Table 5 Description of Complications of Cast Metal and Resin Core Restorations

	Cast metal core, n (%)	Resin core, n (%)	P*
Total	372 (100.0)	1,752 (100.0)	
Core failures	72 (19.4)	193 (11.0)	
1- Core loosening	14 (3.8)	24 (1.4)	.0016
Caries	13 (3.5)	17 (1.0)	.0002
Post fracture	0 (0.0)	4 (0.2)	.3563
Tooth fracture	1 (0.3)	3 (0.2)	.6934
2- Core removal	6 (1.6)	44 (2.5)	.2992
Caries	3 (0.8)	18 (1.0)	.6957
Endodontic retreatment	3 (0.8)	26 (1.5)	.3064
3- Tooth extraction or hemisection	52 (14.0)	126 (7.2)	<.0001
Caries	18 (4.8)	22 (1.2)	<.0001
Tooth fracture	9 (2.4)	13 (0.7)	.0037
Marginal periodontitis	9 (2.4)	17 (1.0)	.0210
Post fracture	0 (0.0)	2 (0.1)	.5144
Periapical periodontitis	12 (3.2)	56 (3.2)	.9766
Unknown	4 (1.1)	15 (0.9)	.6835

*Chi-square test.

Discussion

Study Design

There were three prominent differences between this study and prior long-term studies: *(1)* the prospective 15-year follow-up period and the large study population, *(2)* the applied structured clinical core record that enabled objective and standardized assessment, and *(3)* the cementation of both core restorations with adhesive resin cement, which displayed a better in vitro performance than conventional luting systems previously.[8–11]

Despite a thorough search in the Medline database, this study was the first to show the longitudinal CSRs of cast metal cores luted with adhesive resin cement. Moreover, this study was the first to compare the cast metal core CSRs with the CSRs of resin cores cemented with a similar adhesive luting material.

On the other hand, this study also had some limitations, such as the large number of censored cases, which might occur naturally in long-term studies due to a patient's hesitation or inability to return for periodontal maintenance. Some patients were not able to return due to physical impairment, change of address, or other unknown reasons not identified in the clinical core record. However, a comparison of censored core rates between cast metal and resin core groups showed no statistical differences (chi-square test, $P = .1385$). Therefore, the core survival/failure rates of both groups were not influenced notably by the large number of censored cases. Future studies should use a more rigorous periodontal recall system, such as sending letters to subjects, making phone calls, or even providing additional benefits (eg, transportation costs) to reduce the number of censored cases.

Another limitation was the nonrandomization of core treatment selection, which was determined according to the clinician's preference. This aspect of the study could partially explain the baseline intergroup disparities of the subsample for analysis of risk factors for core failure, particularly in regard to remaining coronal dentin and core margin location (Table 2). However, a subsequent multivariate analysis (Cox proportional hazards test) of the follow-up data hopefully negated the baseline discrepancies because some of the significant factors detected at baseline (core margin location, tooth type, tooth location, and DMFT Index) were not identified as statistically significant risk factors for core failure (Tables 2 and 4). To better control and equalize intergroup baseline data, as well as to obtain more reliable and valid results, randomized clinical trials would be the best clinical design. However, randomization is impossible in some clinical studies due to ethical considerations.

Finally, the clinical classification of the remaining coronal dentin was determined by the clinician's own judgment rather than by the precise categorization of the number of remaining dentin walls or the degree of dentin height and width. Future studies should include more specific and accurate dental anatomical inclusion criteria.[1]

Core Survival Rates and Risk Factors for Core Failure

The null hypothesis that no significant differences in the CSRs between the two core groups would be observed was rejected. The results of the Kaplan-Meier curve clearly demonstrated the higher CSR of the resin core group (log-rank test, $P < .0001$) (Fig 3). The lifetable analysis demonstrated that the 15-year cumulative

CSRs were 55.4% and 78.7% for the cast metal group and the resin core group, respectively (Table 3).

According to a recent systematic review, there has been only one quasi-randomized clinical trial evaluating the CSRs of resin and cast metal cores.[1] The results observed herein are consistent with that clinical study, which demonstrated that the CSR of resin cores was associated with significantly fewer failures than conventional cast metal cores after 4 years of clinical follow-up.[19]

However, previous prospective longitudinal studies demonstrated no differences in the CSRs between the two core restorations, affirming that both treatments have good long-term outcomes.[20,21] One study, however, involved a limited sample size of less than 100 cores,[20] while the cementation techniques were not adequately described in the other study.[21] Two previous systematic reviews reported that the CSR up to 72 months varied from 87.2% to 91.0% for cast metal cores and from 81.0% to 86.4% for resin cores.[4,6] In this study, a CSR of 89.6% for cast metal cores and a notably higher rate of 94.2% for resin cores for the same time interval was observed (Table 3).

There have been very few long-term follow-up studies evaluating CSRs for more than 15 years. As a result, a detailed comparison was not feasible. A recent study reported a 17-year cumulative CSR of 84.0% for cast metal cores luted with zinc phosphate or glass-ionomer cement and a variance from 71.0% to 84.0% for resin core cases with minimal and substantial dentin height, respectively.[7] The patient sample in that study, however, could have been biased due to different selection criteria used by the 17 dental offices that collected the data.

In accordance with previous reviews and longitudinal studies, the authors believe that the major risk factor for core failure is the absence of remaining coronal dentin (Table 4).[1–4,7,20,21] Extensive tooth damage caused by caries, trauma, or consecutive filling failures weakens the structure of the remaining tooth dentin biomechanically, thus increasing the likelihood for tooth or root fracture.[1–3] Several in vitro studies have also shown that a decreased amount of remaining dentin height and thickness is associated with lower tooth fracture resistance independent of the core restoration type.[2,22–25] Therefore, preservation of tooth structure during any dental procedure is a must.[1–3]

For that reason, differences in tooth preparation techniques could have influenced the overall CSR. The cast metal cores required undercut-free tapered root canal preparation, which sometimes required dentin overcutting. However, in the resin core treatment, the tooth could be restored even with internal undercut. Root preparation was therefore more conservative (ie, with minimal dentin cut and axial wall parallelism).[2,26] Moreover, the prefabricated post may have fit better because its standardized diameter size matched the Largo Peeso Reamer.

The Cox proportional hazards test also revealed the cast metal core restoration type as a significant risk factor for core failure, independent of the absence of remaining coronal dentin (Table 4). An additional intergroup comparison among the specific subsample of cores luted only in severely damaged teeth (with an absence of remaining coronal dentin) demonstrated a significantly lower failure rate of resin cores than cast metal cores (log-rank test, $P = .0282$). This finding could be explained partially by the similar elasticity modulus of the resin used and proper tooth dentin, which would absorb more occlusal forces, reduce the probability of disruption of the adhesive layer, and prevent tooth fracture.[27–29]

On the other hand, cast metal cores could presumably increase the probability of tooth fracture, especially in teeth with extensive coronal dentin destruction, due to mechanical properties of greater hardness and lower resilience in comparison to tooth dentin, which would not reduce the intensity of occlusal forces distributed to the devitalized root and coronal dentin.[24,30] This explanation is supported by the higher incidence of complications in the cast metal core group, which experienced a 14.0% incidence of tooth extraction/hemisection and an almost 4.0% incidence of core loosening. In contrast, the resin core group experienced incidence rates of 7.2% and 1.4% for the respective conditions (Table 5). In vitro studies have also demonstrated that endodontically treated teeth restored with cast metal cores had a higher probability of vertical fracture; moreover, the fractures were more catastrophic and usually resulted in tooth extraction.[23,24]

Nevertheless, these results should be analyzed cautiously because of the marked baseline differences of the subsample for risk analysis for core failure (Table 2). There could have also been a possible bias effect due to unknown predictor variables (noninvestigated predictors). Therefore, the extent to which the consequences of sample nonrandomization and the limited number of analyzed predictors could have influenced the CSR is unknown. For example, a recent study demonstrated that dentin contaminated with provisional cements used between appointment intervals reduced resin bond strength significantly in comparison to freshly cut dentin.[31] Therefore, direct resin core cementation might have led to better bond adhesion to the tooth structure, thus resulting in better outcomes. This phenomenon could also explain the significantly lower incidence of caries in the resin core group.

The decreased mechanical strength of aged teeth could explain why age at core installation was an independent predictor for core failure (Table 4).[32–34] For

example, Kinney et al[34] reported an almost 20.0% reduction in dentin fracture resistance in aged teeth. Moreover, elderly patients would have a higher incidence of root canal retreatment and core recementation associated with cumulative deleterious fatigue due to long-term sustained occlusal stress.

Finally, a significantly higher core failure rate was observed in male subjects. This finding may be partially explained by the fact that the occlusal force of men is generally higher than that of women.[35,36] Individual oral care might have played an important role in treatment longevity; however, no conclusion could be drawn concerning that variable because no data were collected in regard to the frequency and quality of oral health maintenance.

Other factors such as tooth location, tooth type, DMFT index, core margin location, and root canal form did not show the statistical significance after the 15-year observation period. Previous studies have drawn attention to tooth type because anterior teeth are loaded nonaxially and therefore may be subject to more damaging occlusal stress.[2,37–39] However, based on the results observed herein, the authors believe that the effects of oblique occlusal loading on the anterior teeth were not likely to be a relevant risk factor for core failure, rather the amount of remaining dentin would be a determinant, independent of tooth type or position.

Conclusion

This clinical comparative cohort study investigated the 15-year CSR of resin and cast metal core restorations. This study showed that the survival rate of resin cores was significantly higher than that of the cast metal cores and the absence of remaining coronal dentin, core restoration type (cast metal), higher age at core insertion, and sex (male) were significant risk factors for core failure. Furthermore, the incidence of core complications such as caries, tooth fracture, and marginal periodontitis was significantly higher in the cast metal core group.

