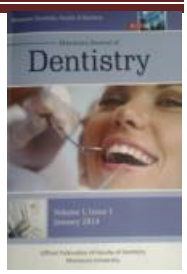
Impact Of Concentrated Growth Factors(CGF) On Clinical outcomes Of Immediately Loaded Dental Implants In Controlled Diabetic Patients



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Abstract:

Problem statement

Diabetes mellitus is considered as a relative contraindication to dental implant therapy. Meanwhile, different platelet concentrates are thought to have a positive impact on implant success. This study was conducted to assess the impact of concentrated growth factors(CGF) on clinical outcomes of immediately loaded dental implants in controlled diabetic patients.

Patient and Method: Sixteen patients seeking for dental implants were divided into the following groups. Negative control group included four healthy nondiabetic patients (HbA1c < 6%) without application of CGF prior to implant insertion. While, twelve well controlled diabetic patients (HbA1c 6.1–8 %) were furtherly and randomly distributed into two equal groups: Positive control group (2nd group) included six well controlled diabetic patients (HbA1c 6.1–8 %) without application of CGF prior to implant insertion. The Study group (3rd group) included six well controlled diabetic patients (HbA1c 6.1–8 %) with application of CGF prior to implant insertion. All implants were subjected to immediate loading within (48-72) hours after fixture installation. All patients were assessed clinically either at baseline (T0), 6 months (T1) or at 12 months (T2) of follow up regarding to implant stability, Modified sulcus bleeding index and peri-implant probing depth and radiographically for assessment of crestal bone loss (CBL).

Result: There were no significant differences between all groups regarding implant at different time intervals of follow up periods either at, (T0), (T1), (T2) (P=0.285, 0.326, 0.341 respectively). However, within the positive control group Statistical significant differences were recorded between (T0) values and those values recorded at (T1) and (T2) (P=0.021, 0.004 respectively). No significant differences were recorded between all groups regarding to mSBI, CBL and PIPD at different time intervals of follow up periods either at, (T0), (T1), and (T2) (P=0.822, 0.211, 0.149 respectively). (P=1.000, 0.367, 0.132 respectively). (P=0.822, 0.211, 0.149 respectively).

Conclusion: Dental implants can be immediately loaded in controlled diabetic patients with acceptable outcomes. Meanwhile, CGF can positively improve implant stability in controlled diabetic patients especially within the early critical phase of healing.

Key Words: **CGF& Diabetic patients and immediate loading.**

Introduction

Dental implant treatment in medically compromised patient stills a point of conflict. According to **Diz et al. (2013)**, there are very limited absolute contraindications for dental implant treatment, but some medical conditions have an increased risk of treatment failure or increased risk of peri-operative complications.[1] One of these conditions is diabetes mellitus.[1] Diabetes mellitus is the most common endocrinal disease. For well-controlled diabetics, implant success is comparable to that of healthy individuals. Also, peri-implant condition is normal and peri-implant bone resorption is comparable to controls.[2] [3] [4] [5] [6] [7] [8] While, for uncontrolled diabetic patients, there is an increased risk of peri-implantitis.[7] [9] However, several studies did not reveal such an impact.[10][11][12]

Currently, implant placement needs less invasive surgical procedures and therefore can be done with minimal risk of significant problems. Additionally, several studies showed that dental implant placement in several diseases is possible, either with or without special measures.[13] Moreover, improvements in implant design and surface treatment lead to increased application of immediate and early loading protocols.[14] Because hyperglycemia impair bone healing, immediate loading is less successful in diabetics when contrasted to conventional loading.[15] Other authors revealed insignificant differences between immediate and delayed loading protocols in diabetic patients.[3]

Meanwhile, the optimistic influences of platelet preparations on healing prompted the production of preparations in different concentrations.[16] One of these preparations is the concentrated growth factor (CGF) that was described by **Sacco in 2006**.[17] CGF has its specific centrifugation protocol that differs from the original PRF. It has a longer and denser fibrin matrix with greater concentration of growth factors.[17] Moreover, local CGF application stimulates FGF-β or VEGF releases, which are important for angiogenesis.[17]

Based on such data, this study was conducted to assess the impact of concentrated growth factors (CGF) on the

clinical outcomes of immediately loaded dental implants in controlled diabetic patients.

