRN delivery in biodegradable scaffold systems
Oral mucositis	Picciolo et al. (2021)	Human gingival fibroblasts and oral mucosal epithelial cells under LPS challenge	LPS 2 μg/mL + PDRN 100 μg/mL ± A2A antagonist	NF-κB, TNF-α, IL-6, IL-10, Wnt/β-catenin, VEGF, EGF	PDRN reduced inflammatory signaling and restored healing-related pathways; A2A antagonist attenuated effects	Mechanistic basis for topical/local PDRN in oral mucositis
Bone regeneration / scaffold	Lim H.K. et al. (2021)	Rabbit calvarial defects	HA/TCP scaffold loaded with PDRN 0.1–10 mg/mL; rhBMP-2 comparator	Radiology, histomorphometry, new bone formation	PDRN showed radiographic improvement at higher concentrations, but histomorphometry did not confirm increased bone formation	Important mixed-result dose-ranging scaffold study
Mandibular bone augmentation	Sato et al. (2020)	Beagle mandibular vertical / saddle-type alveolar ridge defects	Salmon DNA/protamine complex paste	Radiography, micro-CT, histology, bone height, BV/TV, BMD	DNA/protamine paste enhanced bone regeneration compared with blank control and β-TCP	Large-animal craniofacial scaffold evidence, but not PDRN/PN-HA formulation
BRONJ / MRONJ	Lee D.W. et al. (2019)	Rat BRONJ model: ovariectomy, tooth extraction, zoledronic acid	Local PDRN 2, 4, or 8 mg/kg twice weekly for 20 days	Necrotic bone, blood vessels, osteoclasts, gross healing	PDRN reduced necrotic bone and increased vascularity and osteoclast numbers; 8 mg/kg showed strongest effect	Key jaw-specific in vivo evidence for MRONJ/BRONJ-related repair
BRONJ inflammatory mechanism	Han et al. (2018)	RAW 264.7 macrophages under ZA + LPS challenge	ZA 1–100 μM; LPS 0.01–1 μg/mL; PDRN 1–100 μg/mL	NO, iNOS, COX-2, IL-1β, IL-6, TNF-α, VEGF	PDRN reduced inflammatory mediator production and modulated cytokine expression	Macrophage-level support for anti-inflammatory activity in BRONJ-like conditions
DNA scaffold / degradation	Matsumoto et al. (2018)	Rat subcutaneous implantation and rat calvarial defect model	UV-treated salmon DNA/protamine scaffolds	Degradation rate, phosphate release, histology, new bone	Moderate UV pretreatment balanced degradation and bone formation; degradation kinetics influenced regeneration	Supportive evidence that DNA-scaffold release/degradation kinetics matter
Bone regeneration / craniofacial	Buffoli et al. (2017)	Rat calvarial defects	Sodium-DNA alone or with fibrin / Bio-Oss	Histomorphometry, RUNX2, osteocalcin-related staining, osteopontin	Sodium-DNA improved bone regeneration, especially in combination with biomaterials	Craniofacial DNA-based adjunct evidence; material differs from PDRN/PN-HA
Bone regeneration / osteoblast migration	Sato et al. (2017)	MG63 osteoblasts and rat critical-sized calvarial defects	Soluble salmon DNA 50–150 μg/mL; freeze-dried DNA disk	Migration, ALP, Runx2, Osterix, bone formation	Salmon DNA enhanced osteoblast migration and osteogenic gene/protein expression and improved calvarial healing	Mechanistic bridge between DNA scaffold and osteogenic cell recruitment
DDM + PDRN osteoinduction	Kim S.K. et al. (2016)	Nude mouse subcutaneous dorsal pouch implantation	Human demineralized dentin matrix + 1.875% PDRN	H&E, Masson trichrome, new bone-like tissue, osteoblasts, fibroblasts	DDM + PDRN induced bone-like tissue formation; highest new bone ratio at 2 weeks	Dental tissue-derived matrix plus PDRN concept, but ectopic model
DNA scaffold / osteogenesis	Katsumata et al. (2015)	MC3T3-E1 osteoblasts; mouse calvarial defects	Salmon DNA fragments/scaffold; NaPi inhibitor experiments	ALP, Alizarin red, Runx2, Osterix, phosphate release, NaPi cotransporter	Salmon DNA promoted osteoblast differentiation and calcification through phosphate / NaPi transporter-related mechanisms	Mechanistic scaffold evidence distinct from soluble PDRN
Experimental periodontitis	Bitto et al. (2013)	Rat ligature-induced periodontitis	0.75% PDRN gel ± A2A antagonist DMPX	Histology, TNF-α, IL-6, HMGB-1, p-JNK, p-ERK, BAX, Bcl-2	PDRN reduced inflammation and apoptosis and preserved Bcl-2; DMPX blocked benefits	Direct periodontal disease model supporting A2A-mediated anti-inflammatory effect
Bone regeneration / historical supportive	Guizzardi et al. (2007)	Rat tibial cortical defect model	PDRN gel 20 mg/mL, heat-deproteinated bone, or HDB/PDRN paste	Histology, histomorphometric defect fill	HDB/PDRN paste accelerated defect filling and bone repair compared with single components	Historical supportive evidence; non-oral tibial model

Five Years of Dental Education Research: A Comparative Analysis of Thematic Priorities in the European Journal of Dental Education and the Journal of Dental Education (2021-2025)

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Manuscript type: Perspective	**Published:** June 1, 2026	DOI: to be assigned	**Open Access**

Abstract

Background
The landscape of dental education research has undergone substantial transformation over the past five years, driven by the COVID-19 pandemic, accelerating digital innovation, and growing demands for social accountability. A systematic understanding of how leading dental education journals have responded to these forces remains limited.

Purpose
This Perspective presents a comparative thematic analysis of all articles published in the European Journal of Dental Education (EurJDE) and the Journal of Dental Education (JDE) between 2021 and 2025, examining topical priorities, research design patterns, target populations, and evolving publication structures.

Methods
A total of 1,765 articles (EurJDE: 509; JDE: 1,256) were extracted from PubMed. Each article was classified across 11 thematic domains, technology/pedagogy subcategories, seven study design types, and eight target population categories using systematic keyword-based analysis of titles and abstracts. Online-ahead-of-print and 2026-dated articles were excluded. Articles with substantive abstracts (>100 words) were designated as research articles (EurJDE: 502; JDE: 788); all remaining items were classified as non-research publications.

