Randomized Controlled Trials in Implant Dentistry: Assessment of the Last 20 Years of Contribution and Research Network Analysis

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The aim of this study was to evaluate the characteristics of randomized controlled trials (RCTs) regarding implant-supported single tooth or fixed partial dentures. We performed searches (PubMed/MEDLINE and Web of Science) to identify all RCTs published from 1996 to 2016 and assessed publication details, study characteristics, international collaboration networks, and characteristics related to the implant-supported treatment. Two reviewers independently screened the titles/abstracts and selected full texts. A total of 122 RCTs were included, and most of the authors were from Europe (72%). Most trials did not report a trial registering number (89.9%) or sample size calculation (58.2%). The use of the CONSORT Statement increased over the past 9 years. Trials were mostly conducted at universities (54.9%), and only 13.1% compared 2 or more implant brands. Loading protocol was the most prevalent main comparison among the included studies, and most of the RCTs did not clearly report whether they excluded patients with known risk factors. The studies reviewed here presented different methodological and publication characteristics, and many did not show aspects aligned with current research practices.

Key Words: clinical research, clinical trials, dental implants, trial registration, reporting guidelines

INTRODUCTION

During the past couple of decades, implant dentistry moved from being a new technique to a well-established treatment. For many patients, the best treatment option to rehabilitate an edentulous ridge uses dental implants,[1] while considering implant survival, success rates, and patient satisfaction.[2–6] Research efforts were intended to improve the primary stability of implants (eg, different implant geometries), reduce osseointegration time (eg, implant surface treatment), reduce the complexity of surgical procedures (eg, flapless surgeries, different bone graft procedures), and improve the implant-abutment connection, with the goal of reducing marginal bone loss around the implants and/or abutment or screw loosening.[7,8]

For implant dentistry literature, the vast majority of papers were in vitro studies or noncontrolled trials. Although these types of studies are important, they have a lower level of scientific evidence than do either studies with well-designed and well-reported randomized controlled trials (RCTs) or summaries of such studies in systematic reviews and meta-analyses.[9] Systematic reviews are important for showing what is already consolidated in the literature and pointing out some specific issues that need to be clarified and addressed in future research, especially methodological issues.

The objective of the present study was to evaluate the characteristics and international collaborations for RCTs of implant-supported single tooth or fixed partial dentures in the past 20 years by considering publication details and characteristics of the conducted trials.

MATERIALS AND METHODS

This report followed the 4-phase flow set forth in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[10]

Criteria for selecting studies

We included any RCTs published between 1996 and 2016 whose stated primary intent was to test any of the following implant-related characteristics for implant-supported single tooth or fixed partial dentures: implant-abutment connection (external hex, internal connection, platform switch concept, and/or Morse taper connections), implant geometry (cylindrical, tapered, or hybrid), implant surface (machined, acid etched, blasted), loading (immediate loading, early loading, conventional loading), or region of placement (anterior/posterior, maxilla/mandible). All of these specific factors were drawn from

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a recent systematic review that extracted all assessed outcomes for implant dentistry RCTs.[11] We considered an RCT "as a study in which the participants are assigned by chance to separate groups that compare different treatments."[9]

We excluded the following types of articles: nonrandomized trials, trials comparing non–implant-related characteristics (prosthetic and surgical aspects), and all trials testing implant-supported complete dentures.

Electronic searches

Searches were performed without language restriction in 2 databases (PubMed/MEDLINE and Web of Science) and were limited to the period between 1996 and December 2016. The search strategies were drafted based on MeSH terms of PubMed and a specific filter for RCTs and adapted for each database. The search and eligibility criteria were based on a previous study.[11]

Study selection procedure

Duplicates were removed from the records retrieved from databases using specific software (EndNote X7, Thomson Reuters, New York, NY). Two reviewers performed the study selection using the same software. The reviewers began by independently screening all titles and abstracts. These 2 reviewers independently retrieved each citation meeting our eligibility criteria or classified as unclear for a full-text analysis. Discrepancies in the screening of title/abstracts or full texts were resolved through a discussion between the 2 reviewers with help of a third reviewer, if necessary. For studies identified in multiple articles, we have included only the article with longer follow-up.

