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Implications of bisphosphonate calcium ion depletion interfering with desmosome epithelial seal in osseointegrated implants and pressure ulcers

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ABSTRACT

Osteoporosis (OP) is a global bone disease prevalent in aging in humans, especially in older women. Bisphosphonates (BPs) are commonly used as therapy for OP as it influences hard and soft tissues calcium metabolism. Mucosal and dermal ulceration with exposure of underlying bone arises from incomplete epithelial recovery due to reduced desmosome formation deriving from lack of available calcium. Pathological situations such as bisphosphonate-related osteonecrosis of the jaw have been described. This hypothesis states other situations which demand intact functional desmosomes such as healing skin over chronic pressure points leading to pressure ulcers (as well-known as bedsores, pressure sores, pressure injuries, decubitus ulcers), and hemidesmosomes such as epithelial seals in contact with titanium surfaces will have a higher prevalence of breakdown among patients being treated with BPs. This may be proven through the diminished modulation of calcium ions due to BPs, and its effect on the formation of intercellular gap junctions.

Background

Osteoporosis (OP) is a global bone disease, and is prevalent among the aged among all ethnic groups. OP presents in both genders, but onset is earlier by a decade or more in women than in men [1,2]. OP develops thinning of bone cortices and trabeculae, with the consequent brittleness of the skeleton, changes in posture, proneness to bone fractures, and chronic pain. Bisphosphonates (BPs) are commonly used to slow down the loss of calcium from bone and bone reserves. BPs influence metabolism of hard and soft tissues, including direct toxicity on epithelia dependent on calcium for health viability and sustainability [3].

What are a desmosome and a hemidesmosome?

Human cells do not simply adhere to each other only through chemical bonds. There are highly specialized cell membrane structures which ensure organ integrity and function. Cells interconnect through a variety of highly specialized intercellular connections. These include desmosomes, gap junctions and protein zones of adherence (zonula occludens) and patterned reticulated attachments (zonula adherens) [4]. A complete desmosome is formed by two hemidesmosomes, interconnecting between cells, but may exist as a hemidesmosome as a structure binding to an inanimate surface like titanium [5].

Most of these cell membrane constructs are constituted by specialized proteins and they are involved in the transfer of intra- and inter-cellular nutrients and other constituent elements [6]. Membrane pumps and gates act selectively for transport of intracellular metabolites, food molecules, and inorganic ions, from one side of a cell-membrane to the other. The best known of these is the sodium-potassium pump (Na+, K+-ATPase) that renders low sodium and high potassium intracellular levels and uses ATP as its energy source in combination with proteins to sustain these pumps [7].

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Desmosome and hemidesmosome failure

Desmosomes and hemidesmosomes function differently, allowing higher concentrations of molecules and ions to flow passively from higher to lower gradients of metabolites. For example, the gap-junctions are formed by hexagonal dumb-bell protein tubes and acts as a cell membrane pore by an aggregation of identical peptides to form a channel through which small molecules flow [4–7]. A channel about 15–20 Ao in diameter forms, through which many small molecules like sugars, amino acids, and small sized proteins, flow unimpeded from one intracellular environment to another. However, the gap junctions do not always remain open. When the normally very low (10–8 M) intracellular calcium levels rise, the gap junctions undergo conformation changes that close the gap junctions channel, inhibiting the transfer of other metabolites [5]. When low calcium concentrations exist due to BPs, epithelialization is compromised with dysfunctional intercellular-connections leading to inadequate calcium ions available. Then, desmosomes and hemidesmosomes will break down, repair poorly and result in functional failure [8,9].

What are bisphosphonates and why are they used?

BPs are ubiquitously and frequently prescribed for OP, and BP-therapies are also often used for controlling breast, prostate, multiple myeloma and metastatic bone cancers, fibrous dysplasia and Paget disease. BPs slow osseous resorption, but do not cure the diseases [10]. Yet BPs are reliably successful at reducing lesions in these diseases and are successful at relieving associated pain. BPs bond available calcium ions and inhibit osteoclasts from the resorbing bone, by binding available calcium released from the bone, ensuring it is minimally ionized and consequently inactivated.

