Critical Size Defects for Bone Regeneration Experiments in the Dog Mandible: A Systematic Review

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Objectives: *To perform a systematic literature review of studies involving critical size defects (CSDs) in the dog mandible and calvarium to find out the common characteristics of CSDs.*

Materials and Methods: *Internet search of the literature was performed on June 2016 based on specific keywords. The search process included 5 databases. The Animal Research Reporting In Vivo Experiment (ARRIVE) guidelines was used to assess the quality of the included studies.*

Results: *Nine studies have met the inclusion criteria and subjected to quality evaluation. All the defects (N = 156) were located in the mandible. Only 2 articles showed randomized controlled studies, whereas the remaining 7 were nonrandomized controlled studies. The geometry of the defects was either rectangular, box, cylindrical (circular), arch, or saddle shaped.*

Conclusion: *There is a lack of homogeneity in reporting data on CSDs in the dog mandible. Future animal studies should include a negative control group for an objective comparison and evaluation of any new biomedical materials. More awareness is needed for the Animal Research Reporting In Vivo Experiment (ARRIVE) guidelines to improve data reporting, which can facilitate comparison and reproducibility of future studies. (Implant Dent 2018;27:135–141)*

Key Words: mandibular defect, bone healing, animal model

The concept of critical size defect (CSD) was developed more than 25 years ago as an attempt to standardize research on bone regenerative materials. Originally, it referred to the smallest defects that would not heal by natural process during the lifetime of the animal.[1] Because healing can involve fibrous tissue formation, the CSD concept was clarified few years later to involve any defect that has less than 10% of bone regeneration during the first year of defect healing. Such period was considered to indicate that bone union is not expected to occur during the animal lifetime, and such defect was considered as a true CSD.[2] Because the animal lifetime in most of clinical research is bounded by the completion of the study, the CSD concept was revisited recently to refer to the smallest size of a defect that does not heal spontaneously when left untreated for a certain period.[3]

Linking the defect size to the duration of the study opened the gate to animal studies that have reported healing of different defect sizes over different durations within the same animal model, and all the nonhealing sites were still considered as CSDs. Delgado-Ruiz et al[4] reviewed systematically CSDs on rabbit calvariae and found a lack of homogeneity between different studies. Moreover, the authors advocated that all animal research protocols should follow the quality checklist of Animal Research Reporting In Vivo Experiment (ARRIVE) guidelines to increase uniformity and to enable comparison and the reproducibility of the studies.

Describing the CSD by referring only to the size of the surgical site has been appraised by Cooper et al,[3] as such description undermined other factors such as the age of the animal, blood supply during the healing process, and the topography of the defect, which have a direct impact on bone healing. Multiple studies confirmed that the healing requirements of the vertical defects are different than those of the horizontal defects,[5] and 3D defects with loss of continuity are higher than monocortical defects created by trephine burs.[6,7] Moreover, preserving the

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periosteum influences the healing process in different defect sizes,[8] which indicates that healing of CSDs of the same sizes could be manipulated also by the manner in which the defect is created.

Misinterpretation of results that may happen due to the abovementioned variability in reporting CSDs, and the recent advances in standardizing and evaluating bone defects highlighted a need for evaluation of the reporting quality of CSD experimental studies. Although Delgado-Ruiz et al[4] have explored the most common practice among high-quality studies in rabbit calvariae, there is still a need to find out the consensus among studies that have reported CSDs in both weight-bearing bone and weight nonbearing bone in a bigger animal model to cover various clinical conditions.

