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Evaluation of Bone Morphogenetic Protein-2 Level in Immediate Versus Delayed Placement of Dental Implants

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Abstract:

Background: Significant progress in the field of dental implants as successful alternative to replace missing teeth is a fact nowadays. Primary stability is a major factor toward successful implant. Traditionally, delayed implant is the most commonly applied; however an immediate implant procedure began to be used, as it reduces time, number of surgical procedures added to increased patient satisfaction. ***Objective***: this study aims to evaluate Bone Morphogenetic Protein-2 (PMP-2) level in immediate compared to delayed placement dental implants. ***Methods:*** Twenty patient; each patient revealed edentulous site at one jaw side, while the other side reveal hopeless tooth indicated for extraction. They were classified into 2 Groups, applying split mouth design: *First group:* edentulous sites received delayed implant placement, and *Second group:* site with hopeless tooth was extracted and replaced by immediate implant placement in other sides. The implants were followed up clinically, radiographically and biochemically to evaluate (BMP-2) level in immediate compared to delayed placement dental implants. ***Results:*** Significant differences in (BMP-2) level was noted between the two implant technique groups, involving implant stability measured by ISQ values, crestal bone change around implants, Plaque index, periimplant probing depth, modified sulcular bleeding index. **Conclusion**: An immediate implant placement into freshly extraction sockets under favorable post-extraction conditions seems to be valuable successful technique.

Keywords: Bone Morphogenetic Protein-2 Level, Immediate placement, Delayed Placement, Dental Implants

Introduction

Dental implants have been acknowledged as a successful maneuver to effectively restore both an oral function as well as esthetics, and they became a fundamental technique for rehabilitation of fully edentulous or partially dentate patients. This field witnesses a great advance during the past four decades, building on the pioneer work of Branemark and other researchers attempting to provide simple / clear understanding of

Osseointegration process and its role in obtaining an efficient dental implant. In this respect, it was postulated that post-extraction healing period of at least six months should be passing prior to perform the placement of an implant. [1] This recommended period of time was based on the belief that complete soft and hard tissue healing following tooth extraction is a mandatory in achievement of successful Osseointegration process. Hence, implants are to be placed 3 to 4 or 8 to 12 weeks after extraction to allow for complete healing of the soft tissues. Delayed implants exhibited a lower incidence of soft tissue dehiscence during guided bone regeneration compared to immediately placed implants. [2]

It should be of value to mention that, although immediate implant placement is an attractive technique, as it reduces the time and number of surgical procedures as well as increased patient satisfaction; it is still injustice to conclude firm long-term results of this approach. However, when implants are immediately placed at time of tooth extraction, major issues relate to the discrepancy between the alveolus walls and the implant may be raised. Such discrepancy was considered to have negative impacts in terms of initial implant stability, amount of Osseointegration, and soft and hard tissue support.

Bone augmentation procedures can be frequently performed simultaneously with immediate implant installation in an attempt to overcome or reduces such discrepancies. Additionally, another neglected aspect in this regard is that tooth extraction is a sequence of either trauma or a disease process; in many cases tooth extraction is accompanied by severe loss of alveolar bone with presence of significant microbial contamination of the affected area. [3] An integral component of tissue engineering (growth factors) include a large family of polypeptide molecules that regulate cell responses as cell attachment / adhesion, cell survival, proliferation, chemotaxis, and differentiation. [4] Thus, bone morphogenetic proteins (BMPs) have been studied extensively regarding their pivotal role in bone formation process. BMPs can stimulate angiogenesis, proliferation, differentiation, and migration of stem cells from the surrounding tissues into cartilage and bone-forming cells in an area of injury. They regulate the expression of many target genes involved in bone physiology, such as alkaline phosphatase, osteocalcin, osteopontin, and osterix. [5] More than 20 BMPs have been described, and many of them have osteogenic ability. In view of these, it seems likely that performing a clinical trial utilizing of BMPs simultaneously at the time of dental implant insertion to restore the missing teeth either on the upper jaw or the lower jaw, may provide data that may be of value in better clarification of this aspect. Hence, the present study was designed and undertaken in this regard.

