The Pharma Innovation Journal 2018; 7(7): 694-696

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(7): 694-696

www.thepharmajournal.com
Received: 15-05-2018
Accepted: 17-06-2018

Dr. Himani Sharma
Post-Graduate student
Department of Periodontology, Subharti Dental College and Hospital, Meerut. Uttar Pradesh, India

Dr. Anamika Sharma
Professor and Head
Department of Periodontology, Subharti Dental College and Hospital, Meerut, Uttar Pradesh, India

Correspondence
Dr. Himani Sharma
Post-Graduate student
Department of Periodontology, Subharti Dental College and Hospital, Meerut. Uttar Pradesh, India

Soft tissue complications associated with the application of 1% metformin gel around dental implants: A report of two cases

Dr. Himani Sharma, Dr. Anamika Sharma

Abstract
The surface modifications of dental implants have gained an important place in ensuring their long term success. Metformin is one of the first line of drugs for the treatment of type 2 diabetes mellitus. Recent discoveries on the effect of metformin on the proliferation of osteoblast have lead the researchers to use this drug in the cases of periodontitis for enhancing bone formation rendering positive results regarding the bone healing. However, little is known about its effect on the soft tissue. The present article reports its use around dental implants as surface modifying agent, and its associated soft tissue complications.

Keywords: Metformin, dental implants, surface modification, bone, wound healing

Introduction
Since the late 1960s due to the focused work of PI Branemark the phenomenon of interfacial bone formation associated with titanium surfaces was revealed. Since then, the osseointegrated implants are used widely in the various fields including dentistry for the replacement of missing tooth. Various techniques have been employed during the past 30 years aiming for improved osseointegration from a physical or chemical stand point.

Implant surface character is one of the most important factor affecting the rate and extent of osseointegration. Therefore, modification of the titanium implant surface seems to be a promising way to achieve stronger and faster osseointegration of the implants. Currently, surface roughening and/or surface coating are commonly used techniques in clinical practice [1].

Metformin, is one of the routinely prescribed oral anti-hyperglycemic drug for the treatment of type II diabetes mellitus. It belongs to second generation of biguanides that inhibits gluconeogenesis and, decreases the peripheral tissue resistance to insulin thus, decreasing the blood glucose level [2].

Recent clinical trials have indicated the effect of metformin on the bone forming cells, by stimulating their differentiation, via adenosine 5′-monophosphate-activated protein kinase (AMPK) activation following the induction of endothelial nitric oxide synthase (eNOS) and bone morphogenetic protein-2 (BMP-2) expression. Metformin was also found to regulate an orphan nuclear receptor, SHP which interacts with the transcription factor Runx2 and stimulates osteoblastic bone formation [3].

More recently, researchers have used metformin as an adjunct to surgical and non-surgical periodontal therapy to treat or arrest the bone loss in chronic periodontitis patients and it has demonstrated success [4]. However, little is known about the role of metformin on epithelial cell keratinocytes and wound epithelization.

In our research we used 1 % metformin gel around dental implants as a surface modifying agent in two patients. Delayed loading protocol was followed in both the cases and the patients were also administered amoxicillin (500mg) plus clavulanic acid (125mg) twice daily and Paracetamol (500mg) thrice daily for five days. 0.2% chlorhexidine mouthwash was advised twice daily for 10 days and were recalled after 10 days for suture removal.

The first patient demonstrated a delayed soft tissue healing with lesser approximation of the flap margins at 10days. (Fig 1b) To check for the stability of implants radiofrequency analysis was done which revealed good primary stability. Flap re-approximation was not done and gingival former was placed on the implant for supporting the soft tissue healing around it. The patient was recalled after 3 weeks demonstrating good healing and formation of soft tissue margins around the gingival former.

