

THE EFFECT OF SURFACE TREATMENT OF THE DENTAL IMPLANT ON THE OSSEINTEGRATION IN MANDIBULAR POSTERIOR MISSING TEETH: A RANDOMIZED CONTROLLED CLINICAL TRIAL

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ABSTRACT

INTRODUCTION: Dental implants have lately emerged as a feasible therapeutic alternative for replacing missing teeth. Implants have undergone continuous improvement to increase their functionality and longevity to meet patients' needs for shorter treatment periods and the need to deal with increasingly complex clinical situations. Surface modifications have been the focus of continuous improvement in modern implants, guiding a new era of surface treatment with chemically modified hydrophilic surfaces.

OBJECTIVES: To evaluate the impact of "Hydrophilic Surface Implants (HSI)" on osseointegration in comparison to "Nonhydrophilic Surface Implants (NSI) in the mandibular posterior area. Methodology: This randomized controlled clinical trial was executed on twelve patients with missing mandibular posterior teeth, randomly allocated into two groups. Group I: six patients received hydrophilic dental implants (HSI), while Group II: six patients received "Nonhydrophilic Surface Implants (NSI). Implant stability, bone density, marginal bone loss, and biochemical analysis of bone formation using Runt-related transcription factor 2 (RUNX2) were all assessed for both groups.

RESULTS: There were no significant differences between the two groups concerning implant stability ($P=0.381$), bone density around the implants ($P=0.326$), marginal bone loss around the implants ($P=0.416$), or biomarkers of bone formation (RUNX2) ($P=0.828$) along the course of the clinical trial.

CONCLUSION: The Hydrophilic Surface Implants (HSI) showed better results compared to Nonhydrophilic Surface Implants (NSI) in all investigated parameters, although the difference was not statistically

KEYWORDS: hydrophilic, dental implant, Implant stability, bone formation.

RUNNING TITLE: Surface treatment of dental implant and osseointegration

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INTRODUCTION

Branemark coined the term "osseointegration" as "a direct structural and functional connection between organized live bone and the surface of a load-bearing implant." (1).

Osseointegration is a complex process involving all biological interactions between the host and the implant surface. Consequently, the procedure is influenced by several variables, including the biomaterials of the dental implants, surface treatment, implant design, surgical techniques, and bone quality (2).

Surface treatment features including morphology, roughness, topography, surface energy, chemical composition, the presence of impurities, and titanium oxide layer thickness have all been investigated to improve the quality and pace of

osseointegration and the success rate of dental implants (3).

A diversity of surface modification treatments has been developed, including mechanical (such as machining and grit blasting), chemical (such as acid etching), electrochemical (such as anodic oxidation), vacuum, thermal, laser, or different combinations of these techniques, such as surfaces that have been both grit-blasted and acid-etched (4).

Manufacturing sandblasted acid-etched (SLA) implants involves a rigorous blasting process followed by etching with sulfuric and hydrochloric acids. It creates a rough surface with superior bone integration (5).

The hydrophilic implant surface is created using the same sandblasting and acid etching procedures. However, it is washed under nitrogen protection and then stored in a tightly sealed bottle containing an isotonic NaCl solution to avoid contamination by atmospheric particles (6).

Hydrophilicity is related to the implant surface's wettability, determined by the water contact angle. Hydrophobic surfaces possess a contact angle greater than 90°, hydrophilic surfaces have a contact angle of less than 90°, and superhydrophilic surfaces possess values below 5° (7).

Several studies have emphasized the significance of the wetting characteristics of the implant surface in promoting osteoblast cell-implant contact, which leads to the rapid diffusion of blood on the implant surface, covering it entirely with bioactive chemicals that could enhance early cell attachment, multiplication, and differentiation by altering the bonding strength, total amount, and formation of adsorbed proteins. Consequently, promoting osteogenesis (8,9). Recent research has uncovered synergistic impacts of nanostructured surfaces and hydrophilicity on the biological reaction (4).

