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Fat Graft in Surgical Treatment of Medication-Related Osteonecrosis of the Jaws (MRONJ)

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Abstract: Background: Although the published literature has grown exponentially during the last few decades, managing medication-related osteonecrosis of the jaws (MRONJ) remains challenging. Since the first description of adipose-derived stem cells, cell therapy showed promising perspectives in surgical treatment of MRONJ. In this study, the beneficial effect of fat graft in surgical treatment of stage 2 and 3 MRONJ patients was assessed. Methods: A retrospective analysis of the evolution pattern of the disease was conducted comparing the outcomes of MRONJ patients who underwent sequestrectomy followed by fat graft (n = 9) and those who received sequestrectomy alone (n = 12). Results: Improvement of the disease stage was observed in 77.8% vs. 22.2% cases in group A and B, respectively (p = 0.030); disease stability was documented in 11.1% vs. 25.0% cases in group A and B, respectively (p = 0.603); worsening of MRONJ stage was observed in 11.1% vs. 50.0% cases in group A and B, respectively (p = 0.159). Conclusions: Despite the small sample size, this study suggests that fat graft may represent a promising low-risk and cost-efficient adjunctive therapy in the surgical treatment of MRONJ patients.

Keywords: medication-related osteonecrosis of the jaws; MRONJ; BRONJ; fat graft; adipose tissue graft; adipose-derived stem cells; adipose-derived stromal cells; ASC; ASCs; mesenchymal stem cells

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1. Introduction

Medication-related osteonecrosis of the jaws (MRONJ) represents an unfortunate adverse event that may follow systemic bone-modifying agents (BMAs) or antiangiogenetic therapies in patients affected by solid tumors or osteoporosis. In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) outlined an updated definition based on three essential criteria: (1) current or previous treatment with BMAs or angiogenetic inhibitors, (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the head and maxillofacial region and that has persisted for longer than 8 weeks, and (3) no history of radiation therapies to the jaws or metastatic diseases to the jaws [1]. Although the etiopathogenesis is considered to be multifactorial, inflammatory and infective conditions affecting the jaws or the periodontal tissues seem to represent the far most dangerous risk factors for the development of the disease [1–3].

According with the AAOMS, MRONJ severity is defined combining clinical and radiological findings [1]. Pain referred to the jaws with or without objective radiological modifications of the bony structures, in the absence of macroscopic evidence or exposure of

necrotic bone, should be considered a stage 0 MRONJ. Exposed and necrotic bone or fistulas that probe to the bone in asymptomatic patients (without infections) should be considered stage 1, while the presence of symptoms—such as pain, infections, erythema, purulent drainage—constitutes stage 2 MRONJ. In case these symptoms and signs coexist with the extension of the osteonecrosis beyond the alveolar process, or with a pathological fracture, or with an extraoral fistula, or with the development of oral antral/nasal communication, stage 3 can be diagnosed [1].

Historically, treatment protocols were based on practitioners' knowledge and expertise. In 2019, the Multinational Association of Supportive Care in Cancer (MASCC), the International Society of oral Oncology (ISOO), and the American Society of Clinical Oncology (ASCO) outlined a joined practice guideline based on the AAOMS staging system [4]. According with their comprehensive recommendations, and with the retrieved literature, full mucosal healing above the exposed bone may be considered as an indicator to reflect the resolution of the disease, along with the absence of referred pain and signs of infection. However, this may represent a challenging goal to achieve, as a significant percentage of treated patients typically do not benefit from the received treatments. Moreover, some ongoing controversies exist regarding how the surgeon should decide between a conservative or aggressive treatment [5]. During the last few years, the research in cell therapy revealed interesting perspectives. Mesenchymal stem cells (MSCs) have been proposed as a candidate for MRONJ management due to their capability to differentiate into other mesenchymal tissue, such as bone, cartilage, and adipocytes [6,7]. Adipose tissue represents an abundant source of autologous MSCs, called adipose-derived stem cells (ASCs), which are easy to be harvested and processed [8]. This cell population has been widely investigated since they were firstly characterized by Zuck et al. in 2001 [9], who demonstrated their in vitro differentiation potential. Following the first in vivo investigation by Lee et al. [10], ASCs potential in wound treatment was widely documented [11]. These cells are capable of differentiating into several cell types reproducing ectodermal [12], endodermal [13], and mesodermal [14] tissues to exert numerous paracrine effects on the recipient tissues [15,16] and to modulate the immune system [17]. ASCs are recognized to be ideally suited for regenerative medicine and meet all the criteria proposed by Gimble et al. for the medical applicability of stem cells [18].

