



## Research Article

## Recombinant Human Bone Morphogenetic Protein-2 as Bone Additive and its Relation with the Dental Implant Dimensions and Stability: Split-Mouth Randomized Clinical Trial

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## Abstract

**Background:** The bone morphogenetic protein belongs to transforming growth factor beta (TGF- $\beta$ ), and it is regarded as one of the biological factors that play major roles in the process of osteogenesis. **Objective:** To measure the effect of recombinant human bone morphogenetic protein-2 with an absorbable collagen sponge carrier (rhBMP-2/ACS) on secondary implant stability and study the relation of other parameters like implant receipt jaws, implant diameter, and implant length with implant stability. **Methods:** Ten participants were enrolled in the study after a selective diagnosis. Forty-seven implants were classified into two groups: the study group included twenty-three dental implants with an additive of rhBMP-2/ACS, and the control group included twenty-four dental implants without an additive. Each patient received at least two implants on each ipsilateral side. The primary implant stability was measured at the surgical phase, and the secondary implant stability was recorded after 16–24 weeks by using the Resonance Frequency Analysis device. **Results:** There was a weak but not significant correlation between implant dimensions and stability, except in the control group. Concerning the ISQ relation to the jaw, the mandible showed a significant increase in primary stability for the study group compared to that in the control group, but no statistical relation was recorded. **Conclusion:** The mandible had higher ISO values for primary stability than the maxilla in both groups, with a non-significant connection. The maxilla in both groups had improved secondary stability, whereas the mandible had decreased. ([clinicaltrials.gov-NCT05719181](https://clinicaltrials.gov/NCT05719181)).

**Keywords:** Absorbable collagen sponge, Implant stability, Osseointegration, Resonance frequency analysis, rhBMP-2.

البروتين المخلوق للعظام البشرية المؤتلف من النوع الثاني كإضافة للعظام وعلاقته بأبعاد زراعات الأسنان واستقرارها: تجربة سريرية عشوائية منقسمة الفم

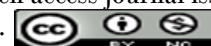
## الخلاصة

**الخلفية:** ينتمي البروتين المخلوق للعظام إلى عامل النمو التحويلي بيتا ويعتبر من العوامل البيولوجية التي تلعب أدوارًا رئيسية في عملية تكوين العظم. **الهدف:** قياس تأثير البروتين المخلوق للعظام البشري المؤتلف 2- مع حامل إسفنجي كولاجين قابل للامتصاص (rhBMP-2/ACS) على ثبات الغرسة الثانوية ودراسة علاقة العوامل الأخرى مثل موقع الفك المستلم للزرعة وقطر الزرعة وطول الزرعة مع استقرار الزرع. **الطريقة:** تم تسجيل عشرة مشاركين في الدراسة بعد التشخيص الانتقائي. تم استخدام سبعة وأربعين زرعة من نوع (Neobiotech®، كوريا) وتم تصنيفها إلى مجموعتين؛ تضمنت مجموعة الدراسة ثلاثة وعشرين زراعة أسنان مع مادة مضافة rhBMP-2/ACS وتضمنت المجموعة الأساس أربعة وعشرين زراعة أسنان بدون مادة مضافة. تلقى كل مريض غرستين على الأقل لكل جانب من الجانب المقابل. تم قياس ثبات الغرسة الأولى عند خط الأساس (المرحلة الجراحية) وثبات الغرسة الثانوية المسجلة بعد 16-24 أسبوعًا باستخدام جهاز تحليل تردد الرنين. **النتائج:** أظهرت علاقة ضعيفة ولكن غير معنوية بين أبعاد الزرعة وثباتها إلا في مجموعة الدراسة. وفيما يتعلق بعلاقة ISQ بالفك، فقد أظهر الفك السفلي زيادة ملحوظة في الثبات الأولى لدى مجموعة الدراسة مقارنة بالمجموعة الأساس ولكن لم يتم تسجيل أي علاقة إحصائية. **الاستنتاج:** لم يثبت وجود زيادة معنوية في ثبات الغرسة مقارنة مع مجموعة الأساس. يؤثر طول زراعة الأسنان على ثبات الزرعة في المجموعة الأساس لتحقيق الثبات الثانوي وبالعلاقة معنوية. قطر زراعة الأسنان ليس له أي تأثير على ثبات الزرعة. قدمت كلا المجموعتين قيمة ISO أعلى في الفك السفلي لتحقيق الاستقرار الأولي من الفك العلوي، ولكن بدون أهمية.

