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HISTOLOGICAL ASSESSMENT OF DEPROTEINIZED BOVINE BONE-BONE MARROW ASPIRATE VERSUS DEPROTEINIZED BOVINE BONE ALONE FOR GUIDED SINUS FLOOR AUGMENTATION. A RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Purpose: To histologically and radiographically compare the newly formed bone (NFB) yielded following sinus floor augmentation using bone marrow aspirate concentrate (BMAC) loaded on bovine bone graft versus bovine bone graft.

Methods: The current randomized clinical trial included ten patients with maxillary posterior atrophy who were presented at outpatient's clinic of the faculty of dentistry, Cairo university. NFB was histologically assessed 4 months following sinus augmentation using BMAC/ deproteinized bovine bone (DBB) (study) versus DBB graft (control). **Covariates** included residual ridge height, age and sex. *At second stage surgery (after 4 months) core biopsies were harvested and submitted for histologic analysis*.

Results: The sample included 10 eligible patients with mean age of 46.8 years. Both groups showed thin irregular bone trabculae with intervening wide bone marrow spaces, areas of woven bone and material remnants were observed. Higher magnification revealed a high inflammatory cell infiltration in contol group). Moreover, radiographic bone height on CBCT for the study group (13.34±2.76) was higher than that of the control group (10.10±2.46) after 4 months (p>0.05).

Conclusions: BMAC /DBB yielded comparable bone gain to the control group. BMAC utilization for sinus floor augmentation supported healing and maintained the grafted sinus height.

KEYWORDS Sinus floor elevation, lateral approach, bone marrow aspirate, histological.

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INTRODUCTION

Sinus pneumatization aggravates the natural resorption process that follows dental extraction. **Lin et al., 2019** & **Lyu et al., 2023** Studies show that dental implants placed in bone-augmented sinuses have higher survival rates than those in non-augmented ones **Chiapasco et al. 2009, Jensen & Terheyden 2009, Nkenke & Stelzle 2009.**

Bone grafting materials act as a scaffold for new bone formation, leading to better implant stability, osseointegration, and long-term success. **Henkel et al., 2013.** Various materials can be used for sinus floor augmentation, yet autogenous bone, particularly cancellous bone, has long been considered the gold standard due to its osteogenic, osteoinductive, and osteoconductive properties. It consolidates rapidly due to the presence of resilient mesenchymal stem cells (MSCs). **Liat Chaushu et al,2021.**

However, autografts have drawbacks like limited availability and donor site morbidity. Autograft substitutes have been developed to address these issues including allografts (freeze-dried bone allograft - FDBA), xenografts (deproteinized bovine bone - DBB) and alloplasts (calcium phosphates, bioactive glass). **Gual- Vaqués et al., 2018, Ferraz.,2023** All share the osteocoductive property, however, an ideal substitute should also be osteoinductive **Chaushu et al., 2021.**

Tissue engineered grafts utilization for reconstructive surgery focus on the use of scaffold (osteocoductive material) seeded with specialized cells (MSCs) to form new tissue, with the help of growth factors recruited from surrounding tissues for bone healing **Stamnitz et al., 2021**

Ideal TE scaffold for bone regeneration should be biocompatible, possess similar mechanical properties to bone, have a suitable architecture for cell and vessel ingrowth, and biodegrade at a rate similar to natural bone **Almouemen et al., 2019.** DBB is most commonly utilized, osteocoductive material for sinus augmentation with moderate cost. **Ferreira at al., 2009** Among different mesenchymal stem cells (MSCs) sources like bone marrow (BM), adipose tissue, bone, and dental tissue that have been explored for bone tissue engineering, **Asutay** et al.,2015 Bone marrow is still the preferable one for its differentiation ability that was shown to be superior to adipose-derived MSCs (ADSCs) in animal models. **Zhang et al., 2013, Schafer et al. 2019, Costela- Ruiz et al., 2022**