These data are helpful for understanding the long-term prognosis of adhesively cemented cast metal and resin cores and may be useful in clinical decision making. Future studies are necessary to evaluate the relationship between the core survival rate and the influence of as yet unidentified risk factors, such as the degree of remaining coronal and root dentin structure (wall number and thickness), occlusal force, parafunctional habits (clenching and bruxism), type of prosthetic treatment loading the treated tooth, post length, post diameter, and strict periodontal condition.

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References

1. Bolla M, Muller-Bolla M, Borg C, Lupi-Pegurier L, Laplanche O, Leforestier E. Root canal posts for the restoration of root filled teeth. Cochrane Database Syst Rev 2007;(1):CD004623.
2. Fernandes AS, Dessai GS. Factors affecting the fracture resistance of post-core reconstructed teeth: A review. Int J Prosthodont 2001; 14:355–363.
3. Dietschi D, Duc O, Krejci I, Sadan A. Biomechanical considerations for the restoration of endodontically treated teeth: A systematic review of the literature, Part II (Evaluation of fatigue behavior, interfaces, and in vivo studies). Quintessence Int 2008;39:117–129.
4. Heydecke G, Peters MC. The restoration of endodontically treated, single-rooted teeth with cast or direct posts and cores: A systematic review. J Prosthet Dent 2002;87:380–386.
5. Goodacre CJ, Bernal G, Rungcharassaeng K, Kan JY. Clinical complications in fixed prosthodontics. J Prosthet Dent 2003; 90:31–41.
6. Creugers NH, Mentink AG, Käyser AF. An analysis of durability data on post and core restorations. J Dent 1993;21:281–284.
7. Fokkinga WA, Kreulen CM, Bronkhorst EM, Creugers NH. Composite resin core-crown reconstructions: An up to 17-year follow-up of a controlled clinical trial. Int J Prosthodont 2008; 21:109–115.
8. Bolhuis HP, de Gee AJ, Pallav P, Feilzer AJ. Influence of fatigue loading on the performance of adhesive and nonadhesive luting cements for cast post-and-core buildups in maxillary premolars. Int J Prosthodont 2004;17:571–576.
9. Hagge MS, Wong RD, Lindemuth JS. Retention strengths of five luting cements on prefabricated dowels after root canal obturation with a zinc oxide/eugenol sealer: 1. Dowel space preparation/cementation at one week after obturation. J Prosthodont 2002;11: 168–175.
10. Ayad MF, Rosenstiel SF, Salama M. Influence of tooth surface roughness and type of cement on retention of complete cast crowns. J Prosthet Dent 1997;77:116–121.
11. Naumann M, Sterzenbach G, Rosentritt M, Beuer F, Frankenberger R. Is adhesive cementation of endodontic posts necessary? J Endod 2008;34:1006–1010.
12. Balbosh A, Ludwig K, Kern M. Comparison of titanium dowel retention using four different luting agents. J Prosthet Dent 2005; 94:227–233.
13. Prati C, Chersoni S, Pashley DH. Effect of removal of surface collagen fibrils on resin-dentin bonding. Dent Mater 1999;15:323–331.
14. Wakabayashi Y, Kondou Y, Suzuki K, Yatani H, Yamashita A. Effect of dissolution of collagen on adhesion to dentin. Int J Prosthodont 1994;7:302–306.
15. Kaneshima T, Yatani H, Kasai T, Watanabe EK, Yamashita A. The influence of blood contamination on bond strengths between dentin and an adhesive resin cement. Oper Dent 2000;25:195–201.
16. Inoue S, Murata Y, Sano H, Kashiwada T. Effect of NaOCl treatment on bond strength between indirect resin core-buildup and dentin. Dent Mater J 2002;21:343–354.
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Asses 1958;53:457–481.
18. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data, ed 1. New York: John Wiley & Sons, 1980.

19. Ferrari M, Vichi A, García-Godoy F. Clinical evaluation of fiber-reinforced epoxy resin posts and cast post and cores. Am J Dent 2000;13 (spec no.):15B–18B.
20. Jung RE, Kalkstein O, Sailer I, Roos M, Hämmerle CH. A comparison of composite post buildups and cast gold post-and-core buildups for the restoration of nonvital teeth after 5 to 10 years. Int J Prosthodont 2007;20:63–69.
21. Creugers NH, Mentink AG, Fokkinga WA, Kreulen CM. 5-year follow-up of a prospective clinical study on various types of core restorations. Int J Prosthodont 2005;18:34–39.
22. Arunpraditkul S, Saengsanon S, Pakviwat W. Fracture resistance of endodontically treated teeth: Three walls versus four walls of remaining coronal tooth structure. J Prosthodont 2009;18:49–53.
23. Varvara G, Perinetti G, Di Iorio D, Murmura G, Caputi S. In vitro evaluation of fracture resistance and failure mode of internally restored endodontically treated maxillary incisors with differing heights of residual dentin. J Prosthet Dent 2007;98:365–372.
24. Pontius O, Hutter JW. Survival rate and fracture strength of incisors restored with different post and core systems and endodontically treated incisors without coronoradicular reinforcement. J Endod 2002;28:710–715.
25. Sornkul E, Stannard JG. Strength of roots before and after endodontic treatment and restoration. J Endod 1992;18:440–443.
26. Sorensen JA, Martinoff JT. Clinically significant factors in dowel design. J Prosthet Dent 1984;52:28–35.
27. Holmes DC, Diaz-Arnold AM, Leary JM. Influence of post dimension on stress distribution in dentin. J Prosthet Dent 1996;75:140–147.
28. Ausiello P, Apicella A, Davidson CL. Effect of adhesive layer properties on stress distribution in composite restorations—A 3D finite element analysis. Dent Mater 2002;18:295–303.
29. Asmussen E, Peutzfeldt A, Sahafi A. Finite element analysis of stresses in endodontically treated, dowel-restored teeth. J Prosthet Dent 2005;94:321–329.
30. Fokkinga WA, Kreulen CM, Vallittu PK, Creugers NH. A structured analysis of in vitro failure loads and failure modes of fiber, metal, and ceramic post-and-core systems. Int J Prosthodont 2004;17:476–482.
31. Magne P, Kim TH, Cascione D, Donovan TE. Immediate dentin sealing improves bond strength of indirect restorations. J Prosthet Dent 2005;94:511–519.
32. Ager JW 3rd, Nalla RK, Balooch G, et al. On the increasing fragility of human teeth with age: A deep-UV resonance Raman study. J Bone Miner Res 2006;21:1879–1887.
33. Senawongse P, Otsuki M, Tagami J, Mjör I. Age-related changes in hardness and modulus of elasticity of dentine. Arch Oral Biol 2006;51:457–463.
34. Kinney JH, Nalla RK, Pople JA, Breunig TM, Ritchie RO. Age-related transparent root dentin: Mineral concentration, crystallite size, and mechanical properties. Biomaterials 2005;26:3363–3376.
35. Braun S, Bantleon HP, Hnat WP, Freudenthaler JW, Marcotte MR, Johnson BE. A study of bite force, part 1: Relationship to various physical characteristics. Angle Orthod 1995;65:367–372.
36. Waltimo A, Könönen M. A novel bite force recorder and maximal isometric bite force values for healthy young adults. Scand J Dent Res 1993;101:171–175.
37. Sorensen JA, Martinoff JT. Intracoronal reinforcement and coronal coverage: A study of endodontically treated teeth. J Prosthet Dent 1984;51:780–784.
38. Naumann M, Blankenstein F, Kiessling S, Dietrich T. Risk factors for failure of glass fiber-reinforced composite post restorations: A prospective observational clinical study. Eur J Oral Sci 2005;113:519–524.
39. Naumann M, Reich S, Nothdurft FP, Beuer F, Schirrmeister JF, Dietrich T. Survival of glass fiber post restorations over 5 years. Am J Dent 2008;21:267–272.

Literature Abstract

The economic value of teeth

This is a rare but interesting paper published by nondental individuals on a community-based dental topic. This paper examined the economic value and the effect of oral health on labor market outcomes by exploiting variation in access to fluoridated water during childhood. The authors studied US populations with local water district fluoridation from the 1960s onward. Since this study was conducted by nonclinicians, oral health was not evaluated in the data. It was assumed that children who live in a district with water fluoridation have better teeth in general. The 1992 Water Fluoridation Census, compiled by the Center of Disease Control, contained details on the fluoridation status of every public water system in the United States (eg, date, population served, natural or chemically adjusted). The authors combined several secondary data sets in this study to obtain information on fluoridation status, earnings, and background demographics. Their results showed that children who grew up in a district with fluoridated water earn more than a comparable cohort without fluoridated water. Fluoride exposure during childhood until four anterior teeth have erupted has a statistically significant effect on the hourly earnings of women; the effect for men is statistically insignificant. The beneficial economic effect is almost limited exclusively to women from a low socioeconomic status. There was little evidence to support occupational sorting, statistical discrimination, and productivity as potential channels of these effects.

