OPTIMIZED PATIENT CARE:
Converting Osseo integration to Patient integration
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OPTIMIZED PATIENT CARE: Converting Osseointegration to Patientintegration

August 8–10, 2018
Oak Brook Hills Resort
Oak Brook, Illinois

Summit Chair
Clark M. Stanford, DDS, PhD
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INTRODUCTION

Optimized Patient Care:
Converting Osseointegration to Patientintegration

The Academy of Osseointegration (AO) is the global leader in research and clinically relevant information relative to oral implant and associated care for optimal outcomes. In addition to a series of meetings per year focused on education and dissemination, the Academy in 1996 began holding a Workshop or Summit every 4 years. The driving question behind the purpose of this Summit, held August 8–10, 2018 in Oak Brook, IL, was to determine if there may be elevated risk factors attributable to local or systemic issues, suggested by recent literature.

This 3-day workshop was the culmination of dedicated work by 70 international clinician-scientists working in three teams under the guidance of three chairpersons. There were also professional member dental organizations represented, including the American Association of Oral and Maxillofacial Surgeons (AAOMS), the American Academy of Periodontology (AAP), and the American College of Prosthodontists (ACP).

The Summit received strong financial and participatory support from the Academy of Osseointegration Foundation (AOF) along with strong financial support from many corporate friends of the AO. The AO board and the membership of the Academy sincerely thank both the AOF and our corporate friends for their support. The AO content experts and our corporate leaders in the fields of implant therapy and biologics listened and learned as all the content experts debated the three topic areas.

Participants discussed three questions for the Summit, each researched and presented by one of three working groups. Framed around outcomes or impact on long-term osseointegration, the questions addressed: Primary Stability and Osseointegration (Group 1); Inflammation and Osseointegration (Group 2); and Systemic Health, Medications, and Osseointegration (Group 3). Leading the groups were Drs John B. Brunski (Biomaterial/Bioengineering), Stanford University, CA (Group 1); Joseph P. Fiorellini (AO Director and Periodontist), University of Pennsylvania, Philadelphia, PA (Group 2); and Tara L. Aghaloo (AO Secretary and Associate Professor, Oral and Maxillofacial Surgery), UCLA, Los Angeles, CA (Group 3). Prior to the meeting, the three teams built formal systematic reviews on the three topic areas and came prepared to debate within the general session. After an initial breakout session, each of the chairs provided an overview of their group’s outcomes, followed by a 60-minute plenary presenter and a clinical presentation for the entire audience. A moderated and dynamic discussion followed each plenary speaker and the clinical case presentation. The plenary presenters were Dr Rick Sumner, Mary Lou Bell McGrew Presidential Professor for Medical Research and Chair of the Department of Cell and Molecular Medicine at Rush University Medical Center in Chicago (Group 1); Dr Flavia Teles, Associate Professor, Department of Microbiology, University of Pennsylvania School of Dental Medicine (Group 2); and Dr Susan Bukata, Orthopedic Surgeon, Ronald Reagan UCLA Medical Center, Department of Orthopedic Surgery, Santa Monica, CA (Group 3).

Following the meeting, the outcomes of the debates were incorporated into the final three papers published in this special supplemental edition of JOMI as a service to the AO membership. Thank you to all of the experts who worked very hard in preparing for this Summit and the AOF and Corporate friends of the AO who supported this important contribution to patient care.

Clark M. Stanford, DDS, PhD
Summit Chair & AO President-Elect
Distinguished Professor and Dean
College of Dentistry
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Primary Stability and Osseointegration

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**Observers**
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Priya Menon, Dentsply Sirona
Thaddeus Picklo, Osstell
Relationship Between Primary/Mechanical and Secondary/Biological Implant Stability

Alberto Monje, DDS, MS, PhD1,2/Andrea Ravidà, DDS, MS3/Hom-Lay Wang, DDS, MS, PhD3/Jill A. Helms, DDS, PhD4/John B. Brunski, PhD4

Purpose: This systematic review was prepared as part of the Academy of Osseointegration (AO) 2018 Summit, held August 8–10 in Oak Brook Hills, Illinois, to assess the relationship between the primary (mechanical) and secondary (biological) implant stability. Materials and Methods: Electronic and manual searches were conducted by two independent examiners in order to address the following issues. Meta-regression analyses explored the relationship between primary stability, as measured by insertion torque (IT) and implant stability quotient (ISQ), and secondary stability, by means of survival and peri-implant marginal bone loss (MBL).

Results: Overall, 37 articles were included for quantitative assessment. Of these, 17 reported on implant stability using only resonance frequency analysis (RFA), 11 used only IT data, 7 used a combination of RFA and IT, and 2 used only the Periotest. The following findings were reached:

• Relationship between primary and secondary implant stability: Strong positive statistically significant relationship (P < .001).
• Relationship between primary stability by means of ISQ and implant survival: No statistically significant relationship (P = .4).
• Relationship between IT and implant survival: No statistically significant relationship (P = .2).
• Relationship between primary stability by means of ISQ unit and MBL: No statistically significant relationship (P = .9).
• Relationship between IT and MBL: Positive statistically significant relationship (P = .02).
• Accuracy of methods and devices to assess implant stability: Insufficient data to address this issue.

Conclusion: Data suggest that primary/mechanical stability leads to more efficient achievement of secondary/biological stability, but the achievement of high primary stability might be detrimental for bone level stability. While current methods/devices for tracking implant stability over time can be clinically useful, a robust connection between existing stability metrics with implant survival remains inconclusive. Int J Oral Maxillofac Implants 2019;34(suppl):s7–s23. doi: 10.11607/jomi.19suppl.g1

Keywords: alveolar bone, bone homeostasis, dental implants, diagnostic, implant stability, mechanical, resonance frequency analysis

Accepting that osseointegration involves a dynamic orchestration of de novo bone formation and remodeling of pre-existing interfacial bone under implant function,1 the significance of achieving mechanical (“primary”) stability is imperative.2 Under ideal conditions, there will be a cascade of cellular and molecular phenomena—including blood clot formation, angiogenesis, osteoprogenitor cell migration, woven bone apposition in bone-implant gaps, secondary remodeling of the woven bone, and remodeling of pre-existing peri-implant bone—all of which play a role in the stabilization of the implant in its site.3,4 However, under non-ideal conditions, such

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as conditions of excessive micromovements of the implant due to lack of mechanical stability, this cascade of events can be perturbed, resulting in fibrous encapsulation, earlier described as fibroplasia, which in turn may lead to implant failure.

From a different perspective, the achievement of “high” mechanical stability—with the term “high” signifying the use of a “larger-than-normal” insertion torque—involves the risk of causing a deleterious effect upon peri-implant tissue stability. For example, recent studies in animal models have focused on the interplay between biology and mechanics in osseointegration. Based on these findings, the insertion of dental implants under “high” torque triggers an increased spatial extent of interfacial microfractures and related bone resorption, which in turn can compromise osseointegration. On the other hand, implants placed with “low” insertion torque (ie, lower than typically used) showed significantly smaller compressive strains in peri-implant bone and minimal cell death, which, in turn, may blunt the oft-reported “dip” in plots of implant stability over time.

In light of these issues surrounding stability and measurements thereof, a search for a quantitative metric that would enable clinicians to predict successful performance of dental implants—regardless of their placement and/or loading protocols—has represented an active thrust in dental research within the last two decades. For instance, it has resulted in the development of vibration tools (ie, resonance frequency analysis) or devices using impact to measure tooth stability (ie, Periotest). Along these lines, an operator’s clinical perception of insertion torque achieved during implant placement has also become a metric of stability.

In the contemporary era of implant dentistry, where protocols such as immediate placement and/or immediate loading are common, these protocols are carried out mainly based on pre- and intraoperative determinants, including judgments about bone characteristics (ie, trabecular density or proportion of cancellous and cortical bone) and implant stability. In addition, numerous bone-condensing approaches are gaining popularity among clinicians due to the actual or perceived enhancement in intraoperative stability or the perception thereof. Nonetheless, the fate of these techniques is still unknown, given that it is yet to be elucidated whether there is a threshold of insertion torque or implant stability quotient value beyond which implant stability is compromised. Hence, the primary purpose of this systematic review was to shed light on the relationship of mechanical (primary) to secondary stability by means of quantitative data. Moreover, the nature, accuracy, and reliability of the devices to measure implant stability were analyzed as the secondary purpose.

**MATERIALS AND METHODS**

**Protocol**
The protocol followed the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement. The review protocol was registered and allocated the identification number CRD42018094624 in the PROSPERO International Prospective Register of Systematic Reviews hosted by the National Institute for Health Research, University of York, Centre for Reviews and Dissemination.

**Focused Questions**
1. What are the relationships between mechanical (primary) stability—by means of implant stability quotient (ISQ) or insertion torque (IT)—and biological stability in humans—by means of implant stability quotient?
2. What are the relationships between implant mechanical (primary) stability—by means of ISQ and IT—and implant survival (≥ 12 months) and peri-implant bone stability?
3. What is the reliability/accuracy of the available quantitative tools to monitor implant stability?

**PI(E)CO (Patient, Intervention [Exposure], Comparison, Outcome) Question 1**
- **P:** Partially or completely edentulous patients
- **I(E):** Placement of dental implants to restore function and/or esthetics with high ISQ
- **C:** Placement of dental implants to restore function and/or esthetics with low ISQ
- **O (Primary outcome):** Biological stability (by means of ISQ)
- **O (Secondary outcome):** Implant survival (or implant failure), peri-implant marginal bone stability (or loss)

**PI(E)CO Question 2**
- **P:** Partially or completely edentulous patients
- **I(E):** Placement of dental implants to restore function and/or esthetics achieving primary stability
- **C:** Placement of dental implants to restore function and/or esthetics not achieving primary stability
- **O (Primary outcome):** Biological stability (by means of ISQ)
- **O (Secondary outcome):** Implant survival (or implant failure), peri-implant marginal bone stability (or loss)

**PI(E)CO Question 3**
- **P:** Partially or completely edentulous patients
- **I(E):** Placement of dental implants under high IT
- **C:** Placement of dental implants under low (or no) IT
- **O (Primary outcome):** Biological stability (by means of ISQ)
O (Secondary outcome): Implant survival (or implant failure), peri-implant marginal bone stability (or loss)

Case Definition for Primary/Mechanical and Secondary/Biological Stability

- **Primary/mechanical stability:** The mechanical engagement (interlock) attained at the time of implant placement; it is governed by implant macro-design (diameter/length and thread design), implant drilling protocol, and bone macro-architecture.
- **Secondary/biological stability:** The biological engagement and homeostasis by means of bone apposition to implant, which occurs after implant placement, influenced by factors including implant micro-design (surface characteristics) and bone macro- and micro-architecture plus implant loading.

Eligibility Criteria

**Inclusion Criteria**

- Randomized and nonrandomized prospective or retrospective human case-control or cohort comparative studies evaluating implants reporting on the relationship between implant primary and secondary stability
- ≥ 12 months after implant placement
- ≥ 10 participants
- Quantitative implant stability value recorded by any commercialized device/method

**Exclusion Criteria**

- Studies in which primary and/or secondary stability are not reported by means of a quantitative value
- Studies in which the primary outcome is not reported
- Studies that assess the impact of bone grafting on primary and/or secondary stability (ie, maxillary sinus floor elevation)
- < 12 months
- < 10 participants

In addition, in order to gain more insight about the findings from human evidence, the screening of the electronic databases also tried to find preclinical and in vitro studies that could corroborate human findings at mechanobiological, cellular, and molecular levels.

Interventions/Methods to Assess Implant Stability

Primary and secondary implant stability were assessed using the following tools and methods (Table 1):

- **Traditional clinical methods:** percussion, two instruments, radiograph, vibration analysis, Periotest (damping effect), Ostell (resonance frequency analysis [RFA])
- **Torque test:** insertion torque, reverse torque

Information Sources

**Electronic Search.** Electronic databases were used as sources in the search for studies satisfying the inclusion criteria: (1) National Library of Medicine (MEDLINE via PubMed), (2) Cochrane Central Register of Controlled Trials, and (3) EMBASE database. These databases were searched for studies published until January 2018. The search was not filtered/limited by language.


**Grey Literature Search.** The System for Information on Grey Literature in Europe (SIGLE) database, through the “OpenGrey” www.opengrey.eu web page, was screened for potential data yet not published.

| Table 1  Tools and Methods to Assess Implant Primary and Secondary Stability |
|-------------------------------------|----------|----------|--------------------------|
| **Reliability** | **Feasibility** | **Major concern** |
| **Traditional clinical methods** | | |
| Percussion | Low | Good | No actual value |
| Two instruments | Medium | Good | Low sensitivity |
| Radiograph | Low | Poor | Low sensitivity |
| **Vibration analysis** | | |
| Periotest (damping effect) | Low | Low | Not reliable |
| Resonance frequency analysis | Medium | Good | Low specificity |
| **Torque test** | | |
| Insertion torque | High | Good | One-time assessment |
| Reverse torque | High | Fair | Too destructive |
Search Strategy
A search strategy applying MeSH keywords when possible and title/abstract keywords was carried out as follows: (((((((((((((((“jaw, edentulous”[MeSH Terms] OR “mouth, edentulous”[MeSH Terms]) OR “jaw, edentulous, partially”[MeSH Terms]) AND “dental implantation, endosseous”[MeSH Terms]) OR “dental implantation, endosseous”[MeSH Terms]) OR “dental implantation, endosseous”[MeSH Terms]) OR “dental implantation, endosseous”[MeSH Terms]) OR “dental implants”[MeSH Terms]) OR “dental implantation”[MeSH Terms]) AND primary stability[Title/Abstract]) OR mechanical stability[Title/Abstract]) OR high stability[Title/Abstract]) AND survival[Title/Abstract]) OR resonance frequency analysis[Title/Abstract]) OR insertion torque[Title/Abstract]) OR failure[Title/Abstract]) OR marginal bone loss[Title/Abstract]) OR crestal bone loss[Title/Abstract] AND (Clinical Trial[ptyp] AND “humans”[MeSH Terms]).


Screening Methods
Three reviewers (AM, AR, and HLW) did the primary search by independent screening of the titles and abstracts. The same reviewers selected for evaluation the full manuscript of those studies meeting the inclusion criteria, or those with insufficient data in the title and abstract to make a clear decision. Any disagreement was resolved by discussion with the rest of the authors. The Cohen’s kappa interexaminer agreement (percentage of agreement and kappa correlation coefficient) of the screening method was calculated and reported.

Data Extraction
Two reviewers (AM and AR) extracted the data. Authors of studies were contacted for clarification when data were incomplete or missing. If agreement could not be reached, data were excluded until further clarification emerged. When the results of a study were published more than once, the data with the longest follow-up were included only once.

Quality Assessment (Risk of Bias in Individual Studies)
A quality assessment of the included randomized clinical trials (RCTs) and controlled clinical trials (CCTs) was performed according to the Cochrane Handbook for Systematic Reviews of Interventions and by the CONSORT statement. Six main quality criteria were assessed: sequence generation, allocation concealment, blinding treatment outcomes to outcome examiners, completeness of follow-up, selective outcome reporting, and other sources of bias. These criteria were rated to be in low, unclear, or high risk of bias depending on the descriptions given for each individual field.