Bone marrow aspirate concentrate (BMAC) has also shown to preserve the augmented alveolar ridge height when added to autografts compared to autografts alone as a control **Naujokat et al., 2022.** For sinus floor augmentation, BMAC was loaded on DBB in few studies to add the osteogenic and osteoinductive potential to the osteocoductive property of DBB. **Sauerbier et al., 2010, Sauerbier et al. 2011, Payer et al., 2014, Wildburger et al., 2014, Pasquali et al., 2015 and de Oliverira et al., 2016. The fore mentioned studies** comprised vast heterogenicity regarding source of BMA, concentration method, centrifugation protocol, number of grafted sinuses and the follow up period, making the ideal management approach still open to research **Ting et al., 2018.**

The posterior iliac crest (PIC) was the main source for BM aspiration in most of the forementioned studies. Only **payer** et al., 2014 utilized tibia as a BM source. Anterior iliac crest (AIC) was not utilized as a source of BM harvesting for sinus augmentation, despite of better accessibility in obese patients and feasibility of simultaneous oral surgical procedures (under local or general anesthesia) with relatively decreased operative time (changing patient position is unnecessary). **Abla et al.,2008.**

Regarding the centrifugation protocol to concentrate the BM aspirate (single vs. double centrifugation), **De oliveria et al., 2016** suggested that centrifugation may lead to better vital tissue formation. All previous studies performed morphometric analysis of the newly formed bone

(NFB). A single study of those relevant articles showed promising positive results in terms of newly formed bone (NFB) compared to the control (unloaded DBB) group **Pasquali et al., 2015** while others found no significant difference among groups. **Sauerbier et al. 2011, Payer et al., 2014, Wildburger et al., 2014**.

Radiographic criteria for successful maxillary rehabilitation include structural stability of graft via maintaining its height and volume and absence of perimplant radiolucency (**Karthik et al., 2013).** This should coincide with the clinical success criteria that include absence of mobility, persistent pain or infection. Sufficient alveolar bone height is hence essential for primary implant stability. The forementioned studies focused on histological assessment of NFB and didn't correlate it with radiographic assessment of NFB quantity.

So, the purpose of the current study was to compare DBB loaded with BMAC (harvested from AIC) to DBB for maxillary sinus floor augmentation via histological and radiographic analysis.

PATIENTS AND METHODS

Study design

The current randomized clinical trial was approved by the ethical committee of faculty of dentistry, Cairo University that follows the declaration of Helsinki guidelines) IRB number: 7 10 22). The current research is registered on ClinicalTrials.gov (registration number: NCT05730400**).**

Patients who were indicated for dental rehabilitation of posterior maxilla were recruited from clinic of oral and maxillofacial surgery department of faculty of dentistry, Cairo University. A written informed consent was obtained from all patients after detailed procedure explanation.

Sample size calculation

According to a previous study (**Pasquali et al., 2015**), a total sample of ten eligible patients (twelve sinuses) were found sufficient to detect an effect size of 1.82, a power of 0.8, a two-sided hypothesis test, and a significance level of 0.05. Sample size was calculated using G*power program, Germany**.**

Variables

Preoperatively, all patients had to have posterior maxillary alveolar ridge height less than 4 mm on the preoperative CBCT to be included in the study. Patients with history of previous sinus augmentation surgery, sinus infection, any systemic disease that might compromise normal bone healing, any local pathosis or bone marrow disease were excluded.

Preoperative panoramic radiograph was ordered for patients to exclude any local pathosis at the surgical intraoral site to check eligibility. Prophylactic antibiotic was prescribed the day before and one hour before surgery for eligible patients.

Random numbers were generated electronically using (www.randomizer.org) by the senior investigator who wasn't directly involved in the trial. The generated numbers were then saved in sealed envelope for later patient allocation by the main investigator. The eligible ten patients were then equally assigned into two groups: study group where sinuses were augmented with BMAC loaded on DBB and control group, where they augmented with DBB only.

