Relationship Between Primary/Mechanical and Secondary/Biological Implant Stability

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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 frequncy 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*

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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

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,[5] 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.[6–12] 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.[13–15]

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).[16] 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.[17,18] 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.[19,20] 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.[21] 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)

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

- 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.

Manual Search. All reference lists of the selected studies were checked for cross-references. The following journals were hand-searched from year 2016 to 2018: *Journal of Clinical Periodontology, Journal of Periodontology, Clinical Oral Implants Research, The International Journal of Oral & Maxillofacial Implants, European Journal of Oral Implantology, Implant Dentistry, International Journal of Oral and Maxillofacial Surgery, Journal of Oral and Maxillofacial Surgery,* and *Clinical Implant Dentistry and Related Research*.

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.

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 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]).

Due to the unsatisfactory/insufficient result yielded when using MeSH keywords on the proposed screening, another wider screening was carried out to ascertain accuracy in the screening of all potential manuscripts. The secondary screening was typed as follows: (“dental implants”[Title/abstract] OR (“dental”[All Fields] AND “implants”[All Fields]) OR “dental implants”[All Fields] OR (“dental”[All Fields] AND “implant”[All Fields]) OR “dental implant”[All Fields]) AND (primary[All Fields] AND stability[All Fields]) OR (mechanical[All Fields] AND stability[All Fields]) OR “insertion”[All Fields]) AND (“torque”[MeSH Terms] OR “torque”[All Fields])) AND ((“biology”[MeSH Terms] OR “biology”[All Fields] OR “biological”[All Fields]) AND stability[All Fields]) OR (“osseointegration”[MeSH Terms] OR “osseointegration”[All Fields]) OR stability[All Fields] AND (implant[All Fields] AND failure[All Fields]) OR (implant[All Fields] AND success[All Fields]) OR (implant[All Fields] AND (“mortality”[Subheading] OR “mortality”[All Fields] OR “survival”[All Fields] OR “survival”[MeSH Terms])) OR (“resonance frequency analysis”[MeSH Terms] OR (“resonance”[All Fields] AND “frequency”[All Fields] AND “analysis”[All Fields]) OR “resonance frequency analysis”[All Fields]) OR (implant[All Fields] AND stability[All Fields] AND quotient[All Fields]) OR (retrieval[All Fields] AND (“torque”[MeSH Terms] OR “torque”[All Fields])) OR (marginal[All Fields] AND (“bone diseases, metabolic”[MeSH Terms] OR (“bone”[All Fields] AND “diseases”[All Fields] AND “metabolic”[All Fields]) OR “metabolic bone diseases”[All Fields] OR (“bone”[All Fields] AND “loss”[All Fields]) OR “bone loss”[All Fields])) OR (crestal[All Fields] AND (“bone diseases, metabolic”[MeSH Terms] OR (“bone”[All Fields] AND “diseases”[All Fields] AND “metabolic”[All Fields]) OR “metabolic bone diseases”[All Fields] OR (“bone”[All Fields] AND “loss”[All Fields]) OR “bone loss”[All Fields])) 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[22] and by the CONSORT statement.[23] 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 used for the assessment of risk of bias in individual observational studies.[24] This scale includes five main categories: representativeness of the exposed cohort, ascertainment of exposure, assessment of outcome, follow-up long enough for the outcome of interest, and adequacy of follow-up.

