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Systematic Review

Cold Plasma Treatment on Titanium Implants and Osseointegration: A Systematic Review

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Abstract

Background/Objectives: Osseointegration of titanium dental implants is essential for the long-term success of prosthetic treatments. Cold atmospheric pressure plasma (CAP) has recently emerged as a promising surface modification technique aimed at enhancing early osseointegration by improving implant surface properties and exerting antimicrobial effects. This systematic review aims to critically evaluate the in vivo preclinical evidence on the effects of CAP or similar cold plasma treatments on titanium dental implant surfaces with regard to osseointegration outcomes. **Methods**: A systematic literature search was conducted in PubMed and Scopus databases for preclinical in vivo studies published between 2005 and 2025 investigating the effects of cold plasma on titanium dental implant surfaces. The primary outcome assessed was the bone-to-implant contact (BIC), followed by secondary outcomes including implant stability quotient (ISQ), removal torque, bone area fraction occupancy (BAFO), peri-implant bone density (PIBD), interfacial bone density (IBD), bone-implant direct weight (BDWT) and bone loss measurements via histology and micro-CT. Risk of bias was evaluated using the SYRCLE Risk of Bias tool. **Results**: Nine eligible studies involving 310 titanium implants in 71 animal models (dogs, pigs and mice) were included. CAP-treated implants consistently demonstrated significant improvements in early osseointegration parameters compared to controls, with statistically significant increases in BIC (up to +20%), BAFO and biomechanical fixation metrics (removal torque and ISQ). Micro-CT analyses revealed enhanced peri-implant bone density and architecture. No adverse biological events or implant failures related to plasma treatment were reported. However, heterogeneity in plasma protocols, animal species and short follow-up durations (2–12 weeks) limited comparability and long-term interpretation. **Conclusions**: Preclinical evidence seems to support CAP as a safe and potentially effective surface treatment for enhancing early osseointegration of titanium dental implants. Further standardized long-term studies involving functional loading and clinical trials in humans are needed to confirm clinical efficacy and optimize treatment protocols.

Keywords: dental implants; titanium; cold atmospheric plasma; osseointegration; implant surface treatment; implant stability; animal models; systematic review

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1. Introduction

Osseointegration of titanium dental implants constitutes a pivotal biological process essential for the long-term success of prosthetic rehabilitations [1]. This phenomenon facilitates the formation of a direct, stable and functional interface between viable bone tissue and the implant surface, thereby ensuring mechanical stability, optimal distribution of masticatory loads and long-term prosthetic durability [2].

In light of the increasing prevalence of dental implant therapies worldwide and the demographic shift toward an aging population with complex systemic conditions, optimizing the biological integration of titanium implants has become a critical objective [3–5]. Early and stable osseointegration not only ensures long-term implant success but also helps reduce the incidence of complications that can lead to costly revision surgeries [6].

The quality and efficiency of osseointegration are modulated by a multitude of factors, notably the topographical, chemical and physical properties of the implant surface [7–10]. Surface modifications play a central role in regulating osteoblast adhesion, proliferation and differentiation, ultimately influencing the integrity and functionality of the bone-implant interface [11,12].

In this context, cold atmospheric pressure plasma (CAP), also referred to as non-thermal atmospheric pressure plasma (NTAPP), emerges as an innovative modality for surface modification aimed at enhancing osseointegration. Its composition allows interaction with biomaterial surfaces without compromising their structural or thermal integrity [13,14].

The mechanism of action of CAP is twofold: firstly, it induces controlled alterations of titanium surface properties, including increased hydrophilicity, surface energy and nanoscale roughness, leading to enhanced osteoblastic activity [15–18]; secondly, it exerts potent antimicrobial and decontaminating effects that contribute to the maintenance of a microenvironment conducive to bone regeneration by mitigating bacterial colonization, thereby potentially preventing peri-implantitis [19–26].

Moreover, CAP's ability to modify surface chemistry and reach complex implant micro-architectures enhances early cell-surface interactions, a key step in initiating and advancing osseointegration [27]. Extensive investigations have substantiated that CAP treatment upregulates osteogenic markers such as alkaline phosphatase (ALP), osteocalcin and runt-related transcription factor 2 (Runx2), promotes the deposition of mineralized matrix and enhances osteoblastic metabolic functions [28,29].

Complementary in vivo studies have begun to corroborate these findings, showing statistically significant improvements in BIC and peri-implant bone density in animal models subjected to CAP treatment, suggesting a favorable influence on both the qualitative and temporal aspects of osseointegration.

Despite the compelling preclinical evidence, the absence of clinical trials in human subjects currently limits the extrapolation of these results to routine clinical practice.

Nonetheless, the aggregate data indicate that CAP represents a promising surface treatment technology capable of enhancing bone-implant interactions, particularly in clinical scenarios characterized by elevated risk profiles or where expedited healing is desirable [30–35].

It should be noted, however, that the majority of extant studies have employed generic implant surfaces or simplified experimental models rather than fully representative dental implants in clinically relevant contexts [36–41]. This limitation restricts the capacity to draw definitive conclusions concerning the clinical efficacy of CAP in implant dentistry.

Furthermore, systematic reviews rigorously evaluating in vivo evidence on CAP application in implantology remain scarce or nonexistent.

Accordingly, the present systematic review endeavors to address this gap by providing a comprehensive and up-to-date analysis of the in vivo literature regarding the application of cold plasma to titanium implant surfaces, with a focused assessment of its biological effects and clinical implications on osseointegration. This work aims to provide meaningful insights into the potential and future clinical applicability of this emerging surface modification technology in dental practice.