Resolution of the infection, control of the inflammatory process, and optimal vascularization are the main aspects that may determine the outcome of the surgical treatment of MRONJ patients. Considering their well-documented properties, ASCs may be considered a useful adjuvant in this regard [11,19], as they have already been used as a successful method to prevent MRONJ development in murine models [20]. The current hypothesis is that introducing an autologous fat graft into the surgical field after necrotic bone removal is likely to promote the healing processes. Some authors found optimal outcomes providing a multilayer coverage of the surgical field by using the pedicled buccal fat pad [21,22]. However, the observed results may obviously be related to the preserved vascularization of the transferred tissue and do not demonstrate the role of ASCs. In this study, the outcomes of MRONJ patients who underwent surgical treatment were retrospectively analyzed, comparing those patients who received surgical sequestrectomy and fat graft and those who received sequestrectomy alone. The purpose was to assess if fat grafts could represent a beneficial adjunctive procedure in MRONJ patients who need a surgical intervention by evaluating eventual differences concerning the healing process and the evolution of the disease.

2. Materials and Methods

The authors performed a retrospective comparative study according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines of patients diagnosed with MRONJ attended to our Maxillofacial Surgery Unit since 2007. The following inclusion criteria were considered during patients' selection: confirmed MRONJ diagnosis, administered BMAs (i.e., zoledronic acid, pamidronic acid, or associations of

both), unresponsiveness after 8 weeks of systemic antibiotic therapy and oral hygiene, performed surgical treatment, and available follow-up for at least 1 year after surgery. On the other hand, reasons for the exclusion were history of radiation therapy to the head and neck region, surgical treatment refused or not performed due to contraindications to local/general anesthesia or surgery, incomplete follow-up (Table 1).

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	• Confirmed MRONJ diagnosis • Confirmed administration of BMAs • Unresponsiveness after 8 weeks of systemic antibiotic therapy and oral hygiene • Performed surgical treatment • Available follow-up: at least 1-year
Exclusion criteria	• History of radiation therapy to the head and neck region • Surgical treatment refused or not permitted • Incomplete follow-up

The selection included only those patients who were operated on by the same surgeon and met the inclusion and exclusion criteria. The following data were retrieved from the clinical database: age, gender, reason for BMAs assumption (i.e., oncological disease or osteoporosis), localization of the primary tumor (in case of oncological disease), MRONJ localization, MRONJ stage, type of assumed BMA, therapy duration, comorbidities, type of surgical treatment received (i.e., sequestrectomy alone or sequestrectomy and adipose graft), and pattern of disease evolution during the follow-up period.

According with the performed surgical procedure, all patients that met the inclusion and exclusion criteria were divided in two groups:

- Group A (n = 9)—patients who received sequestrectomy and autologous fat graft;
- Group B (n = 12)—patients who received sequestrectomy alone.

Bivariate appropriate tests (Fisher test) have been used to assess the associations between each of the independent characteristics and the performed surgical procedure. After performing the exploratory bivariate analyses, only those variables found to be associated at the p-value < 0.25 level were introduced into a multivariate regression model performed to assess the independent predictors of sequestrectomy surgical procedure followed by autologous fat graft. Analyses were performed using Stata 15 software (StataCorp, 2017. Stata Statistical Software: Release 15.1. College Station, TX, USA. StataCorp LLC).

Treatment Protocol

Patients included in both groups were treated with the same systemic antibiotic therapy with amoxicillin 1.75 g, clavulanic acid 250 mg, and metronidazole 1.5 g daily, starting from the first visit, for at least 8 weeks. All of them suspended the BMA therapy before surgery. All surgical procedures were conducted under general anesthesia. In both groups, a sequestrectomy was performed achieving vital bone margins. Sharp bone edges were removed to minimize the trauma to the overlying soft tissues. Patients included in group B received an advancement mucosal flap taken from the surrounding areas and sutured above the surgical site, while patients included in group A also received an autologous fat graft, which was introduced in the surgical site before the advancement mucosal flap was sutured.

The adipose tissue graft was harvested from the abdominal subcutaneous compartment, similarly to the technique described by Coleman [23–25]: through a 3 mm cutaneous incision, the subcutaneous adipose compartment was infiltrated with a tumescent solution (lidocaine 1000 mg/L, epinephrine 1 mg/L, and sodium bicarbonate 10 mEq/L in 1 L of saline 0.9% NaCl). Then, the adipose tissue was aspirated manually with a 3 mm cannula connected to a 60 mL syringe, under moderate negative pressure (Figure 1). In contrast with Coleman's technique, the harvested fat was not processed by centrifugation but drained

of oil and liquid by gravity (Figure 2) and transferred to a 5 mL syringe. This procedure has been demonstrated to not affect the outcomes of patients receiving fat autografts [26]. Finally, it was introduced in the surgical site before the closure of the mucosal flap or through the wound margins after the mucous lining was sutured (Figure 3).

The same postoperative protocol was administered (amoxicillin 1.75 g, clavulanic acid 250 mg, and metronidazole 1.5 g daily, oral rinses with 0.2% chlorhexidine solution) for at least two weeks. In those cases where the surgical treatment determined the complete healing of the surgical wound, the antibiotic therapy was suspended 2 weeks after surgery (continued until suture removal). On the other hand, it was extended until at most 8 weeks in case of postoperative dehiscence or relapse of bone exposure.

