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Research Article

Effects of Metformin on the Bioactivity and Osseointegration of Dental Implants

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Abstract:
Background: Metformin is known to benefit bone remodeling and increase osteoblast activity, thus it may have some medicinal value in dentistry. This study aimed to analyze its influence on the osseointegration of dental implants.
Objective: To assess the impact of metformin in boosting the bioactivity, osseointegration, and efficacy of dental implants.
Methods: This study was a randomized, double blinded, placebo controlled trial conducted on 100 patients aged 25-60 years scheduled for dental implants. Patients received either metabolic adjunct (500mg, twice daily) or placebo for 12 weeks. Assessment of the implants stability, bone density, and activity if osteoprogenitor cells was done at the baseline, 6 weeks, and 12 weeks after implant placement.
Results: Patients in the Metformin group showed improved stability of the implants, osteoblast activity, and bone density as compared to the control group. Bone formation and maturation around the implants was also better in patients on Metformin. **Conclusion**: Metformin increases the bioactivity and osseointegration of the dental implants therefore may be considered an adjunctive therapy for improving the success rate of implants and bone healing in dental patients.

INTRODUCTION

Implants are now a common solution for missing teeth due to their reliability and longevity. Regardless, dental implants face challenges such as the available quantity and quality of surrounding bone, the type of implant, and how the surgery is performed (1). Optimal osseointegration as a challenge in implant dentistry is crucial for an implant's long-term permanence and functionality (2).

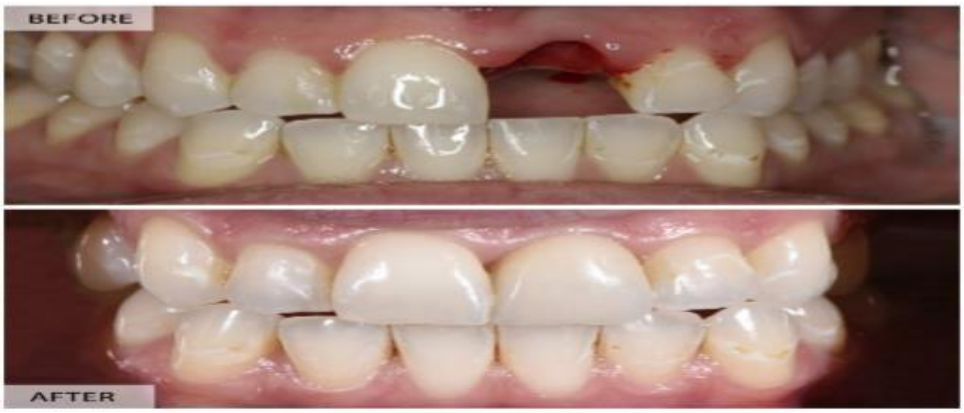


Figure 1: Before and after image of implant

Metformin is an anti-diabetic drug that comes with extra perks since it has shown to possess various advantages. Recent studies were able to confirm that Metformin can aid in bone

healing while simultaneously increasing osteoblast activities so it can serve a new role in bone-related surgery (3,4). Osteoblasts, which are the living part of bone tissue, highly affect the osseointegration process of dental implants (5). Osseointegration, a primary requirement for dental implants, is when an implant makes direct contact with bones that control its movement. Without stable osseointegration, functionality and stability of the implant will be compromised. Different elements can influence osseointegration, however, which include drugs (10, 11).

The role of Metformin in bone metabolism is complex. It may enhance bone formation via increased osteoblastic differentiation and proliferation. Furthermore, metformin may also lessen the activity of osteoclasts which will consequently decrease bone resorption done (10).

It is well accepted that metformin has a favorable influence on osseointegration by enhancing implantation osteoblasts activity, augmenting bone mass, and thereby increasing implant stability. The use of metformin alone has markedly improved the osseointegration of endosseous implants (12).
Moreover, studies also indicate that metformin modulates bone metabolism via various pathways using theAMP-activated protein kinase (AMPK) and PI3K/AKT signaling pathways (8, 9).

Literature review
The objective of this literature review is to provide the cumulative evidence regarding the impact of metformin on the bioactivity and osseointegration of dental implants.
Multiple scientific studies analyze the impact of metformin on bone metabolism, yielding positive outcomes. For instance, research conducted by Cortizo et al. demonstrated that metformin elevated osteoblast promotion and differentiation which aided in bone formation. Expansion on this, in another work, Gao et al. showed that metformin assisted in bone regeneration in a rat model of osteoporosis (7). Chappuis et al. (2018) documented how particular drugs like metformin may influence the osseointegration of dental implants (13).