Bone marrow aspiration & concentration method

For the study group and under strict aseptic conditions, the BM harvest site was swabbed with 10% betadine then 70% alcohol and draped. Under field block local anesthesia (Articaine 4% including 1:100 000 epinephrine BM was aspirated from the AIC **Abla et al., 2008**.

A stab incision down to the periosteum of the anterior superior iliac spine (ASIS) was performed. Once the proper angulation was achieved (medial and caudally), the bone marrow needle (gauge 15) was advanced through the incision site till contacting bone. A clockwise-counterclockwise, back and forth turning motion while maintaining gentle forward pressure through the bone Trabeculae and monitoring patient response was performed.

Once the marrow cavity was reached, the stylet was removed and a 20 cm pre-heparinized syringe was attached to the end of the aspiration needle and 10 ml bone marrow was aspirated. Slight repositioning of the aspiration needle was performed for each 10 ml BMA to access different areas of cancellous bone marrow utilizing the same cortical access hole.

An average of 30 ml bone marrow was aspirated and transferred from the syringes to be collected in 2 (15 ml) pre-heparinized falcon tubes. Then, centrifugation at 2800 rpm for 15 min for concentration of the BMA was followed. The superficial clear layer was discarded and the intermediate layer buffy coat (mononuclear cell fraction, MNC-F) was aspirated, recentrifuged at the same parameters to obtain the cell pellet (Fig. 1).

Sinus floor augmentation

For both groups and following antiseptic mouth rinse (chlorohexidine gluconate 0.1% for 3 minutes) and under local anesthesia (Articaine 4%, 1:100 000 epinephrine), full thickness, two Incision line flap was elevated on the buccal side **Tartaglia**, **et al., 2021**. On maxillary surface, the lateral antrostomy window was delineated with a small round diamond bur under copious irrigation. The sinus membrane was inspected for tears then elevated carefully using sinus elevation curettes of different angulations along the floor, lateral and medial wall of the sinus. (**Fig.** 1). For control group, DBB (Tutobone ®) only was utilized for augmentation of the sinus floor while for the study group, the obtained cell pellet was loaded on the bovine graft (DBB) before sinus augmentation.

In both groups, the osteotomy window was covered with platelet rich fibrin (PRF) membrane which was prepared by 20 cc venous blood sample collection from antecubital vein and its centrifugation at 3000 rpm for 10 minutes [**Xu et al., 2021**]. The PRF membrane was stabilized with periosteal sutures and flap was then repositioned and sutured in an interrupted fashion.

Patients were instructed to follow strict oral hygiene measures and avoid any positive or negative pressure on the nasal cavity. Postoperative antibiotic (Clindamycin 300 mg cap., 3td for 1 week) & analgesic (Ibuprofen 400 mg cap., 3td for 3 days, then PRN) were prescribed for oneweek post-operative, then patients were recalled on regular follow up intervals (immediate/ 2 days, 1 week,1 month and monthly for the remaining 3 months) to assess surgical site healing.

Post-operative radiographic height assessment

CBCT scans were requested immediately and 4 months postoperatively. The same CBCT machine with the same exposure parameters (0.7mm Cu, 120kv, 5.0mA, 12.0s, 388mGy.cm^2) were utilized to standardize measurements. Images were reconstructed using Mimics software (version 21, Materialize, Leuven, Belgium) to evaluate graft consolidation, existence of any biologic complication, height of new bone formation and surgical guide fabrication at 4 months.

Newly formed (NF) bone height was measured from the crest of the ridge to the sinus floor on the coronal cuts of 4 months radiograph. The coronal orientation line was adjusted mesial, distal and at the middle of the graft on the axial and sagittal cuts. The average of all measurements was recorded for statistical analysis. (Fig. 2) Measurements were performed by senior investigator who was blinded to patient' group assignment. Radiographic height assessment was performed by M.H. who was blinded to the surgical procedure.