Findings
Both journals shared curriculum development, competency assessment, and student wellbeing as dominant themes among research articles. COVID-19-related articles peaked in 2022-2023 before declining sharply. Artificial intelligence emerged as the fastest-growing topic from 2023 onward. EurJDE placed greater emphasis on technology integration, qualitative inquiry, and European competency frameworks, while JDE showed stronger coverage of diversity-equity-inclusion and evidence-based practice. Notably, 37.3% of JDE articles were non-research items, compared with only 1.4% in EurJDE.

Conclusion
The two journals share a common intellectual core but serve distinctly different editorial missions. Understanding these distinctions can guide manuscript targeting, help educators identify research gaps, and inform future agendas in dental education scholarship.

Keywords: dental education; thematic mapping; trends; descriptive analysis; journals

INTRODUCTION

As the biblical saying goes, “there is nothing new under the sun”; many so-called innovations in education are better understood as reconfigurations of long-standing concerns. A variety of studies and advocacy papers over the past 25 years have identified or described similar challenges facing dental education in many nations of the world. The fact that these challenges persist signals the urgent need for curricular and infrastructure reform (Annamma et al., 2024).

Dental education research has experienced a period of unusual intensity and disruption since 2020. The COVID-19 pandemic forced dental schools worldwide to rapidly redesign curricula, shift to remote and hybrid delivery, and reconsider fundamental assumptions about clinical training, assessment, and student welfare (Hendricson, 2021; Quinn et al., 2020). Simultaneously, the emergence of immersive simulation technologies, the proliferation of artificial intelligence (AI) tools in clinical and educational settings (Chan & Zary, 2019; Schwendicke et al., 2020), and an intensifying conversation about diversity, equity, and inclusion (DEI) have placed new and sometimes conflicting demands on dental educators and researchers.

In this context, the two most prominent English-language journals dedicated to dental education - the *European Journal of Dental Education* (EurJDE) and the *Journal of Dental Education* (JDE) - serve as primary mirrors of the field's intellectual priorities. EurJDE, the official journal of the Association for Dental Education in Europe (ADEE), represents the European perspective on dental education scholarship. JDE, the official journal of the American Dental Education Association (ADEA), not only publishes peer-reviewed research but also serves as ADEA's official communication platform, encompassing policy statements, annual proceedings, and institutional position papers.

Despite the central role these journals play in shaping dental education discourse, no systematic comparative analysis of their recent thematic trajectories has been published. Such an analysis is timely for multiple reasons. First, it provides an evidence-based map of where scholarly attention has been directed - and where it may be lacking. Second, it illuminates how different institutional contexts shape what gets studied and published. Third, for researchers preparing manuscripts, understanding journal identity and thematic density can meaningfully improve submission quality and targeting.

This Perspective presents a comprehensive keyword-based classification of all 1,765 articles published in EurJDE and JDE between January 2021 and December 2025. We characterise thematic distributions, temporal trends, research design patterns, and target populations, and offer interpretive commentary on what these findings reveal about the current state and future directions of dental education research.

METHODS

Data source and article selection

All articles published in EurJDE and JDE between 2021 and 2025 were retrieved from PubMed using journal-specific search filters. Articles listed as Online Ahead of Print and those with a 2026 publication date were excluded, yielding a final dataset of 509 EurJDE articles and 1,256 JDE articles (total: 1,765).

Each article was classified as a research article - defined as having a substantive abstract of more than 100 words - or a non-research item. The latter category encompasses editorials, letters to the editor, policy statements, proceedings, educational innovation reports, and other items without a formal abstract. This distinction is critical: 468 of 1,256 JDE publications (37.3%) fall into the non-research category, reflecting JDE's dual role as

both a scholarly journal and ADEA's official organ. All percentage figures in thematic analyses use research articles as the denominator (EurJDE: n=502; JDE: n=788).

Classification framework

Research articles were classified across four dimensions using systematic keyword matching against titles and abstracts:

(1) Thematic domains: Eleven mutually non-exclusive domains were defined - curriculum and program development; technology and digital education; assessment and competency; student wellbeing and professional identity; clinical skills training; COVID-19 and pandemic response; global and international perspectives; diversity, equity and inclusion; evidence-based practice and research skills; faculty development; and AI-related research. Multiple domains could be assigned to a single article.

(2) Technology and pedagogy subcategories: Simulation and manikins; video and multimedia; e-learning and online delivery; virtual/augmented reality; AI and machine learning; 3D printing; problem- and case-based learning; and flipped classroom.

(3) Study design: Survey and cross-sectional; qualitative; observational and retrospective; educational intervention; systematic review and meta-analysis; experimental and in vitro; and randomised controlled trials.

(4) Target population: Undergraduate dental students; postgraduate students and residents; faculty and educators; practicing clinicians; dental hygienists and allied personnel; patients and the general public; institutional and program-level analyses; and continuing professional development participants.

Non-research items in JDE were separately classified into five types: educational innovation reports, policy/advocacy/vision commentaries, ADEA official records and proceedings, editorials and letters, and conference poster abstract collections.

F I N D I N G S

Publication volume and composition

Table 1 summarises the basic publication profile of both journals. EurJDE published 509 articles, of which 502 (98.6%) were research articles. JDE published 1,256 articles, but only 788 (62.7%) met the research article criterion. The 468 non-research items in JDE represent a defining structural feature of that journal and require explicit acknowledgment in any comparative analysis of publication output.

Annual output in EurJDE increased from 95 articles in 2021 to a peak of 132 in 2023, declining thereafter to 73 in 2025. JDE maintained a more consistent output of 241-274 research articles annually throughout the study period.

Thematic distribution

Table 2 presents the distribution across 11 thematic domains among research articles only. Since articles can fall under multiple domains, percentages reflect the proportion of research articles in which each theme appeared, with EurJDE (n=502) and JDE (n=788) as respective denominators.

Curriculum and program development was the single most prevalent domain in both journals (EurJDE 75.9%; JDE 70.7%), confirming that foundational questions of what to teach and how to organise dental training remain central to the field. Assessment and competency ranked second in EurJDE (62.0%) and third in JDE (55.8%), while student wellbeing and professional identity emerged as the third most common domain in EurJDE (38.2%) and matched this proportion almost exactly in JDE (38.5%).