Glied S, Neidell M. *J Human Resources* 2010;45:468–496. **References:** 38. **Reprints:** Sherry Glied, Mailman School of Public Health, Columbia University, Department of Health Policy and Management, 600 West 168th Street, Room 610, New York, NY 10032—*Ansgar C. Cheng, Singapore*

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ORIGINAL ARTICLE

Test–retest reliability of MRI-based disk position diagnosis of the temporomandibular joint

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Abstract This study evaluated the test–retest reliability for determining the temporomandibular joint (TMJ) disk position, diagnosed using magnetic resonance imaging (MRI). These assessments were done as a base-line measurement for a prospective cohort study, which examines the risk factors for precipitation and progression of temporomandibular disorders. Fifteen subjects (mean age, 24.2±0.94 years; male/female=8/7) were recruited from the students of Okayama University Dental School. Sagittal MR TMJ images were taken with a 1.5-T MR scanner (Magneton Vision, Siemens) in close and maximal open positions twice at about 1-week (6–11 days) interval. The images were displayed using 200% magnification on a computer screen with a commercially available image software package (OSIRIS, UIN/HCUG). Three calibrated examiners diagnosed the disk positions using the standardized criteria. The disk position of each joint was classified as normal, anterior disk displacement with or without reduction, and others. The first and second disk position diagnoses were compared, and the test–retest reliability level was calculated using the kappa index. The second disk position diagnosis was consistent with the first in 27 out of 30 joints. The calculated kappa value representing the test–retest reliability level between the first and second disk position diagnosis was 0.812. These results indicated that the test–retest reliability of MRI-based diagnosis of TMJ disk positions at about 1-week interval was substantially high, even though they were not completely consistent.

Keywords Temporomandibular disorders (TMD) · Magnetic resonance imaging (MRI) · Temporomandibular joint disk position · Diagnosis · Reliability

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Introduction

Magnetic resonance imaging (MRI) can accurately depict the temporomandibular joint (TMJ) disk position. One major advantage of MRI over all other radiographic imaging techniques is that it does not expose the patient to radiation. It is also non-invasive, painless, and of minimal risk potential in comparison to other imaging techniques [1–7]. However, the most crucial element is that the image accurately depicts the TMJ disk position and configuration. The validity of MRI in the assessment of the

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TMJ disk position has been evaluated using autopsy specimens. Westesson et al. [8] first compared the disk position of sagittal and coronal MR images with corresponding sagittal cryosections using 15 fresh TMJ autopsy specimens. They demonstrated that MRI correctly delineated the position of the disk in 11 (73%) joints [8]. This accuracy rate is slightly lower than has been reported for arthrography [9, 10]. However, there have been substantial improvements in imaging hardware, coupled with several software upgrades. Schwaighofer et al. [11] reported that MR images accurately assess the TMJ disk position at the rate of 86%. In addition, the most recent study using a larger number of samples (55 joints) by Tasaki and Westesson [12] demonstrated that MRI was 95% accurate in the assessment of disk position and disk form and 93% accurate in the assessment of osseous changes. They concluded that MRI should therefore be considered the prime imaging modality for analyzing the soft- and hard-tissue changes of the TMJ.

On the other hand, with regard to the reliability of disk position assessment, some studies evaluated the effect of examiner calibration on inter-examiner agreement levels on disk position assessment. These studies suggested that performing the suitable examiner calibration programs can reduce the examiner variation [13, 14]. Another study evaluated whether the difference of TMJ disk status influences inter-examiner reliability of the disk position assessment. Nebbe et al. [15] reported that the kappa statistics of agreement indicated moderate agreement among all four examiners for both the medial and lateral components of the joints. In addition, they demonstrated that disk displacement without reduction was the category with the greatest agreement among all examiners (kappa= 0.914). Furthermore, the inter-examiner reliability was excellent for diagnosing disk displacements with reduction (kappa=0.78) and for disk displacement without reduction (kappa=0.94), when the image analysis criteria developed by Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Validation Project was utilized [16].

However, no study has so far attempted to assess the test–retest reliability of plurally MRI-scanned individual joint disk positions. Such information is useful and indispensable, because an MRI-based disk position assessment would be questionable for clinical and research application if the test–retest reliability is not reliable. Therefore, this study investigated the test–retest reliability levels of MRI-based disk position assessment in asymptomatic volunteers. The study subjects underwent MRI scanning of the TMJ twice with the jaws in closed and maximally open positions in a 1-week interval, and the results of the disk position assessment were compared between the initial and second scans. Plural examiners participated to assess the disk positions in order to evaluate the disk position accurately, and an examiner calibration program was performed to standardize the inter-examiner assessment ability before the investigation. In addition, since the three-dimensional assessment using sequential multi-slice images of each joint may possibly diagnose the disk position more accurately, this study detected the disk position using seven sequential images of each joint.

Materials and methods

Subjects

This study was incidentally conducted as a base-line measurement of a prospective cohort study on risk factors for the precipitation and progression of TMD. The study subjects of this large cohort study are the students of Okayama University Dental School. The participants in the current study were recruited from the above larger subject population. In total, 30 subjects (male/female=16/14; mean age, 24.1±2.97) participated in this study, and all of them fulfilled the following subject criteria. The inclusion criteria were (1) willing to participate in the study and (2) less than 30 years old. The exclusion criteria of this study were (1) having claustrophobia and (2) not willing to undergo MR imaging twice. Half of those subjects (male/female=8/7; mean age, 23.9±0.24) were involved in the preliminary examiner calibration program. MR images of their TMJs were taken twice, and the mean interval between the initial and second MRI scanning was 38.4±1.24 (from 31 to 48) days. Another 15 subjects (male/female=8/7; mean age, 24.2±0.24) participated in the main study in this report. They also had MR images of their TMJs taken twice with a mean interval of 7.1±0.3 days (range from 6 to 11 days). This study protocol was approved by the Ethical Committee for Human Research in Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (No. 13).

Clinical examination

The clinical signs and symptoms of each subject were examined by any of two examiners (C.S-N and T.O) before the MR images were obtained. Both two examiners were TMD specialists, and the calibration was performed before the experiment. The clinical examination involved the mouth opening range measurement and the palpation of the TMJ noise. In addition, the subjects provided information concerning pain in the TMJ and the history of the TMJ noise. This process was also performed twice before each scan was performed, and the examiner was randomly assigned at each examination.

MRI scanning technique

Bilateral sagittal MR images of the TMJs with intercuspal and maximally jaw-opening positions were taken twice in each subject. Scans were performed with a 1.5-T MR imaging system (Magnetom Vision: Siemens, Erlangen, Germany) by the same technical expert (H.Y.). Sagittal proton density-weighted images were taken with a fast spin echo technique (repetition time, 2,400 ms; slice thickness, 3 mm; field of view, 125 mm; matrix, 256×80) and through the use of a unilateral surface coil (127 mm). Each subject's head was placed with the Frankfort plane parallel to the opening of the scanner. The head was fixed in position with adhesive tape on a foam rubber support.

Criteria to interpret the disk status

Continuous multi-slice images (at intervals of 3 mm) were obtained in both the close and open jaw positions. The images were magnified (200%) and displayed on a computer screen using a commercially available imaging software program (OSIRIS, UIN/HCUG, Geneva, Switzerland). First, the individual disk position of the images was examined separately by three examiners (T.K., T.O., and C.N.) All examiners were the TMD and orofacial pain specialists. All examiners were blinded to age, gender, symptoms of each subject, and the results of the disk position assessment by other examiners. The criteria for disk position on the image were in accordance with the IZ (intermediate zone) criteria described by Orsini et al. [17, 18]. These criteria determine the disk position by judging the position in relation to the line where the center of two circles is connected and the posterior and anterior bands [19] (Fig. 1). The position of the disk was considered to be normal if the IZ was located between the anterior-superior aspect of the condyle and the posterior-inferior aspect of the articular eminence in the middle or above a line that joined the centers of two imaginary circles which were fitted to these structures. These circles were positioned to closely approximate the condyle and the eminence outlines [20]. On the other hand, the judgment of the disk position was "anterior disk displacement" when the posterior band was located anterior from the line (Fig. 2). Furthermore, the judgment of the disk position

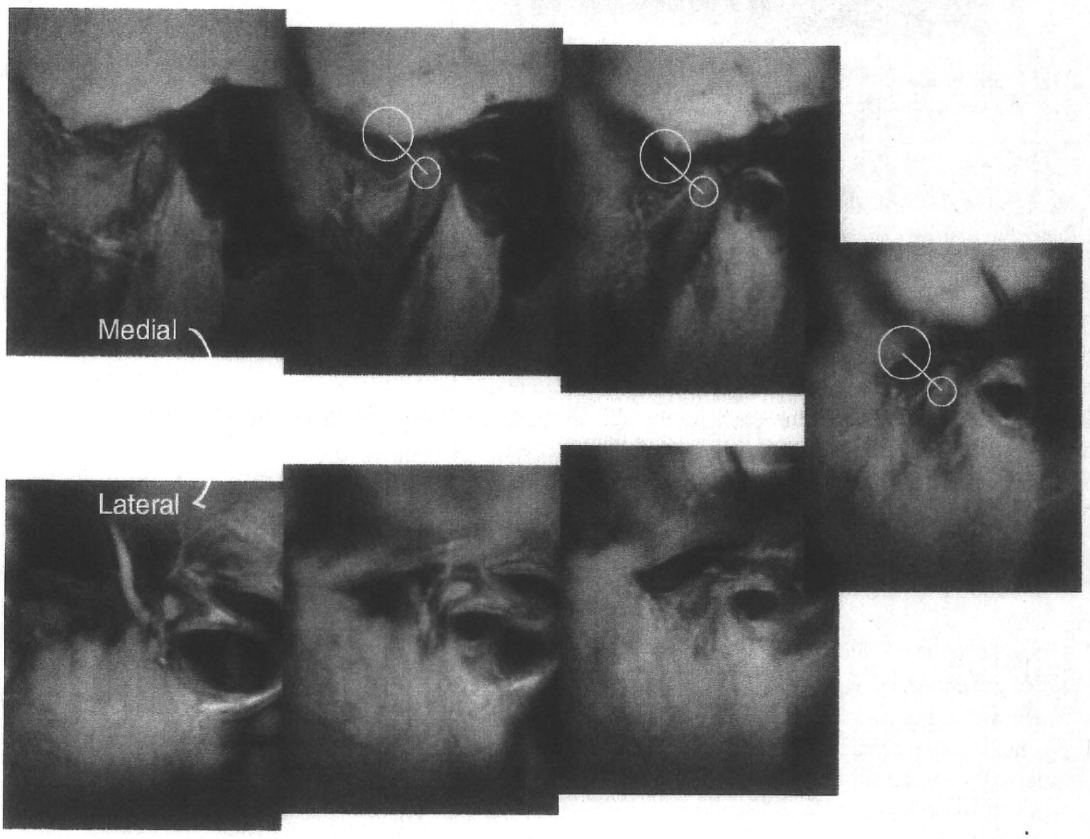

Fig. 1 The images of the subject who was diagnosed as normal disk position using the criteria in this study. The images reveal that the *line*, connecting the center of the two *circles*, is located between the anterior and posterior bands

