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Review Article

Integrating Osteoimmunology into Modern Clinical Implantology: The Immune Blueprint of Osseointegration

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Abstract

Study Design: Narrative review (non-systematic, qualitative synthesis; no meta-analytic pooling performed). Background: Osteoimmunology describes the reciprocal regulation between the immune system and bone and is increasingly recognized as central to the biology of osseointegration and peri-implant bone loss. Objective: This review summarizes current osteoimmunological knowledge relevant to oral implants, including biomaterial-specific immune interactions and proposes how this knowledge can be applied in daily clinical practice. Materials and Methods: A structured literature search of PubMed/MEDLINE and Scopus (2000-2026) was performed using combinations of osteoimmunology, RANKL, macrophage polarization, peri-implantitis, titanium hypersensitivity, zirconia and dental implant risk factor terms; 39 sources meeting relevance and quality criteria were retained, including the narrative and case-based literature of Wiedemann and colleagues on titanium corrosion, metal hypersensitivity and zirconia alternatives. Results: Osseointegration and peri-implantitis represent two ends of a shared immune-bone continuum governed by the RANKL/RANK/OPG axis, macrophage M1/M2 polarization and the Th17/Treg balance. Implant surface characteristics, implant material (titanium versus zirconia), smoking, diabetes and antiresorptive or biologic medications all measurably shift this balance. Discussion: These findings support a clinical approach combining pre-surgical osteoimmune risk screening, biomaterial selection informed by individual hypersensitivity risk, surgery designed to shorten the pro-inflammatory window and maintenance that treats early bone loss as a possible immune rather than purely infectious event. Conclusion: Incorporating osteoimmunological reasoning, including awareness of material-specific immune reactivity, into routine implant practice offers a mechanistic framework that complements conventional surgical and prosthetic planning.

Keywords: Osteoimmunology; Dental Implants; Osseointegration; Peri-Implantitis; RANKL; Macrophage Polarization; Th17/Treg; Foreign Body Reaction; Titanium Hypersensitivity; Zirconia Implants; Implant Risk Factors

Introduction

For decades, osseointegration was described mainly in mechanical and histological terms: a direct, functional connection between living bone and a load-bearing implant. This classical framework does not explain why implants with near-identical surface chemistry produce markedly different peri-implant outcomes in different patients, nor why some patients lose marginal bone in the absence of detectable biofilm [1-9]. The discipline of osteoimmunology has filled this explanatory gap by formally recognizing that osteoblasts, osteoclasts and osteocytes share cytokines, transcription factors and signaling receptors with cells of the innate and adaptive immune system, so that every peri-implant bone response is, at its core, an immune response [3,4]. Translating this concept into implant dentistry requires clinicians to reconsider osseointegration not as a purely passive mechanical outcome but

as the favorable resolution of a controlled foreign body reaction [10-22].

A further, often underappreciated, dimension of this biology is that the immune response is not generic but partly material-specific: titanium, titanium alloys and zirconia elicit measurably different local and systemic immune profiles and a subset of patients demonstrate clinically relevant hypersensitivity to titanium corrosion products [23-37]. The aim of this review is to synthesize the mechanistic evidence linking osteoimmunology, including biomaterial-driven immune reactivity, to implant outcomes and to describe, in practical terms, how this knowledge can be integrated into daily implant placement.

Materials and Methods

A structured, narrative literature search was conducted in PubMed/MEDLINE and Scopus for articles published between January 2000 and June 2026. Search terms combined "osteoimmunology," "RANKL," "RANK," "OPG," "macrophage polarization," "Th17," "Treg," "foreign body reaction," "peri-implantitis," "osseointegration," and "dental implant" with recognized systemic risk factors (diabetes mellitus, smoking, bisphosphonates, biologic therapy) and with biomaterial-specific terms ("titanium hypersensitivity," "titanium corrosion," "zirconia implant," "metal allergy"). Reference lists of retrieved systematic reviews, meta-analyses and narrative reviews were hand-searched for additional sources. The full search and selection process is summarized in Fig. 1.