Data collection process

A standardized data extraction form was used to collect the following data:

- Publication details: authors, affiliation country of all authors and coauthors of the study, year, and journal of publication
- Characteristics of study: duration of follow-up, clinical setting, register of trial protocol, reported sample size calculation, use of the CONSORT Statement to report the study, main comparisons, number of patients/implants included, implant-abutment connection design, implant brand, and exclusion criteria of trial patients

First, all items were discussed by the 2 reviewers to ensure consistency in interpretation of data items. Subsequently, each reviewer extracted half of the included articles, and when in doubt, a reviewer gathered the opinion of the other reviewer.

Data synthesis

Tables and graphs were generated to summarize the included studies and findings. We considered the register of trial protocol, sample size description, and use of the CONSORT Statement as dichotomous "yes/no" data based on the reporting of study. Data regarding the register of protocol was collected since 2005, the year that the International Committee of Medical Journal Editors (ICMJE) began requiring trial registration as a condition for publication. Main comparisons, implant-abutment connection design, and implant brand were categorized by similarity, and the exclusion criteria for trial patients was categorized as "yes" or "unclear" if the study mentioned exclusion of patients with known parafunction, with alcohol or substance abuse, who were smokers (>10 cigarettes/d), with a presence of systemic diseases, with active periodontal disease, who were bisphosphonate users, and who underwent head and neck radiotherapy in the past 10 years or not. The authors' affiliations were categorized by country and continent. Each study that presented at least 2 countries of affiliation was considered in the international research network analysis. All relationships among countries for each study were recorded in a spreadsheet. Pajek software (http://vlado.fmf.uni-lj.si/pub/networks/pajek/) was used to identify the frequency of interactions among countries and to analyze and visualize the research network.[12]

Also, we considered the year of publication as dichotomous data (1996–2006 and 2007–2016) to compare the use of the CONSORT Statement during both periods, given that the first version of that statement was published in 1996. The software STATA version 14.0 (Stata Corporation, College Station, TX) was used for the analysis.

Results

Figure 1 summarizes the study selection. There were 6379 articles identified by the initial search. After screening of the title and abstracts and subsequent full-text assessment, 122 RCTs fulfilled the eligibility criteria.[11]

Publication details

Figures 2 and 3 feature publication details regarding the journal of publication and the location of the corresponding author, respectively. In total, 122 RCTs were published in 21 journals during the past 20 years. Most of the trials were published in the journal *Clinical Oral Implants Research* (n = 36) and the *European Journal of Oral Implantology* (n = 21). Most of the corresponding authors were from Italy (n = 39, 32%) and the United States (n = 13, 10.7%), and 72% of corresponding authors were from Europe, followed by Asia (13%) and the Americas (13%).

Research network analysis

A total of 686 authorships were recorded. The mean average of participation was 5.67 authors per study, ranging from 2 to 13. For all 686 authors, 35 countries were represented in the authors' or coauthors' affiliations. Italy had the highest number of author/coauthorship (178), and the mean average was 19.6 authors per country.

Figure 4 shows number of authors per country and the research network between countries. For each of the 35 countries presented in the figure, the sizes of the vertices (countries) are proportional to the number of authors from that country. The research network shown in the center of the figure indicates the number and relationships between the 9 countries that had 3 or more international collaborations.