Angiogenesis plays a significant role in bone remodeling during wound healing, positively influencing osseointegration by delivering nutrients, oxygen, and osteoprogenitor cells. RUNX2, an intermediate bone formation marker, provokes angiogenesis and demonstrates a crucial role in osteogenesis by directing multipotent mesenchymal precursor cells toward the osteoblastic lineage and encouraging early osteoblast differentiation. Additionally, it has a critical role in osteoblastic function (10,11).

Previous studies assumed that the modified hydrophilic implant surface might further reduce titanium implants' healing time (9,12).

Thus, the purpose of this research was to evaluate the effect of hydrophilic surface treatment of dental implants placed in posterior missing teeth in the mandible on the osseointegration: clinically by implant stability, radiographically by marginal bone loss and bone density around the dental implant; and biochemically by measuring the RUNX2 compared to non-hydrophilic surface implants.

MATERIALS AND METHODS

This study was performed as a randomized controlled clinical trial and reported according to CONSORT guidelines (13). And carried out following the Ethics Research Board (IRB No. 001056-IORG 0008839-0183-10/2020), Faculty of Dentistry, Alexandria University. This study was registered in an ICMJE-approved registry (<https://clinicaltrials.gov/>) and granted an ID of NCT05194813.

The study was conducted on 12 patients with missing mandibular posterior teeth who were candidates for implant placement. Patients were chosen from the Department of Oral and Maxillofacial Surgery outpatient clinic, Faculty of

Dentistry, Alexandria University. All patients were informed of the study's purpose, procedure steps, and time intervals. Each patient signed informed consent.

Sample size estimation: The sample size was estimated using the NCSS-PASS program version 20. A minimal hypothesized total sample size of 12 patients with missing posterior teeth who are indicated for implant placement admitted to the outpatient clinic of the oral and maxillofacial surgery department (6 per group) is needed to detect the proportional difference in Implant Stability Quotient (ISO) between the two groups, taking into consideration 5% level of significance and 80% power using Chi Square-test (14,15).

Randomization and allocation concealment

Patients were randomly assigned to one of the two groups through an online randomizer. (www.randomizer.org). **Group I (test):** six patients received Hydrophilic Surface Implants (HSI) (Acqua, AlvimCM, Neodent, Brazil).

Group II (control): six patients received Nonhydrophilic Surface Implants (NSI) (Neoporous, Alvim CM, Neodent, Brazil).

Patients were assigned using sequentially numbered, opaque, sealed, and stapled envelopes (SNOSE).

Inclusion criteria:

(a) Patients with missing mandibular posterior teeth with good oral hygiene (plaque index less than 10%) (16); (b) Good compliance with the treatment; (c) Free from local or systemic disease (6); (d) Adequate bone width (at least 1 mm on the buccal and lingual aspect, 1.5 mm from the adjacent teeth); (e) Adequate bone height (at least 10 mm of bone height from the inferior alveolar canal to the crest of the ridge); (f) At least three months after tooth extraction; and (g) Sufficient interocclusal space (17).

Exclusion criteria

(a) The presence of persistent and unresolved infection in the implant site (18); (b) Parafunctional habits (17); (c) Heavy smokers (19); and (d) Uncontrolled systemic disease that impedes bone healing (19).

Surface morphological and chemical analysis of the dental implants by scanning electron microscopy (SEM)

Both implants were inspected by the use of scanning electron microscopy (SEM) (JSM-IT200in touch scopeTM; JEOL Ltd) at magnifications of $\times 15$, $\times 1000$, $\times 5000$, and $\times 10,000$.

After observing the implant surfaces with SEM, they were subjected to an element analysis with energy-dispersive X-ray spectroscopy (EDX) to examine the chemical components of dental implants (20).

Presurgical Phase

Personal data and past medical and dental history were collected and recorded in complete detail; then, patients were examined extra and intraorally. To assess the implant sites, a radiographic examination was done using cone-beam computerized tomography (CBCT) (Veraview X800; J. Morita).