Inclusion criteria were: (i) original research, systematic reviews, meta-analyses or narrative reviews addressing bone-immune crosstalk or biomaterial-immune interaction in the context of endosseous implants or closely related periodontal/orthopedic bone biology; (ii) English language; (iii) peer-reviewed or indexed academic publication. Preclinical (*in-vitro*/animal) studies were included when they provided mechanistic insight not yet available from clinical data. Case reports were included selectively when they illustrated a mechanistically informative and otherwise rare clinical phenomenon, such as aseptic bone necrosis associated with metal allergy. Non-peer-reviewed sources and articles unrelated to bone-immune interaction were excluded. Thirty-nine sources satisfied these criteria and form the evidence base for this review.

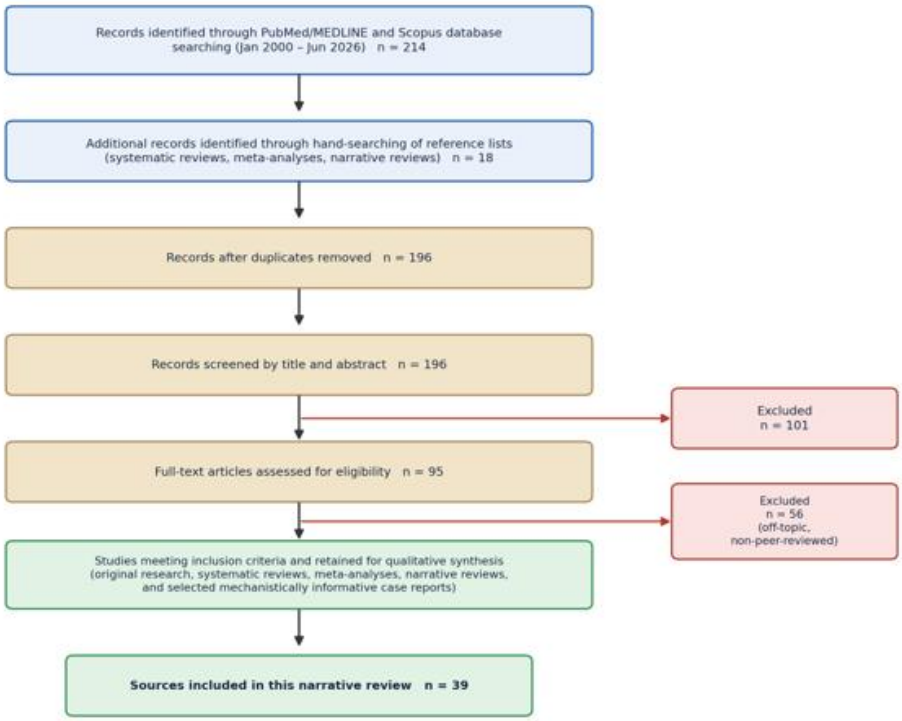

Figure 1: Literature search and study selection flow diagram, summarizing database identification, deduplication, screening, full-text eligibility assessment and final inclusion of 39 sources.

Statistical Considerations

As this review is qualitative and narrative rather than systematic, no original statistical analysis, formal risk-of-bias scoring or meta-analytic pooling was undertaken. Where quantitative effect estimates (e.g., relative risks, odds ratios) are presented in the Results, these are reported exactly as published in the cited primary meta-analyses, without recalculation, re-pooling or adjustment for heterogeneity; readers are directed to the original sources for confidence intervals and statistical methodology.

Results

The Osteoimmune Axis: Core Mechanisms

Bone remodeling and immune defense converge on a shared molecular language. The RANKL/RANK/OPG axis is the central node: RANKL, expressed by osteoblasts, osteocytes and activated T cells, binds RANK on osteoclast precursors to drive their differentiation and activation, while OPG acts as a soluble decoy receptor that neutralizes this signal [5]. Pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 amplify RANKL expression and directly potentiate osteoclastogenesis, whereas Th2 and regulatory T-cell (Treg) populations favor an anti-resorptive, pro-osseointegrative milieu through IL-4, IL-10 and TGF-β2. Th17 cells occupy a particularly important position at the implant interface: through IL-17 they recruit neutrophils and up-regulate RANKL and clinical studies of peri-implant tissue have found a hybrid Th17/Treg transcriptional profile, with elevated RORγT and FOXP3 expression, in diseased compared with healthy peri-implant sites [29,39]. A reduced or dysregulated Treg compartment has similarly been linked to peri-implant tissue destruction and implant loss [36,39]. Fig. 2 illustrates this cellular and molecular crosstalk directly at the bone-implant interface.