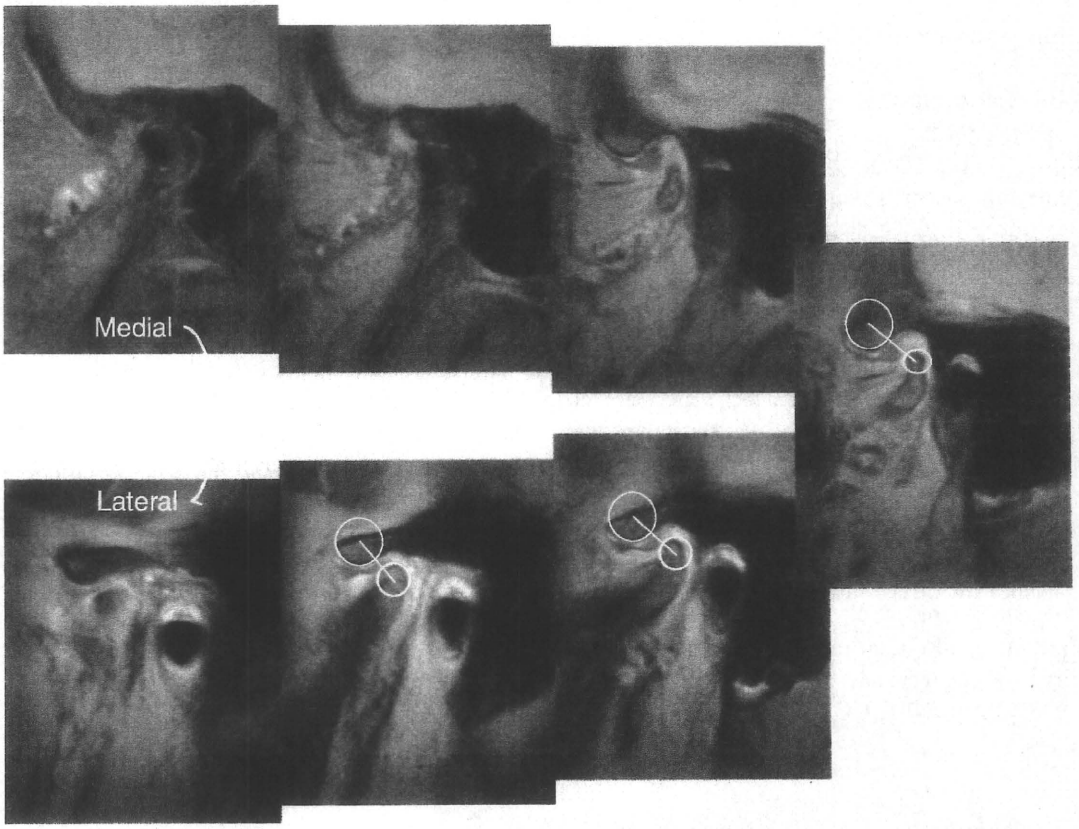

Fig. 2 The images of the subjects who were diagnosed as anterior disk displacement using the criteria in this study. The posterior band was located anterior from the *line*, connecting the center of the two *circles*

was "posterior disk displacement" when the anterior band was located from the line backward, and others were regarded as normal position. The disk position of the joint was considered displaced when at least one of the seven slices in each TMJ was diagnosed as displaced. The disk position, assessed in both the open- and the closed-mouth, was combined, and the final categorization of the joint disk status was formulated for each joint, e.g., normal, anterior disk displacement with or without reduction (ADDwR or ADDwoR), or posterior disk displacement either with or without reduction (PDDwR or PDDwoR).

Calibration procedures for the three examiners

First, the three examiners separately diagnosed the initial set of the 30 MR images with the aforementioned criteria. Then, all examiners discussed the result of their joint disk position assessment, and when disagreement existed, a mutual consensus on the disk position assessment criteria was reached. This calibration discussion took approximately 2 min for each joint disk position. Therefore, 1 h was necessary to assess 30 joints. Next, the three examiners diagnosed the second set of the 30 joints' MR images. The inter-examiner agreement before and after calibration were calculated by using a kappa index. Those indices were calculated between the examiners (A, B, and C) two by two (AB, AC, and BC).

Test–retest reliability of the categorization of TMJ disk status

The three calibrated examiners next assessed another 30 TMJ disk status (15 subjects) using the MR images scanned twice at a week interval (mean interval, 7.1± 0.3 days). This new examination was performed under the same conditions as the previous calibration program. A diagnosis was considered to have been achieved for the final individual joint disk position when at least two of the three examiners agreed on the diagnosis. The results of diagnosed disk position at both the initial and second scans were compared, and these agreements were evaluated using the kappa index calculations (Fig. 3).

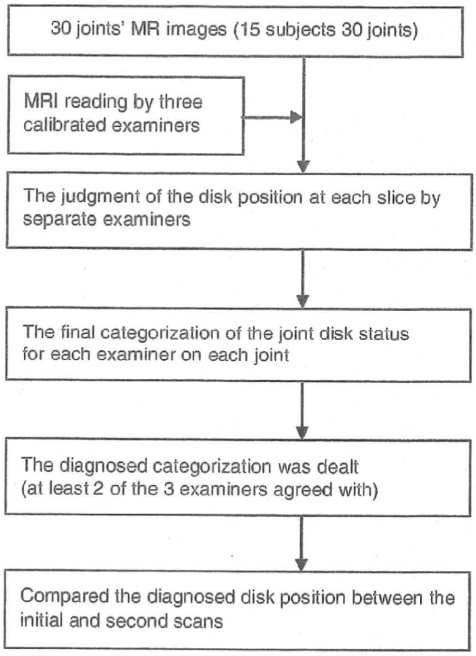

Fig. 3 A flow sheet for the test–retest reliability assessment of the MRI-based diagnosis of the TMJ disk position

Results

Effect of examiner calibration on the TMJ disk status assessment

The comparisons of inter-examiner agreement between before and after calibration are shown in Fig. 4. The mean kappa values among the three examiners increased from κ= 0.377 (before) to κ=0.812 (after) as a result of the calibration program. This kappa value after the calibration program reached almost the perfect level, which was proposed by Landis and Koch [21]. These results clearly suggest that the inter-examiner agreements significantly improved by the examiner calibration utilized in this study.

Test–retest reliability levels of MRI-based assessment of TMJ disk status

Table 1 shows the comparisons of the joint disk status and clinical signs and symptoms between the initial and the second MRI scan in each subject of the main study. Nineteen of 30 joints were diagnosed to be in a normal position, and others were regarded as disk displacement in both the initial and second scans. However, the results of the disk position status of several joints were not consistent between the initial and second scans. While the disk position of 27 joints were consistently diagnosed same positions between initial and latter scans, the disk position of the three joints varied between two scans. The kappa value calculated using the results obtained from two scans was κ=0.812. These results suggest that the test–retest reliability of MRI-based classification of TMJ disk status at 1-week interval was substantially high, even though it was not completely consistent.

A couple of subjects showed a fluctuation between the examinations performed at a 1-week interval. While one of the subjects (subject No. 1) did not show any joint clicking at the first examination (at the initial MRI scanning), it was seen at the second examination (at the second MRI scanning) on the right side TMJ. The joint disk status diagnosed by MRI was also changed from ADDwoR (initial scan) to ADDwR (second scan) in this subject. On the other hand, two subjects showed a fluctuation of joint clicking between the initial and second examination (right side TMJ of subject Nos. 2 and 15). Interestingly, the joint disk statuses of those subjects were both in the normal position and did not change between the initial and the second MRI scanning. In addition, the joint disk statuses of two of the subjects (Nos. 3 and 5) changed from normal to ADDwR between initial and second scanning. However, none of those subjects showed any joint clicking during both the initial and second clinical examination.

