

## Periodontal changes following distraction osteogenesis in patients with cleft lip and palate: a clinical trial

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### ABSTRACT

**Objectives:** To evaluate inflammatory mediator levels and periodontal changes following distraction osteogenesis (DO) in patients with cleft lip and palate (CLP) using mid-maxillary distraction (MMD).

**Materials and Methods:** A total of 20 healthy patients with CLP with Class III malocclusion were included. Segmental forward advancement of the anterior maxilla from the second premolars on both sides using DO was performed. A custom-made, tooth-borne distractor connecting buccal molar segments to the anterior maxilla was used for 7 days with 0.5-mm distraction for the first 2 days and then increased to 1 mm daily until overcorrection. Crevicular interleukin IL-1 $\beta$  and tumor necrosis factor TNF- $\alpha$  levels were measured during distraction. Periodontal clinical parameters and indices were recorded at baseline and 3 and 6 months postoperatively. Soft tissue healing was evaluated histologically at 2 and 4 weeks after distraction.

**Results:** The periodontal parameters remained stable during the follow-up periods. Insignificant increases in the level of inflammatory cytokines compared with the control were observed. Histological findings revealed mild inflammatory and structural changes in the gingiva immediately after distraction, whereas regeneration was noticed after 4 weeks.

**Conclusions:** MMD was an effective technique in treating patients with CLP, leading to new bone and soft tissue formation without significant detrimental effect on the periodontium of the adjacent teeth. (*Angle Orthod.* 2022;92:764–772.)

**KEY WORDS:** Cleft lip and palate; Maxillary distraction; Healing; Periodontium; Distraction osteogenesis; Inflammatory mediators

### INTRODUCTION

Primary cleft lip and palate (CLP) repair by conventional orthognathic surgery improves patients' facial appearance, feeding, and speech, but may contribute to maxillary growth impairment.<sup>1</sup> However, a 25%–40% relapse rate in cleft maxillary hypoplasia was reported as a result of severe scarring that limited maxillary mobilization.<sup>2</sup>

Distraction osteogenesis (DO) was originally used in the treatment of mandibular deficiency<sup>3</sup> and subsequently has been used to treat a hypoplastic maxilla through internal distractors that can be maintained for long periods during consolidation.<sup>4,5</sup> Interdental osseous distraction is based on distracting the dento-osseous segment posterior to the cleft site and narrowing the large alveolar defect with mesial movement of the segment. In addition, the technique provides maxillary advancement in a forward direction to correct Class III malocclusion and generate new alveolar bone and soft tissue.<sup>6,7</sup>

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However, rapid maxillary expansion (RME) in adults has been associated with complications such as alveolar bending, periodontal ligament compression, and buccal root resorption of the anchor teeth.<sup>8</sup> Therefore, in adults, the alternative is surgically assisted RME with tooth-borne banded orthodontic appliances and corticotomies of the areas of skeletal resistance such as the pterygoid junction and mid-palate suture. Today, this is an accepted treatment option for maxillary hypoplasia, and almost 79% of patients with tooth-borne distractors have no complications.<sup>9</sup>

Few studies have evaluated the effect of tooth-borne distractors on the periodontium of the involved teeth. The newly formed gingiva from clinical cases has not yet been histologically evaluated. Hence, the objective of this study was to evaluate the health status of the periodontium in patients with CLP using mid-maxillary distraction (MMD), including the level of inflammatory mediators and soft tissue healing in the distraction site.

## MATERIALS AND METHODS

This study is presented in accordance with the Transparent Reporting of Evaluations with Non-randomized Designs statement.<sup>10</sup>

### Trial Design

The study was a prospective, nonrandomized, single-center, one-arm clinical trial. The protocol for this trial was registered at ClinicalTrials.gov with identifier number NCT02901678. The study protocol conformed to the ethical guidelines of the Helsinki Declaration of 1975 as revised in 1983. Ethical approval was obtained from the Faculty of Dentistry, Alexandria University, Egypt (institutional review board approval 00010556).

### Participants, Eligibility Criteria, and Settings

The study sample was randomly selected from patients visiting the Orthodontic Clinic, Faculty of Dentistry. The inclusion criteria were systemic healthy patients with bilateral or unilateral CLP, primary lip and palate repair in infancy and/or early childhood, antero-posterior maxillary hypoplasia, and Class III malocclusion and negative overjet resulting in a concave profile. Participants were also required to be nonsmokers and not pregnant. The exclusion criteria included a history of alveolar ridge augmentation procedure, secondary bone graft surgery in the cleft area, the presence of a physical disability that hindered proper plaque control, and noncompliant patients. A total of 20 patients (four males and 16 females) with a median age of 20 years (16–25 years) were included, and informed written

consent was obtained after explaining the study design.

### Distractor Design

Custom-made rigid, tooth-borne, intraoral distraction devices connecting buccal molar segments to the anterior maxilla were designed and used in all patients (Figure 1).

