KEY WORDS
Reanalysis, Secondary Analysis, Individual Patient Data, Meta-Analysis, Phoenix analysis

PHOENIX ANALYSIS: REANALYSIS OF OLD STUDIES IN DENTISTRY

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PURPOSE. This study explores an inexpensive method of obtaining useful information by reprocessing individual patient data reported in old clinical studies by means of secondary analysis.

MATERIALS AND METHODS. Three areas of interest in dental research were chosen (gnathology, endodontics, and periodontology). A manual search was conducted on Oral Surgery, Oral Medicine, and Oral Pathology from 1960 to 1970. Only articles reporting individual patient data (IPD) and published at least 50 years ago were considered. One article concerning a controversial topic in each area was selected. Three old articles were chosen to be subjected to new statistical analyses not available at the time of the original publication. Specifically, the IPD from each selected study was entered into an electronic database for further analysis, performed via the appropriate current statistical techniques.

RESULTS. The new analyses confirmed the conclusions drawn by the original authors were correct in some cases, while contradicting them in others. In particular, a lack of relationship between pulp alterations and periodontitis was confirmed, as was hypothesis that the roots of immature teeth grow after transplantation. However, a lack of correlation between maximum mouth opening and condyle location was disproved, as was the notion of intra-individual variation in pulp morphology.

CONCLUSIONS. Phoenix analysis is a useful and inexpensive method of updating interpretations of old dental literature, and can provide a springboard for further research.

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INTRODUCTION

Any scientific study involves collecting and analysing data. Three subsequent levels of analysis may be carried out on the same data set according to the following classification[1]:

- Primary analysis, which is "the original analysis of data in a research study";
- Secondary analysis, which is "the reanalysis of data for the purposes of answering the original research question with better statistical techniques or answering new questions with old data. Secondary analysis is an important feature of the research and evaluation enterprise […]";

- Meta-analysis, the third level of analysis, which is "the statistical analysis of a large collection of analysis that results from individual studies for the purpose of integrating the findings".

Both primary analysis and meta-analysis have become very common in the medical environment, while secondary analysis is seldom encountered in the medical literature. Secondary analysis is not commonly used because it must be performed on individual patient data (IPD), or raw data, which is rarely available (either on paper or electronically) for use by other investigators. Hence, secondary analysis is mainly performed on large databases collected by public agencies[2-6], or when investigators decide to conduct new analyses on their own data[7,8]. Nevertheless, secondary analysis may lead to important discoveries, or contradict previously reported conclusions based on statistics employed in primary analysis that we now know to be superseded or inappropriate. In such cases, reanalysis reveals that previously drawn conclusions may be misleading, which is particularly important to know when suggesting potential benefits to patients[9].

Individual patient data (IPD) has progressively gained importance in the dental and periodontal literature, especially for the purposes of meta-analysis[10-12]. However, IPD from old scientific articles has rarely been subjected to reanalysis for other purpose. The databases remain, but the ways of analysing the information, as well as the clinical issues involved, may change over time; hence, an old publication may acquire new importance through secondary analysis of its IPD.

The main objectives of secondary analysis are: to test the hypotheses proposed in the old studies by applying appropriate modern statistical techniques, and to analyse the same data in light of new theories, in order to explore new relationships and new related hypotheses. Secondary analysis is also a powerful tool for preparing old data for modern meta-analysis, for example when aggregate parameters were not evaluated in the original publication (e.g., standard deviation). Thus, as in the myth of the phoenix, new analysis may breathe new life into the ashes of old data.

The aim of this article is to illustrate and promote the use of this form of research, by reviewing several old articles on different controversial topics from the dentistry literature, and applying "phoenix" analysis to the individual patient data reported therein.

MATERIALS AND METHODS

One of the authors (MN), experienced in methodological evaluation of scientific articles, selected three areas of interest in dental research (gnathology, endodontics, and periodontology). A manual search was conducted on *Oral Surgery, Oral Medicine, and Oral Pathology* from 1960 to 1970. Only articles reporting IPD were considered. One article concerning a controversial topic in each area was selected.