Risk of Bias Across Studies

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

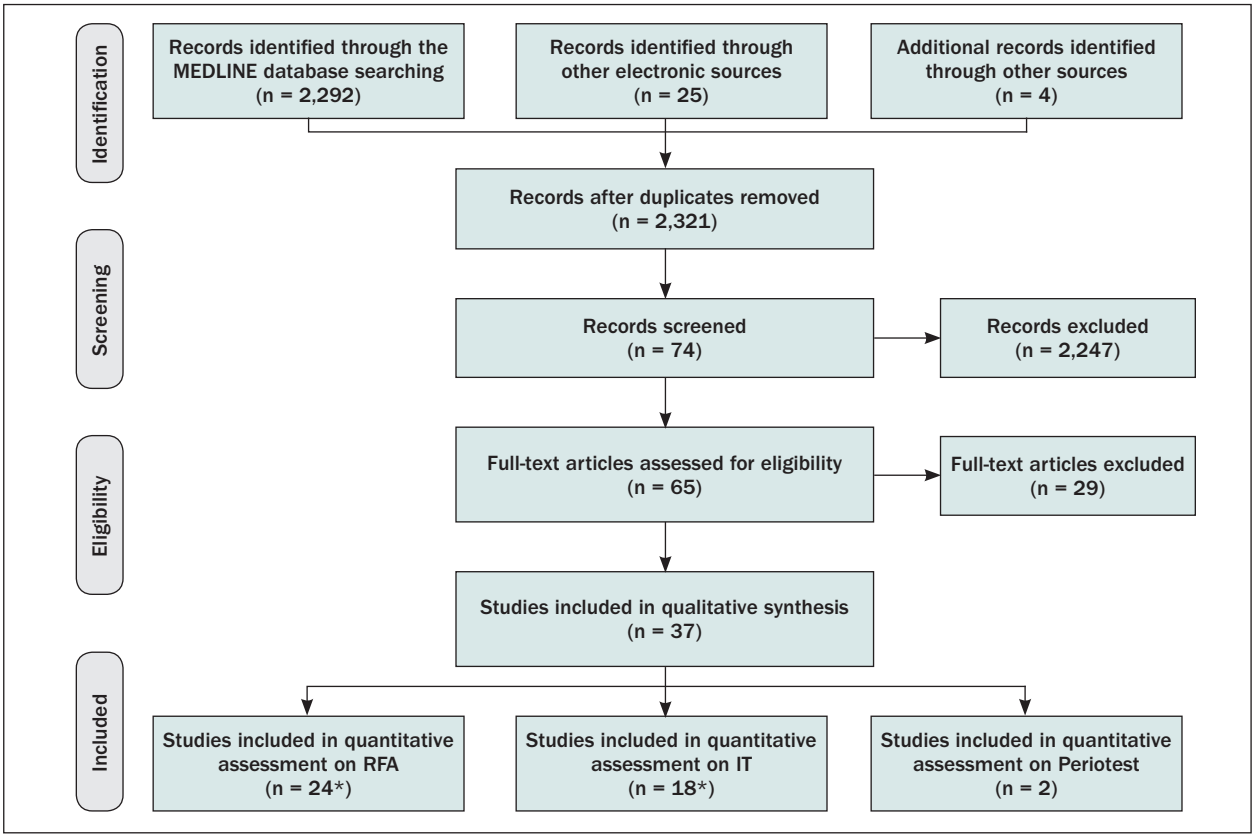

Fig 1 PRISMA Flowchart of the screening process. *Seven trials evaluated and reported implant stability with resonance frequency analysis (RFA) and insertion torque (IT).

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,[25] leaving 37 studies[26–62] eligible for inclusion in the qualitative and quantitative analyses (Fig 1; Tables 2 to 4).

Of these, 17 reported implant stability only using RFA,[28,29,31,32,36,38,40,46–48,50,52,54,55,58,60,62] 11 only IT,[33–35,39,42,44,45,51,53,56,59] 7 a combination of RFA and IT,[27,30,41,43,49,57,61] and 2 the Periotest.[26,37] Of the 36 studies included in the qualitative and quantitative evaluation, 22 were prospective cohort (PC) studies,[27–29,32–35,39,42,45–52,54,57,60–62] 1 was a retrospective cohort (RC) study,[37] and 14 were RCTs.[30,31,36,38,40,41,43,44,53,55,56,58–60]

- 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[28]; Kronstrom et al[41]). The mean implant survival rate was 98.4% (95% CI: 97.3%–99.3%).

