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Title: Optimization of the Oral Microbial Environment to Prevent Jaw Osteonecrosis: The Role of Microbial Balance in Modulating Adverse Effects

Background and Purpose: Bisphosphonates (BPs) are widely administered as antiresorptive agents in the management of osteoporosis and cancer-related bone metastases. Nitrogen-containing BPs are particularly prevalent; however, their use is associated with adverse effects, including inflammation and medication-related osteonecrosis of the jaw (MRONJ). Emerging evidence suggests that these complications may be mediated by interactions with oral microorganisms, such as periodontopathogenic bacteria and *Candida* species, common oral commensal fungi. *Candida* species exhibit low pathogenicity although the fungi can cause opportunistic infections under immunosuppressed conditions and influence cancer patient survival. Furthermore, interactions between *Candida* species and the immune checkpoint molecule PD-L1 have recently attracted attention. Interestingly, observational studies have reported a reduced incidence and severity of COVID-19 among BP users, although the underlying mechanisms remain unclear. Thus, we investigated the potential effects of BPs on interferon-β (IFN-β) production, an essential antiviral cytokine.

Research Outline: Our findings demonstrated that BP alone did not induce IFN-β production by macrophage-like cells; however, pretreatment with BP significantly augmented lipid A-induced IFN-β production. In addition, BP upregulated the expression of cyclic GMP-AMP synthase (cGAS) and retinoic acid-inducible gene I (RIG-I), both critical viral nucleic acid sensors. These results indicate that BP may potentiate antiviral immune responses. Conversely, BPs appeared to exacerbate inflammation mediated by periodontopathogenic bacteria and induce pyroptotic cell death. The inflammatory responses may contribute to the pathogenesis of MRONJ. Importantly, maintaining oral hygiene and controlling the oral microbial burden could mitigate these risks, thereby improving the safety profile of BP therapy.

Future Prospects: Recent studies indicate that BPs exhibit synergistic antifungal activity with azole-class agents via inhibition of the mevalonate pathway. Furthermore, in oncology, combined administration of BPs and PD-L1 inhibitors has shown promise for enhancing therapeutic efficacy. Ultimately, the prevention of MRONJ will require integrated strategies that include effective microbial control and maintenance of oral health. Future research will further explore BP-mediated modulation of immune checkpoint pathways, including PD-L1.

Reference:

1. *Candida* Infections: The Role of Saliva in Oral Health-A Narrative Review. *Microorganisms* doi: 10.3390/microorganisms13040717. 2025
2. Pretreatment with alendronate augments lipid A-induced IFN-β production via upregulation of cGAS expression. *Pharmacological Reports* doi: 10.1007/s43440-025-00773-y. 2025