2. Materials and Methods

This systematic review aimed to critically evaluate the effects of cold plasma treatments on titanium dental implant surfaces in preclinical in vivo studies. Comparisons were made against untreated surfaces or those subjected to alternative surface modification techniques. The primary outcome of interest was bone-to-implant contact (BIC), while secondary outcomes included implant stability quotient (ISQ), bone area fraction occupancy (BAFO), removal torque, peri-implant bone density (PIBD), interfacial bone density (IBD), bone-implant direct weight (BDWT) and bone loss, as assessed through histological and micro-computed tomography (micro-CT) analyses.

The review protocol was prospectively specified in an internal document and subsequently registered in the PROSPERO database (CRD420251130327) after the initial searches. No protocol deviations occurred between the pre-specified protocol and the conduct of the review. The review was conducted in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure methodological rigor, transparency, and reproducibility [42].

2.1. Search Strategy

A comprehensive electronic search of the PubMed and Scopus databases was performed, with the final update conducted on 2 July 2025.

The following search strategy was employed to systematically retrieve relevant studies: *(“non-thermal plasma” OR “cold atmospheric plasma” OR “non-thermal atmospheric pressure plasma” OR “NTAPP” OR “argon plasma” OR “argon cold plasma” OR “cold atmospheric argon plasma” OR “oxygen plasma” OR “plasma gases” OR “gas plasma”) AND (“dental implants” OR “oral implants” OR “dental implant fixtures” OR “dental implant screws”) AND (“osseointegration” OR “bone-to-implant contact” OR “BIC” OR “implant stability quotient” OR “ISQ” OR “cell proliferation” OR “bacterial reduction” OR “antibacterial effect”) NOT (“zirconia implant” OR “zirconia implants” OR “zirconia surface” OR “zirconia”).*

Reference lists of selected articles were manually screened to identify additional relevant studies.

2.2. Inclusion and Exclusion Criteria

Studies were considered eligible for inclusion if they were published between 2005 and 2025 and focused on the application of non-thermal atmospheric pressure plasma (also known as cold plasma) on titanium dental implant surfaces prior to their placement. Only preclinical in vivo primary research studies were included, specifically those that compared plasma-treated titanium implants to either untreated implants or implants treated with alternative surface modification methods. To be eligible, studies were required to assess osseointegration using one or more recognized evaluation methods, such as bone-to-implant contact (BIC), implant stability quotient (ISQ), removal torque, bone area fraction occupancy (BAFO), peri-implant bone density (PIBD), interfacial bone density (IBD), bone-implant direct weight (BDWT) and bone loss assessed through histological or micro-CT analysis.

In order to maintain a clear focus on titanium dental implant surfaces, studies that investigated prosthetic components like abutments or non-implant titanium substrates (such as discs or plates) were excluded. Furthermore, only studies published in English with full-text availability were considered for inclusion, to ensure the accessibility and quality of data.

Studies were excluded if they utilized thermal plasma or plasma generated under non-atmospheric pressure conditions, as these do not correspond to the non-thermal atmospheric pressure plasma technology of interest. Likewise, studies applying plasma treatments directly to soft tissues, such as the oral mucosa, were excluded. Research that failed to specify the type of plasma used, or that focused on zirconia implants or zirconia surfaces, were also excluded to maintain homogeneity of the implant material.

Studies that did not assess osseointegration were excluded from this systematic review. Additionally, in vitro studies, preliminary reports, narrative and systematic reviews, meta-analyses, editorials, and case reports were not considered eligible, as the focus was strictly on primary preclinical in vivo research.

Finally, articles published in languages other than English or available only as abstracts were excluded to ensure comprehensive data extraction and analysis.

2.3. Article Selection Process

The initial database search yielded 140 records, 55 from Pubmed and 85 on Scopus.

A total of 44 studies were removed as duplicates identified across the two databases.

One study was excluded for being published before 2005 and 3 were excluded due to language (non-English). Thus, 92 studies were screened by title and abstract. In total, 4 studies were excluded due to lack of full-text availability.

Of the full-text articles assessed for eligibility, 29 were excluded based on study type. Of the remaining 59 articles, 20 were excluded because they did not involve dental implants, 14 because they did not investigate cold atmospheric plasma and 16 due to being in vitro studies.

Ultimately, nine preclinical in vivo studies met all inclusion criteria and were included in the systematic review.

The selection process was performed independently by two expert reviewers. Any disagreements were resolved through discussion with a third reviewer. The overall selection workflow is presented in a PRISMA flow diagram (Figure 1).

2.4. Data Extraction and Quality Assessment

Two independent reviewers performed data extraction using a standardized Excel spreadsheet.

The following information was collected from each included study: first author, year of publication, journal, study design, animal model, number of implants, type of plasma treatment, follow-up duration, comparison and the main outcomes evaluated through various indicators of osseointegration such as implant stability quotient (ISQ), removal torque, bone-to-implant contact (BIC), bone area fraction occupancy (BAFO), histological and micro-CT analyses.

Any discrepancies between the two reviewers regarding study selection or risk of bias assessment were resolved through discussion with a third reviewer.

The methodological quality and risk of bias of the included in vivo studies were assessed using the SYRCLE Risk of Bias tool, which is specifically tailored for animal research [43]. This tool evaluates ten domains: sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers/investigators, random

outcome assessment, blinding of outcome assessors, incomplete outcome data, selective reporting and other sources of bias.