Table 2 Studies Included in the Systematic Review Using Resonance Frequency Analysis (RFA) to Assess Primary and Secondary Implant Stability

					Primary stability		
Study (year)	Study design	Follow-up	Participants (n)	Implants (n)	Method	IT	Value
Alghamdi et al[27] (2011)	PC	12 mo from IP	29	26	RFA	35.19 ± 4.79	68.5 ± 4.81
				26		34.62 ± 5.82	66.6 ± 5.41
Atieh et al[28] (2014)	PC	12 mo from IP/PL	28	28	RFA	NA	79.7 ± 4.4
Balleri et al[29] (2002)	PC	12 mo from PL	14	45	RFA	NA	NA
Barewal et al[30] (2012)	RCT	36 mo from IP	38	8	RFA	10.01 ± 45.81	58 ± 5.5
				13		32.28 ± 11.04	72 ± 3.1
				19		16.61 ± 7.78	70 ± 4.2
Bechara et al[31] (2017)	RCT	36 mo from IP	33	45	RFA	NA	68.2
Becker et al[32] (2013)	PC	24 mo from IP	76	100	RFA	NA	72.1
Hof et al[36] (2014)	RCT	12 mo from IP	21	42	RFA	NA	75.5
				42		NA	78.5
Karabuda et al[38] (2011)	RCT	12 mo from PL	22	48	RFA	NA	55.46 ± 8.29
				48		NA	56.63 ± 8.19
Kim et al[40] (2015)	RCT	12 mo from PL	21	22	RFA	NA	66.8 ± 7.4
		12 mo from PL		24		NA	66.2 ± 6.5
Kronstrom et al[41] (2010)	RCT	12 mo from IP/PL	36	3	IT	20	74.1
				42		30	
				1		35	
				9		40	
Malchiodi et al[43] (2016)	RCT	12 mo from IP	40	40	RFA	49.0 ± 9.95	63.95 ± 8.81
Norton[62] (2017)	PC	12 mo from IP	22	3	RFA	< 5	66.83
				9		5–10	63.22
				18		> 10	67.11
Olsson et al[46] (2003)	PC	12 mo from PL	10	61	RFA	NA	60.1 ± 3.6
Östman et al[47] (2005)	PC	12 mo from PL	40	123	RFA	NA	62.9 ± 4.9
				120		NA	61.3 ± 8.8
Östman et al[49] (2013)	PC	12 mo from IP	21	139	RFA	53.1	73.1 ± 6.3
Östman et al[48] (2008)	PC	12 mo from PL	77	257	RFA	NA	72.2 ± 7.5
Pieri et al[50] (2012)	PC	24 mo from PL	25	61	RFA	NA	67.35 ± 6.67
Rao and Benzi[52] (2007)	PC	12 mo from PL	46	51	RFA	NA	71.9
Sennerby et al[54] (2012)	PC	12 mo from PL	90	218	RFA	NA	73.7 ± 7.6
Shayesteh et al[55] (2013)	RCT	12 mo from IP	30	23	RFA	NA	70.9
				23		NA	64.7
Tatli et al[57] (2014)	PC	12 mo from PL	23	77	RFA	36.8 ± 3.8	73.6 ± 5.8
Turkyilmaz et al[58] (2008)	RCT	12 mo from IP	20	20	RFA	NA	76.2 ± 2.8
	RCT	12 mo from IP		20		NA	75.6 ± 4.5
Zix et al[60] (2005)	PC	12 mo from IP	35	120	RFA	NA	52.5 ± 7.9
Zwaan et al[61] (2016)	PC	12 mo from PL	97	163	RFA	41.3 ± 12.0	73.7 ± 6.4