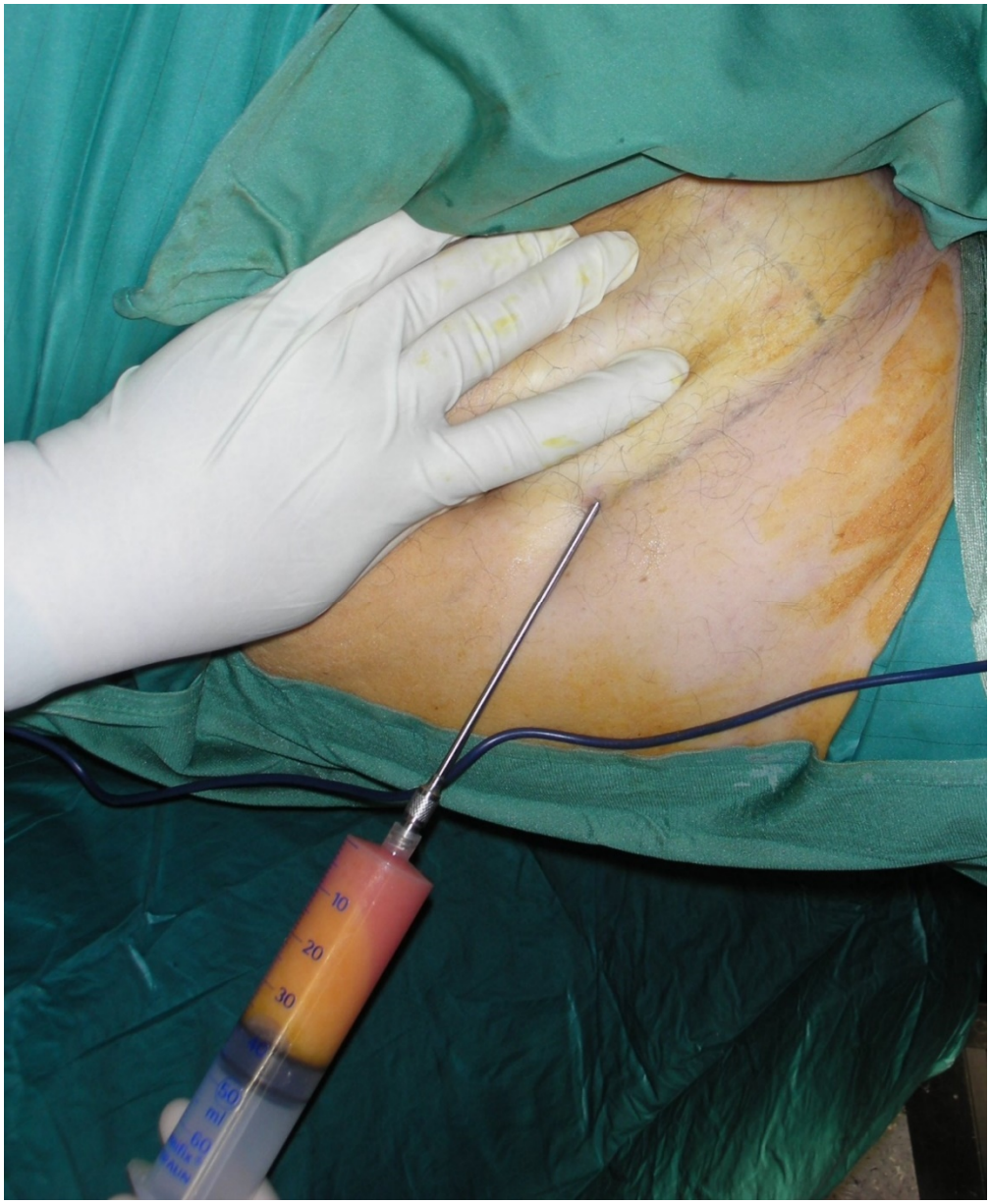

Figure 1. Fat harvesting technique. The adipose tissue is aspirated under moderate manual negative pressure, using a 60 mL syringe connected to a 3 mm cannula.