Core biopsy& implant placement

After 4 months and under the same aseptic conditions, local anesthesia was administered. Following conservative flap elevation. A surgical guide was used initially to mark the biopsy site using the trephine bur. Core biopsy specimens were harvested under copious irrigation and speed of 600 rpm from the grafted (proposed implant) site using a trephine bur (3mm external diameter). The specimens were transferred in 10% formalin for histological analysis. Dental implants were then installed and the flap was repositioned and sutured. Four months after implant installation, the final prosthesis was completed.

Histological processing

After specimens were fixed in formalin, specimens were then decalcified in 10% ethylene diamine tetra-acetic acid (EDTA) for 4-5 weeks. After the decalcification was completed, specimens were then dehydrated in ascending grades of alcohol, cleared in xylol, embedded in paraffin blocks and were cut into sections of 4-5μ thickness, mounted on glass slides and stained by Hematoxylin and Eosin (H&E) stain.

Data analysis:

Data were expressed as mean and standard deviation (SD). 2 samples independent t-test was used to assess significance between groups. The significance level was set at $p < 0.05$. Statistical analysis was performed with SPSS 18.0 (Statistical Package for Scientific Studies, SPSS, Inc., Chicago, IL, USA) for Windows.

RESULTS

Radiographic results

Preoperatively, the mean residual alveolar bone height± SD in BM aspirate groups was (4.14±1.248), while in control group was (5.018±1.013). The mean postoperative alveolar bone height ±SD for control group was (10.10±2.46), while for BM aspirate was (13.34±2.76). Paired T test revealed a significant increase in alveolar bone height postoperatively as compared to preoperative bone height in both control and BM aspirate groups (P<0.05). While no significant difference was detected between groups regarding alveolar bone height postoperatively (P=0.06) **(Table 1).**

Histological results

Histological examination of control group revealed newly formed irregular, bone trabeculae, separated by wide bone marrow spaces, areas of woven bone with wide osteocytic lacunae, and graft material remnants were observed. Higher magnifications showed heavy chronic inflammatory cells infiltration. Several Howship's lacuna and intact layer of osteoblasts indicating bone remodeling could be seen (Fig. 3). Similarly, histological examination of the study group revealed the presence of wide bone marrow spaces with interspersed newly formed bone trabeculae, woven bone with wide osteocytic lacuna was observed. Remnants of material were also detectable. Higher magnifications showed signs of bone resorption and Howship's lacuna, in addition to osteoblasts denoting active bone remodeling. Few chronic inflammatory cells were detectable (Fig. 4).

TABLE (1) Descriptive statistics and comparison between groups radiographic alveolar bone height (independent T- test).

PARAMETER	GROUP	MEAN	STD. ERROR	MIN	MAX	P VALUE
ALVEOLAR BONE HEIGHT	Control	10.10±2.46	1.00	7.43	13.52	0.06
	BM aspirate	13.34±2.76	1.13	10.06	17.35	

Significance level P<0.05, *significant ***Means with different superscript letters are significantly different.***

Fig. (1) Sinus augmentation for study group A) The BM aspiration needle advanced into the cancellous bone of AIC & 20 ml plastic syringe is attached for aspiration B) BMA is collected C) Following centrifugation to concentrate the BMA with buffy coat in the middle (arrow) D) Creation of the lateral osteotomy for sinus augmentation E) BMAC mixed with DBB F) Sinus augmentation with BMAC/ DBB

