The Challenge of Predictable Vertical Alveolar Ridge Augmentation for Dental Implant Site Development

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Dental implants are the standard of care for replacing missing teeth and their long-term clinical success is dependent upon the quality and volume of bone and degree of osseointegration that can be achieved. Bone height and volume is often diminished in patients due to periodontal disease and/or trauma and the patho-physiological bone loss that occurs with time after tooth extraction[1]. The lack of sufficient bone height and volume is a major limitation impacting dental implant treatment success[2]. Several surgical techniques and biomaterials have been developed for dental implant site

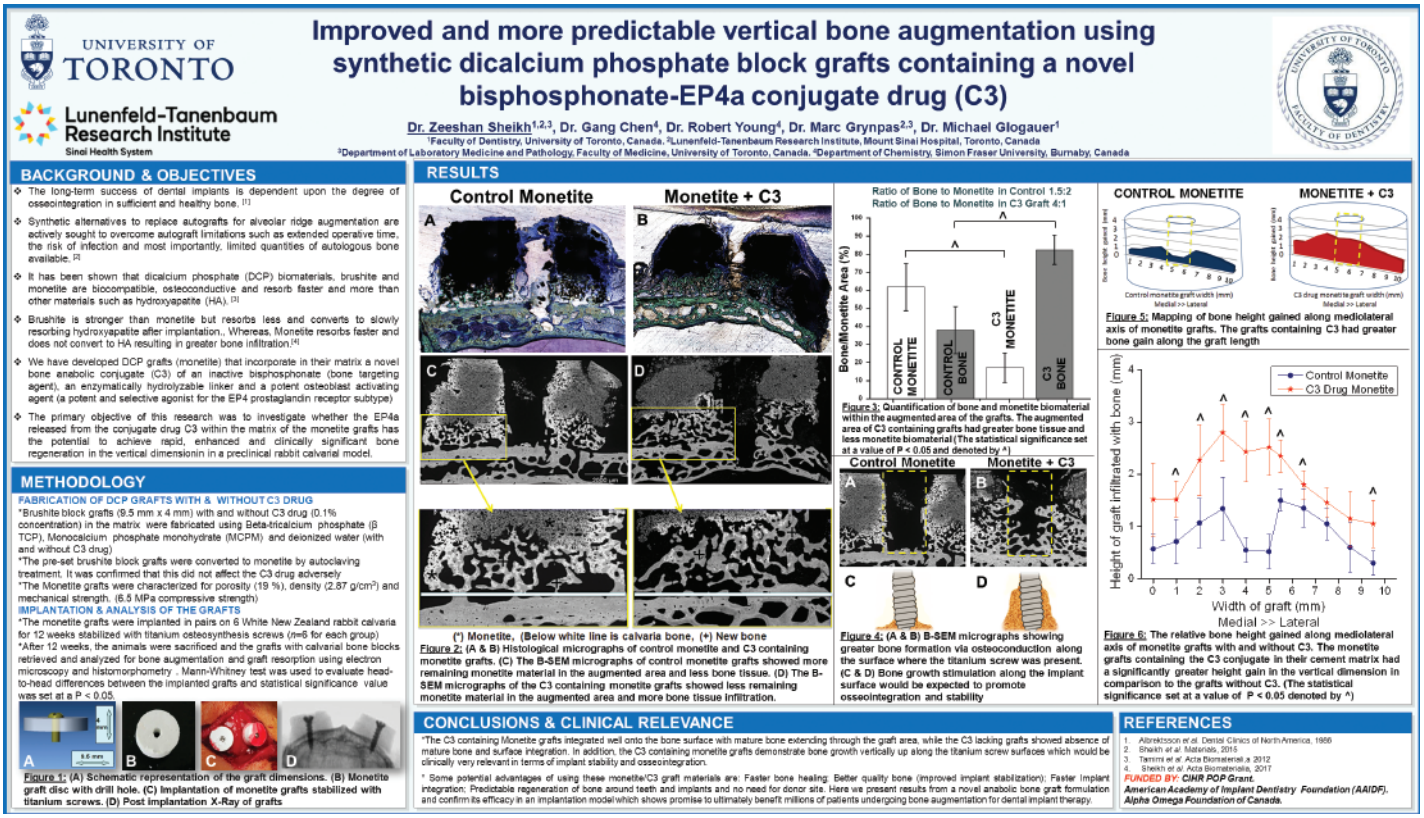

Figure 1: ePoster presented at the AAID 66th Annual Conference

development in the resorbed alveolar jaw[2,3]. Some of the commonly used surgical techniques used are:

1. Osteoperiosteal flap technique (OPF);
2. Distraction osteogenesis (DO);
3. Block grafting;
4. Guided bone regeneration (GBR) using membranes;
5. Subperiosteal tunneling for minimally invasive approach to GBR.

The material options for bone augmentation procedures are divided into natural transplants (autografts, allografts and xenografts) and synthetic biomaterials (alloplasts).[4,5] These grafting materials are used for clinical applications because they are osteogenic, osteoinductive, osteoconductive or possess a combination of these properties.[2,6] Although preclinical and clinical investigations using various surgical techniques in combination with the available bone replacement graft materials have reported promising results, vertical ridge augmentation procedures still continues to be unpredictable and experience a high rate of failure in clinical dental practice.[7] Distraction osteogenesis produces greater bone height than GBR and onlay block grafting, but it has a higher rate of complication associated with it.[8] Although the results of GBR for vertical ridge augmentation are promising, clinical success is limited due to the procedure being highly technique-sensitive, and often failing due to wound dehiscence.[9] Onlay block grafting to increase the vertical height of the mandible and maxilla usually requires extraction of an autologous bone block from donor site and its fixation with screws onto the recipient site.[10] Autologous onlay grafting is associated with complications such as donor site morbidity and are also vulnerable to rapid resorption in sites that receive mechanical load and soft tissue tension.[7] Difficulty in creation and maintenance of space in the defect area where bone regeneration is intended also proves to be detrimental. Bone loss often generates non self-containing defects covered by soft tissues which ultimately collapse onto a grafting site if not supported.[2] Also, epithelial cells have a higher turnover rate than bone tissue, resulting in the defect space being filled with soft tissue if barrier membranes are not used.[11-13] Hence, in larger defects, barrier membranes are used in combination with graft materials to allow for migration of osteoblasts and ingrowth of blood vessels from adjacent