The Newcastle-Ottawa scale for cohort studies and a modification of the scale for cross-sectional studies were included only once.

The Publication Bias was evaluated using a funnel plot and the Egger’s linear regression method. A sensitivity analysis of the meta-analysis results was also performed.

RESULTS
Study Selection
A total of 2,292 records were identified through the electronic search after removal of duplicates; they
were supplemented with 25 citations from the manual search and 4 citations through screening bibliographies of relevant included/excluded articles, as illustrated in Fig 1.

Upon exclusion of reports deemed ineligible, this left 2,247 titles and abstracts, and 65 studies remained for full-text evaluation. Finally, 28 studies were excluded for not meeting the inclusion criteria and one further study could not be included as it did not report the exact values, but rather reported ranges, leaving 37 studies eligible for inclusion in the qualitative and quantitative analyses (Fig 1; Tables 2 to 4).

Of these, 17 reported implant stability only using RFA, 8, 11 only IT, 7 a combination of RFA and IT, and 2 the Periotest. Of the 36 studies included in the qualitative and quantitative evaluation, 22 were prospective cohort (PC) studies, 7 was a retrospective cohort (RC) study, and 14 were RCTs.

- For the evaluation of RFA, 24 studies comprised a total of 892 participants. The participants had a total of 2,137 implants that were assessed.
- For the evaluation of IT, 18 studies comprised a total of 1,387 participants. The participants had a total of 2,646 implants that were assessed.
- For the evaluation of Periotest, 2 studies comprised a total of 56 participants. The participants had a total of 128 implants that were assessed.

Relationship Between Primary and Secondary Implant Stability

The study demonstrated a strong positive statistical significance between primary and secondary stability ($P < .001$) with a coefficient of 0.847 when using the RFA tool. In other words, roughly, there is 85% of variation from primary to secondary stability. No relationship between primary and secondary stability could be evaluated using the other methods (Fig 2).

Primary Outcome on Implant Survival

The inter-study heterogeneity reached 99.9% of the total variability ($I^2 = 0.999; P < .001$). Due to this issue, two studies were excluded from the analysis (Atieh et al, 2018; Kronstrom et al, 2019). The mean implant survival rate was 98.4% (95% CI: 97.3%–99.3%).

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Fig 1. PRISMA Flowchart of the screening process. *Seven trials evaluated and reported implant stability with resonance frequency analysis (RFA) and insertion torque (IT).
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study design</th>
<th>Follow-up</th>
<th>Participants (n)</th>
<th>Implants (n)</th>
<th>Method</th>
<th>IT Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alghamdi et al27 (2011)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>29</td>
<td>26</td>
<td>RFA</td>
<td>35.19 ± 4.79 68.5 ± 4.81</td>
</tr>
<tr>
<td>Atieh et al28 (2014)</td>
<td>PC</td>
<td>12 mo from IP/PL</td>
<td>28</td>
<td>28</td>
<td>RFA</td>
<td>34.62 ± 5.82 66.8 ± 5.41</td>
</tr>
<tr>
<td>Balleri et al29 (2002)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>14</td>
<td>45</td>
<td>RFA</td>
<td>NA</td>
</tr>
<tr>
<td>Barewal et al30 (2012)</td>
<td>RCT</td>
<td>36 mo from IP</td>
<td>38</td>
<td>8</td>
<td>RFA</td>
<td>10.01 ± 45.81 58 ± 5.5</td>
</tr>
<tr>
<td>Bechara et al31 (2017)</td>
<td>RCT</td>
<td>36 mo from IP</td>
<td>33</td>
<td>45</td>
<td>RFA</td>
<td>32.28 ± 11.04 72 ± 3.1</td>
</tr>
<tr>
<td>Becker et al32 (2013)</td>
<td>PC</td>
<td>24 mo from IP</td>
<td>76</td>
<td>100</td>
<td>RFA</td>
<td>NA</td>
</tr>
<tr>
<td>Hoff et al33 (2014)</td>
<td>RCT</td>
<td>12 mo from IP</td>
<td>21</td>
<td>42</td>
<td>RFA</td>
<td>NA</td>
</tr>
<tr>
<td>Karabuda et al38 (2011)</td>
<td>RCT</td>
<td>12 mo from PL</td>
<td>22</td>
<td>48</td>
<td>RFA</td>
<td>55.46 ± 8.29 56.63 ± 8.19</td>
</tr>
<tr>
<td>Kim et al40 (2015)</td>
<td>RCT</td>
<td>12 mo from PL</td>
<td>21</td>
<td>22</td>
<td>RFA</td>
<td>66 ± 7.4</td>
</tr>
<tr>
<td>Kronstrom et al41 (2010)</td>
<td>RCT</td>
<td>12 mo from IP/PL</td>
<td>36</td>
<td>3</td>
<td>IT</td>
<td>20</td>
</tr>
<tr>
<td>Malchiodi et al43 (2016)</td>
<td>RCT</td>
<td>12 mo from IP</td>
<td>40</td>
<td>40</td>
<td>RFA</td>
<td>49.0 ± 9.95 63.95 ± 8.81</td>
</tr>
<tr>
<td>Norton45 (2017)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>22</td>
<td>3</td>
<td>RFA</td>
<td>&lt;5</td>
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<tr>
<td>Olsson et al46 (2003)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>10</td>
<td>61</td>
<td>RFA</td>
<td>NA</td>
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<tr>
<td>Östman et al47 (2005)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>40</td>
<td>123</td>
<td>RFA</td>
<td>NA</td>
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<tr>
<td>Östman et al48 (2013)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>21</td>
<td>139</td>
<td>RFA</td>
<td>NA</td>
</tr>
<tr>
<td>Östman et al49 (2008)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>77</td>
<td>257</td>
<td>RFA</td>
<td>NA</td>
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<tr>
<td>Pieri et al50 (2012)</td>
<td>PC</td>
<td>24 mo from PL</td>
<td>25</td>
<td>61</td>
<td>RFA</td>
<td>NA</td>
</tr>
<tr>
<td>Rao and Benzi52 (2007)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>46</td>
<td>51</td>
<td>RFA</td>
<td>NA</td>
</tr>
<tr>
<td>Sennerby et al54 (2012)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>90</td>
<td>218</td>
<td>RFA</td>
<td>NA</td>
</tr>
<tr>
<td>Shayesteh et al55 (2013)</td>
<td>RCT</td>
<td>12 mo from IP</td>
<td>30</td>
<td>23</td>
<td>RFA</td>
<td>NA</td>
</tr>
<tr>
<td>Tatl et al57 (2014)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>23</td>
<td>77</td>
<td>RFA</td>
<td>36.8 ± 3.8 73.6 ± 5.8</td>
</tr>
<tr>
<td>Turkyilmaz et al58 (2008)</td>
<td>RCT</td>
<td>12 mo from IP</td>
<td>20</td>
<td>20</td>
<td>RFA</td>
<td>NA</td>
</tr>
<tr>
<td>Zix et al60 (2005)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>35</td>
<td>120</td>
<td>RFA</td>
<td>NA</td>
</tr>
<tr>
<td>Zwaan et al61 (2016)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>97</td>
<td>163</td>
<td>RFA</td>
<td>41.3 ± 12.0 73.7 ± 6.4</td>
</tr>
</tbody>
</table>

PC = prospective cohort study; RCT = randomized clinical trial; IT = insertion torque; IP = implant placement; PL = postloading.
### Table 2  Studies Included in the Systematic Review Using Resonance Frequency Analysis (RFA) to Assess Primary and Secondary Implant Stability

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study design</th>
<th>Follow-up</th>
<th>Participants (n)</th>
<th>Implants (n)</th>
<th>Primary stability</th>
<th>Secondary stability</th>
<th>Confounders</th>
<th>Success rate (%)</th>
<th>MBL follow-up (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary stability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>15.42 ± 3.04</td>
<td>11.52 ± 2.03</td>
<td>NA</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>RFA 73.4 ± 12.4</td>
<td>NA</td>
<td>8 wk</td>
<td>68.5 ± 4.81</td>
<td>NA</td>
<td>NA</td>
<td>78.6</td>
<td>21.4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>RFA 69 ± 6.5</td>
<td>12 mo</td>
<td>NA</td>
<td>100</td>
<td>0</td>
<td>NA</td>
<td>0.3 ± 0.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>87.5</td>
<td>12.5</td>
<td>NA</td>
</tr>
<tr>
<td>RFA 71.6</td>
<td>3 y</td>
<td>21</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>100</td>
<td>0</td>
<td>NA</td>
<td>0.89 ± 0.25</td>
</tr>
<tr>
<td>RFA 72.6</td>
<td>24 mo</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>93</td>
<td>7</td>
<td>NA</td>
<td>0.6</td>
</tr>
<tr>
<td>RFA 80.5</td>
<td>12 mo</td>
<td>NA</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td>97.6</td>
<td>2.4</td>
<td>NA</td>
<td>0.69</td>
</tr>
<tr>
<td>RFA 81.3</td>
<td>12 mo</td>
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</tr>
<tr>
<td>NA</td>
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<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>84</td>
<td>16</td>
<td>NA</td>
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<td>RFA 81.7</td>
<td>12 mo</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>100</td>
<td>0</td>
<td>NA</td>
<td>0.44 ± 0.4</td>
</tr>
<tr>
<td>RFA 67.48 ± 5.95</td>
<td>3 mo</td>
<td>25</td>
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<td>NA</td>
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<td>100</td>
<td>0</td>
<td>100</td>
<td>0.54 ± 0.38</td>
</tr>
<tr>
<td>RFA 84.83</td>
<td>3 mo</td>
<td>4.5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>100</td>
<td>0</td>
<td>NA</td>
<td>0.07</td>
</tr>
<tr>
<td>78.22</td>
<td>79.30</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>RFA 62.8 ± 1.6</td>
<td>4 mo</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>93.4</td>
<td>6.6</td>
<td>N/A</td>
<td>1.3 ± 0.6</td>
</tr>
<tr>
<td>RFA 64.5 ± 4.8</td>
<td>6 mo</td>
<td>5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>99.6</td>
<td>0.4</td>
<td>NA</td>
<td>0.78 ± 0.90</td>
</tr>
<tr>
<td>62.6 ± 7</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.91 ± 1.04</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>99.4</td>
<td>0.6</td>
<td>NA</td>
<td>1.01 ± 0.85</td>
</tr>
<tr>
<td>RFA 72.5 ± 5.7</td>
<td>6 mo</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>98.4</td>
<td>1.6</td>
<td>82.9</td>
<td>0.7 ± 0.78</td>
</tr>
<tr>
<td>RFA 72.91 ± 5.07</td>
<td>24 mo</td>
<td>16</td>
<td>NA</td>
<td>13.6</td>
<td>&lt; 2 mm (2 implants)</td>
<td>96.8</td>
<td>3.2</td>
<td>96.8</td>
<td>0.6 ± 0.13</td>
</tr>
<tr>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>100</td>
<td>0</td>
<td>NA</td>
<td>1.12 ± 1.06</td>
</tr>
<tr>
<td>RFA 76.7 ± 5.2</td>
<td>12 mo</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>98.6</td>
<td>2.4</td>
<td>NA</td>
<td>0.6 ± 0.8</td>
</tr>
<tr>
<td>RFA 76.4 ± 2.5</td>
<td>12 mo</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>100</td>
<td>0</td>
<td>NA</td>
<td>1 ± 0.3</td>
</tr>
<tr>
<td>RFA 76.4 ± 2.8</td>
<td>12 mo</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>100</td>
<td>0</td>
<td>NA</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>22.8</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.7 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>RFA 75.0 ± 4.5</td>
<td>6 mo</td>
<td>24.5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>96.9</td>
<td>3.1</td>
<td>NA</td>
<td>0.5 ± 0.4</td>
</tr>
</tbody>
</table>

PC = prospective cohort study; RCT = randomized clinical trial; IT = insertion torque; IP = implant placement; PL = postloading.
### Table 3  Studies Included in the Systematic Review Using Insertion Torque to Determine Primary Stability

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study design</th>
<th>Follow-up</th>
<th>Participants (n)</th>
<th>Implants (n)</th>
<th>Primary stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alghamdi et al\textsuperscript{27} (2011)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>29</td>
<td>26</td>
<td>IT</td>
</tr>
<tr>
<td>Barewal et al\textsuperscript{30} (2012)</td>
<td>RCT</td>
<td>36 mo from IP</td>
<td>38</td>
<td>8</td>
<td>IT</td>
</tr>
<tr>
<td>Vanden Bogaerde et al\textsuperscript{59} (2016)</td>
<td>RCT</td>
<td>36 mo from IP</td>
<td>11</td>
<td>11</td>
<td>IT</td>
</tr>
<tr>
<td>Calandriello et al\textsuperscript{33} (2003)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>26</td>
<td>20</td>
<td>IT</td>
</tr>
<tr>
<td>Degidi et al\textsuperscript{34} (2012)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>13</td>
<td>51</td>
<td>IT</td>
</tr>
<tr>
<td>Grandi et al\textsuperscript{38} (2013)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>102</td>
<td>114</td>
<td>IT</td>
</tr>
<tr>
<td>Khayat et al\textsuperscript{39} (2013)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>6</td>
<td>9</td>
<td>IT</td>
</tr>
<tr>
<td>Kronstrom et al\textsuperscript{41} (2010)</td>
<td>RCT</td>
<td>12 mo from IP/PL</td>
<td>36</td>
<td>3</td>
<td>IT</td>
</tr>
<tr>
<td>Maiorana et al\textsuperscript{42} (2015)</td>
<td>PC</td>
<td>46 mo from IP</td>
<td>189</td>
<td>377</td>
<td>IT</td>
</tr>
<tr>
<td>Malchiodi et al\textsuperscript{43} (2016)</td>
<td>RCT</td>
<td>12 mo from IP</td>
<td>40</td>
<td>40</td>
<td>IT</td>
</tr>
<tr>
<td>Marconcini et al\textsuperscript{44} (2018)</td>
<td>RCT</td>
<td>36 mo from IP</td>
<td>116</td>
<td>58</td>
<td>IT</td>
</tr>
<tr>
<td>Norton\textsuperscript{45} (2011)</td>
<td>PC</td>
<td>46 mo from IP</td>
<td>61</td>
<td>68</td>
<td>IT</td>
</tr>
<tr>
<td>Norton\textsuperscript{62} (2017)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>30</td>
<td>22</td>
<td>IT</td>
</tr>
<tr>
<td>Östman et al\textsuperscript{46} (2013)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>42</td>
<td>139</td>
<td>IT</td>
</tr>
<tr>
<td>Rabe et al\textsuperscript{51} (2007)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>263</td>
<td>408</td>
<td>IT</td>
</tr>
<tr>
<td>Rizkallah et al\textsuperscript{53} (2013)</td>
<td>RCT</td>
<td>15 mo from IP</td>
<td>145</td>
<td>390</td>
<td>IT</td>
</tr>
<tr>
<td>Stanford et al\textsuperscript{56} (2016)</td>
<td>RCT</td>
<td>12 mo from PL</td>
<td>120</td>
<td>79</td>
<td>IT</td>
</tr>
<tr>
<td>Tatli et al\textsuperscript{57} (2014)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>23</td>
<td>77</td>
<td>IT</td>
</tr>
<tr>
<td>Zwaan et al\textsuperscript{61} (2016)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>97</td>
<td>163</td>
<td>IT</td>
</tr>
</tbody>
</table>

PC = prospective cohort study; RCT = randomized clinical trial; IP = implant placement; PL = postloading.

