

Clinical Validity of Tooth Size Measurements Obtained via Digital Methods with Intraoral Scanning

Mohammed Alnefaie^{id}, Sun-Hyung Park^{id}, Jung-Yul Cha^{id}, Sung-Hwan Choi^{id}

Department of Orthodontics, Institute of Craniofacial Deformity, Yonsei University College of Dentistry, Seoul, Korea

Purpose: Dental diagnostic records derived from study models are a popular method of obtaining reliable and vital information. Conventional plaster models are the most common method, however, they are being gradually replaced by digital impressions as technology advances. Moreover, three-dimensional dental models are becoming increasingly common in dental offices, and various methods are available for obtaining them. This study aimed to evaluate the accuracy of the measurement of dental digital models by comparing them with conventional plaster and to determine their clinical validity.

Materials and Methods: The study was conducted on 16 patients' maxillary and mandibular dental models. Tooth size (TS), intercanine width (ICW), intermolar width (IMW), and Bolton analysis were taken by using a digital caliper on a plaster model obtained from each patient, while intraoral scans were manually measured using two digital analysis software. A one-way analysis of variance test was used to compare the dental measurements of the three methods.

Result: No significant differences were reported between the TS, the ICW and IMW, and the Bolton analysis through the conventional and two digital groups.

Conclusion: Measurements of TS, arch width, and Bolton analysis produced from digital models have shown acceptable clinical validity. No significant differences were observed between the three dental measurement techniques.

Key Words: Dental impression technique; Dental models; Digital technologies; Three-dimensional imaging

Corresponding Author: **Sung-Hwan Choi**, ^{id} <https://orcid.org/0000-0002-1150-0268>

Department of Orthodontics, Institute of Craniofacial Deformity, Yonsei University College of Dentistry, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea

TEL : +82-2-2228-3102, FAX : +82-2-363-3404, E-mail : selfexam@yuhs.ac

Received for publication October 9, 2022; Returned after revision December 5, 2022; Accepted for publication December 8, 2022

Copyright © 2022 by Korean Academy of Dental Science

© This is an open access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Diagnostic records based on plaster dental models are popular in dentistry, providing a reliable and vital source of information. For many years, study model analysis has been the gold standard for diagnostic procedures¹. The use of plaster dental models is a common procedure used for orthodontic diagnosis or to evaluate orthodontic treatment outcomes. Furthermore, successful orthodontic treatments rely heavily on the use of accurate measurements and study model analysis. The assessment of the degree and severity of dental malposition and/or malocclusions in three dimensions, as well as the “determination of spaces, crowding, rotations, tooth sizes, tooth size discrepancies, arch form, arch symmetry, arch dimensions, tooth-arch discrepancies,” aid in diagnosis and dental treatment planning².

Traditionally, dental models have been analyzed using conventional plaster models, which require an impression tray and materials such as alginate. Plaster dental models are the cornerstone of orthodontics, and are used beyond diagnosis for teaching, research, and clinical documentation³. In addition to illustrating the dentition dimensionally, plaster dental models can be used to analyze discrepancies in tooth size (TS) and arch length as well as to predict permanent TS. However, the high precision of plaster models is reportedly affected by factors such as the processing method and impression technique. Moreover, plaster models are more prone to breakage and deterioration, and take up a lot of space for storage². Furthermore, volumetric deformation is associated with plaster dental models, increasing the possibility of errors¹.

However, digital models are gaining popularity among dentists, with many options for obtaining three-dimensional (3D) dental models. The recent advances in computer science have enabled many orthodontic practices to replace traditional methods with technology, which offer more reliable diagnos-

tic tools at an affordable cost². The intraoral scanners and software used in the digital dental impression technique allow the dental clinician to directly acquire patient data³. Moreover, digital models are distinguished by their ease of use and good mobility, as well as their ability to eliminate many difficulties associated with plaster models⁴. While plaster models depict occlusion in 3D, the digital storage feature in digital models makes the model more accessible, and allows easier data retrieval¹.