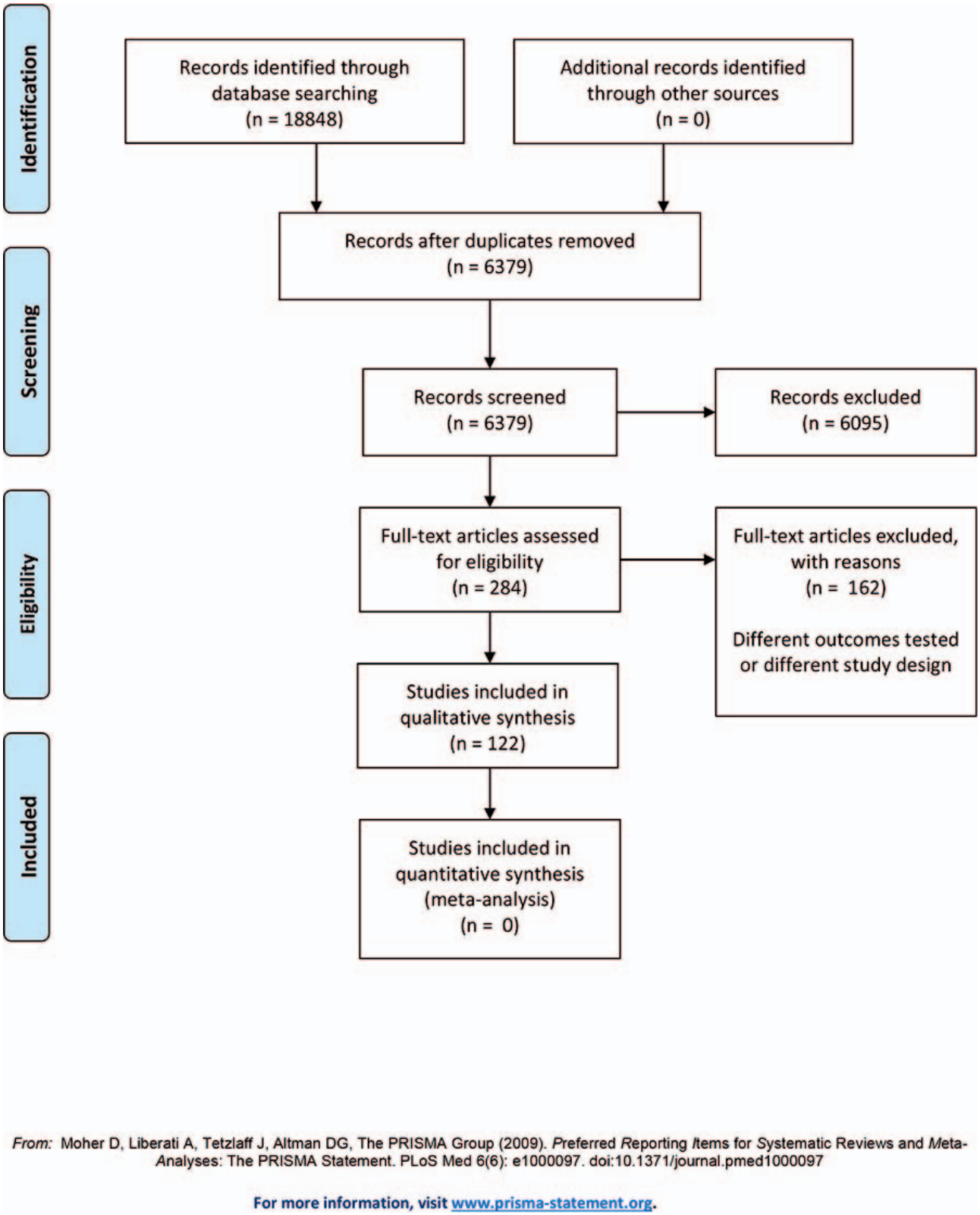

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.[10]

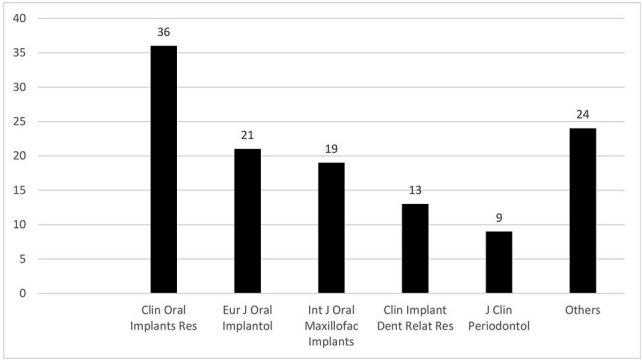

Figure 2. Randomized controlled trial distribution according to journals.

Characteristics of the study

The median number of patients included was 40 (ranging from 4 to 239), and the median number of implants tested was 69 (ranging from 12 to 1413). The mean time of follow-up was 2.2 years (ranging from 0.125 to 16).

Table 1 demonstrates that most of trials (89.9%, n = 98) did not report the register of trial protocol and the sample size calculation (58.2%, n = 71). During the first 11 years (1996–2006), no trial reported using the CONSORT Statement, but during 2007–2016, 105 trials were published, with 70 reporting using the CONSORT. Most of the trials were performed in a university setting (54.9%, n = 67), followed by private practice (18%, n = 22), and 21 trials (17.2%) were classified as unclear.

For all included trials, 44 different brands of implants were tested, and in 2 trials, the implant brand was considered unclear. Table 2 features the implanted-related characteristics of included studies. Nobel Biocare (18.9%, n = 23) and Straumann (14.7%, n = 18) were the most tested implant brands, while 16 trials (13.1%) compared 2 or more different brands. The implant-abutment connection design was classified as unclear in most of the studies (45.1%, n = 55), while the most tested connection was internal hex (16.4%, n = 20) and platform switch (12.3%, n = 15). For the trials published between 1996 and 2006 and between 2007 and 2016, different loading protocols were the most prevalent main comparison in both time periods. Also, no trials comparing different implant-abutment connections were published between 1996 and 2006, but between 2007 and 2016, 20 trials were published. In the first time period, only 3 trials tested the implant surface, while 14 tested implant surfaces in the second time period.

