Review

Dental Implant Failure Rate and Marginal Bone Loss in Transplanted Patients: A Systematic Review and Meta-Analysis

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Abstract: This systematic review investigates the failure rate and marginal bone loss (MBL) of dental implants placed in Solid-organ transplant (SOT) patients compared to healthy controls. Three databases (PubMed, Web of Sciences and the Cochrane Library) were searched up to June 2020 (PROSPERO CRD42019124896). Case-control and cohort studies reporting data failure rate and marginal bone loss (MBL) of dental implants placed in SOT patients were included. The risk of bias of observational studies was assessed through the Newcastle-Ottawa Scale (NOS). Four case-control studies fulfilled the inclusion criteria, all of low risk of bias. Meta-analyses revealed consistently lower implant failure rate than control populations at patient and implant levels. SOT patients had a significant difference of -18% (p-value <0.001) of MBL towards healthy patients. SOT status poses no serious threat to implant survival. Overall, this group of patients presented lower levels of dental implant failure rate and marginal bone loss compared to otherwise healthy patients. Further intervention trials with wider sample size and longer follow-ups are necessary to confirm these summary results.

Keywords: transplantation; dental implant; marginal bone loss; implant failure rate; systematic review; periodontitis; periodontal diseases; oral health

1. Introduction

Dental implants are predictable in restoring missing teeth, in both partially and fully edentulous patients [1–3]. Further, implants have consistent long-term success, with high survival rates and evidencing significant improvements in the patient's function, aesthetics and quality of life [4,5].

It is, however, unclear what is the impact of systemic diseases on the outcome of implant therapy and whether medically compromised patients may have different success and survival rates [6,7]. Systemic diseases and medications may directly affect oral tissues, either by increasing the susceptibility to infections or by interfering with wound healing or bone metabolism, which may directly influence implant osseointegration and result in early or late implant failures [8,9].

The replacement of a damaged organ by a healthy organ has been one of the most extraordinary medical achievements ever achieved [10,11]. According to the Global Observatory on Donation and Transplant (GODT), the number of solid organ transplants (SOT) increased 7.5% in 2016 [12]. According to GODT, in 2017 more than 139 thousand organ transplants were performed, corresponding to 16 organ transplants per hour. To prevent organ rejection, these patients undergo a chronic regimen of immunosuppressants, which puts them at higher risk of infections and

inflammation [13–16]. In patients taking these medications, there is evidence that wound healing and bone metabolism may be impaired, due to either inhibition of osteoblast function and osteogenesis or to a concomitant increase of bone resorption and osteoporosis, which may result in decreased bone-to-implant contact [17–20]. In addition, these patients also often take concomitant systemic steroid medication, which can also cause wound healing alteration and opportunistic colonisation by oral pathogens [10,21].

The overall medical improvements have contributed to high standards of quality of life in SOT patients, and hence, it is very common that these patients seek for implant therapy once recovered from the surgical procedure [10,11].

The evidence on the outcome of implant therapy in SOT patients is scarce [4], mostly reported in cases of liver transplant patients [8,22]. There are some prospective controlled studies evaluating dental implants in these patients [23], or in liver transplant patients [24], or in a combined sample of heart and liver transplant patients or in renal transplant patients [25]. These publications have reported successful outcomes of implant therapy in SOT individuals; however, the existing evidence on the long-term outcome of implant therapy, in large samples of these populations, is scarce.

Therefore, the aim of this review was to evaluate the failure rate and marginal bone loss (MBL) of dental implants placed in SOT patients compared to healthy controls.

2. Materials and Methods

2.1. Protocol and registration

This review was submitted to the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Review database (ID number: CRD42019124896). We planned this review under the PRISMA statement (Supplemental File S1) [26].

2.2. Focused question and eligibility criteria

We set the following research question: "In adults, do dental implants placed in solid-organ transplanted individuals have comparable survival rates to systemically healthy individuals?" with the following PICO:

- P (Population): Solid-organ transplanted adult humans (≥ 18 years old).
- I (Intervention): Dental implant placement.
- C (Comparator): Adult healthy controls.
- O (Outcome): Implant failure rate and marginal bone loss.

To address this PICO question, the following inclusion criteria were applied:

- Randomised clinical trials (RCTs) and non-RCTs (retrospective and prospective case-control and cohort studies);
- Studies reporting implant survival, or otherwise failure, in transplanted patients, with or without non-transplanted patients as reference;
- Studies reporting marginal bone loss data;
- Defined SOT patients;
- Studies reporting follow-up period of placed dental implants;
- Studies with follow-ups of, at least, 6 months after placement of the dental implant.