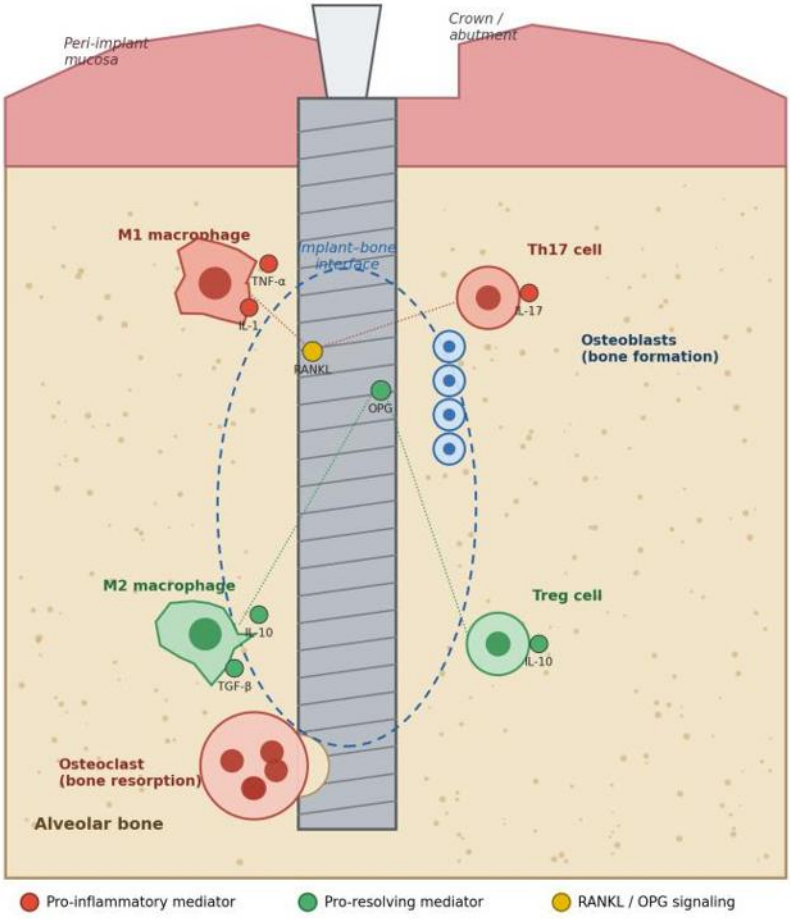

Figure 2: The Bone-Implant-Immune Interface: Illustrative cross-section of the bone-implant-immune interface, depicting M1 and M2 macrophages, Th17 and Treg lymphocytes, osteoclasts, osteoblasts and the RANKL/OPG signaling molecules that together determine whether peri-implant bone is resorbed or preserved.

Macrophage Polarization, Implant Surface Design and Implant Material

Macrophages provide the second pillar of this crosstalk. Upon contact with any implant surface, resident and recruited macrophages polarize along a continuum between a pro-inflammatory M1 phenotype and a reparative, pro-angiogenic M2 phenotype [32]. Early, transient M1 polarization is a normal and necessary step in debris clearance, but persistent M1 dominance sustains a chronic foreign body reaction that culminates in fibrous encapsulation or progressive marginal bone loss, while a timely shift toward M2 polarization is associated with stable, mineralized osseointegration [10,21]. Nanostructured and moderately rough, hydrophilic titanium surfaces have been shown experimentally to favor faster M2 polarization, less peri-implant inflammation and greater bone-to-implant contact compared with rougher or highly hydrophobic surfaces [10,32].