Patients and Methods

The present study was designed as an inter-venational comparative study. Twenty patients with partially edentulous areas were recruited from the Department of Oral Medicine, Periodontology, Oral Diagnosis and Oral Radiology, Faculty of Dental Medicine, Al Azhar University (Assiut branch). They were selected according to the following criteria: each patient had a single site on one side of the jaw indicated to have dental implants (tooth extracted from long time) and the other side had hopeless tooth indicated for extraction and implant placement was done on that site at the time of tooth extraction in one jaw

Inclusion criteria:

1. Adult patients with single partially edentulous area on one side of the jaw and having a single hopeless tooth on the other side of the same jaw, indicated for extraction due to trauma, periodontitis, endodontic or un-restorable caries; both areas were restored with dental implants ***(Fig 1)*.**
2. They were free from any known systemic disease that affect bone status, surgical procedure as well as wound healing capacity, and had adequate quantity of native bone to achieve primary stability;
3. They presented with reasonable and satisfactory level of oral hygiene status. Each patient complies with complete periodontal treatment, if necessary.
4. They did not showed clinically symptomatic periapical radiolucency, acute abscesses or chronic sinus tracts at the site of extraction.

5. Each patient possessed an adequate mesio-distal space for implant placement (7-9mm), sufficient band of keratinized mucosa to allow surgical manipulation and suturing and will be available for follow up ***(Fig 2).***

Exclusion Criteria:

1. Patients with systemic diseases that may influence the outcome of therapy as: pregnancy, heavy smokers, parafunctional habits and radiation.

2. Patients with neglected oral hygiene as well as those had previous periodontal surgical treatment.

Grouping:

Twenty patients; revealed edentulous site in one side and the side reveal hopeless tooth indicated to be extracted were classified into two groups applying the split mouth design: ***First group*****:** Twenty partially edentulous sites indicated to receive delayed implant placement on one sides. ***Second group*****:** Twenty sites with hopeless tooth that was extracted and replaced by immediate implant placement in other sides.

Ethical consideration: After ethical approval, all participants were verbally informed about the nature of the study, and written informed consent was obtained from each patient for participation into the study.

Preoperative preparation:

All included patients were received initial periodontal therapy; including supra and subgingival scaling, subgingival debridement if needed, and polishing. They were instructed in proper plaque control measures and advised to use teeth brushing and interdental cleaning devices. Preoperative assessment of all patients was carried out including history taking, clinical and radio-graphic examination.

Surgical Procedure:

At the appointed time for dental implant procedure, each appointed subject was pre-medicated with 2 g of amoxicillin-clavulanic acid (or an appropriate alternative for patients with allergy), and 50 mg of diclofenac (or 500 mg of paracetamol). Implant placement and implant diameter choice was restorative drive to maximize aesthetics and function. Tooth indicated to have extraction, was performed in a standardized way as previously mentioned; papilla preservation flaps with intra-sulcular incisions were raised to expose 2–3 mm of alveolar bone, luxation was carried out with fine periotome, paying an attention to avoid trauma to the alveolus. Following tooth extraction, every effort was paid to verify the feasibility of immediate implant placement on the basis of absence of acute infection or purulence and presence of an adequate quantity of alveolar bone to allow immediate implant placement with primary stability ***(Fig 3 & 4).***

Delayed dental implant placement on the other side was done as following: para-crestal incisions with releasing incisions were done at surgical sites and full-thickness flaps were reflected exposing the alveolar ridge; a sequential drill was applied until the final drill under constant continuous irrigation. Healing abutments were installed at time of surgery, and flaps were closed by interrupted sutures using 4"0" silk; dental implants was placed at bone level. Suture removal was carried out after two weeks ***(Fig 5& 6).***

Post-operative care and Medication: Patients were informed in proper oral hygiene measures and were asked to follow the oral hygiene instructions.

Clinical Evaluation: Patients were followed up and examined at 3, 6 and 9 months after implant insertion using, Osstell® ISQ device to measure the stability, [6] Plaque index (PlI), [7] Modified Sulcus Bleeding Index (BI) [8] and Peri-implant Pocket Depth (PPD). [9]

Biological Evaluation: Peri- implant crevicular fluid (PICF) samples were collected at 1, 2, 4 week and 3, 6, 9 months and Bone Morphogenetic Protein-2 levels were assessed. BMP-2 in the PICF samples was measured using a human BMP-2 Enzyme Linked Immunosorbent Assay (ELISA) kit according to the manufacturer's protocol. The principle of this assay was depending upon measurement of an antibody specific for human BMP-2 coated on a 96-well plate ***(Fig 7).***

Radiographic Evaluation: Intra-oral digital periapical radiographs were carried out to evaluate the crestal bone changes. All radiographs for each case were taken under standard method at baseline, 6 and 9 months

post-surgically. Readings were obtained by drawing vertical line from reference point at implant shoulder to bone level mesially and distally ***(Fig 8 - 11).***

Statistical analysis

Data were collected and analyzed statistically with suitable tests to draw the significance and to compare between the two techniques applied in the study. The significance level was set up at 5% ($p < 0.05$).

