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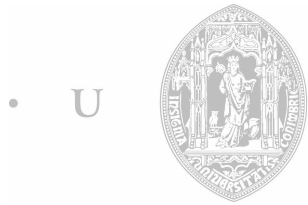
Integrated Master in Dental Medicine

OSSEOINTEGRATION OF ZIRCONIA IMPLANTS
SYSTEMATIC REVIEW AND META-ANALYSIS

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I - Abstract

Introduction: Osseointegration is one of the most primordial factors in implant rehabilitation. Although osseointegration of titanium implants is considered a reference of implantology some disadvantages of them as the potential presence of allergic reactions or the dark color that may compromise aesthetics when there is an unfavorable mucosa, have led to the development of alternatives. Zirconia, a well studied bioinert structure derived from the Zirconium metal, has been used in medicine and dentistry. Zirconia implants may be an alternative due to the aesthetics, biocompatibility and high fracture resistance. **Objective:** This systematic review and meta-analysis aimed to evaluate the survival and success rates of zirconia implants in humans. **Methodology:** A PICO question was defined "*In patients subjected to tooth replacement with single unit zirconia implant does the survival rates do compare to single unit titanium implant?*", followed by a search in primary databases PubMed / MEDLINE, Cochrane and Embase with the following keywords: "dental implantation, osseointegrated", "implantation, osseointegrated dental", "osseointegrated dental implantation", "osseointegration", "zirconium", "titanium", "dental implants", "dental implants, single tooth", "single tooth dental implants", "dental implantation, endosseous"; using the appropriate boolean operators, "OR" and "AND". Wherever possible the MeSH terms were used. The search criteria did not include a time limit or restrictions on the language or type of publication. **Results:** A total of 1465 articles were obtained from which 71 were selected for full text reading, after exclusion of the duplicates and reading the title and abstract. Of these articles, nine were included on this systematic review. The outcomes evaluated were the survival rate, the success rate and the Marginal Bone Level; others parameters were extracted to complement the review. **Discussion:** Recently, the option for zirconia implants has increased exponentially due to the inherent characteristics of the material. Regarding the parameters, survival and success rates as well as the Marginal Bone Level, translation of an effective osseointegration, present values very similar to that of titanium implants. **Conclusion:** Considering the limits of this systematic review, it is possible to conclude that zirconia implants can be a safe and viable option, and an alternative to titanium implants in single unit implant-supported restorations. However, more multicentre randomized clinical trials with scientific quality and validity, with a larger follow-up, are needed to accurately prove the success of these implants.

Key-words: osseointegration; zirconia implant; success rates; survival rates; marginal bone level

Introdução: A osteointegração é um dos factores preponderantes no sucesso da reabilitação com implantes. A osteointegração dos implantes de titânio é considerada a referência da implantologia; contudo, algumas desvantagens dos mesmos como a potencial presença de reacções alérgicas ou a sua cor escura que pode comprometer a estética quando existam condições desfavoráveis da mucosa, levaram ao desenvolvimento de alternativas. A zircónia, uma estrutura bionerte bem estudada que deriva do metal Zircónio, tem sido usada amplamente na Medicina e na Medicina Dentária. Os implantes em zircónia podem constituir essa alternativa devido à sua estética, biocompatibilidade e elevada resistência à fractura.

Objectivo: Este trabalho pretende fazer uma revisão sistemática e meta-análise para avaliação das taxas de sobrevivência e sucesso dos implantes de zircónia, em humanos.

Metodologia: Foi definida uma questão PICO "Em pacientes submetidos à substituição dentária com um implante unitário de zircónia, as taxas de sobrevivência podem-se comparar com a dos implantes unitários de titânio?", seguida de uma pesquisa nas bases de dados primárias da PubMed/MEDLINE, Cochrane e Embase com as seguintes palavras-chave: "*dental implantation, osseointegrated*", "*implantation, osseointegrated dental*", "*osseointegrated dental implantation*", "*osseointegration*", "*zirconium*", "*titanium*", "*dental implants*", "*dental implants, single tooth*", "*single tooth dental implants*", "*dental implantation, endosseous*"; com os conectores booleanos "AND" e "OR". Sempre que possível foram utilizados os termos MeSH. Os critérios de pesquisa não incluíram um limite cronológico nem foram feitas restrições quanto à língua ou tipo de publicação.