A literature review reveals a lack of consistency regarding the accuracy of digital models, as well as the methodology, such as the measurements selected, and the scanners or software used for analysis³. Pertaining to the comparison of the digital model's accuracy with the plaster model, several studies have reported the clinical acceptability of digital models, and that they can be used instead of plaster models for diagnosis and treatment planning⁵. For example, Zhang et al.³ used iTero[®] (Align Technology, San Jose, CA, USA) and reported no significant differences between intraoral scans and plaster models, except in one measurement, which is the lower interdental width measurement. Conversely, Camardella et al.⁶ reported significant differences between the measurements taken using a plaster model and the digital measurements scanned with TRIOS Color intraoral scanner (3Shape[®], Copenhagen, Denmark) and measured with Ortho Analyzer software (3Shape[®]). According to their results, the highest measurement error occurred when measuring the crown height of the upper central incisors. In contrast, Tomita et al.⁷ utilized multiple scanners to compare the two models and reported greater accuracy in reported digital models than in conventional plaster models.

There have been many similar studies so far, but according to the inconsistency of the results, this study aimed to evaluate the accuracy of the measurement of dental digital models by comparing them with conventional plaster and to determine their clinical

acceptability. In this paper, one conventional and two digital methods will be used to analyze tooth measurements to compare the accuracy of conventional models with the accuracy of digital models. The plaster model was the first gold standard method used, followed by two digital models with different ways of tooth segmentation, one generated by Ortho Analyzer software (3Shape®), and the other generated by the Autolign program (Diorco, Yongin, Korea).

Materials and Methods

This study included 16 patients who finished orthodontic treatment at Yonsei University Dental Hospital. Informed consent and all experimental protocols were approved by the Institutional Review Board of Yonsei Dental Hospital (IRB No. 2-2021-0030) and adhered to the Declaration of Helsinki (2013).

The inclusion criteria for all patients who underwent alginate impression-taking and intraoral scanning at one appointment were as follows: complete adult dentition from the first molar to the contralateral first molar, and no missing or malformed teeth. The sample selection method and the software utilized to obtain and analyze the dental impressions, for both the plaster and digital models, are shown in Fig. 1.

1. Measurements

To evaluate the accuracy and efficiency of measurements for the three groups, measurements were obtained using a digital caliper on a plaster model obtained from each patient referred to as the manual group (Fig. 2A) and digital impression generated by iTero 5D Element (Align Technology) were manually measured using digital analytics software such as Ortho Analyzer (3Shape®) referred to as the LS group (landmark-based tooth segmentation), and

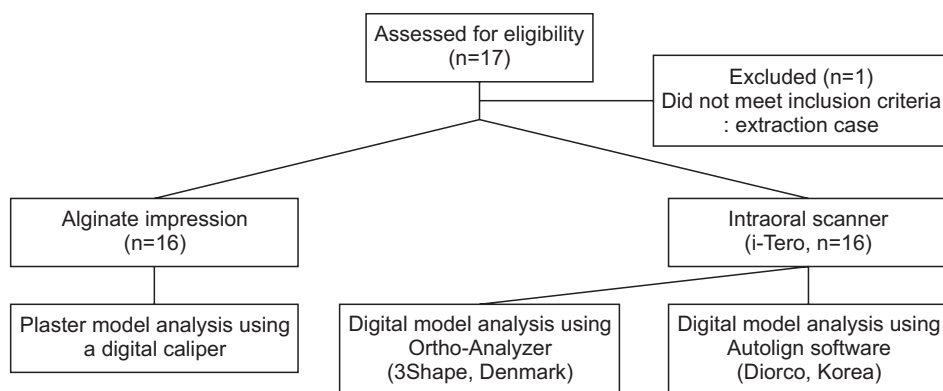


Fig. 1. Study selection flow diagram.



Fig. 2. Model types used for the measurements; (A) manual measuring on a plaster model with a digital caliper (Manual group); (B) measuring the upper arch using Ortho Analyzer software (3Shape®, Copenhagen, Denmark) (LS group); (C) measuring the upper arch using Autolign software (Diorco, Yongin, Korea) (DS group).

Autolign software (Diorco) referred to as the DS group (tooth designation and segmentation) (Fig. 2B, C). For landmark-based tooth segmentation, the tooth is segmented only when the mesial and distal points of each tooth are accurately set after orientation through the virtual coordinate system. In contrast, tooth designation and segmentation methods differ in that they are segmented when the approximate mesial and distal points of individual teeth are set after orienting the digital model⁹⁾.

These measurements were used in model analyses to determine the TS (mesiodistal width for each individual tooth), intercanine width (ICW; distance between the canine tips in each arch), and intermolar widths (IMW; distances between the central fossa of the first molars in each arch), and Bolton analysis (Bolton ratio 6 and 12). Bolton ratio 6 is the percentage obtained by summing the widths of the six mandibular teeth divided by the widths of the six maxillary teeth, and Bolton ratio 12 is the percentage obtained by summing the widths of the twelve mandibular teeth divided by the widths of twelve maxillary teeth.

