Impact of Platform Switched Implants on Marginal Bone Level in Mandibular Overdentures: A Six-Year Follow-Up Longitudinal Study

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Purpose: To evaluate the impact of the platform-switched implant on marginal bone loss (MBL) and the probing pocket depth (PPD) in patients wearing mandibular overdenture.

Patients and Methods: This longitudinal study included 40 completely edentulous patients aged 51–64 years. All patients received complete dentures and were distributed into two groups randomly; 20 patients each. The first group GI received two platform switched implants; however, the 2nd group GII received two platform matched implants (3.6 × 11.5 mm) in the canine region of the mandible. The radiographic evaluations were carried out every year for six years, whereas probing pocket depth was evaluated every six months for 72 months for both groups. The data were analyzed by repeated ANOVA, Friedman’s, and Student’s t-test.

Results: This study included 36 patients; 56 ± 3.6 years was the mean age; 17 females (47%) and 19 males (53%) completed the study. Statistically significant differences were observed in MBL and PPD in each of GI and GII after 6 years, p ≤ 0.05. Between GI and GII after 6 years, a statistically insignificant difference was detected in MBL or PPD, p ≥ 0.05, except in PPD at loading, 2 and 6 years, p ≤ 0.05.

Conclusion: Time positively affected MBL and PPD in platform switched and matched implants retained mandibular overdentures. Platform switching influences probing pocket depth in implants retained mandibular overdentures.

Keywords: dental implant, platform switching, overdenture, supporting structures, COVID-19

Introduction

Complete edentulism is known as a globally common obstacle. Speech, nutrition, perceived aesthetics, and self-esteem are severely compromised. The loss of teeth significantly impacts the individual quality of life. Although oral problems are more severe and chronic, they have been always over-sighted, especially in the aged.

Complete dentures are performed for oral rehabilitation of complete edentulism, it is considered for long as the only prosthodontics treatment option. Osseo-integrated implants and the overdentures installation are used as an alternative to enhance stability, retention, and accordingly functions of complete dentures. With the increasing prevalence, availability, and utilization of dental implants a great variety of treatment approaches have been opened, especially with advanced demands for preferable function and adequate replacement of teeth. Mandibular overdentures retained by two implants are considered a treatment option already approved in the literature.

The connection between abutment and implant was further improved through the “platform switching (PS)” concept. This was all simply about decreasing the abutment diameter at the implant’s platform. This includes horizontal inward relocation of abutment-implant interface, in relation to the implant platform. That type of implant carries several advantages like repositioning of gingival papillae and preserving the peri-implant tissues.
The PS concept is believed to decrease bone loss around the implant. By moving the concentration of stress from the cervical region to the abutment’s interface and compact to cancellous bone, this concept was regarded to reduce stresses around the implant neck. Elimination of bacterial micro-leakage at the implant neck area is performed by platform switching. In addition, the PS interrupts infiltration of the inflammation and consequently prevents the migration of the tissues around the implant apically.9–11

Preservation of bone around the dental implant is a challenge. Comprehensive research concerning the assessment of marginal bone loss around implants has been established. It remains a principal aspect in anticipating the survival and prognosis of an implant. Marginal bone preservation promotes soft tissue stability, which is important for implant survival for long period. Accordingly, the clinician’s responsibility is to demand the least crestal bone loss.11,12

Bone loss around an implant around 1 mm during 1st year of service is considered to be unavoidable. Within the 1st year of implant loading, crestal bone physiology changes, it becomes mature and denser. Occlusal forces that induce initial marginal bone loss are not sufficient to induce additional bone resorption.11,13 Preservation of crestal bone should be arranged before implant placement. The PS system is considered one of the approaches which are recommended to minimize marginal bone loss.14

Moreover, it was reported that the clinical success of dental implant osseointegration will affect the soft tissue changes. This is particularly through pocket depth as well as mobility of the implant. Probing depth was used as a diagnostic tool to assess mucosa around an implant. A long follow-up period is essential to observe all these variables.15,16

There is a relative scarcity of literature, especially regarding implant-retained removable prostheses. Therefore, long-term studies are needed to identify the ideal implant-abutment junction design recommended to be used with implants retained removable prostheses.11

That longitudinal study was planned to evaluate the impact of the platform-switched implant on marginal bone loss (MBL) and probing pocket depth (PPD) in patients wearing mandibular overdenture as compared with that of the platform-matched implant during 6 years follow-up period.