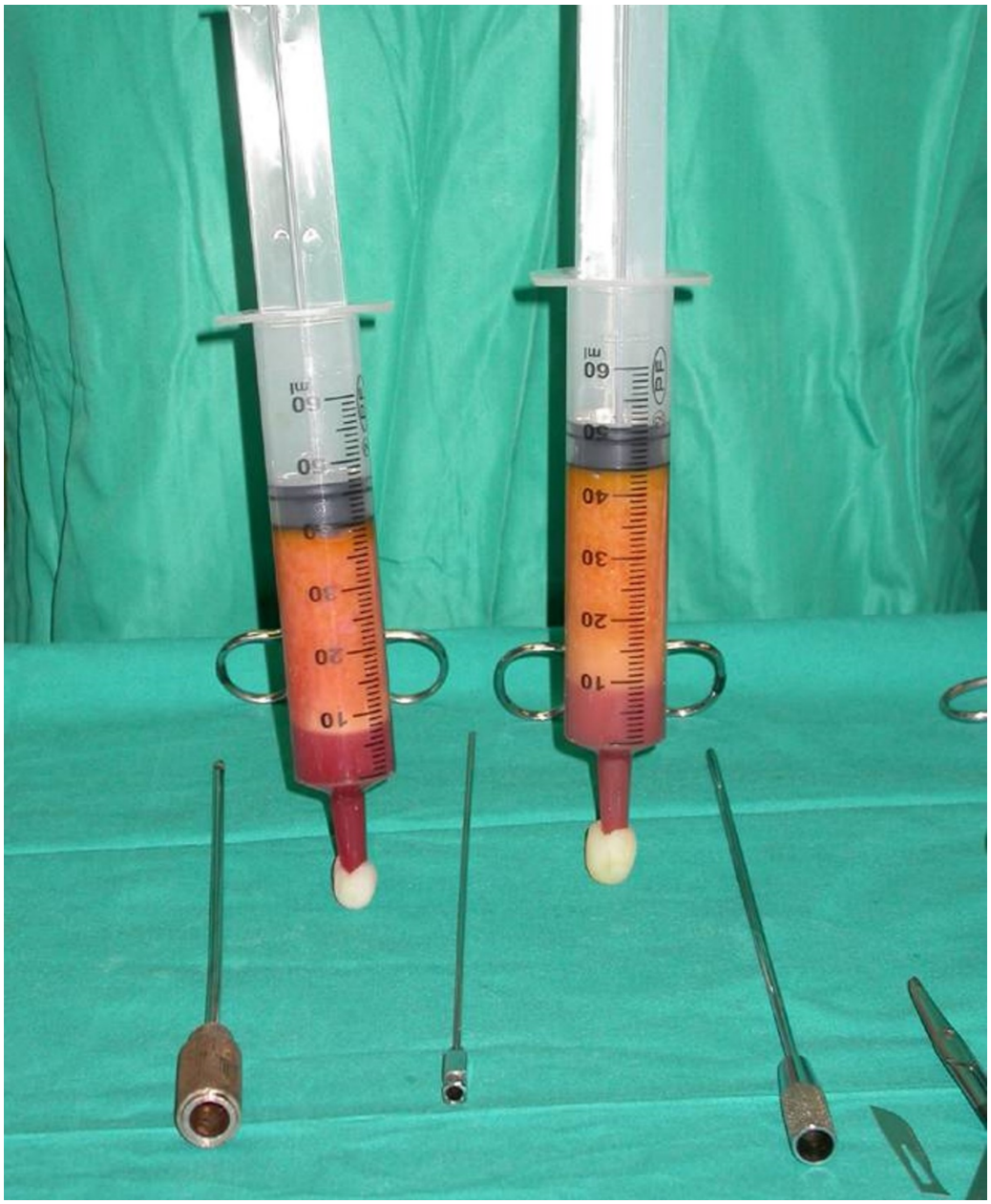

Figure 2. The harvested fat is drained by gravity.