Rabbits differ in their bone microarchitecture and biomechanics, skeletal anatomy, and healing of critical-sized defects when compared with large animal models. Large animal models have well-developed haversian and

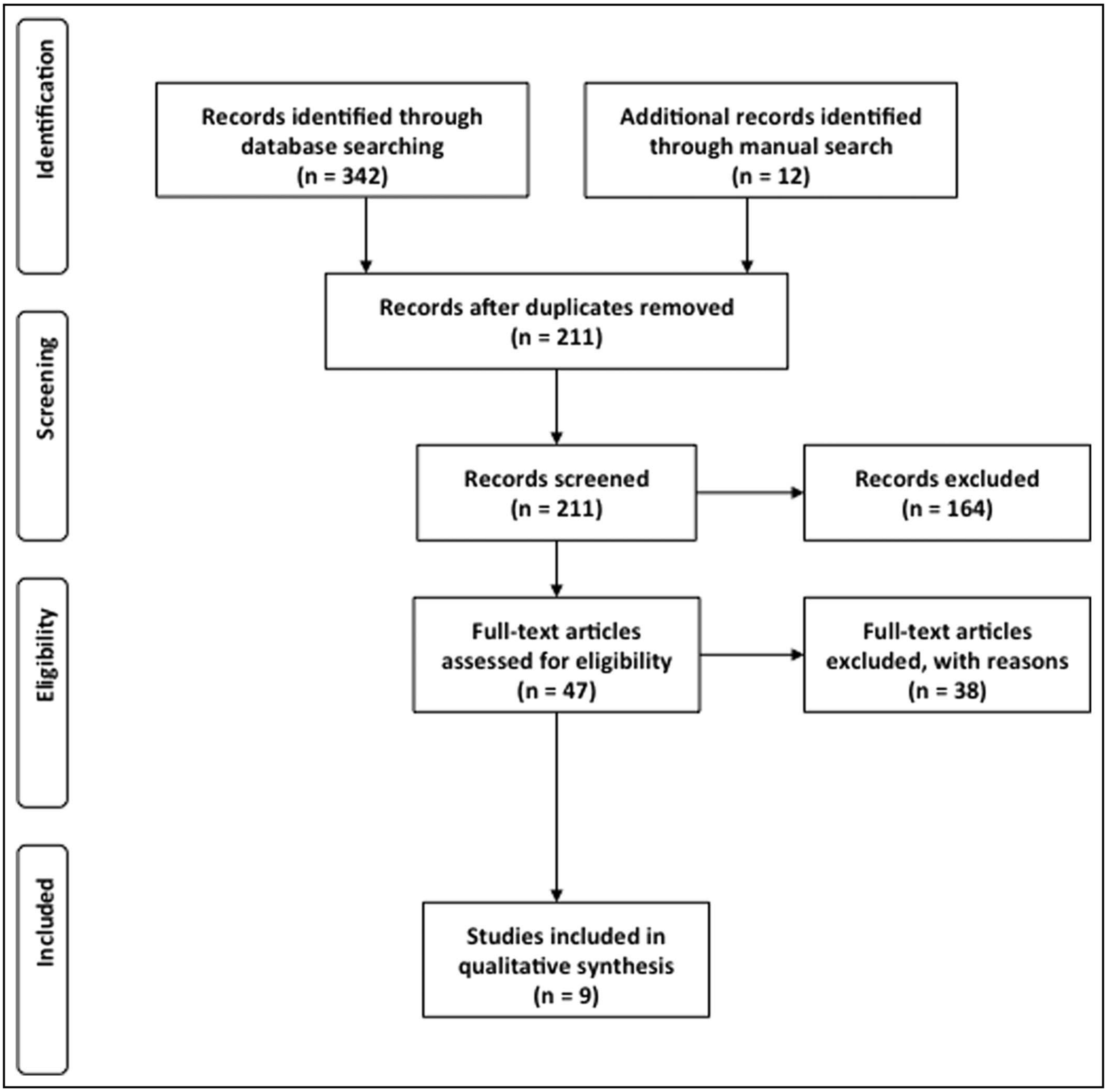

Fig. 1. Flowchart for the search process. Three hundred fifty-four articles were identified, of which, there were 143 duplicate articles resulting in 211 articles ready for screening. One hundred sixty-four articles involved defects in other anatomical sites and other animal models. Full text of 47 articles was subjected to in-depth reading and evaluation. Nine studies fulfilled the inclusion criteria.

trabecular bone remodeling; large skeletal surface areas; and volumes that allow testing of prosthetic devices and similar skeletal disuse atrophy results to human.[9] Therefore, the aim of this study was to perform a critical, systematic literature review of studies involving CSDs in the dog mandible and calvarium and to assess the quality of the selected studies using the ARRIVE guidelines to provide a consensus that can improve the homogeneity and comparison of future studies.

