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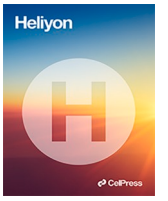

Research article

Effect of buccal fat autotransplantation on improving the alveolar socket bone regeneration: An in-vivo study☆

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ABSTRACT

Background: There are various materials used for socket preservation following dental extraction. The aim of the present animal study was to histologically investigate the efficacy of buccal fat autotransplantation on alveolar bone regeneration following dental extraction.
Study design: In this prospective, double-blind laboratory experiment with a split-mouth design, 16 mandibular second premolar teeth in eight beagle dogs were extracted, and half of the extraction sockets were randomly filled using buccal fat autotransplantation. Other samples were left untouched to heal normally by the formed blood clot. Buccal fat autotransplantation was the primary predictor variable, and the type and amount of newly formed bone were the primary outcome variables. Assessment methods were the H & E coloring technique and histomorphometric evaluation. The significance level was set at 0.05, and data was subjected to Chi-Square and Wilcoxon signed-rank tests using SAS statistical software version 9.4.
Results: From the total number of 16 samples in 8 dogs, 50% of the samples in the intervention group represented inflammation with lower intensity compared to 33% in the control group; however, this difference was not considered statistically significant (Chi-Square test, P-value = 0.55). Wilcoxon test results showed no statistically significant difference between the two groups regarding the mean amount of total bone formation (Z = 0.00, P-value = 1.00).
Conclusion: It was inferred from the outcomes of the present study that when compared to the normal healing of the socket, buccal fat autotransplantation did not represent with superior outcome concerning the socket bone regeneration.

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1. Introduction

Alveolar bone resorption is an inevitable consequence of tooth extraction [1]. Alterations and resorption of the alveolar crestal bone result in bone deformity, especially in the mandibular buccal bone [2]. Bone loss in the first six months following the tooth extraction is extremely significant in a way that up to 40% of the height and 60% of the width of the alveolar bone could be lost [3]. These morphohistologic alterations may interfere with future treatment plans, including dental implants [4].

Although the exact amount of bone loss under different circumstances might not be predictable, some evidence supports the idea of the positive effects of ridge preservation on maintaining the ridge dimensions and improved socket healing following dental extractions [5]. However, this has remained a controversial issue among clinicians, and there are several studies available reporting contradictory results in this regard.

Thakkar et al. [6] implemented a clinical trial on extraction sockets of 36 single-root teeth. In the intervention group, Demineralized Freeze-Dried Bone Allograft (DFDBA) plus Platelet-Rich Fibrin (PRF) was placed into the extraction socket, followed by a collagen membrane to cover the material. In the control group, however, DFDBA was the only material used for filling the extraction socket, covered with a collagen membrane. After six months, vertical and horizontal alveolar bone loss was measured. Despite the positive effect of PRF in reducing bone loss, differences in vertical and horizontal alveolar bone loss between the two groups were not considered statistically significant ($P = 0.056$).

On the other hand, a six-month postoperative evaluation of the application of PRF and β-Tricalcium Phosphate (β-TCP) [7] for socket preservation showed a statistically significant difference in bone loss between the two groups (P-value = 0.001) and superiority of β-TCP, while bone formation quality was reported to be higher in PRF group.

Despite the vast number of evidence evaluating various materials and techniques for alveolar ridge preservation and bone regeneration [8–11], the buccal fat might be considered an appropriate autologous source for intraoral tissue regeneration [12]. Furthermore, buccal fat grafting has been suggested for pulp tissue regeneration in immature permanent teeth [13] and maxillofacial reconstructions, including maxillary sinus lift and closure of the oroantral fistula [14], reconstruction of bony defects [14], and periodontal regeneration [15].

The buccal fat pad has also been used for primary closure of the augmented site and improving soft tissue thickness, as well as preventing soft tissue dehiscence [16]. Moreover, Free fat graft harvested from Buccal Fat Pad (BFP) has been used for the management of peri-implant lesions, and promising functional and aesthetic outcomes have been reported in this regard [17].