As exclusion criteria, we defined: studies with patients with necessary bone graft and/or guided bone regeneration procedure, and patients undergoing radiation treatment of the head and neck.

There were no restrictions concerning race, origin, year of publication or language. Only published, peer-reviewed journal articles were considered eligible.

2.3. Search strategy

We conducted a computerised literature search using the electronic databases of PubMed, Web of Sciences and the Cochrane Library from the earliest data available until June 2020. We merged keywords and subject headings in accordance with the thesaurus of each database and applied exploded subject headings. The following syntax was made to conduct a search in PubMed: ("dental implants") AND ("survival rate" OR survival OR "marginal bone loss" OR "marginal loss" OR "bone loss") AND (transplantation OR "organ transplantation" OR "transplantation, organ" OR "tissue transplantation" OR "transplantation, tissue" OR "heart transplantation" OR "kidney transplantation" OR "liver transplantation" OR "lung transplantation" OR "pancreas transplantation"). Additional relevant literature was included after a manual search across the selected articles reference lists.

There were no restrictions other than the search terms.

2.4. Study process

Two independent investigators (M.P. and P.M.) examined the title and abstract of available studies for the first inclusion phase. We resolved disagreement through a third reviewer. The final selection of the studies was carried out independently by the authors, who reviewed the full text of the selected papers according to the inclusion criteria mentioned above.

A predefined table was created to extract essential data from each eligible article, including the first author's name, study design, publication year, inclusion/exclusion criteria, number of participants and rationale for failure. Clinical implant measures included implant failure rate and marginal bone loss. All data were extracted independently by two reviewers. The authors were contacted when necessary for additional data clarification.

2.5. Risk of bias (RoB) in individual studies

Methodological quality was independently performed by two calibrated authors (V.M. and J.B.) using Newcastle-Ottawa Scale (NOS) for cohort studies. Regarding this tool, we scored across three categories: studies with 7-9 stars as of low RoB, studies with 5-6 stars as of moderate RoB, whilst studies with fewer than 5 stars were deemed of high RoB. Any doubt was resolved by discussion with a third author.

2.6. Statistical analysis

All statistical analyses were performed in R version 3.4.1 (R Studio Team 2018). Incidence rate ratios (IRR) and mean ratios (MR) calculations, including confidence intervals and plots, were calculated through the metafor R package with control data as reference (denominator). Meta-analysis procedures followed Random-effects Restricted Maximum Likelihood models with log transformed data. Overall results were displayed in exponentially back transformed data forest plots. Due to the reduced number of studies selected for the quantitative synthesis, sensitivity and publication bias analysis was skipped. Heterogeneity was evaluated by means of the I2 index. Assumption of statistical significance was set at $p<0.05$.

3. Results

3.1. Characteristics of included studies

The search strategy identified a total of 970 possibly relevant articles. After duplicates removal, 947 papers were judged against the eligibility criteria and 867 were excluded. Out of eight papers, four were further excluded with reasons (Appendix S2), and a total of four case-control studies was included for quantitative and qualitative synthesis (Figure 1) (Table 1). Inter-examiner reliability was considered as excellent (kappa score=0.9754, 95% CI: 0.9656-0.9852).
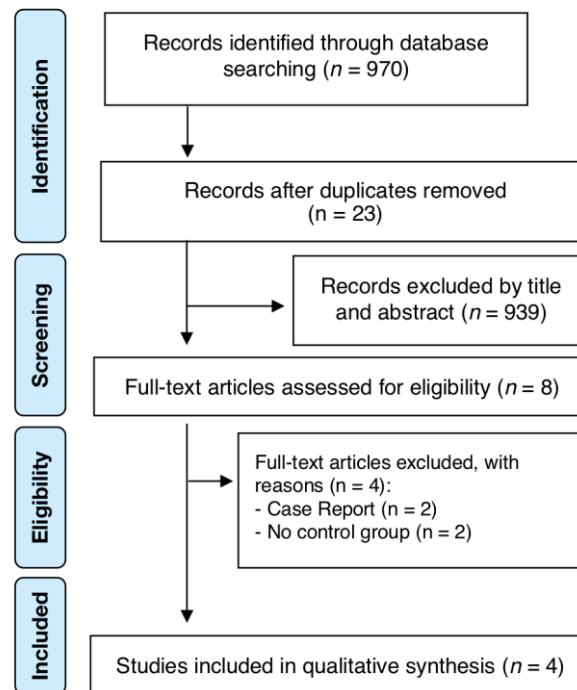
Figure 1. PRISMA flow chart.