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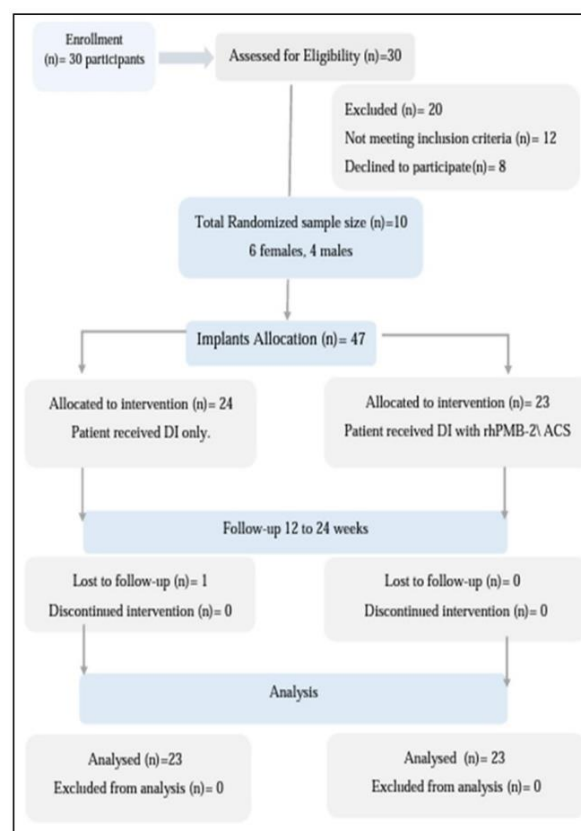
## INTRODUCTION

Branemark described "osseointegration" to explain the successful interaction of bone reinforcement with an implant body in the late 1960s [1,2]. It provides a structural and functional interaction between the living bone and the surface of a load-bearing implant [2,3]. The stability of the implant is one of the requirements for its clinical success [4]. Rao and Gill (2012) defined implant stability as an assessment of an implant's anchoring quality in alveolar bone, and it is regarded as the most important successful parameter in implants [5]. Implant stability can be grouped into two categories: mechanical (primary) stability and biological (secondary) stability. Primary stability is a mechanical concept characterized as the tightening of a dental implant instantly following the insertion in its designated osteotomy, in which the implant is regarded as having initial stability when it is clinically immovable at the time of insertion [6,7]. IPS is generally regarded as a necessity for osseointegration [8]. While biological stability is called secondary stability, it is the outcome of osseointegration (OI) [9,10]. Secondary stability is caused by bone apposition to the implant following implant insertion. It is obtained when a biological attachment and hemostasis start to form between both the host bone tissue and the implants, as well as between the implant and the host bone [11]. A most popular approach for assessing implant stability is resonance frequency analysis (RFA) [12], which involves measurement of the initial bending resonance frequency of a rod screwed into the implant [13]. The Osstell device is focused on the RFA method for determining an implant's harmonic response via the implant stability quotient (ISQ), which gives an estimation of the stiffness of the bone-implant structure [14]. Most clinicians utilize the concept of implant stability for osseointegration to evaluate the outcome of the treatment. Many methods have been proposed to do so, with the RFA being one of the most popular [15]. In order for dental implant treatments to be successful, stability as assessed by RFA must be taken into account. This may be determined by the implant stability quotient (ISQ) [16]. The release of the BMP protein from the surface of the implant has been aided in increasing "in vitro" bone cell proliferation, differentiation, and mineralization; it has also improved "in vivo" bone healing [17]. Urist *et al.* discovered the BMPs in 1965, and he was the first to describe "osteo-induction" [18]. rhBMP-2 is costly and has a limited level of stability and biological activity in vivo. According to this, we must increase the cells' ability to absorb it by incorporating them into slow-release delivery systems [19]. In previous studies, the concentration of rhBMP-2 varied from 0.75 to 2.0 mg/mL, which was equal in effect to the autogenous bone graft due to its ability to form de novo bone in addition to its clinical outcomes when prepared and used [20–22].