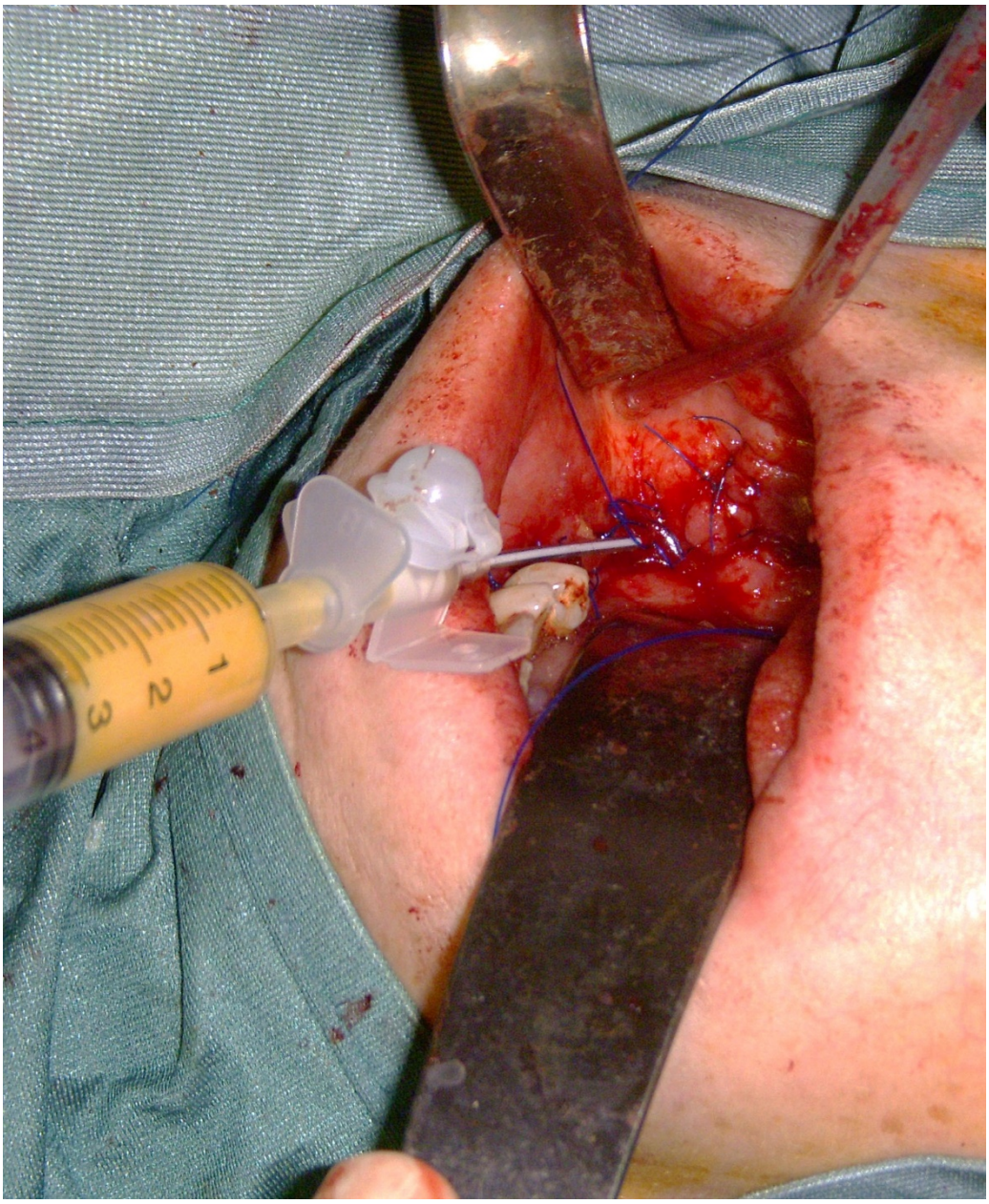

Figure 3. After the fat is transferred to a 5 mL syringe, it is injected through the sutured mucosal margins of the surgical wound until the underlying space is filled.

3. Results

The search retrieved a total of 21 treated patients: nine receiving sequestrectomy with autologous fat graft (group A) and 12 receiving sequestrectomy alone (group B). All included patients were operated by the same surgeon between 2007 and 2012. Thus, the retrieved data were based on the AAOMS guidelines in force at the time [27].

Group A was represented by three males and six females, in a range of age 45 and 75 years; three patients had multiple myeloma, three had breast cancer, two had prostate cancer, and one had lung cancer. The mandible was affected in seven cases, while the maxilla was affected in two. Pamidronic acid was administered in six patients, zoledronic acid was administered in two patients, and one patient received a combination therapy of both. The mean BMA therapy duration was 38 weeks. One patient was affected by diabetes, one was affected by cardiac disease, and one was affected by both. Four patients presented a stage 2 MRONJ, while the remaining five had a diagnosis of stage 3 MRONJ.

Group B was represented by four males and eight females, in a range of age 48 and 86 years; three patients had multiple myeloma, six had breast cancer, one had prostate cancer, and two had lung cancer. The mandible was affected in nine cases, while the maxilla was affected in two, and one patient had the involvement of both. Pamidronic acid was administered in seven patients, zoledronic acid was administered in three, while two patients received a combination therapy of both. The mean BMA therapy duration was 41 weeks. One patient was affected by diabetes, two were affected by cardiac disease, and one was affected by both. Six patients presented a stage 2 MRONJ, while the remaining six had a diagnosis of stage 3 MRONJ. Sociodemographic and disease-related data are summarized in Table 2.

Table 2. Sociodemographic and disease-related variables.

	Group A	**Group B**
Cases (*n*)	9	12
Gender (*n*)		
Male	3	4
Female	6	8
Age (years)		
Median	58	60
Range	45–75	48–86
Smoking (*n*)	0	0
Reason for BMAs assumption (*n*)		
Multiple myeloma	3	3
Breast cancer	3	6
Prostate cancer	2	1
Lung cancer	1	2
Osteoporosis	0	0
MRONJ localization (*n*)		
Mandible	7	9
Maxilla	2	2
Mandible and maxilla	0	1
Assumed BMAs (*n*)		
Zoledronate	6	7
Pamidronate	2	3
Zoledronate + Pamidronate	1	2
Duration of administration (months)		
Median value	38	41
Range	(4–65)	(3–90)
Comorbidities (*n*)		
Diabetes	1	1
Cardiopathy	1	2
Diabetes and cardiopathy	1	1
Baseline MRONJ stage (*n*)		
Stage 2	4	6
Stage 3	5	6

The disease evolved toward a complete resolution in seven patients in group A (Figures 4 and 5), and a complete mucosal healing was achieved; the disease remained stable in one patient, who developed the relapse of the bone exposure; one patient experienced a progression toward more severe conditions.

Among patients in group B, three demonstrated a complete resolution of the disease, and a complete mucosal healing was achieved; the disease remained stable in three patients, who developed the relapse of the bone exposure; the remaining six experienced a progression toward more severe conditions.