### Interventions

The operation was performed under general anesthesia. Local anesthesia was administered, and a buccal flap was raised using sulcular and vertical incisions distal to the first molars. The osteotomy was made vertically using piezosurgery at the premolar area and extended horizontally above the apices of the roots, keeping the palatal mucosa intact. Then, segmental forward advancement of the anterior maxilla from the second premolars on either side was performed. Patient characteristics are listed in Table 1. The flap was closed with interrupted interdental sutures. The distractor was cemented in place immediately after surgery, and bands were cemented to the maxillary first premolar and first molar on the left and right sides with glass ionomer cement while the patients were still under general anesthesia.

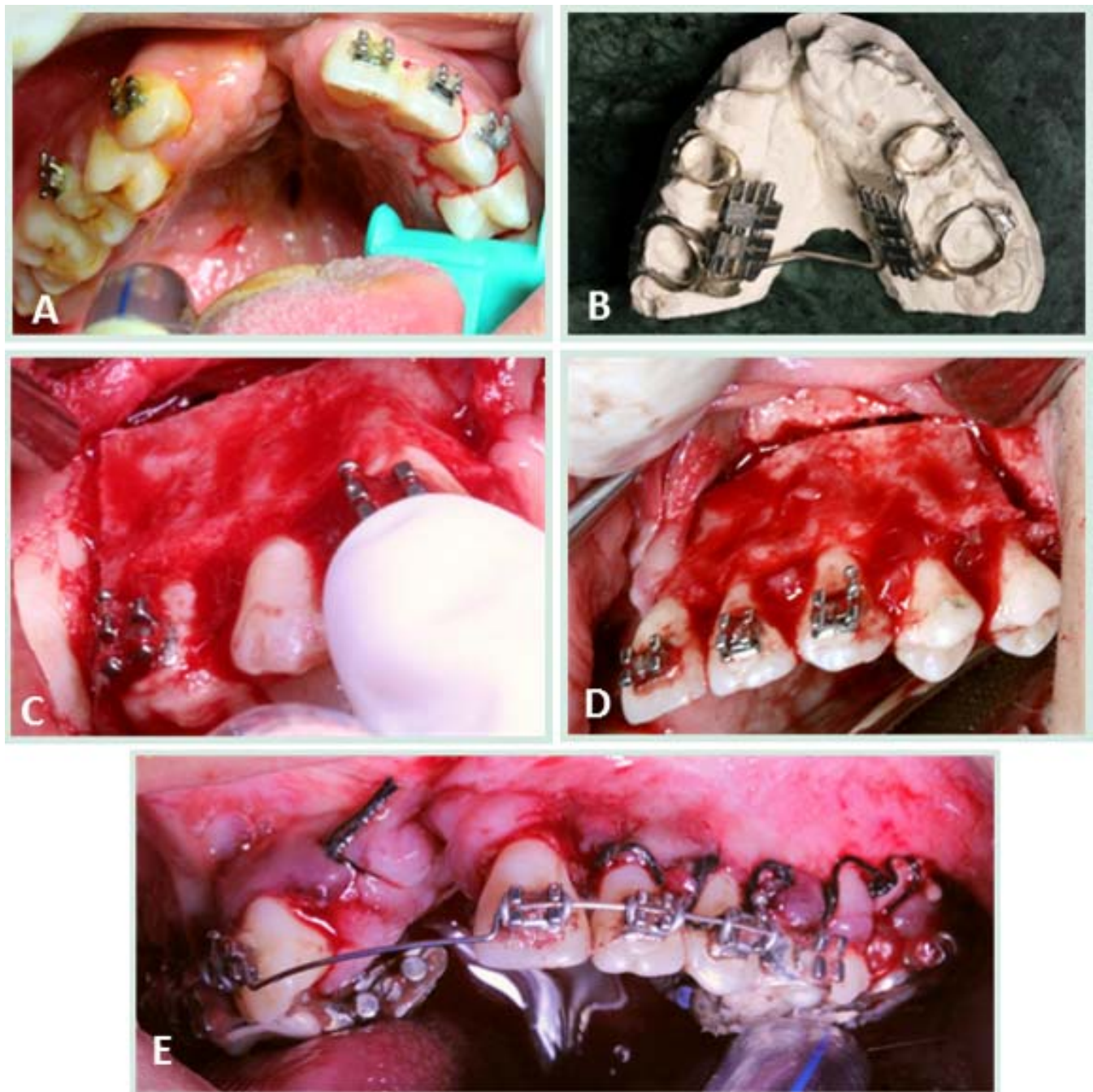
The screw was oriented in an anterior-posterior direction to move the anterior maxillary segment forward. The distraction appliance served to distract the osteotomized segment forward and to secure the anterior segment to the posterior segment of the maxilla (Figure 1). Postoperatively, 1 g of amoxicillin/clavulanic acid (GlaxoSmithKline, London, England) and 600 mg of Brufen (Abbott GmbH, Wiesbaden, Germany) twice per day were prescribed for the patients for the following 7 days.