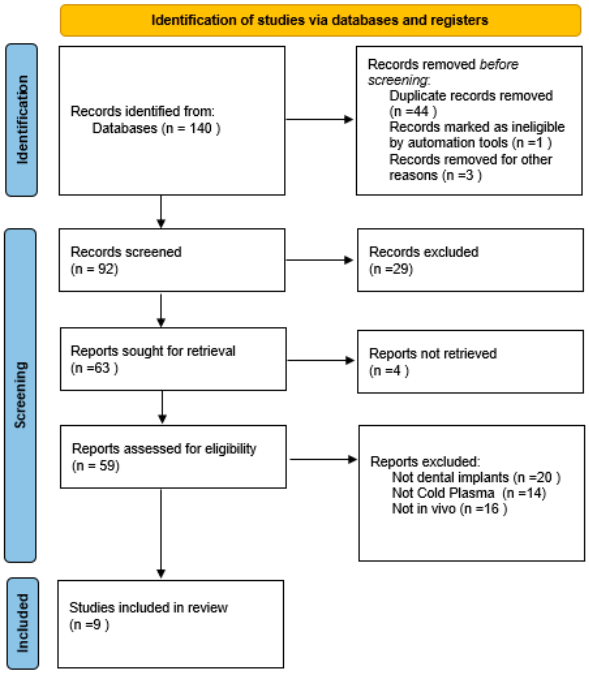

Figure 1. This diagram illustrates the systematic process of identifying, screening and selecting studies for inclusion in the systematic review.

Each domain was rated as "low risk", "high risk" or "unclear risk" according to the available information. A summary table ("traffic light" format) was generated to visualize the risk of bias across studies (Figure 2).

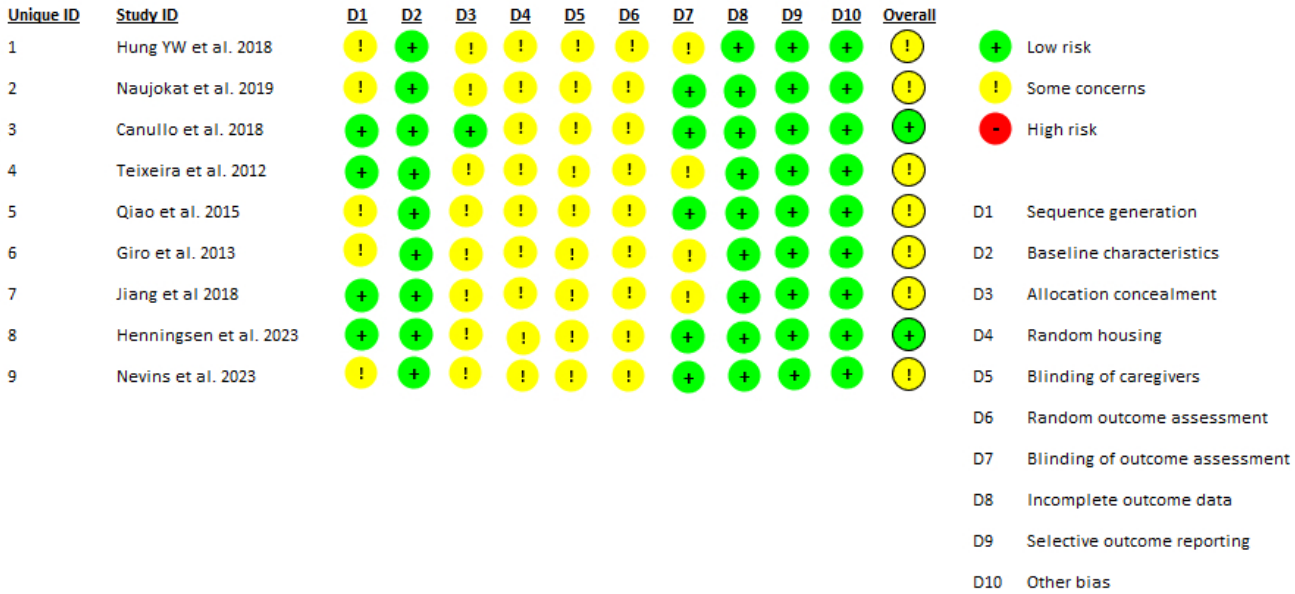

Figure 2. This table presents the assessment of the risk of bias for each included study, evaluated across the ten domains of the SYRCLE Risk of Bias tool [44–52].

3. Results

This systematic review included nine preclinical in vivo studies involving a total of 71 animals, comprising 41 dogs (Beagles, Labrador, Foxhounds), 4 Göttingen minipigs,

6 pigs and 20 mice in which 310 titanium dental implants were placed. Among these, 164 implants underwent surface modification using cold atmospheric pressure plasma (CAP) or silver-ion plasma immersion ion implantation (Ag-PIII), while the remaining 146 implants served as controls or received alternative treatments such as UV light activation. Follow-up periods ranged from 2 to 12 weeks. No adverse clinical events such as inflammation, implant instability, or soft tissue complications were reported, confirming the biological safety of plasma surface treatments under experimental conditions (Table 1).

