Evaluation of Mineralized Plasmatic Matrix Prepared from Xenogeneic Bone in Mandibular Defects Grafting after Cystectomy in Diabetic Patient: A Prospective Randomized Clinical Trial

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ABSTRACT: Objective: To evaluate the usage of Mineralized Plasmatic Matrix prepared from Xenogeneic Bone (MPM-XB) in the healing process of mandibular defects after cystectomy in diabetic patients by using density measuring and volumetric analysis with cone beam computed tomography (CBCT). **Patients and Methods:** This study involved 12 diabetic cases with cystic lesions of the mandible. MPM-XB is used to fill the cavity after cystectomy. At the post-operative 3rd and 6th months, the implanted bone was evaluated by matching the CBCT scan in terms of density and volume compared with the mandibular cystic lesion volume. **Results**: Mean bone density was increased after 6 months as compared to 3 months postoperative with statistically significant difference p value ≤0.05. Bone density increased by mean value 41.75±20.43, ranged from 18 to 102, while volumetric analysis showed a non-significant difference between preoperative and 6 months after, regarding cystic volume and graft volume as well as the ratio between both (P > 0.05). **Conclusion:** Mineralized plasmatic matrix prepared from xenogeneic bone appeared to be stable with appropriate bone density and minimal complications in filling bone defects after cystectomy in diabetic patients with mandibular cystic lesions.

Keywords: Mineralized Plasmatic Matrix, xenogeneic graft, cystic mandibular lesion.

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Introduction:

Healing of the bone is a sequence of complex orchestrated biologic processes. Bone healing includes osteo-induction and osteoconduction mediated by intra-cellular and extra-cellular signaling pathways [1]. A bone defect can be congenital or related to infection, trauma or malignancy [2]. Usually, spontaneous healing of small bone defect does occur; however, in critical bone defect, there is a limited healing capacity; thus, surgery is necessary [3].

Large sized jaw defect might cause significant deformities of the face, as well as lingual and masticatory dysfunction. Accordingly, their reconstruction and repair are important issues for plastic and maxillofacial surgeons [4,5,6]. Bone grafting thus has an important role and is necessary for reconstructing the massive defect [7]. Autograft, allograft, xenograft, and synthetic bone graft substitute material (alloplastic) have been used [8].

A xenograft involves grafting from an animal to another of other species or to human [9]. Osteogenesis, osteoconduction, osteo-induction, and osteointegration are biologic processes essential for new bone formation [10]. There are limitations related to the utilization of autograft and allograft [10,11]. Both xenografts and tissue engineering material with enhanced properties could overcome such limitations [12]. Bone-derived xenografts are extensively utilized in maxillofacial surgery [13].

MPM is significantly concentrated in platelets and fibrin in liquid form and combined with bone powder or bone substitute [11]. MPM is a variant of platelet-rich fibrin [14]. Platelet concentrates are appropriate bioactive material due to providing growth factors and cytokines that help in healing process [15,16]. Furthermore, fibrin promotes migration and proliferation of the cells as well as angiogenesis [17]. MPM is more advantageous than platelet concentrates due to incorporation of graft particles into the fibrin meshwork, thus forming sticky bone. The latter is flexible and easy to shape, and it provides high stability to bone particles and prevents soft tissue deposition in the defect [18].

Diabetes mellitus (DM) is common in dental patients. Hyperglycemic microenvironment can delay the healing of post-surgical jaw defects, and is associated with poor outcomes in many oral diseases [19]. Novel improvements have been made in various treatment strategies and medications for managing wound healing in diabetes. Topical plasma-rich growth factor, platelet-rich fibrin, leukocyte- and platelet-rich fibrin and hyaluronic acid is regarded as a promising strategy for diabetics who require jaw surgeries [19].

This study aimed at evaluating the usage of MPM-XB in healing process of mandibular defects after cystectomy in diabetic patients by using volumetric analysis and density measuring with CBCT.

Patients and Methods

This prospective, interventional study involved 12 cases with mandibular cyst in succession who approved to be studied and fulfilled the inclusion criteria. The study was performed in the Dental clinics of Aswan University Hospital at the period from April 2022 to May 2023.

The study included adult diabetic patients more than 18 years of age, both sexes included, they had mandibular cystic bone lesions (large cysts >2.5 cm). Other forms of jaw diseases, pediatric patients, previous dental surgery and major systemic diseases or autoimmune diseases as well as non-diabetic patients were excluded.

The procedures were performed according to ethics research committee, Faculty of oral and dental medicine, Cairo University. Informed consents were taken from all participants and included details about the purpose of this study, and a simple and easy explanation of the technique, possible complications, and benefits of the procedure.