### Table 4  Studies Included in the Systematic Review Using Periotest to Assess Primary and Secondary Implant Stability

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study design</th>
<th>Follow-up</th>
<th>Participants (n)</th>
<th>Implants (n)</th>
<th>Primary stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Hashedi et al\textsuperscript{26} (2016)</td>
<td>RCT</td>
<td>12 mo from PL</td>
<td>20</td>
<td>20</td>
<td>Periotest –1.61 ± 2.02</td>
</tr>
<tr>
<td>Norton\textsuperscript{46} (2011)</td>
<td>PC</td>
<td>46 mo from IP</td>
<td>61</td>
<td>68</td>
<td>Periotest –2.19 ± 2.23</td>
</tr>
<tr>
<td>Norton\textsuperscript{62} (2017)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>30</td>
<td>22</td>
<td>Periotest –1.02 ± 2.83</td>
</tr>
<tr>
<td>Östman et al\textsuperscript{46} (2013)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>42</td>
<td>139</td>
<td>Periotest –0.74 ± 2.69</td>
</tr>
<tr>
<td>Rabe et al\textsuperscript{51} (2007)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>263</td>
<td>408</td>
<td>Periotest –1.09 ± 2.83</td>
</tr>
<tr>
<td>Rizkallah et al\textsuperscript{53} (2013)</td>
<td>RCT</td>
<td>15 mo from IP</td>
<td>145</td>
<td>390</td>
<td>Periotest –1.02 ± 2.83</td>
</tr>
<tr>
<td>Stanford et al\textsuperscript{56} (2016)</td>
<td>RCT</td>
<td>12 mo from PL</td>
<td>120</td>
<td>79</td>
<td>Periotest –1.02 ± 2.83</td>
</tr>
<tr>
<td>Tatli et al\textsuperscript{57} (2014)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>23</td>
<td>77</td>
<td>Periotest –1.02 ± 2.83</td>
</tr>
<tr>
<td>Zwaan et al\textsuperscript{61} (2016)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>97</td>
<td>163</td>
<td>Periotest –1.02 ± 2.83</td>
</tr>
</tbody>
</table>

RCT = randomized clinical trial; RC = retrospective cohort study; PL = postloading.
Table 3  Studies Included in the Systematic Review Using Insertion Torque to Determine Primary Stability

<table>
<thead>
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<th>Study (year)</th>
<th>Study design</th>
<th>Follow-up</th>
<th>Participants (n)</th>
<th>Implants (n)</th>
<th>Primary stability Value</th>
<th>Success rate %</th>
<th>Implant failure (%)</th>
<th>MBL follow-up (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alghamdi et al (2011)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>29</td>
<td>26</td>
<td>IT</td>
<td>35.19 ± 4.79</td>
<td>0</td>
<td>15.42 ± 3.04</td>
</tr>
<tr>
<td>Barewal et al (2012)</td>
<td>RCT</td>
<td>36 mo from IP</td>
<td>38</td>
<td>8</td>
<td>IT</td>
<td>10.01 ± 4.58</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
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<td>IT</td>
<td>38 ± 11.4</td>
<td>27.2</td>
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<tr>
<td>Calandriello et al (2003)</td>
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<td>12 mo from IP</td>
<td>26</td>
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<td>IT</td>
<td>66.3 ± 8.4</td>
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<tr>
<td>Degidi et al (2012)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>13</td>
<td>51</td>
<td>IT</td>
<td>12.6 ± 3.6</td>
<td>NA</td>
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<td>Grandi et al (2013)</td>
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<td>12 mo from IP</td>
<td>102</td>
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<td>74.8 ± 7.9</td>
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<td>NA</td>
</tr>
<tr>
<td>Khayat et al (2013)</td>
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<td>12 mo from IP</td>
<td>6</td>
<td>9</td>
<td>IT</td>
<td>37.1</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Kronstrom et al (2010)</td>
<td>RCT</td>
<td>12 mo from IP/PL</td>
<td>36</td>
<td>3</td>
<td>IT</td>
<td>20</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Maiorana et al (2015)</td>
<td>PC</td>
<td>46 mo from IP</td>
<td>189</td>
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<td>RCT</td>
<td>12 mo from IP</td>
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<td>49.0 ± 9.95</td>
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<td>Marconcini et al (2018)</td>
<td>RCT</td>
<td>36 mo from IP</td>
<td>116</td>
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<td>29.1 ± 6.6</td>
<td>30.1</td>
<td>NA</td>
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<tr>
<td>Norton (2011)</td>
<td>PC</td>
<td>46 mo from IP</td>
<td>61</td>
<td>68</td>
<td>IT</td>
<td>22.5</td>
<td>25</td>
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<tr>
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<td>12 mo from PL</td>
<td>30</td>
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<td>&lt;20</td>
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<td>NA</td>
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<td>PC</td>
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<td>42</td>
<td>139</td>
<td>IT</td>
<td>53.1</td>
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<td>NA</td>
</tr>
<tr>
<td>Rabel et al (2007)</td>
<td>PC</td>
<td>12 mo from IP</td>
<td>263</td>
<td>408</td>
<td>IT</td>
<td>28.8 ± 15.2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rizkallah et al (2013)</td>
<td>RCT</td>
<td>15 mo from IP</td>
<td>145</td>
<td>390</td>
<td>IT</td>
<td>72</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Stanford et al (2016)</td>
<td>RCT</td>
<td>12 mo from PL</td>
<td>120</td>
<td>79</td>
<td>IT</td>
<td>31 ± 13</td>
<td>14.1</td>
<td>NA</td>
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<tr>
<td>Tatli et al (2014)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>23</td>
<td>77</td>
<td>IT</td>
<td>36.8 ± 3.8</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Zwaan et al (2016)</td>
<td>PC</td>
<td>12 mo from PL</td>
<td>97</td>
<td>163</td>
<td>IT</td>
<td>41.3 ± 12.0</td>
<td>24.5</td>
<td>NA</td>
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Table 4  Studies Included in the Systematic Review Using Periotest to Assess Primary and Secondary Implant Stability

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study design</th>
<th>Follow-up</th>
<th>Participants (n)</th>
<th>Implants (n)</th>
<th>Primary stability Value</th>
<th>Secondary stability Value</th>
<th>Timing</th>
<th>Confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Hashedi et al (2016)</td>
<td>RCT</td>
<td>12 mo from PL</td>
<td>20</td>
<td>20</td>
<td>Periotest –1.61 ± 2.02</td>
<td>Periotest –2.19 ± 2.23</td>
<td>12 mo from PL</td>
<td>NA</td>
</tr>
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<td>Jeong et al (2015)</td>
<td>RCT</td>
<td>5 y from PL</td>
<td>36</td>
<td>88</td>
<td>Periotest –1.02</td>
<td>Periotest –0.74</td>
<td>5 y from PL</td>
<td>NA</td>
</tr>
</tbody>
</table>

PC = prospective cohort study; RCT = randomized clinical trial; IP = implant placement; PL = postloading.
A statistically significant relationship was not yielded between mechanical stability determined by ISQ and implant survival ($P = .511$) (Figs 3 and 4).

No statistically significant relationship was reached between the IT and implant survival ($P = .227$) (Fig 5).

The inter-study heterogeneity reached 98.6% of the total variability ($I^2 = 0.986; P < .001$). It was found that one study (Rao and Benzi$^2$) accounted for the highest heterogeneity. Mean marginal bone loss was estimated to be 0.69 mm (95% CI: 0.56–0.84 mm). (See Supplementary Figs S1 and S2, in online version of article at www.quintpub.com.)
Relationship Between Primary Stability by Means of ISQ Unit and Marginal Bone Loss
No relationship could be established between the ISQ unit and marginal bone loss based on the existing evidence \( (P = .970) \) (Fig 6).

Relationship Between IT and Marginal Bone Loss
A statistically significant relationship between IT and marginal bone loss was yielded \( (0.027) \), favoring lower IT values. Each increase of 1 IT unit stands for a marginal bone loss of 0.01 mm. The coefficient of determination \( (R^2) \) was found to be low \( (30.8\%) \) (Fig 7).

Relationship Between Periotest Values and Implant Survival
Due to the limited data of implant primary stability using the Periotest, and the high level of heterogeneity \( (98\%) \), no clear results could be obtained of this relationship. The mean implant survival rate was 99.4\% \( (95\% \text{ CI: 98.4\%–100\%}) \).

Risk of Bias
Risk of bias is presented in Supplementary Tables S1 and S2 in the online version of this article at www.quintpub.com.

DISCUSSION

Main Findings
Findings of the present systematic review illustrated the role that mechanical stability in vivo plays on the achievement of biological stability. Moreover, it shed light on the detrimental effect that high implant IT may have upon peri-implant bone stability. Interestingly, the meta-regression analysis failed to identify a statistically significant relationship between the implant mechanical (primary) stability—as recorded using ISQ units or, instead, by the IT value—and the survival rate. It can be suggested that this controversial finding might be due to the inaccuracy of the currently used quantitative methods to evaluate implant stability in vivo.

Clinical Implications
Given the fact that mechanical stability is advised to successfully achieve biological stability, it is recommended to tailor implant macro-design and drilling protocol according to the bone characteristics. In this sense, advances in personalized medicine (precision medicine) offers the potential to condition the patient to achieve successful mechanical and biological stability by modifying bone biologic characteristics. Nevertheless, it should be kept in mind that the high IT values may jeopardize peri-implant marginal bone stability. Moreover, it is worth noting that the suggested degree of mechanical stability sought by the clinician should take into account the implant placement and intended loading protocol.

In addition, RFA has shown to be useful in monitoring the dynamic transition (time course) from mechanical to biological stability. Hence, it is advisable to use RFA as a reference tool in monitoring to evaluate the short-term changes from baseline; that is, clinical decisions should not be based solely on an isolated ISQ value without considering any initial measurement. Along these lines, it is worth noting that this device was not developed to guarantee long-term stability, since after the achievement of biological stability, a myriad of confounding factors might be associated with implant failure, such as changes in prosthetic design or occlusal habits.
Are Our Findings Plausible? Biological and Biomechanical Mechanisms Underlying Our Findings

On the Relationship of Primary and Secondary Stability. The dynamic process of osseointegration is initiated at the moment the implant is inserted within the alveolar bone. The prerequisite of mechanical stability has been a matter of debate, in particular the threshold of stability that assures adequate biologic anchorage. Given our understanding that the peri-implant healing in an aseptic environment arises from an orchestration of cellular events triggered by the damage of the pre-existing substratum and ending with new bone formation and remodeling at the implant surface, it is logical to consider that any physical disruption such as micromovement (above some threshold) might compromise this process. This was clearly depicted in a canine preclinical study where, after a healing period of 9 months, none of the non-stable implants reached osseointegration, with a layer of connective tissue interposed between the implant and the newly formed bone. Such findings confirmed earlier clinical observations. The present meta-regression analysis on clinical trials assessing the influence of primary over secondary stability is consistent with the direct relationship between these two. Hence, in order to strengthen the odds of the achievement of osseointegration, mechanical (primary) stability must be a first step. However, this begs the as-yet incompletely answered question of what exactly is the threshold value of implant micromotion—as measured by some appropriate method—that will interfere with proper osseointegration.

On the Relationship Between IT and Primary and Secondary Stability. Classically, it has been thought that a higher IT—ie, “higher than the standard recommended value”—might lead more predictably to osseointegration. In light of this perspective, techniques that attempt to improve osteotomy viability and fit to the implant, eg, modified specialized cutting tools or the use of osteotomes, have been proposed. Nevertheless, while it would intuitively make sense that increasing the interfacial bone volume and bone-implant contact could provide better primary mechanical support to the implant, it is also known that condensing cancellous bone using an osteotome will result in significant damage to the bone, which in turn can lower the bone’s modulus and strength, thus weakening the bone-implant interface.

It should also be noted that, besides implant macro-design (ie, governed by factors such as diameter, length, thread pattern, and cutting design), IT is directly related to bone characteristics. While it is true that the anatomic location is not synonymous with bone quality, nonetheless, type I bone predominates in the anterior mandible while types III and IV are more frequently found in the posterior maxilla. Hence, generally speaking, if all other factors are equal, IT is assumed to be higher in the mandible compared to the maxilla, with greater bone-implant contact (BIC) in the former than the latter. Now the question that remains unanswered is the following: If one tries to achieve a higher IT—and thus supposedly a higher stability—by increasing the BIC by employing an undersized osteotomy, will this approach guarantee the process of osseointegration? The short answer is: no. At a cellular level, higher IT (> 50 Ncm), owing to undersized drilling or the insertion in compact bone, has been demonstrated to develop microfractures that may lead to tissue breakdown or even to an erratic process of osseointegration. On the other side, although lower IT may lead to lesser primary stability, it does not affect the process of osseointegration as long as the healing is not disrupted by undue movement/load.

On the Relationship Between IT and Clinical Peri-Implant Bone Stability. Many investigations have focused on the identification of the “ideal” IT that would guarantee peri-implant bone stability. As noted previously, this begs the question of the exact meaning of “low” vs “high” IT—a question that is only answered in the context of each paper dealing with that topic. Early findings suggested that low IT at implant placement might be associated with future fibrous encapsulation of the implant, as a result of the occurrence of implant micromotion. This idea has been a matter of debate, since osseointegration has been demonstrated in animal models when an IT < 30 Ncm was applied, or even with a lack of IT (0 Ncm). However, these results do not reflect the trend observed in human trials, where a correlation between the lack of rotational primary stability and decreased overall survival rate was reported.

As aforementioned, high IT has been linked to higher stresses in the surrounding bone, which induces microfractures, bone necrosis, and remodeling. Similar to what was previously reported with low IT, this idea has been challenged in a preclinical study, where implants placed under 110 Ncm survived for 6 weeks, reaching the peak of lesser stability after 7 days. In addition to this, a prospective investigation failed to demonstrate a statistical significance between marginal bone loss in nonsubmerged implants using low (30 to 50 Ncm) and high torque (> 70 Ncm) 1 year after placement. However, contrary to these findings, the results of a RCT displayed that implants placed with high IT (≥ 50 Ncm) in healed alveolar ridges had more peri-implant bone remodeling and buccal soft tissue recession than implants inserted with a regular IT (< 50 Ncm). In summary, the overall clinical outcomes elucidate the uncertain impact that IT may have...
upon osseointegration and on the fate of the peri-implant bone. Generally, there is a linear correlation between the mechanical (primary) and the secondary stability; nevertheless, as demonstrated in the present systematic review, high IT is frequently associated with increased peri-implant bone loss.