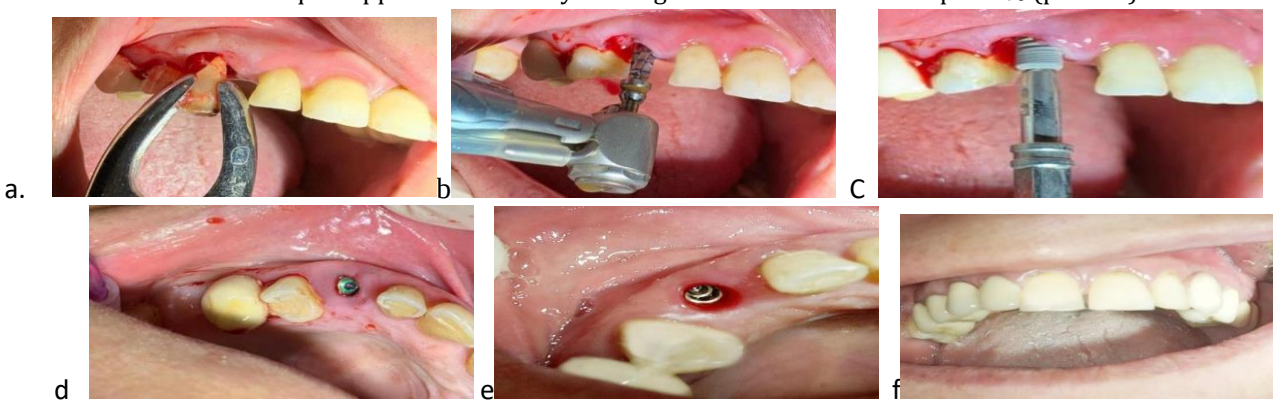

Fig .(1): Showing immediate implant placement in upper right canine :(a)Extraction of hopeless tooth on upper right canine.(b)Sequential drilling at implant site.(c) Implant Insertion.(d) Cover Screw.(e)Complete healing by using gingival former.(f) Final restoration.

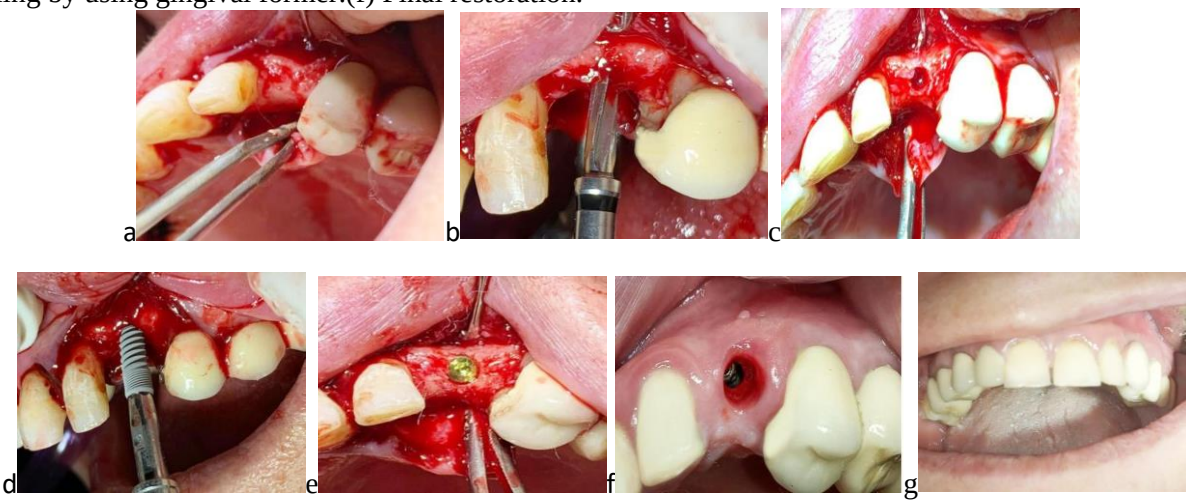

Fig (2): Showing delayed implant placement in upper left canine :(a)para-crestal incisions with releasing incisions at surgical sites and full-thickness flaps were reflected exposing the alveolar ridge.(b)Sequential drilling at implant site.(c)Osteotomy site after drilling.(d) Implant Insertion.(e) Cover Screw.(f)Complete healing by using gingival former.(g) Final restoration.