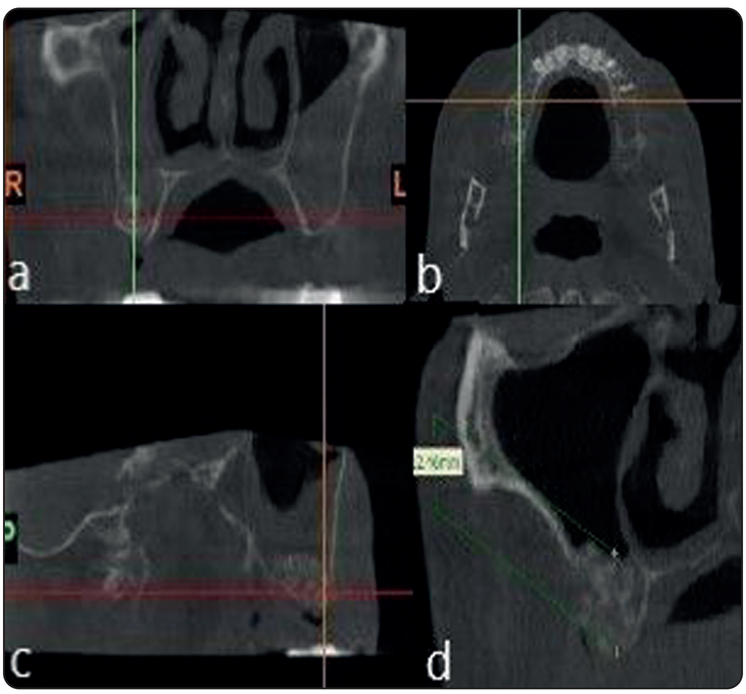

Fig. (2) CBCT image revealing orientation line is adjusted on the Cross-sectional views A) Coronal B) Axial C) Sagittal D) Measuring the height on the coronal cut at 4 months postoperative

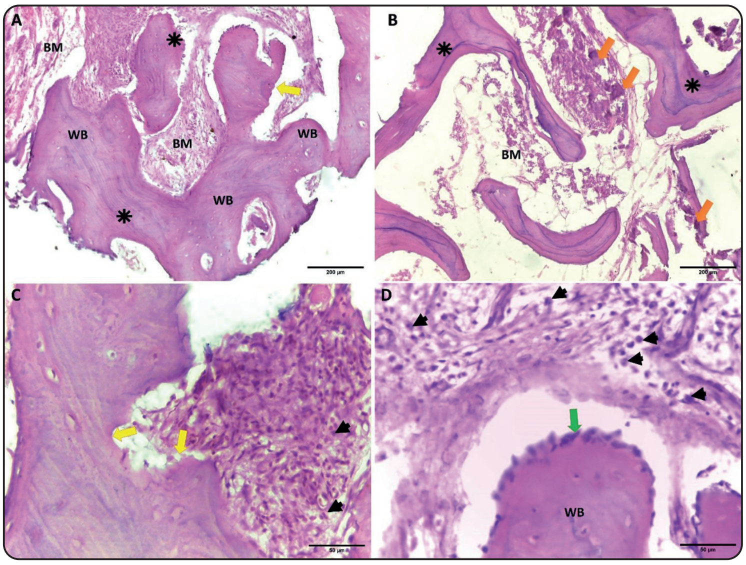

Fig. (3) Light microscopic picture of the control group showing newly formed bone trabeculae (asterisks), bone marrow spaces (BM), remnants of material (orange arrows), chronic inflammatory cells (black arrows), areas of woven bone (WB) showing wide osteocytic lacunae (WB), intact osteoblastic layer (green arrows) and Howship's lacuna (yellow arrows) (figures A&B original magnification x10, figures C&D original magnification x40).