Temporal analysis revealed a notable divergence in the trajectory of curriculum-related research: EurJDE showed a slight downward trend as attention shifted toward technology and simulation topics, while JDE showed a modest upward trend, reflecting ongoing systemic curriculum reform debates in North American dental education. COVID-19-related research followed a consistent decline across both journals from 2022 onward - by 2025 fewer than five articles per journal per year addressed pandemic-specific themes.

The fastest-growing domain across both journals was AI-related research. From a near-zero baseline in 2021-2022, annual outputs more than doubled by 2024-2025. The majority addressed large language model applications (including ChatGPT) in student learning, examination preparation, and faculty feedback, alongside institutional policy responses to AI in academic settings.

A notable divergence appeared in diversity, equity, and inclusion (DEI): JDE published proportionally more DEI-related research than EurJDE (21.4% vs. 12.5%), and showed an upward trend across the study period. This contrast reflects structural differences between the North American and European contexts - specifically the more prominent national DEI discourse in the United States and ADEA's explicit institutional commitment to equity and inclusion goals.

Research design

Table 3 summarises the distribution of study designs. Survey-based and cross-sectional studies were the most common design across both journals, though considerably more pronounced in EurJDE (56.8%) than JDE (35.6%). Qualitative research appeared in EurJDE at nearly twice the rate of JDE (19.9% vs. 10.9%), reflecting a stronger orientation toward interpretive and exploratory inquiry in the European literature. Randomised controlled trials remained rare in both journals (EurJDE 1.8%; JDE 1.1%), consistent with the broader health professions education literature.

Target population and educational stage

Undergraduate dental students constituted the most frequently studied population in both journals (EurJDE 58.6%; JDE 50.5%). Program- and institutional-level analyses were more prominent in JDE (37.9% vs. 25.1% in EurJDE), consistent with JDE's role in evaluating dental school policies and accreditation processes. Dental hygienists and allied dental personnel featured in only 3.2% of EurJDE research articles but 7.6% of JDE articles, with the JDE proportion increasing steadily from 2021 to 2025. Patients and the general public were the primary study population in fewer than 3% of articles in either journal.

Non-research content in JDE

Of the 468 non-research items in JDE, the largest category was educational innovation reports (61.5%) - short practice-based narratives describing novel teaching tools or approaches without formal empirical methodology. Policy and advocacy commentaries (13.5%) covered topics including student debt, licensure reform, racial justice in dental schools, and the future of

Table 1. Publication profile of EurJDE and JDE, 2021-2025

Journal	Total articles	Research articles	Non-research items	%
Eur J Dent Educ	509	502 (98.6%)	7 (1.4%)	1.4
J Dent Educ	1,256	788 (62.7%)	468 (37.3%)	37.3
Total	**1,765**	**1,290**	**475**	-

Table 2. Thematic domain distribution in EurJDE and JDE research articles, 2021-2025

Thematic domain	EurJDE (n=502)	Trend	JDE (n=788)	Trend
Curriculum & program development	381 (75.9%)	↓	557 (70.7%)	↑
Assessment & competency	311 (62.0%)	→	440 (55.8%)	↑
Student wellbeing & professional identity	192 (38.2%)	→	303 (38.5%)	↑
Clinical skills training	151 (30.1%)	↑	191 (24.2%)	↑
Technology & digital education	121 (24.1%)	↑↑	183 (23.2%)	↑
COVID-19 & pandemic response	104 (20.7%)	→	152 (19.3%)	↓
Global & international education	89 (17.7%)	↑↑	86 (10.9%)	→
Diversity, equity & inclusion	63 (12.5%)	→	169 (21.4%)	↑
Evidence-based practice & research	62 (12.4%)	↑↑	120 (15.2%)	↑↑
Faculty development	54 (10.8%)	↑	96 (12.2%)	↑
AI-related research	13 (2.6%)	↑↑	20 (2.5%)	↑

Trend symbols - ↑↑: moderate increase; ↑: slight increase; →: stable; ↓: slight decrease. Trends derived by comparing mean annual rates in 2021-2022 versus 2024-2025.

Table 3. Study design distribution in EurJDE and JDE research articles, 2021-2025

Study design	EurJDE	JDE	Comment
Survey / cross-sectional	285 (56.8%)	281 (35.6%)	Dominant in both; higher in EurJDE
Qualitative study	100 (19.9%)	86 (10.9%)	Notably higher in EurJDE
Observational / retrospective	70 (13.9%)	69 (8.7%)	Comparable
Educational intervention	33 (6.6%)	32 (4.1%)	Similar
Systematic review / meta-analysis	26 (5.2%)	21 (2.7%)	Similar
Experimental / in vitro	24 (4.8%)	38 (4.8%)	Identical proportion
Randomized controlled trial	9 (1.8%)	9 (1.1%)	Rare in both journals

the oral health workforce. ADEA official records and proceedings comprised a further 11.5%. By contrast, EurJDE's seven non-research items consisted primarily of editorials and one invited commentary on European curriculum policy.

DISCUSSION

Two journals, one field, two editorial identities

The most fundamental insight to emerge from this analysis is that EurJDE and JDE, while sharing a common intellectual domain, serve distinctly different editorial functions. EurJDE operates as a focused European academic research journal with a strong emphasis on curriculum frameworks, qualitative inquiry, and the translation of educational theory into practice. Its orientation is shaped by the ADEE's mission to harmonise dental education quality across European nations and by the competency-based framework of the Graduating European Dentist (GED) (Cowpe et al., 2010; Walmsley et al., 2023).

JDE functions as the comprehensive communication organ of ADEA and the broader North American dental education enterprise. In addition to publishing original research, it serves as a vehicle for institutional policy, workforce analysis, advocacy, and professional community building. This function aligns with longer historical analyses of curriculum structure, the dental education environment, and innovation in doctoral training (Haden et al., 2006; Kassebaum et al., 2004).

To borrow a journalistic analogy: EurJDE resembles a specialist academic journal; JDE is closer to a trade journal with a strong and rigorous research section. This structural difference has direct implications for bibliometric comparisons: raw article counts between the two journals are not commensurable without accounting for the 37.3% of JDE content that does not constitute peer-reviewed research.

This distinction has practical consequences for researchers. Those seeking evidence on specific pedagogical questions - virtual reality simulation, AI-assisted feedback, or competency-based assessment - will find literature distributed comparably across both journals. Those seeking to understand systemic issues in North American dental education - tuition burden, DEI climate, interprofessional policy, or workforce projections - will find JDE's non-research content uniquely informative and largely without European equivalent. In particular, JDE's attention to DEI aligns with longer histories of dental education pipeline and community-responsiveness initiatives in the United States (Formicola et al., 2009).