Surgical Phase

Before any surgical procedure, patients in both groups were directed to gargle their mouths with Hexitol mouthwash (Chlorhexidine 125mg/100ml, Arabic drug business, ADCO). The surgery was performed under local anesthesia (Articaine hydrochloride 40 mg/ml with adrenaline 1:100,000). A crestal incision was performed on the ridge's crest with bard parker blade number 15. The ridge was exposed by gently reflecting a full-thickness mucoperiosteal flap using a sharp mucoperiosteal elevator. The osteotomy was accomplished using a sequence of drills with a profuse quantity of normal saline according to the treatment plan based on CBCT data. Implants were inserted using a Neodent ratchet wrench with an insertion torque of 30–50 Ncm. The smart peg Type 48 specific for Alvim Neodent was attached to the implant. The primary stability of the dental implant was evaluated using a resonance frequency analysis (RFA) (Osstell ISQ, Osstell, Gothenburg, Sweden) by holding the measurement probe close to the head of the smart peg in buccolingual and mesiodistal directions without touching it. A smart peg was removed, then a healing abutment was tightened to the implant using a manual screwdriver. The flap was repositioned with suturing of the edges by a 3/0 black silk suture. The implant stability was assessed during surgery and three months later using the Osstell. (Figure 1)

Immediately Post-surgery phase

Post-surgical patient instructions included using cold packs extra orally every ten minutes for two hours on the first day. For a week, consume soft foods and refrain from brushing and trauma. Sutures were removed 7–10 days later.

Patients were instructed to take 1gm tablets of Augmentin (Amoxicillin 875 Clavulanic acid 125; GlaxoSmithKline, UK), 50 mg tablets of Cataflam (Diclofenac potassium; Novartis, Switzerland) every 12 hours for five days, and rinse their mouths with the Hexitol mouthwash (Chlorhexidine 125mg/100ml, Arabic drug business, ADCO) for one minute, five times each day, for two weeks beginning on the second post-operative day.

After a three-month healing period, the patients were recalled for prosthetic treatment. The prosthetic procedures involved making a closed-tray impression technique using an additional silicone impression material (Zhermack; Dentsply Sirona), then fabrication and cementation of porcelain fused to metal crowns. All patients were monitored for six months.

Pain assessment

The pain was evaluated through telephone interviews in the first three days and after one week through a visual analog scale (VAS) from 0 to 10 ("0" is no pain and "10" is intolerable pain) (21).

Wound closure

The wound closure was evaluated after one week and two weeks according to Landry healing Index (22).

Implant stability

The stability of the dental implant was assessed with resonance frequency analysis (RFA) immediately post-operative (primary stability) and after three months (secondary stability).

Radiographic evaluations

The radiographic findings were evaluated to estimate any evidence of success or failure for the implants. CBCTs were taken at two different time points: Immediate post-operatively, this was considered the baseline CBCT; another CBCT was taken for the patient six months post-operatively (three months after loading) to evaluate:

- A) **The Bone density** was measured with an implant planning software program (On-demand 3D software).
- B) **Marginal bone loss**
 - b) The height of the marginal bone was determined immediately after surgery (baseline) and three months after loading the final restoration (six months later). The distance from the alveolar bone crest to the implant apex was measured on the mesial, distal, buccal, and lingual aspects. The difference between the two measurements represented a marginal bone loss.

Biochemical assessment of the bone formation by (RUNX2) (23)

Isolation of selected implants and teeth using a cotton roll placed in the mucobuccal fold, then air-dried gently, absorbent paper strip Periopaper (Oraflow, Smithtown, New York) was placed in the peri-implant sulcus until resistance was sensed and kept in situ for 30 seconds to collect the peri-implant sulcular fluid (PISF) samples. Blood-contaminated absorbent paper strips were discarded. The periopaper strip was preserved in a 1.5-ml Eppendorf tube containing 200µl phosphate-buffered saline (PBS). The tubes were labeled, maintained on ice, and then stored at -20 °C until the data were analyzed. The same operator collected the peri-implant crevicular fluid at two weeks, one month, two months, and three months after implant placement. The contralateral molar was considered the negative control group. The RUNX2 obtained from gingival clavicular fluid (GCF) around the dental implant was measured by the ELISA method, the sandwich technique using platinum ELISA (Bioneovan Co.Ltd., Beijing, China (100000)).