The null hypotheses were that no differences were observed in MBL or probing pocket depth in each of the platform-switched and -matched implants retained mandibular overdentures in their influences on supporting structures during 6 years.

**Materials and Methods**

**Study Design**

A longitudinal study was performed from July 2015 to December 2021. A total of 40 completely edentulous patients, 18 females, and 22 males, aged (51–64 years) participated in this study. The calculation for power size detected a sample size (N = 40) at power 0.80, confidence interval 0.95, and alpha level 0.05.8,17 Selection of patients followed a specific inclusion and exclusion criteria; exempt from any systemic or local diseases, temporomandibular joint disorders (TMJDs), neuromuscular disease or bone disease. All patients had Angle’s class I jaw relationship and sufficient inter-arch space. They had well-developed maxillary and mandibular alveolar ridges with tough mucosa exempt from flappy tissues, ulceration, and inflammation. To prevent the adverse effects on the musculatures and oral functions, any patient with bruxism, clinching, or abnormal tongue habits was excluded. All patients accepted the treatment. Written, informed consents were received from all patients. This was approved by the Research Ethics Committee of the Faculty of Dental Medicine (Girls), Al Azhar University, Review Board (Code REC19-022). The current study complied with the Declaration of Helsinki.
Clinical Protocol
Cone-beam computed tomography CBCT and a preoperative panoramic radiograph was performed on all selected patients to evaluate the height, quantity, and quality of bone. Upper and lower complete dentures have been performed for the patients. Dentures constructions were performed following standard clinical and laboratory procedures. Patients were instructed to use their upper and lower complete dentures for 3 months following delivery for adaptation. The quality, height, and buccolingual width of bone available for implant placement were determined with CBCT using a radiographic template. All patients were divided randomly into 2 groups twenty in each. Group I (GI) received 2 self-tapping, tapered, endosteal (3.6 × 11.5 mm) platform switched implants in the mandibular canine region (Deyna Dental Engineering BV, Holland). Group II (GII) received 2 self-tapping, tapered, endosteal (3.6 × 11.5 mm) platform switched implants in the mandibular canine region (Deyna Dental Engineering BV, Holland). In both groups, two stages surgical techniques were performed for implants installation and implants remained submerged for 3 months to allow osseointegration. After 3 months, exposure of the implant was performed, and the cover screw of the implant was unthreaded and exchanged with a healing collar. After 10 days ball and socket attachments (Dyna Dental Engineering BV, Holland) replaced the healing collars. The female housing of attachments was picked up with the lower denture. GI was obtained, two ball and socket attachments connected to two platform switched dental implants retained mandibular-overdenture, while GII was obtained, two ball and socket attachments connected to two platform matched dental implant-retained mandibular overdenture, Figure 1.

![Figure 1](https://example.com/image1.png)

**Figure 1** Two platform switched dental implants at canine areas of mandibular ridge.

After implants loading, radiographic evaluation of MBL and periodontal pocket depth measures were performed for each patient. In both groups, all patients utilized their dentures for 6 years a follow-up period. Radiographic evaluation was performed at loading and every year for 6 years for each group while periodontal pocket depth measures were performed at loading and every 6 months for 72 months.

Radiographic Evaluation
Intraoral Indirect Digital Radiographic Measurements
For each patient, a radiographic template was performed and checked in the patient’s mouth. Both mesial and distal bone heights were assessed for every implant during each follow-up appointment. A standardized radiograph for the lower alveolar ridge was performed using The Orix x-ray machine (Orix-Aet, ARDET, S.V.R, Milano, Italy) at radiographic exposure (10-milliampere, 65-kilovolt, and 0.4-seconds). That was standardized for
all patients at each follow-up appointment. The measurements of bone height were performed using Digora’s computerized system and image processing software (Orion Corporation, Soredex Medical Systems, Helsinki, Finland). The radiographic images for each patient were interpreted and analyzed to record the marginal bone height at the mesial and distal sides of the implant. The crest alveolar bone and the shoulder of the implant were utilized as reference points. The distance between these 2 reference points is considered vertical MBL and measured for mesial and distal sides. That was carried out at each scheduled follow-up visit. The data were collected and statistically analyzed.