**On the Relationship of IT and Peri-implant Bone Stability from the Standpoint of Basic Biomechanics.** To what degree is IT an accurate measure of implant mechanical (primary) stability? On the one hand, everyday experience with tightening bolts and screws makes it intuitively attractive to think that “tightening a screw” with torque is synonymous with achieving “stability.” However, as discussed below, everyday experience with threaded fasteners is not always fully transferable to the case of dental implants in bone. A more complete discussion of the relationship between torque and stability involves familiarity with basic mechanics underlying torque, interfacial pressure, misfit, mechanical properties of bone, and the very concept of stability itself. These topics are now discussed in more detail.

Starting with IT, an equation of Norton\(^7\) gives some initial insight (equation 1):

\[ T = \frac{\mu \pi D^2 p}{2} \]

Here \( T \) is insertion torque (IT), \( \mu \) is the coefficient of friction between implant and bone, \( \pi \) is the constant pi, \( H \) is the length of the implant in contact with bone (which varies as an implant is inserted deeper into bone), \( D \) is implant diameter, and \( p \) is the pressure at the bone-implant interface. This equation 1 is based on assuming that: (1) the implant is a cylinder of uniform circular cross section with diameter \( D \), and (2) the resistance to the applied torque \( T \) only arises from friction at the bone-implant interface, where the pressure, \( p \), arises from a normal force caused by fitting the cylinder into its hole. Since this equation predicts a linear relationship between IT and interfacial pressure \( p \), it confirms a clinician’s intuition that “more IT equals more pressure on bone.” However, this intuition is not fully correct if cutting occurs during placement of the implant; for example, in the case of an implant that is self-tapping, its placement also involves torque from cutting threads in the bone. The Norton equation also neglects other complexities arising from the size/shape of implant vs osteotomy, eg, using a tapered implant. Therefore, overall, the Norton equation provides limited insight into the origin of IT and its relationship to interfacial pressure. Moreover, it gives essentially no insight into any relationship that is sometimes presumed to exist between IT and mechanical (primary) stability of dental implants.

Additional perspective on IT comes from examining the concept of “misfit” of an implant in its osteotomy. Skalak and Zhao\(^7\) defined misfit as the difference between the radius of the implant and the radius of the osteotomy \((r_2 - r_1)\) and derived an equation showing that the interfacial pressure \( (p) \) that develops between implant and bone depends upon misfit as well as the mechanical (elastic) properties of the bone and implant. Their equation for the interfacial pressure \( p \) is (equation 2):

\[ p = (r_2 - r_1) \left[ \frac{(1 + v_1)}{E_1} r_1 + \frac{(1 + v_2)(1 - 2v_2)}{E_2} r_2 \right]^{-1} \left( \frac{\mu \pi D^2}{2} \right) \]

Here subscripts 1 and 2 refer to the bone in which the implant is placed and the material of the implant, respectively; likewise, the subscripted \( E \) and \( v \) refer to Young's elastic modulus and Poisson's ratio of the bone and implant, respectively.

The Skalak-Zhao analysis is instructive because it reveals that the bone-implant interfacial pressure, \( p \), is linearly proportional to both the misfit \((r_2 - r_1)\) and the bone's modulus \((E)\). This means that as either the misfit or the bone's modulus increases, so does the interfacial pressure. So as an example, for the same implant placed with the same misfit in “hard” (higher modulus) vs “soft” (lower modulus) bone, the pressure will be larger in the hard bone. Moreover, added insight comes from substituting Skalak-Zhao's equation for \( p \) into the Norton equation, which yields the following equation for insertion torque (equation 3):

\[ T = (r_2 - r_1) \left[ \frac{(1 + v_1)}{E_1} r_1 + \frac{(1 + v_2)(1 - 2v_2)}{E_2} r_2 \right]^{-1} \left( \frac{\mu \pi D^2}{2} \right) \]

This equation 3 predicts that for the same misfit \((r_2 - r_1)\) and same implant material, the IT will increase with increasing elastic modulus of the bone. Notably, this prediction about IT is consistent with clinicians' experience as well as data from controlled experiments with implants in Sawbones.\(^7\)

So how does this knowledge about IT relate to implant “stability”? This begs the question: What is the most direct and relevant measure of implant stability? As noted, several candidate measures have been suggested, but at present none of the available methods/devices provides a clinical measurement of how much an implant moves when the implant is loaded in the various ways that it may be loaded in vivo, eg, laterally, axially, rotationally. The motivation for seeking a metric on implant movement under load is this: There is already significant support around the hypothesis that implant micromotion and related interfacial strain fields are key determinants of interfacial mechanobiology and related bone healing.\(^5\)–\(^11\) So ultimately, this
leaves the question of how IT—and related factors such as misfit and mechanical properties—do or do not relate to "stability" as best we can currently measure it.

Currently, the most commonly used metrics of stability are the RFA (Oststell) and percussion (Periotest) methods. For the sake of argument, we can focus on the Osstell method, which is based on excitation of small-magnitude implant vibrations (displacements) of the implant in bone. On this basis, it has been suggested that the ISQ value is sensitive to the local interfacial elastic properties (eg, the elastic modulus) of the bone surrounding the implant. So if this is true, and if, as already shown by the Skalak-Zhao and Norton analyses in equation 3, the IT depends on the elastic properties of the interfacial bone, then it follows that there should be some relationship between IT and ISQ.

In exploring this, Bayarchimeg et al conducted experiments in which the same implant was placed with the same degree of misfit \((r_\text{m} - r_\text{i})\) in samples of Sawbones having different values of the Young’s elastic modulus. They observed that IT and ISQ both increased with modulus, ie, IT correlated with ISQ. This result is also consistent with equation 3 on IT as well as Osstell’s background about the ISQ: both metrics should increase with elastic modulus of the bone.

However, what do IT and ISQ data say when it comes to the common clinical scenario in which a clinician attempts to increase the IT of an implant in a given sample of bone (typically cancellous bone) by undersizing the osteotomy (ie, increasing the misfit)? In this clinical approach, does ISQ correlate with IT?

On the one hand, equation 3 predicts that IT will increase with increasing misfit. And in fact, this prediction is confirmed by experiments in both Sawbones (Bayarchimeg et al) and porcine iliac bone samples in vitro. However, both of these studies showed that when implants were tested in the same modulus material but with increasing misfit, IT increased but ISQ did not—it was there was no correlation between IT and ISQ.

This last finding is significant because it is at odds with the common clinical practice of undersizing the osteotomy for an implant, ie, increasing misfit in porous cancellous bone—a practice that has evidently been premised on the intuition that “higher IT means higher stability.” The mechanics and data reveal, however, that this intuition is not always correct. On the one hand, equation 3 does reveal that IT should increase with increasing misfit. But on the other hand, the Oststell literature indicates that ISQ (a popular metric for stability) should only increase if there is an increase in the elastic modulus of the interfacial bone; the Osstell literature is silent about whether misfit increases the modulus and therefore the ISQ. The simplest explanation of the results of Bayarchimeg et al and Sakoh et al—is no correlation between IT and ISQ when misfit increases in the same type of Sawbones or porcine bone—is that increasing misfit does not increase the peri-implant bone’s elastic modulus, which is a main determinant of the ISQ value. So while IT can increase from increasing misfit, that doesn’t mean the ISQ will increase.

**On the Relationship of IT and Peri-implant Bone Stability at Molecular and Cellular Levels.** From analyses of the mechanics underlying measurements of mechanical stability with methods such as RFA and Periotest, it is appreciated that these methods have some connection to implant micromotion, which in turn begs the question noted earlier of whether there is a threshold of micromotion below which osseointegration can be guaranteed. Research has revealed, however, that micromotion needs to be understood at a deeper level; for example, it is not so much the micromotion per se that is the key metric behind interfacial events but rather the local (microscopic) states of interfacial strain that are engendered by the micromotion. Indeed, a number of recent papers have examined the role of interfacial strain as the decisive biomechanical variable in interfacial events. So at this time it is not possible to offer a reliable borderline between “safe” vs “dangerous” micromotion.

**On the Accuracy of RFA to Monitor Peri-implant Tissue Stability.** RFA was developed to provide a quantitative value for implant stability. Assuming that greater implant osseointegration should lead to higher stability, RFA was suggested as a tool useful to monitor peri-implantitis. Accordingly, it was shown that a linear relationship existed between peri-implant vertical bone defect depths. Furthermore, Sennery et al showed in an experimental study in dogs that ISQ exhibited a linear correlation to radiographic peri-implant bone loss. It was further demonstrated that the ISQ values are dependent on the implant surface, showing a greater reduction with sandblasted acid-etched implants compared with turned implants. A recent canine study yielded findings that are in agreement with previous results. The baseline ISQ increased during the healing phase, and thereafter, the ISQ values significantly decreased to 69.5 ± 1.30, showing a mean drop of 5.8%. The correlation between ISQ-MBL reached strong statistical significance \((r = –0.58; P < .001)\). Nevertheless, it is important to note that the ligature-induced peri-implantitis applied in such study, courses with advance lesions. Therefore, as the ISQ value remained high, the usefulness of RFA in monitoring progressive bone loss remains debatable. Due to the gap of knowledge in clinical studies, the present systematic review could not address this question. Hence, this represents a promising research field to validate the use of RFA to monitor peri-implant bone loss.
CONCLUSIONS

Data suggest that primary stability leads to more efficient achievement of secondary stability. However, data are inconclusive concerning the effect of the degree of primary stability on implant survival and marginal bone loss. Furthermore, while insertion torque seems to influence positively on implant survival, high thresholds of insertion torque have demonstrated to have a detrimental effect on peri-implant marginal bone stability. The accuracy of the available methods and devices to assess implant stability remains to be answered.

DISCLAIMER

The authors have no direct financial interests with the products and instruments listed in the paper.

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**SUPPLEMENTARY INFORMATION**

![Galbraith graph on marginal bone loss.](image1)

![Funnel plot showing the dispersion of studies on marginal bone loss.](image2)

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**Table S1**  
Newcastle Ottawa Scale for Nonrandomized Clinical Trials

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<th>Comparability</th>
<th>Outcome/ Exposure</th>
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<td>★★</td>
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Inflammation and Osseointegration

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Peri-implant Mucosal Tissues and Inflammation: Clinical Implications

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Purpose: The purpose of this review was to explore the available literature and compile studies that discuss the relevance of the biofilm, onset and progression of disease, critical peri-implant pocket depth, frequency of supportive implant therapy, excess cement, and keratinized peri-implant tissues as related to peri-implant disease. Materials and Methods: PubMed, Cochrane Oral Health Group Specialized Trial Register, and hand searches of related journals were performed in relationship to the focused question. Reports describing techniques, preclinical studies, and case reports were excluded. Results: Due to the absence of controlled studies, a meta-analysis could not be performed. Summaries of relevant publications were completed for each topic area. Clinical recommendations were developed to provide guidance to the practitioner. Conclusion: The importance of proper diagnosis, planning, and clinical treatment cannot be overstated. Patient factors including systemic disease, periodontal status, and oral hygiene significantly impact peri-implant health. Clinician factors such as implant position, excess cement, and restorative design can contribute to development of peri-implant disease. Surveillance of implant status is essential and can be assisted by the assessment of risk factors, establishment of a proper recall program, and monitoring changes in bone and peri-implant pocket depths. Int J Oral Maxillofac Implants 2019;34(suppl):s25–s33. doi: 10.11607/jomi.19suppl.g2

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Over the past almost five decades, dental implants have been a predictable therapy to replace missing teeth. The field has also evolved to include more aggressive loading protocols, osseous augmentation of deficient bone areas, and modification of the implant designs. These, along with other factors, have led to an expansion in the number of implants placed and their more widespread use by both general practitioners and dental specialists. The importance of proper diagnosis, planning, and clinical treatment cannot be overstated. However, survival/success have been found to be affected by a number of risk factors resulting in peri-implant diseases. Peri-implant diseases have been characterized as a condition of the tissues around osseointegrated implants with signs of inflammation (bleeding and/or suppuration on probing) with or without loss of supporting bone.

Early on, Meffert (1992) described the ailing and failing implant.¹ The ailing implant had bone loss with pocketing but was static at maintenance visits, whereas the failing implant also demonstrated bone loss with pocketing but presented additionally with bleeding on probing, purulence, and continued bone loss despite therapy. Misch (1998) also utilized clinical parameters to assess implant health.² A continuum of health to disease was described with disease status related to a progressive worsening of clinical parameters...
such as probing depth, bone loss, and pain. Froum and Rosen (2012) established thresholds for clinical parameters as a basis for classification of peri-implantitis.\(^3\) Combinations of bleeding on probing and/or suppuration, probing depth, and radiographic bone loss were utilized to classify peri-implantitis into early, moderate, and advanced categories. Recently, a classification system based on etiology was proposed.\(^4\) Its results indicated that the majority of bone loss was related to biofilm, followed by iatrogenic factors, exogenous irritants, absence of keratinized tissue, and extrinsic pathology.

Although the literature denotes many risk factors associated with peri-implant diseases, the purpose of this review was to explore the available literature and compile studies that discuss the relevance of the biofilm, onset and progression of disease, critical peri-implant pocket depth, frequency of supportive implant therapy, excess cement, and keratinized peri-implant tissues as related to peri-implant disease.

**MATERIALS AND METHODS**

**Rationale**

This systematic review evaluated the relationship of various risk factors as they pertain to dental implant disease.

**Focused Question**

In patients with dental implants, what is the relationship of biofilm, onset and progression of disease, critical peri-implant pocket depth, frequency of supportive implant therapy, excess cement, and keratinized peri-implant tissues with peri-implant disease?

**Search Protocol**


**Selection Criteria**

Publications reporting mucositis of dental implants related to biofilm, keratinized peri-implant tissues, peri-implant pocket depth, frequency of recall, and residual cement were included in the analysis. Reports describing techniques were excluded.

**Data Collection and Analysis**

Due to the absence of controlled studies, a meta-analysis was not performed.