Patients and Methods

Sixteen patients seeking for single tooth replacement in the posterior mandibular region were divided into the following groups. Negative control group (1st group) included four healthy nondiabetic patients (HbA1c < 6%) without application of CGF prior to implant insertion. While, twelve well controlled diabetic patients (HbA1c 6.1–8 %) were furtherly and randomly distributed into two equal groups. Positive control group **(2nd group)** included six well controlled diabetic patients (HbA1c 6.1–8 %) without application of CGF prior to implant insertion. The Study group (3rd group) included six well controlled diabetic patients (HbA1c 6.1–8 %) with application of CGF prior to implant insertion. Patients in both groups were received final restoration with immediate functional loading within 48-72 hours after implant installation.

Surgical procedures

Standardized periapical radiographs were taken to evaluate the residual bone height, and to clarify that the future implant place was not having any local pathology. All surgical procedures were performed under local anesthesia (2% Mepivacaine Hydrochloride with 1:20000 levonordefrine)[1] by the same operator. A full-thickness mucoperiosteal flap was elevated. Implant osteotomy sites was prepared according to the manufacturer instructions. In the control group, implants (Conventional, two pieces, screw-type titanium dental implant was used) [2] were placed without addition of any material. While in the study group, the implant osteotomy site was filled with CGF membranes all around. CGF membranes were prepared according to the following protocol. Traditional, one-use, 10-ml non-anticoagulant tubes and a corresponding centrifugation machine were used. The tubes were placed in the centrifuge and the centrifugation protocol procced as follow acceleration for 30 s, centrifugation at 2700 rpm for 4 min, 2400 rpm for 4 min, 2700 rpm for 4 min, and 3000 rpm for 3 min, and deceleration for 36 s. Three layers were obtained: bottom red blood cell layer, top platelet poor plasma layer, and fibrin gel with concentrated growth factor in the middle. First, the top platelet-poor layer was eliminated with a sterile syringe. The concentrated growth membrane was grasped with artery forceps, detached from the bottom layer by cutting with a scalpel and then compressed to produce a membrane.(18) The mucoperiosteal flap was reapproximated and sutured. An immediate postoperative periapical X ray was done to confirm the correct implant position. Definitive porcelain fused to metal crowns were manufactured and cemented with permanent cement on the abutment within 72 hours.

[1] MepivacaineHydrochloride with 1:20000 levonordefrine; manufactured by Alexandria Co, Egypt.

[2] Neobiotec IS II active implant system, Korea.