The univariate analysis showed that the type of intervention was significantly associated with the clinical course after surgery of the patient, with the improvement (77.8 vs. 22.2%; Fisher's exact $p = 0.030$) with no modification (11.1 vs. 25%; Fisher's exact $p = 0.603$) and with worsening (11.1 vs. 50%; Fisher's exact $p = 0.159$) (Table 3).

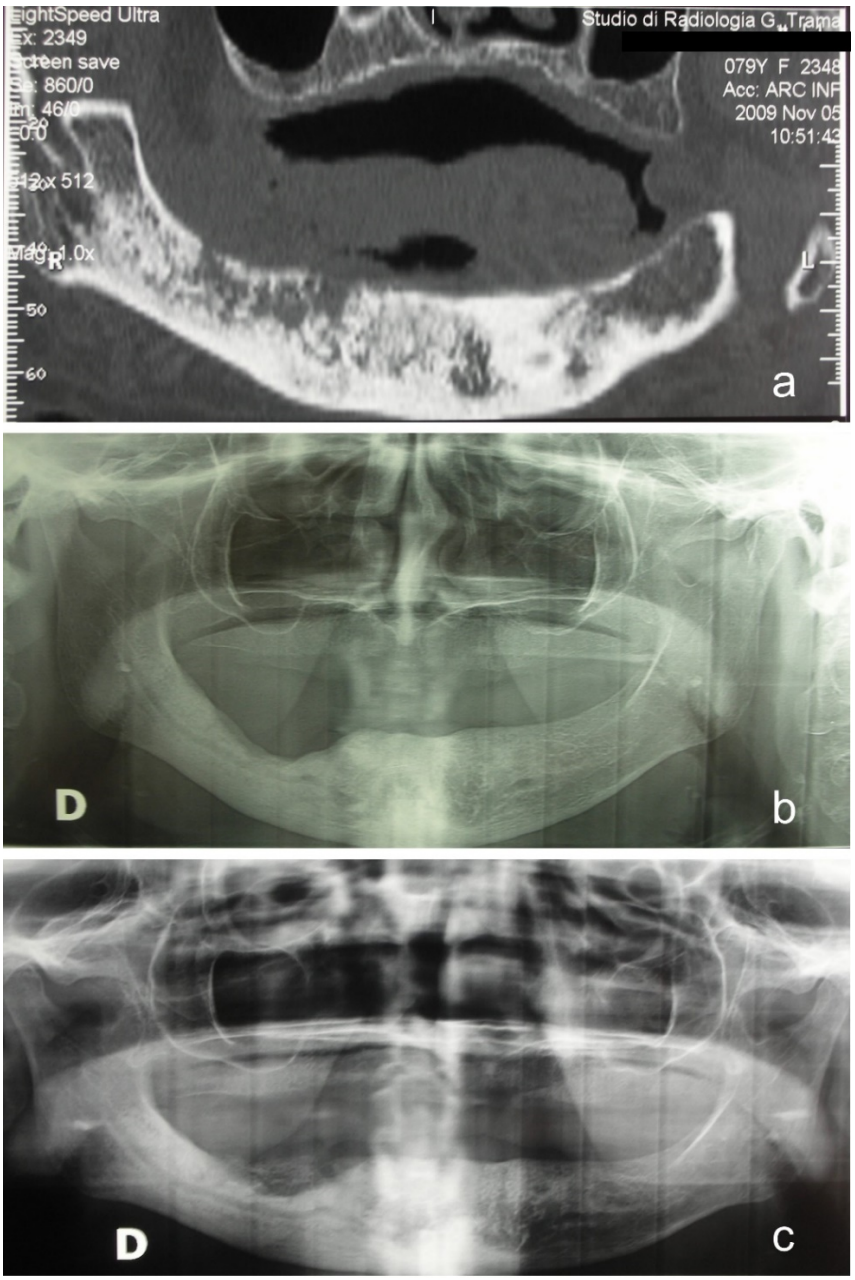

Figure 4. Radiological examination of a treated patient: (**a**) baseline CT taken before surgery; (**b**) postoperative panoramic X-ray, taken 7 days after surgery; (**c**) postoperative panoramic X-ray taken 6 months after surgery.