**Biofilm and Inflammatory Response to Peri-implant Disease**

The biofilm related to peri-implant diseases has not been extensively documented. The literature for peri-implant diseases follow those of gingivitis and periodontitis with regard to microflora and inflammatory response. As Loe et al (1965) induced an experimental gingivitis,\(^5\) several studies have described the response around dental implants.\(^6\text{-}9\) They indicate that the response to the cessation of oral hygiene around implants and its onset are similar to that around the natural teeth. The classic signs of inflammation—Gingival Index, bleeding on probing, and Plaque Index—were increased. Salvi et al (2012) also induced an experimental peri-implant mucositis and found similar results.\(^6\) However, the Gingival Index was higher around dental implants when compared to teeth. The authors postulated that the inflammatory response for dental implants is more severe than for the natural dentition. In addition, they found that with the reintroduction of oral hygiene measures, the soft tissues recovered to baseline values.\(^6\) Zitzmann et al (2001) evaluated the cellular response with an experimentally induced peri-implant mucositis with tissue biopsies.\(^7\) The response of T- and B-cells was similar to that around teeth. At 21 days, there was an increase in the volume of these lymphocytes. Lastly, host biomarkers including IL1-β, TNF-α, and TGF-β2 have been evaluated in the induced peri-implant mucositis model.\(^10\) Only IL-1β increased over the 3-week period in the gingival crevicular fluid. Following reinstatement of oral hygiene, IL1-β levels returned to baseline. In natural longstanding peri-implant mucositis lesions, sites that bled on probing and had some degree of redness and inflammation demonstrated on biopsy infiltrate in the connective tissue.\(^11\)

The biofilm conversion from peri-implant mucositis to peri-implantitis has been only documented with cross-sectional studies describing the characteristics of peri-implantitis. The microbiome of healthy and/or diseased implants have been compared.\(^12,13\) In general, species of the red complex such as *Porphyromonas gingivalis* and *Tannerella forsythia* have been found in diseased sites. Sanz-Martín et al (2017) studied healthy and diseased implants, illustrating that both states had a core microbiome, while health had taxa consistent with periodontal health and peri-implantitis had taxa consistent with periodontitis.\(^14\) In addition, the findings regarding peri-implantitis biofilm have shown species including *Synergistetes* and *Tannerella*. In a systematic review by Lafaurie et al (2017), peri-implantitis was an infection with a diversity of microorganisms including periodontal pathogens, anaerobic Gram-negative rods, and rarely, entric rods and *Staphylococcus aureus*.\(^15\) Overall, the majority of information
available indicates that a shift occurs from health to disease with regard to the biofilm. The biofilm associated with the diseased dental implant seems to be more pathogenic and somewhat like those in periodontitis.

Clinical Recommendations
- The clinician should be aware that a shift in the biofilm and inflammatory response occurs with the conversion of a healthy to diseased implant state. For example, with the deepening of a peri-implant pocket, the practitioner should consider additional measures to monitor and/or treat the failing implant.
- The biofilm associated with peri-implant disease may be similar to that in periodontitis. As a result, the susceptible periodontitis patient with dental implants should be carefully monitored.
- Given the inflammatory basis of peri-implant diseases, the surgical and restorative clinician should carefully consider the contour, function, and overall cleansability of the prosthesis throughout the planning process.

Time to Onset and Progression of Peri-implant Diseases
The development of peri-implant diseases seems dependent on many variables, such as oral hygiene, quality of tissue, and restoration type. However, unlike periodontitis, factors such as position of the implant within the edentulous ridge, implant surface texture, etc, impact the development of both mucositis and/or peri-implantitis. In addition, the pattern and rate of onset do not follow that of periodontal disease but may be influenced by the presence or history of periodontitis.

Studies involving experimentally induced peri-implantitis demonstrate clinical changes as in an induced gingivitis. The cessation of oral hygiene produced increases in plaque, Gingival Index, and bleeding. When oral hygiene was re instituted, clinical parameters recovered. The analysis of biologic responses to the induction of peri-implant mucositis indicates an upregulation of peri-implant crevicular fluid factors and the cellular response involving an increase in the proportions of T and B cells. Overall, these studies indicate that the clinical biologic response as well as timing of progression in the experimental induction of peri-implant mucositis collates with induced gingivitis.

In a retrospective review of dental radiographs, Fransson et al (2010) evaluated the onset and progression of bone loss. A total of 182 patients with 419 implants were assessed for bone loss and had a mean follow-up period of 11.1 years. Bone loss after the first year averaged 1.68 mm. Interestingly, 32% of the implants had bone loss of ≥ 2 mm, and 10% of those had bone loss ≥ 3 mm. Analysis indicated that progression was nonlinear and the rate decreased with time. Derks et al (2016) also found that the pattern of bone loss was nonlinear. A retrospective review of 105 implant dental radiographs indicated that the onset generally occurred within the first 3 years of function. However, compared to Fransson et al (2010), the amount of bone loss was greater with an average of 3.5 mm. Bone loss of more than 3 mm occurred in 51% of the sample. The authors postulated that the bone loss could be related to a prior history of periodontitis. In a shorter-duration study, Schwarz et al (2017) found that of 512 implants, a total of 262 were diagnosed with peri-implant disease. The majority of disease that occurred with implants was found between 12 and 48 months. After 48 months, the rate of disease was similar to that between 1 and 12 months. These results again indicate that peri-implant disease occurs early in the life of a functionally loaded implant. Recently, Sarmiento et al (2018) found that the timing of grafting influenced the rate of peri-implant disease. In a staged grafting procedure where the implant is placed following a healing period, the rate of peri-implant mucositis was 8.1% and the rate of peri-implantitis was 4.4%. However, when grafting occurred at the time of implant placement, the rate of peri-implant mucositis was 7.5% and the rate of peri-implantitis was 9.7%. In addition, the onset of mucositis preceded the statistical detection of radiographic bone loss.

Clinical Recommendations
- Although limited, studies indicate that the onset and the majority of peri-implant disease progressions occur in the life of a functionally loaded implant generally prior to 36 months.
- Since the onset and progression of peri-implant diseases seem not to follow patterns of periodontitis, the clinician should have an enhanced awareness of risk and should structure an individualized recall program for the patient.

Critical Peri-implant Pocket Depth
The establishment of the biologic width with implant healing has been well documented. Although the dimensions seem to vary when compared to the natural dentition, the formation of an epithelial and connective tissue attachment occurs. The healing results in the formation of a peri-implant sulcus. Several factors, such as surface characteristics, implant height above the bone level, platform switching, microgap, abutment size, etc, influence the final measurements. With the onset of peri-implant disease, these structures begin to change much in the same manner as with periodontitis. Gingival inflammation can increase the peri-implant sulcus and with loss of supporting bone, apical migration of the connective tissue and
epithelium occurs. The disease around an implant with bone loss then forms a deepened peri-implant pocket.

Healthy peri-implant mucosa can be altered by factors that progress to conditions of peri-implant mucositis and peri-implantitis. Although clinical assessment can differentiate between a state of health and disease, a critical implant pocket depth can assist in defining this transitional state. Derks et al (2016) described healthy peri-implant tissue by the absence of bleeding on probing, mucositis as presence of bleeding on probing ± suppuration without radiographic bone loss, and peri-implantitis as bleeding on probing ± suppuration and radiographic bone loss > 0.5 mm (45% of cases presented). The onset of disease occurred early, with the majority of peri-implantitis cases/implants occurring within 3 years of function. Schwarz et al (2018) measured peri-implant sulcus/pocket depth values of 1 to 3 mm and 4 to 6 mm for healthy and mucositis implants, respectively. Peri-implantitis implants only recorded pocket values in the 4- to 6-mm range. Schwarz et al (2017) noted that mucositis and peri-implantitis could present within 12 to 48 months after initial implant placement.

Recently, Monje et al (2018) evaluated 1,572 sites around 262 implants in 141 patients. The clinical parameters included the evaluation of pocket depth. In this cross-sectional matched case-control study, healthy implants had a mean pocket depth of 2.63 mm, mucositis-classified implants had a mean pocket depth of 3.26 mm, and peri-implantitis–diagnosed implants had a mean pocket depth of 4.58 mm. The authors concluded that pocket depth might accurately discern between diagnoses among peri-implant conditions. Similarly, Ramanauskaite et al (2018) evaluated 269 dental implants with several different clinical parameters including peri-implant pocket depth. A total of 77 dental implants diagnosed as healthy had a mean pocket depth of 2.95 mm. Peri-implant mucositis implants (n = 77) had a mean pocket depth of 3.10 mm, whereas peri-implantitis implants (n = 115) had a mean pocket depth of 4.91 mm. These differences in pocket depth between the three groups were significantly different.

Clinical Recommendations
- The documentation of dental implant health status is an important component of clinical care. During the treatment process, a baseline radiograph (at final prosthesis insertion) and clinical parameters (pocket depth, bleeding on probing, etc) should be recorded. The frequency of periodic documentation should be based on individual risk factors in order to assess changes in implant health over the life of the implant.
- The apparently healthy implant may still harbor an environment (biofilm, inflammation, etc) that could predispose the implant to convert to disease. Studies indicate that the clinician should be aware of the development of future markers for peri-implant disease and conditions including perfuse bleeding on probing, suppuration, bone loss, and critical implant pocket depth of ≥ 5 mm. This awareness includes but is not limited to continuing routine care, radiographic assessment, oral hygiene instruction, and shortened recall interval.

Frequency of Supportive Implant Therapy
According to contemporary studies, there is an estimated 43% prevalence of peri-implant mucositis and a 22% prevalence of peri-implantitis. A majority of this peri-implant disease may share a pathogenesis with periodontitis. Therefore, peri-implant maintenance seems to be critical to maintain the stability of the tissue around dental implants.

Despite the understanding of the importance of peri-implant maintenance, there have been no well-controlled investigations that refine the peri-implant recall interval; this is due to various definitions of diagnosis, unclear terminology, varying follow-up periods, and ethical considerations. Thus, most of the evidence of supportive implant therapy interval has been obtained from retrospective studies or reviews.

The prevalence rates of peri-implant diseases were evaluated in 89 patients. The patients were assigned to 3-month intervals during the first year after implant placement and later on 6-month intervals. Patients who did not participate in regular supportive implant therapy had an 11-fold higher chance of peri-implantitis than patients showing good compliance. On the contrary, patients who did not have regular supportive implant therapy were reported to have up to 48% of the prevalence of peri-implant mucositis during an observation period of 9 to 14 years. These studies have confirmed the essential role of supportive implant therapy to maintain tissue health and that the lack of supportive implant therapy will lead to a higher prevalence of the peri-implant disease.

A retrospective study done by Frisch et al (2015) evaluated the compliance and the frequency of the supportive post-implant therapy program and indicated a positive correlation between lower compliance and increased probing depth and higher plaque rate. The compliance rates were categorized into five different groups, from a 3-month interval to no compliance at all. The higher rates of patient compliance (86% to 94%) were observed during the first 3 years. A significant correlation was found between lower compliance and increased peri-implant probing depth. In addition,
higher plaque rates were found in individuals with lower compliance rates.

Dental implant patients may have a higher risk of peri-implant disease due to diabetes, poor oral hygiene, and smoking. A history of periodontitis seems to be the most documented risk for future peri-implant disease. Long-term studies done by Roccuzzo and coworkers evaluated the tissue around dental implants with supportive implant therapy for 10 years. The study found that in periodontally healthy patients there were no statistical differences in clinical parameters if subjects adhered to their supportive implant therapy or not. In contrast, the patients who had moderate to severe periodontal disease had higher plaque scores, bleeding scores during the supportive implant therapy, and eventually implant loss. In a systematic review, Monje et al (2016) analyzed 13 studies to evaluate the impact of supportive maintenance on the implant. This review successfully provides positive evidence of the patient with maintenance and concluded a minimum recall post-implant maintenance therapy of 5 to 6 months. However, the studies did indicate that the possibility of biologic complications might still occur and other risk factors should be appropriately considered.

In 2013, Aguirre-Zorzano et al stated that the prevalence of peri-implant inflammatory disease in periodontal patients who regularly undergo supportive implant therapy with a mean recall of 4 months is clinically significantly lower and the peri-implant disease could be even prevented. A similar result was found in a retrospective study by Costa et al (2012), which suggested that the simple fact of enrolling subjects for supportive implant therapy may reduce the risk of peri-implantitis from 43.9% to 18% at the patient level with maintenance at least once a year. These findings provide clinical evidence that the supportive implant therapy interval should be adjusted case by case, particularly in patients with a history of periodontitis.

**Clinical Recommendations**

- In general, a reasonable interval of supportive implant therapy is 5 to 6 months for a patient with low risk of peri-implant disease, but should this be evaluated case by case.
- When considering a patient with a history of risk, such as periodontal disease, it may be necessary to shorten the supportive implant therapy interval.
- During a supportive implant therapy appointment, reinforcement of oral hygiene, modification of factors such as smoking, and removal and cleaning of the prosthesis should be considered.

**Role of Excess Cement in Peri-implant Diseases**

Cemented restorations are commonly used to restore dental implants. It has been shown that excess cement left in the sulcus around implant-supported restorations can cause inflammation, ultimately leading to peri-implant disease. Cemented restorations offer several advantages, such as ease of prosthetic fabrication, reduced costs, increased framework passivity, and improved esthetics due to the absence of the buccal screw access hole. The main disadvantage of cement-retained restorations is the fact that cements are a flowable material that can spread unintentionally to the adjacent gingival tissues, making it difficult for the clinician to properly remove excess subgingival material. Therefore, caution on implant selection, placement, and prosthetic design should play a key role in the initial treatment plan. Although we aim for screw restoration as a primary election to restore a dental implant, it is not always feasible if angulation of the implant body is necessary.

A study published by Wilson (2009) demonstrated how the presence of peri-implantitis caused by dental cements was observed in 81% of cases. Korsch and Walther (2015) compared various types of cements and associated peri-implant disease. The authors found that the frequency of excess cement depended on cement type. For implants that used methacrylate cement, the frequency of excess cement was 62%, whereas the frequency of excess cement for zinc oxide-eugenol cement was 100%. Although several publications have documented different peri-implant complications, few have addressed the causative factor for the biologic breakdown. In a study published by Sarmiento et al (2016), the classification system based on etiologies included 5.5% of cases with peri-implantitis induced by an exogenous factor, eg, residual excess cement. Another retrospective study by Linkevicius et al (2013) concluded that patients with previous periodontal disease may also be more predisposed to peri-implantitis due to excess cement. Other studies have shown that the presence of suppuration around dental implants was greater on crowns that were cemented versus screw-retained. Many authors have shown different techniques to reduce excess cement complications. Linkevicius et al (2013) in a clinical study showed that dental radiographs should not be considered as a reliable method for cement excess evaluation. His results revealed that cement remnants were around 7.5% to 11.5% depending on the location of detection.
on the thickness of the cement, smaller pieces would remain unseen. They suggested placing margins supragingival for proper cement removal.

Challenges for the clinician on when to place a cement-retained restoration should not be based on material selection to achieve higher esthetics, but rather the criteria should be those unique to cementation technique and proper treatment planning. Therefore, avoiding cement-retained restorations in difficult-to-access areas should be recommended for clinicians with less experience.

Clinical Recommendations
• All attempts to reduce excess submarginal cement should be made through the use of screw-retained restorations or abutments designed to minimize the depth of the cement line in relation to the peri-implant tissue architecture. The cement line should be located with a minimal depth for ease of removal and to minimize submarginal excess cement.
• A final radiograph should be carried out routinely to assess unwanted cement beyond the gingival margin.
• Postoperative assessment is recommended within the first weeks post–crown insertion. This should allow immediate clinical detection of excess cement and avoid peri-implant tissue inflammation.