The digital transformation imperative

Across both journals, technology-related themes appeared in roughly one in four research articles - a sustained level of attention that reflects the convergence of multiple forces: the disruption of traditional clinical training by COVID-19, the maturation of simulation and virtual reality platforms, the accessibility of 3D printing and digital workflow tools, and the explosive emergence of generative AI from 2023 onward.

The rise of AI-related research deserves particular emphasis. Its trajectory - near zero in 2021-2022, followed by a rapid increase from 2023 - represents one of the most dramatic topical transitions in recent dental education scholarship. Current articles remain largely exploratory, reporting student and faculty perceptions of ChatGPT, evaluating AI tools for examination item generation, and debating academic integrity policies. This pattern is characteristic of an early technology adoption cycle: descriptive and attitudinal studies precede the intervention research and longitudinal outcome data needed to establish whether and how AI tools improve educational quality.

The field would benefit from moving more rapidly from the descriptive to the evaluative phase. Rigorous studies examining learning outcomes associated with AI-assisted feedback, the equity implications of differential access to AI tools, and the competency frameworks needed to prepare graduates for AI-augmented clinical practice are conspicuously absent from the current literature.

Curricular priorities in transition

The slight downward trend in curriculum-related research in EurJDE - counterbalanced by an upward trend in JDE - warrants interpretive caution. In the European context, the GED framework has provided a stable reference point for curriculum design since its last major revision; the relative decline may reflect maturation of that discourse rather than diminished interest (Cowpe et al., 2010; Walmsley et al., 2023). In North America, by contrast, ongoing debates about competency-based education, accreditation standards, and dental hygiene curriculum integration appear to be sustaining - and indeed amplifying - curriculum-related research output.

Assessment and competency research remained the second most prevalent domain in EurJDE across all five years, with a stable trend. In JDE, this domain showed a modest upward trajectory, driven in part by growing interest in entrustable professional activities (EPAs) and milestone-based frameworks as potential successors to traditional competency models (Chambers, 1994). The parallel stability in student wellbeing research across both journals - at approximately 38% of research articles - suggests that burnout, mental health, and professional identity formation have become structural rather than transient concerns in dental education.

The methodological question

The dominance of survey-based designs and the rarity of randomised controlled trials reflect structural realities of educational research that are unlikely to change substantially. The ethical and logistical challenges of random assignment, the heterogeneity of institutional contexts, and the multifactorial nature of educational outcomes all militate against experimental designs. Nevertheless, the field would benefit from greater investment in intervention studies with pre-post designs and control conditions, longitudinal follow-up studies, and mixed-methods approaches that situate quantitative findings within interpretive frameworks. Methodological strengthening is particularly important for assessment research, where validity, reliability, and self-assessment have long been recognised as central concerns (Cook & Beckman, 2006; Mattheos et al., 2004).

The notably higher proportion of qualitative research in EurJDE (19.9% vs. 10.9% in JDE) suggests that European researchers may be drawing more systematically on educational theory and interpretive methodology. This tradition deserves wider cultivation, particularly as the field grapples with complex questions about professional identity formation, the hidden curriculum, and the social determinants of student wellbeing. As in health professions education more broadly, dental education must be treated as both part of the problem and part of the solution in professional formation (Lucey, 2013).

Persistent gaps

Several important topics remain underrepresented in both journals. Postgraduate and continuing professional education accounted for only 14% of research articles despite the fact that dental training extends well beyond the undergraduate degree. The transition from student to independent practitioner - with its associated challenges of competency consolidation, professional socialisation, and early career wellbeing - has received almost no systematic attention. Faculty development also remains comparatively sparse, despite earlier calls for more formal educational preparation of dental faculty (Haak et al., 2005).

Interprofessional education, while growing in JDE, remains modest in scale relative to the complexity of implementing collaborative practice models and the broader health professions rationale for interprofessional preparation (Holsinger et al., 2012). Patients and communities as subjects of dental education research remain at the margins of both journals, with fewer than 3% of articles adopting a patient or community perspective on the outcomes of student-delivered care.

CONCLUSION

This comparative analysis of 1,765 articles published in EurJDE and JDE between 2021 and 2025 - based on research articles only as the denominator for thematic analyses - reveals both a shared intellectual core and meaningful structural and thematic differences. Curriculum development, competency assessment, and student wellbeing represent the enduring priorities of the field across both geographic contexts. COVID-19 research followed a predictable arc from disruption to resolution; AI-related scholarship has begun a steep ascent that shows no sign of levelling off.

EurJDE and JDE serve different editorial functions: the former as a focused European academic research journal, the latter as a comprehensive professional platform. Neither represents a complete picture of the field alone. Read together - and with careful attention to the proportion of non-research content in JDE - they offer a rich and complementary account of where dental education scholarship has been, and what questions are most urgently awaiting rigorous answers.

For researchers, these findings carry practical implications. Authors targeting EurJDE may expect a receptive readership for qualitative work, curriculum framework analyses, and studies grounded in European competency standards. Authors targeting JDE will find their work most impactful if it addresses systemic questions of workforce, equity, and institutional policy. In both cases, the field calls most insistently for methodological diversification, longitudinal inquiry, and evidence that closes the gap between educational innovation and demonstrated learning outcomes.

ACKNOWLEDGEMENTS

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2021R1I1A2048516), Korea. There is no conflicts of interest.

DATA AVAILABILITY

The full classified dataset is available from the corresponding author upon reasonable request.

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From Digital Planning to Physical Execution: A Scoping Review of Physical AI in Dentistry

Mapping Technologies, Clinical Domains, and Evidence Gaps

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Manuscript type:	Scoping Review	Published:	June 1, 2026 | DOI: to be assigned	Open Access

Abstract

Objectives
Physical AI in Dentistry is defined as artificial intelligence embodied within a physical platform—robotic, haptic, tactile, or actuator-based—capable of sensing, guiding, constraining, or executing dental and oral health procedures. This scoping review aimed to map the current literature on Physical AI in dentistry, characterize major clinical and educational domains, and identify evidence gaps relevant to future research and clinical translation.

Data Sources
A PubMed search (January 2015 – May 2026) using terms related to dental robotics, autonomous and semi-autonomous robotic systems, haptic simulation, tactile robots, force feedback, and robot-assisted surgery was conducted, supplemented by hand-searching of reference lists and key dental journals.