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

Secondary stability			Confounders							
Method	Value	Timing	Smoking (%)	Plaque index (%)	Bleeding index (%)	Keratinized mucosa (mm)	Implant survival (%)	Implant failure (%)	Success rate (%)	MBL follow-up (mm)
NA	NA	NA	0	15.42 ± 3.04	11.52 ± 2.03	NA	100	0	100	NA
					100	NA	100	0	100	NA
RFA	73.4 ± 12.4	8 wk	0	NA	NA	NA	78.6	21.4	NA	NA
RFA	69 ± 6.5	12 mo	NA	NA	NA	NA	100	0	NA	0.3 ± 0.3
NA	NA	NA	0	NA	NA	NA	87.5	12.5	NA	0.22
							100	0		
							100	0		
RFA	71.6	3 y	21	NA	NA	NA	100	0	NA	0.89 ± 0.25
RFA	72.6	24 mo	NA	NA	NA	NA	93	7	NA	0.6
RFA	80.5	12 mo	NA	NA	10	NA	100	0	NA	0.69
	81.3	12 mo					97.6	2.4		0.68
RFA	58.15 ± 6.52	6 wk	NA	NA	NA	NA	100	0	NA	0.46 ± 0.07
	58.21 ± 5.2						97.1	2.9	NA	0.43 ± 0.11
NA	NA	NA	NA	NA	NA	NA	84	16	NA	NA
	NA	NA	NA	N	NA	NA	100	0	NA	NA
RFA	81.7	12 mo	NA	NA	NA	NA	100	0	NA	0.44 ± 0.4
							81	19		
							100	0		
							78	22		
RFA	67.48 ± 5.95	3 mo	25	NA	NA	NA	100	0	100	0.54 ± 0.38
RFA	84.83	3 mo	4.5	NA	NA	NA	100	0	NA	0.07
	78.22									
	79.30									
RFA	62.8 ± 1.6	4 mo	NA	NA	NA	NA	93.4	6.6	N/A	1.3 ± 0.6
RFA	64.5 ± 4.8	6 mo	5	NA	NA	NA	99.6	0.4	NA	0.78 ± 0.90
	62.6 ± 7						100	0		0.91 ± 1.04
NA	NA	NA	NA	NA	NA	NA	99.4	0.6	NA	1.01 ± 0.85
RFA	72.5 ± 5.7	6 mo	NA	NA	NA	NA	98.4	1.6	82.9	0.7 ± 0.78
RFA	72.91 ± 5.07	24 mo	16	NA	13.6	< 2 mm (2 implants)	96.8	3.2	96.8	0.6 ± 0.13
RFA	74.1	12 mo	NA	NA	NA	NA	100	0	NA	1.12 ± 1.06
RFA	76.7 ± 5.2	12 mo	NA	NA	NA	NA	98.6	2.4	NA	0.6 ± 0.8
RFA	72.71	3 mo	0	NA	NA	NA	100	0	NA	0.41 ± 0.22
	71.37						100	0		0.34 ± 0.21
RFA	74.8 ± 5.6	3 mo	NA	NA	NA	NA	100	0	NA	NA
RFA	76.4 ± 2.5	12 mo	NA	NA	NA	NA	100	0	NA	1 ± 0.3
RFA	76.4 ± 2.8	12 mo	NA	NA	NA	NA	100	0	NA	0.9 ± 0.3
NA	NA	NA	22.8	NA	NA	NA	NA	NA	NA	0.7 ± 1.1
RFA	75.0 ± 4.5	6 mo	24.5	NA	NA	NA	96.9	3.1	NA	0.5 ± 0.4

Table 3 Studies Included in the Systematic Review Using Insertion Torque to Determine Primary Stability

Study (year)	Study design	Follow-up	Participants (n)	Implants (n)	Primary stability	
					Method	Value (Ncm)
Alghamdi et al[27] (2011)	PC	12 mo from IP	29	26	IT	35.19 ± 4.79
				26		34.62 ± 5.82
Barewal et al[30] (2012)	RCT	36 mo from IP	38	8	IT	10.01 ± 4.58
				13		32.28 ± 11.04
				19		16.61 ± 7.78
Vanden Bogaerde et al[59] (2016)	RCT	36 mo from IP	11	11	IT	38 ± 11.4
		36 mo from IP		11		39.5 ± 9.1
Calandriello et al[33] (2003)	PC	12 mo from IP	26	20	IT	66.3 ± 8.4
				19		60.9 ± 11
				11		51.3 ± 25.4
Degidi et al[34] (2012)	PC	12 mo from IP	13	51	IT	12.6 ± 3.6
				31		35.4 ± 7.3
Grandi et al[35] (2013)	PC	12 mo from IP	102	114	IT	74.8 ± 7.9
				42		37.4 ± 8.2
Khayat et al[39] (2013)	PC	12 mo from IP	6	9	IT	37.1
			32	42		110.6
Kronstrom et al[41] (2010)	RCT	12 mo from IP/PL	36	3	IT	20
				42		30
				1		35
				9		40
Maiorana et al[42] (2015)	PC	46 mo from IP	189	377	IT	45
Malchiodi et al[43] (2016)	RCT	12 mo from IP	40	40	IT	49.0 ± 9.95
Marconcini et al[44] (2018)	RCT	36 mo from IP	116	58	IT	29.1 ± 6.6
				58		70.6 ± 8.5
Norton[45] (2011)	PC	46 mo from IP	61	68	IT	22.5
Norton[62] (2017)	PC	12 mo from PL	30	22	IT	< 20
Östman et al[49] (2013)	PC	12 mo from IP	42	139	IT	53.1
Rabel et al[51] (2007)	PC	12 mo from IP	263	408	IT	28.8 ± 15.2
				194		25.9 ± 14.7
Rizkallah et al[53] (2013)	RCT	15 mo from IP	145	390	IT	72
Stanford et al[56] (2016)	RCT	12 mo from PL	120	79	IT	31 ± 13
				87		22 ± 9
Tatli et al[57] (2014)	PC	12 mo from PL	23	77	IT	36.8 ± 3.8
Zwaan et al[61] (2016)	PC	12 mo from PL	97	163	IT	41.3 ± 12.0