The second patient showed delayed epithelization, so patient was recalled 21 days postoperatively for suture removal. During this recall visit improper epithelization was observed. (Fig 2b) Therefore this patient was again recalled 2 weeks later. Complete soft tissue healing was observed thereafter. Both the patients were then recalled after 3 months for the crown placement and 6, 9 months for reevaluation. (Fig 1c, 2c)

The usefulness of metformin in lessening the blood glucose was discovered by Stern *et al* 1950. Its efficacy, non-toxicity, effects on cardiovascular system and metabolism, and its ability to arrest the progression of osteoporosis in diabetic patients makes this drug the prime choice as anti-hyperglycemic agent for treating the patients with type 2 diabetes mellitus [5].

Various studies have shown that administration of Metformin, either topically or in systemic form, reduces bone resorption. The exposure of osteoblast-like cell lines to metformin resulted in higher alkaline phosphatase activity, activation of AMPK, increased osteoblastic proliferation and collage type II turnover rate. Moreover, metformin influenced the formation of mineralized bony tissue for up to 3 weeks. Additionally, increased expressions eNOS and BMP-2 were detected, both of which have vital roles in maintaining and controlling bone turnover [3].

Several epidemiological studies have demonstrated a protective action of metformin in the development of various types of cancer. Metformin treatment significantly reduces cell proliferation; colony formation and alterations of the cell cycle by effecting m TOR, AMPK and other targets in those cells. This suggests that, the same phenomenon might occur in non-cancerous cells also and may cause delay in wound closure. In recent clinical trials, metformin has shown to reduce cell proliferation in keratinocytes by different methodologies. Several reports indicate that metformin might also effect immune cells such as CD8+ and endothelial cells and can induce apoptosis [6]. Therefore, it can be said that in similar manner it can be involved in the deregulated vascularization and wound healing observed after administering metformin.

Our results are consistent with these studies showing that metformin treatment delayed the wound healing process and epithelization when applied locally. This can be due to the fact that Metformin can retain in the target compartment for a span of 3-4 weeks [3]. However, none of the above cases demonstrated implant failure. Both the implants achieved good secondary stability as demonstrated by radio frequency analysis, suggesting the potential role of metformin in enhancing osseointegration around dental implants. However, regarding the detained epithelization it can be suggested that the mediators of tissue remodeling such as proteases, inflammatory cells (including Natural killer cells), the inflammatory process and others mediators might also be influenced by metformin application, therefore it is very likely that inflammation is reduced due to its application resulting in delayed wound healing [7].

The findings of present study suggest the potential role of metformin around dental implants by enhancing the deposition of bone around it. However, deteriorating effect of metformin on wound healing and epithelization were observed suggesting its careful use. But further research with larger sample size is needed to clarify whether metformin treatment or other factors are associated with these findings.

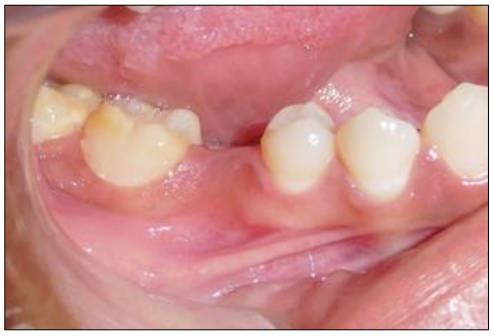

Fig 1: Pre-operative picture of case 1

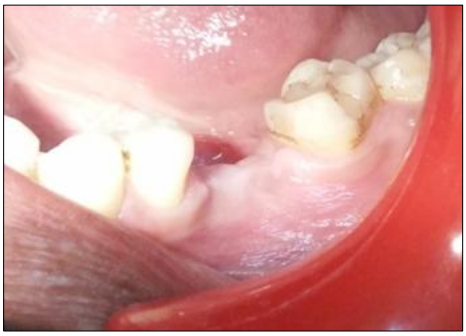

Fig 2: Pre-operative picture of case 2

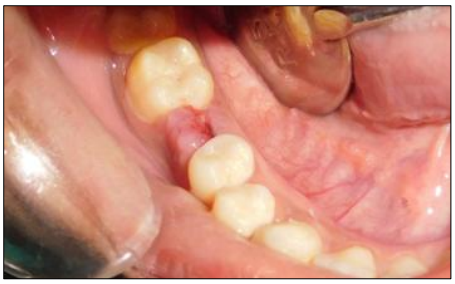

Fig 3: Incomplete flap approximation Case 1 (10 days Post-operative)