Table 3 presents the results about the exclusion criteria used in the identified RCTs. For most of the included trials, it was unclear whether the trial excluded patients with known parafunction, alcohol and substance abusers, smokers (>10 cigarettes/d), with presence of systemic diseases, bisphosphonate users, and patients who underwent head and neck radiotherapy in the past 10 years. However, for most of the trials, the exclusion criteria "patients with active periodontal disease" was the only one used (54.1%, n = 66).

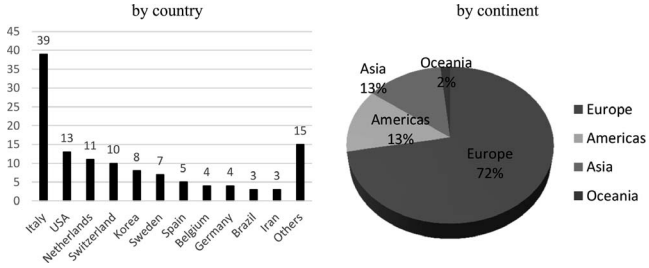

Figure 3 Randomized controlled trial distribution according to countries and continents.

Discussion

To the best of our knowledge, this is the first attempt to assess all RCTs regarding implant-supported single tooth or fixed partial dentures published in the past 20 years. A better understanding of these trials is important as RCTs are considered one of the highest levels of evidence and a key component for making evidence-based decisions in a dental context.

Since 2005, the ICMJE has required prospective trial registration as a condition for publication to help improve the scientific and ethical value of published articles.[13] Also, prospective trial registration is important for assessing possible problems of publication bias and selective reporting bias. The number of trials that were registered at public databases every year since has increased. However, the number of registered trials can vary among different research areas,[14] and dentistry presents a relatively low number of registered trials.[15] Our study demonstrated that most assessed trials did not report the trial register number, which could be considered a source of bias. Although one might suggest that industry-sponsored trials are less likely to be registered,[16,17] a recent systematic review that assessed the influence of industry sponsorship bias in clinical trials in implant dentistry concluded that sponsored trials tended to show a higher quality compared with

Table 1

Trial registration, CONSORT, sample size calculation

Trial registration	n	%
No	98	89.9
Yes	11	10.1
Sample size calculation		
No	71	58.2
Yes	51	41.8
Setting		
University	67	54.92
Private practice	22	18.03
Unclear	21	17.21
Mixed	7	5.74
Clinical centers	4	3.28
Hospital	1	0.82
Reported use of CONSORT		
1996–2006		
No	17	13.9
Yes	0	0
2007–2016		
No	70	57.4
Yes	35	28.7