Regarding the potentiality of stem cells of adipose tissue for differentiation into osteoblast cells and possessing the growth factors required for stimulation of the differentiation process, Adipose tissue can act as a natural scaffold to provide an ideal environment for proper proliferation and differentiation of these stem cells; thus, it is claimed that buccal fat pad has all three osteoinductive, osteoconductive, and osteogenic characteristics required for bone regeneration in the extraction socket. Adipose tissue is rich in Mesenchymal Stem Cells (MSCs). Stem cells isolated from the buccal fat (ADSCs) have self-renewal ability and can differentiate into different lineages of mesenchymal tissue [18]; Various studies have shown that the total number of extracted ADSCs is significantly (100–500 times) higher than stem cells extracted from a similar volume of bone marrow [19]. Also, Bondarava and colleagues [20] showed that adipose tissue stem cells could differentiate into bone in a three-dimensional culture medium.

Khojasteh and Sadeghi [21] utilized BFP accompanied by an iliac bone graft in the block form for the reconstruction of the severe atrophic alveolar process of the jaw. The outcomes of their study showed that the application of BFP increases new bone formation and decreases secondary bone loss.

The application of buccal fat in combination with other biomaterials for socket preservation following dental extraction and bone regeneration has been well-studied in recent years [22,23]; however, the reported results could not be interpreted as the net effect of the buccal fat itself due to the pedicled nature of the graft or accompanied regenerative materials. Regarding various factors affecting the healing process of the extraction socket, there is still no consensus over the beneficial application of buccal fat autotransplantation in improving the clinical and histologic outcomes of ARP compared to the gold standard materials used in intervention for this purpose [24,25].

A combination of a 3D-printed scaffold loaded with Adipose-Derived Mesenchymal Stem Cells (AD-MSCs) has shown improvement in the regenerated bone volume from 18.6% to 28.7% in a 3-month follow-up period. Histologic evaluation reported a lower possibility of fibrous encapsulation of the scaffold and a higher rate of bone formation as a result of adding AD-MSCs in the polycaprolactone–tricalcium phosphate PCL-TCP scaffold [26].

Therefore, concerning the above-mentioned advantages and positional superiority of buccal fat over adipose tissues of other sources (lower risk of infection, better access, and lower cost), the present animal study aimed to perform a histologic evaluation of alveolar socket bone regeneration following application of buccal fat compared to the normal healing of the socket with a blood clot.

2. Material and methods

Study design: To address the research hypothesis, the investigators designed and implemented a double-blind animal study with a split-mouth design in the *Animal Lab* of *the Dental Research Institute* of *Isfahan University of Medical Sciences* in Iran, between January and February 2022. The present study was carried out in accordance with the Arrive Guidelines. Neither the pathologist nor the data analyzer was aware of the type of intervention on each side. Type of intervention on each side-which was encrypted as "*A = Fat Autotransplantation*" and "*B= Normal Healing*"-was only disclosed after the data was analyzed. This study was approved by the Regional Bioethical Board of Isfahan University of Medical Sciences on *January* 10th*, 2022 (IR.MUI.RESEARCH.REC.1400.419)*.

Sample size: The study population was composed of 16 mandibular second premolar teeth of eight beagle dogs between the ages of

2–3 years old randomly allocated to case and control groups using online computer software (*http://www.randomization.com*), which provided a randomized order for application of buccal fat autograft on the left or right side for each dog. Calculation of the sample size was done using the formula for comparison of two means with a significance level of 0.05, and minimum difference of 1.4 in the mean amount of bone formation in two dependent groups.

2.1. Study variables

- Primary predictor variable: Buccal fat autotransplantation
- Primary outcome variables: The type and amount of newly formed bone by calculating the mean number of osteoclast cells as well as the mean number of empty lacunas with no osteocytes inside (8–10 empty adjacent lacunas) in five separated microscopic fields with no overlap and the 40 × magnification
- Secondary outcome variables:

1. Cellular inflammatory response, including the type and intensity of the inflammation (by calculating the mean number of lymphoplasmacytic in five separate microscopic fields without overlap from the alveolar bone surrounding the extraction socket with the 40 × magnification)
2. Soft tissue alterations, including necrosis and hyperemia (by calculating the mean number of vessels defined as the number of arterioles in five separate microscopic fields without overlap with the 40 × magnification)

Inclusion criteria: To be included, young Beagle dogs between the ages of 2–3 years old with sixteen bilateral mandibular second premolar intact teeth with no sign of gingival diseases underwent minimally traumatic dental extraction. Presence of any kind of infectious and/or non-infectious diseases, including Rabies, Parasitic, and fungal diseases, as well as infection arising from tooth extraction, extensive bone resorption in the extraction socket, traumatic tooth extraction, and exposure of socket and extrusion of the grafting material were considered exclusion criteria.