MATERIALS AND METHODS

The present study is a systematic review that has followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in addressing one focused question: What are the common characteristics of CSDs among studies that were conducted on a dog experimental model?

Internet search that is followed by a manual search of the literature by all the authors was performed on June 2016. The search included 5 databases: PubMed, Google Scholar, Web of Science, Ebsco Dentistry, and Scopus. Search terms involved specific keywords, which are (dogs OR canine) AND ("critical size defect" OR "critical size defects" OR "critical defects" OR "bone defects" OR "non-healing defect").

One author (K.M.) independently screened the titles and abstracts of all the identified studies to exclude duplications. Two authors (H.F.M. and K.A.) assessed the titles, abstracts, and full articles identified by the Internet and manual searches. Disagreements were resolved by discussion between the authors, if not, the third author (K.M.) determined the inclusion or exclusion of a relevant article.

The inclusion criteria were as follows: (1) original experimental studies; (2) use of dog model; (3) defects created in the mandible and/or calvariae; (4) inclusion of a negative control group; (5) There was a confirmation either by histomorphometric or radiographic data that the negative control defects did not heal along the entire period of the study; and (6) articles in English language only.

Table 1. List of the 38 Excluded Studies and the Reasons for Exclusion

#	Study	Reason for Exclusion
1	Caplanis N. et al (1997)	Supra-alveolar defects around dental implants
2	Cochran D. et al (1997)	Circumferential defects around dental implants
3	Giannobile W. et al (1998)	Supra-alveolar defects and no size are given
4	Wikesjo E. et al (1998)	Supra-alveolar defects
5	Tatakis D. et al (2000)	Supra-alveolar defects
6	Nagao H. et al (2002)	No negative control
7	Wikesjo U et al (2002)	Supra-alveolar defects
8	Artzi Z. et al (2003)	No negative control
9	Wikesjo E. et al (2003)a	Supra-alveolar defects
10	Wikesjo E. et al (2003)b	Supra-alveolar defects
11	Wikesjo E. et al (2003)c	Supra-alveolar defects
12	Wikesjo E. et al (2003)d	Supra-alveolar defects around dental implants
13	Wikesjo E. et al (2003)e	Supra-alveolar defects and no negative control
14	Polimeni G. et al (2005)	Supra-alveolar defects
15	Tal H. et al (2005)	Complete bone healing in negative control
16	Cui L. et al (2007)	No negative control
17	Yuan J. et al (2007)	No negative control
18	Lai H. et al (2009)	Circumferential defects around implants
19	Weng D. et al (2009)	Circumferential defects around implants
20	Choi S. et al (2010)	No negative control
21	He D. et al (2010)	No negative control group
22	Kwon H. et al (2010)	Supra alveolar defects and no negative control
23	Lee J. et al (2010)	Supra alveolar defects and no negative control
24	Valderrama P. et al (2010)	Circumferential defects around implants
25	Yan X. et al (2010)	Supra-alveolar defects
26	Yuan J. et al (2010)	No negative control
27	Fernandes J. et al (2011)	Supra alveolar defects and no negative control
28	Kawai T. et al (2011)	No negative control
29	Kim S. et al (2011)	Circumferential defects around dental implants
30	Wang L. et al (2011)	Circumferential defects around dental implants
31	Koli K. et al (2012)	Supra-alveolar defects
32	Machtei E. et al (2013)	Complete bone healing in negative control
33	Messora M. et al (2012)	Titanium mesh was placed on the control site
34	Liu X. et al (2014)	No negative control
35	Messora M. et al (2014)	Titanium mesh was placed on the control site
36	Zandi M. et al (2014)	No negative control
37	Jung U. et al (2015)	Circumferential defects around dental implants
38	Tsumanuma Y. et al (2016)	Supra-alveolar defects

The main reasons for exclusion were lack negative control group, complete healing of the negative control, supra-alveolar defects, and circumferential defects around the dental implant.