Beyond surface topography, the implant material itself shapes the immune response. Commercially pure titanium and titanium alloys are highly biocompatible but are susceptible to bio-tribocorrosion, releasing titanium particles and ions into peri-implant tissue that can activate innate immune pathways independent of infection and, in a subset of patients, provoke type I or type IV hypersensitivity reactions with amplified corrosion and osteolysis [23,37]. Documented clinical presentations range from localized inflammation and unexplained marginal bone loss to, rarely, aseptic bone necrosis temporally associated with metal allergy and clinicians should consider titanium intolerance in the differential diagnosis of otherwise unexplained implant complications, particularly in patients with a history of metal sensitivity [30,31]. Zirconia has emerged as an alternative biomaterial with excellent biocompatibility, low bacterial affinity and a comparatively reduced propensity for inducing an inflammatory or hypersensitivity response and one-piece zirconia implants now show clinical indication ranges similar to titanium implants, although long-term data beyond five years, particularly for two-piece designs, remain more limited [19,35,38]. Osteocytes, once regarded as passive bystanders, are now recognized as major local sources of RANKL and as mechanosensors that translate occlusal loading into immune and remodeling signals, linking biomechanics directly to the osteoimmune response regardless of the material chosen [14].

Osseointegration as a Controlled Foreign Body Reaction

Contemporary models describe osseointegration as the favorable resolution of an inevitable foreign body response rather than its absence [13,22]. Implant placement causes local tissue trauma and exposes a non-biological surface, triggering protein adsorption, complement activation and recruitment of neutrophils and macrophages within minutes to hours. When the physiological M1-to-M2 transition fails-due to surface characteristics, particle debris, material-specific hypersensitivity, mechanical overload or an unfavorable systemic immune state-a chronic granulomatous or fibrotic response develops instead, mechanistically continuous with clinical peri-implantitis [22,23]. This reframing implies that peri-implant marginal bone loss is not solely a consequence of bacterial biofilm but can also be provoked or amplified by the material itself, including titanium particles released through corrosion, tribocorrosion or repeated instrumentation [23,37]. The biological rationale for this material-driven pathway is that corrosion products and wear debris behave as Damage-Associated Molecular Patterns (DAMPs), engaging pattern-recognition receptors-such as Toll-like receptors and the NLRP3 inflammasome-on resident macrophages; this triggers IL-1β and TNF-α release and downstream RANKL upregulation independent of any bacterial antigen, offering a mechanistic explanation for biofilm-poor peri-implant bone loss. Consistent with a shared immunopathology, the 2017 World Workshop consensus and subsequent immune-profiling studies describe peri-implantitis as a dysbiosis-driven, Th17/RANKL-dominated lesion that overwhelms Treg/OPG counter-regulation while biofilm composition itself differs meaningfully from that of periodontitis [7,24,36]. Fig. 3 contrasts the cellular environment of stable osseointegration with that of established peri-implantitis, highlighting the reversal of the M1/M2 and osteoblast/osteoclast balance.