The IPD from each selected study was entered into an electronic database for further analysis. One author (MN) set up the strategy for the secondary analysis by selecting appropriate current statistical techniques.

RESULTS

Three articles were selected, dealing with the following topics in gnathology, endodontics and periodontology, respectively: physiology of the temporomandibular joint (Wooten 1966)[13], relationship between pulpal alterations and periodontitis (Mazur and Massler 1964)[14], and the periodontal status of autografted teeth (Galanter and Minami, 1968)[15]. The outcomes of their subsequent secondary analysis are described below.

Data analysis

1. Physiology of the temporomandibular joint (Wooten, 1966)[13]

Original results

Wooten's was a radiological study on the position of the mandibular condyle at the maximum opening of the mouth[13]. Wooten had randomly sampled 100 men from the U.S. Air Force, aged 18 to 30, finding that the condyle, at maximal mouth opening, was sometimes fully anterior to the articular eminence. This was found on the right side in 70% of cases. He concluded that the correlation between the location of the condyle and mouth opening is "completely unreliable", stating that "the position of the condyle cannot be determined by the distance of maximal mouth opening".

However, Wooten did not carry out any inferential statistical analysis, and only calculated descriptive statistics for a few of the variables considered.

Reanalysis

a. The correlation coefficient between the location of the right condyle and the maximum mouth opening was calculated, and a linear regression was drawn between these variables. It was determined that correlation coefficient between the location of the right condyle relative to the articular eminence in millimetres and the maximum mouth opening in centimetres is $r = 0.51$, 95% CI from 0.35 to 0.64, $b = 2.44$ ($P < 0.0001$).
b. Logistic regression was performed to predict the completely anterior location of the right condyle with respect to the maximum mouth opening. This analysis was only introduced in the medical literature at the end of the 1970s, and was therefore not available to Wooten. However, the logistic regression we performed (shown in **FIG. 1**) showed that when the maximum mouth opening is 4 cm, the right condyle will be completely anterior to the eminence in 40% of cases, while a maximum opening of 6 cm is associated with a

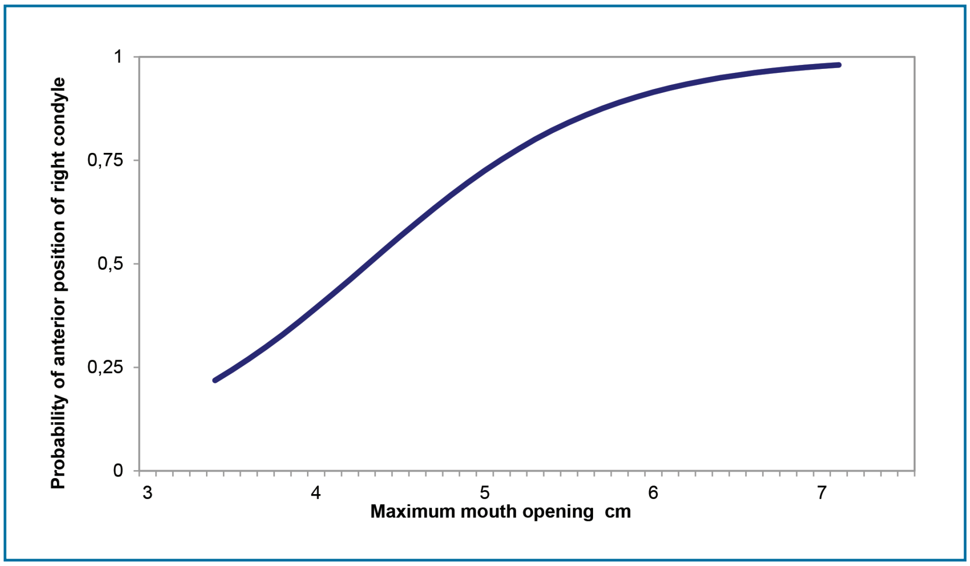

FIG. 1: *Logistic regression of the completely anterior position of the right condyle at maximum mouth opening.*
Logit Right Ant = -6.04 + 1.40 Mouth Op
Mouth Op is the maximum mouth opening in cm. Right Ant is 1 when the right condyle is completely anterior to the articular eminence, otherwise it is zero. The logistic regression line gives the estimated probability of having the right condyle completely anterior to the articular eminence at the various maximum mouth openings expressed in cm.