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

Study (year)	Study design	Follow-up	Participants (n)	Implants (n)	Primary stability	
					Method	Value
Al-Hashedi et al[26] (2016)	RCT	12 mo from PL	20	20	Periotest	–1.61 ± 2.02
				20	Periotest	2.15 ± 2.52
Jeong et al[37] (2015)	RC	5 y from PL	36	88	Periotest	–1.02

RCT = randomized clinical trial; RC = retrospective cohort study; PL = postloading.

Confounders							
Smoking (%)	Plaque index (%)	Bleeding index (%)	Keratinized mucosa (mm)	Implant survival (%)	Implant failure (%)	Success rate %	MBL follow-up (mm)
0	15.42 ± 3.04	11.52 ± 2.03	NA	100	0	100	NA
0	NA	NA	NA	87.5	12.5	NA	0.22
				100	0		
				100	0		
27.2	NA	NA	NA	100	0	NA	0.4 ± 0.7
	NA	NA	NA	90.91	9.09	NA	0.6 ± 0.5
NA	NA	NA	NA	98	2	0	1.22 ± 0.8
NA	NA	NA	NA	98	2	NA	0.6 ± 1
				100	0		0.5 ± 0.8
22.3	NA	NA	NA	100	0	NA	0.41 ± 0.18
23.03	NA	NA	NA	100	0		0.45 ± 0.25
NA	NA	NA	NA	100	0	NA	1.09 ± 0.62
NA	NA	NA	NA	100	0		1.24 ± 0.75
NA	NA	NA	NA	100	0	NA	NA
				81	19		
				100	0		
				78	22		
NA	NA	NA	NA	99.7	0.3	NA	NA
25	NA	NA	NA	100	0	100	0.54 ± 0.38
30.1	NA	NA	NA	98.2	1.8	NA	0.96 ± 0.46
				91.3	8.7		1.16 ± 0.61
8.19	NA	NA	NA	95.5	4.5	NA	NA
NA	NA	NA	NA	96.7	3.3	NA	NA
NA	NA	NA	NA	99.4	0.6	NA	1.01 ± 0.85
NA	NA	NA	NA	98.5	1.5	NA	NA
				99.5	0.5		
NA	NA	NA	NA	97.7	2.3	NA	NA
14.1	NA	NA	NA	94.9	5.1	NA	0.51 ± 0.72
				98.9	1.1		0.34 ± 0.49
NA	NA	NA	NA	100	0	NA	NA
24.5	NA	NA	NA	96.9	3.1	NA	0.5 ± 0.4

Secondary stability			Confounders							
Method	Value	Timing	Smoking (%)	Plaque index (%)	Bleeding index (%)	Keratinized mucosa (mm)	Implant survival (%)	Implant failure (%)	Success rate (%)	MBL follow-up (mm)
Periotest	–2.19 ± 2.23	12 mo from PL	0	NA	NA	NA	100	0	NA	NA
Periotest	1.09 ± 2.83	12 mo from PL	0	NA	NA	NA	100	0	NA	NA
Periotest	–0.74	5 y from PL	NA	NA	N/A	NA	98.9	1.1	NA	NA