Study Selection
A total of 191 records were identified. After independent dual-reviewer screening, 68 records were excluded (software-only AI, pure dynamic navigation, TORS in non-dental ENT contexts, AI-free mechanical systems, and borderline records conservatively excluded for conceptual coherence). A final set of 123 studies was included.

Results
The literature is dominated by autonomous and semi-autonomous robotic implant placement systems (n ≈ 90; ~73%), with smaller clusters in robotic endodontics (~13), robotic prosthodontics (~9), robot-assisted oral and maxillofacial surgery (~6), haptic simulation and dental education (~8), and tactile robotic oral hygiene (~3). Evidence derives primarily from in vitro studies, phantom experiments, single-center clinical series, and case reports. Only two randomized controlled trials were identified. Geographic concentration in Chinese institutions is notable (~63% of studies).

Conclusions
Physical AI in dentistry is transitioning from proof-of-concept toward early clinical translation. Robotic implantology is the most mature domain. The field remains methodologically heterogeneous, with insufficient long-term clinical, patient-centered, and cost-effectiveness data. Standardized autonomy classification, reporting checklists, multicenter trials, and regulatory frameworks are urgently needed.

Keywords: Physical AI; dental robotics; autonomous robotic surgery; robotic implantology; haptic simulation; dental education; embodied intelligence; autonomy level; scoping review

INTRODUCTION

Artificial intelligence has become one of the most visible themes in contemporary dental research. Most dental AI applications, however, remain fundamentally screen-based. They detect caries on radiographs, segment anatomical structures on cone-beam computed tomography, classify oral lesions, predict treatment outcomes, assist diagnosis, or support digital treatment planning. In these applications, AI functions primarily as an analytical or cognitive tool. It sees, calculates, predicts, and recommends. A radiographic AI system may identify the mandibular canal, but it does not place an implant. A treatment-planning algorithm may suggest an ideal implant position, but it does not execute the osteotomy. These software-only systems represent virtual or software-centered AI—intelligence operating through data processing and decision support rather than direct physical engagement.

A different paradigm is now emerging. In this newer paradigm, AI is no longer confined to the screen. It is connected to sensors, robotic arms, force-feedback systems, haptic interfaces, navigation platforms, automated cutting devices, or tactile actuators. It does not merely interpret the clinical world; it physically interacts with it. This emerging convergence is referred to in this review as Physical AI in Dentistry.

This concept is closely aligned with the framework of embodied intelligence, which holds that intelligent behavior does not arise from computation alone but from the dynamic coupling of algorithm, body, and environment. Recent commentary in Nature Machine Intelligence has described a conceptual shift 'from embodied intelligence to physical AI,' highlighting the convergence of robotics, sensing, control, and adaptive computation in systems that move intelligence beyond abstract code and into physical action (Nature Machine Intelligence, 2026). Reviews of embodied intelligence in soft robotics similarly emphasize that perception, materiality, and environmental feedback are not peripheral to intelligence but constitutive of it (Biomimetics, 2024).

Physical AI may therefore be understood as artificial intelligence embodied within a physical system capable of sensing, interpreting, guiding, constraining, or executing real-world actions. In dentistry, this includes autonomous or semi-autonomous implant robots, haptic-guided surgical platforms, robotic tooth preparation systems, robot-assisted endodontic access, autonomous osteotomy, haptic simulation for dental education, and tactile robots for oral hygiene. The defining feature is not simply the presence of a robot or a digital interface, but the translation of digital planning, sensing, or adaptive control into physical dental action.

This distinction is clinically important. Dentistry depends heavily on psychomotor precision, spatial judgment, tactile feedback, fine motor control, and physical interaction with hard and soft tissues. The clinical relevance of AI in dentistry will therefore depend not only on what AI can detect or predict, but also on how AI can safely support, guide, or perform physical procedures.

Despite rapid growth, the Physical AI dental literature remains fragmented. Terms such as 'robotic,' 'autonomous,' 'semi-autonomous,' 'dynamic navigation,' 'AI-assisted,' and 'haptic' are used without clear distinction. A scoping review methodology was selected to map the breadth of evidence, characterize the diversity of Physical AI technologies and clinical domains, and identify gaps warranting future systematic evaluation and primary research.

For this review, Physical AI in Dentistry is defined as any dental or oral-health technology in which AI, robotic control, sensor-guided computation, haptic feedback, tactile perception, or autonomous/semi-autonomous decision-making is integrated with a physical platform capable of guiding, constraining, assisting, or executing a dental, oral, craniofacial, educational, or oral-care task.

METHODS

Study Design and Reporting Framework

This scoping review was conducted in accordance with the PRISMA extension for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018), guided by the Arksey and O'Malley (2005) framework and the refinements of Levac et al. (2010). A scoping review design was selected because the field is heterogeneous in terminology, system architecture, autonomy level, clinical application, and outcome reporting. The aim was to map the breadth, distribution, and maturity of available evidence rather than to estimate a pooled treatment effect. The protocol was not pre-registered in a public registry prior to this submission.

Working Definition and Eligibility Criteria

Eligible systems included, but were not limited to:

- Autonomous or semi-autonomous robotic implant systems
- Robotic systems for endodontic access, post removal, or microsurgery
- Robotic systems for prosthodontic or restorative tooth preparation
- Robot-assisted oral and maxillofacial surgical platforms
- Haptic simulators or force-feedback systems for dental education
- Tactile collaborative robots for oral hygiene or assistive care
- AI-enabled or sensor-guided systems converting digital planning into controlled physical action

Studies were excluded if they: (1) involved software-only AI, diagnostic AI, or treatment planning without physical execution; (2) described pure dynamic navigation without robotic actuation; (3) involved teleoperated TORS without AI autonomy in non-dental ENT/head-and-neck oncology contexts; (4) used 'autonomous' in a professional or administrative sense; (5) described AI-free mechanical testing devices, chewing simulators, or non-adaptive robots; (6) focused on non-dental robotic surgery; or (7) represented borderline cases with insufficiently clear Physical AI integration. A conservative approach was applied to preserve conceptual coherence.