Discussion

A review of the literature suggests that MRI is the optimal way to image the hard and soft tissues of the TMJ in patients with signs and symptoms of TMD [22, 23]. It can accurately depict abnormalities of disk position and morphology, and has therefore been used to substantiate the clinically suspected existence of disk displacement. Although a large number of studies reveal the excellent validity of the MRI-based diagnosis of TMJ disk position [11, 12], few studies have tested the reliability. Several

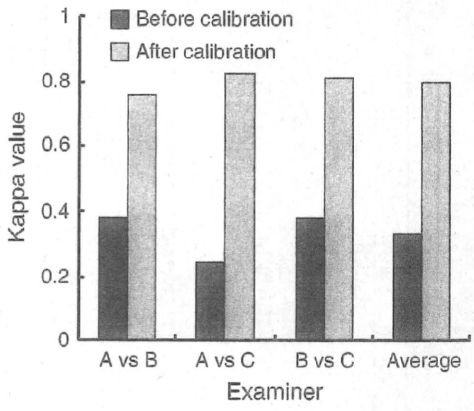

Fig. 4 The comparisons of inter-examiner agreement between before and after the calibration program

Table 1 The comparisons of the joint disk status and clinical signs and symptoms of the second subject group between the initial and second MRI scans

	Gender	Age	Joint disk status				Clicking				History of clicking				TMJ pain during jaw opening					
			Right TMJ		Left TMJ		Right TMJ		Left TMJ		Right TMJ		Left TMJ		Right TMJ		Left TMJ		Maximum range of mouth opening (mm)	
			Initial	Second	Initial	Second	Initial	Second	Initial	Second	Initial	Second	Initial	Second	Initial	Second	Initial	Second	Initial	Second
No. 1	Female	23	ADDwR	ADDwR	ADDwoR[a]	ADDwR[a]	−	−	−[a]	+[a]	−	−	−	−	−	−	−	−	51	52
No. 2	Male	24	Normal	Normal	Normal	Normal	+[a]	−[a]	+	+	−	−	−	−	−	−	−	−	57	56
No. 3	Female	24	Normal	Normal	Normal[a]	ADDwR[a]	−	−	−	−	−	−	−	−	−	−	−	−	40	42
No. 4	Male	23	Normal	Normal	Normal	Normal	−	−	−	−	−	−	−	−	−	−	−	−	64	64
No. 5	Female	23	Normal	Normal	ADDwR[a]	Normal[a]	−	−	−	−	−	−	+	+	−	−	−	−	50	49
No. 6	Male	23	ADDwoR	ADDwoR	ADDwoR	ADDwoR	−	−	+	+	−	−	−	−	−	−	−	−	57	54
No. 7	Female	24	Normal	Normal	Normal	Normal	−	−	−	−	−	−	−	−	−	−	−	−	53	55
No. 8	Female	25	Normal	Normal	ADDwoR	ADDwoR	−	−	+	+	−	−	−	−	+	+	−	−	45	49
No. 9	Male	25	Normal	Normal	Normal	Normal	+	+	+	+	−	−	−	−	−	−	−	−	50	48
No. 10	Male	25	ADDwoR	ADDwoR	ADDwR	ADDwR	+	+	−	−	−	−	−	−	−	−	−	−	44	41
No. 11	Female	24	Normal	Normal	Normal	Normal	−	−	−	−	−	−	−	−	−	−	−	−	43	42
No. 12	Male	25	Normal	Normal	Normal	Normal	−	−	−	−	−	−	−	−	−	−	−	−	48	47
No. 13	Female	24	ADDwoR	ADDwoR	ADDwR	ADDwR	−	−	+	+	−	−	−	−	−	−	−	−	55	51
No. 14	Male	25	Normal	Normal	Normal	Normal	−	−	−	−	−	−	−	−	−	−	−	−	65	64
No. 15	Male	24	Normal	Normal	ADDwR	ADDwR	−[a]	+[a]	+	+	−	−	−	−	−	−	−	−	66	66

ADDwR anterior disk displacement with reduction, *ADDwoR* anterior disk displacement without reduction

[a] Different findings were observed between two examinations or MRI scans

studies have evaluated the inter-examiner reliability of reading MR images of TMJ disk position and morphology [13–15], and reported that inter-examiner agreement is high when an examiner calibration program is performed [14] or a quantification technique is used to interpret MR images. Indeed, the current study also evaluated the effect of an examiner calibration program on the inter-examiner reliability of detecting the TMJ disk position and demonstrated that only one calibration training session substantially improved the inter-examiner reliability levels. However, the test–retest reliability levels of plurally MRI-scanned individual joint disk position have not yet been assessed. The current study is the first report to evaluate the test–retest agreement level of the TMJ disk position using two separate MR images. The results showed that 90% of TMJ disk position diagnosis was consistent between both initial and second images, which were scanned at a week interval. These results provided new evidence that the reliability level of the MRI-based diagnosis of TMJ disk positions at 1-week interval is substantially high. In addition, this reconfirmed that it is sufficiently valuable to apply TMJ disk position diagnosis in clinical and academic settings. In addition to the highly efficient capability of MRI for depicting the TMJ disk, other factors possibly elevated the reliability levels. This study employed sequential multi-slice images of each joint for the detection of the TMJ disk position. This was different from previous studies, which applied a few representative slices from all the images. Therefore, employing an increased number of the slice images might affect the reliability levels for detecting the disk position. However, this study did not evaluate the reliability level of the TMJ disk position using a few selected representative slices from all the images. Future studies which evaluate the influence of the number of the sliced images for detecting the disk position are therefore expected to clarify this point.

On the other hand, this study also demonstrated that a mismatch was observed in three of 30 joints between two scans, and a perfect match was not obtained. One of the possible reasons for these results is that the different detections of the disk position between initial and second MRI scan were due to the examiners' failure. Another possible reason is that the TMJ disk position in some of the participants may have changed within a 1-week interval. Since previous studies reported that existence of TMJ sound fluctuates [24], a positional fluctuation is also a possibility, especially if a patient has an intermittent locking disorder [25, 26]. Indeed, while one of the subjects in this study (No. 1) did not show joint clicking at the initial examination, which was performed prior to the initial MRI scanning, this subject did show joint clicking at the second examination. The joint disk status of this subject actually indicated the changes from ADDwoR to ADDwR. These findings strongly suggested that the disk position of this subject changed within a 1-week interval.

However, the clinical signs and symptoms of two other subjects (Nos. 3 and 5), whose TMJ disk status was different between two scans, did not show obvious changes at a 1-week interval. Although neither subject showed TMJ clicking at both the initial and second clinical examination, the TMJ disk status was diagnosed as ADDwR at either MRI scan. Of course, this might be due to the examiners' failure, but the absence of joint clicking for ADDwR individuals is not a rare finding [27]. In addition, the ADDwR condition has been speculated to develop from an intermittent joint displacement [28]. Therefore, either possibility may explain the difference of disk position status between two scanning. Future studies with larger samples are therefore desirable to clarify this point.

In conclusion, this study indicated the test–retest reliability of MRI-based diagnosis of TMJ disk positions by well-calibrated plural examiners at a 1-week interval and found a substantially high agreement. The reliability level suggested the possibility that MRI-based TMJ disk position diagnosis by the examiners in this study is sufficiently reliable and employs MRI image evaluation in an ongoing prospective cohort study on risk factors of the precipitation and progression of TMDs.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. Cirbus MT, Smilack MS, Beltran J, Simon DC (1987) Magnetic resonance imaging in confirming internal derangement of the temporomandibular joint. J Prosthet Dent 57:488–494
2. Katzberg RW (1989) Temporomandibular joint imaging. Radiology 170:297–307
3. Tasaki MM, Westesson PL, Isberg AM, Ren YF, Tallents RH (1996) Classification and prevalence of temporomandibular joint disk displacement in patients and symptom-free volunteers. Am J Orthod Dentofacial Orthop 109:249–262
4. Katzberg RW, Westesson PL, Tallents RH, Drake CM (1996) Anatomic disorders of the temporomandibular joint disc in asymptomatic subjects. J Oral Maxillofac Surg 54:147–153
5. Nebbe B, Major PW, Prasad NG, Hatcher D (1998) Quantitative assessment of temporomandibular joint disk status. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 85:598–607
6. Takaku S, Sano T, Yoshida M (2000) Long-term magnetic resonance imaging after temporomandibular joint discectomy without replacement. J Oral Maxillofac Surg 58:739–745
7. Guler N, Yatmaz PI, Ataoglu H, Emlik D, Uckan S (2003) Temporomandibular internal derangement: correlation of MRI findings with clinical symptoms of pain and joint sounds in patients with bruxing behaviour. Dentomaxillofac Radiol 32:304–310