Animal housing/conditions: Animals were kept in separate cages while ideal environmental conditions, including air conditioning, diet control, availability of water, and medical and health facilities were provided. A veterinary expert monitored dogs on a daily basis. Vaccination and providing the antiparasitic drugs were completed prior to study implementation. Dogs were kept in an animal shelter following the completion of the experiment. All dogs went through a health examination by a veterinary expert; the vaccination plan was completed, and animals received antiparasitic drugs. Animals were isolated before implementing the research.

Surgical intervention: Anesthesia was induced using Ketamine 10 mg/kg and Acepromazine 1%, 0.02 cc/kg administrated by Intravascular route. Animals were then intubated followed by maintenance of the anesthesia using Isoflurane. Tramadol 10 mg/kg was administered during anesthesia every 8 h and three days postoperatively to provide analgesia. Next, prepping and draping were done. Sectioning of the tooth in the furcation area was done using a surgical bur, and each root was extracted using a surgical elevator and forceps. An experienced surgeon performed all surgical extractions of the teeth. In the control group (n = 8), normal socket healing took place by blood clots filling the socket, and no material was placed into the extraction socket. In the intervention group (n = 8), on the other hand, the buccal fat was isolated and filled the extraction socket to the crestal edge of the bone. Buccal fat pad isolation was done using the following sequence.

1. Mepivacaine 3% was administered to provide local anesthesia
2. A flap was released in the depth of the maxillary vestibular area to provide access to the fat pad
3. Isolation of the fat pad and rinsing with sterile saline was done
4. Copious rinsing of the surgical site and flap was performed
5. Wound closure was done using interrupted Vicryl 4-0 suture
6. Sterile gauze was applied to establish hemostasis.

Afterward, flaps were released to the coronal direction to provide full coverage of the filling material and then sutured using Vicryl 4-0 suture material (Supabon, Supa Company, Tehran, Iran). Ceftriaxone 25 mg/kg was administered intravenously every 12 h for one week in order to prevent infection. Besides, a soft diet was considered for proper healing of the soft tissue and prevention of traumatic injuries to the surgical site.

Data collection methods: Four weeks postoperatively, the second stage of the surgical procedure was done using trephine bur for excising the healed socket bone for histologic and histomorphometric evaluations. For this purpose, samples provided from the healed sockets were cut buccolingually and kept separately in bottles labeled with the recorded information, including the location (left or right side), the ID number of the dogs, and the type of intervention for socket preservation (Buccal fat autotransplantation Vs. Normal healing of the socket). Samples were then fixed using buffered Formaline 10% for 72 h. After the decalcification process using Chloridric Acid 8% and Formic acid, the paraffin blocks of the samples were provided, and the pathologist made serial sections with a width of 6 μm in a buccolingual direction. For each sample, two lamels were prepared and colored using the H & E coloring technique. Cellular inflammatory responses, including the type and severity of the inflammation (by counting the number of inflammatory cells) as well as soft tissue alterations, including necrosis and hyperemia (by counting the number of blood vessels), and the type of newly formed bone were studied by the pathologist using an optical microscope (Olympus, Tokyo, Japan).

Finally, the calculation of the percentage of the newly formed bone was done by the pathologist colleague using Adobe Photoshop Software (San Jose, CA, USA) for histomorphometric evaluation. The number of pixels of the entire image followed by the percentage of newly formed bone was calculated according to the ratio of bone pixels to the entire image pixels.

Data analyses: 'The Shapiro-Wilk Test of normality showed that the quantitative bone variables had no normal distribution; therefore, regarding the small sample size of six dogs (providing 12 histologic samples), nonparametric tests were used for these variables.

Data was subjected to the descriptive analysis, *Chi-Square*, and *Wilcoxon signed-rank* tests performed with SAS statistical software version 9.4 (SAS Institute, Cary, NC, USA). The threshold for statistical significance was set at a P-value of 5%.

3. Results

Of the total number of 8 dogs, one dog (ID #4) expired during the executive phase of the study, and samples of dog #8 were devastated during the decalcification process for histopathologic evaluation.