3.2. Risk of bias (RoB) in individual studies

All cohort studies presented low RoB (two with 9/9, and four with 7/9 scores) (Table 2). The main reason for bias arose from the representativeness of the cases (33.3%, n=2) and controls (50.0%, n=3). In the ascertainment of exposure, this involved demonstration that outcome of interest was not present at start of study, comparability of cohorts on the basis of the design or analysis, usability of the same method of ascertainment for cases and controls, and adequate follow-up.

Table 2. Newcastle-Ottawa Scale assessment.

Study (Year) (Country)	1	2	3	4	5	6	7	8	Score (RoB)
Hernández et al. (2019) (Spain) [24]	a	a	a	a	a/b	b	a	a	9 (Low)
Radzewski and Osmola (2019) (Poland) [27]	d	c	a	a	a/b	b	a	a	7 (Low)
Paredes et al. (2018) (Spain) [23]	a	a	a	a	a/b	b	a	a	9 (Low)
Montebugnoli et al. (2015) (Italy) [28]	c	c	a	a	a/b	b	a	a	7 (Low)

3.3. Synthesis of results

3.3.1. Implant failure rate

To investigate the likelihood of failure rate, four studies were selected to synthesise estimates for implants (Figure 2) and patients prospects (Figure 3). Implant failure was perceived as a very rare event in both SOT and healthy populations. For the implant view, SOT patients presented, on average, consistently lower implant failure rate than control populations (Incidence Rate Ratio 0.52, 95% Confidence Interval (CI): 0.09-2.99). The level of heterogeneity was considered to be residual (I2 = 0%) (Figure 2).

In terms of patient analysis, SOT populations presented half of the overall implant failure rate of healthy controls (Incidence Rate Ratio 0.50, 95% Confidence Interval (CI): 0.09-2.86), with high consistency (I2 = 0%) (Figure 3).

1   Table 2. Studies Characteristics

Study	Effect size	SOT Sample	Control	Exclusion criteria	Clinical environment	Immunotherapy	Implant characteristics	Implant follow-up	Outcome	Funding sources
Hernández et al. (2019) (Spain) [24]	Implant failure incidence rate and MBL	25 partially edentulous Renal TP who received 79 dental implants	28 matched controls who received 86 dental implants	Suffering from untreated periodontitis, being smokers, or having a medical history of radiotherapy, severe or uncontrolled metabolic diseases or lack of compliance.	Private practice	Prednisone, Tacrolimus + Mycophenolate Mofetil (15 patients) Prednisone,Cyclosporine A + Mycophenolate Mofetil (9 patients) Prednisone, Cyclosporine A + Azathioprine (2 patients) Prednisone + Tacrolimus or Prednisone plus Cyclosporine A (2 patients)	Ti Unite, Nobel Biocare 3.75 / 4.00 or 5.00mm diameter and 8 / 8.5 / 10 / 11.5 / 13 or 15mm length	Mean follow-up of 9.7 years	Implant survival rate was over 98% in both test and control groups. Slightly increased marginal bone loss in the control group.	Dentaid S. L. provided partial support
Radzewski and Osmola (2019) (Poland) [27]	Implant failure incidence rate and MBL	21 organ transplant immunosuppressed patients (Kidney, Pancreas and Liver) who received 24 dental implants	15 matched controls who received 15 dental implants	Patient with active periodontal disease, substantial occlusion disorders, bone diseases, blood coagulation disorders, untreated dyslipidemia, or was a smoker.	University based	Tacrolimus (majority) or Cyclosporine, Sirolimus, or Mycophenolate Mofetill, Sirolimus (12 patients)	Naturactis; ETK, Sallanches, France	2 years	Implant stability and bone loss were not any different from those in healthy people	NA
Paredes et al. (2018) (Spain) [23]	Implant failure incidence rate	14 pharmacologically immunosu	16 matched controls who	Suffering from active periodontitis, being smokers, or having a medical history of	Private practice	Prednisone + Cyclosporin A + Azathioprine (2 patients)	Ti Unite ®; Nobel Biocare S.A.,	Mean follow-up of +8 years	100% implant survival in liver	Dentaid S. L. provide