Preoperative evaluation:

Detailed medical and dental history was obtained from each patient including name, age, gender, occupation, address, telephone number.

General examination of systemic condition, blood pressure, temperature and a local examination including jaw inspection and palpation were performed to detect any accompanying infections or lesions.

Laboratory report including complete blood count (CBC), hemoglobin concentration, coagulation study, blood sugar level as well as glycosylated haemoglobin (HbA1c).

Plain X-ray of the jaw (panoramic views) and CBCT (PaX-i3D, Vatech Co., Gyeonggi-do, Republic of Korea) utilizing the following settings: 0.3-mm, 24 s, 106 kV, and 65 mAs was done for all patients for assessment of exact location, size, and extension of jaw cystic lesion.

A sample was taken from the cystic lesion to ensure its histopathological nature before performing its complete surgical removal by using fine-needle aspiration biopsy.

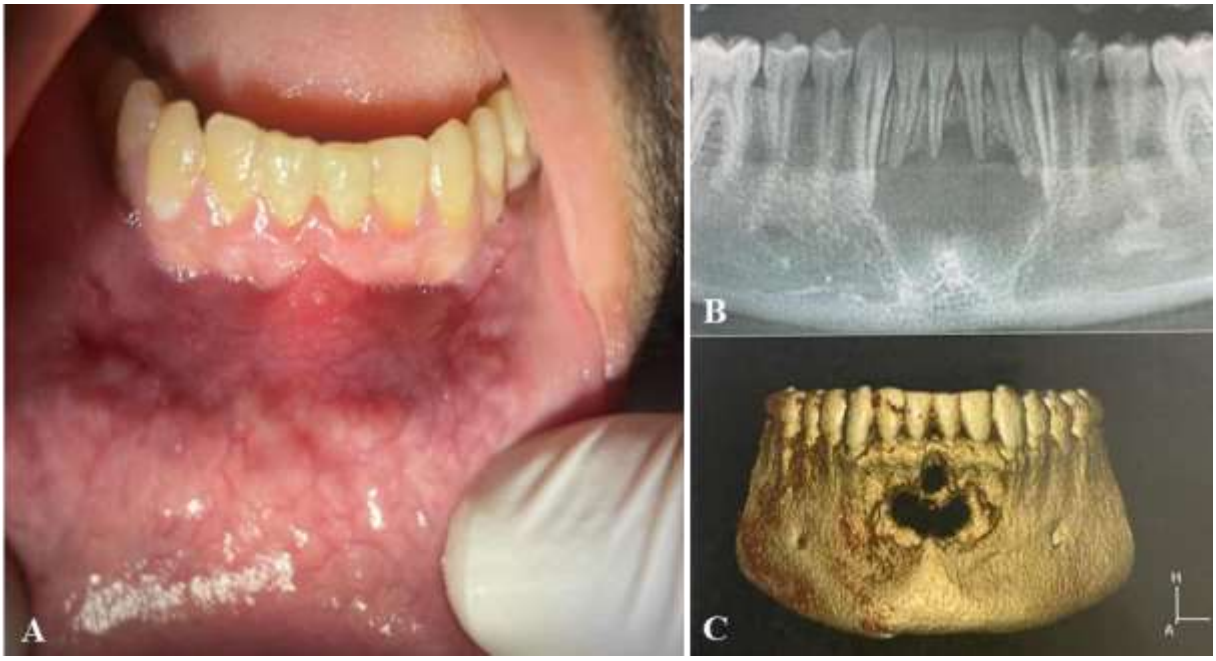

Fig. (1): Preoperative views of mandibular lesion: A. Direct photo. B. Plain x-ray. C. 3D radiographic view.

Operative procedures:

Pre-surgical rubbing and preparation were achieved. Articain (ARTINIBSA 4% 1:100000®)[1] was first injected into the surgical sites. A full 3-lines mucoperiosteal flap was incised and reflected for exposure of the area of cystic lesion. Periosteal releasing incisions were then performed to enable tension-free closure at the end of operation. Small cortical perforations were performed for accessing the lesion if decortication was needed using small round bur. Cysts were excised with adequate curettage and were planned for microscopic examination. Any related restorable teeth were endodontically obturated after apicectomy.

[1] ARTINIBSA® 4% 1:100000 by INIBSA Pharmaceutical Group, Spain.
2 Xenograft ONEXENO GRAFT® by One Graft, Germany.