The exclusion criteria were as follows: (1) animal models other than dog; (2) anatomical locations other than mandible and calvariae; (3) literature reviews; (4) circumferential defects and/or supra-alveolar defects around dental implants.

All the included articles were subjected to extraction of sex, weight, sex of the animals; number, location, geometry, size of the defects; type of osteotomy, time to sacrifice, and the techniques used to evaluate bone healing. Authors HM and KM identified the study design and evaluated the quality of the included studies using the ARRIVE guidelines. The authors followed the procedure described by Kilkenny and Altman[10] and Kilkenny et al.[11]

To describe the quality of each item in the checklist, the quality score/maximum score was calculated and compared with 3 possible quality coefficients: Excellent quality if the score is >80%; average quality if the score is between 50% and 80%; and poor quality if the score is <50%.

Statistical Analysis

Descriptive statistics (mean and SD) were calculated. Kappa statistics

Table 2. List of Included Studies and the Extracted Data

Author/year	Type of Study	Animal Sex	No. of Animals	Age, mo	Weight, kg	No. of Defects per Animal/Geometry
Hunt D. et al (2001)	Pilot study; nonrandomized controlled	Male	3	18–36	25	4/Saddle-type defects
Imbronito A. et al (2002)	Pilot study; nonrandomized controlled	N/P	4	Adult	12	4/Rectangular
Huh J. et al (2005)	Nonrandomized controlled	Female	16	N/P	15–20	2/Segmental defects and continuity defects
Elsalanty M. et al (2009)	Nonrandomized controlled	Male	13	N/P	37	1/Segmental defects and continuity defects
Neamat A. et al (2009)	Nonrandomized controlled	Male	8	18–24	12–15	2/Geometry is not provided
Baba S. et al (2011)	Nonrandomized controlled	Male	7	20–22	N/P	2/2-wall rectangular defects
Birang R. et al (2012)	Randomized controlled	Male	3	N/P	25	8/bilateral/circular (cylinder)
Miura K. et al (2012)	Nonrandomized controlled	Male	9	17	N/P	One/an arc-shaped defect
Park C. et al (2012)	Randomized controlled study	Male	10	15	9–13	2/rectangular 1-wall defects—box shape

Author/year	Total Number of Negative Control Defects/Study	Defect Size Expressed, mm	Method Used to Perform the Osteotomy	Time to Sacrifice in Weeks	Percentage of Healing (Defect Closure as a Percentage of the Defect Area)	Measured Variables (Defect Closure/Bone Regeneration Obtained From Histomorphometric or Radiographic Data)
Hunt D. et al (2001)	2	10 × 15	Reciprocating mini-saw	12	65%	Histomorphometry and radiology
Imbronito A. et al (2002)	1	8 × 12	Low-speed rotatory and chisels	8 & 16	N/P	Histomorphometry
Huh J. et al (2005)	32	5–20, 30–60	N/P	24	N/P	Histomorphometry and radiology
Elsalanty M. et al (2009)	8	33 ± 8.4	Reciprocating minisaw	10	N/P	Histomorphometry and radiology
Neamat A. et al (2009)	8	5	Carbide surgical bur	12, 24	N/P	Histology
Baba S. et al (2011)	7	3 × 3 × 5	Dental round bur	4, 8	N/P	Histomorphometry
Birang R. et al (2012)	6	6 × 6	Trephine	6	N/P	Histomorphometry
Miura K. et al (2012)	3	10	N/P	24	N/P	Histomorphometry and radiology
Park C. et al (2012)	5	4 × 5	N/P	24	N/P	Histomorphometry

Manuscripts that fulfilled the inclusion criteria: type of study, number of animals per study, total number of defects/study, total number of negative control defects/study, type of osteotomy describes the instrument used for creating the CSD, time of sacrifice was expressed in weeks, and percentage of healing, expressed as the healing of the control/whole defect.
N/P, data not provided in results.