3.1. Histomorphometric Bone Response

Most studies assessed bone-to-implant contact (BIC) and bone area fraction occupancy (BAFO) as primary indicators of early osseointegration, generally reporting significant improvements in plasma-treated implants compared to controls or alternative treatments. For example, Canullo et al. (2018) [46] in a Beagle model with 32 implants found that at 2 months, plasma-treated implants exhibited a BIC of 72.5% ± 12.4% compared to 64.7% ± 17.3% in controls, with a statistically significant difference ($p = 0.012$) suggesting enhanced mineralized bone fraction. Similarly, Giro et al. (2013) [49], working with six Beagle dogs and calcium phosphate-coated implants, reported that at 3 weeks plasma treatment doubled BIC and increased BAFO by 82% relative to calcium phosphate coating alone. In Göttingen minipigs, Naujokat et al. (2019) [45] reported BIC values of 90.4% ± 1.24% in plasma-treated implants versus 86.5% ± 1.23% in controls at 8 weeks ($p = 0.053$). Inter-thread bone density (IBD) was significantly higher in the plasma group (72.47% ± 5.21% vs. 63.36% ± 6.21%, $p = 0.002$).In Labrador dogs, Qiao et al. (2015) [48] placed 48 implants and found that at 8 weeks the Ag-PIII plasma-treated implants had significantly greater BIC (73.2% ± 5.2% for 30 min and 69.9% ± 4.1% for 60 min) than controls (62.0% ± 4.7%, $p < 0.01$), with bone density within threads (BDWT) similarly improved. Nevins et al. (2023) [52] working with Foxhounds reported significantly higher BIC (88.3% ± 4.8%) in plasma-treated implants compared to controls at 4 weeks ($p = 0.046$). Henningsen et al. (2023) [51], in minipigs, documented BAFO values of 80.4% ± 7.0% in plasma-treated implants versus 73.9% ± 12.2% in controls at 8 weeks ($p = 0.027$), alongside significantly higher BIC at 4 and 8 weeks. In a murine model, Jiang et al. (2018) [50] found that at 4 weeks plasma-treated implants showed a BIC of 47.8% ± 9.6% versus 39.4% ± 9.0% in SLA controls ($p < 0.05$), with BAFO also significantly improved. Conversely, Hung et al. (2018) [44] reported no statistically significant differences in BIC or crestal bone levels at 4, 8, and 12 weeks, although plasma-treated implants trended towards better values.

3.2. Biomechanical Fixation and Implant Stability

Mechanical implant stability was evaluated by several studies through removal torque testing and Implant Stability Quotient (ISQ) measurements. Teixeira et al. (2012) [47], using plateau-root form implants in Beagle dogs, found significantly higher removal torque values in both 20 s and 60 s plasma-treated groups compared to controls at 2 and 4 weeks ($p = 0.001$), with no significant difference between the two exposure times. Qiao et al. (2015) [48] observed significantly higher ISQ values in plasma-treated implants relative to SLA controls at 8 weeks ($p < 0.01$). Nevins et al. (2023) [52] measured ISQ at baseline and found no significant difference between plasma-treated implants and controls, nor changes over time. Henningsen et al. (2023) [51] reported an initial dip in ISQ values at 2 weeks across all groups, followed by a recovery to baseline levels by 8 weeks, with no significant differences between plasma and control groups. Similarly, Hung et al. (2018) [44] found no statistically significant differences in ISQ values between groups at any time point up to 12 weeks.

Table 1. This table provides an overview of the studies selected for inclusion in the systematic review. It outlines key information for each study.

Title	Authors + Year	Study Design	Animal Model	Number of Implants	Type of Plasma Treatment	Follow-Up	Comparison	BIC (%)	ISQ	BAFO %	Removal Torque	PIBD (Peri Implant Bone Density)%	IBD (Interthread Bone Density) %	BDWT (Bone-to-Implant Distance Within Threads) %	Bone Loss (mm)
Effects of non-thermal plasma on sandblasted titanium dental implants in beagle dogs	Hung et al., 2018 [44]	Preclinical in vivo	9 Beagle dogs	36 implants (18 treated, 18 untreated), 4 implants per dog	Argon NTAPP	T0: placement T1: 4 weeks T2: 8 weeks T3: 12 weeks	Argon NTAPP treated VS Non treated implants	CONTROL GROUP (T1): 65.27% ± 3.62 (T2): 82.10% ± 0.23 (T3): 90.20% ± 3.49 STUDY GROUP (T1): 66.40% ± 3.71 (T2): 80.30% ± 0.66 (T3): 87.38% ± 1.98 (p = non significant)	CONTROL GROUP (T0): 68.04 ± 3.37 (T1): 66.53 ± 7.40 (T2): 69.20 ± 2.55 (T3): 74.20 ± 2.68 STUDY GROUP (T0): 67.36 ± 0.52 (T1): 70.17 ± 0.76 (T2): 71.50 ± 1.41 (T3): 77.00 ± 5.87 (p = non significant)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Surface conditioning with cold argon plasma and its effect on the osseointegration of dental implants in miniature pigs	Naujokat et al., 2019 [45]	Preclinical in vivo	4 mini pigs	16 implants (8 treated, 8 not treated), 4 implants per pig	Argon NTAPP	8 weeks	Argon NTAPP treated VS Non treated implants	CONTROL GROUP 86.5 ± 1.23 STUDY GROUP 90.4 ± 1.24 (p = non significant)	Not reported	Not reported	Not reported	CONTROL GROUP 61.14 ± 6.10 STUDY GROUP 60.48 ± 5.03 (p = non significant)	CONTROL GROUP 63.36 ± 6.21 STUDY GROUP 72.47 ± 5.21 (p = 0.002)	Not reported	Not reported
Hard and soft tissue changes around implants activated using plasma of argon: A histomorphometric study in dog	Canullo et al., 2018 [46]	Preclinical in vivo	8 Beagle dogs	32 implants (16 treated, 16 untreated), 4 implants per dog	Argon NTAPP	T1:1 month T2: 2 months	Argon NTAPP treated VS Non treated implants	CONTROL GROUP (T1): 57.2 ± 13.1 (T2): 64.7 ± 17.3 STUDY GROUP (T1): 60.1 ± 15.6 (T2): 72.5 ± 12.4 p = 0.012 (T2)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Table 1. *Cont.*