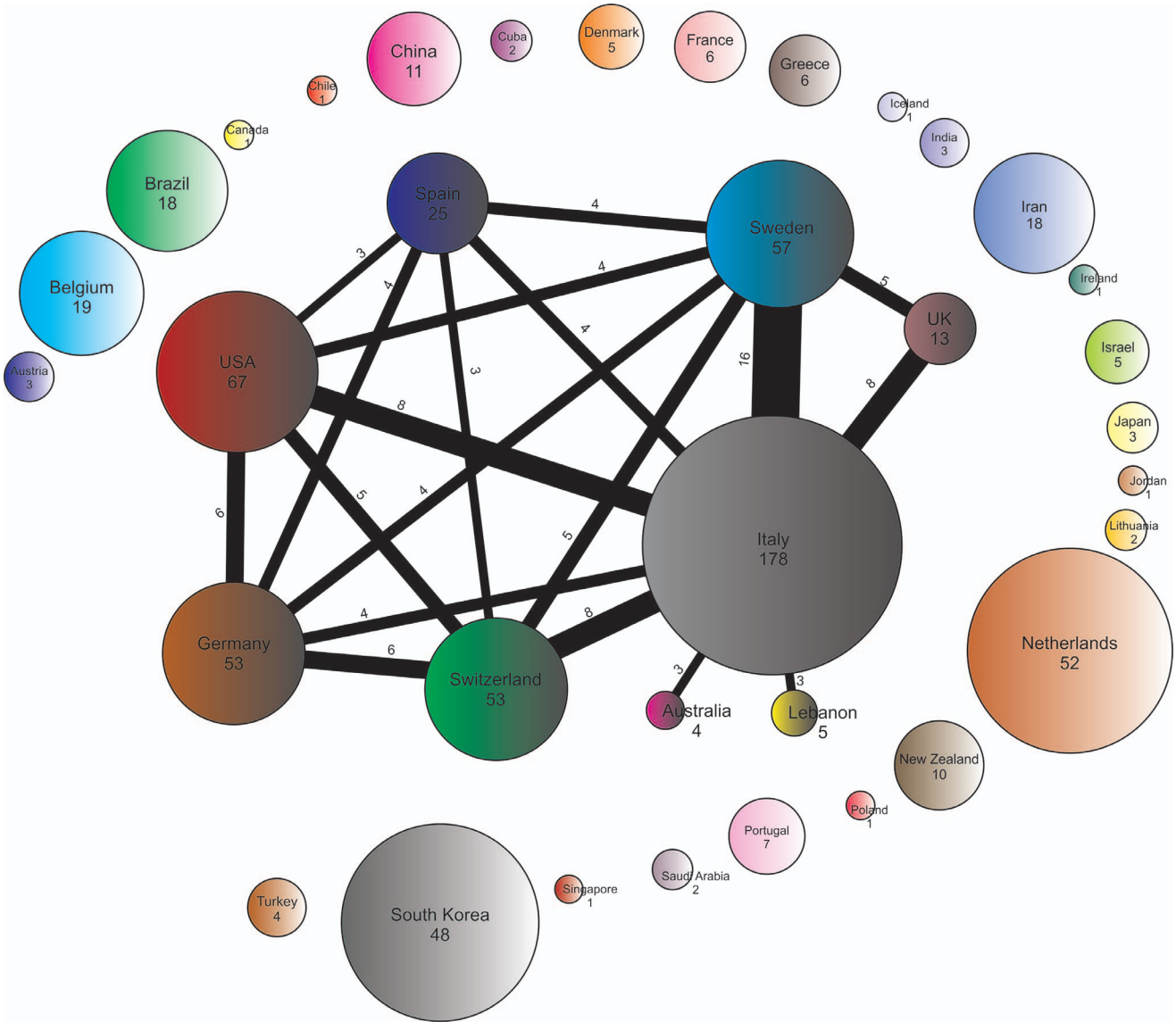

Figure 4. Authors' country of affiliation social network. Only countries with 3 or more collaborations are presented in the network (connected with lines). The sizes of the vertices (countries) are proportional to the number of authors accounted for each country (number below the countries' names). The number that appears in the lines corresponds to the number of international collaborations between different countries.

nonsponsored ones. Also, initiatives supporting trial registration, such as the EQUATOR Network, have not gained traction among oral health researchers.[18]

The present study shows an encouraging increase in the use of the CONSORT Statement in the past 9 years, with almost 70% of published trials reporting according to CONSORT. The CONSORT Statement is the reporting guideline endorsed by most dental journals, including the 2 journals with the highest number of published trials in implant dentistry (*Clinical Oral Implants Research* and the *European Journal of Oral Implantology*). For 2016 metrics presented in the Journal Citation Reports, the impact factor (IF) of the *European Journal of Oral Implantology* is high (3.567) among dental journals, but the number of total citations (TC; 812) is lower than other important journals in the area (*Clin Oral Implants Res*: IF: 3.624, TC: 12 295; *J Clin Periodontol*: IF: 3.477, TC: 12 144; *Clin Implants Dent Relat Res*: IF: 2.939, TC: 3412; *Int J Oral Maxillofac Implants*: IF: 2.263, TC: 8314).

Furthermore, although there are a large number of commercially available dental implants and brands, most of the studies used the leading brands in the market (Nobel Biocare and Straumann).

About 1300 different designs of dental implants are available with variations in shape, thread design, material, surface, and implant-abutment connection.[1] However, only a few of these implant designs are supported by high-level scientific research.[19] The present study supports this conclusion, because only a small percentage of the trials compared design characteristics (implant design: 5.5%; neck design: 6.5%).