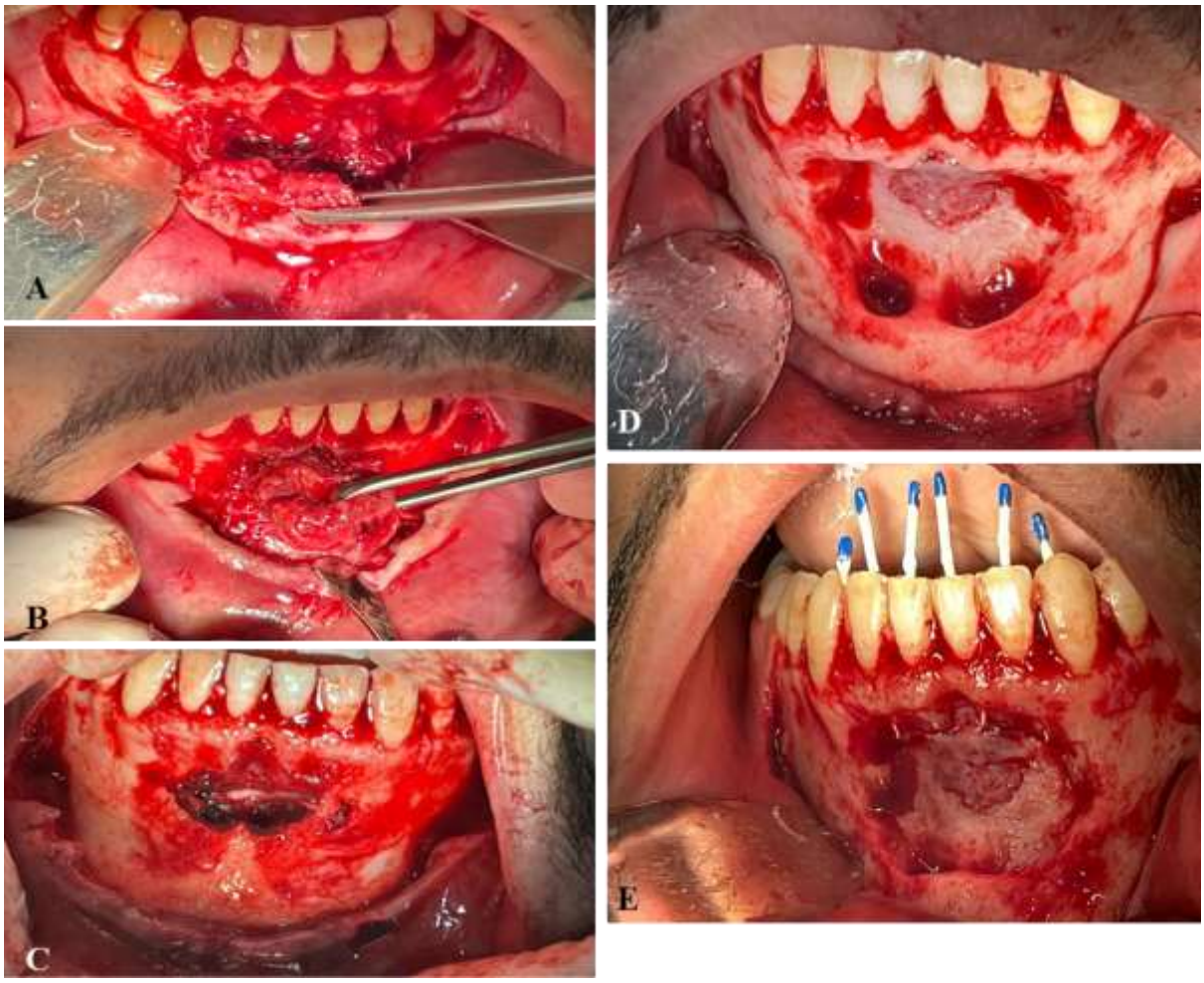

Fig. (2): Steps of cyst removal, curettage, RCT and graft site preparation.

A Xenogeneic cancellous bone particulate was utilized for grafting (OneXeno Graft, Cortico-cancellous Bovine Powder, Germany). It was placed in a sterile mixing bowl and underwent hydration with saline. From the patient, 15ml venous blood was collected in uncoated plastic tubes without anticoagulant (B.D. vacutainer) and underwent centrifugation at (2500 rpm) over three minutes to separates the plasma which is rich in platelets and fibrin concentrates at top of the tube while the red corpuscles at its bottom. Then, plasma collection was done using a syringe and placed over the graft and stirred with a mucoperiosteal elevator until the formation of a bone-fibrin mass.