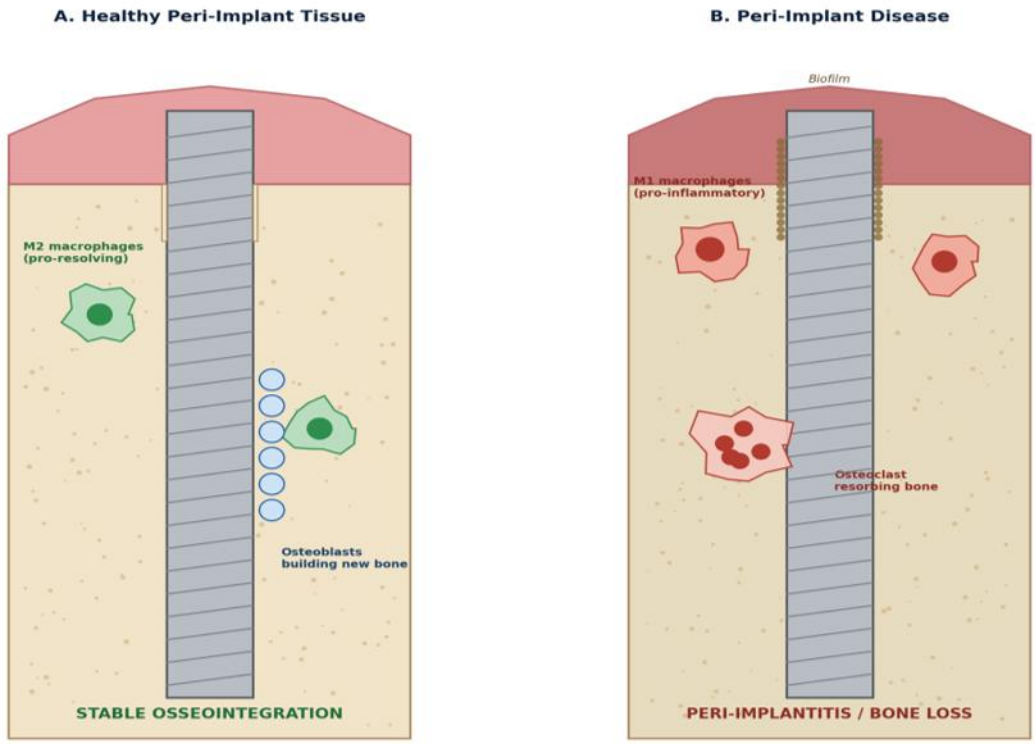

Figure 3: Osteoimmune Contrast: Stable Osseointegration versus Peri-Implantitis: Side-by-side comparison of the peri-implant cellular environment in health (A) versus disease (B), showing the shift from M2-dominated, osteoblast-driven bone formation to an M1-dominated, biofilm-associated, osteoclast-driven resorptive state with crestal bone loss.

Systemic Modulators of the Peri-Implant Immune Response

Several systemic and pharmacological factors shift this balance independent of local hygiene. Meta-analytic data show that smokers have an approximately two-fold higher risk of peri-implantitis at the implant level compared with non-smokers (relative risk approximately 2.0-2.1), although patient-level associations are less consistent and elevated pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) have been measured directly in the peri-implant sulcular fluid of smokers [12,15,26,34]. Diabetes mellitus, particularly when poorly controlled, is associated with a significantly higher implant failure risk (odds ratio approximately 1.8, rising further in type 1 diabetes) and greater marginal bone loss that increases with follow-up time, changes attributable to hyperglycemia-driven chronic inflammation and impaired angiogenesis rather than a purely mechanical phenomenon [8,16,33]. Antiresorptive and immunomodulatory drugs deserve particular attention: current evidence suggests bisphosphonates do not meaningfully reduce implant survival and may even be mildly protective against bone loss, but carry a small, absolute risk of medication-related osteonecrosis of the jaw after implant surgery while systemic disease and its associated medications more broadly, including biologic agents targeting TNF-α or IL-17, can alter osseointegration through mechanisms that remain incompletely characterized in prospective clinical trials [17,18,25,27,28]. Tables 1 and 2 summarize these behavioral/metabolic and pharmacological/material-related modulators alongside their reported effect estimates.

Risk Factor	Effect on Peri-Implant / Osseointegration Outcome	Effect Estimate	Ref.
Smoking	Increased risk of peri-implantitis at implant level; elevated peri-implant IL-1β, IL-6, TNF-α	RR ≈ 2.0-2.1 (implant-level); patient-level association less consistent	12,15,26,34
Diabetes mellitus (poorly controlled)	Higher implant failure risk; greater marginal bone loss increasing with follow-up	OR ≈ 1.8 (higher in type 1 diabetes)	8,16,33

Table 1: Behavioral and metabolic modulators of the peri-implant immune response.