Probing Pocket Depth Measurement
Hawe Neos (3/5/7/9mm) is a color-coded plastic periodontal probe end provided with a flexible tip (Kerr, Lugano, Switzerland). It is specially fabricated to estimate periodontal pocket depth (PPD) around implants. The distance extending from the gingival margin to the tip of the periodontal probe was considered PPD. The estimation of PPD was measured on the facial, lingual, mesial, and distal surfaces of each implant. The PPD measurements were evaluated to the nearest full millimeter, recorded on a specific chart, and become a permanent part of the patient chart. The mean of the PPD measurements with both the right and the left implants for each patient was statistically analyzed.

Statistical Analysis
The computerized data were analyzed using SPSS 20. Shapiro–Wilk normality test was performed to disclose normally distributed data. The quantitative data were represented by the mean and standard deviation (SD). The independent Student’s t-test was used to interpret the significance of differences between two continuous variables and repeated ANOVA test and Friedman test were performed to interpret the significance of differences between the means of three or more groups. The pairwise comparisons were performed using Bonferroni test. The significance level was adjusted at a p-value ≤0.05.

Results
Patients
Forty patients, GI and GII (n=20 in each) participated in this study. A total of 2 male patients in GI and 2 patients (a female and a male) in GII did not continue the follow-up appointments. In GI, a male patient rejected the follow-up appointments at the end of one year and a male patient suffered from a brain stroke following 2 years of loading of the implant and discontinued the follow-up appointments. In GII, a female patient died after 4 years of follow-up appointments and a male patient rejected the follow-up appointments at the beginning of six years. Finally, 36 patients had a mean age (56 ± 3.6 years); 17 females (47%) and 19 males (53%) finished the study, Table 1 and Figure 2.

The follow-up appointments for the 5th year were totally missed due to the complete lockdown caused by COVID-19. The follow-up appointments (July 2019 to July 2020) were delayed six months to December 2020 until the finishing of the lockdown.

<table>
<thead>
<tr>
<th>Table 1 Patient Demographics</th>
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<tbody>
<tr>
<td><strong>Patient Demographics</strong></td>
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<tr>
<td>Male/female</td>
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<tr>
<td>Mean age</td>
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</table>
Effect of Time on MBL in Each Group

The MBL was measured in platform switched (GI) and platform matched (GII) implant-retained mandibular overdenture for patients at the loading of the implants, each year afterward for 6 years. In GI, the mean of MBL (the mesial, distal, right, and left measurements) was increased from the loading of the implants until the 6th year in patients who have received platform switched implant, Figure 3; MBL.1y < MBL.2y < MBL.3y < MBL.4y < MBL.5y < MBL.6y. Statistically significant differences were detected in mean MBL of GI following 6 years follow-up period, \( p \leq 0.05 \), Table 2 and Figure 4.

In GII, the mean of MBL was increased from the loading of the implants until the 6th year in patients who received platform-matched implants. Statistically significant differences were detected in the mean MBL of GII following 6-year follow-up period, \( p \leq 0.05 \), Table 3 and Figure 5.

Effect of Time on Probing Pocket in Each Group

The mean of probing pocket depth (PPD) in platform switched implant was evaluated for (GI) at loading and every six months for 72 months follow-up periods. In GI, the mean of PPD was increased from loading of the implants and each 6 months for 72 months; PPD at loading > PPD.6m < PPD.12m < PPD.18m < PPD.24m < PPD.30m = PPD.36m > PPD.42m < PPD.48m < PPD.54m > PPD.60m < PPD.66m < PPD.72m. Statistically significant differences were detected in PPD in GI following 72 months follow-up period, \( p \leq 0.05 \), Table 4 and Figure 6.
Table 2 Marginal Bone Loss (MBL) in GI During 6 Years Follow-Up Period

<table>
<thead>
<tr>
<th>Patients (n = 18)</th>
<th>Mean(±SD)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Implants (n = 36)</td>
<td>1 y</td>
<td>2 y</td>
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<tr>
<td>Follow Up Period (6 Years)</td>
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</table>

- Right side (n = 18)
  - Mesial MBL
    - Mean MBL (n = 36)
      - 0.61±0.07
      - 0.80±0.08
      - 1.16±0.08
      - 1.50±0.29
      - 1.71±0.35
      - 1.84±0.59
      - 0.001*  

- Left side (n = 18)
  - Mesial MBL
    - Mean MBL (n = 36)
      - 0.60±0.20
      - 0.79±0.20
      - 1.13±0.28
      - 1.39±0.31
      - 1.60±0.34
      - 1.76±0.43
      - 0.001*  

Note: *Significant.  
Abbreviation: SD, standard deviation.