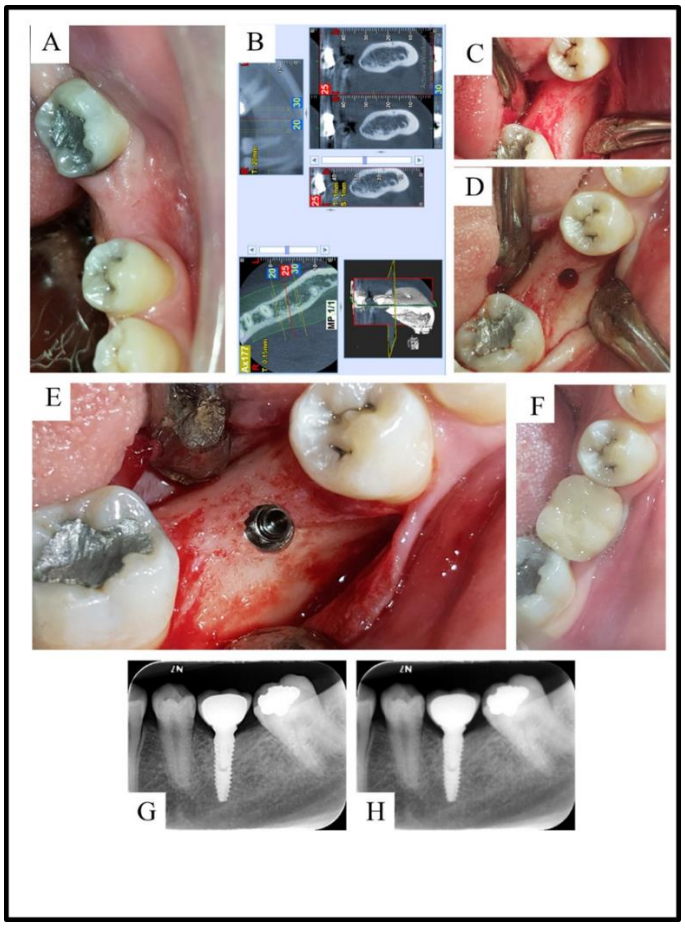

Figure 1 (Negative control group) A- showing preoperative clinical photograph. B- Showing preoperative CBCT. C- Showing mucoperiosteal flap reflection. D- Showing the osteotomy site. E- Showing the implant fixture in place. F- Showing the final ceramometal crown in place . G-showing CBL after 6 months. H- Showing CBL after 12 months.

