Bisphosphonates

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Since the 90s, bisphosphonates (BP) have been used as medication to treat metabolic and oncological bone diseases. BP and other bone antiresorptive therapies still raise concern about oral health, especially implant therapy. During demineralization, the transport of calcium-bisphosphonate, linked by transcytosis performed through clasts, induces biochemical events capable of triggering apoptosis. This process of natural death — in which cells die by structure fragmentation without causing flow of enzymes or molecules that induce inflammation — minimizes bone resorption and slows down the process of remodeling. Thus, bisphosphonates contribute to control bone turnover, thereby preventing osteopenia and consequent osteoporosis.[1]

The advent of bisphosphonates used to treat osteopenia and osteoporosis promoted an avalanche of publications, including extensive and thorough literature reviews. Every detail of this class of medication was duly explored on the book written by Bijvoet et al.[2] A search performed in PubMed database retrieved recent reports on the association between the use of BP and osteonecrosis of the jaws or implant failure. The investigation also found other researches that provide an up-to-date view on recent clinical concerns, as follows.

Two systematic literature reviews[3,4] highlight our limited understanding about the risks involved in BP therapy, especially in regard to implant success. Either one of those two was able to find new evidence that contraindicated implant treatment to patients undergoing BP therapy. Additionally, they did not find evidence that BP therapy onset damages previously placed implants. Their findings suggest an implant survival rate of at least 95% for patients undergoing BP therapy. Despite being encouraging, our enthusiasm about the aforementioned literature reviews remains restrained due to the little evidence they provide for evaluation.

A case-control study,[5] recently published and not included in the aforementioned literature reviews, conducted a retrospective analysis of more than 300 patient records. The study found an increase in implant failure rates among patients with history of

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oral BP therapy. Nevertheless, it should be considered that these results are merely associative and that the potential causes for implant failure are countless. It is also worth noting that no reports on osteonecrosis of the jaws were found, which suggests a subtler effect of BP on implant survival.

An investigation[6] on the use of CTX biomarker for bone resorption suggests that the former is not considered useful to assess the risks undergone by patients using bisphosphonates. However, there are reasons to feel optimistic. Data provided by a cohort prospective study assessing bone augmentation and implant success among older women with osteopenia or osteoporosis are among those.

Another study[7] presented an early report on the relationship established among bone resorption markers, BP therapy and implant integration in 58 women. The research found that, based on bone resorption biomarkers (CTX), patients with history of BP therapy had the lowest levels of bone resorption correlated with improvements in implant stability eight weeks after implant placement. Curiously, this is also supported by another study[8] of which findings revealed that implant surfaces coated with BP led to greater implant osseointegration and reduced marginal bone loss throughout the first six months after implant placement. Consolaro[9] asserts that the use of bisphosphonates induces clinicians to fear and care. These reactions are associated with controversy resulting from lack of deep knowledge on the mechanisms of action as well as lack of a more accurate assessment of side effects.

Fear often results from ignorance. We have to promote knowledge. Scientific wisdom must be based on scientific evidence rather than opinion, words or faith. Personal and clinical experience is valuable when combined with scientific grounds and criteria. Similarly to personal and clinical experience, strictly laboratory and/or experimental trials should not be considered in isolation either. Coherently combining laboratory, experimental and clinical outcomes with experience previously described in the literature allows well-grounded procedures to be established, thereby indicating true evolution. Taken all the aforementioned statements into account, the only thing that remains clear is that we have a long journey ahead of us if we wish to understand the effects of BP therapy on our clinical practice with dental implants. It is worth noting that concerns about osteonecrosis of the jaws and implant failure are two utterly distinct subjects that need individual clarification. We have been working to determine the hurdles posed by BP therapy to implant therapy, and it is encouraging to know that, in the future, BP might be applied in implant therapy with positive outcomes.

The relationship between implant stability and bone health markers in post-menopausal women with bisphosphonate exposure

The authors[10] assessed the relationship between implant stability and bone turn-

over markers in patients with and without a history of bisphosphonate (BP) exposure for treatment of osteopenia/osteoporosis. One dental implant site was evaluated in 58 post-menopausal women with a spectrum of bone health in a "best practice" prospective cohort study. Each site had a previous or simultaneous bone augmentation procedure. BP exposure at enrollment was categorized as "never" or "past/current" exposure. Implant stability was assessed by resonance frequency analysis (RFA ISQ) at surgery and eight weeks post-implant. Bone turnover markers, C-telopeptide collagen crosslinks (sCTX) and procollagen -1 N-terminal telopeptide (P1NP) were measured pre-treatment, one and eight weeks following implant surgery. Mean age was 62.4 ± 6.8 years; 66% were osteopenic/osteoporotic. Average RFA ISQ at placement for all participants was 63.5 ± 11.3, at eight weeks post-surgery 74.2 ± 9.4 ($p < 0.01$). Among "past/current" BP users, there was a significant negative correlation between RFA ISQ values at eight weeks post-implant placement and sCTX and P1NP values at one week ($p = -0.65$ and $p = -0.55$, respectively; $p < 0.01$) and eight weeks ($p = -0.64$ and $p = -0.52$, respectively; $p < 0.05$). RFA ISQ values increased between implant placement and eight weeks post-surgery demonstrating successful osseointegration. Lower bone turnover was associated with better implant stability among patients with a history of BP exposure. Further investigation of the relationship between BP exposure and implant stability is warranted in a larger population, as results may strongly impact clinical practice decisions.