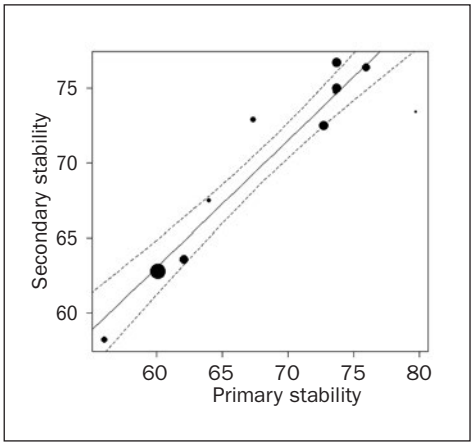

Fig 2 Relationship between primary and secondary stability.

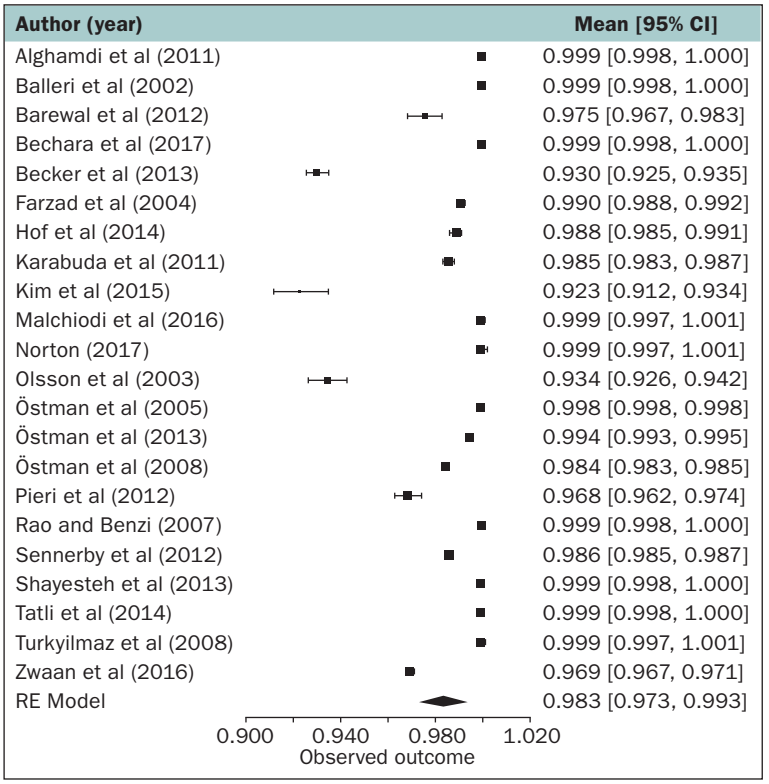

Fig 3 *(Right)* Forest plot *of* relationship between primary stability by means of ISQ unit and implant survival.

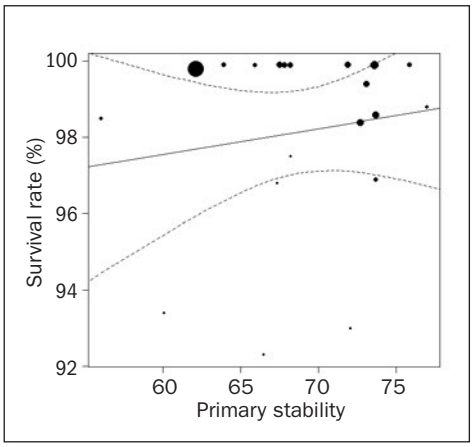

Fig 4 Relationship between primary stability by means of ISQ unit and implant survival.