Fig(3): Radiograph showing edentulous site at upper left canine indicated for delayed implant placement and hopeless upper right canine that will be extracted and to be replaced by immediate implant placement.

Results

The characteristic information of the included sample in the present study, and received either immediate dental implant or delayed dental implants, is presented in Table 1

Table 1: Details of the included sample in the present study.

	Number		Age	
	Males	Females	Range	M+SD
Immediate Implant	4	6	28 - 49	37.8 + 4.78
Delayed Implant	4	6	25 - 49	38.4 +3.89
p	*NS*	*NS*	*NS*	*NS*

NS*: Non-significance (p< 0.05)*

Results of recorded Gingival index scores as mean and standard deviation at 6 months and 9 months after placement of dental implants among the various included groups of patients are presented in Table 2.

Table 2: Mean and SD of Gingival index score measured from the included subjects at two different time post-placement of the dental implant

	Immediate	**Immediate**	**Delayed**	**Delayed**	**Immediate**	**Immediate**	**Delayed**	**Delayed**
	Upper	**Lower**	**Upper**	**Lower**	**Upper**	**Lower**	**Upper**	**Lower**
Time	**6 M**	**6 M**	**6 M**	**6 M**	**9 M**	**9 M**	**9 M**	**9 M**
Range	**0 - 2**	**1 - 2**	**0 - 2**	**0 - 2**	**1 - 2**	**1 - 2**	**1 - 2**	**1 – 2**
M+ SD	*1.4 + 0.38*	*1.5 + 0.42*	*1.1 + 0.37*	*1.3 + 0.34*	*1.6 + 0.33*	*1.7 + 0.42*	*1.4 + 0.35*	*1.5 + 0.38*

Results of recorded Plaque index scores as mean and standard deviation at 6 months and 9 months after placement of dental implants among the various included groups of patients are presented in Table 3.

Table 3: Mean and SD of Plaque index score measured from the included subjects at two different time post-placement of the dental implant

	Immediate	**Immediate**	**Delayed**	**Delayed**	**Immediate**	**Immediat e**	**Delayed**	**Delayed**
	Upper	**Lower**	**Upper**	**Lower**	**Upper**	**Lower**	**Upper**	**Lower**
Time	**6 M**	**6 M**	**6 M**	**6 M**	**9 M**	**9 M**	**9 M**	**9 M**
Range	**0.5 - 1**	**0.65 – 1.10**	**0.25 – 0.98**	**0.25 – 0.80**	**0.90 -1. 25**	**0.95 – 1.25**	**0.50 – 1.25**	**0.50 – 1.25**
M+ SD	*0.793+0.06*	*0.833 +0.08*	*0.748+ 0.04*	*0.555+ 0.05*	*0.975+0.06*	*1.076+0.04*	*0.815+0.03*	*0.904+0.07*

Results of recorded Peri-implant pocket depth as mean and standard deviation at two different times after placement of dental implants among the various included groups of patients are presented in Table 4

Table 4: Mean and SD of Peri-implant pocket depth measured from the included subjects at two different time post-placement of the dental implant

	Immediate	**Immediat e**	**Delayed**	**Delayed**	**Immediate**	**Immediat e**	**Delayed**	**Delayed**
	Upper	***Lower***	***Upper***	***Lower***	***Upper***	***Lower***	***Upper***	***Lower***
Time	***6 M***	***6 M***	***6 M***	***6 M***	***9 M***	***9 M***	***9 M***	***9 M***
Range	**0 - 2**	**1 - 2**	**0 - 2**	**0 - 2**	**1 - 2**	**1 - 2**	**1 - 2**	**1 – 2**
M+ SD	**1.01 +0.45**	**0.91+ 0.39**	**0.71 + 0.28**	**0.81 +0.32**	**0.93**	**1.08 + 0.23**	**0.74 + 0.34**	**0.88 + 0.029**

These are presented in Table 5 (subjects received immediate implants) and Table 6 (received delayed dental implants

Table 5: BMP-2 levels among subjects received immediate dental implants, measured initially and at 1 week, 2 weeks, 4 weeks, 3 months, 6 months and 9 months post placement of the dental implant.