completely anterior condylar location in about 90% of cases. Thus, the conclusion of the original study, that the position of the mandibular condyle cannot be determined by the distance of maximal mouth opening, was erroneous; a lack of appropriate statistics had prevented quantification of this correlation, which, however, becomes clear when appropriate statistics are applied.

2. Relationship between pulpal alterations and periodontitis (Mazur and Massler, 1964)[14]

Original results

That article examined the histological characteristics of the pulp of 128 teeth extracted from 25 patients; all the extracted teeth were associated with periodontal lesions of varying severity[14]. The authors found that: (1) "there was no correlation between the severity of periodontal disease and the pulpal changes" and that no "correlation exists between age and changes in the pulp"; and (2) "the pulps of the teeth, regardless of periodontal involvement, presented very similar pictures" and "the structural morphology of the pulpal tissue is peculiar to the individual person, no matter what the status of the periodontium". Nevertheless, the authors provided no statistics in support of their conclusions[14], and in fact, the appropriate statistical techniques for investigating the correlation among variables in a two-level study (patient, tooth) were not available in 1964.

Reanalysis

a. A new, secondary analysis was performed by constructing a multilevel model to test their first conclusion (1)[16]. Specifically, a two-level analysis (patient and tooth) was performed to investigate the correlation between pulp alterations, age, race, and periodontal disease. The model confirmed a lack of association between pulp alterations and either periodontal disease (P = 0.4849), race (P = 0.6844), gender (P = 0.7023), or age (P = 0.2753) (**TABLE 1**).

TABLE 1 MULTILEVEL ANALYSIS OF PULP ALTERATIONS, AGE, RACE AND PERIODONTAL DISEASE.

Term	Estimate	Std. error	P-value
Intercept (β_{0ij})	1.385	0.624	
Periodontal$_{ij}$ (β_1)	0.044	0.063	0.4849
Race$_j$ (β_2)	-0.126	0.310	0.6844
Gender$_j$ (β_3)	-0.112	0.293	0.7023
Age$_j$ (β_4)	0.012	0.011	0.2753
σ_u^2	0.320	0.120	
σ_e^2	0.392	0.054	

Model Pulpal$_{ij}$ = β_{0ij} + β_1Periodontal$_{ij}$ + β_2Race$_j$ + β_3Gender$_j$ + β_4Age$_j$ which translates as the following estimate

Pulpalij ranges from "mild" = 1 to "severe" = 4; Periodontalij ranges from "0 to ¼ of root exposed" = 1 to "¾ to 1 of root exposed" = 4; Racej is 0 for "white" and 1 for "black", Genderj is 0 for "women" and 1 for "men", Agej is reported in years.

In the model, the subscript "i" refers to tooth level, while the subscript "j" refers to patient level. σ_u^2 and σ_e^2 indicate the variances at patient and tooth levels, respectively

b. The intraclass correlation coefficient[17] was calculated to test Mazur and Massler's second conclusion (2). This was found to be 0.47, suggesting that 47% of the observed variation is explained by the patient features while the remaining 53% is explained by site-level features.

Thus, modern multilevel analysis applied to the available IPD enabled us to confirm the authors' first conclusion that there is no correlation between pulp alterations and either age, race or periodontal disease. However, the new "phoenix" analysis also revealed that the pulp tissues display considerable site-specific variability (53%), indicating that the characteristics of the pulp are not "peculiar to the individual person" as suggested by the authors. This is important to note because the conclusions reported in the original article had influenced all subsequent studies on this topic, despite not being based on appropriate statistics.