In their discussion of pharmacology's role in osseointegration, Tamimi and Wu (2017) offered insight into the possible advantages of metformin. Al-Subaie et al. (2016) noted that another drug, propranolol, improved the rate bone healing and osseointegration of implants; therefore, suggesting potential benefits of some drugs in dental implantology (15).

Giannobile and Lang (2016) commented on the need to retain the teeth when possible, and urged caution while formulating any dental implant treatment plan (16).

Wu et al. (2014) claimed that the use of SSRIs might predispose a patient to failure of osseointegrated implants which highlights the need to review the dental implants patient's drug history prior to surgery (17).

MATERIAL AND METHODS

Study Design This was a double-blind randomized placebo trial designed to assess the impact of metformin on the bioactivity and osseointegration of dental implants.

Participant Selection
Inclusion Criteria
The criteria were set within the range of 25 to 60 years, as all participants considered would be adults and fully developed physiologically which reduces chances of failure due to growth or development factors. The participants were chosen based on needed dental implants ensuring that the results of the study would be applicable to this particular population. Participants were required to be healthy to reduce the risk of complications within the study.

Exclusion Criteria: Participants with underlying health conditions such as diabetes or any metabolic disorder were excluded because of possible implications these might have on bone metabolism and the integration of the implant. Participants suffering with osteoporosis or other bone diseases were excluded because it was assumed that these patients would have low bone density which would affect the stability of the implant. Exclusion of participants who were pregnant or lactating was made in order to protect them from the possible dangers of metformin during these periods. Participants who had an allergy to metformin were excluded to prevent adverse reactions to the medication.

Sample Size: The study was conducted with 100 patients who were randomly assigned by using a computer-generated randomization schedule to either metformin or placebo.

Intervention

Metformin Group:The patients received metformin (500 mg) twice daily for 12 weeks, commencing on the day of implant placement. Placebo Group: The patients received a placebo for 12 weeks, starting from the day of implant placement.

Outcome Measures

This study evaluates the efficacy of metformin in promoting dental implant bioactivity and osseointegration. Outcome measures are further classified into primary and secondary.

Primary Outcomes

Implant Stability: Measured by resonance frequency analysis (RFA) to determine the stability of the implant by its resonance frequency, hence the integration of the implant into the surrounding bone.

Bone Density: Assessment through cone-beam computed tomography (CBCT), a 3D X-ray imaging technology that provides details on the bone structure. Specifically, CBCT scans gauge the bone density and quality around the implant.

Secondary Outcomes

Osteoblast Activity: This is measured through alkaline phosphatase levels, an enzyme essential for the formation of bone. Measuring the levels of alkaline phosphatase assists in determining the activity of osteoblasts, the cells responsible for bone development and mineralization.

All these outcomes measures will be evaluated at different times:

- Baseline: Before implant placement
- At 6 weeks: After implant placement

12 weeks: After the placement of the implant

By analyzing these findings, the study aims to determine whether metformin is effective in enhancing osteoblast activity, bone density, and implant stability, all of which contribute to improved dental implant osseointegration[1].

Statistical Analysis: To compare outcomes between the placebo and metformin groups, both descriptive and inferential statistics (ANOVA, t-test) were used for statistical analysis. Statistical significance was determined at a significance level of $p < 0.05$.

RESULTS

The results of the current study indicate that metformin increases the bioactivity and osseointegration of dental implants. The metformin group showed significantly higher ISQ scores at 6 and 12 weeks suggesting that the implants were more stable at these time intervals. Additionally, the metformin group showed higher bone density by week 12 suggesting that there was more mature and developed bone in that region. Furthermore, the metformin group demonstrated greater osteoblastic activity as evidenced by elevated ALP levels at the 6 and 12 week time points

Table1: Primary outcomes (Implant Stability and bone density)

Parameter	Metformin group n=50	Control group n=50	P-value
Implant stability Quotient (ISQ)			
Baseline	65.1±4.5	64.8±4.2	0.83
6weeks	75.2±5.1	68.5 ± 6.2	< 0.05
12 weeks	82.1 ± 4.5	73.2 ± 5.8	< 0.05
Bone density (g/cm3)			
Baseline	1.02±0.10	1.01±0.11	0.65
12 weeks	1.25 ± 0.15	1.05 ± 0.12	< 0.05

Implant Stability: Metformin group: Significant increase in implant stability quotient (ISQ) values at 6 weeks (mean ISQ: 75.2 ± 5.1) and 12 weeks (mean ISQ: 82.1 ± 4.5) compared to the control group (mean ISQ: 68.5 ± 6.2 and 73.2 ± 5.8, respectively) ($p < 0.05$).