Figure 3 Radiographic measurements for MBL in platform switched implant (GI) after (A) 1 year and (B) 6 years of follow-up.

Figure 4 The mean of MBL in platform switched implant-retained mandibular overdenture during 6 years follow-up period.
In GII, the mean of PPD was increased from loading of the implants and each 6 months for 72 months; PPD at loading < PPD.6m < PPD.12m < PPD.18m < PPD.24m < PPD.30m < PPD.36m < PPD.42m < PPD.48m < PPD.54m < PPD.60m < PPD.66m < PPD.72m. Statistically significant differences were detected in PPD in GII following 72 months follow-up periods, p≤ 0.05,

Table 5 and Figure 7.

Table 3 Marginal Bone Loss (MBL) in GII During 6 Years Follow-Up Period

<table>
<thead>
<tr>
<th>- Patients (n = 18)</th>
<th>Mean(±SD)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>- Implants (n = 36)</td>
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<td></td>
</tr>
<tr>
<td>- Follow Up Period (6 Years)</td>
<td>1 y</td>
<td>2 y</td>
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<tr>
<td>- Right side (n = 18)</td>
<td>Mesial MBL</td>
<td>0.53±0.29</td>
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<td>Distal MBL</td>
<td>0.77±0.25</td>
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<tr>
<td>- Left side (n = 18)</td>
<td>Mesial MBL</td>
<td>0.78±0.26</td>
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<tr>
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<td>Distal MBL</td>
<td>0.70±0.32</td>
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<tr>
<td>- Mean MBL (n = 36)</td>
<td>0.70±0.14</td>
<td>0.85±0.16</td>
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</table>

Note: *Significant.
Abbreviation: SD, standard deviation.

Figure 5 The mean of MBL in platform matched implant-retained mandibular overdenture during 6 years follow-up period.

In GII, the mean of PPD was increased from loading of the implants and each 6 months for 72 months; PPD at loading < PPD.6m < PPD.12m < PPD.18m < PPD.24m < PPD.30m < PPD.36m >PPD.42m < PPD.48m < PPD.54m < PPD.60m > PPD.66m < PPD.72m. Statistically significant differences were detected in PPD in GII following 72 months follow-up periods, p≤ 0.05, Table 5 and Figure 7.

Table 4 Probing Pocket Depth in GI During 6 Years Follow-Up Period

<table>
<thead>
<tr>
<th>- Patients (n = 18)</th>
<th>Mean(±SD)</th>
<th>P-value</th>
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<tr>
<td>- Implants (n = 36)</td>
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<tr>
<td>- Follow Up Period (at Loading-72 Months)</td>
<td>At Loading</td>
<td>6M</td>
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<tr>
<td>- Probing pocket depth</td>
<td>1.5</td>
<td>1.3</td>
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<td></td>
<td>±0.37</td>
<td>±0.47</td>
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</table>

Note: *Significant.
Abbreviation: SD, standard deviation.
Table 5 Probing Pocket Depth in GII During 6 Years Follow-Up Period

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 18)</th>
<th>Implants (n = 36)</th>
<th>Follow up Period (at Loading - 72 Months)</th>
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<tr>
<td></td>
<td>Mean(±SD)</td>
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<tr>
<td>Probing pocket depth</td>
<td>1.0 ±0.35</td>
<td>1.5 ±0.42</td>
<td>1.8 ±0.37</td>
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<td>1.7 ±0.24</td>
<td>1.8 ±0.22</td>
<td>2.1 ±0.35</td>
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<td>2.1 ±0.35</td>
<td>2.3 ±0.49</td>
<td>2.1 ±0.38</td>
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<td>2.4 ±0.47</td>
<td>2.5 ±0.61</td>
<td>2.6 ±0.35</td>
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<td>2.6 ±0.33</td>
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<tr>
<td>p-value</td>
<td>0.001*</td>
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Note: *Significant.
Abbreviation: SD, standard deviation.