3. Periodontal condition of auto-transplanted immature teeth (Galanter and Minami, 1968)[15]

Original results

The authors analysed the periodontal condition of 31 auto-transplanted immature teeth, reporting individual data for transplanted teeth and the contralateral, mesial and distal teeth. They concluded that there were no differences in probing values between transplanted teeth and other teeth in the same patient. They also stated that "some root growth does occur after transplantation" and observed that "root lengths were greater and crown–root ratios more favourable in the transplants that had been in place longer".

Reanalysis

a. A new analysis was performed, constructing a multilevel model[16] (three levels: patient, tooth and site) to test the authors' conclusion that there is no difference in probing depths (PD) between transplanted and control teeth. The mean probing depth was 2.4±1.6 mm at transplanted teeth but 2.2±1.3 mm at control teeth. The estimated difference between transplanted teeth and control teeth was 0.2 mm (95% CI from -0.0 to 0.4 mm), and the P-value was close to the level of statistical significance ($P = 0.0589$), thereby casting some doubt on the authors' conclusions. In this case statistical analysis revealed that their null hypothesis can neither be rejected or accepted with any certainty based on the available data.
b. Their hypothesis that the crown–root ratio diminished over time after transplantation may be tested using a quadratic model, which was considered a sophisticated approach in 1968. The quadratic model that is illustrated in **FIG. 2** supports the authors' observations in this regard.
c. We also employed ordinal logistic regression analysis to investigate the relationship between crown–root ratio and mobility of the transplanted teeth, something that had not been considered by the authors. This indicated the probability of a transplanted tooth having different degrees of mobility for a given crown–root ratio (**FIG. 3**); specifically, at a crown–root ratio of 1, the probabilities of observing mobility 0, 1 or 2 were found to be 22%, 69% and 9%, respectively.

In this case, "phoenix" analysis made it possible to apply statistical tools that were not available at the time of original publication, and to quantify some of the authors' observations, revealing further relationships among the variables.

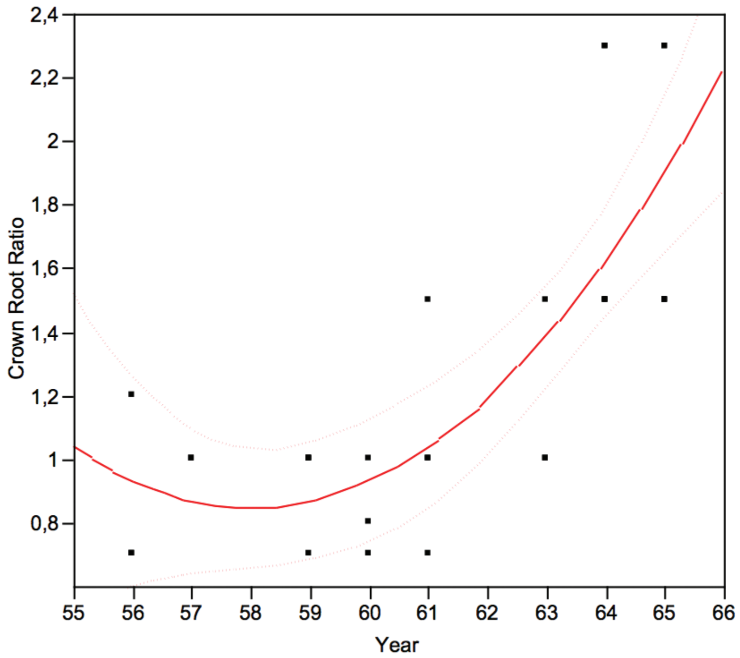

FIG. 2: *Relationship between year of transplant and crown/root ratio.*
CrownRoot Ratio = 73.13 – 2.49year + 0.02year^2
$R^2 = 0.62$
The variable CrownRoot Ratio indicates the crown–root ratio of the transplanted teeth. Year is the time at which the transplant was performed. The quadratic regression indicates that the "older" transplants have a lower crown/root ratio. Root development appears to stop at a definitive crown–root ratio of about 0.9; it is interesting to note that the crown–root ratio of teeth distal to the transplanted tooth is, on average, 0.8.