8. Westesson PL, Katzberg RW, Tallents RH, Sanchez-Woodworth RE, Svensson SA, Espeland MA (1987) Temporomandibular joint: comparison of MR images with cryosectional anatomy. Radiology 164:59–64
9. Westesson PL, Rohlin M (1984) Diagnostic accuracy of double-contrast arthrotomography of the temporomandibular joint: correlation with postmortem morphology. AJR Am J Roentgenol 143:655–660
10. Westesson PL, Bronstein SL, Liedberg J (1986) Temporomandibular joint: correlation between single-contrast videoarthrography and postmortem morphology. Radiology 160:767–771
11. Schwaighofer BW, Tanaka TT, Klein MV, Sartoris DJ, Resnick D (1990) MR imaging of the temporomandibular joint: a cadaver study of the value of coronal images. AJR Am J Roentgenol 154:1245–1249
12. Tasaki MM, Westesson PL (1993) Temporomandibular joint: diagnostic accuracy with sagittal and coronal MR imaging. Radiology 186:723–729
13. Tasaki MM, Westesson PL, Raubertas RF (1993) Observer variation in interpretation of magnetic resonance images of the temporomandibular joint. Oral Surg Oral Med Oral Pathol 76:231–234
14. Orsini MG, Terada S, Kuboki T, Matsuka Y, Yamashita A (1997) The influence of observer calibration in temporomandibular joint magnetic resonance imaging diagnosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 84:82–87
15. Nebbe B, Brooks SL, Hatcher D, Hollender LG, Prasad NG, Major PW (2000) Magnetic resonance imaging of the temporomandibular joint: interobserver agreement in subjective classification of disk status. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 90:102–107
16. Ahmad M, Hollender L, Anderson Q, Kartha K, Ohrbach R, Truelove EL, John MT, Schiffman EL (2009) Research diagnostic criteria for temporomandibular disorders (RDC/TMD): development of image analysis criteria and examiner reliability for image analysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 107:844–860
17. Orsini MG, Kuboki T, Terada S, Matsuka Y, Yamashita A, Clark GT (1998) Diagnostic value of 4 criteria to interpret temporomandibular joint normal disk position on magnetic resonance images. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 86:489–497
18. Orsini MG, Kuboki T, Terada S, Matsuka Y, Yatani H, Yamashita A (1999) Clinical predictability of temporomandibular joint disc displacement. J Dent Res 78:650–660
19. Osborn JW (1995) Internal derangement and the accessory ligaments around the temporomandibular joint. J Oral Rehabil 22:731–740
20. Katzberg RW, Westesson P-L (1994) Normal anatomy. Diagnosis of the temporomandibular joint. WB Saunders, Philadelphia
21. Landis JR, Koch GG (1977) The measurement of observer agreement for categorical data. Biometrics 33:159–174
22. Westesson PL (1993) Reliability and validity of imaging diagnosis of temporomandibular joint disorder. Adv Dent Res 7:137–151
23. Larheim TA (2005) Role of magnetic resonance imaging in the clinical diagnosis of the temporomandibular joint. Cells Tissues Organs 180:6–21
24. Kamisaka M, Yatani H, Kuboki T, Matsuka Y, Minakuchi H (2000) Four-year longitudinal course of TMD symptoms in an adult population and the estimation of risk factors in relation to symptoms. J Orofac Pain 14:224–232
25. Friedman MH (1993) Closed lock. A survey of 400 cases. Oral Surg Oral Med Oral Pathol 75:422–427
26. Yamaguchi T, Komatsu K, Okada K, Matsuki T (2006) The advantageous direction of jaw movement for releasing TMJ intermittent lock. Cranio 24:171–178
27. Porto VC, Salvador MC, Conti PC, Rotta RR (2004) Evaluation of disc position in edentulous patients with complete dentures. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 97:116–121
28. Farrer WB, McCarty WL (1983) A clinical outline of temporomandibular joint diagnosis and treatment, 7th edn. Walker Printing, Montgomery

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Review

The effect of growth factors for bone augmentation to enable dental implant placement: A systematic review

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KEYWORDS
Growth factors;
Dental implant;
Bone augmentation;
Systematic review;
Clinical trial

Summary This systematic review assessed the potential benefits of growth factors for bone augmentation prior to the placement of dental implants in human.

A systematic online review of the Medline database, using the PubMed search machine was performed between 1966 and November 2008 by entering the MeSH terms. The primary outcome of the included studies was bone regeneration of localized alveolar ridge defects.

The initial search identified 119 papers from the electronic database. This review produced seven eligible papers that reported on bone augmentation with recombinant human Bone Morphogenetic Protein-2 (rhBMP-2), recombinant human Platelet-Derived Growth Factor (rhPDGF) and Plasma-Rich Growth Factor (PRGF). The rhBMP-2 affected local bone augmentation with increasing volume for higher doses. Both rhPDGF and PRGF showed a positive effect in favor of the growth factor.

Differing levels and quantity of evidence were noted to be available for the growth factors evaluated, revealing that rhBMP-2, rhPDGF, and PRGF may stimulate local bone augmentation to various conditions. Especially the potential of rhBMP-2 is supportive. However, the confined number of investigators using these techniques and the low number of patient treatments reported in the literature, the generalizability of this approach is limited at this time.

Contents

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Introduction

Dental implants are the most innovative and superior treatment in dentistry, and are widely used for a variety of cases. Most of the techniques that are used are evidence-based and predictable. However, in many cases, the intended implant site is inappropriate due to the poor bone quality or to an insufficient quantity of bone. An insufficient alveolar ridge height is often related to the proximity of the implant site to other anatomical structures, i.e., the maxillary sinus or the mandibular canal.

In order to overcome some of these difficulties, autogenous bone grafts taken from the chin, the ramus of the mandible, or the iliac crest of the same patient have historically been the standard for alveolar reconstruction, specifically, due to their osteoconductive, osteoinductive, and lack of immunogenic properties. However, the adverse events and complications, such as infection, pain, sensory loss, and hematoma formation at the donor site, occur frequently upon autogenous bone graft treatment. In addition, a donor site with a sufficient quantity of bone is not always available. Allograft bones, bones taken from a different person and processed and managed by a tissue bank or commercial supplier, have often been substituted. However, this method also has limitations, including an inconsistent osteoinductive activity, unfavorable host immune responses [1], a delayed resorption, and a risk for prion and virus transmissions [2,3].

An ideal bone graft in implant dentistry should have the following properties: it should be biomimetic; it should have the ability to induce differentiation of the appropriate cells (i.e., endothelial and osteoblastic cells) for the formation of new bone; it should be easily synthesized or produced, rather than extracted from allograft materials (to eliminate all risks of disease transmission); it should be easily and quickly resorbed as the osteogenic response occurs; it should have no immune-provoking properties; it should be easily transported and stored; it should be reasonably cost-effective; it should be capable of achieving consistent and predictable results without being affected by different level of technical ability of the clinician.

In order to meet these demands, dental research has focused on the use of bioactive molecules to induce local bone formation. Since the various growth factors that have an effect on the bone regeneration have been discovered, the number of related studies has increased substantially. In particular, the factors recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) [4–7] and recombinant human Platelet-Derived Growth Factor (rhPDGF) [8–10] have been shown to induce bone formation at the compromised sites in a variety of experimental and clinical situations. These factors have also been approved by the U.S. Food and Drug Administration (FDA) for use in dentistry.

To date, there is only limited evidence to support the application of growth factors for local bone augmentation in dentistry. The aim of this systematic review was to summarize the current literature that describes the use of growth factors in conjunction with dental implants.

Material and methods

Study selection

We conducted an electronic search of the Medline database, using the PubMed search machine, for the relevant selection of studies by entering the following MeSH terms: "Intercellular Signaling Peptides and Proteins;" and "Dental Implants". We limited our results to humans, to articles published in the English language; and, in the time range of 1966 to November 2008. The references of the retrieved articles were also searched.

The inclusion and exclusion criteria

The studies included in this review met the following inclusion criteria: (1) only relevant data on bone augmentation induced by the growth factors; (2) only randomized, non-randomized clinical trials, cohort studies, case–control studies, and case reports; (3) only studies with a clearly written amount and concentration of growth factors or using the kit with fixed concentration of growth factors; (4) only studies with a clearly defined baseline; and (5) only studies with the application of titanium root-form implants. The most recent report was used if more than one publication referred to the same data. The studies that did not meet all the inclusion criteria were excluded from the review. The studies that dealt with the following topics were excluded: (1) *in vitro* animal studies; (2) studies using gene therapy; (3) studies with a focus on periodontal regeneration; (4) studies reporting systemic treatment outcomes; (5) craniofacial surgery for total or partial reconstruction of mandibles/maxillas; (6) cleft lip and palate surgeries; (7) distraction osteogenesis; (8) osseointegration; (9) implant anchor; (10) immediate loading or (11) orthopedic surgeries. Each retrieved citation was reviewed by two independent reviewers (K.S., O.M.). Most of the citations were excluded immediately, due to the information provided by the title or the abstract. If the citation could not be excluded immediately because of its equivocal nature, then the complete article was selected by the two reviewers. Any disagreement between the reviews was resolved by a consensus. To avoid any bias, the search

process was blinded to the names of the authors, to the names of institutions, and to the names of the journals.

The data extraction

The data were independently extracted by two reviewers using data extraction tables. Any disagreements were discussed until they were resolved by a consensus. The following information were extracted: the authors, the year of publication, the study design, the number of patients, the mean age of the patients, the follow-up period, the adverse event, the applied dose of growth factor, the carrier system, the control group, the type and the dimension of the defect, the decrease in the defect of height/increased bone height/width, the newly formed bone, and the new bone density.

Result

The study characteristics

The PubMed search identified a total of 119 citations. However, most of them were excluded immediately due to the information provided by the title or the abstract (Fig. 1). Only 20 articles were selected for further text review [11–30]. The main reasons for excluding some studies ($n = 13$), after the full text was obtained, were as follows: poor-quality data for bone augmentation induced by growth factors, any reports based on animal studies, and a lack of or insufficient discussion of the clinical, radiographic, or histological treatment outcomes (only descriptive presentation of results). Of the seven eligible articles, three studies reported on bone augmentation with rhBMP-2 [14,15,17], three studies discussed the effect of rhPDGF [11–13], and one study examined the effect of Plasma-Rich Growth Factor (PRGF) [16]. Two of the rhBMP-2 studies were randomized control trials (RCT) with a clearly stated random allocation of subjects. The other BMP-2 study was a prospective, human clinical trial without a control. All of three rhPDGF studies and the PRGF study were case reports.