### Distraction Protocol

A latency period of 7 days following the osteotomy was permitted. Distraction was then performed at a rate of 0.5 mm/d for the first 2 days, then increased to 1 mm daily until overcorrection of the crossbite by 3–4 mm was reached. The distraction device was then kept in place for 2 to 3 months to ensure rigid retention. Study casts, cephalograms, and panoramic radiographs were taken before the treatment and 6 months after distraction.

### Clinical Measurements

The clinical periodontal conditions of the patients were evaluated using the following parameters: (1) probing pocket depth (PD), (2) clinical attachment level (CAL), (3) plaque index (PI),<sup>11</sup> and (4) gingival index



**Figure 1.** Clinical photograph showing the surgical procedure. (A) Preoperative view showing cleft defect. (B) Custom-made tooth-borne distractor. (C, D) Osteotomies at the premolar/molar area for both sides. (E) Flap closure with distractor in place.

(GI).<sup>11</sup> Clinical measurements were performed at baseline (before treatment) and at 3 and 6 months after distraction by two precalibrated examiners.

#### Gingival Crevicular Fluid Collection

Gingival crevicular fluid (GCF) was collected on the seventh day after surgery. The osteotomies were performed distal to the maxillary second premolars

(#15 and #25), and GCF was collected from #15 and #25 (test group) and mandibular premolars #35 and #45 to serve as a control.

Sterile filter papers were precut into  $2 \times 8$ -mm strips. Patients were instructed to avoid eating or drinking for 2 hours before sampling. Partial isolation was achieved using cotton rolls. Supragingival plaque was gently removed, and the tooth was dried using a gentle air



**Table 1.** Comparison Between Baseline (Before Treatment) and 3 and 6 Months According to Different Periodontal Parameters<sup>a</sup>

	Baseline	3 Months	6 Months
PD			
Median (minimum–maximum)	2 (0.6–3.3)	1.8 (0.3–3)	1.8 (0.3–2.6)
Mean $\pm$ SD	2.1 $\pm$ 0.8	1.8 $\pm$ 0.7	1.9 $\pm$ 0.7
Significance between periods		$P_1 = .113$ , $P_2 = .141$ , $P_3 = .799$	
CAL			
Median (minimum–maximum)	0.6 (0–2.2)	1.1 (0–2.2)	1.1 (0–2.2)
Mean $\pm$ SD	0.8 $\pm$ 0.8	1.04 $\pm$ 0.9	1.1 $\pm$ 0.92
Significance between periods		$P_1 = .068$ , $P_2 = .046$ , $P_3 = .655$	
PI			
Median (minimum–maximum)	0.6 (0–1.3)	0.8 (0.3–1.5)	0.4 (0–1)
Mean $\pm$ SD	0.7 $\pm$ 0.4	0.8 $\pm$ 0.34	0.5 $\pm$ 0.4
Significance between periods		$P_1 = .034$ , $P_2 = .024$ , $P_3 = .010$ *	
GI			
Median (minimum–maximum)	0.6 (0–1)	0.8 (0.3–1)	0.5 (0.3–1)
Mean $\pm$ SD	0.6 $\pm$ 0.34	0.7 $\pm$ 0.3	0.5 $\pm$ 0.2
Significance between periods		$P_1 = .248$ , $P_2 = .351$ , $P_3 = .034$ *	

<sup>a</sup> Abnormally distributed data were compared using Wilcoxon signed ranks tests.  $P_1$  indicates  $P$  value for comparing between baseline and 3 months;  $P_2$ ,  $P$  value for comparing between baseline and 6 months; and  $P_3$ ,  $P$  value for comparing between 3 months and 6 months.

\* Statistically significant at  $P \leq .05$ .

stream for 5 seconds.<sup>12</sup> Filter paper strips were inserted into the selected pocket until mild resistance was felt, then left for 60 seconds.<sup>13</sup> Strips contaminated with blood or saliva were discarded. Collected strips were put in a sterile plastic Eppendorf tube (Thermo Fisher Scientific, Swindon UK) containing 150  $\mu$ l phosphate-buffered saline and then centrifuged at 4058 g. The concentrations of interleukin 1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) markers in the samples were determined by using a commercially available enzyme-linked immunosorbent assay kit (eBioscience Inc, San Diego, Calif), according to the manufacturer's instructions.

### Histological Evaluation

Five patients agreed to provide a soft tissue sample (3  $\times$  3 mm) from the crest of the edentulous distraction site at 2 and 4 weeks after surgery. Samples were fixed in 10% neutral buffered formalin and processed.

### Sample Size

The sample size was calculated based on detecting a difference in IL-1 $\beta$  and TNF- $\alpha$  with a standard deviation (SD) of 1.2 mm to achieve 80% power with an  $\alpha$  value of 0.05.<sup>14</sup> A minimum sample of 23 was required in each group. Thus, in every patient, two teeth served as tests and two teeth as controls.