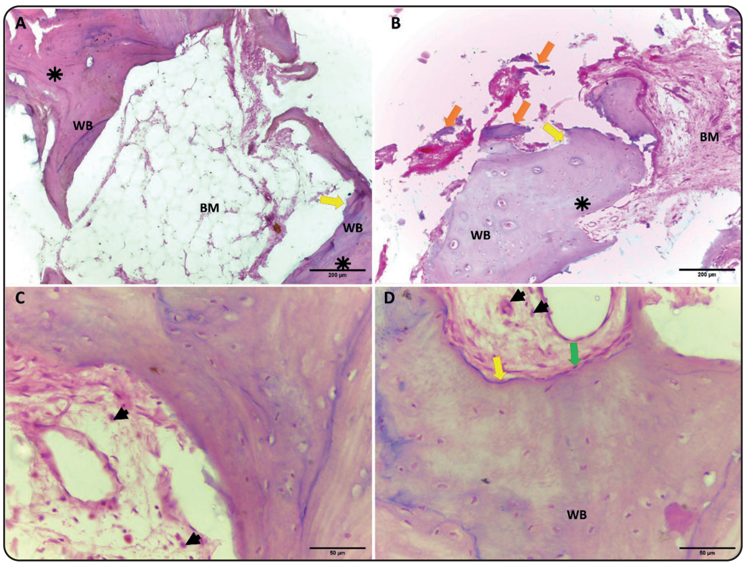

Fig. (4) Light microscopic picture of the study group showing newly formed bone trabeculae (asterisks), bone marrow spaces (BM), remnants of material (orange arrows), few chronic inflammatory cells (black arrows), areas of woven bone (WB) showing wide osteocytic lacunae (WB), intact osteoblastic layer (green arrows) and Howship's lacuna (yellow arrows) (figures A&B original magnification x10, figures C&D original magnification x40).

DISCUSSION

Posterior maxillary rehabilitation is a challenging procedure with a lot of variations regarding the suitable surgical technique or the ideal grafting material for reconstruction. The current study was conducted to assess the application of BMAC loaded on bovine bone graft for SFE compared to bovine bone graft which is the most commonly used bone substitute for grafting procedures.

BMAC was selected as it represents a concentered and safe source of MSCs (that provide an osteogenic potential for the graft) compared to BMA and osteogenically differentiated MSCs obtained from culture respectively (**Ting et al., 2018 & Kadry et al., 2021**). In the present study, chair-side BM aspiration and concentration required an average of ten and thirty minutes respectively. The patients' response to BM harvesting from AIC under local anesthesia ranged from negative to mild discomfort. Pain-free harvest was guaranteed via analgesic premedication, profound local anesthesia (subcutaneous & periosteal) and controlled advancement of BMA trocar to the cancellous bone from the periosteal aspiration site while monitoring patient response.

Coverage of the lateral antrostomy window represents a critical factor for bone formation and avoidance of soft tissue proliferation into the sinus cavity, hence increasing the chances of bone formation (**Oliveira et al., 2012**). It has been documented that utilization of barrier membranes has a positive effect on bone formation (**Tarnow et al., 2000**). In the present study, PRF membrane was used to cover the osteotomy window. It was fixed with periosteal sutures to ensure stabilization of the membrane during initial healing and to hinder the intrusion of unwanted fibrous tissue into the sinus cavity.

The Mechanism of the bone formation in the sinus is not fully clear. Schneiderian membrane is the key role for bone formation and the bone gain is not affected by the type of grafting material utilized as it has osteogenic potential which is the main concept behind bone formation in guided tissue regeneration. The sinus mucosa constitutes important source of bone-forming cells as it contains mesenchymal progenitor cells (**Falah et al., 2016**). That is true and effective for immediate Maxillary rehabilitation with dental implants when minimum alveolar ridge height is more than 4 mm. However, grafting only as a first stage Surgery is necessary in case of severely atrophied ridge (less than 4 mm) with subsequent delayed (secondary stage) implant rehabilitation (**Lyu et al.,2023**).

Having bone that contains osteoprogenitor cells and is osteoinductive and osteoconductive with simultaneous avoidance of donor site morbidity was of prime concern in the current study. As volumetric stability of the space created beneath the elevated membrane represents one of the most critical factors that affect the quantity of NBF, the use of DBB helps to maintain the height of the sinus membrane due to its slow resorption rate (**klijn at al., 2010**).

In the present study, BMAC was used as a source of mesenchymal stem cells to provide osteogenic potential of the selected autograft alternative. At the same time, DBB provided a stable scaffold along which angiogenesis and osteogenesis can occur.