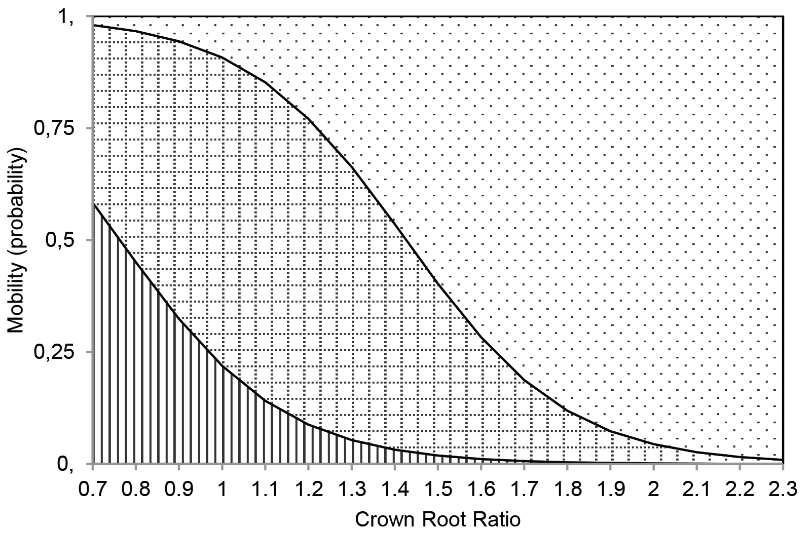

FIG. 3: *Relationship between crown-root ratio and mobility.*
Ordinal logistic regression. Vertical lines indicate mobility = 0. Squares indicate mobility = 1. Dots indicate mobility = 2.
Mobility is clearly lower at teeth with a lower crown–root ratio (P < 0.0001).

DISCUSSION

Secondary analysis is a method of *ex novo* reanalysis that allows scientific knowledge to evolve by applying new computer and statistical technology to IPD reported in old scientific articles. As we have seen, it can be used not only to test the hypotheses formulated in the original articles, but also to explore new hypotheses on the subject that had not been considered by the original authors. This is of particular interest, when, as is often the case, old studies cannot be easily replicated due to ethical concerns (radiation, dangerous interventions, lack of treatment, etc.), long follow-up and/or unrepeatable events.

Indeed, the original data that were retested for this article had been published more than 50 years ago. Secondary analysis using new statistical methods allowed the original authors' conclusions to either be refuted, confirmed or further clarified by discovering new relationships in the data. Thus, "phoenix" analysis can lead to reinterpretation of data provided by old articles that may have influenced clinical behaviour in different areas of dentistry. In cases of misleading data interpretation, this reanalysis is useful in correcting inappropriate clinical approaches, and in promoting future research to clarify the features of each controversial topic.
Phoenix analysis may also serve as a support for meta-analysis; it enables us to compute statistical indices that had not been considered by the original authors, and to check the calculation of the reported indices. For example, several statistical indices were recalculated, using the originally reported IPD, in a meta-analysis of articles on surgical root coverage[18]. This procedure made it possible to correct printing errors, and to obtain data not otherwise available to the reader. For instance, the topic explored by Wooten[13] was investigated later by many other researchers[19-21]; two articles considered the same relationship studied by Wooten and found correlation coefficients similar to that which we found in the reanalysis: 0.56 and 0.46 respectively[20,21]. However, the correlation coefficient for the right condyle was reported in another study[19] as 0.969, which was clearly a misprint, since the correlation coefficient for the left condyle was 0.692[19]. Nevertheless, a lack of reported IPD prevented us from recalculating the correlation coefficient for this study. In fact, this information gap may have led subsequent investigators to discount Wooten's findings: both Obwegeser et al.[19] and Muto et al.[20] referenced Wooten's article, but reported only that it dealt with the same subject, while Meti[21] did not even quote the article. However, Wooten's data could have been very useful to these researchers if secondary analysis had been performed.
On another topic, dental literature has consistently reflected a controversy related to the effect of periodontal disease on the dental pulp[22,23]. To date it is not clear which factors in periodontal disease can affect pulp inflammation. Several authors who conducted human and animal studies have suggested that degenerative pulpal changes develop independently of periodontal disease[24,25], and Mazur and Massler[14] thought that the structural morphology of the pulpal tissue varies on an intra-individual basis, no matter the status of the periodontium. However, secondary analysis of Wooten's work appears to indicate that the characteristics of the pulp are not, in fact, "peculiar to the individual person" as suggested. If so, further studies comparing pulp conditions with periodontitis, race, gender, and age may shed light on potential links.
Similarly, information that can be deduced from Galanter and Minami's article on auto-transplanted teeth can still prove useful[15]. Immature root development of donor teeth has been established as one of the most important factors in the success of tooth transplantation[26], but to date there is not much data on the state of the periodontal tissues around auto-transplanted immature teeth. Hence, the data we do have, including historical data such as Galanter and Minami's, should be considered a precious resource, which can be mined for information via more up-to-date analytical methods, as presented here.
It should be noted, however, that there are certain limitations to the use of secondary analysis. Indeed, this is a *post-hoc* form of investigation using data sets collected by other investigators. Hence, this method offers few possibilities of clarifying terms and actions that were not explicitly indicated in the original article[27]. In other words, secondary analysts are: "prisoners of the decision about conceptualization made by those who originally collected the data"[28]. Furthermore, the fact that some of the statistical tests performed were not contemplated in the original research protocol could give rise to "post-hoc analysis bias"[29].
That being said, publication of IPD does make secondary analysis possible at a minimum cost. Proper reanalysis may provide precious information, also allowing us to calculate the adequa-