Role of Keratinized Tissue Surrounding Dental Implants
Peri-implant health has been defined both clinically and histologically. Peri-implant tissues surround an osseointegrated dental implant and can be divided into hard and soft tissue components. The hard tissue component forms a contact relationship to the implant surface, which contributes to implant stability. The soft tissue component is formed during the healing process following implant/prosthetic placement. The peri-implant tissues protect the bone that supports the implant. With the absence of healthy peri-implant tissues, the long-term implant success and survival becomes compromised and less predictable. However, if there is an insufficient amount of keratinized tissue around implants, is there an increased risk of peri-implant mucositis? If so, what types of modalities are appropriate to address a lack of keratinized tissue of the peri-implant tissues?

Does the Absence of Keratinized Tissue Influence Peri-implant Mucositis? Keratinized tissue or mucosa, which extends from the margin of the peri-implant mucosa to the mucogingival junction, is composed of fibrous connective tissue with fibroblasts; type I, III, IV, V, and VI collagen; and an orthokeratinized squamous epithelium. Keratinized gingiva has been defined as marginal and attached gingiva that excludes soft tissue of the interdental col region—interproximal gingival tissue between posterior teeth where epithelium is devoid of keratinization. One theory explaining the reduction of keratinized tissue is the post–tooth extraction natural loss of crestal bone. The buccal thickness of keratinized tissue is greater at the base of implants than at teeth (2.0 mm vs 1.1 mm, respectively). According to a new classification scheme for periodontal and peri-implant diseases and conditions, peri-implant mucositis is defined as an inflammatory lesion of the mucosa surrounding an endosseous implant without loss of supporting peri-implant bone. This is clinically determined by the presence of redness, swelling, bleeding on probing, and suppuration. The dimensions of peri-implant keratinized mucosa may be a risk indicator for peri-implant mucositis. The need for a minimum amount of keratinized tissue in order to maintain peri-implant tissue health has been a controversial issue. Some studies suggested that plaque accumulation that resulted in marginal inflammation was more frequent at implant sites with < 2 mm of keratinized tissue. However, several studies suggested that the lack of a minimum amount of keratinized tissue was not associated with mucosal inflammation.

A systematic review assessed seven cross-sectional and four longitudinal studies to determine if keratinized mucosa affected implant health, suggesting that a lack of adequate keratinized tissue around endosseous dental implants is associated with plaque accumulation, tissue inflammation, recession, and attachment loss. This supported a meta-analysis that indicated a statistically significant difference between plaque scores and modified Gingival Index in favor of sites with a wider dimension for keratinized tissue. The width of keratinized tissue at implant sites is another area of controversy. The association of keratinized mucosa width at implant sites was studied in a small group of patients 5 to 10 years retrospectively. Statistical analysis failed to indicate an association between keratinized tissue or the mobility of marginal mucosa around implant sites with plaque accumulation, bleeding on probing, or probing depth. Another longitudinal study of 339 implants measuring the amount of keratinized mucosa present over a period of at least 3 years showed a higher Gingival Index (0.9 vs 0.8) and modified Plaque Index (1.5 vs 1.3) in patients with keratinized tissue with < 2 mm and > 2 mm, respectively. A 5-year study involving 307 implants in edentulous mandibles with fixed implant-retained reconstructions assessed sites with < 2 mm and > 2 mm of keratinized tissue. The investigators reported higher plaque scores (0.7 vs 0.4) and bleeding on probing (0.2 vs 0.1) at lingual sites as well as
recession (0.7 vs 0.1) at buccal sites. Another study involving 15 patients with mandibular overdentures on four implants assessed the presence or absence of keratinized tissue on buccal aspects of implants, showing that 19 implants with at least 2 mm of keratinized mucosa had lower plaque (0.3 vs 0.6) and gingival indices (0.1 vs 0.6) than 17 implants without keratinized mucosa. It has been suggested that the evidence is equivocal regarding the effect of keratinized tissue on the long-term health of the peri-implant tissue. The notable advantages are the ease of plaque removal and patient comfort.

Does Grafting Help in the Management of Peri-implant Mucositis? Historically, scientific evidence reported that a lack of keratinized tissue was not critical to maintain peri-implant soft tissue health nor to result in more peri-implant diseases. However, based on current evidence, it has been suggested that an increased amount of keratinized tissue may better preserve both soft and hard tissue stability, resulting in a favorable long-term outcome for dental implants (as well as better oral hygiene maintenance over time). Also, an increased amount of keratinized tissue thickness may decrease the risk of recessions with immediate implants. Therefore, periodontal surgical procedures that augment soft tissue volume are recommended for esthetic and dimensional advantages following tooth extraction and implant therapy for both immediate and delayed placement.

Bleeding on probing was discussed in two studies with respect to grafting and nongrafting treatments after implant placement. According to a long-term study by Roccuzzo et al, there was an insignificant difference (23% and 27%) between groups with or without soft tissue grafting. However, in another study there was notable improvement from mean baseline values of 85% to 30% with autogenous soft tissue grafting compared with 40% to 95% to 25% to 95% without soft tissue grafting. In the same study, the mean Gingival Index shared a similar notable improvement comparing soft tissue grafting with no soft tissue grafting after follow-up periods of 6 to 12 months. Multiple studies indicated that there was a significant benefit to lower plaque values following surgical intervention when increasing keratinized tissue. Conversely, one study compared Plaque Index of treated and untreated groups over time and found no significant difference at baseline and at 12 months.

With regard to probing depth, there were no significant changes over time between the different treatment groups of apically positioned flap versus apically positioned flap plus free gingival graft in a meta-analysis. The mean probing depth values at baseline for soft tissue grafting, 1.97 to 3.09 mm, reduced to 2.08 to 3.18 mm after 6 to 12 months, while no soft tissue grafting ranged from 1.76 to 3.25 mm at baseline and 1.60 to 3.62 mm after 6 to 12 months. Comparing these final probing depth values favored the apically positioned flap plus autogenous tissue. In a clinical study of 30 patients with keratinized tissue of < 1 mm at implant sites, half of the patients underwent surgery to widen the band of keratinized mucosa. After 10 years, there was a significant difference in the gain of keratinized mucosa of 3.1 mm versus 0 mm in patients who underwent surgery and patients who did not, respectively. However, the Plaque Index, bleeding on probing, and presence of peri-implantitis was not different between both groups. Lastly, a meta-analysis assessing three different treatment modalities (autogenous, collagen matrix, and apically positioned flap) used for implant site maintenance with > 2 mm, < 2 mm, or no keratinized tissue resulted in statistically significant differences favoring apically positioned flap plus autogenous tissue in a period of 6 months.

Although there has been an increase of literature to support the use of soft tissue augmentation for keratinized tissue around peri-implant tissues, unfortunately there is a lack of data regarding clinical long-term outcomes associated with peri-implant soft tissue augmentation procedures.

Clinical Recommendations
• The removal of plaque around peri-implant tissues should be performed as part of a routine periodontal maintenance program to prevent the progression of peri-implant diseases and conditions.
• Soft tissue augmentation surgery should be performed around dental implants to provide stable keratinized tissue.

CONCLUSIONS
The importance of proper diagnosis, planning, and clinical treatment cannot be overstated. Patient factors including systemic disease, periodontal status, and oral hygiene significantly impact peri-implant health. Clinician factors such as implant position, excess cement, and restorative design can contribute to development of peri-implant disease. Surveillance of implant status is essential and can be assisted by assessment of risk factors, establishment of a proper recall program, and monitoring changes in bone and peri-implant pocket depths.

DISCLAIMER
The authors have no direct financial interests with the products and instruments listed in the paper.
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Systemic Health, Medications, and Osseointegration

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Since their development, dental implants have become one of the most common procedures to rehabilitate patients with single missing teeth or fully edentulous jaws. As implants become more mainstream, determining the factors that affect osseointegration is extremely important. Medical risk factors identified to negatively affect osseointegration include diabetes and osteoporosis. However, other systemic conditions and medications that interfere with wound healing have not been as widely investigated. The aim of this systematic review was to evaluate the effect of systemic disorders including diabetes and osteoporosis on implant osseointegration. The aim was also to evaluate the effect of other diseases, such as neurocognitive diseases, cardiovascular disease, human immunodeficiency virus (HIV), hypothyroidism, rheumatoid arthritis, and medications, such as selective serotonin reuptake inhibitors (SSRIs), proton pump inhibitors (PPIs), and antihypertensives. Although the literature does not demonstrate that diabetes negatively affects implant osseointegration, most studies focus on well-controlled diabetics and the use of prophylactic antibiotics. In addition, studies have shown increased long-term bone and soft tissue complications. For osteoporosis, recent studies and reviews also fail to demonstrate a lower osseointegration rate. However, caution must be exercised in these patients due to the risk for osteonecrosis of the jaws (ONJ), especially in patients with bone malignancies. There is also no direct evidence that patients with HIV, cardiovascular disease, neurologic disorders, hypothyroidism, or rheumatoid arthritis have a decreased rate of implant osseointegration. However, some preliminary evidence suggests that medications such as SSRIs or PPIs may have a negative effect on implant osseointegration. These studies are fairly recent and must be validated with continuous research. Moreover, disease control, concomitant medications, and other comorbidities complicate implant osseointegration and must guide our treatment approaches and clinical guidelines.
Osseointegration classically occurs after 3 to 6 months with machined or turned titanium implant surfaces; it may occur faster with enhanced or roughened surfaces. This improved osseointegration has sparked an increased use of dental implants, with early or immediate placement and loading, and implants in patients with medical risk factors. However, studies have been unclear and conflicting in terms of osseointegration or short-term survival between healthy and medically compromised patients. Many studies have identified specific medical conditions such as diabetes mellitus and osteoporosis as negative factors for both osseointegration and long-term implant survival. As such, these long-term studies do not examine whether initial osseointegration was affected by systemic diseases.

Diabetes mellitus (DM) is a chronic metabolic disorder that can present in two forms. Patients who suffer from type 1 DM have an autoimmune disorder where their body cannot produce insulin; as such, these individuals must take exogenous insulin to control their blood sugar. Type 2 DM is a multifactorial disease, where a combination of genetics and environment deem the pancreas unable to produce insulin and lead the body to become insulin resistant. In both conditions, chronic high levels of circulating glucose lead to more severe complications, which affect numerous organ systems, including the oral cavity. This condition has classically been associated with an increased risk of dental implant failure, with numerous studies suggesting poor osseous healing in times of hyperglycemia. Indeed, diabetics suffer from increased incidence of periodontitis and gingivitis, and are more subject to dental infections. Despite the lack of clinical evidence, these associations are made and may often limit patient treatment, especially since some previous studies have demonstrated increased short-term implant failure in diabetic patients or increased time required for osseointegration.

Osteoporosis is a musculoskeletal disease of reduced bone mass, low bone mineral density with a T-score ≤ −2.5 standard deviations of lumbar spine (L1-L4) and femoral neck, and susceptibility to bone fractures. Although the diagnosis of osteoporosis includes decreased cortical bone and thin trabecular bone with increased trabecular spacing in the axial and appendicular skeleton, correlation with decreased bone mineral density or thin trabecular and cortical bone in the maxilla and mandible has not been consistent. Moreover, the relationship between systemic bone density and metabolism is not well understood. Indeed, patients with systemic osteoporosis are often seeking dental implant therapy, and studies have suggested an increased failure in those patients, especially in the maxilla. In fact, type IV bone with decreased cortical and increased trabecular bone has been associated with higher implant failure. However, more recently, as enhanced implant surfaces are utilized almost exclusively, osseointegration and long-term peri-implant bone maintenance is favorable in osteoporotic patients.

As more of our implant patients have significant medical problems and take medications that may affect wound healing and bone metabolism, we must be able to evaluate the literature in a systematic way where results can be combined to maximize the information currently available. Therefore, the aim of this systematic review was to evaluate the effect of systemic disorders, including diabetes and osteoporosis, on implant osseointegration. Also evaluated were the effect of neurocognitive diseases, cardiovascular disease, human immunodeficiency virus (HIV), hypothyroidism, and rheumatoid arthritis (RA), as well as medications such as selective serotonin reuptake inhibitors (SSRIs), proton pump inhibitors (PPIs), and antihypertensives.

**MATERIALS AND METHODS**

**Study Selection and Inclusion Criteria**

The focused question was developed following the PICO format (Population: patients with osteoporosis or diabetes, or patients taking systemic medications; Intervention: dental implant therapy; Comparison: healthy patients; Outcome: osseointegration) to evaluate the effect of systemic health conditions and medications on implant osseointegration. Inclusion criteria were determined by the authors before the beginning of the study: human or clinical studies with at least 10 patients, publication in the English literature, a follow-up time of ≥ 3 months to assess implant osseointegration, and defined specific medical problems with data on implant survival (surrogate marker of osseointegration). Studies were excluded if they were animal or in vitro studies, case reports, or small case series; if they lacked specific information on implant survival or osseointegration, specific numbers of patients with systemic illness or medication, or specific numbers of patients and/or implant survival; or were published in non–English-language journals (Table 1).

**Search Strategy**

For this systematic review, PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were utilized. A PubMed electronic search was performed to identify potential articles from 1975 to July 2018 utilizing the keywords of different combinations: “dental implants” and “osteoporosis,” “bisphosphonates,” “diabetes,” “parkinson’s disease or
neurocognitive disease, “rheumatoid arthritis,” “cardiovascular disease or hypertension or coronary artery disease,” “hypothyroidism,” “human immunodeficiency virus or acquired deficiency syndrome,” “depression,” “anti-hypertensive or diuretics or beta-blockers,” “serotonin reuptake inhibitors,” “proton pump inhibitors,” or “thyroid.” In addition to the online search, hand search was performed in specific journals, including The International Journal of Oral and Maxillofacial Implants; Clinical Oral Implants Research; Journal of Oral and Maxillofacial Surgery; International Journal of Oral and Maxillofacial Surgery; Clinical Implant Dentistry and Related Research; Implant Dentistry; Journal of Periodontology; Journal of Clinical Periodontology; and Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics. Titles were screened by two independent investigators (TLA and JPA), and any disagreements between the two authors were resolved by all four clinicians of this review.

Statistical Analysis

For the meta-analysis, forest plots were constructed using the proportion of implants healed for both the diabetic cohort as well as the osteoporotic cohort (which was then stratified by medication usage). Heterogeneity was assessed using the Cochran’s Q statistic and $I^2$ index (the percentage of variation across studies that is due to heterogeneity rather than chance). Since significant heterogeneity was observed, the authors elected to use the random effects meta-analytical model as opposed to the fixed effects pooled estimate. Statistical analyses were performed using R V3.5.1 (www.r-project.org) utilizing the ‘meta’ package. $P$ values < .05 were considered statistically significant.

RESULTS

The analysis of studies for patients with osteoporosis revealed a total of 408 studies, with 21 studies remaining for analysis after further assessment (Fig 1). Four studies were included for osteoporotic patients not on antiresorptive medications (Table 2), and 17 studies were included for patients taking antiresorptives (Table 3). For osteoporotic patients, the pooled estimate for implant survival rate from the meta-analysis was 98% (with a 95% confidence interval [CI] of 96%–99%) (Fig 2). No differences in osseointegration were observed in patients with or without osteoporosis, regardless of antiresorptive therapy.