The overall rate of inflammation was lower in the intervention group compared to the control group; however, considerable changes in the percentage due to the small sample size should also come into consideration, and variable count seems to be a better index to be reported in this case (Table 1).

A greater number of samples represented inflammation with higher intensity in the control group compared to the intervention group; however, severe inflammation was detected neither in the case nor in the control groups (Fig. 1). Similarly, considerable changes in the percentage due to the small sample size should also come into consideration, and variable count seems to be a better index to report in this case (Table 2).

Proportions of the bone in the newly formed tissue in the extraction socket as well as proportions of the lamellar and woven bones are reported in Table 3 (Fig. 2).

Tissue necrosis was seen in none of the samples (n = 0) neither in the normal healing group nor in the fat autotransplantation group.

Chi-Square test results showed no statistically significant difference concerning the type of inflammation between the intervention and control groups (P-value = 0.51); similarly, no statistically significant difference was detected between the two groups regarding the intensity of the inflammation (Chi-Square test, P-value = 0.55).

There was no statistically significant difference reported between case and control groups concerning hyperemia (Wilcoxon Signed-Rank test, Z = −0.55, P-value = 0.56). Similarly, there were no statistically significant differences between the two groups concerning the amounts of the newly formed bone (Wilcoxon Signed-Rank test, P-values >0.05) (Table 4).

4. Discussion

The purpose of the present study was to evaluate whether the application of buccal fat autotransplantation would result in improved socket regeneration compared to normal healing of the socket with the blood clot. The outcomes showed no statistically significant difference in the mean amount of newly formed bone in extraction sockets healed with buccal fat autotransplantation compared to the normal healing with the blood clot.

Considering soft tissue alterations, the overall rates of inflammation occurrence and severity were lower in the intervention group; however, differences were not considered statistically significant.

In a study by Ethan et al., it was reported that the type of material or method of surgery used for mild to moderate defects did not differ statistically significantly concerning the hard tissue aspects of the extraction sockets [27]. Similarly, In a study by Friedmann and colleagues, it was shown that the amount of bone volume formed in extraction sockets filled with bone grafts did not demonstrate a statistically significant difference from those non-contained sockets, and they showed that mere application of ribose cross-linked collagen membrane would suffice for the following healing process [28]. These findings support the outcomes of our study regarding the fact that the normal healing process of the extraction socket with a blood clot in small-size defects and healthy animals would probably suffice, and there might not be a necessity for the application of grafting materials in such cases.

The effects of the application of soft tissue grafting materials on improving bone regeneration have also been well-studied. Recent evidence has shown that conventional hard-tissue grafting biomaterials are no longer considered the only viable options, and soft tissue grafting materials could be considered a good choice due to their proven efficacy and easy application in addition to cost-effectiveness. Buccal fat and its combinations have recently come into consideration for clinical applications by clinicians. Takedachi and associates [29] studied the periodontal regenerative effects of autologous adipose tissue-derived progenitor cells in patients with severe periodontitis and reported a promising impact in this regard; on the contrary, the result of our study does not support their results, which could be justified by the compromised periodontal apparatus and human species in Takedachi's study samples versus

Table 1
Frequency distribution of the type of inflammation in two groups.

			Intervention		Total
			Fat	Normal Healing	
Inflammation Type	**No inflammation**	Count	2	1	3
		%	33.3	16.7	25
	Chronic	Count	4	4	8
		%	66.7	66.7	66.7
	Acute-chronic	Count	0	1	1
		%	0	16.7	8.3