Study	MBL	Test group	Control	Exclusion criteria	Setting	Medication	Implant/Location	Follow-up	Outcome	Funding
	and MBL	ppressed Liver TP with 48 dental implants	received 53 dental implants	radiotherapy, severe or uncontrolled metabolic diseases or lack of compliance.		Prednisone + Cyclosporin A + Mycophenolate Mofetil (5 patients) / Prednisone + Tacrolimus + Mycophenolate Mofetil (8 patients)	Gothenburg, Sweden 3.75, 4 & 5mm diameter		transplant patients after the pharmacological immunosuppression	d partial support
Montebugnoli et al. (2015) (Italy) [28]	MBL	13 organ-transplanted (11 hearts, two livers) patients who received 29 submerged dental implants	15 matched controls who received 15 dental implants	Previous irradiation of the head and neck region, alcohol or drug abuse or psychiatric disorders that made it difficult to obtain informed consent, severe bruxism or clenching habits, smoking, and cyclosporine-induced gingival overgrowth.	University based	Prednisone + Cyclosporin A (1 patient) Cyclosporin (11 patients) and Tacrolimus (2 patients)	Standard tapered implants with anodised surfaces (NobelReplace Tapered Groovy, Nobel Biocare AB, Gothenburg, Sweden). +3.5mm diameter and +8mm length	1 year	Implant failure and bone loss were equivalent to those in control	No funding

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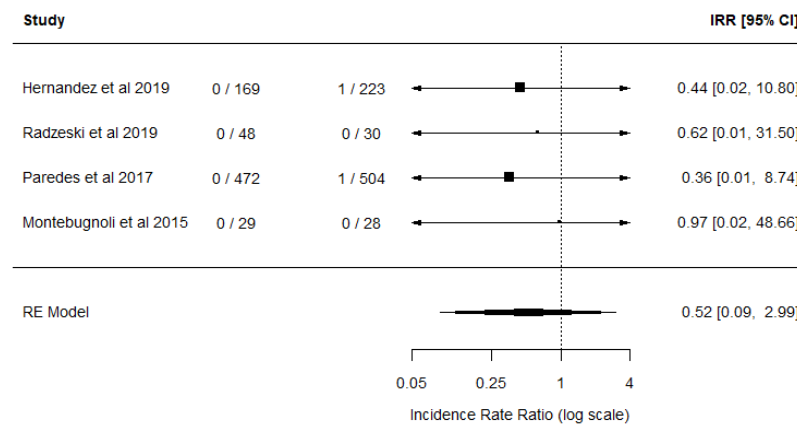
Figure 2. Forest plot of studies with Implants Incidence Rate Ratio values comparing transplanted and healthy patients. Mean effect size estimates have been calculated with 95% confidence intervals and are shown in the figure. Area of squares represents sample size, continuous horizontal lines and diamonds width represents 95% confidence interval.
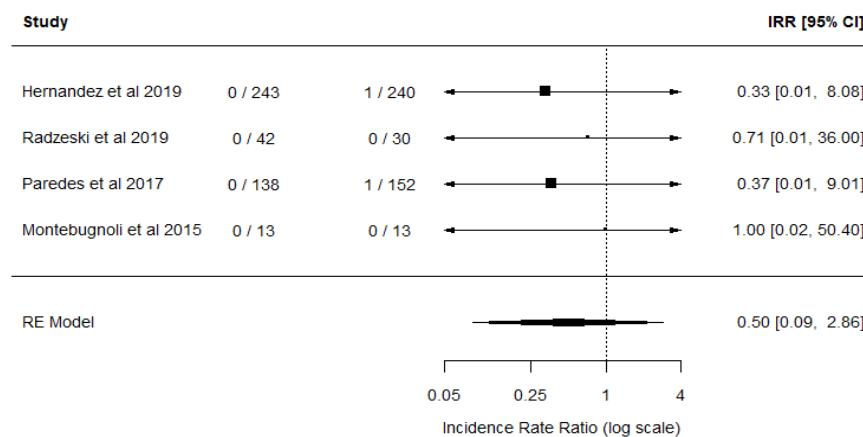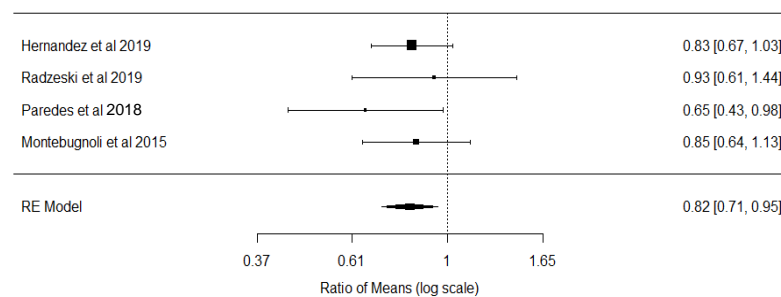

Figure 3. Forest plot of studies with Patients Incidence Rate Ratio values comparing transplanted and healthy patients. Mean effect size estimates have been calculated with 95% confidence intervals and are shown in the figure. Area of squares represents sample size, continuous horizontal lines and diamonds width represents 95% confidence interval.