Table 1. Descriptive statistics of the study sample (N=16)

Variable	Value
Age (yr)	23.1±4.9
Gender	16
Men	9 (56.25)
Women	7 (43.75)

Values are presented as mean±standard deviation or number (%).

Table 2. Reliability analysis of tooth measurement

Group	TS		ICW		IMW	
	ICC	P-value	ICC	P-value	ICC	P-value
Manual	0.871	<0.001	0.987	<0.001	0.997	<0.001
LS	0.983	<0.001	0.999	<0.001	0.996	<0.001
DS	0.916	<0.001	0.996	<0.001	0.999	<0.001

TS: tooth size, ICW: intercanine width, IMW: intermolar width, ICC: intraclass coefficient, Manual: manual measurement on a plaster model, LS: landmark-based tooth segmentation, DS: tooth designation and segmentation.

TS, ICW and IMW, presented as continuous variables, were verified for intra-rater reliability using ICC.

2. Reliability analysis

To check their level of reliability, all measurements were taken twice at intervals of two weeks for the three groups by a single researcher. Intraclass coefficient (ICC) values were calculated to determine the level of reliability.

3. Statistical analysis

All measurements were analyzed with IBM SPSS Statistics 28.0.0.0 (IBM Corp., Armonk, NY, USA). To verify the normality of the data distribution, we applied the Shapiro–Wilk test. The data were normally distributed, a one-way analysis of variance with Tukey’s post hoc test was performed to identify any difference in the measurement values between the three groups.

Result

As shown in Table 1, our data analysis revealed the descriptive statistics of the study sample. The sample had a mean age of 23.1 years with a standard deviation of ±4.9 years. A total of 16 people were included in the study, 9 men (56.25%) and 7 women (43.75%).

ICC values were calculated to determine the level of reliability of the digital models, as seen in Table 2 (less than 0.50, poor reliability; between 0.5 and 0.75, moderate reliability; between 0.75 and 0.9, good reliability; greater than 0.9, excellent reliability)⁹⁾. In the manual group, the ICC value of TS was 0.871, mainly due to a measurement error of approximately 0.2~0.4 mm that occurred when measuring the maxillary second premolar. This may be because it is one

of the teeth with a large variation of TS, so there was a measurement error during repeated approaches with a digital caliper. Nevertheless, ICC showed excellent reliability of 0.8 or more. On the other hand, the LS and DS group values were 0.983 and 0.916, respectively, which indicated excellent reliability for both digital models. However, even with a small difference, the DS method also showed a slightly smaller ICC value than the LS due to the influence of the size diversity of the maxillary second premolar because it uses approximate mesial and distal points of individual teeth. In all three groups, ICW and IMW showed an ICC close to 1, which is because they are simple distance measures.

Table 3 displays a comparison of the maxillary arch TS, ICW, and IMW measurements between the investigated methods. Among the three groups, the central incisors, lateral incisors, canines, premolars, and molars were compared bilaterally. The results revealed no significant difference between TS, ICW, and IMW measurements of the maxillary arch

among the manual, LS, and DS groups. However, although there was no statistical significance, the P-value of the maxillary second premolar was the smallest compared to other teeth due to the diversity of TS.

Table 4 demonstrates a comparison of TS, ICW, and IMW measurements between the investigated methods for the mandibular arch. Among the three groups, the central incisors, lateral incisors, canines, premolars, and molars were compared bilaterally. The results revealed no significant difference between the TS, ICW, and IMW measurements of the mandibular arch among the manual, LS, and DS groups.