## METHODS

### Study design

The RCT was self-funded and actually registered in the Protocol Registration and Results System (PRS) at <https://clinicaltrials.gov> (NCT05719181). Ten participants were assessed for their eligibility according to the inclusion criteria (6 females, 4 males) and were included in the study. Their ages ranged from 28 to 60 years, and a total of 47 dental implants (DI) were inserted with conventional protocol with a triple-blind, split-mouth technique (all patients, surgeons, and data analysts had no idea when the intervention rhBMP-2/ACS was put in). All the parameters included in the study were tested for normal distribution at  $p < 0.05$  via the Shapiro-Wilk test. The intra-group comparison was done in the same group at different intervals of time, and the inter-group comparison was done between the two groups, as shown in the below CONSORT flow chart (Figure 1).



**Figure 1:** The CONSORT flow chart of the study.

### Inclusion criteria

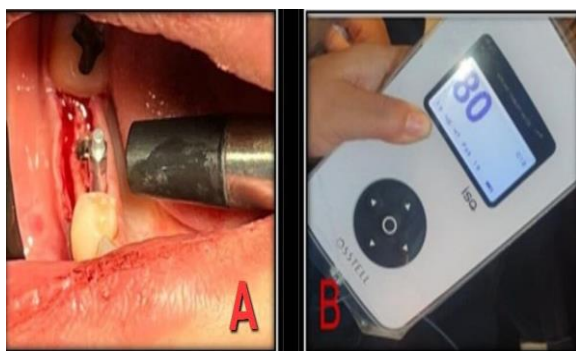
The participants enrolled in the study were selected in relation to the included criteria, which comprise good oral health, being healthy from systemic disease, being older than 18 years, being at least six months after tooth extraction, having the edentulous region healed (delayed implant protocol), and having at least two missed teeth in the unilateral or bilateral jaw from the canine to the 2<sup>nd</sup> molar area.

### Exclusion criteria

The excluded criteria involved the following: the presence of systemic illnesses; previous implantation or augmentation of the same region; additional bone augmentation treatments required (such as maxillary sinus augmentation); a sharp knife-edge ridge that is either completely or partially edentulous; any pathological disease at the implant site or an acute infection; an allergy to one of the materials to be used during the operation; pregnancy; radiation therapy; bisphosphonate drugs; osteoradionecrosis; and unstable periodontitis.

### Surgical procedure

Patients had their blood pressure monitored and reported before surgery. The patient was covered with sterile surgical drapes to reduce the possibility of extra oral contamination sources. Patients were then told to rinse their mouths with a 0.2% chlorhexidine solution. A full-thickness flap was elevated under local anesthesia with Lidocaine 2% (Septodont®, France) by using the infiltration technique only. Then, implant osteotomies were performed with continuous coolant and saline irrigation to prevent heating. In the conventional drilling technique, the first drill pilot drill (Guide Point Drill Ø1.35 PD13) was used for creating the initial hole in the osteotomy implant site. Then, a series of drills with an increasing diameter were used to expand the osteotomy according to the required dimension for implant placement in accordance with the recommendations of the selected implant system (Neobiotech®). The implant micromotor sets the speed (800 rpm) and torque (35 N/cm) [23]. In the study group, the rhBMP-2/ACS (2 mg/ml) formula was directed to implant cavities (Figure 2).



**Figure 2:** Smart peg engaged in correct position inside the fixture and Osstell device head put closely to the Smart peg device. (B) The implant primary stability reading.

While the control group had no additive of rhBMP-2\ASC formula, Then, the implants are inserted with a surgical micromotor with a torque of 35 N/cm and a speed equal to 35 rpm, or with the aid of a ratchet. After that, the implant fixture was applied to the crestal bone level. The primary implant stability (PIS) was measured by the *Osstell* device by screwing the

Smartpeg™ into the implant body, and four readings of ISQ values were recorded (in buccal, lingual, mesial, and distal directions) immediately following the insertion of the implant, and the average was registered for both the study and control groups (Figure 3). Then, after 16–24 weeks, the RFA measurements were repeated for registration of secondary implant stability.