	Baseline	1 W	2 W	4 W	3 M	6 M	9 M
Range ***U***	10.1 - 12.4	14.8 – 16.2	12.9 – 14.5	11.1 – 13.8	9.0 – 12.1	8.9 – 12.1	8.9 – 12.3
L	10.2 – 12.7	15.2 – 17.4	13.1 – 15.8	11.6 – 13.7	9.8 – 12.1	9.6 – 12.3	9.6 – 12.4
Mean +SD ***U***	11.42+1. 02	15.61+1.15	13.66+2.01	12.00+1.86	10.24+2.35	10.22+2.30	10.30+2.74
L	11.76+1.08	16.59+1.24	14.52+2.10	12.74+1.2.12	11.07+2.1	11.17+2.70	11.00 +2.68

Table 6: BMP-2 levels among subjects received delayed dental implants, measured initially and at 1 week, 2 weeks, 4 weeks, 3 months, 6 months and 9 months post placement of the dental implant.

		Baseline	1 W	2 W	4 W	3 M	6 M	9 M
	U	10.0 - 12.5	15.8 – 18.3	13.8 – 16.2	11.4 – 14.6	9.0 – 12.3	8.8 – 12.3	8.8 – 12.4
Range	***L***	10.7 – 12.7	15.8 – 19.9	13.7 – 17.5	10.9 – 14.8	9.2 – 12.3	9.1 – 12.3	9.0 – 12.5
	U	11.40+1.08	17.16+ 1.48	15.00+2.03	12.69+1.89	10.47+ 2.15	10..50+ 2.07	10.40+ 2.15
M+ SD	**L**	12.07+ 1.15	15.85+1.86	15.68+ 2.18	13.29+2.08	10.06+ 2.08	10.95+ 2.05	10.71+ 2.18

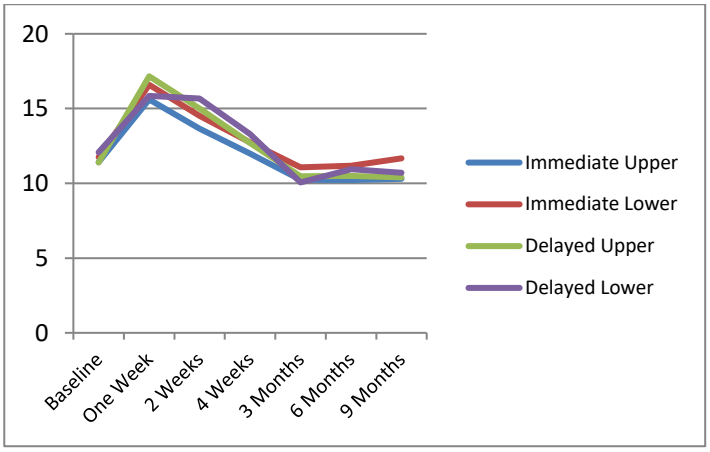

Figure 5: Line chart representing the (BMP-2) levels detected in patients included in the present study and treated either with immediate or delayed dental implants that measured at different time

Results of measured Bone resorption associated with placement of dental implants into upper and lower jaws applying either immediate or delayed implantation (Table 7 & 8)

Table 7: Bone resorption level at mesial and distal aspect, associated with immediate dental implants inserted into either into upper or lower jaw, detected initially as well as during the follow up period.

		Baseline		6 Months		9 Months	
		Mesial	Distal	Mesial	Distal	Mesial	Distal
Range	U	- 0.3 – 0.5	0.3 – 0.5	0.4 – 1.0	0.4 – 1.0	0.5 – 1.1	0.5 – 1.0
	L	- 0.3 – 0.5	0.3 – 0.5	0.2 – 0.6	0.3 – 0.7	0.5 – 0.9	0.5 – 1.0
M	**U**	- 0.39	- 0.39	0.59	0.56	0.74	0.69
	L	- 0.43	- 0.39	0.44	0.54	0.61	0.75

Table 8: Bone resorption level at mesial and distal aspect, associated with delayed dental implants inserted into either into upper or lower jaw, detected initially as well as during the follow up period.