A comparison of the Bolton analysis for the investigation method between manual, LS, and DS methods is shown in Table 5. No significant difference was observed between Bolton ratio 6 and Bolton 12 among the manual, LS, and DS groups. Bolton 6 exhibited a mean of 77.6, 77.6, and 77.7 for the manual, LS, and DS groups, respectively, while Bolton 12 ex-

Table 3. Comparison of TS, ICW and IMW between investigated methods of the maxilla arch

Measurement	Manual		LS		DS		P-value
	Mean	SD	Mean	SD	Mean	SD	
Right (mm)							
Central incisor	8.4	±0.4	8.4	±0.3	8.4	±0.3	0.978
Lateral incisor	7.1	±0.4	7.1	±0.4	7.1	±0.4	0.993
Canine	8.0	±0.3	8.0	±0.3	7.9	±0.4	0.907
First premolar	7.4	±0.2	7.4	±0.2	7.4	±0.2	0.938
Second premolar	6.9	±0.3	7.0	±0.3	7.0	±0.4	0.727
First molar	10.7	±0.5	10.6	±0.5	10.6	±0.5	0.987
Left (mm)							
Central incisor	8.4	±0.4	8.4	±0.3	8.4	±0.3	0.978
Lateral incisor	7.1	±0.4	7.1	±0.4	7.1	±0.4	0.996
Canine	7.9	±0.3	7.9	±0.3	7.9	±0.3	0.977
First premolar	7.5	±0.2	7.5	±0.2	7.5	±0.2	0.994
Second premolar	6.9	±0.4	6.9	±0.3	6.9	±0.9	0.425
First molar	10.4	±0.4	10.4	±0.4	10.4	±0.4	0.987
ICW (mm)	37.0	±1.7	36.9	±1.7	37.0	±1.7	0.993
IMW (mm)	49.6	±2.8	49.6	±2.8	49.6	±2.8	0.999

TS: tooth size, ICW: intercanine width, IMW: intermolar width, Manual: manual measurement on a plaster model, LS: landmark-based tooth segmentation, DS: tooth designation and segmentation, SD: standard deviation.

Table 4. Comparison of TS, ICW and IMW between investigated methods of the mandible arch

Measurement	Manual		LS		DS		P-value
	Mean	SD	Mean	SD	Mean	SD	
Right (mm)							
Central incisor	5.4	±0.2	5.4	±0.2	5.4	±0.2	0.831
Lateral incisor	6.0	±0.3	6.0	±0.3	6.0	±0.3	0.988
Canine	6.8	±0.3	6.8	±0.3	6.8	±0.3	0.989
First premolar	7.4	±0.3	7.3	±0.3	7.4	±0.3	0.932
Second premolar	7.3	±0.3	7.0	±0.3	7.0	±0.4	0.998
First molar	11.2	±0.6	11.2	±0.7	11.2	±0.7	0.999
Left (mm)							
Central incisor	5.4	±0.2	5.4	±0.2	5.4	±0.2	0.972
Lateral incisor	5.9	±0.3	6.0	±0.3	5.9	±0.3	0.989
Canine	6.9	±0.3	6.9	±0.3	6.9	±0.3	0.980
First premolar	7.5	±0.3	7.5	±0.3	7.5	±0.3	0.986
Second premolar	7.2	±0.4	7.2	±0.3	7.2	±0.4	0.998
First molar	11.2	±0.5	11.2	±0.5	11.2	±0.5	>0.999
ICW (mm)	27.5	±1.1	27.5	±1.1	27.5	±1.1	0.993
IMW (mm)	43.7	±2.7	43.7	±2.7	43.6	±2.6	0.999

TS: tooth size, ICW: intercanine width, IMW: intermolar width, Manual: manual measurement on a plaster model, LS: landmark-based tooth segmentation, DS: tooth designation and segmentation, SD: standard deviation.

Table 5. Comparison of the Bolton tooth size discrepancy measurements for investigated method between manual, LS, and DS

Measurement	Manual		LS		DS		P-value
	Mean	SD	Mean	SD	Mean	SD	
Bolton ratio 6 (%)	77.6	±2.2	77.6	±2.4	77.7	±2.2	0.992
Bolton ratio 12 (%)	91.3	±1.4	91.2	±1.4	91.2	±1.4	0.875

Manual: manual measurement on a plaster model, LS: landmark-based tooth segmentation, DS: tooth designation and segmentation, SD: standard deviation.

hibited a mean of 91.3, 91.2, and 91.2, respectively.

Discussion

With technological advances, plaster study models can be displayed as 3D images, which are utilized by many dental clinicians in diagnosis and treatment planning, as well as to obtain specific measurements such as Bolton ratios and TS. However, the literature describes various methods and techniques for digital dental measurements, resulting in varying findings between the studies in terms of accuracy, reliability, and efficiency.