Table 3. Quality Scores of the Included Studies Based on the ARRIVE Guidelines

	Items According to the ARRIVE Checklist																				
References	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Total/study
Hunt D. et al (2001)	1	2	1	1	1	1	1	2	0	0	0	2	2	1	1	0	2	1	1	2	22
Imbronito A. et al (2002)	1	2	1	1	0	1	2	1	0	0	0	2	2	1	1	0	1	2	2	0	20
Huh J. et al (2005)	1	2	1	1	2	2	2	1	0	1	0	2	1	1	2	0	2	2	2	2	27
Elsalanty M. et al (2009)	1	2	2	1	2	2	1	1	0	1	1	2	2	1	2	1	2	2	2	2	30
Neamat A. et al (2009)	1	2	2	1	2	2	2	2	1	1	1	2	2	1	2	2	2	1	1	2	32
Baba S. et al (2011)	1	1	1	1	2	1	2	2	0	0	0	2	1	0	1	0	1	2	2	2	22
Birang R. et al (2012)	1	2	2	1	2	2	2	1	1	0	1	2	2	0	2	1	2	2	2	0	28
Miura K. et al (2012)	1	1	2	1	2	2	2	1	0	1	0	2	2	1	2	1	2	2	2	2	29
Park C. et al (2012)	1	2	2	1	2	2	2	2	1	1	1	2	2	1	2	2	2	2	2	2	34
Total/category	9	16	14	9	15	15	16	13	3	5	4	18	16	7	15	7	16	16	16	14	—
Maximum score/category	9	18	18	9	18	18	18	18	18	18	9	18	18	9	18	18	18	18	18	18	—

Items from 1 to 20 are title (1), abstract (2), introduction—background (3), introduction—objectives (4), methods—ethical statement (5), study design (6), experimental procedure (7), experimental animals (8), housing and husbandry (9), sample size (10), allocation of animals (11), experimental outcomes (12), statistics (13), results—baseline data (14), number analyzed (15), outcome and estimation (16), adverse events (17), discussion—interpretation/scientific implications (18), general applicability/relevance (19), and funding sources and role of the funders (20). Last number on the right side represents the total score of a maximum of 36 points, obtained by each study.

for the qualitative evaluation of the studies was calculated to reflect on the interreviewer agreement. Statistical analysis was performed using SPSS 22 statistical software (IBM Corporation, Armonk, NY).

Results

The Internet search in all the selected databases resulted in 342 titles, whereas 12 titles were found by the manual search. The first round of screening of all the titles resulted in exclusion of 143 titles because of duplications. The second round involved screening of the titles and abstracts of the 211 studies according to the inclusion and exclusion criteria. If any of the identified abstracts did not provide the full information, the full articles were retrieved to check eligibility for inclusion (Fig. 1). The second round of assessment resulted in exclusion of 164 studies because they were dealing mainly with defects in other anatomical sites and other animal models. The full text of the remaining 47 articles was retrieved for in-depth reading and evaluation. The third round of evaluation resulted in exclusion of 38 articles because they lack negative control group, complete healing of the negative control, supra-alveolar defects, and circumferential defects around dental implants (Table 1). Extraction of the required information and quality evaluation based on the ARRIVE guidelines were applied on the remaining 9 studies, which fit our inclusion criteria (Table 2).

The included 9 studies, with experimental sample of 73 dogs (53 males and 16 females and 4 not provided); showed defects in the mandible only. The variability in the shape of the defects among studies made statistical comparison impossible; therefore, descriptive statistics was performed to show the most common characteristics of mandibular CSDs. Only 2 articles showed randomized controlled studies, whereas the remaining 7 were non-randomized controlled studies. The earliest study was published in 2001, whereas the latest one was in 2012. Five studies have mentioned the age of the animals, which ranged from 15 to 36 months. Regarding the weight of the animals, it was reported in 7 articles and varied from 9 to 25 Kg.