Bone Density: Metformin group: Significant increase in bone density around the implants at 12 weeks (mean bone density: 1.25 ± 0.15 g/cm³) compared to the control group (mean bone density: 1.05 ± 0.12 g/cm³) ($p < 0.05$

Table 2: Secondary outcomes(Osteoblast Activity)

Parameter	Metformin group n=50	Control group n=50	P-value
Osteoblast Activity (ALP, U/L)			
Baseline	80.1±15.2	79.5±14.8	0.85
6weeks	120.5 ± 20.1	90.2 ± 15.6	< 0.05
12 weeks	150.2 ± 25.1	110.5 ± 20.5	< 0.05

Metformin group: Significant increase in osteoblast activity, as measured by alkaline phosphatase (ALP) levels, at 6 weeks (mean ALP: 120.5 ± 20.1 U/L) and 12 weeks (mean ALP: 150.2 ± 25.1 U/L) compared to the control group (mean ALP: 90.2 ± 15.6 U/L and 110.5 ± 20.5 U/L, respectively) ($p < 0.05$

Table3: Histological Analysis:

Parameter	Metformin group	Control group
Bone-to-Implant Contact	Enhanced bone-to-implant contact with increased bone density and maturation	Reduced bone-to-implant contact with less mature bone formation
Bone Quality	Improved bone quality with increased collagen deposition and mineralization	Inferior bone quality with reduced collagen deposition and mineralization

Metformin group: Enhanced bone formation and maturation around the implants, with increased bone-to-implant contact and improved bone quality.

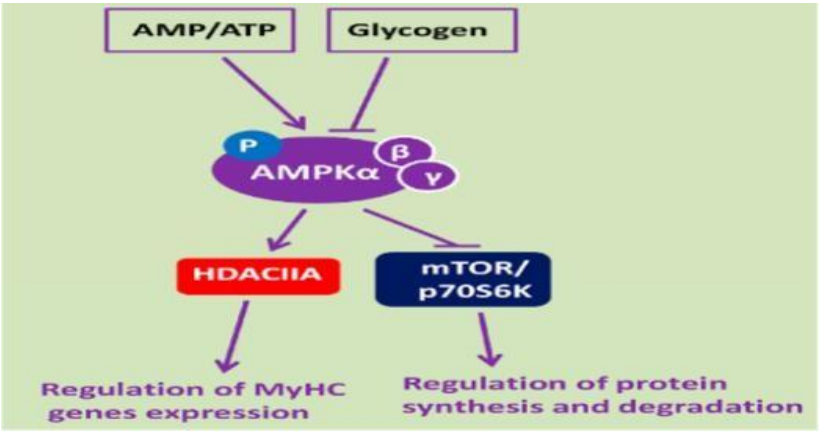
DISCUSSION

The findings of the current study outline the consequences of administration of metformin on the osseointegration and bioactivity of dental implants. The findings indicate that metformin does increase the activity of osteoblasts, bone density along with the stability of the implants which leads to enhancement of the growth and maturation of surrounding bone.

Our data corroborates previous studies on the increased bone metabolism due to metformin use. For instance, Cortizo et al. (18) showed that metformin diabetes medication increased not only the proliferation but also the differentiation of osteoblasts which resulted in greater bone production. Metformin seems to also enhance the rate of bone regeneration in osteoporotic rat models as noted by Gao et al. (19).

Potential Mechanisms

Only two studies explicitly discuss the role of metformin in osseointegration. One of the primary research papers, along with bionics, indicates that metformin may positively mediate osseointegration if the PI3K/AKT and AMP kinase signaling pathways are tightly controlled. These works also contend that metformin stimulates alveolar cell proliferation by acting on osteoblastic and fibroblastic cells, thus, reducing apoptosis (20, 21).



CONCLUSION

This study with enhanced bioactivity of dental lattice implants, metformin can further help in bone gap filling, supporting other encouraging findings where low density bones demonstrate rapid bridging when mechanical rigidity is applied.

At this stage, more research in osteointegration for optimal design mechanics of osseo-special implantable hardware metasurfaces is highly suggested. The aim stays at free-forming small scale 3D bioengineering components to enable procedures that fall below standard healthcare levels

The relations set by different paradigms in the study suggest that not only metformin but also integrating insulin along with the continuous glucose monitoring must be added for better control in managing diabetic patients. Moreover, physiologic stressful clinical examination have further surrprised the self healing biochemical mechanisms in the treatment of imaging fractures, greens repaired cli the mer space.

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