### Blinding

Blinding of the orthodontist and patients was not possible because of the nature of the interventions. However, the histologist and statistician who conducted the histological and data analyses were blinded.

### Statistical Analysis

The data were analyzed using IBM (Armonk, N.Y.) SPSS software package version 20.0. The Kolmogorov-Smirnov test was used to verify the normality of the variable distributions, and the Mann-Whitney test was used to compare the groups for abnormally distributed quantitative variables. The Wilcoxon signed ranks test was used for abnormally distributed quantitative variables in different periods. The significance level was 5%.

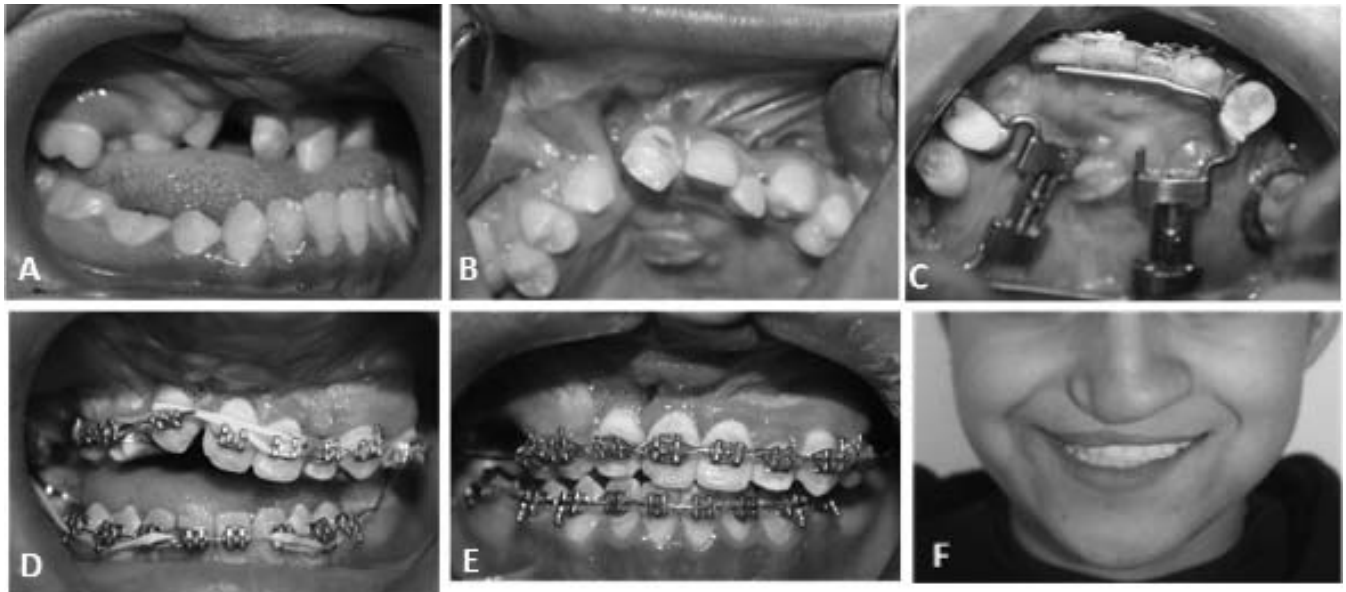
### RESULTS

Clinically, all the patients demonstrated maxillary advancement after DO (Figures 2 and 3). A total of 12 patients had unilateral (three males and nine females), and eight patients had bilateral clefts (one male and seven females). None of the patients had previous bone augmentation. The distracted segment boundaries were the right maxillary second premolar #15 and the left maxillary second premolar #25.

According to the cephalograms and the study casts taken before distraction and 6 months after, the mean increase in the alveolar ridge was 11.5  $\pm$  2.9 mm. The mean maxillary anterior movement measured by dental overjet was 8 mm  $\pm$  1.6 mm, whereas the mean increase in the alveolar ridge was 11.5 mm  $\pm$  2.9 mm. These findings will be reported in another article.

### Periodontal Parameters

PD measurements did not show significant differences among any of the follow-up periods ( $P > .05$ ). CAL was recorded for the teeth adjacent to the



**Figure 2.** Intraoral photographs before and after MMD. (A, B) Preoperative severe maxillary hypoplasia. (C) MMD with distractor in place. (D) Postsurgical view showing crossbite correction. (E) Bite closure. (F) Final tooth restoration.

distracted segments. In one patient, teeth #15 and #25 had 5-mm CAL, and 4-mm CAL was observed in another patient. In five patients, mild CAL (1 mm) was observed. PI measurement increased significantly from baseline to 3 months, and at 6 months it decreased significantly. GI measurements decreased significantly from 3 to 6 months (Table 1), whereas no significant difference was observed regarding the levels of TNF- $\alpha$  and IL-1 $\beta$  (Table 2).