The total number of defects was 156. They were continuity defects (n = 45) that were fixed by 2 miniplates or reconstruction plate, 1 wall defect (n = 44), and 2 wall defects (n = 14), whereas the type of 53 defects was not clearly provided. The geometry of the defects was either rectangular, box, cylindrical (circular), arch, or saddle shaped. For the rectangular defects, the sizes were 3 × 5 mm and 8 × 12 mm; for the box type defects, the sizes were 4 × 5 mm; for the saddle defects, they were 10 × 15 mm; for the arch shaped, they were 10 mm in radius, whereas for the cylindrical defects, they were 6 × 6 mm. All the cylindrical defects were created using trephine burs, whereas the segmental defects were formed using reciprocating mini-saw. For the other defects, dental burs and chisels were used.

The time of sacrifice of the animals ranged from 4 to 24 weeks. The most commonly used healing period was 24 weeks as it was followed in 4 studies. Regarding healing, all studies used histomorphometric analysis for evaluation of bone tissue. Only 1 study has provided the percentage of defect closure in relation to the overall defect volume, but all the studies have reflected on bone volume formation in the studied histological sections, the significant difference between the study and the control sites, and if complete healing was attained in the control defects.

The included studies involved 72 negative control defects. All the defects involved either less than 10% of bone within the healed tissue or did not show complete obliteration within the lifetime of the animal except for mandibular segmental defects that are less than 40 mm in length when the periosteum is preserved, and those that are less than 15 mm in length when the periosteum is excised.

Quality evaluation of the included articles showed a mean score of 27.1 ± 4.8 out of 36. Items that evaluated the housing- and welfare-related assessment interventions (ie, type of cage, bedding material, number of cage companions, light/dark cycle, temperature, and access to food and water) and sample size-total number, details of calculation methods were received in poor quality (score <50%). Items that evaluated experimental animal species, strain, sex, developmental stage, weight, source of animals, allocation of animals to experimental group randomization, baseline data characteristics and health status of animals, outcomes and estimation results for each analysis with a measure of precision have received average quality (score 50%–80%), whereas the remaining items of the checklist have received over 80% indicating excellent quality (Table 3).

DISCUSSION

The aim of this study was to explore the common characteristics of CSDs among studies that were conducted on dog experimental model to provide a consensus that can improve the homogeneity and comparison of future dog studies.

Our search resulted in a total of 211 studies after removal of duplicated titles. Out of them, only 9 articles were included. Such number of studies is considered as low number if compared with the study by Delgado-Ruiz et al[4] that investigated CSDs in rabbit calvarium and showed 350 articles with inclusion of 25 studies. Such difference could be due to the nature of the experimental model under investigation.

Rabbit as an experimental model has more advantages than dog. It is easier to handle and control, cheaper, has shorter bone sigma, and less difficulties with creating large, homogenous samples for statistical testing.[9] It is easier to control the confounding factors in studies investigating weight non–bearing bone (calvarium) than in weight-bearing bone studies. To evaluate CSDs in weight-bearing bone such as mandible, proper fixation and adequate stability of segmental defects are crucial for bone healing to keep the size of the defect as the only independent variable.