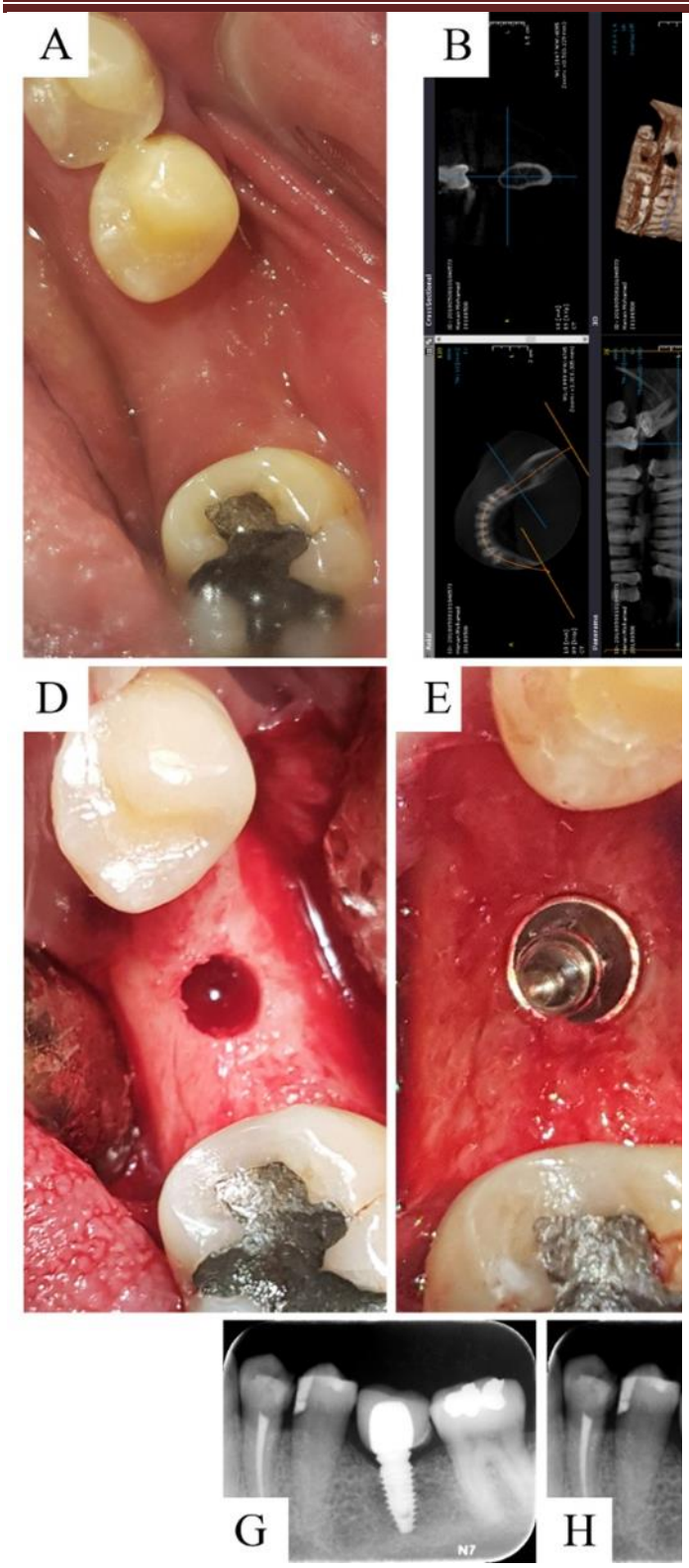

Figure 2 (positive control group) A-showing preoperative clinical photograph. B-showing preoperative CBCT. C-showin mucoperiosteal flap reflection. D-showing the osteotomy site. E- showing the implant fixture in place. F-showing the final ceramometal restoration. G-showing CBL after 6 months. H- showing CBL after 12 months.

Clinical Evaluation

It was done immediately after implant placement, after a period of 6 and 12 months.

Patients were evaluated clinically for:

1. Implant stability

Implant stability was evaluated at all follow-up intervals by means of periotest. The score was determined following ***Lorenzoni et al***[19] Grade I ranges from -08 to 0 indicating that the fixture is well integrated and can be loaded. Grade II ranges from +1 to +9 indicating that loading the implant is not yet possible and need further clinical examination. Grade III varies from +10 to +20 indicating that osseointegration is inadequate and no pressure can be applied to the fixture.[19]

2. Peri-implant probing depth (PD)

In each group, peri-implant PD was determined at six points per implant (mesiobuccal, mid-buccal, distobuccal, mesiolingual,mid-lingual and distolingual) at all follow up periods with light force to avoid undue tissue damage and over-extension into the healthy tissue.[4]

3. Modified sulcus bleeding index(mSBI)

Peri-implant mucosal health was evaluated using modified bleeding index:[20] **Score 0;** absence of bleeding when a periodontal probe was pressed along the gingival margins next to the implant.**Score 1:** Isolated bleeding spots were detected.**Score 2;** Bleeding formed overlapping red lines on the margins. **Score 3 revealed** perfuse bleeding.

Radiographic evaluation

• Standardized periapical radiographic film to evaluate crestal bone loss (CBL) of the surrounding bone in immediate (as a starting point), 6 months and 1year postoperatively. In every group, the average mesial CBL and distal CBL were measured in millimeters on digital radiographic films. Mesial CBL and distal CBL were measured for all implants from the widest supracrestal portion of the fixture to the a crest of the alveolar ridge.[4]

Statistical Analysis

Data were analyzed by means of IBM SPS software package version 20.0**.** **(**Armonk, NY: IBM Corp**)** Qualitative data were expressed using number and percent. The Kolmogorov-Smirnov test was used to confirm the normality of distribution. Quantitative data were expressed using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was considered at the 5% level.

Results

Demographic data

This study was conducted on sixteen individuals; four patients (2 females & 2 males) included within the negative control group. They were healthy nondiabetic individuals (HbA1c < 6%) with an age ranging from 21–40 years and

average mean 31.50 ± 8.10. The remaining twelve well controlled diabetic patients of (HbA1c < 6%) were equally distributed into two groups. Six patients (5 males & 1 female) were included within the positive control group for whom (CGF) was not applied. The patient's ages of this group ranged from 40– 45 years with mean 44.0 ± 2.0. Six patients (1 male & 5 female) were included within the study group for whom (CGF) was applied. The patient's ages of the study group ranged from 40 – 45 years with mean 44.17 ± 2.04.