### Histological Results

The histological changes in the specimens taken after 2 weeks resulted from the tension of the tissue after distraction. This was manifested as decreased epithelium thickness. Some epithelial ridges appeared with deep edges pointing toward the lamina propria, giving an impression of continued cellular proliferation. The cells of the basal cell layer appeared flattened, whereas the cells within the prickle cell layer showed a widening of the intercellular spaces. In addition, areas of epithelial tearing could be seen in the superficial layers of the epithelium. The lamina propria exhibited numerous blood vessels and many inflammatory cells (Figure 4). The same histological findings were observed in all specimens of five patients, whereas one patient showed no epithelial tear.

After 4 weeks, the tissues appeared well adapted to tension. The epithelium showed considerable maturation and was relatively thick. The epithelial ridges recovered their thickness and length, and the basal cell restored its columnar shape. The intercellular spaces were minimal, with prominent intercellular bridges. The

lamina propria showed denser, closely packed collagen bundles. Blood vessels were seen in the connective tissue. In addition, there was a marked decrease in the number of inflammatory cells (Figure 5). These findings were consistent in all patients.

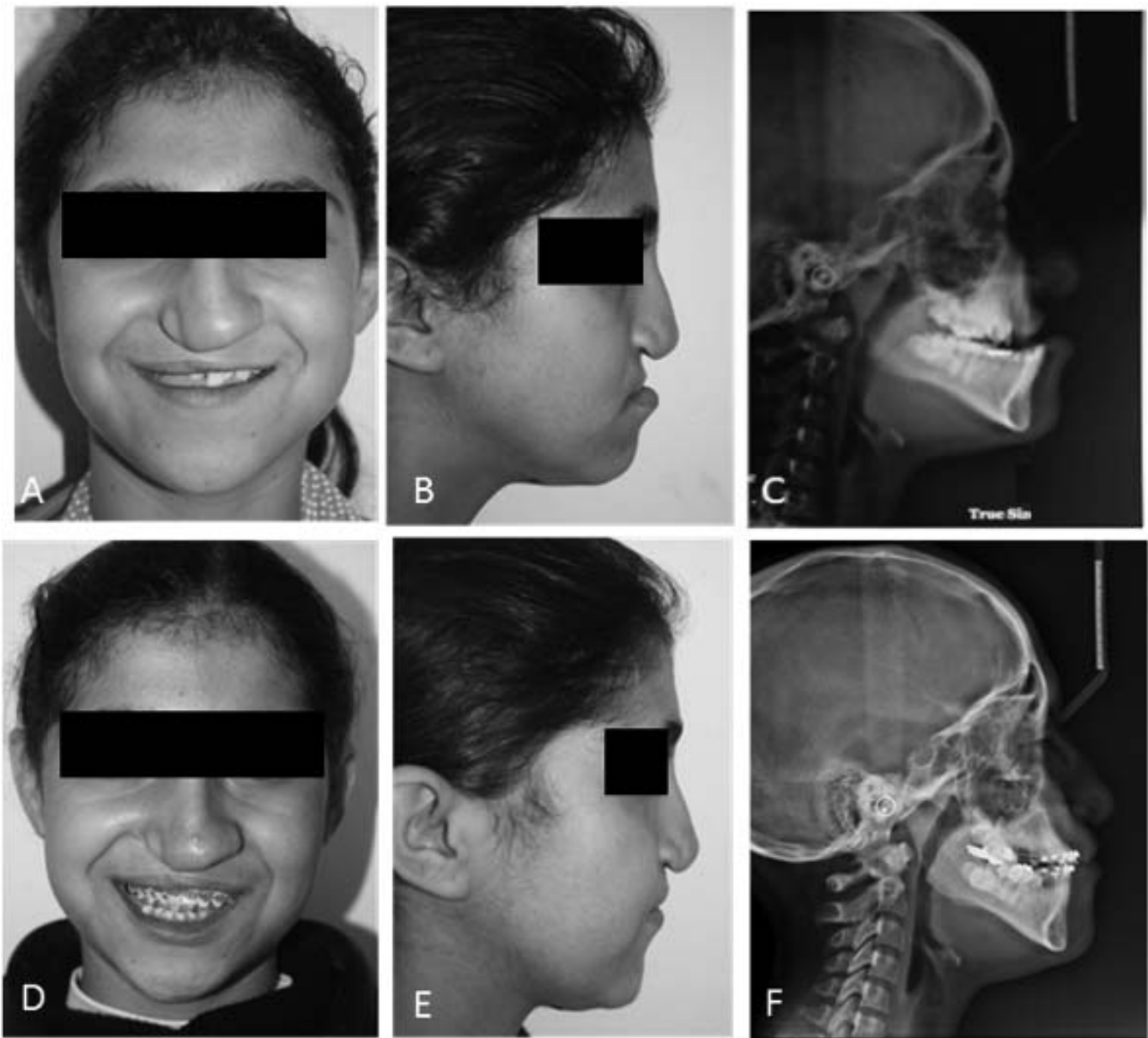
### DISCUSSION

In the present study, the DO technique was used to correct facial deformity and to promote the formation of new bone and healthy soft tissue. Liou et al.<sup>15</sup> reported the first success using a surgically assisted approximation of the alveolar segments with a tooth-borne distraction device in patients with cleft palate.