te sample size for new studies, thereby saving time, effort and money. Phoenix analysis may prove very useful, as such data represents the collective scientific "memory", and could even be a source of new knowledge[30]. Indeed, the power of science can best be exercised by considering past experience. Unfortunately, the loss of IPD, and therefore our "memory", occurs all too often. Phoenix analysis could, however, contribute to building a bridge between the past, present, and future knowledge in science, while saving significant amounts of time and money.

CONCLUSIONS

Phoenix analysis is a useful and inexpensive method of updating interpretations of old dental literature and can provide a springboard for further research.

REFERENCES

1. Glass GV. Primary, secondary, and meta-analysis. Educ Res 1976;5:3-8.
2. Kannel WB, Gordon T, Schwartz MJ. Systolic *versus* diastolic blood pressure and risk of coronary heart disease; the Framingham study. Am J Cardiol 1971;27:335-46.
3. Best AE. Secondary data bases and their use in outcomes research: a review of the area resource file and the healthcare cost and utilization project. J Med Syst 1999;23:175-81.
4. Port S, Demer L, Jennrich R, Walter D, Garfinkel A. Systolic blood pressure and mortality. Lancet 2000;355:175-80.
5. Dragonas P, Kaste LM, Nunn M, Gajendrareddy PK, Weber KM, Cohen M, Adeyemi OM, French AL, Sroussi HY. Vitamin D deficiency and periodontal clinical attachment loss in HIV-seropositive women: a secondary analysis conducted in the Women's Interagency HIV Study (WIHS). Oral Surg Oral Med Oral Pathol Oral Radiol. 2018;125:567-73.
6. Davidson J, Ding Y, Chan E, Dave S, Bjazevic J, Filler G, Wang PZ. Postoperative outcomes of ureteroscopy for pediatric urolithiasis: a secondary analysis of the National Surgical Quality Improvement Program Pediatric. J Pediatr Urol 2021;17:649.e1-649.e8.
7. Paquette DW. Clinical relevance of adjunctive minocycline microspheres in patients with chronic periodontitis: secondary analysis of a phase 3 trial. J Periodontol 2004;75:531-6.
8. Reiniger APP, Maier J, Wikesjö UME, Moreira CHC, Kantorski KZ. Correlation between dental plaque accumulation and gingival health in periodontal maintenance patients using short or extended personal oral hygiene intervals. J Clin Periodontol 2021;48:834-42.
9. Tu YK, Clerehugh V, Gilthorpe MS. Ratio variables in regression analysis can give rise to spurious results: illustration from two studies in periodontology. J Dent 2004;32:143-51.
10. Clauser C, Nieri M, Franceschi D, Pagliaro U, Pini-Prato G. Evidence-based mucogingival therapy. Part 2: Ordinary and individual patient data meta-analyses of surgical treatment of recession using complete root coverage as the outcome variable. J Periodontol 2003;74:741-56.
11. Nieri M, Clauser C, Pagliaro U, Pini Prato GP. Individual patient data (IPD) may be a criterion in grading articles dealing with therapy outcomes. J Evid Base Dent Pract 2003;3:122-6.