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osteogenic tissues.[2,14] Tenting screws, titanium-reinforced membranes or titanium meshes are and can also be used in conjunction with graft materials to increase mechanical support.[15,16]

A requirement for bone regeneration is the presence and/or recruitment of osteoblast precursors and growth factors at sites of bone augmentation. Osteoblast precursors can be provided by the graft material (e.g., cancellous autografts) or by the recipient bed.[6] Growth factors can come from the graft, recipient bed and vasculature and it is believed that intra-marrow penetration of the recipient bed favours both cellular and growth factor migration into the sites where bone is required to be regenerated.[17,18] Host osteoprogenitor cells infiltrate the graft materials within seven days and the early phase of bone regeneration at grafted sites is dominated by active bone resorption and formation throughout the graft.[2] The latter phase of incorporation is characterized by osteoconduction and a process known as creeping substitution.[19] Many of the bone graft materials used today are able to contribute to new bone formation through this biological process.[20] The osteoblast precursors differentiate into mature osteoblasts under the influence of osteoinductors and synthesize new bone during the first weeks after. Growth factors involved in bone formation act on fibroblast and osteoblast proliferation, extracellular matrix deposition, mesenchymal cell differentiation and vascular proliferation.[21] Research on bone augmentation and regeneration is currently focused on molecular, cellular, and gene therapeutics.[22] Bone morphogenetic proteins (BMPs) are differentiation factors and have the ability to differentiate osteoprogenitor cells into mineral forming osteoblasts and stimulate vascular proliferation.[23] BMPs have shown promise for intraoral applications such as ridge preservation and sinus augmentation.[24-26] Platelet derived growth factor (PDGF) has also shown potential for use in bone regenerative applications.[27] However, optimal dosage and carriers for PDGF are still to be determined and extensive preclinical and clinical trials are required in future. A new approach to achieve bone augmentation is the addition of platelet rich plasma (PRP) from the patient blood to graft materials.[28] Initial results have shown more and denser bone compared to autografts used alone for ridge augmentation procedures.[6] In addition, the seeding of constructs with mesenchymal stem cells also holds great promise and merits further in-depth investigation.[29,30]