	Baseline		**6 Months**		**9 Months**	
	Mesial	**Distal**	**Mesial**	**Distal**	**Mesial**	**Distal**
Range	- 0.4 - 0. 6 - 0.3 – 0.6	- 0.5 – 0.6 - 0.4 – 0.6	0.0 – 0.5 0.1 – 0.5	0.0 – 0.3 0.2 – 0.7	0.2 – 1.0 0.2 – 0.9	0.3 – 0.5 0.4 – 1.0
Mean+ SD	- 0.49 - 0.47	- 0.51 - 0.47	0.23 0.28	0.16 0.39	0.47 0.51	0.42 0.49

Results of implant stability measured with OSTEL:

The measured values of implant stability at various visits are presented in (Table 9)

Table 9 Implant stability measured using OSTEL at baseline (immediately following implant placement and then at 3 months, 6 months and 9 months post placement of the dental implant, either immediate or delayed technique.

Patient	**Baseline**		**3 Months**		**6 Months**		**9 Months**	
	Immediate	**Delayed**	**Immediate**	**Delayed**	**Immediate**	**Delayed**	**Immediate**	**Delayed**
1 U	73	75	70	70	82	85	86	89
L	76	79	73	72	85	85	88	90
2 U	75	78	71	75	84	89	90	91
L	77	81	72	78	83	87	90	93
3 U	74	76	70	73	81	85	85	91
L	81	80	76	76	80	85	86	89
4 U	75	77	70	72	82	83	87	92
L	75	78	70	73	81	80	84	85
5 U	78	81	72	76	80	85	86	90
L	79	82	71	78	83	86	89	93
6 U	73	79	70	71	83	84	85	89
L	76	80	74	77	84	87	88	92
7 U	75	78	72	76	84	88	88	92
L	80	79	75	74	85	85	89	91
8 U	74	76	71	74	82	84	86	88
L	75	78	70	75	85	81	87	89
9 U	75	75	71	70	84	86	87	87
L	76	79	74	73	83	86	87	92
10 U	80	80	76	75	83	86	87	89
L	78	82	76	77	88	87	90	94
Range U	73 – 78	75 – 81	70 - 76	70 – 76	80 – 84	83 – 89	85 – 90	87 – 92
L	75 - 81	78 - 82	70 – 76	72 - 78	80 – 85	80 - 87	84 - 90	85- 94
U	*75.20*	*77.50*	*71.30*	*73.20*	*82.50*	*85.50*	*86.70*	*89.80*
Mean + SD	*78.30*	*79.00*	*73.10*	*74.90*	*83.70*	*84.90*	*87.80*	*90.80*

Radiographic measurements of bone density: These values are presented in Table (10)

Table 10: Bone density recorded from either the upper or lower jaw among the included patients

Patient	***Upper jaw***	***Lower jaw***
1	D2	D3
2	D3	D3
3	D3	D2
4	D3	D4
5	D2	D4
6	D4	D3
7	D2	D3
8	D4	D4
9	D3	D3

10	D4	D2		
		D2	**3**	**2**
		D3	**4**	**5**
		D4	**3**	**3**

Discussion

Dental implants represent a reliable treatment option for oral rehabilitation of partially or fully edentulous patients, in order to secure various kinds of prostheses. However, the long-term success of dental implants has been well documented in the literature, as numerous investigators reported markedly the biological factors, surgical procedures, and restorative principles that influence the outcome of implant-supported restorations. [10] Dental implants have been classified in different ways, for example they were classified according to the timing of implant placement into immediate and delayed implants. Placement of dental implants to replace the missing teeth applying the original protocol include waiting several months after tooth extraction prior to implant placement to allow alveolar bone healing process. [11] This recommendation has been based on the thought that complete soft and hard tissue healing after tooth extraction is required to achieve successful osseointegration.[12] However, the need for complete post-extraction healing before implant placement has been rejected and challenged during the last decades, as it was found that reducing the time between extraction of a tooth and placing and / or loading of the implant can be done; this thought has led to the protocol of implant placement classification. [13]