Resultados: Obtiveram-se um total de 1465 artigos dos quais foram seleccionados 71 para leitura integral, após exclusão dos duplicados e leitura do título e abstract. Desses artigos, nove foram incluídos para esta revisão sistemática. Os parâmetros avaliados foram a taxa de sobrevivência, a taxa de sucesso e o nível ósseo marginal e foram extraídos ainda outros que permitiram enriquecer a revisão.

Discussão: Recentemente, a opção por implantes de zircónia aumentou exponencialmente devido às características oferecidas pelo material. Relativamente aos parâmetros, as taxas de sobrevivência e sucesso, assim como o nível ósseo marginal, tradução de uma osteointegração efectiva, apresentam valores muito semelhantes à dos implantes de titânio.

Conclusão: Considerando os limites desta revisão, é possível concluir que os implantes de zircónia podem constituir uma opção segura e viável, e uma alternativa aos implantes de titânio. Contudo, são necessários mais ensaios clínicos randomizados multicêntricos com qualidade e validade científica, apresentando um *seguimento* maior, para provar com exactidão o sucesso destes implantes.

Palavras-chave: osteointegração; implante de zircônia; taxas de sucesso; taxas de sobrevivência; nível ósseo marginal

II - List of abbreviations and acronyms

BIC - Bone Implant Contact

FDPs - Fixed Dental Protheses

FGF - Fibroblast Growth Factor

HIF-1 - Hypoxia Inducible Factor

LTD - Low-Temperature Degradation

MBL - Marginal Bone Level

Mg-PSZ - Magnesium Partially Stabilized Zirconia

PMN - Polymorphonuclear Leucocytes

RCTs - Randomized Clinical Trials

VEGF - Vascular Endothelial Growth Factor

Y-TZP - Yttria-Stabilized Tetragonal Zirconia Polycrystal

ZTA - Zirconia-Thougened Alumina

III - Introduction

1. Osseointegration: a major factor to implant stability

Since ages, people have the concern, because of a functional or aesthetic care, of replacing teeth that were lost. In ancient Egypt, people used animal teeth as the first attempts to replace missing teeth. Ivory was the material of choice, and it was mechanically shaped to look like a tooth. Similar implantation procedures were also found in South America and Europe. ⁽¹⁾ The continuous evolution of implant dentistry, as in dentistry, made possible that currently we can replace missing teeth from other materials that became so popular because of its features, like the biocompatibility.

Implant dentistry has passed from an experimental treatment to a highly predictable and long-term option to treat fully or partially edentulous patients. When compared with conventional fixed or removable prostheses, it offers a significant functional and biologic advantages that turn this rehabilitation an excellent treatment option. Nowadays, it is the best treatment option for many patients and it became the first line of choice for so many dentists and patients.

This change was initiated 50 years ago by the discovery that implants made of commercially pure titanium could achieve anchorage in the bone with functional and direct bone-to-implant contact (BIC). In the 1960s, Branemark, the most important pioneer of modern implant dentistry from the University of Gothenburg (Sweden), and coworkers performed the first preclinical and clinical studies and discovered this anchorage when blocks of titanium placed into the femur of rabbit got ankylosed with the surrounding bone and could not be retrieved. ⁽²⁾

Schroeder, from the University of Bern (Switzerland), and coworkers started to examine the tissue integration. Both were the pioneers that provided evidence for direct bone apposition on the surface of titanium, a phenomenon later termed "osseointegration", which is today widely accepted. A few years later, he reported as well the soft tissues reactions to titanium

implants. ^(1,2)