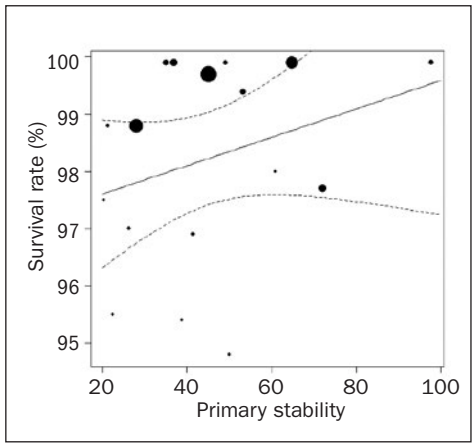

Fig 5 Relationship between implant torque and implant survival.

Relationship Between Primary Stability by Means of ISQ Unit and Implant Survival

A statistically significant relationship was not yielded between mechanical stability determined by ISQ and implant survival ($P = .511$) (Figs 3 and 4).

Relationship Between IT and Implant Survival

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

Secondary Outcome on Marginal Bone Loss

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[52]) 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.)

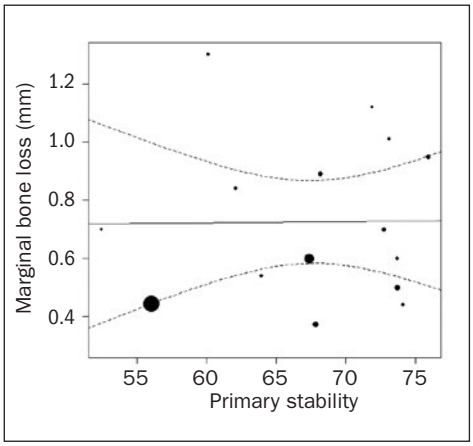

Fig 6 Relationship between primary stability by means of ISQ unit and marginal bone loss.

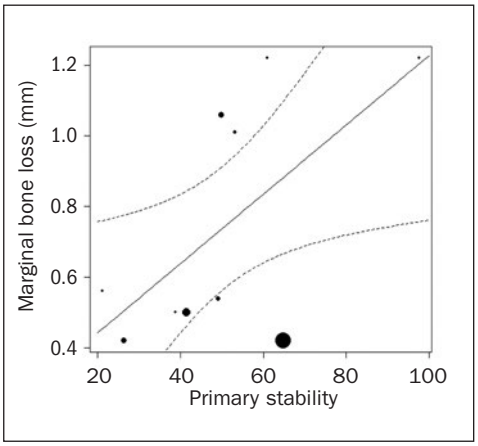

Fig 7 Relationship between insertion torque and marginal bone loss.

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% 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.[2] Such findings confirmed earlier clinical observations.[63,64] 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.[65–68]

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.[6] 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.[69] This idea has been a matter of debate, since osseointegration has been demonstrated in animal models when an IT < 30 Ncm was applied,[70,71] or even with a lack of IT (0 Ncm).[72] 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.[73,74]

As aforementioned, high IT has been linked to higher stresses in the surrounding bone, which induces microfractures, bone necrosis, and remodeling.[17] 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.[75] 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.[39] 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).[76] 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[77] gives some initial insight (equation 1):

$$T = \frac{\mu \pi H D^2 p}{2}$$

Here T is insertion torque (IT), μ is the coefficient of friction between implant and bone, π 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[78] 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):

$$p = (r_2 - r_1)\left[\frac{(1+\nu_1)}{E_1} r_1 + \frac{(1+\nu_2)(1-2\nu_2)}{E_2} r_2\right]^{-1}$$

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 ν 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_1). 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):

$$T = (r_2 - r_1)\left[\frac{(1+\nu_1)}{E_1} r_1 + \frac{(1+\nu_2)(1-2\nu_2)}{E_2} r_2\right]^{-1}\left(\frac{\mu \pi H D^2}{2}\right)$$

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.[79]

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.[6–11] 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 (Osstell) 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.[80,81] 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.[82] 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[79] conducted experiments in which the same implant was placed with the same degree of misfit ($r_2 - r_1$) 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[79]) and porcine iliac bone samples in vitro.[83] 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[83]—ie, 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 Osstell 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[79] and Sakoh et al[83]—ie, 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,[81] 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.[6–11] 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.[84–86] Furthermore, Sennerby 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.[87] A recent canine study[88] 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