Information Sources and Search Strategy

A PubMed search was conducted in May 2026, restricted to publications from January 2015 onward. The search string was:

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("dental robot*"[tiab] OR "robotic dental"[tiab] OR "autonomous
robot*"[tiab] OR "semi-autonomous robot*"[tiab] OR
"task-autonomous"[tiab] OR "robotic implant*"[tiab] OR "robot-assisted
implant*"[tiab] OR "robot-assisted surgery"[tiab] OR "haptic
simulat*"[tiab] OR "force feedback"[tiab] OR "tactile robot*"[tiab] OR
"autonomous robotic system"[tiab] OR "computer-guided robot*"[tiab]) AND
("dentistry"[MeSH] OR "dental"[tiab] OR "oral surgery"[MeSH] OR "dental
implant*"[MeSH] OR "endodont*"[tiab] OR "prosthodont*"[tiab] OR "tooth
preparation"[tiab]) AND ("2015/01/01"[PDat]:"3000/12/31"[PDat]) NOT
("dynamic navigation"[tiab] NOT "robot*"[tiab])
```

Supplementary hand-searching was performed on reference lists of included review articles and key dental journals. No language restrictions were applied.

Study Selection

A total of 191 records were identified. Two reviewers independently screened titles and abstracts. Full texts were retrieved for all potentially eligible records and independently assessed. Disagreements were resolved by discussion; persisting disagreements were adjudicated by a third reviewer. Borderline records—including mixed-reality navigation-only systems and studies with unclear Physical AI integration—were excluded conservatively. The complete selection process is presented in the PRISMA-ScR flow diagram (Supplementary Figure S1).

Data Extraction and Synthesis

A structured extraction form captured: first author; year; country; journal; study design; dental domain; Physical AI category; system type; autonomy level; procedure; sample size; primary outcomes; key findings; reported limitations; and safety events. For implant studies, coronal deviation (mm), apical deviation (mm), and angular deviation (°) were the primary quantitative outcomes. Given heterogeneity in designs and outcome measures, synthesis was narrative. Descriptive statistics were calculated within subgroups where sufficient comparability existed.

RESULTS

Study Selection

The PubMed search retrieved 191 records. After independent dual-reviewer screening, 68 records were excluded and 123 studies were included. The most common reasons for exclusion were: TORS/teleoperated ENT robotic surgery in non-dental contexts (n ≈ 19); borderline cases with insufficient Physical AI integration, conservatively excluded (n ≈ 20); pure dynamic navigation without robotic actuation (n = 8); AI-free mechanical or materials-testing robots (n = 6); 'autonomous' used in a non-technological sense (n = 5); software-only diagnostic AI (n = 4); and non-dental robotic surgery (n = 2). The full PRISMA-ScR flow diagram is provided in Supplementary Figure S1.

Publication Trend and Geographic Distribution

The included studies span 2015 to 2026, with a marked acceleration in annual output from 2022 onward and a cumulative evidence base more than doubling between 2021 and 2024 (Supplementary Figure S2). This confirms that Physical AI in dentistry has transitioned from isolated technical reports toward a rapidly expanding translational research field. Chinese research institutions contributed approximately 63% of included studies, particularly in autonomous robotic implantology (Supplementary Figure S4). Additional contributions came from the United States, Korea, Germany, Japan, Belgium, Saudi Arabia, and Italy.

Distribution by Physical AI Category

Figure 1 shows the distribution of included studies across seven Physical AI categories. Robotic implant systems (Category A) dominate with approximately 73% of included studies. The evidence maturity across domains—showing the stark contrast between the RCT-level evidence in robotic implantology and the in vitro-only evidence in Categories D, E, and F—is detailed in Supplementary Figure S3.

Robotic Implantology

System Architecture and Autonomy

Autonomous dental implant robotic systems (ADIRS) perform the complete osteotomy and implant placement sequence under AI control with the surgeon in a supervisory role. Semi-autonomous systems collaborate through haptic feedback or motion constraints. The two most widely studied platforms are: (1) the Yomi system (Neocis, USA), a haptic-guided arm cleared by the US FDA in 2019; and (2) Chinese-developed fully autonomous systems, most prominently from the Fourth Military Medical University (Xi'an), where the robotic arm autonomously drills and inserts implants according to a preoperative CBCT-IOS fusion plan.

Accuracy Outcomes

Implant placement accuracy was the primary outcome in most Category A studies. Across meta-analyses and comparative studies, pooled mean deviations for autonomous systems were approximately: coronal deviation 0.45–0.77 mm, apical deviation 0.50–0.78 mm, and angular deviation 0.80–1.46°. These compare favorably with dynamic navigation (mean angular ~1.78–3.71°) and static surgical guides (~3.5°).

Clinical Applications

Applications extend beyond standard single-tooth implant placement to include: zygomatic implants; All-on-4 and full-arch edentulous rehabilitation; immediate post-extraction implant placement; maxillary sinus floor elevation with force-feedback membrane breakthrough detection; tilted implants in atrophic ridges; and osseodensification protocols. No cases of major vascular or nerve injury attributable to robotic malfunction were reported across included studies.

Robotic Endodontics and Apical Surgery

Thirteen studies described robot-assisted endodontic procedures. The most investigated application was autonomous robotic system (ATR) guidance for fiber post removal, with multiple in vitro comparisons demonstrating significantly shorter operative time and reduced dentinal loss versus dynamic navigation and conventional microscope-ultrasonic techniques. Robot-assisted endodontic microsurgery in anatomically challenging locations was demonstrated in case reports. A computer-controlled CO_2 laser ablation system integrated with CBCT and augmented reality completed all 20 in vitro access preparations across six preparation designs without iatrogenic error. Evidence remains primarily in vitro and case-level.

Robotic Prosthodontics and Restorative Dentistry

Nine studies reported robot-assisted preparation for prosthetic restorations. The Lupin semi-active robotic system (Peking University) demonstrated RMS preparation errors of 0.15–0.30 mm in veneer preparation, within clinically acceptable thresholds. For removable partial denture guiding plane preparation, a robotic system reduced inter-guiding-plane angular deviation from 13.41° ± 8.86° (freehand) to 1.93° ± 1.04°, a clinically significant improvement for path-of-insertion parallelism.