### Ethical consideration

The protocol (reference number: 528, project number: 528622, in 17/4/2022) was approved by the ethical institution committee of the College of Dentistry, University of Baghdad, according to the Declaration of Helsinki in 1964. Written informed consent was obtained from all participants, which represented "the patient's acceptance" to participate in the study before starting the treatment.



**Figure 3:** The rh-BMP2/ACS formula was directed to the implant cavities.

### Statistical analysis

All data were collected, tabulated, and statistically analyzed using SPSS 26.0 for Windows (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as the mean±SD and median (interquartile range), and qualitative data were expressed as absolute frequencies (number) and relative frequencies (percentage). The Shapiro-Wilk test of normality verified the data's normality. Independent samples A Student's *t*-test was used to compare two groups of normally distributed variables, while the Mann-Whitney U test was used for non-normally distributed variables. A paired sample *t*-test was used to compare paired, normally distributed data. All tests were two-sided.  $p < 0.05$  was considered statistically significant.

### RESULTS

The resulting acceptable sample size consists of 47 implants; the first group consists of 23 implants with rh-BMP2/ACS as the study group; and the second group has no additives and includes 24 dental implants in the control group. The sample consists of 10 subjects aged 28–60 years old (4 males and 6 females) (Table 1).

**Table 1:** Descriptive data of dental implant distribution

Variable		DI n(%)
Group	Study (with rhBMP-2\ACS)	23(48.9)
	Control (without rhBMP2\ACS)	24(51)
Recipient jaw	Maxilla	22(46.8)
	Mandible	25(53.2)
Gender	Male	4(40)
	Female	6(60)
Tooth site No.	13,14,45,46	11(23.3)
	15,16,34,35	11(23.3)
	24,26,36,37	13(27.7)
	23,25,27,47	7(14.9)
	33,44,43	5(10.8)
	Total	47(100)

Regarding the relation of ISQ to the groups, there was an increase in the ISQ clinically, but there was no significant relation between the study and control groups at baseline (surgery time) or after 16–24 weeks ( $p=0.9$ ,  $p=0.6$ , respectively) (Figure 4).

**Table 2:** Descriptive statistic of ISQ among jaw recipient

Variable	DI n(%)	ISQ (mean±SD)					
		Baseline	<i>p</i>	After 16-24 weeks	<i>p</i>		
Jaw	Maxilla	Study	11(23.4)	66.64±9.16	0.7	69.16±4.91	0.8
		Control	11(23.4)	67.98±6.87		68.71±4.08	
	Mandible	Study	12(25.53)	72.02±5.53	0.4	71.65±4.96	0.41
		Control	13(27.66)	70.02±6.26		69.9±5.54	

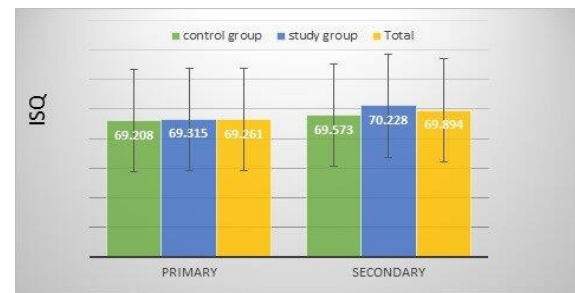
Results showed a weak but not significant relationship between the dimensions of implant stability except in the control group, where the results were weak but significant between secondary stability and implant length (Table 3).

**Table 3:** Comparison of ISQ with different DI dimensions

Groups	Diameter		Length		
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	
Control	Primary stability	-0.239	0.260	0.286	0.175
	Secondary stability	-0.063	0.770	0.471	0.020
Study	Primary stability	0.265	0.222	0.156	0.479
	Secondary stability	0.230	0.292	0.305	0.157

**DISCUSSION**

RCT (split-mouth) has an advantage in that most of the outcome variability among the patients has been eliminated from the intervention effects, which causes a probable increase in the statistical power [24,25]. On the other hand, these studies could be considered costly and time-consuming [26]. Implant surfaces probably have the greatest potential for enhancement in implant dentistry [27]. The study compared two groups, one with local application of rhBMP-2/ACS (study group) and the other without rhBMP-2/ACS (control group). The current study included 6 women (60%) and 4 men (40%), with more women than men. This was done so that there would be less bias when testing new treatments by figuring out how rhBMP-2