Table 1 shows the characteristics of the included studies. A total of 76 patients were treated with growth factors for local intra-oral bone regeneration. The mean age of the patients was 54.8 years and the mean follow-up period was 47.1 months. Table 2 shows the operative data reported in the included studies. The growth factors were always administered locally, and the root form dental implant was used in every study. The applied dose of the rhBMP-2 ranged from 0.43 to 1.5 mg/ml or from 0.2 to 24 mg/patient. However, the rhPDGF and the PRP studies lacked this type of information. Two different carrier systems were used for the application of rhBMP-2. An absorbable collagen sponge (ACS) was used in two studies [14,17], whereas rhBMP-2 was applied to a demineralized bovine bone matrix (xenogenic bone substitute mineral, Bio-Oss^{R}) in another study [15]. With respect to the application of rhPDGF, the carriers used were Bio-Oss^{R}, beta-tricalcium phosphate (β-TCP) and a freeze-dried mineralized bone allograft (FDBA). For the PRGF treatment, a combination of Bio-Oss^{R} and autogenous bone was used. The types of local bone augmentations observed were sinus floor augmentations [14,16,17], preservations of extraction socket [13,17], alveolar ridge bone augmentation [11], and lateral ridge augmentation in combination with simultaneous implant placement [12,15,16]. A meta-analysis of the outcomes was not performed because of the heterogeneity of the studies (various indications, RCT, or cohort)

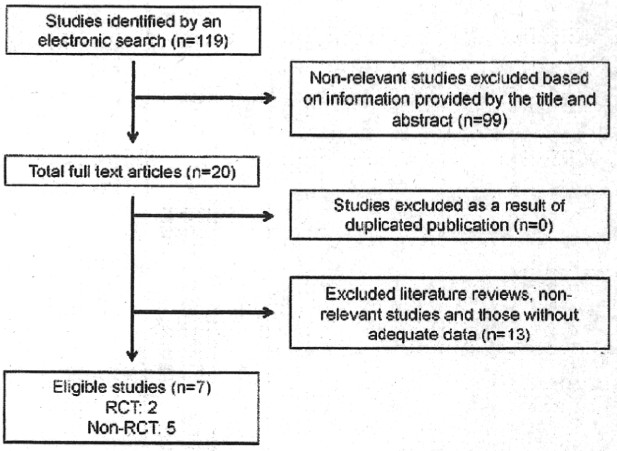

Figure 1 Outline of the literature search.

Bone height increase/defect size decrease

An increase in bone height, ranging from 10.16 ± 4.7 to 9.47 ± 5.72 mm for the sinus lift procedures, and a change in bone depth of 6.8 ± 0.2 mm, for the extraction socket augmentations, were reported for the sites treated with rhBMP-2 (Table 3). Two RCTs included control groups without the application of the rhBMP-2 [14,15]. In comparison to the controls, the effect of rhBMP-2 showed substantial variability. Boyne et al. presented negative data for the bone height, and the average gain in the bone height was 11.29 ± 4.12 mm for the control sites and 9.47 ± 5.72 mm for test sites with a low dose of rhBMP-2, respectively. There were no statistically significant differences in the control group with respect to the increase in ridge height, and the decrease in ridge width with the use of rhBMP-2 [14]. Only one RCT reported a positive effect in comparison to the control group, when the factor was applied to the lateral ridge augmentation [15].

On the other hand, rhPDGF seemed to have a positive role in enhancing the healing of soft and hard tissues, even though there was no clear mention and evaluation of bone regeneration. The result of the bone augmentation was clearly presented by the use of pictures and dental X-rays that showed successfully filled bone defects within 5–7 months after the operation [11–13].

New bone formation

Jung et al. and Boyne et al. reported the new bone formation as a percentage of the original defect or as new bone density, respectively (Table 3). The dose of the applied factor seemed to have an impact on the treatment outcome, with a higher local bone regeneration for the higher doses of rhBMP-2. For a lower dose of rhBMP-2, a positive, but not a statistically significant effect was observed on the bone formation, whereas, for a higher dose, a positive and statistically significant effect was reported. Boyne et al. reported a significant difference in new bone density in favor of the bone

Table 1 Characteristics of included studies.

Study	Year of publication	Type of study	Type of surgical procedure	No. of enrolled patient			Mean follow-up (month)	Mean age		M/F ratio		Outcome
				Treatment group	Control group	Total		Treatment group	Control group	Treatment group	Control group	
Simion et al.	2008	Case report	Alveolar ridge augmentation	1	0	1	14	36 years	–	0	–	X-ray
Byun et al.	2008	Case report	Socket preservation	1	0	1	ND	65 years	–	0	–	X-ray
Fagan et al.	2008	Case report	Socket preservation	1	0	1	3	52 years	–	1	–	X-ray, histology
Boyne et al.	2005	RCT	Sinus floor augmentation	Low dose: 18; high dose: 17	13	48	52	Low dose: 57 years ± 12; high dose: 52 years ± 7	57 years ± 11	Low dose: 0.80; high dose: 0.54	0.625	CT, histology, success and survival rate
Jung et al.	2003	RCT	Alveolar ridge augmentation	11	–	11	ND	53 years ± 16.9	–	0.57	–	Defect filling rate, histology
Anitua	2001	Case report	Alveolar ridge augmentation Sinus floor elevation	2	0	2	36	61 years ± 4.2	–	1	–	Histology
Cochran et al.	2000	Prospective clinical trial	Alveolar ridge augmentation Socket preservation	12	0	12	36	ND	–	ND	–	Defect filling rate, histology

Table 2 Operative data investigated in the included studies.

Study	Treatment group				Control group	Implant system	Number of implant
	Type of growth factor	Dose of growth factor	Delivery vehicle	Concentration of growth factor	Type of bone graft		
Simion et al.	rhPDGF-BB (GEM21S®; BioMimetic)	ND	Bio-Oss® + autogenous bone	1.2 mg/ml	–	MK3 Natural Platform 3.3 mm × 15 mm, Speedy Groovy 4 mm × 15 mm, Nobel biocare	2
Byun et al.	rhPDGF-BB (GEM21S®; BioMimetic)	ND	β-TCPalloplast, autogenous bone	0.3 mg/ml	–	Tapered ScrewVent 3.7 mm × ND mm, Zimmer Dental	1
Fagan et al.	rhPDGF-BB (GEM21S®; BioMimetic)	ND	FDBA	0.3 mg/ml	–	Osseotite implant 4 mm × 13 mm, BIOMET/3i	1
Boyne et al.	rhBMP-2 (Medtronic)	Low dose: 8.9 mg (5.2–12.0 mg); high dose: 20.8 mg (10.8–24.0 mg)	Autogenous bone or ACS	Low dose: 0.75 mg/ml; high dose: 1.5 mg/ml	Autogenous bone graft	ND	219
Jung et al.	rhBMP-2	0.18 mg	Bio-Oss®	0.5 mg/ml	Bio-Oss®	Machine surface, Nobel biocare	34
Anitua	PRGF (PRP)	ND	Bio-Oss® + autogenous bone	ND	–	ND	5
Cochran et al.	rhBMP-2	Alveolar ridge augmentation 0.27 mg (0.1–0.9 mg), Socket preservation 0.83 mg (0.2–1.7 mg)	ACS	0.43 mg/ml	–	Titanium plasma sprayed implant	13

Table 3 Summary of the clinical bone assessment.

Study	Group		Defect fill			Histological analysis			CT analysis	
			Base line (mm)	Change from base line (mm)	Percent vertical defect fill (%)	Woven bone (%)	Lamellar bone (%)	Bone substitute mineral (%)	Bone density at 4 months (mg/cm^3)	Bone density 6 months post-functional loading (mg/cm^3)
Simion et al.										
Control	–	–	–	–	–	–	–	–		
Test	rhPDGF-BB/Bio-Oss® + autogenous bone	Depth	20	ND	ND	ND	ND	ND		
		Width	15	ND	ND					
Byun et al.										
Control	–	–	–	–	–	–	–	–		
Test	rhPDGF-BB/P-TCP + autogenous bone	Depth	ND	ND	ND	ND	ND	ND		
		Width	ND	ND	ND					
Fagan et al.										
Control	–	–	–	–	–	–	–	–		
Test	rhPDGF-BB/FDBA	Depth	15	ND	ND	48	19	14		
		Width	8	ND	ND					
Boyne et al.										
Control	Autogenous bone graft	Height	11.29 ± 4.12	ND	ND				350 ± 243	448 ± 213
		Width at 1/4	4.66 ± 2.75	ND	ND					
		Width at 1/2	10.17 ± 2.98	ND	ND					
		Width at 3/4	10.56 ± 3.17	ND	ND					
	rhBMP-2/ACS 0.75 mg/ml	Height	9.47 ± 5.72	ND	ND				84 ± 50	456 ± 131
		Width at 1/4	2.02 ± 2.73	ND	ND					
		Width at 1/2	8.54 ± 5.47	ND	ND					
		Width at 3/4	11.86 ± 5.15	ND	ND					
Test	rhBMP-2/ACS 1.50 mg/ml	Height	10.16 ± 4.7	ND	ND				137 ± 77	508 ± 126
		Width at 1/4	1.98 ± 2.41	ND	ND					
		Width at 1/2	7.8 ± 3.87	ND	ND					
		Width at 3/4	10.78 ± 4.63	ND	ND					
Jung et al.										
Control	Bio-Oss®	Depth	5.8 ± 1.8	5.4 ± 2.2	91 ± 15.1	13 ± 6.7	17 ± 8.1	17 ± 11.0		
		Width	ND	ND	ND					
Test	rhBMP-2/Bio-Oss®	Depth	7.0 ± 2.7	6.8 ± 0.2	96 ± 6.9	8 ± 5.0	29 ± 11.3	23 ± 11.1		
		Width	ND	ND	ND					
Anitua										
Control	–	–	–	–	–					
Test	PRGF (PRP)	Depth	10	ND	ND					
		Width	ND	ND	ND					
Cochran et al.										
Control	–	–	–	–	–					
Test	Alveolar ridge augmentation Socket preservation	Height	ND	−0.8 ± 2.5	ND					
		Width	ND	0.4 ± 0.9	ND					
		Depth	ND	10.4 ± 6.6	ND					
		Width	ND	4.9 ± 2.4	ND					

graft group (350 ± 243 mg/cm^3) in comparison to the low (84 ± 50 mg/cm^3) and to the high (137 ± 77 mg/cm^3) dose treatment groups at 4 months after the operation. However, after 6 months of functional loading, the density of the newly induced bone increased significantly for the low (456 ± 131 mg/cm^3) and the high (508 ± 126 mg/cm^3) dose treatment groups, and its value was comparable to that of the bone graft group (448 ± 213 mg/cm^3). Jung et al. reported a positive, but not statistically significant, effect of rhBMP-2 on the amount of newly formed bone (37 ± 11.2%) in comparison to the control group (30 ± 8.9%). However, a statistically significant increase in mature lamellar bone (29 ± 11.3%) for the test site was found in comparison to the control site (17 ± 8.1%).