For analysis of osseointegration in diabetic patients, a total of 360 studies were identified, with an additional 11 studies also identified. After exclusion and inclusion criteria were assessed, 20 studies remained (Fig 3). Of the 20 studies, 5 were retrospective, 5 were case-control studies, and 10 were prospective studies (Table 4). For diabetic patients, the pooled estimate for implant survival rate from the meta-analysis was 98% (with a 95% CI of 96%–99%) (Fig 4). No differences were observed in osseointegration rates in diabetic vs non-diabetic patients.
There were an inadequate number of studies to conduct a meta-analysis for patients with neurologic disorders, HIV, cardiovascular disease, RA, selective serotonin receptor inhibitors, or PPIs. However, evaluation of implant survival was performed from available studies. Only one study that was not a case report was available on patients with neurologic disorders. Of the 27 patients with 70 implants in this study, the implant survival rate was 86%.45 Although few studies are available on patients with HIV, two studies demonstrated only 1 implant lost out of 135, for a 99.2% survival rate compared to 100% survival in HIV-negative patients46,47.

For patients with cardiovascular disease, no differences were found in implant survival rate as compared to controls, where one study demonstrated 97.8% vs 100%42 and another demonstrated 87.3% vs 87%.48 In 56 patients with RA, high survival rates between 96.1% to 100% were achieved in 215 implants from two retrospective studies.49,50 For hypothyroidism, two studies were found that demonstrated similar implant survival between healthy and disease patients.51,52

In addition to systemic diseases, certain medications known to affect bone formation and remodeling were evaluated. The use of antihypertensive medications for cardiovascular disease was associated with increased implant survival of 99.4% vs 95.9% in patients not taking these medications.53 In contrast, patients taking SSRIs demonstrated a lower implant survival rate of 89.4% to 94.4% vs 95.4% to 98.15% in control patients, respectively.53,54 Similarly, patients taking PPIs had a decreased implant survival rate of 88% to 93.2% vs 95.5% to 96.8% in PPI naïve patients, respectively.53,55
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DISCUSSION

Dental implants are a first-line therapy to replace single and multiple missing teeth, with many studies documenting short- and long-term survival rates above 95%. As implants become more successful, patients with systemic medical problems are seeking treatment with increased frequency. Although health conditions and medications are known to affect general wound

**Fig 2** (Above) Forest plot of implant survival rate for osteoporotic patients.

**Fig 3** (Right) Search strategy for diabetes articles. Flowchart depicting articles identified, screened, and included in qualitative and quantitative analysis.
healing, compromise the immune system, decrease vascularity, and inhibit bone remodeling, the direct effect on implant osseointegration is not well understood, or well-studied. The focus of this review was to evaluate the available literature for evidence of systemic health conditions and medications that affect implant osseointegration. Even though the search identified studies on osteoporosis, diabetes, neurocognitive diseases, cardiovascular disease, HIV, RA, and hypothyroidism, and medications such as SSRIs, PPIs, and antihypertensives, only diabetes and osteoporosis had enough data to support a systematic review.

As previous studies have identified both diabetes and osteoporosis to have a negative effect on implant survival, more recent papers have failed to confirm these initial findings. Whether it is due to newer enhanced implant surfaces, improved disease control, or some other external factors, implants in patients with diabetes or osteoporosis appear to be a safe and effective treatment option. One caveat in diabetic studies is disease control, where poorly controlled diabetics were either excluded or lacked adequate subject numbers to draw definitive conclusions from most studies. In addition, even though initial implant osseointegration is achieved between 3 and 6 months, long-term survival or success may still be compromised in diabetic patients, with an increased incidence of peri-implantitis.

Dental implant failures, classically defined as early or late, can occur due to a variety of reasons. Early failures generally occur when implants fail to osseointegrate, often due to infection; late failures occur following loading and can be due to a variety of different factors, including retained cement, occlusal loading, and peri-implantitis. While studies identified in this review were often long-term studies, data for osseointegration status at loading was available and utilized for analysis. Consequently, many studies reported late failures 1 to 2 years following placement, after the implant was restored with a dental prosthesis.

### Diabetes

Diabetes, a systemic metabolic disorder, is characterized by high blood glucose levels. In chronic states, pro-inflammatory cytokines and mediators, such as TNF-alpha and IL-6, become locally increased and can reduce osteoblast-osteoclast coupling, two vital cell types needed for implant osseointegration. Similarly, diabetes affects the ratio of receptor activator

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**Table 4  Studies on Implants in Diabetic Patients Included in the Analysis**

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Design</th>
<th>Type of diabetes</th>
<th>Diabetic patients</th>
<th>No. of implants</th>
<th>% Osseointegrated</th>
<th>Control group</th>
<th>No. of implants</th>
<th>% Osseointegrated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkylilmaz115 (2010)</td>
<td>RS</td>
<td>WC</td>
<td>23</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Erdogan et al116 (2015)</td>
<td>PS</td>
<td>WC</td>
<td>22</td>
<td>100</td>
<td>21</td>
<td>100</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dowell et al63 (2007)</td>
<td>CC</td>
<td>Varying levels of control</td>
<td>39</td>
<td>100</td>
<td>11</td>
<td>100</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Eskow and Oates57 (2017)</td>
<td>PS</td>
<td>PC</td>
<td>70</td>
<td>98.6</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Oates et al117 (2014)</td>
<td>CC</td>
<td>Varying levels of control</td>
<td>134</td>
<td>99.2</td>
<td>100</td>
<td>99</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Aguilar-Salvatierra et al118 (2016)</td>
<td>PS</td>
<td>Varying levels of control</td>
<td>52</td>
<td>98.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Farzad et al119 (2002)</td>
<td>RS</td>
<td>WC</td>
<td>136</td>
<td>96.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Al Amri et al120 (2017)</td>
<td>PS</td>
<td>WC</td>
<td>108</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cabrera Domínguez et al121 (2017)</td>
<td>PS</td>
<td>WC</td>
<td>15</td>
<td>100</td>
<td>15</td>
<td>100</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Khandelwal et al122 (2013)</td>
<td>PS</td>
<td>WC</td>
<td>48</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Peled et al123 (2003)</td>
<td>PS</td>
<td>WC</td>
<td>141</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Abdulwassie and Dhanrajani124 (2002)</td>
<td>PS</td>
<td>WC</td>
<td>113</td>
<td>95.6</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Morris et al125 (2000)</td>
<td>RS</td>
<td>WC</td>
<td>255</td>
<td>92.2</td>
<td>2,632</td>
<td>93.2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Olson et al126 (2000)</td>
<td>PS</td>
<td>WC</td>
<td>178</td>
<td>93.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fiorellini et al127 (2000)</td>
<td>RS</td>
<td>WC</td>
<td>215</td>
<td>88.8</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kapur et al128 (1998)</td>
<td>PS</td>
<td>WC</td>
<td>104</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anner et al129 (2010)</td>
<td>RS</td>
<td>WC</td>
<td>177</td>
<td>97.2</td>
<td>1,449</td>
<td>95</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ghiraldini et al130 (2016)</td>
<td>CC</td>
<td>WC</td>
<td>31</td>
<td>100</td>
<td>19</td>
<td>100</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Tawil et al131 (2008)</td>
<td>CC</td>
<td>WC</td>
<td>255</td>
<td>97.6</td>
<td>244</td>
<td>99.6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gómez-Moreno et al132 (2015)</td>
<td>CC</td>
<td>WC</td>
<td>46</td>
<td>100</td>
<td>21</td>
<td>100</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

PS = prospective study; RS = retrospective study; CC = case-control study; PC = poorly controlled; WC = well-controlled.
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of nuclear factor kappa-B ligand (RANKL) and osteoprotegrin (OPG), master regulators of osteoclast function. In times of hyperglycemia, this ratio is disrupted and favors increased bone resorption. Finally, these patients are more susceptible to both systemic and localized infections, and thus are at a risk for osseointegration failure due to infection. Altogether, these changes could be a reason for a potential increase in implant failure in diabetic patients.

Importantly, diabetic control is evaluated by measuring the levels of glycosylated hemoglobin, hemoglobin A1c (HbA1c). Indeed, dental precautions exist for patients with uncontrolled diabetes, and most practitioners limit their placement of dental implants, as well as elective surgical procedures, in patients with uncontrolled diabetes. As such, a majority of studies identified included patients with controlled diabetes (HbA1c < 8). Only two studies were identified comparing implant survival in patients with different levels of HbA1c. One study investigated osseointegration rates in patients with uncontrolled diabetes and found no differences in patients with high or low HbA1c. Another study that included 23 patients with HbA1c from 6 to 13.9 who had a total of 70 implants placed found no difference in osseointegration among groups. In both studies, implant survival rates were comparable, with no statistical differences among groups. However, with low sample sizes, it is difficult to formulate definite conclusions for implants in patients with poorly controlled diabetes.

Indeed, systematic reviews have been conducted for diabetes and dental implant therapy with varied conclusions. One review states that implant osseointegration is delayed in diabetic patients based on two separate reports that investigate resonance frequency analysis (RFA) values during the osseointegration period. In these studies, RFA values are lower in diabetic patients, and patients with poor glycemic control led to delays in implant stabilization. However, survival rates in one study are unreported; in the other, successful osseointegration is reported at 99.2% in diabetic patients and 99% in non-diabetic patients. While there may be a delayed healing process in diabetics, successful osseointegration seems to be achieved. These results are supported by long-term implant survival where no difference in implant survival is noted. However, when evaluating bone changes, both studies report significantly higher marginal bone loss in patients with diabetes.
In the present review, osseointegration was measured at the time of definitive loading, which was at least 3 months after surgical implant placement. In the studies included, no differences were observed between implant osseointegration at 3 months in diabetic and non-diabetic patients. While a vast majority of studies included patients with controlled diabetes, two studies were found that directly compared healthy patients and diabetic patients with both poorly controlled and well-controlled disease. Osseointegration rates in all groups were similar, with no statistically significant differences. In fact, implant survival rates were 97% (95% CI: 94%–98%) in diabetic patients. Although these results are encouraging for osseointegration and short-term implant survival, marginal bone loss and long-term implant success may be affected by diabetic status; this highlights the need to closely follow these patients for maintenance and potential complications.

### Osteoporosis

Since osteoporosis is a disease of decreased bone mass, increased bone fragility, and susceptibility to fracture, the thin cortical bone and increased trabecular spacing is thought to contribute to higher implant failure. This has been shown in previous studies of postmenopausal women on hormone replacement therapy, especially in the less dense maxillary (type IV) bone.\(^ {14,34} \) However, a recent systematic review of 10 studies where both osteoporotic and non-osteoporotic patients were compared (702 implants in 188 osteoporotic patients and 4,114 implants in 348 healthy patients), failure rates were similar, with 4.70% vs 3.57% at the implant level and 5.85% vs 4.89% at the patient level, respectively (\( P > .05 \)).\(^ {33} \) Similarly, our meta-analysis revealed a 97% implant survival rate (95% CI: 94%–98%) in osteoporotic patients.

Osteoporosis therapy most commonly includes an antiresorptive medication such as a bisphosphonate (BP) or denosumab (Dmb). Both BPs and Dmb inhibit osteoclast differentiation and function, leading to reduced bone resorption and remodeling.\(^ {64,65} \) Since millions of prescriptions for antiresorptives are written for osteoporosis, patients and clinicians are concerned about how these medications affect implant osseointegration. Although most studies have failed to show a new effect on implant osseointegration or survival after BP therapy, osteonecrosis of the jaw (ONJ) and alveolar bone loss have been reported after dental implant placement.\(^ {66–74} \) Moreover, patients with previously osseointegrated implants can develop ONJ after antiresorptive therapy is initiated.\(^ {75} \) With the potentially devastating consequences of ONJ, accepted treatment guidelines should be followed, including avoiding elective placement of dental implants in patients on antiresorptive medications for malignancies, and utilizing a prophylactic antibiotic

### Human Immunodeficiency Virus

The life expectancy of people living with HIV has significantly improved over the past two decades. Many people who are HIV-positive now live much longer, healthier lives. In fact, the most common causes of illness and death in people living with HIV are now similar to those of non-HIV patients. They include heart disease, kidney disease, liver disease, diabetes, depression, and cancer. The development of highly active antiretroviral therapy (HAART) in the mid 1990s has not only drastically reduced the mortality rates of HIV-positive patients, but also lessened patient morbidity and transmission of the disease. Nonetheless, there is a positive correlation between HIV-positive individuals and bone metabolic alterations. Reasons for this are low calcium/vitamin D intake, low testosterone, alcohol and opiate abuse, smoking, depression, physical inactivity, and HAART.\(^ {77} \) To date, there is little evidence of the effect of HIV, and more specifically HAART therapy, on osseointegration and long-term success and survival of dental implants. In a pilot study, Oliveira and coworkers\(^ {47} \) aimed to determine the success rate of dental implants placed in patients who were positive for HIV and were receiving different regimens of HAART. The authors assessed the peri-implant health of 59 implants 6 and 12 months after loading. They analyzed success in relation to CD4+ cell counts, viral load, and baseline pyridinoline and deoxypyridinoline values. Finding the higher baseline levels of pyridinoline and deoxypyridinoline in HIV-positive participants did not interfere with osseointegration after 12 months of follow-up, they concluded that the placement of dental implants in HIV-positive patients is a reasonable treatment option, regardless of CD4+ cell count, viral load levels, and type of antiretroviral therapy. In a systematic review, Ata-Ali and colleagues\(^ {78} \) analyzed the impact of HIV infection on dental implant osseointegration. Nine studies finally met the inclusion criteria and were selected for inclusion in the systematic review. A total of 173 dental implants were placed in 80 patients (135 implants in 56 HIV-positive and 38 implants in 24 HIV-negative patients), and a single loss of dental implant osseointegration was recorded in one HIV-positive patient. The results of the systematic review suggested that dental implant placement in HIV-positive patients did not increase dental implant failure. Nonetheless, the authors concluded that prophylactic antibiotic
treatment, the administration of highly active antiretroviral therapy, and control of the CD4+ T lymphocyte counts were key in the successful treatment of these groups of patients.