There was no statistical significance among all groups as regard the patient's sex (P=0.083). But, statistical significant difference was found among all groups regarding the patient's ages (P=0.001). **(Table 1).**

Table (1): Showing comparison between the three studied groups regarding to demographic data

	Control				Study gz		P
	Negative (n = 4)		Positive (n = 6)				
	No.	%	No.	%	No.	%	
Sex							
Male	2	50.0	5	83.3	1	16.7	p=0.083
Female	2	50.0	1	16.7	5	83.3	
Age (years)							
Mean ± SD.	31.50 ± 8.10		44.0 ± 2.0		44.17 ± 2.04		0.001*

Eleven first molars, four second molars and one second premolar were replaced. The most commonly used implant length was 11.5mm (81.25%) followed by 10 mm (18.75%). Moreover, implant diameter in this study was 4 mm. All implants were immediately loaded during the first 24-72 hours following implant insertion with ceramometal crowns. All patients were subjected to clinical and radiographic evaluation immediately after implant placement, after a period of 6 and 12 months.

All fixtures revealed an ankylotic healing indicating a (100%) success ratio, all individuals were subjected to clinical evaluation concerning these parameters:

Implant stability assessment by Periotest

In the 1st group, the periotest values at (T0) varied from -2.10 to -5.0 with an average value -3.0±1.34. At (T1), they varied from -2.0 to -5.40 with an average value -3.28±1.49. At (T2), they varied from -1.9 to -5.4 with an average value -3.25±1.53. While in the 2nd group, the periotest values at (T0) varied from -1.30 to -4.90 with an average value -2.62±1.71. At (T1), they varied from -0.80 to -5.40 with an average value -2.13±1.67. At (T2), they varied from -0.50 to -4.50 with an average value -2.03±1.77.

In the 3rd group, the periotest values measured following implant placement at (T0) varied from 0.0 to -5.10 with an average value -2.05±2.24. At (T1), they varied from -0.50 to -4.0 with an average value -1.97±1.61. At (T2), they varied from -0.50 to -4.0 with an average value -1.95±1.58.

Comparing all groups, no statistical significant differences were found at (T0), (T1), (T2) (P=0.285, 0.326, 0.341 respectively). **Table (2)** Also, within the negative control group no statistical significant difference was found between (T0) values and those documented at (T1) or (T2) values (P=0.420). But, within the positive control group Statistical significant differences were recorded between (T0) values and those values recorded at (T1) and (T2) (P=0.021, 0.004 respectively).

Table (2): Showing comparison between the three studied groups regarding implant stability at different time intervals of follow up

Implant stability (PTVs)	Control		Study group (n=6)	P
	Negative (n = 4)	Positive (n = 6)		
T0 (Initial) Mean ± SD.	3.0 ± 1.34	2.62 ± 1.71	2.05 ± 2.24	0.285
T1 (After 6 months) Mean ± SD.	3.28 ± 1.49	2.13 ± 1.67	1.97 ± 1.61	0.326
T2 (After 12 months) Mean ± SD.	3.25 ± 1.53	2.03 ± 1.77	1.95 ± 1.58	0.341

2- Peri-implant probing depth (PPD)

In the 1st group, the peri-implant probing depth values at (T0) varied from 0.5 to 1.5mm with an average value 1.0±0.41mm. At (T1), they varied from 0.5 to 1.0 mm with an average value 0.75±0.29. At (T2), they varied from 0.5 to 1.0 mm with an average value 0.75±0.29mm. While in the 2nd group, the peri-implant probing depth values at (T0) varied from 0.50 to 2.0 mm with an average value 1.0±0.55mm. At (T1), they varied from 0.50 to 1.50 mm with an average value 1.0±0.32mm. At (T2), they varied from 0.50 to 1.50 mm with an average value 1.17±0.41mm.