Our study utilized two digital software. The results

revealed no significant differences between the measurements of the dental impressions obtained via the conventional method and those obtained via the two digital methods. The comparison of TS, ICW, and IMW measurements revealed no significant differences (Tables 3, 4), indicating the acceptability of using digital models as an alternative to conventional models. This finding was consistent with those of multiple studies that reported clinically non-significant differences between conventional and digital models and supported the clinical use of computer digital models^{7,10-12}.

For example, a similar study by Sfondrini et al.¹⁰ compared measurements obtained via the conven-

tional model with those obtained via digital models analyzed using Ortho Analyzer software, identifying no significant differences in the upper and lower arch measurements, nor in the ICW and IMW between the two models. Another similar study by Murugesan and Sivakumar¹¹⁾ did not report any significant variations in the measurements obtained from conventional and digital methods and argued that both model types are clinically reliable in dental practice, and offer accurate measurements. Another study by Tomita et al.⁷⁾ compared the accuracy of measurements between four groups, *i.e.*, the conventional group, and three other experimental groups including the alginate, silicone, and intraoral scanning groups. The study reported no statistical differences between the measurements among the four groups. Though Ender and Mehl¹²⁾ reported higher accuracy of conventional impression scans to obtain full-arch digital models compared to that of direct digital impression scans, the differences were not significant. Moreover, Schlenz et al.¹³⁾ reported significant differences between conventional and digital models, with digital models showing superior performance and accuracy over conventional models.

As for the Bolton analysis measurements, our study reported no significant difference between Bolton ratio 6 and 12 among the manual, LS, and DS groups (Table 5). This was supported by Kim and Lagravère¹⁴⁾, who compared Bolton analysis measurements and reported the accurate and consistent performance of digital models in Bolton analyses.

Conversely, Lee and Park¹⁵⁾ used alginate impressions for their plaster models and two intraoral scanners (TRIOS and iTero scanners) to analyze the measurements from their digital model, identifying an overall deviation of 0.10 mm between conventional alginate impressions and *in vivo* intraoral scans of the full dental arch. Moreover, Schlenz et al.¹³⁾ reported challenges regarding tooth measurements among periodontal compromised patients and emphasized the importance of considering the challenging aspect

pertaining to impression taking as these patients usually have numerous undercuts and extensive interdental areas.

Furthermore, Lim et al.¹⁶⁾ considered the involvement of different dental restorative materials to measure the accuracy and differences between intraoral scanning impressions and conventional impression groups. The two groups had similar accuracy when it came to non-metallic crowns; however, significant differences were noted between the groups when metallic crowns were utilized. Hence, the study argued the importance of considering the restoration material already placed in the oral cavity when choosing an impression method.

Another important factor for consideration is the effect of lighting conditions on the accuracy and precision of the impressions obtained via digital models. According to Revilla-León et al.¹⁷⁾, the precision and accuracy significantly differs between digital impressions obtained under different lighting conditions. The study argued that different intraoral scanners require different digital impressions, and recommended the use of the appropriate ambient lighting conditions that match the intraoral scanning method selected to avoid distortion to the precision and accuracy of the scans taken.

Regarding the strengths and limitations, the current study adds to the literature by supporting the findings from previous studies that reported digital models and measurements as acceptable tools in dental practices as replacements for the conventional plaster model. Regarding the study limitations, the study had a relatively small sample size and a non-diverse study sample. There was no difference between groups in all the TS, ICW, IMW, and Bolton values in this study, but this may be due to the very small sample size. In addition, since this study was conducted on patients after orthodontic treatment to exclude factors other than the measurement method, such as crowding or rotation at the time of TS measurement, it is expected that patients randomly re-

cruited will show significant differences in TS values between groups¹⁸⁾.

Therefore, future studies must include a larger sample size, and a more diverse study sample, with the utilization of more different digital software and intraoral scanning tools available to support the movement toward the use of digital models. Furthermore, specific attention must be given when measuring patients with specific conditions such as crowding and rotation of the tooth, and the type of restoration material that exists in the oral cavity, as these may contribute to the variations in findings.

Conclusion

After the development of computer-aided design and computer-aided manufacturing systems, especially intraoral scanners, digital models have become increasingly important and were successful in producing dental impressions that have high accuracy similar to the dental impressions obtained via conventional methods. Most of the literature supports the use of digital models and measurements as acceptable tools in dental practices that can replace the conventional plaster model. Our study also supports this fact as no significant differences were reported between the TS, the ICW and IMW, and the Bolton analysis through the conventional and two digital groups. Measurements of TS, arch width, and Bolton analysis produced from digital models have shown acceptable clinical validity.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgement

This research was supported by a grant from the Korea Health Technology R&D Project through the

Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI20C0611).