Robot-Assisted Oral and Maxillofacial Surgery

Six studies described robot-assisted orthognathic and maxillofacial procedures. A foundational phantom study from Seoul National University developed a six-degree-of-freedom autonomous bone repositioning robot that executed CT-based plans with submillimeter accuracy (Woo et al., 2017). Robot-assisted mandibular reconstruction with fibula flap transfer achieved mean deviation of 1.22 mm versus 1.58 mm (navigation) and 2.31 mm (freehand). Evidence remains at proof-of-concept level.

Haptic Simulation and Dental Education

Eight studies examined haptic simulation platforms providing adaptive, real-time AI feedback for dental skill training. A distinctive study of postgraduate trainees using robotic computer-assisted implant surgery (r-CAIS) found that accuracy metrics showed no statistically significant deterioration across training days while preparation times improved significantly—reframing Physical AI as a precision scaffold that preserves safety while accelerating efficiency learning.

Tactile Robots and Oral Hygiene

Three in vitro studies from the Hannover group demonstrated that a seven-axis tactile collaborative robot achieved interproximal and buccal plaque removal statistically comparable to a trained human operator, using integrated force-torque sensing to maintain safe contact dynamics. Authors highlighted translational potential for patients with limited manual dexterity or neurodegenerative disease.

DISCUSSION

Principal Findings

This scoping review mapped 123 studies on Physical AI in dentistry, providing the first systematic evidence map applying the Physical AI framework across robotic, haptic, tactile, and sensor-actuated dental technologies. Robotic implantology is clearly the most mature domain, while other domains—endodontics, prosthodontics, oral and maxillofacial surgery, dental education, and oral hygiene robotics—remain at earlier stages. This imbalance is captured visually in Figure 1 (category distribution) and in the evidence maturity matrix (Supplementary Figure S3).

From Software Intelligence to Embodied Clinical Action

Physical AI represents a fundamentally different form of intelligence from software-only dental AI. A radiographic AI system may identify the mandibular canal, but it does not place an implant. A treatment-planning algorithm may suggest an ideal position, but it does not execute the osteotomy. A robotic implant system translates digital planning into physical action. The risk profile, validation requirements, ethical implications, and professional responsibilities are therefore categorically different. When AI physically acts on human tissue—drilling bone, resecting tissue, guiding a scaler—questions of safety, accountability, informed consent, and liability enter entirely new territory.

The Autonomy Problem: A Proposed Classification Framework

A major challenge across the included literature is inconsistent use of terminology. 'Robotic,' 'autonomous,' 'semi-autonomous,' 'computer-assisted,' and 'navigation-guided' are used without clear distinction—with significant clinical and regulatory consequences. A static surgical guide, a dynamic navigation system, a haptic-constrained robotic arm, and a task-autonomous drilling robot represent profoundly different levels of physical agency.

This review proposes a seven-level autonomy classification framework for Physical AI in dentistry (Figure 2), adapted from analogous frameworks in surgical robotics and autonomous vehicles. Most current dental Physical AI systems operate at Levels 3–4. Future studies should report autonomy level explicitly using a defined framework.

Accuracy Is Necessary but Not Sufficient

Figure 1. Distribution of Included Studies by Physical AI Category

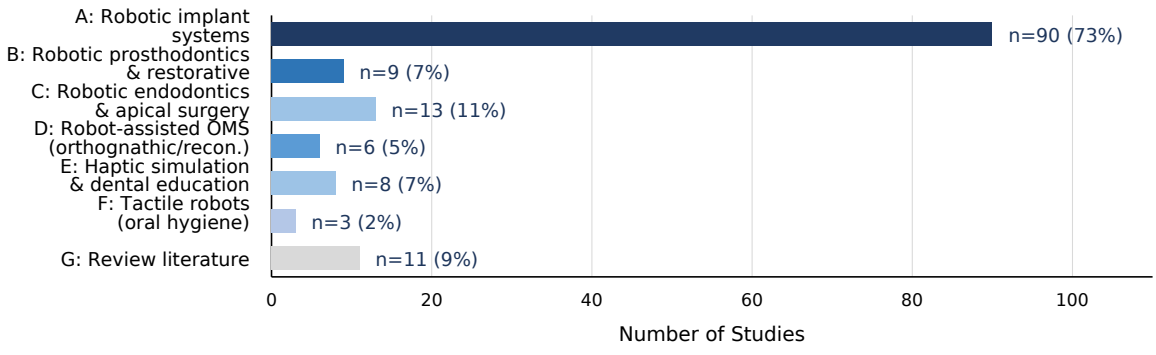

Figure 1. Distribution of included studies by Physical AI category (n = 123). Percentage values represent proportion of total included studies.

The included literature is dominated by accuracy metrics. Positional and angular deviation data are measurable and relevant—but accuracy alone does not establish clinical superiority. Future research must determine whether Physical AI improves outcomes that matter to patients and health systems: complication rates, pain, swelling, healing, implant survival, prosthetic success, tooth survival, tissue preservation, peri-implant bone loss, anxiety levels, patient satisfaction, clinician fatigue, training efficiency, cost-effectiveness, and access to care. None of these patient-centered endpoints are well-addressed in the current Physical AI dental literature.

Evidence Maturity and Geographic Concentration

The field is highly concentrated geographically, primarily in Chinese institutions (see Supplementary Figure S4). This concentration has accelerated innovation but raises concerns about external validity. Independent replication, multicenter studies across diverse clinical and anatomical contexts, and international regulatory evaluation are needed before reported accuracy data can be considered broadly generalizable.

Underdeveloped Domains and the Role of Academic Institutions

The concentration of evidence in implant dentistry reflects commercial priorities. Physical AI in endodontics could improve access accuracy and tooth preservation. Robotic prosthodontics could standardize minimally invasive preparations. Haptic simulation could address faculty shortages and provide objective psychomotor assessment. Tactile oral hygiene robots could assist patients with disability, neurodegenerative disease, or age-related functional decline.

These underdeveloped areas are unlikely to attract commercial investment commensurate with their public health significance. They require investigator-initiated, publicly funded, long-horizon research that national and public universities are best positioned to conduct. The foundational orthognathic robotic surgery work from Seoul National University (Woo et al., 2017) and the Dentronics tactile robot studies from Hannover exemplify this academic imperative. As Physical AI transitions from laboratory curiosity to clinical infrastructure, academic dental institutions have both the opportunity and the responsibility to shape its development toward broad patient benefit.

Implementation, Safety, and Accountability