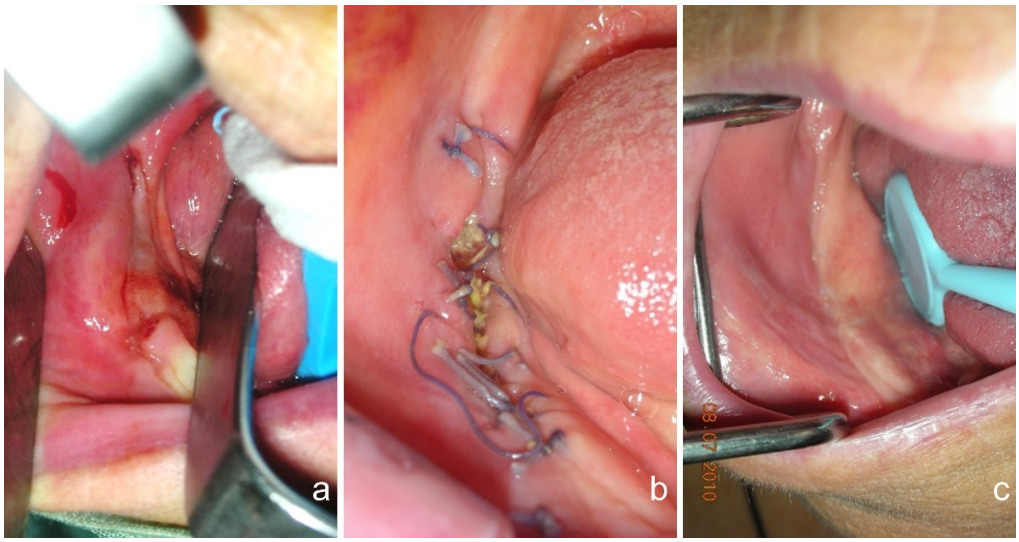

Figure 5. Clinical examination of a treated patient: (**a**) a fistula is present on the alveolar crest, through which the bone could be probed; (**b**) clinical control 7 days after surgery; (**c**) 6 months follow-up demonstrating the perfect healing of the musical lining.

Table 3. Sequestrectomy with autologous fat graft and relative clinical trend after surgery.

Characteristics	Total *n* = 21		Improvement *n* = 10 (47.6%)		No Modification *n* = 4 (19.1%)		Worsening *n* = 7 (33.3%)	
	n	%	*n*	%	*n*	%	*n*	%
Group A	9	42.9	7	77.8	1	11.1	1	11.1
Group B	12	57.1	3	25	3	25	6	50
			Fisher's exact $p = 0.030$		Fisher's exact $p = 0.603$		Fisher's exact $p = 0.159$	

4. Discussion

The goal of a successful management of patients affected by MRONJ is to control pain, solve eventual infections, and prevent complications or disease progression. The proposed treatment algorithms have historically represented a field of wide controversies. Following the publication of the AAOMS update in 2009 [28], several studies have been published searching for stronger evidence regarding the best management strategy. According with today's concept, recommended by MASCC/ISOO/ASCO guidelines [4] and the 2014 update from the AAOMS [1], established MRONJ should undergo initial conservative management with accurate oral hygiene and systemic antibiotics (in the presence of evident signs of infection) and conservative interventions (such as the removal of superficial bone spiculae), reserving more aggressive treatments to refractory cases.

Surgical treatment aims to obtain a complete healing of the mucosal lining. This goal needs two essential steps: to remove the necrotic bone (trying to achieve vital margins) and to cover the defect with healthy mucosa, avoiding any tension that might compromise the healing process. This can be particularly difficult when the maxillary bone is affected. Allowing the patient to wear a mobile prosthesis—given that also minimally invasive implantology [29] could be contraindicated—could be considered to obtain a tension-free mucosal flap by the palatal aspect. This could be realized adapting a partial thickness palatal flap similarly to the technique described by Freda et al. [30] to treat residual palatal fistulas after a push-back palatoplasty.

4.1. Adjunctive Therapies and Procedures

Despite the efforts in the field, the proposed recommendations demonstrated moderate to weak evidence quality [4]. Concerning the usefulness of adjunctive therapies/materials during and after the surgical treatment, many issues remain to be addressed.

Some studies have investigated the use of hyperbaric oxygen therapy associated with the surgical treatment, and some improvements have been reported concerning wound healing, pain, and quality of life [31,32]. However, the evidence quality of these studies is strongly impaired by the small sample sizes, and even analyzing larger ones, as performed by Watanabe et al. [33], no conclusive indications can be drawn. Further studies, designed in a prospective fashion, will enhance the evidence in the field [34].

Ozone therapy has been scantly discussed in the current literature as a post-surgical adjuvant treatment [35]. Despite the published studies documented some promising perspectives, the small sample sizes and the chosen study designs do not permit providing conclusive recommendations [36,37].

Low-level laser therapy represents another discussed post-surgical adjuvant therapy, which was recently renamed photobiomodulation. Its effect on treated tissues has been widely studied by Mester [38], who demonstrated the induction of neo-angiogenesis and protein synthesis in open wounds. Investigations on patients affected by MRONJ found some effect on remission from the disease, even though the studied samples remain too small to gather sufficient evidence [39].

Autologous platelet concentrates (APCs) have also been proposed as an adjuvant treatment modality [40]. When introduced in the surgical field, the growth factors released by platelets stimulate the healing process by stimulating cell proliferation and neo-angiogenesis [41]. Despite the promising results retrieved from animal studies [42], the real effectiveness of APCs in MRONJ management does not seem to fulfill the initial expectations, as demonstrated by Fortunato et al. [43].