**Figure 4:** The relation of ISQ with groups.

Concerning the ISQ relation to the jaw, the mandible showed a significant increase in primary stability for the study group compared to that in the control group, but there was no statistical relation recorded, as illustrated in Table 2. On the other hand, the maxilla showed an increase in ISQ values after 16–24 weeks for the study group.

affected stability around DI in a triple-blinded study design. The explanation could also be agreed with by (28) who declared in his study that the highest percentage of females were attributed to 66.7%. The fact that females suffer from continuous hormonal changes during different periods of their lives, such as pregnancy and the postmenopausal period, which produce a negative effect on dental and periodontal health, causes earlier tooth loss, and this makes females more enthusiastic and seek the esthetic and functional replacement of teeth [29]. The implant's stability would change over the course of healing or osseointegration. The stability of ISQ values would change from higher primary stability to slightly decreased stability based on ISQ values due to the physiologic phenomena of bone modeling or remodeling, then return to equal or higher ISQ values than those originally observed [30]. The physiologic drop in ISQ values has been referred to as a "dip." Typically, a dip ranges between 3 and 9 ISQ units [31]. The change in stability over time referred to the biological event associated with the bone-implant interface [32]. Findings in the current study show that in the study group there is an increase in implant stability at the surgical phase, but with no significant change. Both stability levels (primary and secondary) are higher in the study group than in the control group, but there is no significant difference. The current study resulted in a positive correlation between implant length and stability (primary and secondary) within the control group. While in the control group, there was no relation between stability and implant length. The relationship between length and primary

stability has been a controversial issue for many years [33]. Much of the studies suggested that increasing the length played a critical role in reducing bone stress and stability in the poor density area (type IV) [34], and it could play an important role in the formation of the bone-to-implant contact (BIC) [35]. In spite of the fact that the diameter of implants has been identified as an influence on implant stability, when the implant diameter increased, the ISQ values also increased [36,37]. The current results demonstrate a weak but not significant relationship between implant diameter and stability (primary and secondary). While other studies showed a statistical correlation between implant diameter and ISQ, especially with a 4 mm diameter [38], Also, in the recent study, no statistical significance was observed between the implant stability and jaw recipient (maxilla, mandible) in regard to both groups (study and control), due to  $p > 0.05$ , in spite of the noticed increase in RFA (primary stability) in the mandibular arch, and the result coincided with the other study by Bischof *et al.* in 2004, who observed that the ISQ value was in general higher in the mandible than in the maxilla [36]. In the other studies, implants inserted in the mandibular arch had higher stability in comparison to those placed in the maxilla ( $p < 0.05$ ) [37]. A study in Iraq by Duha *et al.* in 2021 showed no significant effect of the recipient jaw on dental stability except for the primary implant stability, where the maxillary implants demonstrated higher stability values [38]. Further clinical studies evaluating the effects of rhBMP-2 on bone density in the bone-implant interface measured by CT and histologically Also, further studies considering concentration, dosages, and alternative delivery methods of rhBMP-2, use of rhBMP-2 in combination with other growth factors to evaluate their effects on acceleration of bone formation and implant stability, a comparative study for measurement of rhBMP-2 in delayed implant placement by utilization of flapless and flap techniques, and the comparative study for measurement of BMP in delayed implant placement in comparison with an immediate loading implant to measure the rhBMP-2 on stability.

### Study Limitations

Comparing the results of the study to the existing literature was rather difficult, as most studies used animal models in addition to the heterogeneity of the agents, concentrations, local application formulas, indications for use, variables of interest, and evaluation tests.

### Conclusion

In both groups, the mandible showed higher ISO values for primary stability than that in the maxilla, with a non-significant correlation. In both groups, the maxilla showed increased secondary stability, while in the mandible it had decreased.

### ACKNOWLEDGMENT

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### Conflicts of interest

There are no conflicts of interest.

### Funding source

The authors did not receive any source of fund.

### Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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