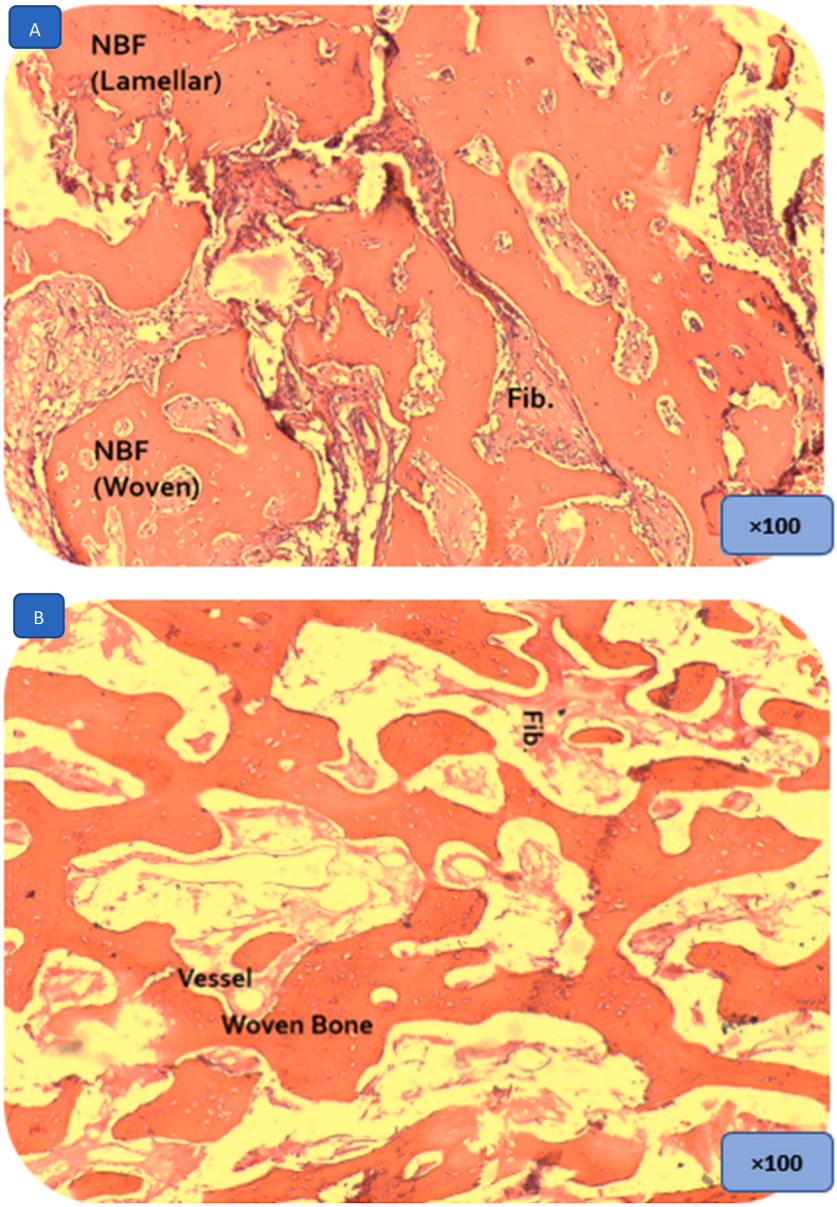

Fig. 1. Histologic evaluation - A: Control sample; B: Case Sample.

Table 2
Frequency distribution of the intensity of inflammation in two groups.

			Intervention		Total
			Fat	Normal Healing	
Inflammation Intensity	**Mild (<30 cells)**	Count	3	2	5
		%	50	33.3	41.7
	Moderate (30 to 60 cells)	Count	3	4	8
		%	50	66.7	58.3
	Severe (>60 cells)	Count	0	0	0
		%	0	0	0

Table 3
Mean and Standard deviation of the amount of newly formed bone in two groups.

Intervention		Total_bone (%)	Total_Lamellar (%)	Total_Woven (%)	Pure_Lamellar (%)	Pure_Woven (%)
Fat	**Mean**	44.17	21.41	22.75	34.17	65.83
	SD	12.00	8.93	11.32	6.64	6.64
Normal healing	**Mean**	44.17	24.83	19.33	35.00	65.00
	SD	4.91	10.24	6.43	7.74	7.74
Total	**Mean**	44.17	23.12	21.04	34.58	65.42
	±SD	8.74	9.33	8.95	6.89	6.89