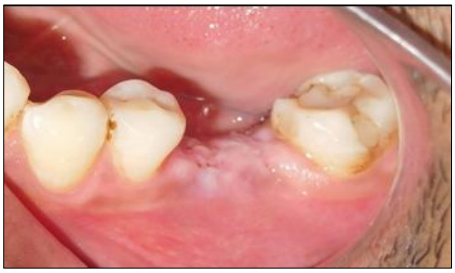

Fig 4: delayed epithelization Case 2 (21 days post-operative

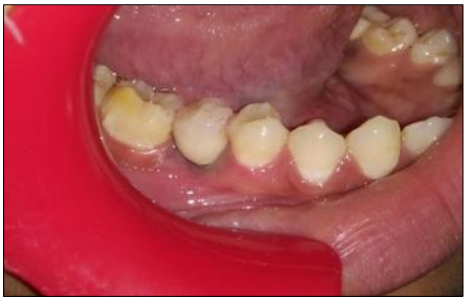

Fig 5: crown placed (6 month- post operative) Case 1

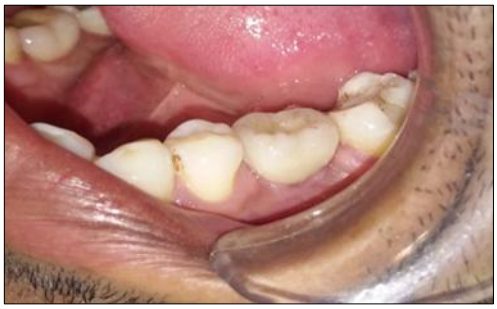

Fig 6: crown placed (6 month- post operative) Case 2

References

1. Goel M, Mehta R, Kumar A, Kumar V, Bhayana G, Wadhwa S. Implant Surface Modification and Osseointegration-Past, Present and Future. J Oral Health comm Dent. 2014; 8:113-118.
2. Marycz K, Tomaszewski KA, Kornicka K, Henry BM, Wroński S, Tarasiuk J *et al*. Metformin Decreases Reactive Oxygen Species, Enhances Osteogenic Properties of Adipose-Derived Multipotent Mesenchymal Stem Cells *In Vitro*, and Increases Bone Density *In Vivo*. Oxidative Medicine and Cellular Longevity 2016; 2016:9785890. doi:10.1155/2016/9785890
3. Pradeep AR, Rao NS, Naik SB, Kumari M. Efficacy of varying concentrations of subgingivally delivered metformin in the treatment of chronic periodontitis: A randomized controlled clinical trial. J Periodontol. 2013; 84:212-220.
4. Pradeep AR, Nagpal K, Karvekar S, Patnaik K, Naik SB, Guruprasad CN. Platelet-Rich Fibrin With 1% Metformin for the Treatment of Intrabony Defects in Chronic Periodontitis: A Randomized Controlled Clinical Trial. J Periodontol. 2015; 86:729-737.
5. Ochoa-Gonzalez F, Cervantes-Villagrana AR, Fernandez-Ruiz JC *et al*. Metformin Induces Cell Cycle Arrest, Reduced Proliferation, Wound Healing Impairment *In Vivo* and Is Associated to Clinical Outcomes in Diabetic Foot Ulcer Patients. Veves A, ed. PLoS ONE. 2016; 11(3):e0150900.
6. Eikawa S, Nishida M, Mizukami S, Yamazaki C, Nakayama E, Udono H. Immune-mediated antitumor effect by type 2 diabetes drug, metformin. Proc Natl Acad Sci U S A. 2015; 112(6):1809-14.
7. Cameron AR, Morrison VL, Levin D, Mohan M, Forteath C, Beall C *et al*. Anti-Inflammatory Effects of Metformin Irrespective of Diabetes Status. Circulation Research. 2016; 119(5):652-665.