There are many surgical techniques with various combinations of natural and synthetic graft materials that are currently used in an attempt to successfully achieve ridge augmentation in the vertical dimension. However, there exists no single ideal technique or graft material which consistently provides reproducible results in all case types. There is a need to develop treatment modalities that involve less invasive vertical ridge augmentation procedures that provide reproducible results. The existing biomaterials require the addition of supplemental pharmacotherapuetics that are able to promote improved bone quality in the resulting grafted site thereby leading to a more predictable long-term result for the dental implant placed into that newly developed bone. The development of these new chemical modulators of bone development will facilitate the fine-tuning of the physico-chemical properties of the bone graft materials and should improve the predictability of bone regeneration therapeutics.[12]

A novel approach for achieving more predictable alveolar ridge augmentation: Calcium phosphates are similar to bone in composition and hence considered as good bone substitutes graft options.[31,32] Dicalcium phosphate cement based biomaterials (brushite and monetite) have been shown to be osteoconductive and have improved resorption profiles when compared to other calcium phosphates.[33-35] Brushite has been investigated for vertical bone augmentation[36-38], but they tends to re-precipitate as insoluble HA after implantation which limits resorption and graft replacement by bone tissue ultimately.[39] The anhydrous form of brushite is monetite, and this after implantation does not to transform to insoluble hydroxyapatite and resorbs more than brushite graft materials.[39-42]

Prostaglandin E_2 (PGE_2) has been previously shown to induce anabolic bone effects in animals and humans[43] through agonism at the EP4 receptor[44] but its clinical usefulness is limited by systemic side effects. Potent EP4-selective agonists (EP4a)[45], while being more potent than PGE_2, still possesses the side effects that limit their utility in bone augmentation therapy. Our collaborative group has identified two bone targeting EP4a-bisphosphonate conjugates (C1 and C3) which link the EP4a via a linker group which is in turn bound to a bone targeting bisphosphonate such as alendronate. These conjugates bind strongly to bone tissue to provide sustained release (half-time in vivo of 4-7 days) of active EP4a via action of local esterase enzymes. C1 releases alendronate[46,47] (a proven inhibitor of bone resorption) but the C3 does not owing to its amide-capped alendronic acid[48], hence allows for localized bone and graft remodelling to take place. Due to the bisphosphonate component, this C3 conjugate can be bound to bone substitutes *in vitro* to form a very stable complex and the loading of conjugate can be varied essentially at will.

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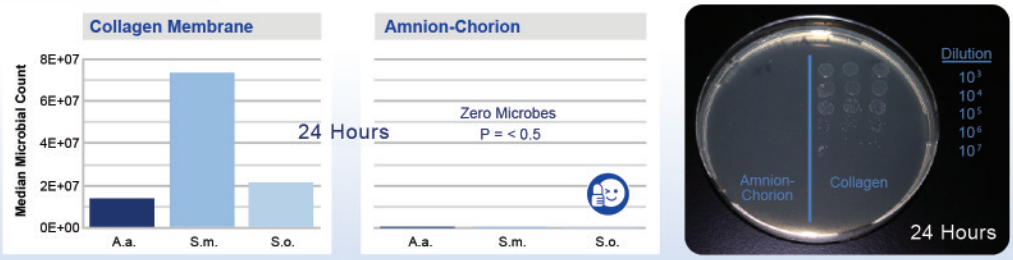