Delayed implant placement (DIP) into healed bone can be considered as a straightforward surgical procedure. In addition, long-term clinical and aesthetic outcomes have been reported as a result; DIP is often used as a reference treatment modality in scientific research. [14] Immediate implant placement (IIP) is a popular treatment concept in dental practice for the both patient and clinician, since it reduces the number of surgical interventions as well as total treatment time. In these situations, it has been assumed for many years that an immediate insertion of the implant into a fresh extraction socket could counteract the three-dimensional alterations involving the alveolar process as a result of tooth extraction that may lead to a lack of buccal convexity and even mid-facial recession. These soft tissue alterations have been demonstrated by prospective and retrospective clinical research. [15] Osseointegration of dental implants has been regarded for long time following the pioneering studies by *Breinmark* as a structural and functional connection between newly formed bone and implant surface, which became a synonym for the biomechanical concept of secondary stability. Secondary stability of a dental implant largely depends on the degree of new bone formation at the bone-to-implant interface. Such bone to-implant contact and is widely used in research to measure the degree of osseointegration. [16]

It is of value to mention that, different agents were suggested to induce bone stimulation as; Hydroxyapatite (HA), Type-I collagen (CO) and Bone Morphogenetic Proteins (BMP). Collagen was found to be a major component in bone composition, increases in tissue vascularization, and decreases in inflammation by decelerating macrophage and osteoclast activity. [17] BMPs belong to transforming growth factor beta (TGF-β) superfamily, are biological factors that play major roles in the osteogenesis process through the regulation of osteogenic cells and differentiation of bone mesenchymal stem cells (MSCs). They were widely used as an additive for bone graft material; its addition contributes for the bone to implant contact (BIC) procedure. [18]

The present study selected bone morphogenetic protein-2 (BMP-2) enzyme due to secreted by osteoblastic cell, and can be found in high concentrations. The expression of this enzyme by osteoblastic cell is very important in mineralization process of bone and ostiointegration needed to dental implant success [19], enhance the bone tissue regeneration [20] and induce augmentation of alveolar ridge. [21] RhBMP-2 has also been reported to significantly enhance alveolar bone augmentation. [22] In addition it induces differentiation of mesenchymal cells into chondrogenic and osteogenic cells, and promotes osteoblast proliferation. [23, 24]

In the present study an attention was paid toward an evaluation or measuring of the Bone Morphogenetic Protein-2 (PMP-2) level associated with immediate compared to delayed placement dental implants. The present study included twenty patients that were selected according to the following criteria: each patient had a single site on one side of the jaw indicated to have dental implants (tooth extracted from long time) and the other side had hopeless tooth indicated for extraction and implant placement was done on that site at the time of tooth extraction in one jaw and free from any known systemic disease that affect bone status, surgical procedure as well as wound healing capacity, and had adequate quantity of native bone to achieve primary stability; and hence deviation of the results. Cone-Beam Computed Tomography (CBCT) was used in this study that has advantages. The main reason is the quality of the imaging, CBCT provides more views and angles of three-dimensional images to evaluate more complex structures such as bones and soft tissues, Low radiation (much less than traditional CT scan) ,Convenient and painless for patients , Cost effective and Safe for patients of all ages. [25]

The present study used peri-implant crevicular fluid (PICF) sampling that suitable for understanding the local cellular metabolism through the detection of biochemical indicators and inflammatory products that are useful for proper diagnosis of both peri-implant disease activity and the outcome of therapy. [26] In addition, the implant loading for all patients was done after three months depending on the healing time of 3 to 6 months was recommended for the conventional protocol of implant loading. [27] The present study measured implant stability at day of placement, 3, 6 and 9 months to evaluate the degree of osseointegration. These studies reveal, there was statistically significant difference between the two groups regarding ISQ baseline (primary stability) and after 3 months (secondary stability). Implants placed in healed sites had higher average ISQ values at implant placement when compared to immediately placed implants, however there was no significant difference between the two groups in stability (ISQ) at 6 and 9 months and this result concluded in other studies. [28, 29]

The obtained results showed that, within each group, there was significant increase in stability (ISQ) over time and similar studies showed that implant stability usually undergoes a transfer from a decrease in primary mechanical stability to a gradual increase in biological integrated stability, which is associated with bone healing response. [30, 31] The dimensions of bone defects present after completion of positioning of immediate and delayed implants. On average, both immediate and delayed implant sites displayed inadequate bone diameters. In the immediate implant group, these were due to: (i) the resorption of the alveolar crest associated with the reason for tooth extraction; and/or (ii) the presence of a gap between the dimension of the alveolus and the restorative driven choice of implant diameter and implant position in the immediate implant group. In the delayed implant group, these were due to the pattern of bone healing. Significant differences were observed comparing the two groups. Not unexpectedly, the more obvious differences related to the larger depth or width of defects associated with immediate implants. [32]