3.3.2. Marginal bone loss

Regarding the assessment of MBL of implants, SOT patients had a significant difference of -18% (p-value <0.001) of MBL towards healthy patients (Ratio of Means 0.82, 95% CI: 0.71-0.95). Overall, this outcome resulted from a very homogeneous synthesis (I2 = 0%) (Figure 4).

Figure 4. Forest plot of studies with Marginal Bone Loss Rate of Means comparing transplanted and healthy patients. Mean effect size estimates have been calculated with 95% confidence intervals and are shown in the figure. Area of squares represents sample size, continuous horizontal lines and diamonds width represents 95% confidence interval.

4. Discussion

Summary of Main Findings

This systematic review provides a comprehensive assessment of implant failure rate and marginal bone loss (MBL) of dental implants placed in SOT patients compared with otherwise healthy individuals. The quantitative analysis provided by case-control studies revealed that SOT patients had lower incidence of implant failures and marginal bone loss than control patients. Nevertheless, these implant clinical shortcomings were collectively seen as rare events and are consistent with previous reviews [29,30].

Our results are novel as, to the best of our knowledge, this is the first systematic review to provide concrete evidence on the dental implant success characteristics in SOT patients. A previous systematic review on immunocompromised patients reported a dental implant success of 100% in SOT patients [31]; however, this result accounted for case reports, which is highly discouraged. In addition, the number of SOT cases is expected to increase globally in the years to come [12] and, therefore, implantology care in SOT cases will become more standard in daily practice.

When compared to healthy patients, the lower rates of dental implant failure and MBL in SOT patients are intriguing.

Nevertheless, the obtained implant failure results differences between SOT and control patients were not significant ($p > 0.05$), and chance may have had a role in here, probably due to implant failure being a very rare event in the studied conditions, and the limited sample size from the selected studies. Furthermore, in a previous meta-analysis in immunocompromised patients, no significant effect of Immunosuppressant therapy was found on implant survival [31].

Regarding MBL, it has been known from studies in immunosuppressed animal models that this condition apparently does not disturb bone density and implants osseointegration [32,33].

Quality of the Evidence, Limitations and Potential Biases in the Review Process

Drawing parallels with available reviews, some comparable populations are immunocompromised patients (HIV, chemotherapy, autoimmune diseases, for instance), given the consequences of the long lasting post-transplant medications (Ref). Under this assumption, dental implant survival was found to be very high in immunocompromised patients [31]. Also, HIV infection is recognised as a non-serious threat to implant survival on short-term evaluation [31,34].

No significant effect of immunocompromised conditions on implant survival was detectable. Implant-based therapy in immunocompromised patients should not aggravate the general morbidity and must not interfere in life-saving therapies. A careful risk stratification prior implant therapy is

fundamental. To further decipher the role of immunosuppression on dental implantology, more data from controlled and randomised studies are needed.

In respect of the type of transplant recipients included in this study, several types of transplants were included, two on liver [23], one on renal [24] and two with mixed transplants types [27,28]. Overall, these results account for the most prevalent types (renal and liver transplantation) (WHO, 2016), but also the infrequent cases.

Despite the comprehensive protocol conducted in this review to appraise all evidence on dental implant failure rate and MBL in SOT populations, some limitations should be discussed. The number of available articles was small and none of the included studies present intervention designs. Future studies should consider intervention designs and longer prospective registers to further confirm our results. Further, the rationale used to categorise implant failure was very dissimilar, although it was not reflected in the levels of heterogeneity. Thus, future studies should employ up-to-date case definitions [35] as well as more detailed clinical data. However, the shortage in available studies precluded additional tests in biological surrogates comparison, for instance cytokines, as they were previously reported as increased in SOT patients [16], and publication bias inspection.

Notwithstanding, several strengths are worth mentioning. The residual level of heterogeneity observed in the reported estimates and the strict protocol endorse the validity of quantitative analyses. In addition, studies were carried out both in hospital and private-practice settings, which allows for generalised conclusions.

5. Conclusions

Solid-organ transplant patients pose no serious threat to implant survival. Overall, this group of patients presented lower levels of dental implant failure rate and marginal bone loss compared to otherwise healthy patients. Further intervention trials with wider sample size and longer follow-ups are necessary to confirm these summary results.

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