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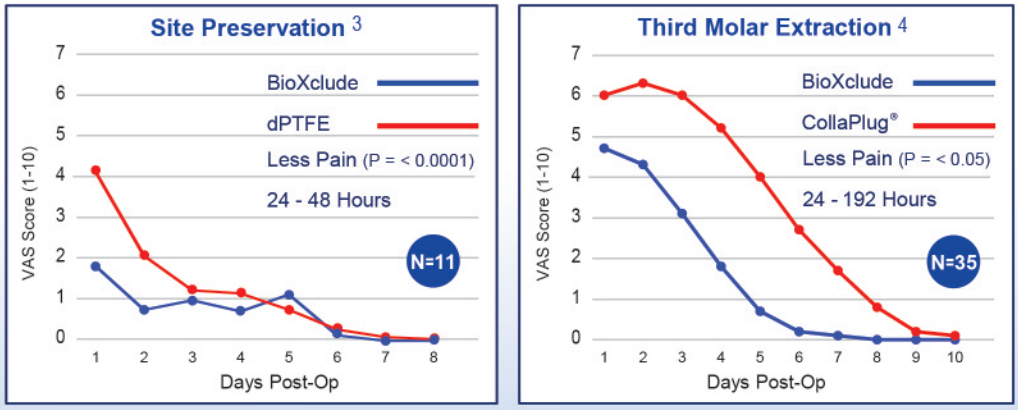

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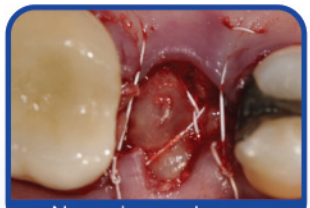
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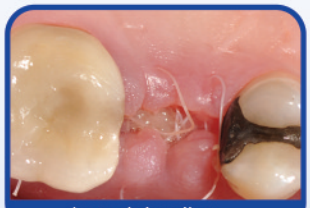
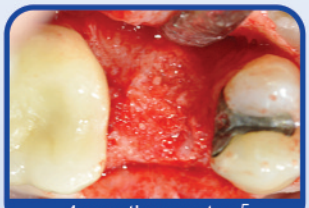

1 week healing


4 month re-entry [5]

AAID 2018

New Trends Session: Weds. 10:40 - 11:00 AM - Dr. Dan Holtzclaw - Rise of Placental Tissue Products: Implications in Dentistry & Medicine

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We have confirmed that loadings of from 0.1 to 5% (w/w) can be achieved for binding of C3 to brushite and monetite during the preparation of the cements from its components. The conjugate not only binds successfully to the grafts, it remains unchanged over time and EP4a released without chemical structure degradation. Implantation of monetite grafts preloaded with C3 conjugate can therefore offer a method to localize the anabolic effects of the conjugate and improve alveolar bone augmentation.

Our research study investigated the monetite grafts fabricated with and without C3 conjugate and implanted on rabbit calvarium to evaluate the ability to integrate and grow bone vertically into the graft area. Our hypothesis was that monetite block grafts loaded with the C3 conjugate would result in greater and more predictable de novo bone formation in the vertical dimension when compared with the grafts without the drug. After the study was completed and results analyzed, it was revealed that the monetite graft materials containing the C3 in their matrix resulted in significantly greater and more predictable de novo bone formation when compared with their counterpart grafts without the conjugate. The increase was statistically significant and would be clinically important if reproduced in human subjects. The novel bone anabolic conjugate drug released via the matrix of the bioresorbable monetite grafts was shown the potential to achieve rapid, enhanced and significant bone regeneration in the vertical bone augmentation model. In the long-term, this research is expected to allow development of clinical treatments using conjugate loaded graft materials that provide more predictable bone regeneration results for patients undergoing bone augmentation, and implant placement procedures.

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