In this study, when delayed implants were placed, they had reduced loss of bone when compared with the group receiving immediate implants. There was statistically significant difference between the two groups regarding crestal bone loss and this is in harmony with other research. [33] On the contrary, other studies suggest when immediate implants were placed; they had reduced loss of bone when compared with the group receiving delayed implants. This may be due to reduced threat of resorption of alveolar bone immediately following extraction of tooth and positioning of the implant in a recent extraction socket. Additionally, the architecture of gingiva and crestal bone is preserved. [34] On the other hand, there was study suggest that difference in Marginal Bone Loss (MBL) between the groups was not statistically significant. One might expect that the MBL around implants placed in fresh extraction sockets would be higher than in healed sites, as there is resorption of the alveolar bone after the extraction of a tooth. However, there is a tendency of bone gain around an implant placed in a socket, as blood clot fills up the space between the implant and the bone walls, resulting in the formation of new bone, which increases in a coronal direction and finally apposes

around the neck of the implant as healing takes place. This could help to explain the reason why there was no clear difference in MBL between the approaches. [35, 36]

It is worthy note to mention that, results of the probing depths (PD) were significantly deeper in the immediate implant group than in the delayed implant group. Deeper probing depths were observed in the immediate implant group at the 9 month follow-up compared with the delayed and these result are similar to other studies. [37-38] On the contrary, other studies suggest when immediate implants were placed, The probing depth (PD) was considerably no significant differences between two groups regarding probing depth (PD) when compared to delayed implants. [39] Regarding the result of pocket depth may be explained by apical migration of the soft tissue margin mainly occurred during the first 6 months of observation period. They suggested that recession of periimplant soft tissue margin mainly may be the result of a re-modelling of the soft tissue. [40] In addition the increase probing depth in both groups may due to more sensitivity of peri-implant tissues to force variation than the corresponding measurements around teeth or due to a higher degree of inflammation of the peri-implant mucosa. [41] Furthermore the present study revealed that there is no differences between the two groups were observed in the frequency of implants bleeding on probing at crown insertion or 9 month follow-up and this is consistent with other studies. [37, 39] While in the present study plaque index (PI) showed statistically greater in delayed implants compared to immediate implants. On the other side the results showed that the average amount of BMP-2 progressively increased from baseline to 3– 5 days post-surgery in the delayed implant group than the immediate implant group and reached a statistical significant elevation at 7 ± 1 days post-surgery. BMP-2 then declined to levels that were not significantly different between the two groups in 3, 6, 9 months. These findings were supported by evidence of biological role of BMP-2 could be affected by several factors, including the presence of BMP inhibitors in the surrounding tissues. The actions of BMPs are tightly regulated by natural inhibitors (BMP antagonists) that can bind to BMPs, thereby inhibit the binding of BMPs to their signaling receptors. [42] Additionally, these findings also explained by mechanical injury were found to upregulate BMP-2, as well as BMP-2 signaling. [43]

The clinical parameters probing depth (PD), modified bleeding index (MBI), and modified plaque index+ (MPI) served as indicators for bone resorption and inflammation. The clinical parameters and BMP-2 were assessed soon after surgery and were chosen for the PICF sampling times, the evidence indicated that major role of inflammatory biomarkers occur in the first month after surgery and complete epithelial healing with a well-defined epithelial attachment can be occurred one month after flap surgery. In addition, woven bone is the first bone tissue that is formed in osseointegration and its formation clearly dominates the healing area within the first 4 to 6 weeks after surgery. [44] In spite to presence of some controversy regarding the efficacy of BMP in bone formation, as several factors are known to affect the osteoinductive ability of BMP-2, the finding indicates that the presence of BMP-2 at a consistently high level in the surgical implant sites over a short period of time may affect the final wound healing outcome.

Conclusion

The amount of BMP-2 progressively increased post-surgery in delayed implant group than immediate implant group. Implant stability at the baseline (primary stability) and after 3 months (secondary stability) in the delayed implant group higher than the immediate implant group. Dental implants can remain functionally accepted applying either delayed and immediate implant technique. Further studies are needed to obtain thorough knowledge regarding the aspect of the value of assessing the biomarker validity in determination of dental implant stability. This line of investigation necessitate establishing research protocol utilizing larger sample size and followed up for longer period and using various biomarkers and determination methods.

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