Clinical adoption will require more than technical feasibility. Implementation barriers include cost, training, calibration, registration errors, patient movement, workflow complexity, and regulatory approval. Safety reporting is currently insufficient: future studies should systematically report device malfunctions, registration failures, aborted procedures, override events, soft-tissue injuries, thermal injury, neurological complications, and operator interventions. Accountability—the distribution of responsibility among clinician, manufacturer, software developer, institution, and regulator when a robotic system acts on human tissue—is almost entirely absent from current literature but will become urgently relevant as autonomy levels increase.

A Proposed Standardized Reporting Checklist for Physical AI in Dentistry

A standardized reporting checklist would substantially improve comparability and accelerate evidence synthesis. At minimum, future reports should include:

- System name, manufacturer, and software version
- Autonomy level (using a defined framework, e.g., Levels 0–6 as proposed above)
- Sensing modalities (optical tracking, force/torque sensing, imaging, etc.)
- Registration workflow and imaging inputs (CBCT, IOS, CBCT-IOS fusion)
- Planning software and version
- Actuator type and degrees of freedom
- Haptic or force-feedback mechanism (if applicable)
- Calibration method and reported calibration error
- Human override mechanism description
- Intraoperative monitoring and safety boundaries
- Failure handling protocol
- Operator training criteria (hours, cases, proficiency thresholds)
- Primary outcome definitions and measurement method
- Adverse event definitions and systematic reporting
- Follow-up duration and long-term outcome data where applicable

Such reporting would distinguish true technological improvement from differences caused by study design, operator experience, or measurement approach. A consensus reporting extension tailored to Physical AI dental studies—analogous to CONSORT or STROBE—should be developed through coordinated effort among dental research organizations, engineering societies, and regulatory bodies.

Limitations

- The search was primarily PubMed-based. Relevant engineering conference proceedings, IEEE publications, robotics journals, and non-indexed technical papers may have been missed. Future updates should include Embase, Scopus, and IEEE Xplore.
- The definition of Physical AI is necessarily evolving and not universally standardized. Borderline technologies—particularly mixed-reality navigation systems and dynamic navigation with emerging AI components—were excluded conservatively. This may have excluded some studies qualifying under a broader definition.
- Study designs and outcome measures were highly heterogeneous, precluding quantitative synthesis across the full dataset. Cross-study comparisons should be interpreted cautiously.
- The included evidence is likely affected by publication bias. Early robotic studies are more likely to report successful feasibility outcomes. Neutral or negative results may be underrepresented.
- The rapid pace of development means the evidence base may change substantially within a short period. New commercial platforms, regulatory approvals, and clinical trial results may alter the conclusions of this review.
- The review protocol was not pre-registered in OSF or a similar public registry prior to the search and data extraction, limiting transparency and increasing the risk of post-hoc modification of eligibility criteria.

CONCLUSION

This scoping review maps 123 studies on Physical AI in dentistry, providing the first systematic evidence map that defines and applies the Physical AI framework across robotic, haptic, tactile, and sensor-actuated dental technologies. The field is characterized by rapid growth and technical maturation in autonomous robotic implant systems, with compelling accuracy data and an emerging body of clinical evidence including two randomized controlled trials.

Beyond implant robotics, Physical AI applications in prosthodontics, endodontics, orthognathic surgery, haptic simulation, and oral hygiene robotics represent smaller but meaningful clusters that demonstrate the breadth of the emerging paradigm. The evidence base remains dominated by in vitro studies, single-center clinical series, and geographically concentrated research outputs. High-quality multicenter trials, standardized outcome frameworks, long-term clinical data, and patient-centered outcome research are the priorities for the next phase.

*Table 1. Representative implant placement accuracy data by technology type. NS = not statistically significant; DNS = dynamic navigation system; * p < 0.01.*

Technology	Coronal Dev. (mm)	Apical Dev. (mm)	Angular Dev. (°)	Study Design
Autonomous robot (pooled meta-analysis)	0.45-0.60	0.50-0.63	0.80-1.24	Meta-analysis
Semi-autonomous robot (clinical)	0.60-0.91	0.60-1.06	1.46-3.07	Clinical retrospective
Robot vs. DNS (RCT)	NS vs. DNS	NS vs. DNS	1.01 vs. 1.78*	RCT (n=40)
Dynamic navigation (comparator)	0.99-1.26	0.70-1.51	1.78-3.71	Various
Static surgical guide (reference)	~1.1	~1.3	~3.5	Systematic review

The autonomy level framework and standardized reporting checklist proposed in this review offer practical tools for improving comparability, guiding regulatory evaluation, and establishing clearer professional expectations about the role of human oversight in physically autonomous dental systems.

Physical AI should be viewed neither as a distant fantasy nor as a fully established clinical standard. It is an emerging translational field with substantial promise, but its future depends on rigorous validation, transparent reporting, careful autonomy classification, and a commitment to clinical value beyond technological novelty.

The essential question is no longer whether AI can assist dentistry from the screen. The next question is how safely, responsibly, and meaningfully AI can enter the physical space of dental care.

ACKNOWLEDGEMENTS

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2021R1I1A2048516), Korea.

There is no conflicts of interest.

DATA AVAILABILITY

The full classified dataset is available from the corresponding author upon reasonable request.

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Figure 2. Proposed Autonomy Level Framework for Physical AI in Dentistry

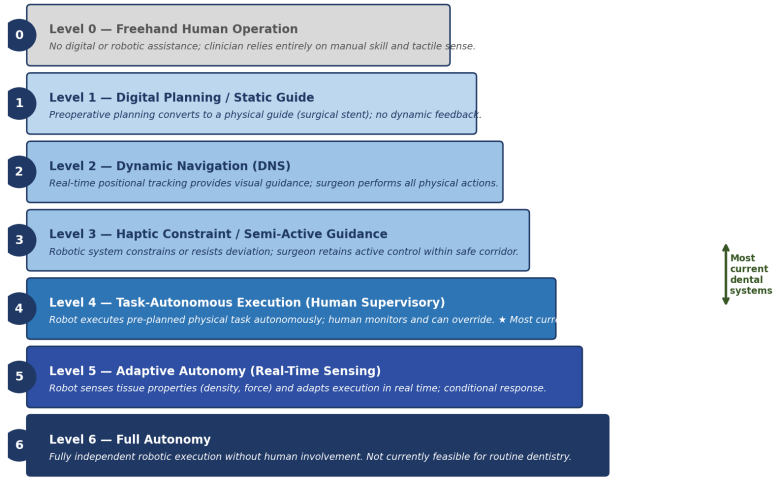

Figure 2. Proposed autonomy level framework for Physical AI in Dentistry (Levels 0-6). Most current dental robotic systems operate between Levels 3 and 4. Level 6 full autonomy is not currently clinically feasible.

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