In the present study, MMD using DO was not observed to adversely affect the periodontal health of the teeth. Although the GI and the PI initially increased during the first months after surgery, they decreased significantly after 6 months. The increase in PI and GI following surgery could be attributed to limited performance of plaque control at the surgical site. The presence of orthodontic appliances, as well as the mechanical orthodontic force applied to the teeth, were challenging factors for maintaining oral hygiene.<sup>16</sup>

Although a significant increase in CAL was detected from baseline to 6 months, the mean change was less than 1 mm, perhaps because attachment loss was calculated as the mean of the six tooth surfaces. Usually, detectable attachment loss occurred on only one surface of the affected tooth close to the distraction site.

GCF levels for TNF- $\alpha$  and IL-1 $\beta$  were assessed to evaluate the effect of DO on the involved teeth. TNF- $\alpha$



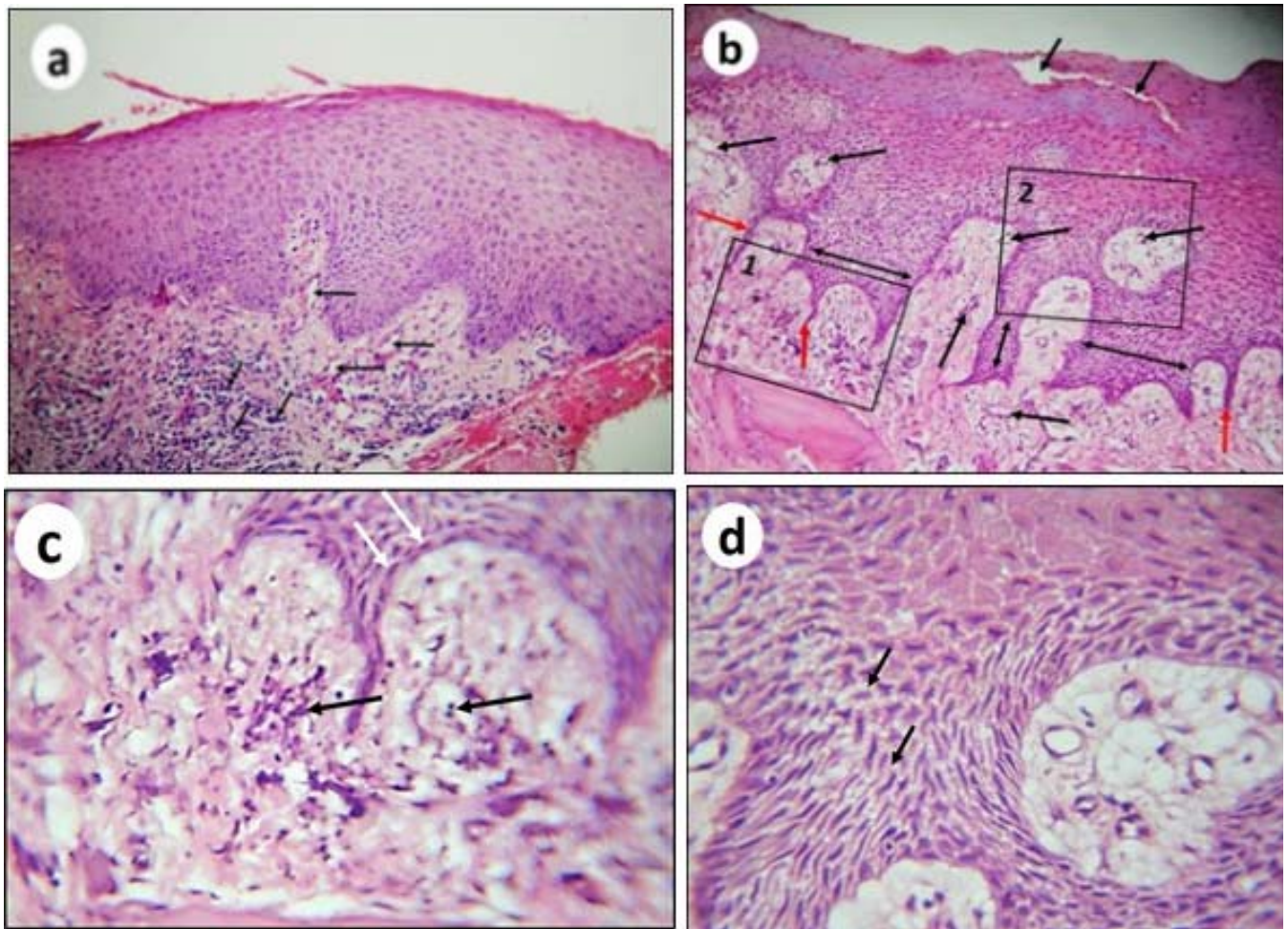
**Figure 3.** Clinical and radiographic pictures before and after MMD. (A) Facial and (B) lateral views of the patient (D) before and (E) after surgery. (C) Preoperative and (F) postdistraction radiographs of correction of crossbite.