12. Chambrone L, Pannuti CM, Tu YK, Chambrone LA. Evidence-based periodontal plastic surgery. II. An individual data meta-analysis for evaluating factors in achieving complete root coverage. J Periodontol 2012 Apr;83(4):477-90.
13. Wooten JW. Physiology of the temporomandibular joint. Oral Surg Oral Med Oral Pathol 1966;21:543-53.
14. Mazur B, Massler M. Influence of periodontal disease on dental pulp. Oral Surg Oral Med Oral Pathol 1964;17:592-603.
15. Galanter DR, Minami RT. The periodontal status of autografted teeth. A pilot study of thirty-one cases. Oral Surg, Oral Med Oral Pathol 1968;26:145-59.
16. Goldstein H. Multilevel Statistical Models. London: Edward Arnold, 1995.
17. Fleiss JL. The design and analysis of clinical experiments. New York: John Wiley & sons, 1986:2-3.
18. Pagliaro U, Nieri M, Franceschi D, Clauser C, Pini-Prato G. Evidence-based mucogingival therapy. Part 1: A critical review of the literature on root coverage procedures. J Periodontol 2003;74:709-40.
19. Obwegeser HL, Farmand M, Al-Majali F, Engelke W. Findings of mandibular movement and the position of the mandibular condyles during maximal mouth opening. Oral Surg Oral Med Oral Pathol 1987;63:517-25.
20. Muto T, Kohara M, Kanazawa M, Kawakami J. The position of the mandibular condyle at maximal mouth opening in normal subjects. J Oral Maxillofac Surg 1994;52:1269-72.
21. Meti M. Position of mandibular condyle at maximal mouth opening in symptom free subjects. Indian J Dent Res 2002;13:135-41.
22. Gautam S, Galgali SR, Sheethal HS, Priya NS. Pulpal changes associated with advanced periodontal disease: a histopathological study. J Oral Maxillofac Pathol 2017;21:58-63.
23. Sabeti M, Tayeed H, Kurtzman G, Mashhadi Abbas F, Talebi Ardakani M. Histopathological investigation of dental pulp reactions related to periodontitis. Eur Endod J 2021;6:164-9.
24. Bergenholtz G, Lindhe J. Effect of experimentally induced marginal periodontitis and periodontal scaling on the dental pulp. J Clin Periodontol 1978;5:59-73.
25. Fatemi K, Disfani R, Zare R, Moeintaghavi A, Ali SA, Boostani HR. Influence of moderate to severe chronic periodontitis on dental pulp. J Indian Soc Periodontol 2012;16:558-61.
26. Almpani K, Papageorgiou SN, Papadopoulos MA. Autotransplantation of teeth in humans: a systematic review and meta-analysis. Clin Oral Investig 2015;19:1157-79.
27. Brown JS, Semradek RN. Secondary data on health-related subject: major sources, uses, and limitations. Public Health Nurs 1992;9:162-71.
28. Jacob H. Using published data: errors and remedies. Beverly Hills, CA: Sage, 1984:16.
29. Choi BC, Pak AW. Bias, overview. In: Armitage P, Colton T, editors. Encyclopedia of Biostatistics, Vol 1. Chichester, England: John Wiley & Sons, 1998:337.
30. Smith GD. Increasing the accessibility of data. BMJ 1994;308:1519-20.