Surface characteristics of an implant have become an important point because of the decisive influence on the cascade of the osseointegration. Modifications of these surfaces were found to influence both the speed and the process of osseointegration. It is necessary to understand the mechanisms by which bone may be formed on an implant surface. Osseointegration is in a comprehensive way "a direct structural and functional connection between ordered, living bone and the surface of a load-bearing implant", which is based on the principle of bone regeneration and on the osteoconductivity of the biomaterial. ⁽³⁾

Intraoral bone healing of an implant wound comprises four phases: the hemostasis (minutes to hours), the inflammatory phase (hours to days), the proliferative phase (days to weeks) and finally the remodeling phase (approximately 3 weeks and lasts for years). ⁽⁴⁾ Cells have an important role in this process.

Hemostasis phase begins with the dental implant drill that will allow the insertion of the implant and which cause a surgical trauma. The implant surface interacts with water molecules and ions, which are followed by plasma proteins like albumin, present at high concentrations in blood, globulins or fibrin. These will be slowly replaced by proteins with lower concentrations such as vitronectin or fibronectin. Cells are able to attach to the implant surface, after proteins absorption and initial coating of the surface implant with blood proteins. ⁽⁵⁾

The inflammatory phase begins with the degranulation of platelets which will lead to a release of cytokines. The innate host defense systems are activated and consists of molecular and cellular elements: polymorphonuclear leucocytes (PMN) and macrophages. PMN have different roles, such as kill bacteria through reactive radicals or secrete digestive enzymes like collagenase and elastase. They have short-lived and are replaced by lymphocytes and macrophages. ⁽⁵⁾

It is necessary to attempt to a cleanest possible surgical work as well as antibacterial measures including antibiotics and local disinfection, to limit this phase and to move as quickly as possible into the proliferative phase. Macrophages have the potential to eliminate bacteria but can act as a switch to the inflammatory phase, by secreting angiogenic and fibrogenic growth factors.

New extracellular matrix and angiogenesis will characterize the proliferative phase. The first one is ensured by the fibroblast growth factor (FGF) that produce metalloproteinases and insoluble cellular fibronectin and other soluble proteins of the extracellular matrix like collagens, vitronectin, and others. Hypoxia will stimulate angiogenesis. That process occurs because of the macrophages that are attracted by hypoxia and an intracellular transcription factor called hypoxia inducible factor (HIF-1) will stimulate the expression of vascular endothelial growth factor (VEGF) which stimulates the production of the endothelial cell. Newly formed vessels, which are a prerequisite for osteogenesis, will connect to existing blood vessels. New bone can only form when a blood vessel is not far than 200 μm away. This process of new bone formation close to a new blood vessel is designated angiogenic osteogenesis. ⁽⁵⁾

It is important to understand that an osteoblast does not directly attach to the surface of the implant, but to the protein layer on the top of the implant. An insoluble cellular fibronectin is produced by cellular attachment. Osteoprogenitor cell becomes secretory active when firm attachment to the surface and it is called osteoblast. Osteoblast starts to express osteocalcin and alkaline phosphatase as a molecular marker. The new bone formation begins with the secretion of a collagen matrix by osteoblasts. ^(4, 7)

Dental implant present primary stability after implant insertion. In particular, mechanical implant stability is regarded as a prerequisite for the short- and long- term clinical success of osseointegrated implants. ⁽³⁾ This primary stability, which provides a passively stabilized implant, is given by the bone wound through friction being mechanical, not biological.

Woven bone will be the first bone to form and the primary bone contacts will be supplemented by a newly formed secondary bone contacts, building up of the secondary stability. ⁽³⁾

Usually, this happens along the existing bone surfaces and the implant surface. The woven bone is characterized by the fact that its collagen fibers are randomly oriented and not parallel. Because of being a process of intramembranous ossification, the bone formation is starting by the secretion of collagen type III. This matrix is subsequently mineralized by hydroxyapatite.