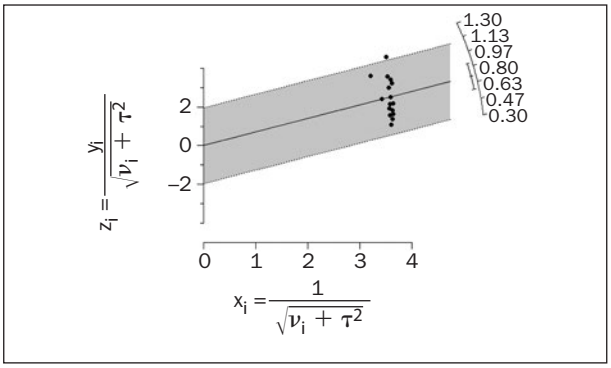

Fig S1 Galbraith graph on marginal bone loss.

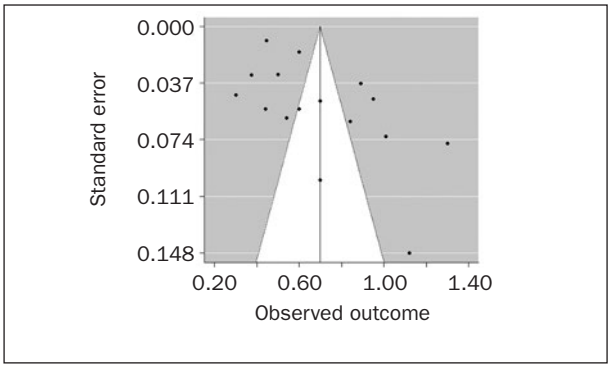

Fig S2 Funnel plot showing the dispersion of studies on marginal bone loss.

Table S1 Newcastle Ottawa Scale for Nonrandomized Clinical Trials

Study (year)	Selection	Comparability	Outcome/ Exposure
Alghamdi et al[27] (2011)	★★	★★	★★★
Atieh et al[28] (2014)	★★★★	★★	★
Balleri et al[29] (2002)	★★	★★	★
Becker et al[32] (2013)	★★★	★	★★
Olsson et al[46] (2003)	★★★★	★★	★
Östman et al[47] (2005)	★★	★	★
Östman et al[49] (2013)	★★	★	★
Östman et al[48] (2008)	★★★★	★	★★★
Pieri et al[50] (2012)	★★	★★	★★
Rao and Benzi[52] (2007)	★★	★	★
Sennerby et al[54] (2012)	★★★★	★★	★★
Tatli et al[57] (2014)	★★	★	★
Zix et al[60] (2005)	★★★	★★	★★
Zwaan et al[61] (2016)	★★★	★★	★
Calandriello et al[33] (2003)	★★★★	★★	★★
Degidi et al[34] (2012)	★★	★★	★
Grandi et al[35] (2013)	★★★	★★	★★
Khayat et al[39] (2013)	★★	★★	★
Maiorana et al[42] (2015)	★★★★	★★	★★
Norton[45] (2011)	★★★★	★	★★★
Rabel et al[51] (2007)	★★	★★	★
Zwaan et al[61] (2016)	★★★	★★	★★
Jeong et al[37] (2015)	★★	★	★★★

Table S2 Bias Risk Assessment for the Included RCTs Using *t* Cochrane Risk of Bias Tool for Randomized Controlled Trials

Study (year)	Random sequence generation	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addresses	Selective reporting	Other bias	Overall risk of bias
Bechara et al[31] (2017)	Low	Low	High	Low	Low	Low	Moderate
Karabuda et al[38] (2011)	Low	Low	Low	Low	Low	Low	Low
Kim et al[40] (2015)	Low	High	Low	Low	Low	Low	Moderate
Malchiodi et al[43] (2016)	Low	High	Low	Low	Low	Low	Moderate
Shayesteh et al[55] (2013)	Low	High	Unclear	Low	Low	Unclear	High
Turkyilmaz et al[58] (2008)	High	High	Unclear	Low	Low	Unclear	Low
Hof et al[36] (2014)	High	Low	Low	Low	Low	Low	Moderate
Al-Hashedi et al[26] (2016)	Low	High	Unclear	Low	Low	Low	High