Safety

From the various studies, Boyne et al. [14] and Cochran et al. [17] reported the adverse events of the rhBMP-2 application that occurred during the procedure (Table 4). The most frequent adverse events occurred during the first 4 months after the operation. These events were transient and consistent with the surgical procedures performed (a maxillary sinus floor augmentation procedure, or a bone graft harvest procedure). The majority of the events were equally distributed among the treatment groups. However, the incidence of edema, rash and pain in the bone graft group were much higher than in the rhBMP-2 groups. These complaints of edema, rash (erythema), and pain were experienced from the autograft harvest site. Notably, the 1.50 mg/ml rhBMP-2/ACS treatment group had significantly greater facial edema during the first 4 months after surgery than did the bone graft group and the 0.75 mg/ml rhBMP-2/ACS group.

Discussion

This systematic review assessed the potential benefits of growth factors for bone augmentation prior to the placement of dental implants. The rhBMP-2 (INFUSE^R, Medtronic) and the rhPDGF (GEM21S^R, BioMinetic Therapeutics) have been approved by the FDA for dentistry. In addition, the rhBMP-7 (OP-1, Stryker Biotech) has been approved in Australia and Europe, and by the orthopedic community in the USA. Various growth factors are now entering clinical practice in dentistry. Hence, a systematic assessment of the effect of the growth factors on the bone augmentation for dental implants is very important.

The number of satisfactory studies was assumed to be low; therefore, in this systematic review with the prospective cohort studies and case reports, a lower level of evidence was used. Instead of performing a formal quality assessment of the included studies and a sensitivity analysis, this review used stringent inclusion criteria. The electronic search selected the studies, that used growth factors for bone augmentation prior to the placement of dental implants in human, by applying the following MeSH terms: "Dental Implant" and "Intercellular Signaling Peptides and Proteins". The term, "Intercellular Signaling Peptides and Proteins", belongs to the chemical and drug category, and is located at the upper level of the MeSH tree that contained all the growth factors. However, only seven studies of the

Table 4 Number of frequent adverse experiences according to the body system.

Study	Group	Body as a whole			Digestive system				
		Dehiscene	Edema	Face edema	Headache	Pain	Infection	Mouth pain	Oral edema	Oral erythema	Colitis
Boyne et al. (*n* = number of patient)	Bone graft (*n* = 13)	2	6	5	0	5	ND	8	8	6	ND
	rhBMP-2/ACS 0.75 mg/ml (*n* = 18)	2	0	7	2	1	ND	14	10	3	ND
	rhBMP-2/ACS 1.50 mg/ml (*n* = 17)	1	0	14	3	3	ND	15	8	4	ND
Cochran et al. (*n* = number of event)	Alveolar ridge augmentation (*n* = 532)	ND	ND	ND	ND	ND	1	6	1	ND	2
	Socket preservation (*n* = 528)	ND	ND	ND	ND	ND	1	4	2	ND	0

rhBMP-2, the rhPDGF, and the PRGF were available for an analysis. Two human RCTs for rhBMP-2 were found, but for rhPDGF and PRGF no human RCT was found. Almost all the articles were old, and no RCT evaluation of the effect of the growth factors for the dental implants had been published recently. Seven eligible articles demonstrated that the application of growth factors was safe and effective for bone formation.

Three articles related to rhBMP-2, includes this systematic review, showed a positive effect on the rhBMP application for bone formation. Cochran et al. reported a prospective, human clinical trial without a control in order to examine the effect and safety of rhBMP-2/ACS on the alveolar ridge augmentation and on the socket preservation. This study showed that bone formation was successful when using rhBMP-2/ACS at a concentration of 0.43 mg/ml. Jung et al. reported a prospective, controlled, randomized, double-masked clinical study on alveolar ridge augmentation. This study was designed to investigate the test site and the control site of the same patient's jaw, which required a lateral ridge augmentation. Despite the small number of patients, this experimental design allows the direct comparison of the test site and the control site by eliminating the differences such as the patients and the doctors or other possible variables. In addition, this is the only report that tested rhBMP-2 with grafting material (xenogenic bone substitute; Bio-Oss^{R}) for lateral bone augmentation. The report concluded that the combination of Bio-Oss^{R} with the rhBMP-2 was able to enhance the maturation process of bone regeneration and increase the graft-to-bone contact in humans. The most recent RCT study was reported by Boyne et al., and it was designed to evaluate the effect of two different concentrations of BMP-2 on the safety and efficacy of the sinus floor augmentation. It was demonstrated that the higher dosage produced better results. Based on the data, they concluded the following: (1) both the high (1.50 mg/ml) and the low (0.75 mg/ml) concentrations of rhBMP-2 were safe, with a safety profile similar to that of bone graft; (2) both concentrations of rhBMP-2 induced a similar amount of bone formation which was similar to that induced by the bone graft; and (3) the higher concentration of rhBMP-2 induced bone formation more rapidly in comparison to the lower concentration. The results support the use of rhBMP-2/ACS at a concentration of 1.50 mg/ml for the future studies of maxillary sinus floor augmentation. In these studies, the most frequent adverse events occurred within the first 4 post-operative months [14,17]. The majority of the events were equally distributed among the treatment groups and control groups. However, the high (1.50 mg/ml) concentration of rhBMP-2 treatment group had a significantly greater facial edema during the first 4 months after surgery in comparison to the bone graft group and the 0.75 mg/ml rhBMP-2/ACS group. On the other hand, we could not obtain a clear outcome from the three case reports that evaluated the rhPDGF efficacy and that met our inclusion criteria. However, the results of every study were consistent with respect to the positive effect of rhPDGF. In addition, there is no well-designed RCT study of rhPDGF. Therefore, the information was not sufficient to draw any definitive conclusions, particularly with respect to the long-term evaluation.

In addition to this systematic review, we also obtained another six eligible articles [31–36] by means of a hand-search of the articles listed in the retrieved list of References. These studies assessed – only the bone grafts. They were most likely automatically excluded on the PubMed during our selection process because the word "Dental Implant" was not associated strongly with these articles. The first studies were clinical trials, one of which was a multicenter cohort study of the effect of rhBMP-2 maxillary sinus floor augmentation and socket preservation [31,32] that supports the beneficial effect of BMPs. Fiorellini reported a randomized, masked, placebo-controlled multicenter clinical study to evaluate the effect of two concentrations of rhBMP-2 on the safety and efficacy of socket preservation [33]. The trend of this study was the same as that of the Boyne's study; 1.5 mg/ml of rhBMP-2 was safe for clinical application and the higher dosage produced better results. Van den Bergh et al. [34] and Groeneveld et al. [35] have used rhBMP-7 as an aid to increase the bone height in sinus, prior to the placement of implants. The results from these clinical trials indicated that the OP-1 (2.5 mg in 1 g of collagen carrier) had the potential to initiate bone formation in the human maxillary sinus within 6 months after a sinus floor elevation operation. However, the behavior of this material cannot be fully predicted.

Dickinson et al. [36] reported about the economic result of the rhBMP-2 treatment on the alveolar bone grafting in the older cleft patients, in order to improve poor wound healing, graft exposure, recurrent fistula, and failure of tooth eruption. According to the report for the autogenous bone graft group, seven of the nine patients underwent the procedure on an outpatient basis. The procedure was applied to the iliac bone graft patients on an inpatient basis. The donor-site pain intensity and the frequency were significant in the traditional iliac bone graft, but it was not significant in the rhBMP-2 treated group. Furthermore, the mean length of stay was greater for the iliac bone graft patients at 1.8 ± 0.8 days in comparison to the patients treated with rhBMP-2 at 0.4 ± 0.4 days ($p < 0.05$). Hence, the mean overall cost of the procedure, including the surgeon, the facility, the equipment, and the anesthesia fees, was greater for the iliac bone graft group ($21,800) in comparison to the rhBMP-2 treated group ($11,100).

On the other hand, the price of those growth factors is still relatively costly for treatment. The price of INFUSE^{R} kit which contains 4.9 mg of rhBMP-2 cost more than $3000 in the United States. The rhBMP-2 and the rhBMP-7 have been used in orthopedic spinal surgery with decreased donor-site morbidity. In addition, these proteins showed promise for the tissues that are characterized by poor wound healing, such as irradiated tissue [37]. However, there are several reports on the side effects associated with the high BMPs dosage and the repeated regimens, which are required for the stable bone regeneration in the orthopedic field [38–40]. As shown here, the use of growth factors in humans undergoing craniofacial and oral maxillofacial procedures has only recently been documented. There have been investigative reports of ectopic bone growth with rhBMP-2 and, consequently, its use in growing patients is being studied carefully [41]. In order to overcome some of these difficulties, a variety of pre-clinical studies are carried out; such as testing new optimized carrier systems to decrease the dosage of growth factors, producing the growth factors by using *E-coli* system [42,43], or finding the new bioactive small peptide which have osseoinduction