Risk Factor	Effect on Peri-Implant / Osseointegration Outcome	Effect Estimate	Ref.
Bisphosphonates / denosumab	No meaningful reduction in implant survival; small absolute risk of MRONJ after surgery	Survival largely unaffected; MRONJ risk low but non-zero	17,18,25,27
Biologic therapy (anti-TNF-α, anti-IL-17)	May alter osseointegration through incompletely characterized mechanisms	Effect size not yet established in prospective trials	28
Titanium hypersensitivity / corrosion products	Biofilm-poor inflammation, unexplained marginal bone loss; rare aseptic osteonecrosis	Population prevalence uncertain (case-report level evidence)	23,30,31,37

Table 2: Pharmacological and material-related modulators of the peri-implant immune response.

Discussion

From Mechanism to Daily Implant Placement

The evidence summarized above has direct, actionable consequences for everyday implant practice. Before surgery, an osteoimmune risk screen-glycemic control (HbA1c), smoking status, vitamin D status, autoimmune disease, a structured medication review for bisphosphonates, denosumab or biologic agents, and, where relevant, a history of metal sensitivity or previous reactions to jewelry, piercings or orthopedic hardware-should accompany the conventional radiographic and periodontal work-up [17,28,30,33]. Patients identified as having elevated osteoimmune risk benefit from pre-operative optimization (glycemic control, smoking cessation counselling, and, where feasible, coordination with the prescribing physician regarding antiresorptive or biologic therapy) rather than blanket contraindication, since most of these factors shift probability rather than guarantee failure [8,25].

Implant material selection is itself an osteoimmunological decision in daily practice, not merely an esthetic or mechanical one. For patients with no history of metal sensitivity and standard risk profiles, titanium and titanium alloy implants remain the well-validated default, given their extensive long-term outcome data [19]. However, in patients reporting prior reactions to metal-containing jewelry, dental or orthopedic hardware or in those with unexplained inflammatory complications around a previous titanium implant, a one-piece zirconia implant-a ceramic oxide biomaterial introduced as a metal-free alternative to titanium-represents a reasonable, immunologically motivated alternative, given its lower propensity to provoke hypersensitivity and its comparable clinical performance in appropriate indications [19,35,38]. Clinicians should also recognize that not all unexplained peri-implant inflammation is infectious: persistent, biofilm-poor inflammation, especially with a compatible allergy history, warrants consideration of titanium intolerance or, in rare cases, an aseptic osteonecrotic process related to metal hypersensitivity [30,31].

At surgery, atraumatic technique and minimization of surface contamination remain fundamental, but osteoimmunology adds a further, practical criterion for implant selection: surfaces with documented capacity to shorten the M1 (pro-inflammatory) phase and accelerate the shift to M2 polarization should be preferred, particularly in patients whose baseline immune profile is already skewed toward chronic inflammation, such as those with poorly controlled diabetes or active smoking [10,32,33′. This is a shift in emphasis from selecting implants purely for primary mechanical stability toward also weighing their immunomodulatory behavior and, where indicated, their material-specific immune reactivity.

During healing and long-term maintenance, clinicians should treat unexplained, early marginal bone loss-particularly when probing depths and visible biofilm are minimal-as a possible sign of an unresolved foreign body or osteoimmune reaction, not only as an infection to be mechanically debrided [9,23]. In practice, this means broadening the differential diagnosis at the first sign of radiographic bone loss to include particle-related and hypersensitivity reactions, occlusal overload acting through osteocyte RANKL signaling and undiagnosed systemic disease and considering host-modulatory strategies analogous to those used in periodontology or a switch to a lower-reactivity material on re-treatment, when biofilm control alone fails to arrest progression [14,36,37]. Fig. 4 summarizes this three-phase, osteoimmunology-informed clinical algorithm.