Statistical analysis

The data was entered into the computer and analyzed with IBM SPSS version 20.0 software (Armonk, NY: IBM Corp.). The Shapiro-Wilk test was used to examine the normality of quantitative data (implant stability, marginal bone loss, and bone density). Data was presented using (minimum and maximum), mean and standard deviation (SD). The Mann-Whitney and Friedman tests, followed by a post hoc test, were used to determine changes in pain scores over time, while ANOVA with repeated measures was used to assess changes in RUNX2 expression over time. The significance of the obtained results was judged at * $P \leq 0.05$.

RESULTS

Twelve patients with missing mandibular posterior teeth participated in the study. The patients were 10 females and 2 males with a mean age of 36.0 ± 3.79 years. The Flowchart of the patients is presented in Figure 1.

In the case of Hydrophilic Surface Implants (HSI), scanning electron microscopy (SEM) revealed aggregation of dried salt (NaCl) on the implant's surface. Aside from that, the micrometric examination revealed that the surfaces of both implants were standard, well-defined, rough surfaces Figure 2.

The EDX examination of the two implant groups revealed that both had high titanium peaks. However, the Hydrophilic Surface Implants (HSI) had a low percentage of sodium (Na) and chlorine (Cl) and no carbon on their surface; the Nonhydrophilic Surface Implants (NSI) had carbon. Figure 3

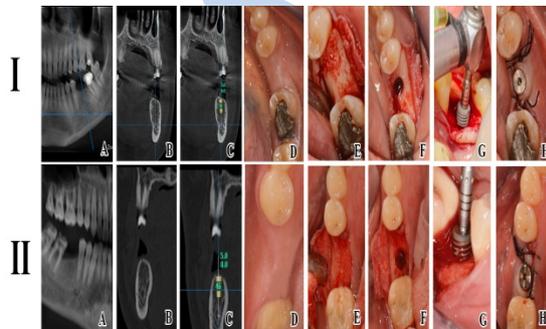


Figure (1): Pre-operative planning and surgical procedure for implant placement. (I) NSI (II) HSI. (A) pre-operative CBCT (panoramic view); (B) pre-operative CBCT (cross section); (C) pre-operative CBCT with virtual implant planning ;(D) photograph showing the preoperative clinical view; (E) reflection of a full mucoperiosteal flap;(F) osteotomy preparation ;(G) implant insertion into the osteotomy site; (H) healing abutment placed over the dental implant and closure of the flap.

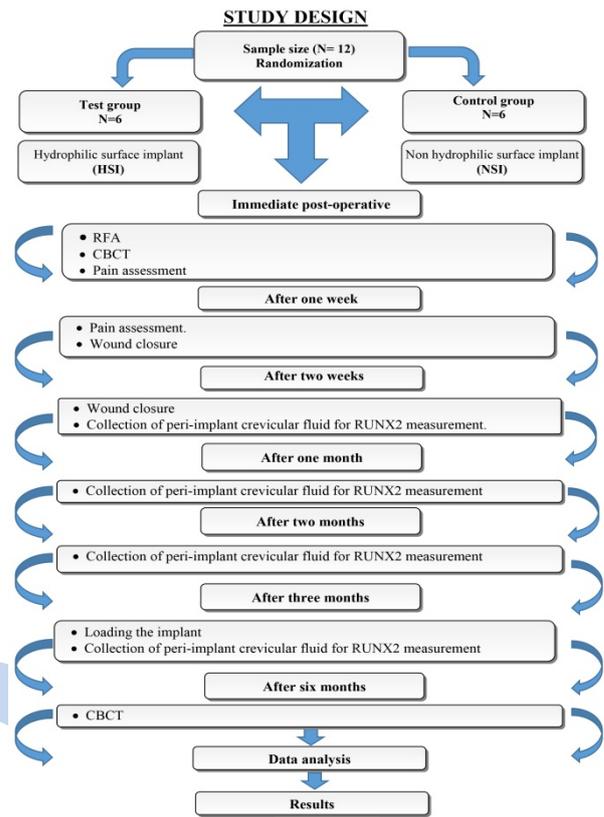


Figure (2): Flowchart Diagram of the study.