Osteoclast has an important role during the remodelling phase. First, they start to create space for the new bone formation and remove primary bone contacts. The new bone is called lamellar bone, named after the parallel orientation of its collagen fibers under polarized light. ⁽³⁾

It is important to highlight that the so-called bone-implant contact can decrease during the remodelling phase and the balance between osteoclasts and osteoblasts have to be maintained. This phase only finishes when most woven bone and old bone from the primary bone contact is removed and replaced by newly bone.

The unique mechanical and biological properties of bone are due to its nanostructural architecture, making it rigid enough to resist pressure and traction forces while maintaining elasticity. ⁽³⁾

Another notion that has to be pointed is the concept of distance and contact osteogenesis. Osborn and Newesley in 1980 described those terms and refer, essentially, two different phenomena by which bone can become juxtaposed to the implant surface. In distance osteogenesis, new bone is formed on the surfaces of bone in peri-implant site. ⁽⁴⁾

In contact osteogenesis, new bone forms first on the implant surfaces, which must become colonized first by a population of osteogenic cells before initiation of bone matrix formation. ⁽⁴⁾

2. State of art - implant evolution

Till the 1980s, implant therapy was mostly used in fully edentulous patients. After the first clinical publications, that appeared around 1990, partially edentulous patients have become the dominant patient group. Consequently, and because of the differences between the research teams concerning the implant surfaces or material, industry answered by producing and improving dental implants, enhancing physical, mechanical, chemical and even optical properties, until today.⁽²⁾

Titanium implants have so far been the material of choice in implant dentistry. However, the potential to development undesirable allergic reactions, cellular sensitization, galvanic current formation and aesthetics gray hue, in particular for titanium alloys, in the presence of thin mucosal biotype,^(1, 8) have raised demands for more aesthetic and biocompatible implant material.

In order to improve aesthetic, aluminum oxide (Al_2O_3) was the first ceramic material used in implant dentistry, due to its good osteointegrative properties. In follow-up examinations after 10 years, the success of those implants was between 87 and 92,5%.⁽¹⁾ However, these systems, that were used particularly for immediate implantation in the areas where chewing forces were relatively weak, were retired from the market for apparent mechanical weakness and due to inadequate osseointegration resulting in a poor clinical outcome.^(1, 10)

Yttrium-stabilized tetragonal zirconia polycrystals (Y-TZP), a well-studied bioinert structure, appear to offer advantages over aluminum oxide for dental implants because of their higher fracture resilience, higher flexural strength, low temperature conductance, esthetic with tooth-like color and biocompatibility.⁽¹¹⁻¹³⁾

Zirconia, which is a Zirconium oxide, was isolated the first time in an impure form by Jons Jakob Berzelius in 1824. Initially, zirconia was used in Medicine in various orthopedic surgical procedures like ball heads for total hip replacements. Later it was introduced in

dentistry and has received an exponent interest as a dental material. ⁽⁸⁾ From crown to aesthetic orthodontic brackets, it has been an exponent demand to use zirconia-based dental implants, especially for aesthetics, which is an advantage over titanium. It was only in 1987, that the first ceramic implant known as the Sigma implant (Sandhause, Incermed, Lausanne, Switzerland) was developed by Sandhaus.

There are two major ways to found zirconia in the pure form: a crystalline or amorphous form. The amorphous form, which is bluish-black powder, will be refined and treated at high temperatures to obtain the crystalline zirconia. Concerning the structure of zirconia, there are three crystalline phases, depending on the temperature: monoclinic (M), tetragonal (T) and cubic (C). Till 1170°C, the M phase is stable and above this mark, it changes to T phase with 5% decrease in volume. At 2370°C the C phase starts appearing. It is important to remark that upon cooling stress generates and causes it to become unstable at room temperature (M phase). ^(8, 10, 13)