Effect of dental implants on bisphosphonate-related osteonecrosis of the jaws

Bisphosphonate (BP)-related osteonecrosis of the jaw (BRONJ) is a side effect of BP therapy. Dental implants are believed to be a risk factor for developing BRONJ. In the present study,[11] we analyzed the interval to the development of BRONJ in patients treated with BP who had received dental implants. Patients with dental implants and established BRONJ were evaluated at the Oral and Maxillofacial Surgery Department (Medical University of Vienna). In addition, studies from 1978 to 2012 were included in a meta-analysis. Three groups were created: implantation before BP treatment, implantation after BP treatment, and implantation during BP treatment. The outcomes were evaluated using linear regression analysis. Patients who underwent dental implantation during ($p < 0.001$) and after ($p < 0.001$) treatment with BPs developed BRONJ more rapidly. The treatment duration with oral BPs was significantly related to the rapidity of developing BRONJ ($p = 0.03$). The insertion of dental implants during or after BP treatment accelerated the development of BRONJ. BRONJ occurred less frequently when the implants had been inserted before BP therapy had been started.

Prospective biomarker evaluation in patients with osteonecrosis of the jaw who received bisphosphonates

Bone biomarkers have been suggested for the risk assessment for osteonecrosis of the jaw, a serious complication associated with bisphosphonate (BP) use; however, no consensus has been reached. This study[12] investigated the possible associations between bone biomarkers and the development of bisphosphonates-related osteonecrosis of the jaw (BRONJ). This is a case control study of 37 patients with BRONJ (age = 73.6 ± 11.2years) who had at least one sample available at diagnosis, out of which, 35 were taking BPs for osteoporosis and two patients for bone metastasis. Age- and gender-matched 37 patients who had been exposed to BPs for > 24 months and had no evidence of BRONJ after dentoalveolar surgery served as control group. The association between biomarkers (osteocalcin [OC], deoxypyridinoline [DPD], C-terminal telopeptide of collagen I [CTX], N-terminal telopeptides [NTX], bone-specific alkaline phosphatase [BAP], and parathyroid hormone [PTH]) and BRONJ development, the effects of BP discontinuation on biomarkers, and the performance of biomarkers for risk assessment were investigated. In our study, the PTH levels were found to be significantly higher in BRONJ patients compared to controls ($p < 0.05$). But the OC, DPD, CTX, NTX, and BAP levels were not significantly different between the two groups ($p > 0.05$). The CTX level in reference to a 150 pg/mL cutoff was also not significant for BRONJ development ($p > 0.05$). Among BRONJ patients who discontinued BP, in a linear mixed model, only CTX showed a significant increase over time ($\beta = 0.002$, $p = 0.007$). The cutoff PTH level was > 41.52 pg/mL (AUC = 0.719, $p = 0.009$), and that of CTX was ≤ 0.094 ng/mL (AUC = 0.619, $p = 0.069$). In conclusion, there is insufficient evidence for the risk prediction for BRONJ of current bone biomarkers; additional research is necessary.

Bone regeneration associated with non-therapeutic and therapeutic surface coatings for dental implants in osteoporosis

Oral implantology is considered as the treatment of choice for replacing missing teeth in elderly people. However, implant complications may occur in patients with osteoporosis. The pathogenesis underlying osteoporosis is due to an alteration in bone cell response to hormonal, nutritional, and aging factors. For such challenging situations, improved bone regeneration has been shown around dental implants for certain surface modifications.[13] These modifications include coatings of titanium implants with calcium phosphate (CaP) ceramics. Surface coating developments also allow for the addition of organic biomolecules, like growth factors, into the inorganic coatings that increase the bone formation process

at the bone-implant interface. The application of therapeutic-based coatings is becoming a rapidly growing research field of interest. CaP-coated implants have the ability to incorporate anti-osteoporotic drugs, which then can be locally released over time from an implant surface in a controlled manner. Thus, it can be anticipated that non-therapeutic and/or therapeutic coated implants can significantly increase low bone density as well as improve impaired bone regeneration in osteoporosis. This review aimed to provide a thorough understanding of the underlying mechanisms for impaired bone regeneration around dental implants in osteoporosis. Secondly, the review focused on biological interactions and beneficial role of the surface-coated (i.e., non-therapeutics and therapeutics) bone implants in osteoporotic bone tissue.

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