4.2. ASCs Potential

In 2001, Zuck et al. [9] firstly demonstrated that a cellular fraction from human lipoaspirate, named processed lipoaspirate (PLA), could be expanded in vitro and provides a multilineage differentiation toward adipogenic, chondrogenic, myogenic, and osteogenic cells, depending upon the chosen lineage-specific differentiation factors. In this pioneering study, the authors recognized a heterogeneous mesenchymal cell population, but ASCs were marked and clearly observed only in 2002 [14]. During the following years, the research showed a huge interest in the field, and several investigations into the mechanism of action and into the therapeutic possibilities were undertaken. Despite the well-documented multilineage differentiation potential, ASCs demonstrated their ability to modify the micromilieu and modulate the immune system [44,45]. These aspects are believed to play an essential role in the therapeutic effect of this kind of cell therapy and promote the research in the acellular therapy using only the exosome that are responsible for the paracrine effects of ASCs [46]. These extracellular vesicles have been found to release miR-21, miR-181b, matrix metalloproteinases, milk fat globule EGF (MFG-E8), angiopoietin-like 1, and miR-375 to promote the neoangiogenesis during soft tissue healing and induce osteoblast differentiation and bone regeneration [47–49]. This expanded knowledge strongly promoted the initial enthusiasm in ASCs-based therapy, and during the following years, several investigations studied their clinical applicability to treat, among the others, osteoarthritis [50], Parkinson's disease [51], stroke [52,53], diabetic kidney disease [54], spinal cord injury [55], cutaneous scars [56], chronic skin wounds and soft tissues defects [57], burn wounds [58], alveolar ridge regeneration [59], Chron's disease [60], liver regeneration after partial hepatectomy [61], Graft-versus-Host disease [62], facial nerve regeneration [63], and intervertebral disc degeneration [64]. Nevertheless, it should be underlined that most of the initial expectations regarding the osteogenic properties of ASCs have been downsized by the following researchers, who demonstrated their limited differentiation potential toward osteogenic lineage [65].

In this scenario, ASCs may represent an interesting opportunity as an adjunctive therapy during the surgical treatment of MRONJ patients to improve the healing processes toward a complete resolution. The scope of reconstructive and regenerative procedures is to restore the injured tissues to allow for the aesthetic and functional recovery of the affected site and organs. Although MRONJ patients might have limited expectations and treatment possibilities, allowing them to receive dental prostheses would ensure improvements in quality of life [66] and cognitive performances [67–75].

4.3. Findings and Study Limitations

In this study, fat graft was found to have an influence on the evolution of the disease toward better stages or complete resolution, which is perhaps due to the described effects of the included ASCs. Exciting results have been reported by Lemound et al. [21] and Ristow et al. [22] using the buccal fat pat to cover the surgical site. In their studies, the complete resolution of the disease was documented over a middle postoperative follow-up for almost all the operated patients. Being a pedicled tissue flap, the optimal results probably may be justified by the preserved vascularization more than their biological properties, or both. The buccal fat pat surely represents an optimal solution in case of small to moderate-sized defects in the oral cavity. However, it is not always available in sufficient volume, or it could not be fully mobilized depending on subjective variabilities. It is also more commonly indicated for maxillary defects, while mandibular ones could be addressed by using a mylohyoid muscle flap [21,22], which might endanger the lingual nerve causing discomfort or pain [21].

The knowledge from current literature suggests that ASCs may lead the process of influencing the micromilieu, causing a significative improvement on the vascularization of the residual bone and the overlying mucosa and reducing the inflammation on the surgical site. It should be underlined that the patients included in group A received a fat graft, which do not represent a cellular therapy as well as the local delivery of isolated ASCs. This obviously implies a much lower amount of stem cells introduced in the surgical site, potentially reducing the effects of the ASCs. However, using a purified ASCs population implies complex purification processes that implicate costs, time, expertise, and dedicated materials, which might not be available. Future studies focusing on the comparison between fat grafts, stromal vascular fraction, and ASCs would be of utmost interest.

Several limitations do not permit defining the reliability of the studied treatment protocol. Firstly, the small sample size precluded a reliable analysis of the retrieved results and a multivariate analysis that would have addressed the potential issues deriving from the existence potential baseline confounding. A more extensive population would have allowed an assessment of the risk of bias by a more complex statistical design. Although in this study, both groups were comparable with respect to diabetes and MRONJ stages, these would represent the most probable sources of bias that should be investigated.

Another limitation is represented by the relatively short follow-up period considered for the study groups. Part of the included patients was lost after the 12-month follow up, because of the progression of the oncological disease or because they voluntary quit.

5. Conclusions

To the best of our knowledge, this article describes the first application of fat graft harvested from distant sites in patients affected by MRONJ. Fat graft might represent a cost-efficient, largely available, and low-risk procedure that might redefine the treatment strategy of patients affected by MRONJ. The current literature supports the hypothesis that ASCs might lead the observed results, and future studies should focus on the comparison between the local delivery of the entire adipose tissue, SFV, and ASCs on larger sample sizes.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are available upon request.

Conflicts of Interest: The authors declare no conflict of interest.

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