It is well known that BPs remain active for years in patients. It takes over 12 years for BPs to clear out of a patient's system. One major complication of BP-therapy is the development bisphosphonate-related osteonecrosis of the jaw (BRONJ). Consequently, patients on BPs are notorious for slower than usual healing with minor trauma, cuts, and scratches [11–14].

Most of the BPs currently used are derivatives of zoledronic acid [3]. Some of the commercially available nitrogen-containing bisphosphonates (N-BPs) are Alendronate (Fosamax), Risedronate (Actonel), Pamidronate (Aredia, Pamisol), and Zoledronate (Zometa); whereas the non-N-BPs are mostly Clodronate (Bonefos, Loron), Etidronate (Didronel) and Tiludronate sodium (Tildren) [10].

Who will be prone to desmosome and hemidesmosome breakdown?

Patients being treated with BP for OP will have signs and symptoms of epithelial breakdown. For example, BRONJ forms exclusively in these patients [8,9].

What are pressure ulcers?

Pressure ulcers (as well-known as bedsores, pressure sores, pressure injuries, decubitus ulcers) form in bed-ridden, debilitated or immobilized patients confined to bed, on weight bearing sites, when they cannot move to change the pressure points. This is particularly found in the elderly patients as the skin becomes less dense and less vascular [15]. Pressure ulcers (PUs) are a localized ulcerated skin with central necrosis, often exposing underlying bone, with margins in a simultaneous process of breakdown and healing [12,13]. Pressure-relieving support surfaces are used to assist in preventing ulcer development [16]. The PUs are often explained away by ischemic necrosis, but their formation is variable, unpredictable and poor nursing is often unfairly blamed arising from lack of frequency-of-turning. Ischemia and regular nursing practices do not fully explain the reason some patients develop PUs more rapidly and easily than others [12–14,17–19]. From a health care system perspective, PUs inflict a major financial burden, in addition to affecting negatively the quality of life [15,16,20]. For instance, PUs' prevalence in Canada is 25% and 30% in acute care hospitals and long-term care facilities, respectively [15].

What are osseointegrated oral implants?

Osseointegration is defined as "a time dependent healing process whereby clinically asymptomatic rigid fixation of alloplastic materials is achieved, and maintained, in bone during functional loading" [21]. Osseointegrated implants can be used to support dental prostheses to replace missing teeth intraorally. Titanium or Zirconium screws are placed into the bony alveolar jaws, and form a foundation on which functional teeth are reconstructed. Osseointegrated implants have a high survival rate (>95%) [22,23], even in patients with a history of aggressive periodontitis [24]. Placing the implants into thick keratinized gingiva (as opposed to thin alveolar mucosa) is highly desirable as this attached epithelium contains desmosomes binding the keratinized cells and form many hemidesmosomes as a seal in the junctional epithelium against the titanium surface of the implant [25]. However, there are many failures which occur in spite of adhering to strict surgical placement and post-surgical maintenance protocols, and explaining these failures remains obscure [26].

Statement of this hypothesis

The hypothesis laid out here states: other sites will also be susceptible, such as neglected osseointegrated implants which have a hemidesmosomal failure of the seal against oral microbial influences, and poor epithelialization healing which allows PUs because of inadequate epithelial repair contributing to ischemic pressure dermal necrosis. Discussion and guidelines over the failure of osseointegrated implants because of desmosomal growth in patients on BP-therapy are scarce [27–30]. In addition, little is known on how BP-therapy impacts malformation of desmosomes in the development of PUs [17].

Objective

Reinterpretation of known facts with this hypothesis explains not only the occurrence and progression of BRONJ [8,9] but also the existence of unexplained PUs and many failed osseointegrated implants (e.g. dental implants) in the elderly. The central gist of this hypothesis focuses on epithelial cell junctions, explains that BPs induces a lack of necessarily available calcium ions, and the consequent dysfunction of epithelial desmosomes which leads to PUs, and hemidesmosomes which result in BRONJ and failure of osseointegrated implants.

Discussion

Pathophysiology of break down

BPs binds calcium ions, both intracellular and extracellular, and inhibits osteoclasts from resorbing calcified bone. The resultant increase of intracellular calcium forces closure of gap junctions, and consequent disruption of the flow of vitally needed cellular metabolites for normal cell function, growth, and differentiation. Gap junctions, necessary for cell adhesion and organ integrity in