The MPM was adapted to the labial surface of the alveolar bone, then the flap was repositioned and closed using 4-0 Vicryl sutures.

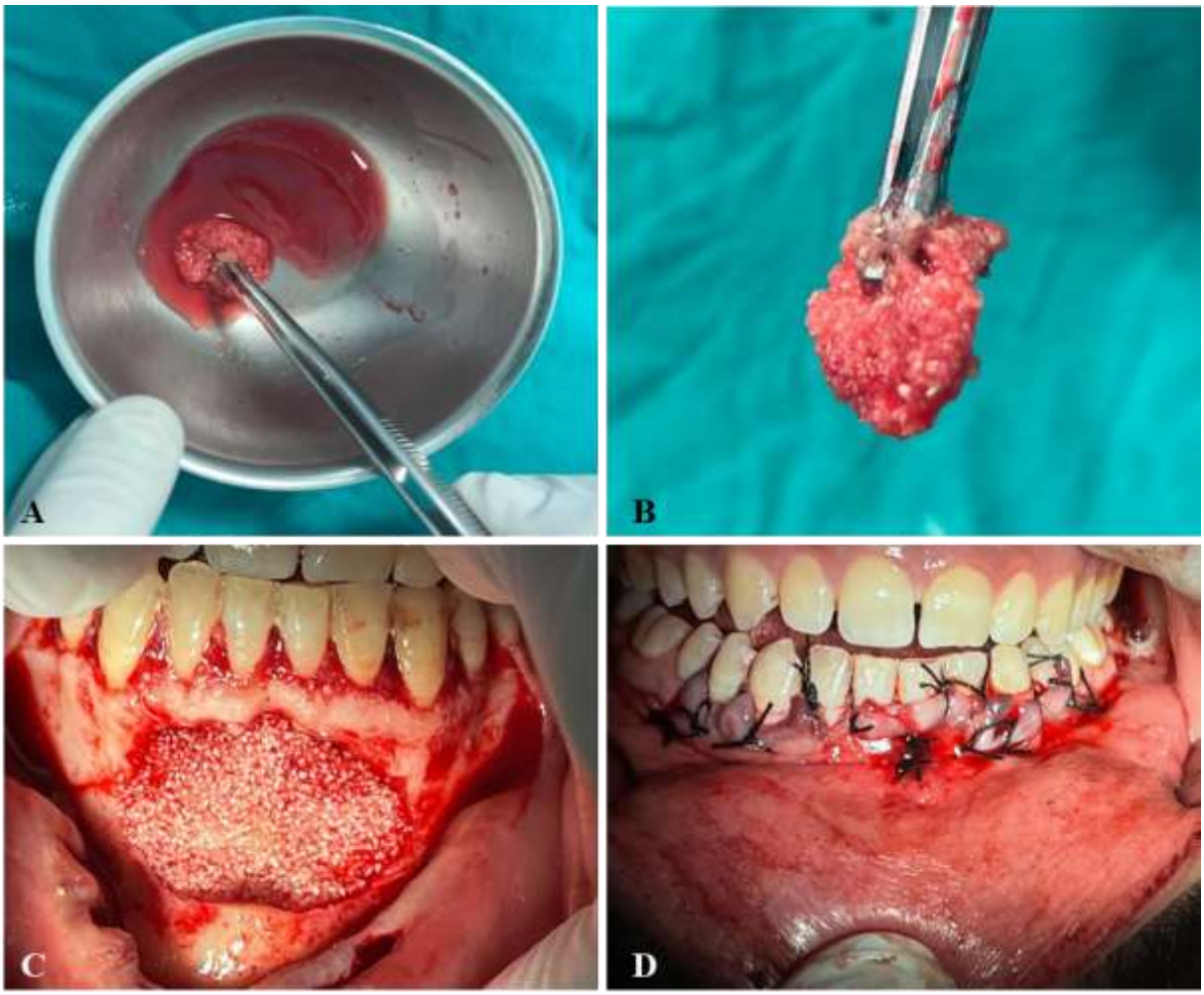

Fig. (3): A & B. Mineralized Plasmatic Matrix Preparation from Xenogeneic Bone. C. Graft insertion in bone defect. D. Wound suturing.

The excised biopsy was sent to pathology department for pathological differentiation. Antibiotics (Amoxicillin-clavulanate) were prescribed (Augmentin 1gm, SmithKline Beecham, Egypt) two times daily for each patient to prevent infections. An analgesic (Brufen 400mg, Abbot Pharmaceuticals, Egypt) [2] was also prescribed to relieve pain.

Augmentin 1gm, SmithKline Beecham, Egypt.