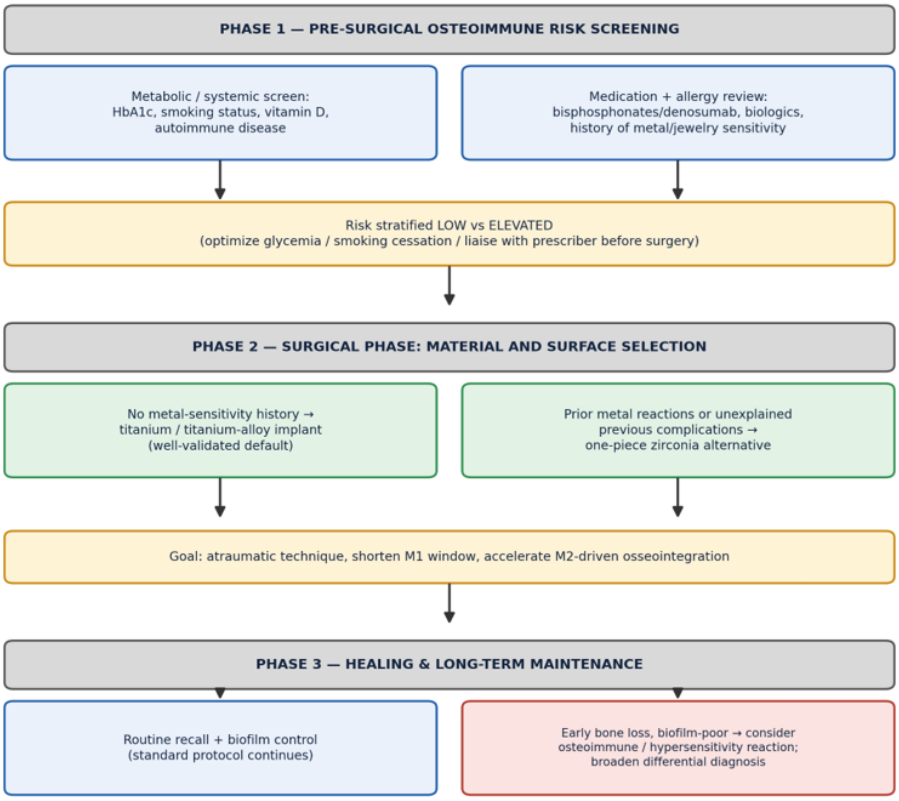

Figure 4: Osteoimmunology-informed clinical algorithm for daily implant placement, integrating pre-surgical risk screening, material and surgical decision-making and maintenance-phase differential diagnosis.

Potential Future Complications

If osteoimmune-guided protocols are applied prematurely or indiscriminately, they carry their own risks: unvalidated hypersensitivity testing could lead to unnecessary material switches or delayed treatment and over-attribution of routine early bone remodeling to an immune reaction could prompt unwarranted surgical intervention. Prospective validation of these protocols against conventional care, rather than uncritical adoption, should guide how quickly these concepts move from bench to chairside.

Limitations

This review is narrative rather than systematic; formal risk-of-bias assessment and quantitative pooling were not performed and publication bias affecting the underlying primary literature cannot be excluded. Much of the mechanistic evidence for macrophage polarization and RANKL/OPG signaling derives from preclinical or short-term human studies and long-term prospective trials directly testing osteoimmunology-guided protocols against conventional care are still lacking. Because much of what is known about titanium hypersensitivity comes from narrative accounts and isolated case reports rather than large, controlled cohort studies, how common clinically significant titanium intolerance actually is in the general implant population cannot yet be stated with confidence. The systemic risk factors discussed act through overlapping and only partially separable pathways, so the individual contribution of each mediator to any given clinical outcome remains difficult to isolate.

Conclusion

Osseointegration and peri-implantitis represent two ends of the same osteoimmune continuum, governed by the balance between pro-inflammatory and pro-resolving cytokine networks, macrophage polarization and the RANKL/OPG axis, with implant biomaterial itself acting as a modifiable immunological variable rather than an inert scaffold. Incorporating osteoimmunological screening, evidence-based surface and material selection and a broadened differential diagnosis for early bone loss into everyday implant practice offers a mechanistic, rather than purely empirical, framework for improving long-term implant survival and represents a logical next step in the evolution of clinical implantology.

Conflict of Interest
The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Acknowledgement
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Data Availability Statement
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement
The project did not meet the definition of human subject research under the preview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement
Informed consent was obtained from all participants included in the study.

Authors' Contributions
All authors contributed equally to this paper.

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