In the 3rd group, the peri-implant probing depth values at (T0) varied from 0.50 to 1.50mm with an average value 1.08±0.38mm. At (T1), they varied from 1.0 to 1.0 mm with an average value 1.0±0.0mm. At (T2), they varied from 1.0 to 1.5 mm with an average value 1.08±0.20 mm.

Comparing all groups, no statistical significant differences were found at (T0), (T1), (T2) (P=0.822, 0.211, 0.149 respectively). **Table (3)** Moreover, within all groups no statistical significant differences were found between (T0) values and those recorded at (T1) or (T2) values (P=0.368, 0.368 and 0.667 respectively). **Table (6)**

Table (3): Showing comparison between the three studied groups regarding peri-implant probing depth at different time intervals of follow up

Peri-implant probing depth (PD)	Control		Study group (n=6)	P
	Negative (n = 4)	Positive (n = 6)		
T0 (initial) Mean ± SD.	1.0 ± 0.41	1.0 ± 0.55	1.08 ± 0.38	0.822
T1 (after 6 months) Mean ± SD.	0.75 ± 0.29	1.0 ± 0.32	1.0 ± 0.0	0.211
T2 (after 12 months) Mean ± SD.	0.75 ± 0.29	1.17 ± 0.41	1.08 ± 0.20	0.149

Modified sulcus bleeding index (mSBI)

In the 1st group, the modified sulcus bleeding index values at (T0) varied from 1.0 to 2.0 with an average value 1.75±0.50. At (T1), they varied from 0.0 to 1.0 with an average value 0.25±0.50. At (T2), they varied from 0.0 to 1.0 with an average value 0.25±0.50. While in the 2nd group, modified sulcus bleeding index values at (T0) varied from 2.0 to 2.0 with an average value 2.0±0.0. At (T1), they varied from 0.0 to 1.0 with an average value 0.83±0.41. At (T2), they varied from 0.0 to 1.0 with an average value 0.67±0.52.

In the 3rd group, the modified sulcus bleeding index values at (T0) showed an average value 2.0±0.0. At (T1), they varied from 0.0 to 1.0 with an average value 0.50±0.55. At (T2), they varied from 0.0 to 1.0 with an average value 0.50±0.55.
Comparing all groups, no statistical significant differences were found at (T0), (T1), (T2) (P=0.822, 0.211, 0.149 respectively). **Table (4)** On the other hand, within each group statistical significant differences were found between (T0) values and those recorded at (T1) (P=0.034, 0.014, 0.009 respectively).

Table (4): Showing comparison between the three studied groups regarding to Modified sulcus bleeding index at different time intervals of follow up

Modified sulcus bleeding index (mBI)	Control		Study group (n=6)	P
	Negative (n = 4)	Positive (n = 6)		
T0 (initial) Mean ± SD.	1.75 ± 0.50	2.0 ± 0.0	2.0 ± 0.0	0.223
T1 (after 6 months) Mean ± SD.	0.25 ± 0.50	0.83 ± 0.41	0.50 ± 0.55	0.197
T2 (after 12 months) . Mean ± SD.	0.25 ± 0.50	0.67 ± 0.52	0.50 ± 0.55	0.458

4- Crestal Bone Loss (CBL)

In the 1st group, the crestal bone loss values at (T1) varied from 0.30 to 0.40mm with an average value 0.35±0.06 mm. At (T2), they varied from 0.40 to 0.70mm with an average value 0.53±0.13 mm. While in the 2nd group, the crestal bone loss (T1) varied from 0.30 to 1.0 mm with an average value 0.63±0.32mm. At (T2), they varied from 0.50 to 1.50mm with an average value 0.97±0.45mm. **In the 3rd group,** the crestal bone loss values at (T1) varied from 0.30 to 1.0mm with an average value 0.48±0.27mm. At (T2), they varied from 0.50 to 1.50mm with an average value 0.73±0.39mm.