[2] Brufen 400mg, Abbot Pharmaceuticals, Egypt.

Postoperative follow-up:

All patients were assessed in the 1st post-operative day looking to exclude any complication and to confirm the proper use of post-operative prescribed drugs. Patients wound was observed one week post-operatively. Then, the follow up was after 1 and 3 months.

CBCT-scans for density measuring and volumetric analysis were carried out and underwent reviewing after 3 and 6 months in relation with the preoperative CBCT-scans.

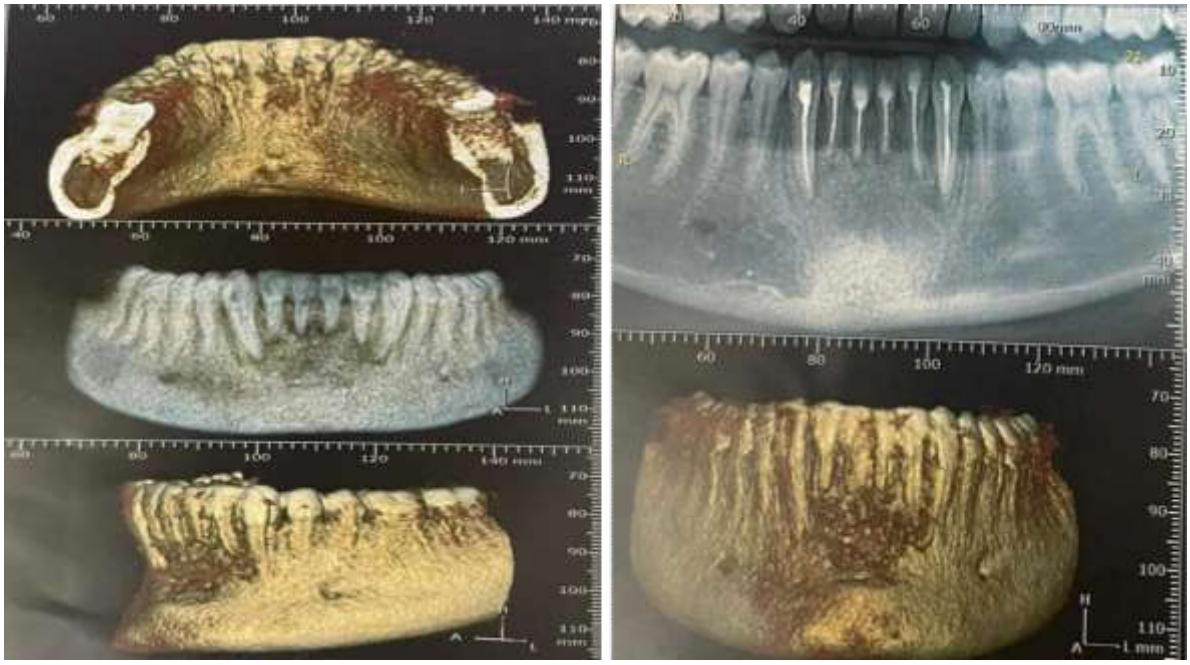

Fig. (4): Cone beam computed tomography (CBCT) during follow-up.

3D volume measurement method consisted of using the INVESALIUS software. A 3D surface of the graft was created from a 2D mask which contains all the pixels of graft and defect. This 2D mask was obtained by customized thresholding tool and then using manual segmentation tool adjusted in all orthogonal plans by interpolation and filling hole of the software, then finally mask was translated into a 3D surface model with volume in mm^3.

Alterations in buccal and lingual bone density of the cystectomy defect (relative) were evaluated from the coronal sagittal cuts whereas the mesial and distal alterations were evaluated from the panoramic cuts using the density measurement tool to determine the region of interest (ROI) then the software automatically calculated bone density. Relative bone density was measured then the average bone density was calculated [20].