Figure 6 The mean of probing pocket depth during 72 months follow-up periods in GI.

Figure 7 The mean of probing pocket depth during 72 months follow-up periods in GII.
Effect of the Group on MBL
The mean MBL in platform switched (GI) and platform matched (GII) implants-retained mandibular overdenture were compared. No statistically significant differences were detected in the mean MBL between lower overdentures retained by two platform switched implants (GI) and that retained by two platform matched implants (GII) after 6 years follow-up periods, p≥0.05, Table 6 and Figure 8.

Table 6 Marginal Bone Loss (MBL) in GI and GII During 6 Years Follow-Up Period

<table>
<thead>
<tr>
<th>Mean(±SD)</th>
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<td>1 y</td>
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<td>3 y</td>
<td>4 y</td>
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<td>GI</td>
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<td>0.61±0.07</td>
<td>0.80±0.08</td>
<td>1.16±0.08</td>
<td>1.50±0.29</td>
<td>1.71±0.35</td>
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<td>GII</td>
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<tr>
<td>0.70±0.14</td>
<td>0.85±0.16</td>
<td>1.02±0.15</td>
<td>1.36±0.26</td>
<td>1.61±0.29</td>
<td>2.00±0.27</td>
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<tr>
<td>p-value</td>
<td>0.33</td>
<td>0.98</td>
<td>0.86</td>
<td>0.72</td>
<td>0.77</td>
<td>0.75</td>
</tr>
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</table>

Abbreviation: SD, standard deviation.

Figure 8 The mean of MBL in GI and GII during 6 years follow-up period.

Effect of the Group on Probing Pocket Depth
No statistically significant differences were detected in probing pocket depth (PPD) between lower overdentures retained by two platform switched implants (GI) and that retained by two platform matched implants (GII) after 72 months follow-up period, p≥0.05. However, statistically significant differences in PPD between GI and GII at loading, 24 months, and 72 months follow-up periods, p≤0.05, Table 7 and Figure 9.

Table 7 Probing Pocket Depth in GI and GII During 6 Years Follow-Up Period

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<tr>
<th>Mean(±SD)</th>
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<tbody>
<tr>
<td>6M</td>
<td>12M</td>
<td>18M</td>
<td>24M</td>
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<td>36M</td>
<td>42M</td>
<td>48M</td>
<td>54M</td>
<td>60M</td>
<td>66M</td>
<td>72M</td>
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<td>GI</td>
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<tr>
<td>1.5±0.37</td>
<td>1.3±0.47</td>
<td>1.6±0.09</td>
<td>1.90±0.53</td>
<td>2.3±0.27</td>
<td>2.4±0.21</td>
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<td>2.1±0.45</td>
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<td>2.5±0.28</td>
<td>2.2±0.57</td>
<td>2.3±0.18</td>
<td>2.4±0.15</td>
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<td>GII</td>
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**Table 7** (Continued).

<table>
<thead>
<tr>
<th>- Patients (n = 18)</th>
<th>- Follow Up Periods (at Loading-72 Months)</th>
<th>Mean(±SD)</th>
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</thead>
<tbody>
<tr>
<td>- Probing Pocket Depth</td>
<td>At Loading</td>
<td>6M</td>
</tr>
<tr>
<td>• Matched implants (GI) (n = 36)</td>
<td>1.0 ±0.35</td>
<td>1.5 ±0.42</td>
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<tr>
<td>P-value</td>
<td>0.004*</td>
<td>0.29</td>
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**Note:** *Significant.
**Abbreviation:** SD, standard deviation.

**Discussion**

The current longitudinal study was planned to evaluate the impact of the platform-switched implant on marginal bone loss (MBL) and probing pocket depth (PPD) in patients wearing mandibular overdenture as compared with that of the platform-matched implant during 6 years follow-up period.

Carefully standardized inclusion and exclusion measures were designed for this study. Parameters including patients’ age, quantity and quality of bone, design of the implant, surgical techniques, and implant loading protocol, which can affect the outcome results of the study, were standardized. This study was caught in the clinical dilemma known because of the Covid-19 pandemic, during the follow-up period from 2019 to 2021.