**Table 2.** Comparison Between the TNF- $\alpha$  and IL-1 $\beta$  Levels Collected From Maxillary Second Premolars #15 and #25 (Test Group) and Mandibular Second Premolars #35 and #45 (Control)<sup>a</sup>

	Test	Control	P Value
TNF- $\alpha$			
Median (minimum–maximum)	18 (13–31)	15 (7–22)	.274
Mean $\pm$ SD	19.6 $\pm$ 6.5	15 $\pm$ 4.7	
IL-1 $\beta$			
Median (minimum–maximum)	17 (6–41)	18 (9–28)	.723
Mean $\pm$ SD	22.1 $\pm$ 12.8	18.7 $\pm$ 6.8	

<sup>a</sup> Abnormally distributed data were compared using Wilcoxon signed ranks tests.





**Figure 4.** Light micrograph (LM) of soft tissue sample after 2 weeks. (A) Blood vessels (long arrows) and many inflammatory cells (short arrows) are seen within the lamina propria. (B) The epithelial ridges appear broad (↔) and some appear relatively thin (†). The deeper edges of the epithelial ridges are pointed toward the connective tissue (red arrows). An area of epithelial tearing (short arrows) is seen in the superficial layers. Numerous blood vessels (long arrows) are scattered in the connective tissue. (C) Higher magnification of inset 1 in Figure 4B. The cells of the basal cell layer appear flattened (white arrows). Numerous inflammatory cells (arrows) in the lamina propria. (D) Higher magnification of inset 2 in Figure 4B showing widening in the intercellular spaces (arrows) of the prickle cells. (Hematoxylin–eosin: A and B, 100×; C and D, 400×.)

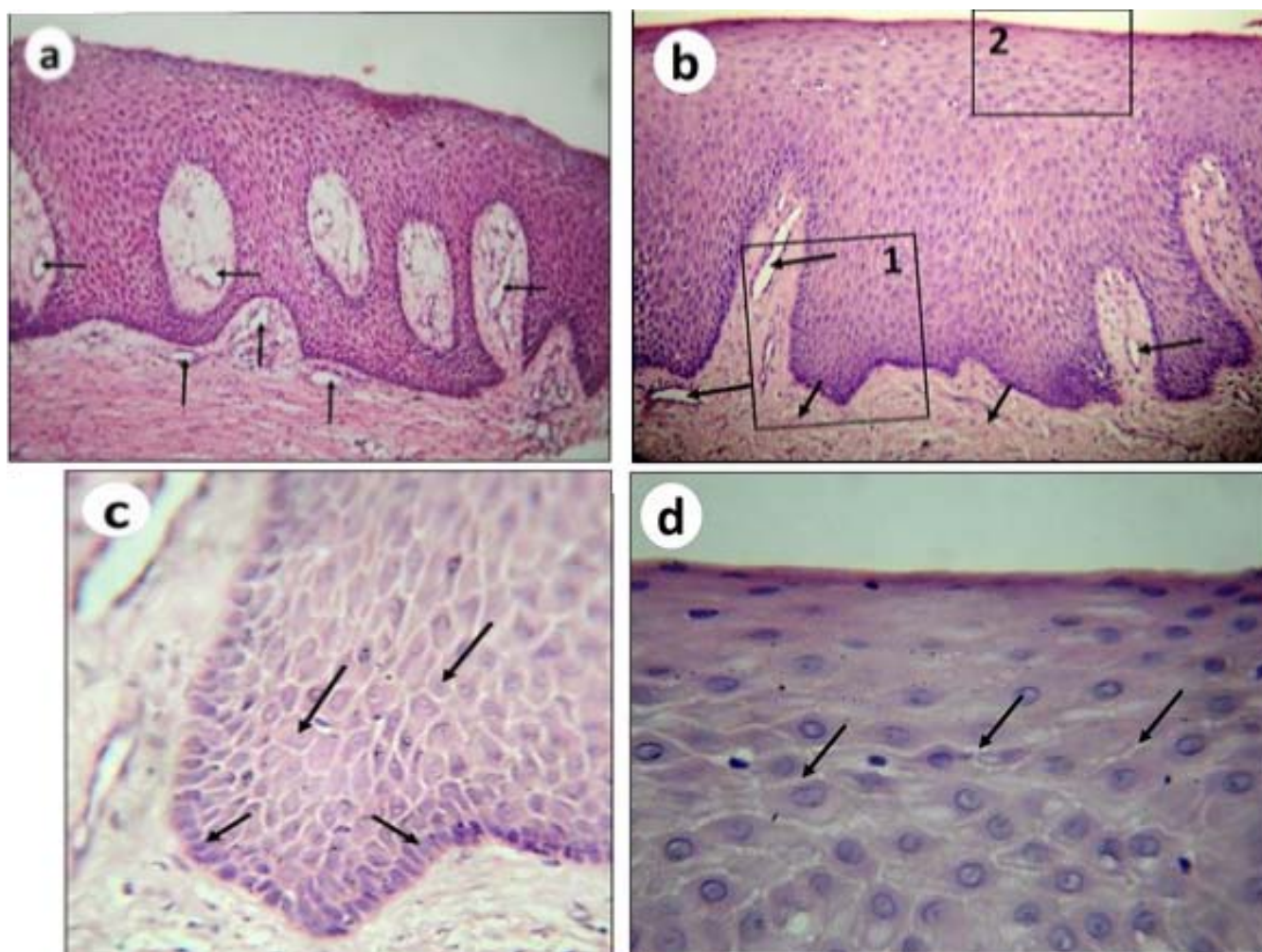
is a typical mediator of inflammatory response that has been shown to be involved in the process of bone resorption.<sup>17</sup> Lowney et al.<sup>18</sup> observed the elevation of  $\text{TNF-}\alpha$  attributed to orthodontic force. One week after distraction, there was no statistically significant difference between the test and control sites. This signified the safety of the procedure and the limited effect on the teeth used to anchor the appliance.