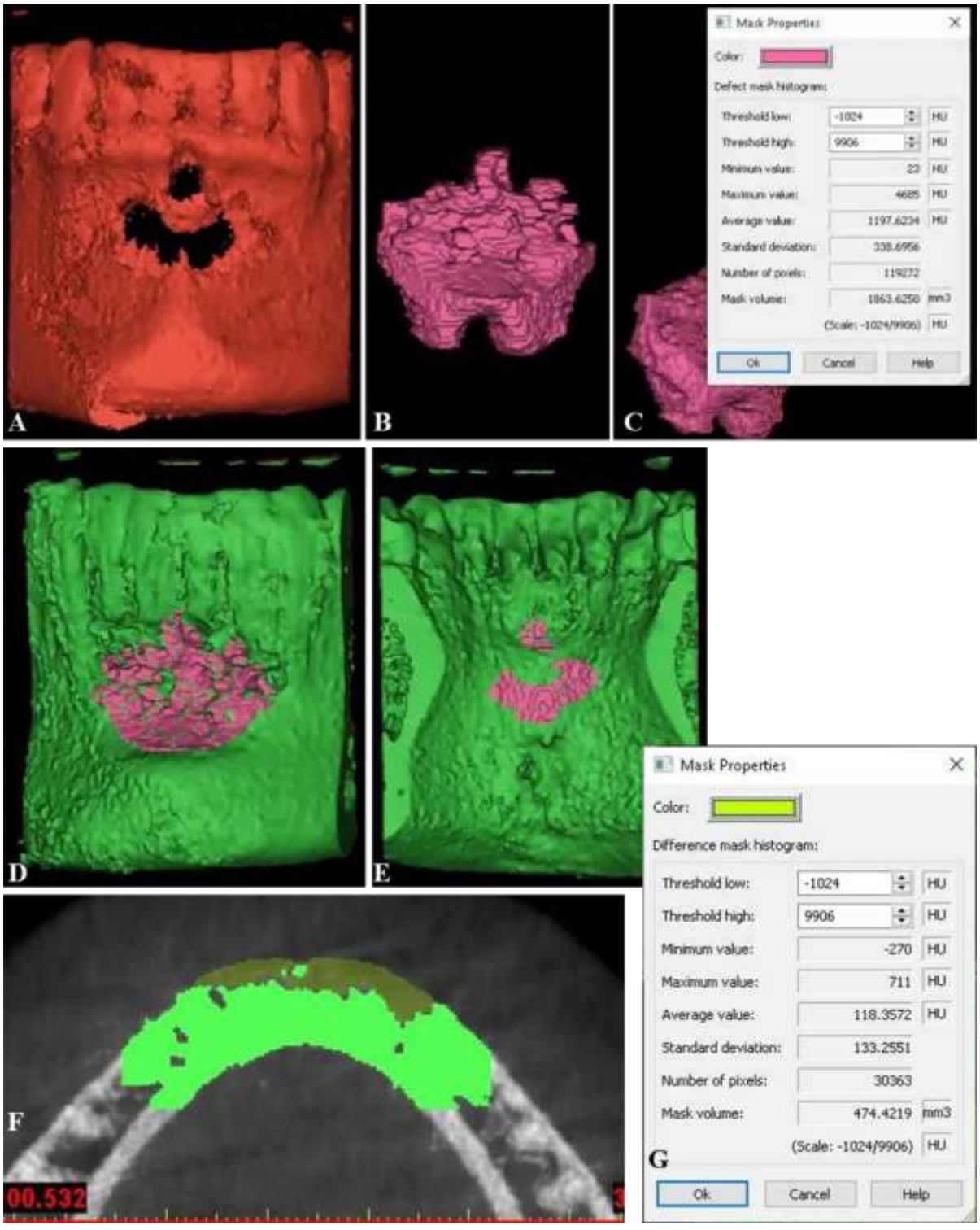

Fig. (5): Examples of X-ray volumetric analysis.

Statistical analysis:

Data were analysed by IBM SPSS software package v 25 (Armonk, NY: IBM Corp). Frequencies and percents were utilized for qualitative data. The Kolmogorov-Smirnov test was utilized to confirm the normality of distribution; the paired groups were compared with paired

t test. Ranges (minimum and maximum), means and standard deviations (SDs) were utilized for quantitative data. Significance of a result was set at $p \leq 0.05$.

Results

This study included 12 diabetic patients with mandibular cystic lesion: They were 5 males (41.7%) and 7 females (58.3%). The ages ranged between 31 to 65 years with mean ± SD of 52.3 ± 6.42 years. Patients' characteristics are presented in (table1).

Mean bone density was increased after 6 months as compared to 3 months postoperative with statistically significant difference p value ≤0.05. Bone density increased by mean value 41.75±20.43, ranged from 18 to 102 (table2), while volumetric analysis shows there a non-significant difference between preoperative and 6 months after, as regard cystic volume and graft volume as well as the ratio between both (P > 0.05) (table 3).

Postoperative complications were minimal. Pain was significantly decreased (p <0.001) from 4.12 ± 0.79 by VAS during the first week decreased to 1.09 ± 0.04 in the first month, then disappeared at 3 months of follow-up. Also, cheek edema significantly decreased (p = 0.001) from 14.7 ± 3.17 in the first postoperative week to 7.75 ± 7.51 at one month and disappeared at the 3rd month. No other complications were found in the follow-up period (table 4).