Comparing all groups, no statistical significant differences were recorded at (T0), (T1), (T2) (P=1.000, 0.367, 0.132 respectively). **Table (5)** Moreover, within all groups no statistical significant difference were recorded between (T0) values and those recorded at (T1) (P=0.157, 0.083, 0.083 respectively). Also, no statistical significant differences were recorded between (T1) values and those recorded at (T2) (P=0.157, 0.083, 0.083 respectively). But, there were significant differences between (T0) and (T2) values P=0.005, 0.001, 0.0001 respectively). **Table (6)**

Table (5): Showing comparison between the three studied groups regarding crestal bone loss at different time intervals of follow up

Crestal bone loss (CBL)	Control		Study group (n=6)	P
	Negative (n = 4)	Positive (n = 6)		
T1 (after 6 months) Mean ± SD.	**0.35 ± 0.06**	**0.63 ± 0.32**	**0.48 ± 0.27**	**0.367**
T2 (after 12 months) Mean ± SD.	**0.53 ± 0.13**	**0.97 ± 0.45**	**0.73 ± 0.39**	**0.132**

Discussion

Dental implant therapy for diabetics is debatable.[21] However, it is known that controlled diabetic patients have comparable success rates of dental implants as normal

people.[22] Other authors have revealed contrasting outcomes.[23] On the other hand, it was believed that

immediate loading is less successful in diabetics when compared with conventional loading.[24] However, other authors recently revealed no significant differences between immediate and delayed loading in diabetic patients.[4]

Based on the aforementioned controversy, this study aimed to assess the impact of concentrated growth factors (GGF) on clinical outcomes of immediately loaded dental implants in controlled diabetic patients.

There was no statistical significance among all groups as regard the patient's sex (P=0.083). On the other hand, there were statistical significant differences between negative control and both positive control and study groups as regard the patient's ages (P=0.001). This statistical significant difference can be attributed to the fact that type 2 diabetes mellitus is commonly diagnosed at later age and all patients included in the negative control group were young adults in contrast with older patients included in both diabetic groups.

Regarding to implant stability assessment by periotest, in this study all implants showed successful osseointegration characterized by implant stability increased with time at follow-up examination periods from T0 to T2 for the negative control group. But, there were no intra-group statistical differences when comparing different time intervals against each other within the negative control group (P=0.420). This increase of PTVs established at follow-up periods was confirmed by **Kim et al** who revealed that implant stability increases with time as a result of bone maturation and the increase in bone-implant contact.[25]

On the other hand, the regression of periotest values of the positive control group was recorded through the follow up intervals. A statistical significant differences were recorded between (T0) values and those values recorded at (T1) and (T2) (P=0.021, 0.004 respectively). Such regression in the periotest values can be attributed to the influence of diabetes on osseointegration. It was recognized that hyperglycemia can reduce osteoblastic differentiation and negatively affect the response of the parathyroid hormone which controls phosphorus and calcium metabolism.[26] It negatively affect the bone matrix and its components and also impairs the adhesion, growth and accumulation of extracellular matrix.[27]

Additionally, another explanation for the regression of periotest values was due to decrease in the bone-implant contact in diabetics. This was compatible with the result of **McCracken et al.** and Nevins et al who found a decrease in bone to implant contact (BIC) in diabetic rats.[28] In contrast, **Casap et al.** found no difference between diabetic and control animals in osseointegration but in this study the implants were not subjected to immediate loading as in our study.[29]

In the study group, the impact of diabetes was minimized due to the effect of concentrated growth factors (CGF) which seem to have positive effects on periotest values. No statistical significant difference was found between (T0) values and those documented at (T1) or (T2) values

(P=0.949). This was in accordance with Pirpir et al who showed that CGF enhances implant stability and accelerates osseointegration within the early period.[16]

From our point of view, concentrated growth factors is more effective than other platelet preparations. In an experimental study, CGF, PRF, and PRP were applied separately in bone defects created in the rabbit skull while in the control group the defects were left empty. Histological evaluation showed statistically significant differences among control and study

groups in the bone regeneration at 6 and 12 weeks intervals. In the study group, the maximum bone regeneration was detected in the CGF group but this difference was not statistically significant.[30]