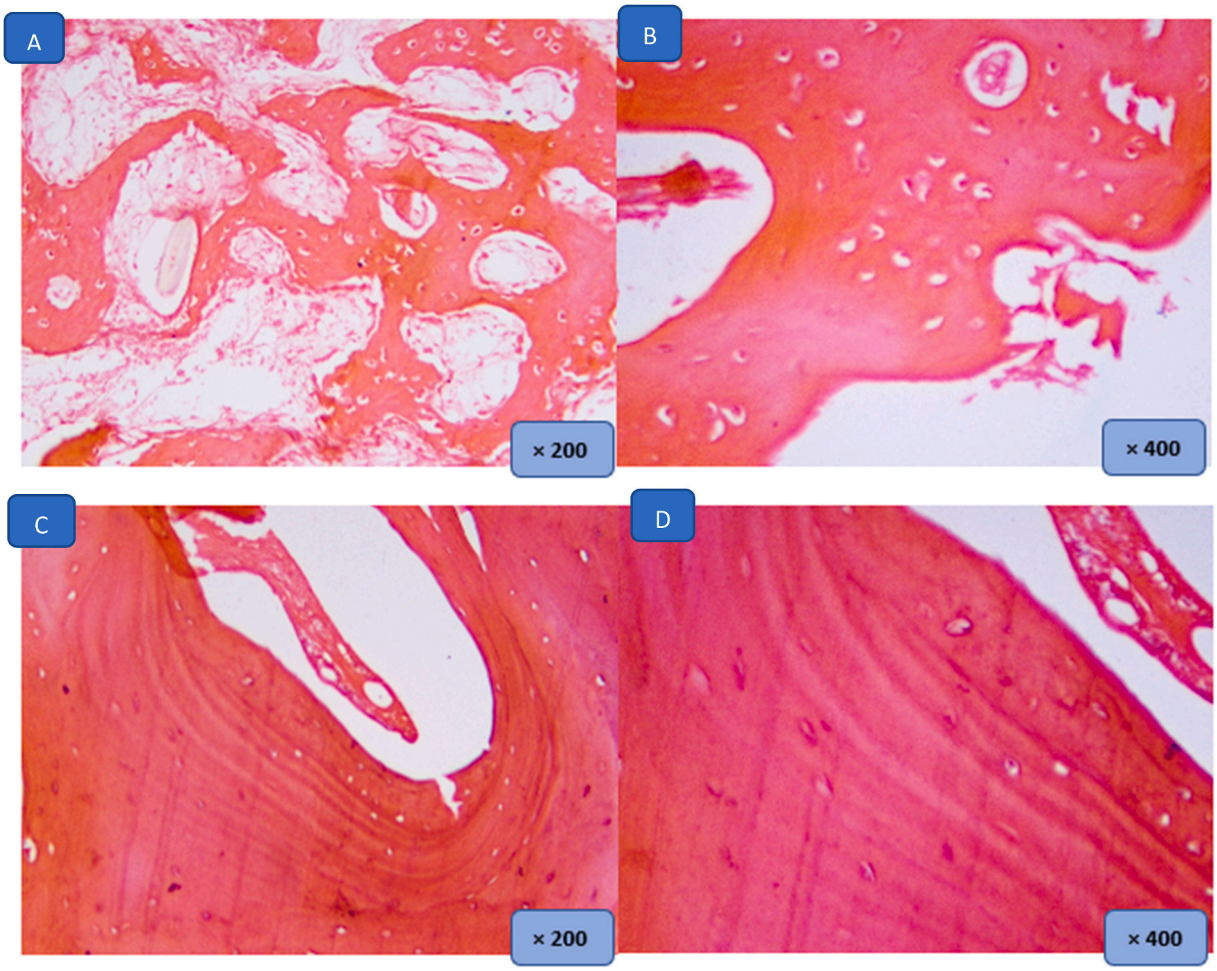

Fig. 2. Histologic evaluation of NBF of a case sample – A, B: Woven Bone; C, D: Lamellar Bone.

Table 4
Results of the Wilcoxon test regarding the evaluation of the differences between the case and control group concerning bone formation variables.

	Normal_TOTAL_bone Fat_TOTAL_bone	Normal_TOTAL_Lamellar Fat_TOTAL_Lamellar	Normal_TOTAL_Woven Fat_TOTAL_Woven	Normal_PURE_Lamellar Fat_PURE_Lamellar	Normal_PURE_Woven Fat_PURE_Woven
Z	0.00 [a]	−0.13 [b]	−0.31 [c]	−0.41 [c]	−0.41 [b]
P-value	1.00	0.89	0.75	0.68	0.68

[a] The sum of negative ranks equals the sum of positive ranks.
[b] Based on positive ranks.
[c] Based on negative ranks.

intact metabolic and immunological characteristics in our animal samples. Moreover, in our study, histomorphometric evaluations were performed alongside the clinical assessment as opposed to the mere clinical examination in Takedachi's study.