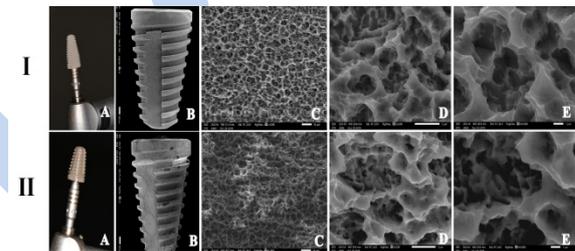


Figure (3): General features and morphology analysis of NSI and HSI. (IA) Macrogeometry of NSI implant (dry and dull surface). (IIA) Macrogeometry of HSI (wet surface). (IB) SEM image for NSI at magnification $\times 15$ (IIB) SEM image for HSI at magnification $\times 15$ showing aggregation of NaCl salts on the surface. IC and IIC SEM at magnification $\times 1000$. ID and IID SEM at magnification $\times 5000$. IE and IIE SEM at magnification $\times 10000$.

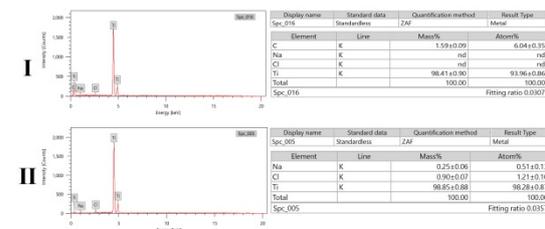


Figure (4): Chemical Analysis of Dental Implants by Energy-Dispersive X-ray spectrometry (EDX) (I) EDX for NSI showing carbon on the surface. (II) EDX for HSI showing Na and Cl on the surface.

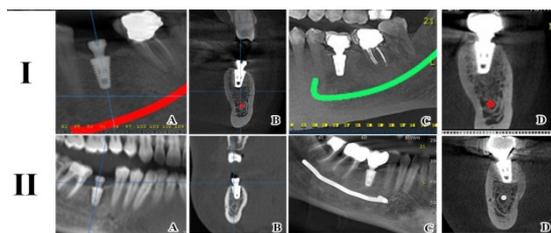


Figure (5): Radiographic evaluation (I) NSI (II)HSI. (A) immediate post-operative CBCT (panoramic view); (B) pre-operative CBCT (cross section) showing implant with healing abutment; (C) CBCT (panoramic view); (D) CBCT (cross section) after 6 month showing implant loading with final restoration.

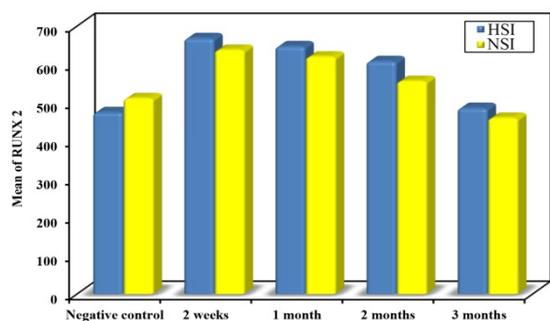


Figure (6): Comparison between the different studied periods according to RUNX 2 in each group.

According to the findings, the two groups did not significantly differ from one another. in pain during the first week following implant placement; however, in the (HSI) group, about 66.7% of patients reported mild pain, and 33.3% had moderate pain on the day of surgery. On the second day, all patients had mild pain; on the third day, 16.7% experienced mild pain. On day seven, no patients displayed any pain. On the other hand, 83.3% of patients in the (NSI) group reported mild pain, and 16.7% had moderate pain after surgery. On the second day, all patients had mild pain; on the third day, 33.3% experienced mild pain. On day seven, no patients displayed any pain.

Regarding wound closure, 83.3 % of patients had very good wound healing one week after surgery, while only 16.7% had good healing. Two weeks after surgery, 83.3% of patients had excellent wound healing, while only 16.7% had very good healing in both groups.

Both the (HSI) and (NSI) groups showed a significant increase in implant stability six months later compared with immediately post-implant placement ($P<0.001$). Although the (HSI) group had higher mean implant stability than the (NSI) group, there was no significant difference in implant stability between the two groups, either immediately after implant placement or six months later ($P=0.381$), as shown in Table (1).