Following implants installation and loading, all implants attained the criteria accepted for a successful implant. All 72 implants in GI and GII (36 in each) survived in accepted function without any detected signs of peri-implant soft tissue infection, pain, or mobility. The survival rate was 100%. Radiographically, there was no persistent mesial or distal radiolucency around the implant. This was in accordance with 5 years of follow-up delayed implants loading results in disparate designs, implants’ survival rate was 98.3%–100%.

The results of the present study clarified that the first null hypothesis was rejected, as there were no differences detected in MBL or changes in probing pocket depth, in each platform switched (GI), and matched implants (GII) retained mandibular overdentures after 6 years follow-up period. Statistically significant differences were detected, in both MBL and probing pocket depth in GI and GII during the 6 years’ follow-up periods.

The mean MBL was significantly increased in GI and GII during the 6 years follow-up period. Following the results of this study, after the 6th-year follow-up, the mean MBL was (1.84±0.59 mm) for GI and (2.00±0.27 mm) for GII. This was in agreement with the criteria of success of an implant which found that bone loss equal to 1–1.5 mm within 1st year.
following loading and annual 0.2 mm subsequently is considered accepted.\textsuperscript{20–22} The MBL, from the loading of the implant, equivalent to or more than 2 mm was estimated as a biological problem and not as an implant failure. Also, these results can be attributed to limitations of measurements rather than biological factors.\textsuperscript{23–25}

The mean probing pocket depth was significantly increased during the 6 years follow-up period in GI and GII. It was reported that generally, peri-implant pocket depths should be \( \leq 5 \) mm. If the increased probing depth is not associated with other symptoms; it will be with a poor diagnostic value. In the current study, all measured preimplant probing pocket depths showed a pocket depth of \( \leq 4 \) mm.\textsuperscript{26–28}

These results are in agreement with an earlier study held by the same authors over five-year follow-up. This study reported a positive long-term effect of mandibular two implants retained overdentures on OHRQoL, MBL, probing pocket depth, and implant stability.\textsuperscript{29}

The second null hypothesis was that no differences between platform switched (GI) and matched implants (GII) retained mandibular overdentures in their influences on MBL or the probing pocket depth after 6 years follow-up period. That hypothesis was accepted. No statistically significant differences were detected between GI and GII after 6 years follow-up period. These results are in accordance with the results of three-year follow-up study held by the same authors.\textsuperscript{30}

The results of the current study found that the marginal bone resorption is not affected by platform switching (PS). This may be attributed to the resorption of bone being almost associated with biological aspects, such as biological bone width regeneration more than to biomechanical aspects, such as the size of the abutment in relation to the implant neck.\textsuperscript{23} These are in accordance with previous studies that revealed that PS may be less important for peri-implant crestal bone-level maintenance as supposed. Also, the contribution of PS is still arguable; resorption of crestal bone is to be affected by various factors.\textsuperscript{6,18,31}

On the other hand, the concept of platform switching has been considered by many other authors as a primary factor in the positive or even dramatic preservation of crestal bone loss. These articles included humans and animals, original studies, and systematic reviews, but these did not include completely edentulous patients restored with implant-retained mandibular overdenture treatment modalities, especially with long-term follow-up periods.\textsuperscript{13,32,33}

The results of probing pocket depths in the current study revealed no statistically significant differences between GI and GII during 6 years follow-up period except at loading, after 24 months, and 72 months. This indicates that probing pocket depth is not influenced by platform switching during the whole follow-up period except at loading, after 24 months, and 72 months. That was in agreement with the study revealed that insignificant values of probing pocket depth were observed at 4 and 5 years follow-up periods between platform-switched and -matched implants.\textsuperscript{23} It was reported that peri-implant probing pocket depths if not combined with signs and/or symptoms such as radiographic radiolucencies, purulent exudate, bleeding, pain, or discomfort, maybe a poor diagnostic value. Accordingly, marginal bone loss over time is associated with increasing probing depths without any signs of implant endosteal disease.\textsuperscript{26}

**Conclusion**

Within the parameters of this study design, time positively affected MBL and PPD in platform switched and matched implants retained mandibular overdentures. Platform switching influences probing pocket depth in implants retained mandibular overdentures. It is recommended to conduct further studies with longer study periods and larger sample sizes to validate the concept of this study.

**Data Sharing Statement**

Datasets related to this study will be available from the corresponding author upon request.

**Disclosure**

The authors report no conflicts of interest in this work.
References