Table (1): Preoperative patients' criteria of the study population.

	Males		Females		Significance	
	No.	%	No.	%	χ^2	P
Total (n = 12)	5	41.7	7	58.3	0.192	0.542
	Anterior mandibular cysts		Posterior mandibular cysts			
Site of lesion	10	83.3	2	16.7	12.37	0.000*
	Range		Mean ± SD			
Age (years)	31 – 65		52.3 ± 6.42			
systolic blood pressure (mmHg)	102 – 157		135.9 ± 13.4			
diastolic blood pressure (mmHg)	59 – 92		78.8 ± 8.65			
Fasting blood sugar (mg/dL)	118 – 151		127.6 ± 21.4			
postprandial blood sugar (mg/dL)	135 – 232		176.5 ± 42.7			
HbA1c (U/L)	5.5 – 13.1		8.63 ± 3.41			

χ^2 = Chi square, P >0.05: non-significant. *p<0.001: highly significant.

Table (2): Bone density measuring outcome during the follow-up period.

Density Measuring	**After 3 months (n=12)**	**After 6 months (n=12)**	**T6-T3**	**Paired t-test**	**P-value**
Bone density Mean ± SD	852.42±96.91 712-1095	894.17±112.7 750-1197	41.75±20.43 18-102	t =7.08	≤0.001*

Mean bone density was increased after 6 months as compared to 3 months postoperative with statistically significant difference p value ≤0.05. Bone density increased by mean value 41.75±20.43, ranged from 18 to 102.

Table (3): Volumetric analysis outcome during follow-up period.

Outcome	Values	Significance

		F	P
Cystic volume (mm^3)	27.91 ± 9.97	0.364	0.494
Graft volume (mm3)	21.52 ± 6.42	0.398	0.463
Graft ratio (%)	85.6 ± 14.2	0.221	0.185

F: Friedman test, * p <0.05 = significant.

This table showed that the cystic volume was 27.91 ± 9.97, while the graft volume was 21.52 ± 6.42. The mean graft ratio was 85.6 ± 14.2%.

Table (4): Postoperative complications during the follow-up period.

Complication	1 week	1 month	3 months	Significance	
				F	P
Pain (VAS)	4.12 ± 0.89	1.09 ± 0.04	0.00	21.6	0.000*
Cheek edema	14.7 ± 3.17	7.75 ± 7.51	0.00	15.73	0.001*
Infection	0.00	0.00	0.00	-	-
Graft exposure	0.00	0.00	0.00	-	-
Graft rejection	0.00	0.00	0.00	-	-
Dehiscence	0.00	0.00	0.00	-	-

F: Friedman test, * p <0.05 = significant. VAS: visual analogue score.

Discussion

Cystectomy is the standard technique for treating bone cysts and might be performed in combination with decompression [21]. After cystectomy, healing does occur spontaneously to repair bone defects [22]. However, decompression and enucleation are not always adequate for achieving complete bone regeneration, and thus healing time could be extended. This increases the risk of fractures and infections.

Spontaneous bone regeneration requires an adequate blood supply and mesenchymal cells. But, because of the absence of mechanical support, the massive defect cannot completely heal [23,24]. In agreement with our study, another study by Perić Kačarević Ž et al. stated that under previously mentioned conditions of critical sized defects, external materials are required for the regeneration process [25].

Different bone substitute materials have been generally utilized [26]. However, there is little evidence to support certain treatment or which material to be utilized. Bovine-derived hydroxyapatite and synthetic hydroxyapatite were found to be associated with optimal healing over six months [27]. Other supernatants, like plasma-rich gel, have also been found to have efficacy [28].

Autologous platelet concentrates contain growth factors, which promote healing. These growth factors include platelet derived growth factor, tumor growth factor beta, vascular endothelial growth factor, and other cytokines. For that, autologous platelet concentrates are commonly used in conditions requiring rapid tissue repair and regeneration and they have shown positive outcomes. The autologous platelet concentrates are applied in the form of fibrin network will lead to confinement of growth factors secretion to the ROI [29].

MPM preparation features the simplicity of the PRF protocol, but provides a liquid platelet/fibrin concentrate which can bind to bony particles. Scanning electron microscopy (SEM) shows that MPM forms a fibrin meshwork around the mineral blocks. Bone graft can

be readily conformed and the surgical site refreshed by different contained products. The surgical technique is often not changed and it becomes easier and safer. MPM involves the usage of plastic tubes with no additives, thus initiating the intrinsic coagulation pathway. The high Ca^{+2} and thromboplastin levels in plasma induce the extrinsic coagulation pathway. Usefully, a homogeneous filling material, a fibrin membrane, and the valuable biological properties of PRF become simultaneously available [30].