Regarding the peri-implant probing depth, no statistical significant differences were documented between all groups at all intervals (T0), (T1) or (T2) (P=0.822, 0.211, 0.149 respectively). Also, in all groups there were no intra-group significant differences when comparing all time intervals of follow up versus each other. This is in harmony with **Bhardwaj et al. in 2016** who revealed insignificant changes in probing depths at 3, 6, 9 and 12 months of implant loading.[31] Such finding was based on the fact that formation and maturation of the barrier function of junctional epithelium around implant abutments requires 6-8 weeks of healing and stabilization which acts as a barrier between the contaminated oral cavity and marginal bone.[32]

Regarding the modified sulcus bleeding index, no statistical significant differences were found between all groups at (T0), (T1), (T2) (P=0.822, 0.211, 0.149 respectively). Also, there were no statistical significant differences between (T1) (T2) values in all groups (P=1.000, 0. 773, 1.000 respectively). But, there were significant intra-group improvement in all groups from T0 to T1 (P=0.034, 0.006, 0.009 respectively). Such findings can be attributed to non-surgical periodontal treatment (NSPT) that applied for all patients which is thought to have an important role in decreasing oral soft tissue inflammation and decreasing blood glucose levels in diabetic individuals.[33] Moreover, the annual NSPT, the use of hypoglycemic drugs and diet control play a significant role in avoiding the development of a chronic hyperglycemia in the included patients.[34]

Regarding the crestal bone loss (CBL), in our study, there were no significant differences in crestal bone loss between all groups at (T0), (T1), (T2) (P=1.000, 0.367, 0.132 respectively). There are many factors that have contributed to these results. It is known that chronic hyperglycemia is complicated by a high rate of formation and accumulation of advanced glycated end products (AGEs) in oral tissues that increase inflammation and if left uncontrolled can contribute to alveolar bone resorption.[35] Additionally, our results are in harmony with a systematic review concluded that under optimum glycemic control, dental implants can osseointegrate and function for long times in diabetics.[37]

A supplementary cause that led to minimize the crestal bone loss around implants placed in normal and diabetic

patients was the proper oral hygiene measures that the patients received. Also, oral hygiene maintenance instructions were confirmed for all patients. This was in accordance with

Javed et al who concluded that in addition to decreasing of BOP and PD, it has been stated that NSPT decreases the systemic effect of inflammatory mediators, therefore

reducing the hyperglycemia in diabetic patients leading to a marked decrease in CBL.[38]
On the other hand, our study showed that (CGF) does not significantly minimize the crestal bone loss. This agrees with **Huang et al.** who stated that although there were no significant diffirence in bone resorption rate between alloderm (ADM) and CGF used for alveolar cleft grafting when applied with autogenous bone chips harvested from the

iliiac crest, there was a remarkable higher bone denisty improvement in the CGF group.[39]

Such similarity in our finding for well controlled diabetic patients included within second and third group in comparison with normal patients included within the first group was in agreement with **Hamano et al.** who showed that the improving poorly controlled hyperglycemia modified bone turnover, reducing bone resorption markers (urinary deoxypyridinoline (Dpd) and type I collagen carboxy-terminal telopeptide (CTx) and increasing OC(osteocalcin).[40] In addition to playing an significant role in bone deposition, OC has an important impact on regulating glucose metabolism.[41][42][43]
Based on the aforementioned, from our point of view well controlled diabetic patients can benefit from dental implant treatment. But, to achieve better outcomes especially if immediate loading protocol is desired, CGF can be used to accelerate osseointegration especially during the early critical phase of healing.

Conclusion:

Dental implants can be immediately loaded in controlled diabetic patients with acceptable outcomes. Meanwhile, CGF can improve implant stability in controlled diabetic patients within the early phase of healing.

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