Between 1996 and 2006, no published trials compared

Table 2

Implant-related characteristics

Implant Brand	n	%
Others	28	22.95
Nobel Biocare	23	18.85
Straumann	18	14.75
2 or more	16	13.11
Biomet 3i	12	9.84
Dentsply	9	7.38
Thommen Medical	4	3.28
Institut Straumann	3	2.46
JDEvolution	3	2.46
MegaGen Implant	3	2.46
Southern Implants	3	2.46
Implant connection design		
Unclear	55	45.08
Internal hex	20	16.39
Platform switch	15	12.30
External hex	14	11.48
Morse taper	13	10.66
Morse taper vs external hex	3	2.46
1-piece prep implant	1	0.82
Internal hex vs external hex	1	0.82

	1996–2006		2007–2016	
Main Comparison	n	%	n	%
Loading protocol	5	4.1	30	24.6
Implant connection	0	0.0	20	16.4
Implant surface	3	2.5	14	11.5
Implant systems	2	1.6	9	7.4
Neck design	2	1.6	6	4.9
Implant design	3	2.5	4	3.3
Submerged vs nonsubmerged implants	0	0.0	6	4.9
Implant length	0	0.0	5	4.1
Implant placement depth	1	0.8	3	2.5
Others	1	0.8	8	6.4

Table 3

Distribution of exclusion criteria in the included studies

Exclusion of patient risk factors	n	%
Parafunction		
Unclear	70	57.4
Yes	52	42.6
Alcohol/drugs		
Unclear	76	62.3
Yes	46	37.7
Smoking (>10 cigarretes/d)		
Unclear	69	56.6
Yes	53	43.4
Systematic diseases		
Unclear	76	62.3
Yes	46	37.7
Active periodontal disease		
Unclear	56	45.9
Yes	66	54.1
Bisphosphanate		
Unclear	85	69.7
Yes	37	30.3
Head and neck radiotherapy		
Unclear	76	62.3
Yes	46	37.7

different implant-abutment connections. Although different connections were designed during this time, the topic was not considered relevant until about 10 years ago, and since then, 20 trials have been published to verify whether an implant-abutment connection design/concept could reduce marginal bone loss, microleakage, reduce the chance for screw loosening or micromotion of the abutments, and improve esthetics.[20]

Loading the protocol and implant surface together represented 42.7% of the main outcomes assessed in the included studies. Both outcomes have been heavily studied, mainly in the past decade, to improve the predictability of the results with immediate loading and reduction of the healing period in delayed implants. Scientific evidence currently shows that an immediate loading and reduced healing period could be considered a safe treatment modality when prescribing dental implants.[21] However, 2 Cochrane reviews[1,21] pointed out 3 important aspects: (1) in general, the failure rate of implant interventions is low; (2) most RCTs present high/unclear risk of bias, demonstrating an important limitation of the evidence; and (3) more high-level RCTs are required, especially for assessing patient satisfaction and decreased treatment time.

Given that 54.9% of the included RCTs were based in universities, the external validity of the study may be limited by the setting since the experiments were conducted in selected populations and in a highly controlled setting, and consequently, the results cannot be considered real-world evidence.[22] Also, the large number of adopted exclusion criteria in the included RCTs might influence the external validity of such studies, since only patients with good health and absence of well-known risk factors were included. However, it is important to point out that in some situations, it is difficult to classify the design of clinical studies, as explanatory or pragmatic, in implant dentistry because they did not report clearly whether or not they included these risky patients.

When the research network of international collaborations was assessed, 6 countries (Germany, Italy, Spain, Sweden, Switzerland, and the United States) presented with more than 30 international collaborations each. Although some countries were not included in the network report (the ones with fewer than 3 international collaborations), the number of RCTs in implant dentistry from South Korea and the Netherlands was noteworthy, with 48 and 52 author/coauthorship affiliations, respectively. Previous studies have suggested that international collaborations are associated with higher academic output,[23] enhancing publication productivity and research quality.[24] As such, international collaborations should be encouraged. Also, trials conducted in a practice-based network should be made to improve the external validity of implant research and shed more light in this area.[25]

Future recommendations

Based on the results of this study, the following recommendations for future studies are warranted:

- Implant dentistry journals should require the prospective register of a trial as a condition for publication.
- Authors should be trained to use the CONSORT Statement.
- An active implementation of the CONSORT Statement by implant dentistry journals should be encouraged.

- Trials assessing the effectiveness of implant interventions in practice networks are strongly recommended./
- Eligible patients presenting some known risk factors should be included in future trials, and the inclusion/exclusion criteria should be reported more clearly.

Conclusions

A large number of RCTs was published in implant dentistry over the past 20 years regarding implant-supported single tooth or fixed partial dentures. In general, the studies had different methodologies and publication characteristics. Also, most trials did not align with good research practices, which negatively affected the quality of studies.

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Note

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