For bone grafting success, many conditions must be ensured including the space maintaining, the scaffolding, graft's stability and the appropriate closure. Platelets' concentration has a little role in the regeneration process as their lifetime is only 4 - 8 days. Thus, few days following the placement of platelet concentrates, their concentration becomes decreased significantly reaching the normal concentration in the body. So, what must be considered in such products is neither the biologic portion, nor is the contained cells, but the significant consideration is the biomechanical part. The MPM is the only natural and autogenous product which offers stability to bony particles. The PRF alone or when mixed with a bone graft, will not achieve adequate stability or the required resistance to chewing forces, and thus is not helpful for bone regeneration [31]

Diabetics have a high risk of hyperlipidaemia, infections, and delayed tissue healing. DM is the 3rd most prevalent chronic oral disease [32]. In contrast, hyperglycaemia decrease the concentrations of insulin growth factor-1 (IGF-1), transforming growth factor-β3, epidermal growth factor receptor, and ciliary neurotrophic factor, contributing to poor healing [33].

Delayed tooth extraction socket healing is usually observed in diabetic subjects [33]. Oral wound healing is slower in diabetic cases compared with those without DM, especially on the post-operative 7th day [34]. However, not all publications concluded that diabetic patients have increased healing disorders [35].

To avoid longstanding healing procedures and their subsequent complications we used in our study MPM-XB to fill the cavity after cystectomy in 12 diabetic patients with Mandibular jaw cyst of critical size aiming to spare autografting with similar outcome and less complications.

Feichtinger and co-workers had recommended the use of 3D CT to obtain specific results on the volume and width of bone bridge [36].

Bornstein et al. concluded that CBCT could be utilized in dentistry for preoperative anatomical assessment, site design, and planning of treatment, as well as for post-operative evaluation [37]. Also, it was found that CBCT is more advantageous than CT because of less radiation dose and less costs [38].

Osman et al. (2019) study shows that cone beam CT scoring method for assessing the outcomes of alveolar bone graft was an excellent radiographic evaluation. Moreover, CBCT is accurate in terms of quantitative analysis of buccal and lingual alveolar bone thickness at different vertical levels [39].

So CBCT was used in our study instead of conventional CT pre-operatively and postoperatively. Regarding bone density using CBCT, a significant increase in bone density was found after 3 months up to the maximum at 6 months, while volumetric analysis shows that there had a non-significant difference between preoperative and 6 months after, regarding cystic volume and graft volume as well as the ratio between both. This is in accordance with

Abo Serie et al., Sultan et al. [40] and Elbokle et al. [41], who concluded that MPM achieved positive results in terms of bone density. Also, Cinar et al. [42] reported that MPM increased new bone formation.

Other earlier studies assessed the grafted bone alterations following alveolar bone graft through assessing the height, Labio- Lingual Thickness, and volume of the grafted bone pre-grafting in comparison to 3 months and one year after grafting [36]. Other studies assessed the resorption of alveolar bone graft through measuring the graft volume at 30 days and 6 months [43].

In our study, regarding the time of healing we had favorable outcomes as we found MPM-XB can fill the cystectomy cavity with good healing and less complications in diabetic patients. The same results were addressed by Abo Serie et al. [44] who studied 16 cases with anterior maxillary horizontal alveolar defect and concluded that MPM provided a more durable and stable structure which helped new bone formation without utilizing a covering collagen membrane.

Our results show that pain and edema were reduced markedly in the 1st month and disappeared by the 3rd month. This agrees with Mansour et al. [38] who reported that MPM reduces post-operative infections, oedema, pain, Graft exposure and/or loss and soft tissue dehiscence. Pain in the first month was controlled by analgesics. No infection found in our study as we adequately controlled diabetes with strict sterile condition pre- intra- and postoperatively with systemic broad-spectrum antibiotics. Also, we did not find any graft exposure and soft tissue dehiscence.

Conclusion

For bone grafting success, many conditions must be fulfilled including the space maintaining, scaffolding, graft's stability and the appropriate closure. MPM prepared from xenogeneic bone is significantly effective in restoring critical sized mandibular cystectomy defects in diabetic patients with ease and less complications. Moreover, work with more patients, however, is essential, and the biological qualities of MPM should be appropriately defined.

Conflict of interests: None.

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