BM derived MSCs possess a multi-lineage potential to different mesenchymal tissues with the highest osteogenic differentiation potential and hence the most frequently used compared to other stem cells sources (**Xu et al.,2017**).

Regarding selection of BMAC rather than MSCs obtained from culture methods; the latter option was intentionally avoided as it adds additional lag period of MSCs isolation and culture (additional average of one month) (**Tondreau, et al., 2004**). Therefore, concentration of BMA was selected as it's a closed, time saving method in comparison to the open method of laboratory MSCs isolation and culture. Utilization of BMAC loaded on xenograft material for SFA has been documented in few clinical trials with vast heterogeneity **Sauerbier et al., 2010, Sauerbier et al., 2011, Payer et al., 2014 Wildburger et al., 2014, Pasquali et al., 2015, de Oliveira et al.,2016, pelegrine et al., 2016.** Study conducted by **Sauerbier et al., 2011** utilized different control group from the present study, being a mixture of bovine graft and autogenous bone.

Moreover, the BM source differed from the present study, represented by tibia as it could be performed chair-side with no need for even sedation as conducted by **Payer et al., 2014.** PIC was preferentially selected in the remaining studies owing to its high cellularity, non-weight-bearing location, and distance from vital organs.

AIC was chosen in the current study as a source of BM-MSCs as it has proved to be a rich source compared to anteromedial surface of tibia (**Ting et al., 2018**). Moreover, BMA from AIC is accessible and convenient under local anesthesia at the outpatient clinic compared to PIC **Abla et al., 2008.**

In the present study, the bone quantity was verified by CBCT while its quality was verified by histological examination. Using BMAC to enhance bovine grafting material was found to be cost-effective and time-saving when compared to other grafting materials or titanium meshes used in other studies. Histological evaluation of core biopsies obtained from the grafted sinuses were the primary outcome of the current study that coincides with that of the forementioned trials.

In the current study, the follow up period was 4 months which was within the healing period of autogenous bone (4-6 months) (**Pasquali et al., 2015**). On the other hand, despite the healing period of xenografts between 6 to 8 months, this was expected to decrease with the addition of cell source that would help graft consolidation and speed up new bone formation.

Follow up of the previous similar studies ranged from 3 to 6 months. **Only Sauerbier et al., 2011** evaluated core biopsies at 4 months post-operative.

In previous studies, BMAC increased viability of the graft with subsequent concomitant enhanced neovascularization, faster new bone formation and rapid graft resorption and bone turnover. However, lack of standardization of time frame with the reminder of studies prohibited the correlation of results of the present study with theirs'.

Residual alveolar height has been documented to be the most determining factor for implant survival and successful maxillary rehabilitation via sinus floor elevation **Rosen et al.,1999**. Therefore, NFB height was also assessed in the present study. At 4 months, there was non- significant difference of NFB height between the studied groups. Unfortunately, NFB height was not one of the outcome measures of the former similar studies to correlate with.

Relatively short follow up period is from the limitations of the current study. Hense, extended follow up period with larger sample are suggested for future research.

CONCLUSION

Results of the current research revealed that quantity of bone yielded by BMAC/ DBB augmentation are comparable to that yielded by DBB. Chair-side BMA harvesting from AIC and concentration is minimally invasive and feasible under local anesthesia to be performed as a routine in the everyday practice.

Declarations

Competing interests

Authors declare no conflict of interest

Funding

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Ethical approval

It was provided by the institutional ethics committee of the faculty of dentistry, Cairo University, Cairo, Egypt (IRB no.: 7 10 22)

Data availability

Data supporting the findings of current research are available within the article. Raw data are available from the corresponding author upon reasonable request.

Patient consent

All patients provided a written informed consent

Authors' contributions

All authors W.K., H. E, I. A, M. H. planned the project. M.H. performed randomization. All authors contributed to data acquisition, interpretation and writing of the manuscript. H.E, W.K. performed the surgical intervention. I. A. performed the histologic analysis of core biopsy specimens. All authors revised and approved the final version of manuscript.

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