Title	Authors + Year	Study Design	Animal Model	Number of Implants	Type of Plasma Treatment	Follow-Up	Comparison	BIC (%)	ISQ	BAFO %	Removal Torque	PIBD (Peri Implant Bone Density)%	IBD (Interthread Bone Density) %	BDWT (Bone-to-Implant Distance Within Threads) %	Bone Loss (mm)
Assessment of a chair-side argon-based non-thermal plasma treatment on the surface characteristics and integration of dental implants with textured surfaces	Teixeira et al., 2012 [47]	Preclinical in vivo	6 Beagle dogs	36 implants (24 treated, 12 untreated), 6 per dog (2 plasma 20′, 2 plasma 60′, 2 untreated)	Argon NTAPP	T1: 2 weeks T2: 4 weeks	Implants treated with NTAPP for 20′ VS Implants treated for 60′ VS Non treated	Not reported	Not reported	Not reported	CONTROL (mean rank) (T1): 8.48 ± 2.08 (T2): 9.50 ± 1.96 PLASMA 20′ (m.r) 9.75 ± 2.40 PLASMA 60′ (m.r) 12.33 ± 2.40 (p = 0–001)	Not reported	Not reported	Not reported	Not reported
Ag-plasma modification enhances bone apposition around titanium dental implants: an animal study in Labrador dogs	Qiao et al., 2015 [48]	Preclinical in vivo	6 Labrador dogs	48 implants (4 types: Control, Ag-PIII 30 min, 60 min, 90 min)	Silver-ion plasma immersion (Ag-PIII)	T0: placement T1:4 weeks T2: 8 weeks T3: 12 weeks	Ag-PIII 30 min VS Ag-PIII 60 min VS Ag-PIII 90 min VS Control Group	CONTROL GROUP (T2): 61.99 ± 4.66 Ag-PIII 30 MIN (T2): 73.18 ± 5.23 Ag-PIII 60 MIN (T2): 69.92 ± 4.10 Ag-PIII 90 MIN (T2): 66.05 ± 3.97	CONTROL GROUP (T0): >65 (T1): <59 (T2): ~65 (T3): ~70 STUDY GROUPS (T0): >65 (T1): <59 (T2): significant increase (p = 0.01) (T3):~ 70–72	Not reported	Not reported	Not reported	Not reported	CONTROL GROUP (T2): 66.52 ± 3.46 Ag-PIII 30 MIN (T2): 77.58 ± 4.3 Ag-PIII 60 MIN (T2): 77.97 ± 3.34 Ag-PIII 90 MIN (T2): 69.69 ± 3.68	Not reported
Osseointegration assessment of chairside argon-based nonthermal plasma-treated Ca-P coated dental implants	Giro et al., 2013 [49]	Preclinical in vivo	6 Beagle dogs	12 implants (6 treated, 6 untreated), 2 implants per dog (1 treated, 1 untreated)	NTAPP on CaP	T1: 1 week T2: 3 weeks	CaP coating (control group) VS CaP+ NTP coating (study group)	T1: no differences T3: increase of 100% Vs Control Group	Not reported	T1: no differences T3: increase of 82% Vs Control Group	Not reported	Not reported	Not reported	Not reported	Not reported
Effect of Plasma Oxidation-Treated TiOx Film on Early Osseointegration	Jiang et al., 2018 [50]	Preclinical in vivo	20 rats	40 implants (20 treated, 20 untreated)	Anodic oxidation plasma (PO-SLA)	4 weeks	SLA surface VS PO-SLA surface	CONTROL GROUP 39.41 ± 9.00 STUDY GROUP 47.79 ± 9.59 (p < 0.05)	Not reported	CONTROL GROUP 29.01 ± 7.24 STUDY GROUP: 39.10 ± 10.01 (p < 0.05)	CONTROL GROUP 9.05 ± 1.42 STUDY GROUP 12.68 ± 1.07 (p < 0.05)	Not reported	Not reported	Not reported	Not reported