Furthermore, preserving or excising the periosteum could be another confounding factor. In one study, segmental defects of 30 and 40 mm in length showed gap obliteration, whereas gap persisted in defects greater than 50 mm over 24 weeks when the periosteum was preserved. In the same study, defects in which the periosteum was excised showed no healing for segmental defects longer than 15 mm in length.[8]

Our study has included only studies with a negative control group in their design. Although the purpose of some of these studies was not to test the CSD, the negative control group in these studies has still reflected on the healing of a defect that has specific shape and size. Our inclusion criteria were consistent with those in the study conducted by Delgado-Ruiz et al.[4]

The included studies had 53 male and 16 female dogs with age range from 15 to 36 months and their weights varied from 9 to 25 Kg. The reviewed literature showed that animal age, weight, and sex influenced bone mineral concentration (BMC) and bone mineral density (BMD), therefore affecting healing potential of any bony defect. In general, middle-aged dogs (3–10 years) revealed the highest BMC and BMD levels. Mean BMC and BMD were higher in males compared with females.[12] Moreover, in aging dogs, the skeletal exchange of calcium falls to a very low level with an increase in osteoclastic bone resorption and loss of skeletal mass.[13] On the other side, bone defects in skeletally immature dogs heal at a faster rate than skeletally mature individuals, which could result in misleadingly high potentials of a tested material if skeletally immature dogs have been used. Therefore, Hollinger and Kleinschmidt[2] recommended that biological age that is confirmed by radiographic investigation of epiphyseal closure be used in conjunction with chronological age and body weight to establish skeletal maturity, before CSD creation.

The current study investigated the results of 72 negative control defects of 156 mandibular defects that have different sizes, types, and geometries. Although there was a great heterogeneity among the included studies that made statistical comparison impossible, all the defects still fell in 2 groups, which are segmental and nonsegmental defects. In segmental defects, there was a lack of agreement between 2 studies in regard to defect size. One study considered 33 ± 8.4 mm as the size of CSD,[7] whereas the other considered 50 mm and more.[8] Such difference could be related to the time of animal sacrifice. In the first study, the animals were killed at 10 weeks, whereas the animals were left to 24 weeks in the second study. Hollinger and Kleinschmidt[2] mentioned that CSD could be as great as 45 mm. The positive correlation between percentage of healing and time of sacrifice was confirmed in a systematic review on CSD in a rabbit model.[4]

In nonsegmental defects, there were 5 different defect shapes, which are rectangular, box, arc, saddle, and cylindrical. Comparison between different sizes for statistically calculating the mean CSD is difficult because all the experimented animals were killed at different time point. These results were different from those of the study conducted by Delgado-Ruiz et al[4], which revealed that the most common CSD used in experimental procedures in calvarium rabbit is 15 mm in diameter. Reciprocating saw, round dental burs, and trephine burs created all the bony defects. It was found that round/fissure dental burs were the most commonly used method for square and rectangular defects, whereas circular trephines were the most commonly used method to create cylindrical defects.

Quality evaluation of the included studies revealed a mean score of 27.1 ± 4.8 and ranged from 20 to 34. Although the ARRIVE guidelines have been published in 2010, some of the earlier studies in our review have still shown high quality score. The most common data that were missed in all studies were relevant to housing- and welfare-related assessment interventions and sample size calculation. We advocate that more awareness in future about the ARRIVE guidelines could improve the quality of reporting animal studies.

The main limitation in our study was the low number of the included studies for final analysis. Inclusion of only 9 studies could be due to the strict inclusion and exclusion criteria that were followed in the study. Moreover, the study involved high level of agreement between authors, which ensured minimal subjectivity in the selection and quality evaluation process. Within the limitation of our study, we support the previous recommendations that were suggested by Coopper et al.[3] The authors advocated the discontinuing use of the term CSD because of the various confounding factors (age, weight, sex, blood supply, defect shape, periosteum, and time of killing the animals) that affect the healing process resulting in a model with a limited clinical applicability.

CONCLUSION

There is a lack of homogeneity in reporting data on CSDs in the dog mandible. Future animal studies should include a negative control group for an objective comparison and evaluation of any new biomedical materials. More awareness is needed for the Animal Research Reporting In Vivo Experiment (ARRIVE) guidelines to improve data reporting, which can facilitate comparison and reproducibility of future studies.

DISCLOSURE

This research did not receive any grants from any funding agencies. The authors claim to have no financial interest, either directly or indirectly, in the products or information listed in the article.

APPROVAL

The Institutional Review Board exempted the study from ethical approval.

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