References

1. Kumar AA, Ananthakrishnan MG, Kumar S, Divakar G, Sekar S, Dharani S. Assessing the validity and reliability of tooth widths and bolton ratios obtained from digital models and plaster models. *J Pharm Bioallied Sci.* 2022; 14(Suppl 1): S148-51.
2. Gül Amuk N, Karsli E, Kurt G. Comparison of dental measurements between conventional plaster models, digital models obtained by impression scanning and plaster model scanning. *Int Orthod.* 2019; 17: 151-8.
3. Zhang F, Suh KJ, Lee KM. Validity of intraoral scans compared with plaster models: an in-vivo comparison of dental measurements and 3D surface analysis. *PLoS One.* 2016; 11: e0157713.
4. Park SH, Byun SH, Oh SH, Lee HL, Kim JW, Yang BE, Park IY. Evaluation of the reliability, reproducibility and validity of digital orthodontic measurements based on various digital models among young patients. *J Clin Med.* 2020; 9: 2728.
5. Choi SH, Koh K, Lee KJ, Hwang CJ, Cha JY. Analysis of the morphological characteristics of the palatal rugae for three-dimensional superimposition of digital models in Korean subjects. *Biomed Res Int.* 2018; 2018: 3936918.
6. Camardella LT, Breuning H, de Vasconcellos Vilella O. Accuracy and reproducibility of measurements on plaster models and digital models created using an intraoral scanner. *J Orofac Orthop.* 2017; 78: 211-20.
7. Tomita Y, Uechi J, Konno M, Sasamoto S, Iijima M, Mizoguchi I. Accuracy of digital models generated by conventional impression/plaster-model methods and intraoral scanning. *Dent Mater J.* 2018; 37: 628-33.
8. Im J, Kim JY, Yu HS, Lee KJ, Choi SH, Kim JH, Ahn

- HK, Cha JY. Accuracy and efficiency of automatic tooth segmentation in digital dental models using deep learning. *Sci Rep.* 2022; 12: 9429.
9. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med.* 2016; 15: 155-63. Erratum in: *J Chiropr Med.* 2017; 16: 346.
 10. Sfondrini MF, Gandini P, Malfatto M, Di Corato F, Trovati F, Scribante A. Computerized casts for orthodontic purpose using powder-free intraoral scanners: accuracy, execution time, and patient feedback. *Biomed Res Int.* 2018; 2018: 4103232.
 11. Murugesan A, Sivakumar A. Comparison of accuracy of mesiodistal tooth measurements made in conventional study models and digital models obtained from intraoral scan and desktop scan of study models. *J Orthod.* 2020; 47: 149-55.
 12. Ender A, Mehl A. In-vitro evaluation of the accuracy of conventional and digital methods of obtaining full-arch dental impressions. *Quintessence Int.* 2015; 46: 9-17.
 13. Schlenz MA, Schubert V, Schmidt A, Wöstmann B, Ruf S, Klaus K. Digital versus conventional impression taking focusing on interdental areas: a clinical trial. *Int J Environ Res Public Health.* 2020; 17: 4725.
 14. Kim J, Lagravère MO. Accuracy of Bolton analysis measured in laser scanned digital models compared with plaster models (gold standard) and cone-beam computer tomography images. *Korean J Orthod.* 2016; 46: 13-9.
 15. Lee KC, Park SJ. Digital intraoral scanners and alginate impressions in reproducing full dental arches: a comparative 3D assessment. *Appl Sci.* 2020; 10: 7637.
 16. Lim JH, Mangal U, Nam NE, Choi SH, Shim JS, Kim JE. A comparison of accuracy of different dental restorative materials between intraoral scanning and conventional impression-taking: an in vitro study. *Materials (Basel).* 2021; 14: 2060.
 17. Revilla-León M, Subramanian SG, Özcan M, Krishnamurthy VR. Clinical study of the influence of ambient light scanning conditions on the accuracy (trueness and precision) of an intraoral scanner. *J Prosthodont.* 2020; 29: 107-13.
 18. Yoon JH, Yu HS, Choi Y, Choi TH, Choi SH, Cha JY. Model analysis of digital models in moderate to severe crowding: in vivo validation and clinical application. *Biomed Res Int.* 2018; 2018: 8414605.