Table 1. *Cont.*

Title	Authors + Year	Study Design	Animal Model	Number of Implants	Type of Plasma Treatment	Follow-Up	Comparison	BIC (%)	ISQ	BAFO %	Removal Torque	PIBD (Peri Implant Bone Density)%	IBD (Interthread Bone Density) %	BDWT (Bone-to-Implant Distance Within Threads) %	Bone Loss (mm)
Osseointegration of titanium implants after surface treatment with ultraviolet light or cold atmospheric plasma in vivo	Henningsen et al., 2023 [51]	Preclinical in vivo	6 pigs	54 implants (18 untreated, 18 UV treated, 18 plasma treated), 9 implants per pig	CAP	T0: placement T1: 2 weeks T2: 4 weeks T3: 8 weeks	UV treated VS CAP treated VS untreated	CONTROL GROUP (T1): >69% (T3): 73.0 ± 2.8 STUDY GROUP (T1): ($p < 0.05$) (T3): 80.6 ± 5.0	CONTROL GROUP (T0): 90.4 ± 7.2 (T3): 93.1 ± 5.4 STUDY GROUP (T0): 92.4 ± 5.9 (T3): 89.2 ± 8.3	CONTROL GROUP (T3): 73.9 ± 12.2 STUDY GROUP (T3): 80.4 ± 7.0 ($p = 0.027$)	Not reported	Not reported	Not reported	Not reported	Not reported
Gas Plasma Treatment Improves Titanium Dental Implant Osseointegration—A Preclinical In Vivo Experimental Study	Nevins et al., 2023 [52]	Preclinical in vivo	6 Foxhounds dogs	36 implants (18 treated, 18 untreated)	Argon NTAPP	T0: placement T1: 2 weeks T2: 4 weeks T3: 6 weeks	Argon NTAPP treated VS non treated implants	CONTROL GROUP (T2): 88.3 ± 4.8 STUDY GROUP (T2): 93.7 ±3.3 ($p = 0.046$)	CONTROL GROUP (T0): 79.39 ± 2.95 STUDY GROUP (T0): 79.53 ± 4.05 ($p = 0.6$, non significant)	Not reported	Not reported	Not reported	Not reported	Not reported	CONTROL GROUP (T3): 0.79 ± 0.20 STUDY GROUP (T3): 0.56 ± 0.24 ($p = 0.016$)

3.3. Bone Quality and Radiographic Outcomes

Selected studies also evaluated bone quality and architecture using micro-CT and histological imaging. Qiao et al. (2015) [48] reported significantly higher bone volume fraction, bone mineral density, trabecular thickness, and trabecular number in plasma-treated groups compared to controls ($p < 0.01$). Naujokat et al. (2019) [45] observed similar fluorescent labeling patterns between plasma and control groups, yet plasma-treated implants exhibited higher BIC and IBD (Interthread Bone Denisity) values. Henningsen et al. (2023) [51] noted BAFO exceeding 75% at 2 weeks in all groups, with plasma-treated implants achieving 80.4% ± 7.0% at 8 weeks ($p = 0.027$), supported by micro-CT scans showing dense mature bone around all implants. Nevins et al. (2023) [52] showed significantly reduced bone loss at 6 weeks in plasma-treated implants (0.56 mm ± 0.24) compared to controls (0.79 mm ± 0.20, $p = 0.016$), alongside surface chemistry analyses indicating a 31% reduction in carbon contamination and increased oxygen and titanium peaks, suggesting enhanced surface bioactivity.

3.4. Safety and Adverse Events

Across all nine studies, no adverse clinical events related to plasma treatment were reported. All animals tolerated the implant placement and surface treatment procedures without signs of peri-implant inflammation, wound dehiscence or systemic complications. Henningsen et al. (2023) [51] noted significant weight gain in animals and absence of implant loosening or inflammation, with micro-CT confirming consistent osseointegration. Nevins et al. (2023) [52] reported only one minor event in a control implant that lost its healing abutment without infection; all other implants remained stable. Jiang et al. (2018) [50], Qiao et al. (2015) [48] and Teixeira et al. (2012) [47] also confirmed clinical stability and mature bone formation without complications. Similarly, Hung et al. (2018) [44], Canullo et al. (2018) [46], Giro et al. (2013) [49] and Naujokat et al. (2019) [45] reported no adverse events, supporting the biocompatibility and safety of plasma-based surface treatments. Surface analyses from Nevins et al. [52] and Giro et al. [49] showed that plasma treatments effectively reduced carbon contamination and increased oxygen content without introducing harmful residues or causing structural damage.

3.5. Limitations

Despite the encouraging results, some limitations must be acknowledged. The short follow-up periods of 2 to 12 weeks limit the evaluation of long-term osseointegration durability, peri-implant bone stability and implant performance under physiological loading. None of the animal models included functional occlusal loading, which is critical to assess implant behavior in clinical contexts. Considerable heterogeneity in plasma treatment protocols across studies precluded a quantitative meta-analysis, as pooling data under such diverse conditions could have led to misleading conclusions. The use of different animal species, implant sites, and implant numbers per subject further introduces variability and may reduce translational applicability to humans. Inconsistent outcome measures and timing across studies also hinder meta-analytical synthesis. This review was based on PubMed and Scopus databases, a deliberate choice that ensured coverage of the main biomedical literature, although it may still represent a limiting factor. Finally, as all evidence comes from preclinical animal models, cautious interpretation is warranted, and well-designed clinical trials are needed to confirm the efficacy and safety of plasma surface modifications in human patients.

4. Discussion

4.1. Biological Effects of CAP on Osseointegration

This systematic review aimed to provide a comprehensive analysis of the current in vivo evidence regarding the application of cold atmospheric plasma (CAP) treatments on titanium dental implant surfaces, with particular emphasis on their biological effects on osseointegration. The included preclinical data consistently seem to indicate favorable outcomes associated with CAP treatment, notably enhanced bone-to-implant contact (BIC), improved biomechanical fixation, and superior bone quality parameters when compared to untreated control surfaces. Across a range of animal models (including Beagle dogs, Labrador dogs, Foxhounds, Göttingen minipigs, pigs and mice) CAP application was shown to improve early and mid-term osseointegration outcomes. Several studies reported statistically significant increases in BIC within 2 to 8 weeks post-implantation, with improvements of up to 20% over controls (Canullo et al. [46], Qiao et al. [48], Nevins et al. [52]). These results align with previous systematic reviews (Pesce et al. [53]) highlighting plasma and photofunctionalization's ability to modify surface energy and chemistry, thereby accelerating cellular adhesion and bone healing. In particular, Pesce et al. [53] reported that studies using non-thermal plasma did not show significant improvements at the earliest follow-up (1 week), but consistently demonstrated higher BIC values at later stages (3–8 weeks). Our findings corroborate this time-dependent effect, as most of the included studies indicated that plasma-related benefits become more evident during the early to mid-term phases of osseointegration.