There was no significant difference in bone density surrounding the implants between the (HSI) and

(NSI) groups, either immediately after implant placement or six months later ($P=0.326$), even though the (HSI) group had a higher mean bone density six months later. The (HSI) group displayed a significant increase in bone density surrounding the implants six months later compared with immediately post-implant insertion ($P=0.004$), whereas the (NSI) group had no significant difference ($P=0.369$).

Six months post-implant placement, the (HSI) group demonstrated lower mean marginal bone loss than the (NSI) group, although the difference was not statistically significant ($P=0.416$), as shown in Table (2).

Table (1): Comparison between the two studied groups according to implant stability.

Stability	HSI (n = 6)	NSI (n = 6)	P
Immediately			
Min. – Max.	62.50 – 72.50	62.50 – 76.50	0.795
Mean ± SD.	69.0 ± 3.49	68.25 ± 5.9	
3 months later			
Min. – Max.	77.0 – 87.50	70.0 – 86.0	0.381
Mean ± SD.	81.33 ± 4.08	78.67 ± 5.84	
p0	<0.001*	<0.001*	

*: Statistically significant at $p \leq 0.05$

Table (2): Comparison between the two studied groups according to bone density and bone loss.

	HSI (n = 6)	NSI (n = 6)	P
Immediately bone density			
Min. – Max.	659.8 – 1439.0	480.8 – 1425.6	0.833
Mean ± SD.	865.5 ± 290.5	906.3 ± 359.8	
6 Months later Bone density			
Min. – Max.	858.1 – 1839.0	503.3 – 1658.6	0.326
Mean ± SD.	1228.6 ± 345.4	1009.4 ± 388.7	
P0	0.004*	0.369	
Bone loss			
Min. – Max.	0.29 – 1.24	0.70 – 1.45	0.416
Mean ± SD.	0.86 ± 0.39	1.03 ± 0.32	

Regarding RUNX2 expression, the (HSI) group presented a higher expression of RUNX2 than the (NSI) group during the different studied periods. However, there was no significant difference between the two groups. Both groups showed increased expression of RUNX2 in comparison to the negative control (contralateral side). RUNX2 had the highest expression on the fifteenth day post-implant placement, then gradually decreased at one month, two months, and three months.

DISCUSSION

Many investigations have been conducted over the years to evaluate factors influencing osseointegration. Many factors were identified to influence osseointegration, including surgical technique, the quality and quantity of peri-implant

bone, implant design, and implant surface treatments (2). Improved hydrophilicity is one of the benefits of treating the surface of an implant, which has captivated the interest of many researchers due to its potential effect on the osseointegration process and shorter treatment duration (8,24).

SEM study of the (HSI) implant revealed the aggregation of dried salt (NaCl) on the implant surface as a result of immersion in NaCl solution to maintain the hydrophilicity of the implant surface, which forms a salt aggregate across the titanium surface when dried. This outcome is consistent with Sartoretto et al. (25). Both implants showed standard, well-defined, rough surfaces due to sandblasting and acid etching, which is an important factor influencing bone formation.

According to the EDX results, the predominant element in both implants was titanium. While carbon was discovered on the surface of the (NSI) group, once the implant was exposed to air, it adsorbed carbon and hydrocarbons, making it hydrophobic. Na and Cl were found on the surface of the (HSI) as it was immersed in a NaCl solution to shield the implant from the air and prevent carbon and hydrocarbons from contaminating it, allowing the implant to retain its hydrophilicity (26).

Even though the (HSI) group had higher mean implant stability than the (NSI) group, there was no significant difference in primary or secondary implant stability between the (HSI) and (NSI) groups, as established by the clinical findings of the current investigation. These findings are per previous researches (27,28).

On the contrary, Shams et al. discovered that the primary stability of the (HSI) group was statistically superior to that of the (NSI) group. However, there was no significant difference in secondary stability (29). This might be because the primary stability was determined by its macrostructure, not its surface treatment, and could be acquired mechanically during implant placement (28). In contrast, secondary stability is achieved through a series of processes, including bone deposition and remodeling at the bone-implant interface. (Gained biologically) (30).