Similarly, Bone morphogenetic protein-2 (BMP-2)-loaded decellularized human adipose tissue matrix demonstrated to have bone regeneration features in calvaria defects in rats and is recommended for critical-sized bone defects when the insufficient supply of grafting material is the issue [30]. Besides, in a study by Lee and colleagues, the utilization of pedicled buccal fat flap in large-size defects in the posterior mandible due to the surgical excision demonstrated promising outcomes and was suggested as a convenient and reliable method for reconstruction of such defects [31]. Furthermore, the Buccal fat and included stem cells are considered an ideal tool for maxillofacial surgeons for the reconstruction of the full-thickness bony defects in the maxilla and mandible due to the pathologic lesion and faster bone regeneration as well as higher bone density and better bone trabecular formation alongside well-organized and well-vascularized lamellar bone all of which resulting in superior functional and aesthetic outcomes [32]. Contradictory results of our experiment might be justifiable by the different sites of surgery, nature of the defect, various forms of autologous fat with a controlled and higher number, the concentration of stem cells and other effective ingredients, and considerably larger defect size in these studies.

Additionally, the application of stem cells of BFP combined with bioceramics is shown to be effective in critical-sized mandibular defects in both healthy and osteoporotic rats [33]. However, the size of the defect and the pure form of stem cells used in this study compared to the defect in the extraction socket and unprocessed form of BFP in our study could explain the different results of our experiment. Moreover, outcomes are controversial in this regard as in an experiment by Dziedzic et al. [34], it was shown that adipose-derived stromal cells (ASCs) do not play a critical role in bone regeneration in periodontal furcation defects since similar results were achieved by the application of Decellularized Human Amniotic Membrane (DAM) alone when compared to the combination of ASCs and DAM. Also, Garcés and colleagues showed insignificant long-term differences in Bone-to-Implant Contact (BIC) between biomaterials coated with particulate β-tricalcium phosphate with a combination of Fibronectin and ADSCs (β-TCP-Fn-ADSCs) and the control group. They concluded that dehiscence-type defects associated with simultaneous implant insertion might not benefit from the application of ADSCs in BIC when compared to other commonly used biomaterials [35]. These results are in favor of our study regarding the fact that autotransplantation of fat does not necessarily lead to superior outcomes concerning bone regenerative aspects of treatment, and defect size might play a significant role in the efficacy of this technique.

Regarding the split-mouth design of the study, more reliable outcomes were achieved owing to the controlled confounding factors. Other confounding factors, including the difficulty of surgery, operation time, and surgeon's experience were also controlled by having just one experienced surgeon performing all surgeries. Nevertheless, this study had some limitations. Increasing the number of samples as well as implementing research on human samples could lead to more comprehensive evaluations of the efficacy of autotransplantation of buccal fat in improving socket healing following dental extraction. Also, the aesthetic drawback of this technique might be a concern in more severe cases in need of more extensive bone regeneration; although aesthetic concerns were not of significant importance due mainly to the fact that only a small amount of buccal fat pad is harvested for such small defect sizes and bilateral harvesting of the buccal fat pad is an option in more extensive cases. Moreover, including other available bone materials in the study design could result in a more comprehensive comparison of the potentials of various materials in alveolar bone regeneration. Also, combining buccal fat with other available regeneration materials might result in more promising outcomes in this regard.

5. Conclusion

It could be inferred from the outcomes of the present study that buccal fat autotransplantation might not significantly benefit small defects, including extraction sockets among perfectly healthy animal samples when compared to the normal healing of the socket with a formed blood clot.

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Data availability statement

Please select why. Please note that this statement will be available alongside your article upon publication. as a follow-up to "Data Availability.

Sharing research data helps other researchers evaluate your findings, build on your work, and to increase trust in your article. We encourage all our authors to make as much of their data publicly available as reasonably possible. Please note that your response to the following questions regarding the public data availability and the reasons for potentially not making data available will be available alongside your article upon publication.

Has data associated with your study been deposited into a publicly available repository?"Data will be made available on request.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Iman Mohammadi: Writing – review & editing, Visualization, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Amir Najafi:** Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Formal analysis, Conceptualization. **Sayed Mohammad Razavi:** Writing – review & editing, Validation, Supervision, Project administration, Data curation, Conceptualization. **Saber Khazaei:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Golnaz Tajmiri:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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