4.2. Biomechanical and Radiographic Outcomes

Biomechanical assessments further supported these findings. Removal torque values and implant stability quotient (ISQ) measurements were generally higher in plasma-treated implants, suggesting enhanced mechanical integrity of the bone–implant interface. However, discrepancies across studies were observed. For example, Hung et al. [44] did not find significant mechanical improvements, suggesting CAP efficacy may depend on specific treatment parameters and implant location. Radiographic and micro-CT analyses revealed positive effects of CAP on peri-implant bone volume, mineral density and trabecular architecture, all features that contribute to long-term implant success under functional loading. Importantly, none of the included studies reported adverse biological reactions or signs of peri-implant inflammation and surface characterization consistently demonstrated reductions in organic contaminants and favorable surface chemistry changes. These findings are consistent with Alqutaibi et al. (2023) [54], who highlighted the dual role of CAP as both an antimicrobial agent and a surface activator.

4.3. The Current Vision of CAP in the Literature

A key issue in the literature is whether CAP should be viewed primarily as a decontamination strategy or a true biofunctionalization tool. While some studies emphasize only its antimicrobial potential in managing peri-implantitis (Alqutaibi et al. [54]), others, including this review, focus on its ability to enhance osseointegration by improving surface wettability, chemistry and energy (Pesce et al. [53]). This duality creates conceptual ambiguity regarding its main mechanism of action. It is important to note that the beneficial effects of CAP do not result from the long-term presence of plasma on the implant surface. Rather, CAP induces transient physicochemical changes, such as increased hydrophilicity and surface energy, that appear to improve early cell adhesion and reduce initial bacterial colonization. However, these effects may diminish over time, and current evidence does not support a lasting antimicrobial action capable of preventing peri-implantitis in the long

term. As Najeeb et al. (2015) [55] pointed out, the lack of standardized surface treatment protocols and outcome measures remains a major challenge in CAP research.

4.4. Limitations of Current Preclinical Evidence

A significant limitation identified across studies is the lack of standardization in CAP treatment parameters, such as gas type, exposure time, power, delivery method, and implant distance, which complicates cross-study comparisons (Table 2). Treatment efficacy is strongly influenced by how plasma is generated and applied, with critical variables including modality (e.g., atmospheric jets, vacuum reactors, RF oxidation, or ion implantation), gas composition (argon, oxygen/air, silver), operating conditions (power, pressure, flow, exposure time, nozzle–surface distance) and timing relative to implant insertion.

Table 2. This table summarizes the plasma parameters used in each study.

Title	Authors	Type of Plasma Treatment	Parameters
Effects of non-thermal plasma on sandblasted titanium dental implants in beagle dogs	Hung et al., 2018 [44]	Argon NTAPP	**Device:** Yih Dar Technology, Hsinchu County, Taiwan (ISO 9001 certified) **Electrodes:** Aluminum tape electrodes on quartz tube (4 mm inner diameter, 10 mm spacer) **Argon flow rate:** 1.8 L/min **Oxygen flow rate:** 0.01 L/min **Voltage:** High-voltage mono-polar square pulses **Repetition rate:** 0.5–4 kHz **Duration:** 60 s per implant
Surface conditioning with cold argon plasma and its effect on the osseointegration of dental implants in miniature pigs	Naujokat et al., 2019 [45]	Argon NTAPP	**Pressure:** 2 bar **Flow rate:** 4.3–4.4 L/min **Frequency:** 20 kHz **Voltage:** 115–230 V **Temperature:** <40 °C at the point of application **Distance:** 7 mm **Duration:** 240 s total (60 s per quadrant, from the neck to the tip of the implant)
Hard and soft tissue changes around implants activated using plasma of argon: A histomorphometric study in dog	Canullo et al., 2018 [46]	Argon NTAPP	**Power:** 75 W **Pressure:** −10 mbar **Temperature:** room temperature **Duration:** 12 min
Assessment of a chair-side argon-based non-thermal plasma treatment on the surface characteristics and integration of dental implants with textured surfaces	Teixeira et al., 2012 [47]	Argon NTAPP	**Pressure:** atmospheric **Temperature:** room temperature **Duration:** 20 or 60 s per quadrant (KinPen™ device, Neoplas tool GmbH, Greifswald, Germany)
Ag-plasma modification enhances bone apposition around titanium dental implants: an animal study in Labrador dogs	Qiao et al., 2015 [48]	Silver-ion plasma immersion (Ag-PIII)	**Cathode rod:** Pure silver (99.99% purity, 10 mm diameter) **Temperature during silver release test:** 37 °C **Duration of silver release test:** 3 months (samples in 10 mL water) **Analysis:** Silver release quantified by Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES)
Osseointegration assessment of chairside argon-based nonthermal plasma-treated Ca-P coated dental implants	Giro et al., 2013 [49]	NTAPP on CaP	**Pressure:** atmospheric **Temperature:** Room temperature **Duration:** 20 s per quadrant (KinPen™ device, portable, length 155 mm, diameter 20 mm, weight 170 g)
Effect of Plasma Oxidation-Treated TiOx Film on Early Osseointegration	Jiang et al., 2018 [50]	Anodic oxidation plasma (PO-SLA)	Plasma oxidation treatment technical parameters not specified in detail
Osseointegration of titanium implants after surface treatment with ultraviolet light or cold atmospheric plasma in vivo	Henningsen et al., 2023 [51]	CAP	**Device:** Yocto III CAP reactor (Diener electronic GmbH, Ebhausen, Germany) **Power:** 24 W **Pressure:** vacuum of –0.5 mbar **Duration:** 12 min
Gas Plasma Treatment Improves Titanium Dental Implant Osseointegration—A Preclinical In Vivo Experimental Study	Nevins et al., 2023 [52]	Argon NTAPP	**Device:** ACTILINK Reborn (Plasmapp Co., Ltd., Daejon, Republic of Korea) **Vacuum base pressure:** ~5 torr reached within 30 s **Operating pressure:** 5–10 torr (optimal range for hydrocarbon removal) **Electrical input:** sinusoidal power, frequency 100 kHz, voltage 3 kV **Treatment time:** 8 s plasma exposure **Additional cycle:** Vacuum generation: 30 s, Plasma treatment: 8 s, Purification/by-product elimination: 17 s, Venting: 5 s **Total cycle:** ~60 s **Gas management:** chamber vented via HEPA filter to prevent reattachment of impurities