According to Velloso et al., implants with hydrophilic surfaces inserted in the posterior mandibular area had greater secondary stability than non-hydrophilic surface implants (31). Many variables might contribute to the variance in the clinical outcomes, such as bone density in the implant region, implant design, and surgical technique (27).

The Hydrophilic Surface Implants (HSI) and Nonhydrophilic Surface Implants (NSI) groups showed a significant increase in implant stability three months later compared to immediately post-implant placement. That was because both implants had the same sandblasted and acid-etched (SLA) surface treatments. This modified surface stimulates osteoblasts to multiply and attach to the implant

surface, improving implant stability and speeding up the healing process (32).

The radiographic findings of the current study showed no significant difference in bone density surrounding the implants between the (HSI) and (NSI) groups, either immediately after post-implant placement or six months later. However, the (HSI) group had a higher mean bone density six months later. Another finding showed that the (HSI) group displayed a significant increase in bone density surrounding the implants six months later compared to immediately post-implant insertion, whereas the (NSI) group did not. These findings were in line with the previous study by Shams et al. (29) which suggested that (HSI) group can increase and enhance bone density due to their hydrophilic properties. An interpretation of the enhanced osseointegration of hydrophilic implant surfaces is the enriched adherence and retention of the blood clot, which enables the early migration of mesenchymal cells through the clot to the implant surface, where they differentiate into osteoblasts and initiate the deposition of collagen matrix for mineralization directly on the implant surface (33).

Moreover, the hydrophilic surface possesses active hydroxyl ions (OH⁻), which increase the wettability and surface energy of the implant surface up to the moment of implant insertion, which contributes to a greater affinity for protein adsorption than a hydrophobic one (4). Hydrophilic surfaces have shown enhanced angiogenesis during the early stage of osseointegration, increased platelet activation, increased osteogenic differentiation of mesenchymal cells through upregulation of genes associated with osteogenesis and suppression of osteoclastogenesis, and down-regulation of inflammatory cytokines, thus reducing healing time and hastening osseointegration (34). Another possible explanation is that the surface roughness tends to increase when an implant's surface is chemically altered to be hydrophilic. Therefore, it is believed that the enhanced osseointegration may be attributed to the increased surface roughness (33).

The (HSI) group demonstrated lower mean marginal bone loss than the (NSI) group, although the difference was not statistically significant, as already evidenced in a previous study (35). Although it was anticipated that some bone loss would occur within the first year of function due to remodeling and adaptation, the degree of bone loss appears to be affected by implant design, patient characteristics, and clinical procedures (36).

RUNX2 represents a premature osteogenic differentiation marker as it activates angiogenesis, extracellular matrix formation, and mineralization (37). Although there was no significant difference between the (HSI) and (NSI) groups in the current study, the (HSI) group had higher RUNX2 expression. These findings indicate that osteoblast differentiation and responses during

osseointegration vary depending on implant surface treatment (11), and hydrophilic surfaces can accelerate bone formation (38). As an early osteogenic indicator, RUNX2 expression was highest on the fifteenth day post-implant placement and gradually decreased at one month, two months, and three months. Runx2 is necessary for guiding multipotent mesenchymal precursor cells toward an osteoblastic lineage and enhancing osteoblast differentiation during the earliest phase of bone formation (39).

Both groups showed increased expression of RUNX2 compared to the negative control (opposite side) because both implants had a sandblasted acid-etched surface that had been shown in a previous in vitro study to increase RUNX2 expression and promote cell adhesion, proliferation, angiogenesis, and osteogenesis (40).

CONCLUSIONS

Hydrophilic surface implants (HSI) exhibited superior implant stability, bone density, RUNX2 expression, and lower mean marginal bone loss, than non-hydrophilic surface implants (NHI), although the difference was not statistically significant (NSI). Furthermore, hydrophilic surface implants exhibited a significant increase in bone density surrounding the implants six months later compared to immediately post-implant insertion, demonstrating that it can improve the bone density surrounding them. We recommend further trials with poor bone quality, immediate implantation, and a more extended follow-up period.

CONFLICT OF INTEREST

The authors declared no conflicts of interest.

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