Lee et al.<sup>19</sup> reported that the  $\text{TNF-}\alpha$  level increased significantly 24 hours after surgery. However, in the current study,  $\text{TNF-}\alpha$  declined after 1 week. This could be attributed to the adaptation of periodontal tissues to the orthodontic force and the possibility of negative feedback mechanisms that prevented the mediators from increasing excessively.  $\text{IL-1}\beta$  was reported to reach a maximum on day 3 and declined thereafter.<sup>17,18</sup> Although this inflammation is considered relatively

aseptic, additional inflammation, such as that induced by plaque accumulation, must be avoided during orthodontic and orthognathic treatment. In this study, GCF was compared between test and control groups rather than before and after treatment to avoid the potential influence of patient dietary and oral hygiene habits.

In the present study, histological examination of the gingival tissue at the distraction site revealed healthy, mature gingiva. This indicated an optimum distraction protocol resulting in regeneration of gingival tissue without signs of necrosis or degeneration.

After 2 weeks of distraction, the epithelium showed changes in its structural organization. Cope et al.<sup>20</sup> explained this as being because, during the initial phases of distraction, the gingival tissue overlying the bone stretches to compensate for the tension that



**Figure 5.** LM of soft tissue sample after 4 weeks. (A) The epithelium appears thicker, and the lamina propria shows fewer inflammatory cells, thicker collagen bundles, and scattered blood vessels (arrows). (B) The epithelium shows adequate thickness with well-developed epithelial ridges. Blood vessels are scattered in the connective tissue (long arrows). The lamina propria contains densely packed collagen bundles (short arrows). (C) Higher magnification of inset 1 in Figure 5B showing the short columnar cells of the basal cell layer (short arrows). The overlying prickles are well organized (long arrows) with minimal intercellular spaces. (D) Higher magnification of inset 2 in Figure 5B showing normal stratification of the epithelium with intercellular bridges (arrows). (Hematoxylin–eosin: A and B, 100 $\times$ ; C and D, 400 $\times$ .)

results from distraction. Thus, the basal and prickles cell layers undergo a reorganization of the intercellular junctions, which results in an increase in intercellular spaces.

In addition, at 4 weeks after distraction, the gingival epithelium had nearly regained its normal thickness, with the reemergence of long and broad epithelial ridges. The epithelial cells exhibited minimal intercellular spaces with prominent intercellular bridges. This indicated that the gingival epithelial cells adapted very well to tension, which stimulated cellular proliferation to regain thickness. This finding was also consistent with another report<sup>20</sup> in which new histogenesis and adaptation of gingival tissues was observed to occur at the distraction gaps 8 weeks after distraction. In addition, the collagen fibers became denser in 4 weeks compared with 2 weeks. This could be attributed to the

tension that occurred during distraction, which led to the mechanical stimulation of fibroblasts and therefore an increase in fibroblast proliferation and the secretion of collagen and extracellular matrix to support the overlying epithelium.<sup>20</sup> After 4 weeks, the epithelium showed considerable maturation, and the lamina propria showed denser, closely packed collagen bundles. Blood vessels were seen in the connective tissue, with a marked decrease in the number of inflammatory cells. Thus, the surgical procedure performed in the current study did not compromise the healing process, and mature tissue was observed at 4 weeks.

A limitation of this study was the sample size. In addition, using two parallel study groups would be recommended for future studies.



## CONCLUSIONS

- Forward MMD with custom-made distractors was an easy, affordable, and predictable technique for treating patients with CLP.
- No significant detrimental effect on the periodontium of adjacent teeth was observed while using this technique.

## DISCLOSURE

There is no financial conflict of interest to be declared for any of the authors.

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