Immediate post-treatment placement appears essential, as the super-hydrophilic state induced by plasma rapidly decays with time. However, many reports under-specify these variables, thereby limiting reproducibility and comparability. Additional shortcomings of the current evidence include short follow-up periods (2–12 weeks), absence of functional loading and considerable variability in animal models, which together reduce generalizability to humans. This limitation had already been highlighted by Pesce et al. [53], who

noted that although qualitative improvements with plasma were evident, heterogeneity in gas types, exposure times and animal models prevented a pooled meta-analysis. Our systematic review confirms this scenario, showing that despite a larger number of studies now available, the absence of protocol harmonization continues to hinder quantitative synthesis. To improve reproducibility and translational relevance, future studies should clearly report device type, gas chemistry, pressure conditions, exposure duration, treatment-to-insertion interval, baseline surface characteristics and objective verification of activation.

4.5. Translational Perspectives

Although current evidence is limited to preclinical models, the promising enhancements in osseointegration suggest potential clinical relevance. Integrating CAP into chairside workflows could provide a rapid and effective surface biofunctionalization step prior to implant placement, potentially improving early stability and bone healing. However, translation to human patients requires careful consideration of key variables not addressed in animal studies, including systemic conditions, oral microbial diversity and functional occlusal loading. Standardization of CAP protocols is essential to ensure reproducibility and safety in clinical practice. Moreover, combination strategies that pair CAP treatment with other surface modifications, such as growth factor coatings or nanostructured topographies, may offer synergistic effects. Well-designed clinical trials are urgently needed to evaluate not only the efficacy of CAP-treated implants but also their long-term performance, safety, and potential to reduce complications such as peri-implantitis. Addressing these translational gaps will be critical for moving CAP technology from preclinical promise to practical application in dental implantology.

In light of these concerns, future research should focus on developing standardized and clinically relevant CAP protocols. Long-term preclinical studies incorporating functional loading are needed to better simulate oral biomechanics. Moreover, combining CAP with other surface biofunctionalization strategies (such as growth factor coatings or nanostructured topographies) may yield synergistic effects that further improve osseointegration and long-term implant success.

5. Conclusions

This systematic review of preclinical in vivo studies shows that cold atmospheric pressure plasma (CAP) and related plasma-based surface treatments consistently promote early osseointegration of titanium dental implants, as evidenced by improved histomorphometric parameters such as bone-to-implant contact and bone area fraction occupancy. These treatments also show promising effects on implant stability and biomechanical fixation without any reported adverse biological reactions, confirming their safety in animal models. Despite these encouraging findings, the current body of evidence is constrained by several limitations, including short observation periods, absence of functional loading conditions and considerable heterogeneity in both treatment protocols and outcome assessments. As such, while plasma surface modifications show potential as a strategy to enhance implant integration, their routine clinical application requires further validation. Future research should prioritize well-designed clinical trials with standardized methodologies, longer follow-up periods and functional loading to better replicate real clinical conditions. Furthermore, the evaluation of patient-reported outcomes and cost-effectiveness will be essential to fully assess the clinical relevance and practical feasibility of these treatments in dental implantology.

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Abbreviations

The following abbreviations are used in this manuscript:

CAP	Cold Atmospheric Plasma
BIC	Bone-to-implant-contact
BAFO	Bone Area Fraction Occupancy
ISQ	Implant Stability Quotient
CT	Computed Tomography
NTAPP	Non-thermal Atmospheric Pressure Plasma
ROS/RNS	Reactive oxygen and nitrogen species
ALP	Alkaline Phosphatase
Runx2	Runt-related transcription factor 2
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Ag-PIII	Silver-ion plasma immersion ion implantation
BDWT	Bone density within threads
SLA	Sandblasted Large-grit Acid-etcher
PBID	Peri Implant Bone Density
IBD	Interthread Bone Density

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