Cardiovascular Disease and Antihypertensive Medications

According to the Centers for Disease Control and Prevention, about 610,000 people die of cardiovascular disease in the United States every year, or one in every four deaths. In fact, heart disease is the leading cause of death for both men and women, and coronary heart disease is the most common type, killing over 370,000 people annually.5 Of the different forms of cardiovascular disease, hypertension, atherosclerosis, vascular stenosis, coronary artery disease, and congestive heart failure seem to have the most direct effect on peripheral blood supply. These manifestations translate into lack of oxygen supply to local tissues, decreasing fibroblast activity, collagen synthesis, capillary growth, and macrophage activity.79 It would therefore be expected to have a direct influence on the process of bone healing and osseointegration following dental implant surgery. In a retrospective analysis of 246 consecutively treated patients, Khadivi et al.48 analyzed the relationship between cardiovascular disease and risk for implant failure. The patients comprised a cardiovascular disease interest group of 39 patients and control subgroups of 98 healthy and 109 patients with a history of other systemic disease. Differences in implant failure rates between the groups were not found to be statistically significant. Though the sample size was small, the authors concluded that cardiovascular disease may not be a risk factor for successful osseointegration. In a retrospective study analyzing nearly 7,000 implants, Alsaadi and coworkers analyzed the impact of local and systemic factors on the incidence of oral implant failures, up to abutment connection.42 They concluded that certain factors, such as cardiac diseases, coagulation problems, hypertension, or hypercholesterolemia, did not lead to an increased incidence of early failures. In a review paper by Diz and coworkers,80 the success and survival rates of dental implants were observed in medically compromised patients. The authors could find no evidence of cardiac disorders as contraindications to dental implants. The authors highlighted the importance of considering other issues, such as the occurrence of bleeding or cardiac ischemic events during surgery, and recommended that consultation with a cardiologist be arranged prior to surgery. When considering the favorable effect of antihypertensive drugs on bone formation and remodeling and decreased risk of bone fractures, the possible positive effect on dental implant osseointegration is intriguing. A recent retrospective cohort study with 1,499 implants in 728 patients (327 implants in 142 patients taking antihypertensive medications and 1,172 implants in 586 healthy patients) demonstrated a lower implant failure rate (0.6%) in medicated patients vs 4.1% failure in healthy patients.53

Neurologic Disorders

According to the American Neurological Association, neurologic diseases impact an estimated 100 million Americans every year. The most common neurologic diseases cost the United States $789 billion in 2014, and this figure is projected to grow, as the elderly population is estimated to double by 2050. Historically, patients suffering from neurologic diseases have been excluded from receiving dental implants. The main reason for the exclusion has been the association with poor access to oral health care, poor oral hygiene, oral parafunctions such as bruxism, harmful habits, and behavioral problems. Treatment of edentulism with removable dentures may present a challenge for these patients due to the aforementioned reasons. Edentulism can lead to deficient nutritional intake, dietary enjoyment, self-esteem, social interaction, and social acceptability. These problems are likely to aggravate existing difficulties during eating and swallowing.

Modern technology and advances in medicine have allowed for vast improvements in patient care and quality of life, including patients suffering from neurologic disorders. Advances in pain and symptom management, access to hospice and assisted care, and emotional and spiritual assistance have allowed these patients to regain a sense of normalcy. This improvement in patients’ psychological and social well-being has been a decisive factor in the reintroduction of dental implants, allowing them to function in a similar manner to their natural teeth. Unfortunately, there is little evidence to support the use of dental implants in patients affected by neurologic disorders. Two reports evaluated the use of osseointegrated dental implants in patients with Parkinson’s disease. In the first one, Chu et al describe the use of a magnetic attachment system in an implant-supported mandibular overdenture for an edentulous patient.81 After the implant osseointegrated, the patient was followed during a 12-month maintenance period. The authors recorded looseness of one magnet on one occasion. This did not recur after retightening. The patient was satisfied with the functional improvement achieved by the prostheses, and family members noted an improvement in the patient’s selection of foods. Heckmann et al described a follow-up period of up to 42 months on three patients rehabilitated with implant-assisted mandibular overdentures retained by non-rigid telescopic attachments.82 No implants were lost during...
their observation period, and the patients reported remarkable improvement in their chewing ability. Both studies agreed that dental implants appear to be a useful adjunctive treatment in edentulous Parkinson’s disease patients and may be considered for patients with diseases similarly affecting motor skills.

In a prospective study, Ekfeldt et al evaluated the medium- to long-term outcome of dental implant therapy in patients with neurologic disabilities. Twenty-seven patients with different disabilities and in need of prosthodontic treatment were treated with various implant-supported prostheses. Altogether, 88 threaded titanium implants were placed, of which 70 were available for examination at the final follow-up. A total of 12 implants (14%) were lost, 3 before loading and 9 after insertion of the implant-supported fixed prostheses. The cumulative survival rate for implants placed was 85.8% after 10 years. Peri-implant mucositis was diagnosed in 10 patients and for 14 of the 70 implants. Three of the 15 patients with measurable radiographs and 4 implants were diagnosed with peri-implantitis. The studies also looked at prosthetic aspects of the treatment. Prosthetic complications occurred, from minor and easily correctable to more severe and requiring retreatment. Nonetheless, the authors concluded that implant therapy can be a valid option for the rehabilitation of patients with neurologic disabilities.

Hypothyroidism

Hypothyroidism is a common endocrine disorder, with an increased prevalence in women and in advanced age. Since most organs have receptors for thyroid hormone, its deficiency interferes with many of the body’s metabolic processes. In addition to regulating temperature, generalized energy, metabolism, skin moisture, gastrointestinal motility, muscle metabolism, mental and memory ability, libido, and menstrual cycle, thyroid hormone affects bone metabolism. Thyroid hormone helps maintain adult bone mass and stimulates production of insulin-like growth factor-1 (IGF-1), which increases osteoblast formation and differentiation, and bone remodeling. Specifically for bone metabolism, hypothyroidism has been associated with delayed bone regeneration, increased fracture risk, and delayed fracture repair. Treatment for hypothyroidism, including long-term levothyroxine, has also been associated with increased risk for osteoporosis and delayed fracture recovery in animal studies, making the condition and its therapy a cause for concern in patients seeking dental implants. Studies that have investigated implant survival in patients with hypothyroidism did not demonstrate a significantly higher rate of implant failures as compared to control patients.

Rheumatoid Arthritis

RA is an autoimmune disease in which the body’s immune system creates inflammation that causes the synovium to thicken, resulting in edema and pain in and around the joints, eventually affecting the bone itself. RA is frequently accompanied by osteoporosis as a result of increased systemic bone turnover and anti-inflammatory and/or combined anti-immune treatment regimens. Approximately 1.5 million people in the United States have RA and nearly three times as many women as men have the disease. Although the cause of RA is not yet fully understood, there is evidence that genetics, hormones, and environmental factors are involved in the process. Researchers have shown that people with a specific HLA shared epitope have a fivefold greater chance of developing RA than those without the marker. Other genes connected to RA include: STAT4, a gene that plays important roles in the regulation and activation of the immune system; TRAF1 and C5, two genes relevant to chronic inflammation; and PTPN22, a gene associated with both the development and progression of RA. Researchers continue to investigate other factors that may play a role. Some include exposure to cigarette smoke, air pollution, insecticides, and occupational exposures to mineral oil and silica. It is well known that patients with RA with or without concomitant corticosteroid treatment will develop localized osteopenia and generalized osteoporosis in 30% to 50% of all cases. Despite this, there is little evidence on the effect of RA on osseointegration and dental implant outcomes.

In a case series, Weinlander et al evaluated implant and prosthodontic treatment outcomes of patients suffering from rheumatic disorders such as RA and connective tissue diseases (CTDs). Overall, 89 implants were inserted for rehabilitations such as single-tooth replacement (n = 8), fixed partial dentures (n = 14), complete dentures (n = 5), and overdentures (n = 2). The mean evaluation period was 42.6 months. The evaluation focused on the cumulative implant survival and success rates and peri-implant conditions, as well as incidence and type of prostodontic complications. The authors reported a high implant survival rate during follow-up, with a cumulative 3-year implant success rate of 96.1%. Patients with RA demonstrated acceptable marginal bone resorption (mean: 2.1 ± 0.5 mm) and good soft tissue conditions, while CTD patients showed increased bone resorption (mean: 3.1 ± 0.7 mm). This was especially noted in scleroderma patients, as were major peri-implant soft tissue alterations (Bleeding Index) in patients suffering from Sjogren’s syndrome. The authors concluded that a high implant and prosthodontic success rate can be anticipated, even for patients suffering from autoimmune rheumatic disorders such as RA and CTDs.
Nonetheless, the authors also encourage a rigorous maintenance program, including optimal oral hygiene, to assist in ensuring stable long-term results for CTD patients with more vulnerable soft tissue conditions. These results were confirmed in another study of 34 patients with RA, demonstrating 100% implant survival and 93.8% success after 3.5 years, which was similar even in the presence of concomitant connective tissue disease. However, peri-implant soft tissue alterations and some bone resorption were seen in patients with combined RA and CTDs.50

**Selective Serotonin Reuptake Inhibitors**

Introduced in 1988, SSRIs are the most commonly prescribed antidepressants, increasing levels of serotonin in the brain. They accomplish that by blocking the re-absorption (reuptake) of serotonin in the brain, making more serotonin available. They act by preventing the reuptake of 5-hydroxytryptamine (5-HT) (serotonin) through the inhibition of the 5-HT transporter (5-HTT) located on the presynaptic neuron, thereby increasing levels of 5-HT within the synaptic cleft and modulating neurochemical signaling, releasing 5-HT directly.

SSRIs have a broad range of indications, including depression, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, social anxiety disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, and bulimia nervosa.92 Recent investigations have also shown a wider role for the SSRIs, as 5-HT plays an active role in numerous pathways including that of bone metabolism.93 Osteoblasts and osteoclasts express 5-HT receptors and can be exposed to 5-HT via autocrine, paracrine, and endocrine pathways. Clinical studies have shown a relationship between the use of SSRIs, reduced bone mineral density, and an increased risk of bone fracture.94–96 Despite the mounting evidence of the effect of SSRIs on bone and bone metabolism, little evidence exists of their effect on the process of osseointegration and ultimately, dental implant outcomes.

In a retrospective cohort study conducted by Wu et al, 94 implants placed in 51 patients using SSRIs were evaluated to estimate the risk of failure associated with the use of SSRIs.97 After 3 to 67 months of follow-up, 10 implants failed and 84 survived in the SSRI-users group. SSRI usage was associated with an increased risk of dental implant failure (hazard ratio, 6.28; 95% CI = 1.25–31.61; \( P = .03 \)). The failure rates were 4.6% for SSRI nonusers and 10.6% for SSRI users. Their findings indicated that treatment with SSRIs was associated with an increased failure risk of osseointegrated implants, and they went on to suggest a careful surgical treatment planning for SSRI users.

Altay and coworkers conducted a retrospective cohort study to investigate the association between systemic intake of SSRIs and failure of osseointegration in patients rehabilitated with dental implants.98 A total of 2,055 osseointegrated dental implants in 631 patients (109 implants in 36 SSRI users and 1,946 in 595 nonusers) were evaluated. Median duration of follow-up was 21.5 (range, 4–56) months for SSRI users and 23 (range, 3–60) months for nonusers (\( P = .158 \)). The failure rate was 5.6% for the SSRI users and 1.85% for the nonusers. The difference between the two groups failed to reach statistical significance at patient and implant levels (\( P = .166 \) and \( P = .149 \), respectively). The odds of implant failure were 3.123 times greater for SSRI users compared to nonusers. Patients using SSRIs were found to be 3.005 times more likely to experience early implant failure than nonusers. The results of this study suggested that SSRIs may lead to an increase in the rate of osseointegration failure, although not reaching statistical significance.

**Proton Pump Inhibitors**

PPIs are among the most commonly used drugs in the world. About 15 million people in the United States use PPIs every year. They are used for the prevention and treatment of acid-related conditions such as esophageal, duodenal, and stomach ulcers; NSAID-associated ulcer; gastroesophageal reflux disease (GERD); and Zollinger-Ellison syndrome. They also are used in combination with antibiotics for eradicating Helicobacter pylori, a bacterium that together with acid causes ulcers of the stomach and duodenum. Chronic use of PPIs could have potential detrimental effects, mainly due to the effect of chronic acid suppression on the absorption of vitamins and nutrients. Gastric acid secretion can affect the absorption of a number of nutrients, drugs, and vitamins, particularly Vitamin B12, iron, calcium, and magnesium. Recent studies showed a possible association between chronic PPI use and increase in bone fractures, possibly by decreasing calcium absorption.99 The most widely assumed mechanism is that long-term PPI use leads to decreased intestinal absorption of calcium, resulting in negative calcium balance, increased osteoporosis, development of secondary hyperparathyroidism, increased bone loss, and increased fractures. Even though evidence exists on the negative effects of PPIs on bone, there is little evidence on their effect on osseointegration and dental implants.

In a retrospective cohort study, Wu et al investigated the association between PPIs and the risk of osseointegrated implant failure.100 The analysis included a total of 1,773 dental implants in 799 patients (133 implants in 58 PPI users and 1,640 in 741 nonusers). Statistical analysis revealed that the failure rates were 6.8% for people using PPIs compared to 3.2% for nonusers. Subjects using PPIs had a higher risk of dental
implant failure (hazard ratio: 2.73; 95% CI = 1.10–6.78) compared to those who did not use the drugs. The findings suggested that treatment with PPIs may be associated with an increased risk of osseointegrated dental implant failure. Chrcanovic and coworkers conducted a retrospective cohort study based on patients consecutively treated between 1980 and 2014 with implant-supported/retained prostheses. A total of 3,559 implants were placed in 999 patients, with 178 implants reported as failures. The implant failure rates were 12.0% (30/250) for PPI users and 4.5% (148/3,309) for nonusers. A total of 45 out of 178 (25.3%) failed implants were lost up to abutment connection (6 in PPI users, 39 in nonusers), with an early-to-late failure ratio of 0.34:1. The intake of PPIs was shown to have a statistically significant negative effect for implant survival rate (hazard ratio = 2.811; 95% CI = 1.139–6.937; P = .025). In their conclusions, the authors also suggested that the intake of PPIs may be associated with an increased risk of dental implant failure.

CONCLUSIONS

Altogether, there is not sufficient data to conclude that diabetes affects the ability of dental implants to osseointegrate. However, most diabetes studies focus on well-controlled disease, especially as measured by HbA1C. Long-term studies evaluating dental implants in diabetic patients do report an increase in marginal bone loss and peri-implantitis in these patients, clearly differentiating the role of diabetes in the osseointegration process vs bone remodeling or soft tissue responses over the long term. This review also failed to uncover direct evidence that dental implant osseointegration is impaired in patients with osteoporosis. Although the disease itself has no direct effect, osteoporosis is generally treated with antiresorptive medications that can increase the risk of osteonecrosis of the jaws. This is a devastating complication that is widely understudied in the literature, either from the lack of elective implant surgical procedures performed in cancer patients receiving antiresorptives, or the insufficient patient numbers included in studies of osteoporosis patients receiving antiresorptives, to adequately assess ONJ risk.

In addition, there is no direct evidence that patients with HIV, cardiovascular disease, neurologic disorders, hypothyroidism, or RA have a decreased rate of implant osseointegration. However, some preliminary evidence suggests that medications such as SSRIs or PPIs may have a negative effect on implant osseointegration. These studies are fairly recent and lacked the body of literature necessary to perform a systematic review, and therefore must be validated with continuous research. Moreover, disease control, concomitant medications, and other comorbidities complicate implant osseointegration, and must guide our treatment approaches and clinical guidelines.

DISCLOSURE

The authors have no conflicts of interest related to this study.

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