Various stabilizing oxides [16 mol% magnesia (MgO), 16mol% of limestone (CaO) or 8 mol% Yttria (Y₂O₃)] are added to zirconia, what remarkably increases the crack resistance, fracture toughness, and longevity of zirconia endosseous implant. Zirconia, for biomedical purpose, can be classified into three types: magnesium partially stabilized zirconia (Mg-PSZ), Y-TZP and zirconia-thougened alumina (ZTA). To improve the resistance of zirconia to low-temperature degradation (LTD) and "ageing" and to enhance more mechanical strength, high wear resistance, fracture toughness, by means of the improvement in the durability and stability of zirconia crystals, alumina has been added to Y-TZP in low quantities (0.25 wt%) to yield ZTA. ⁽¹³⁾

3Y-TZP, which is formed by doping zirconia with 2-3 mol% of Y₂O₃, are the mainly form used in dental applications, like in zirconia implants. This type of zirconia, among zirconia ceramics, present the highest toughness and strenght. ^(8, 10, 13)

Besides the numerous modification methods that have been proposed to enhance mechanical properties of zirconia some surface modifications to enhance osseointegration as been proposed as well. These changes includes optimization of surface microroughness with

sandblasting and/or acid etching, sinterization of particles onto the implant surface, bioactive coatings like calcium phosphate, and laser surface modifications. ⁽¹²⁾

By far, histomorphometric analysis has been the gold standard in evaluating the bone-implant interface. ^(12, 14) However, only in cases of failure it is possible to apply those techniques to humans and evaluate them. In vivo investigations were designed with animal models to draw some clinical implications on the performance in humans.

Sivaraman et al. ⁽⁸⁾ also refer that animal and humans' clinical studies have evaluated and confirmed the deposition of newly formed mature bone. In addition, they have also revealed the osteoconductive nature in of zirconia implant surfaces with no cytotoxic, oncogenic or mutagenic effects on the bone cells and fibroblasts after implantation into muscles or bones. Further, cell culture studies demonstrated that zirconia surface is well tolerated by osteoblasts and integrates into bone tissue. ⁽¹²⁾ Gahlert et al. confirmed that the increased surface roughness of sandblasted and acid etched zirconia implants not only has an important influence on bone integration but also is associated with increased removal torque strength and bone stability in minipigs. ⁽¹²⁾ Scarano et al., on an experimental study in New Zealand male rabbits, demonstrated a good bone response to zirconia implants with a percentage of Bone Implant Contact (BIC) of nearly 68,4% at four weeks. Dubruille et al. compared the BIC of three different materials and found BIC to be 54% for titanium, 64,6% to zirconia and 68% for alumina, which translates on no statistically significant difference between the three types of implants. ⁽¹²⁾

In a recent systematic review, for the BIC analyses of titanium and zirconia implants, values varied between 0% after one week in pig maxillae and 89,09% after 90 weeks in rabbit femurs when evaluating both materials. When the data of both materials were evaluated separately, it was shown that titanium implants has a BIC of 60,70% and zirconia implants showed a 3,47% lower BIC. ^(10, 14) However, it is still not defined what values of the BIC are better.

Recently the demand for zirconia-based implant system is rising tremendously due to the features offered by the material that allows to obtain excellent in vivo results and may elicit

also good clinical results The objective of the present systematic review was to assess the survival rates of single unit zirconia implants when compared to single unit titanium implants.

IV - Materials and Methods

Protocol and Registration

This systematic review was performed and reported as prescribed by the Preferred Reporting Items for Systematic Review (PRISMA) guidelines, to answer the following focused question: *In patients subjected to tooth replacement with single unit zirconia implant does the survival rates do compare to single unit titanium implant?*

Initially, a population intervention/exposure comparison outcome (PICO) assessment worksheet was used to define the topic and plan the search strategy considering:

- Population: Patients subjected to tooth replacement with a unitary implant
- Intervention: Rehabilitation with a single unit zirconia implant
- Comparison: Single unit titanium implant
- Outcome: Survival rates of single unit zirconia implant

Eligibility criteria

The inclusion criteria for this systematic review were studies with implant survival rates and measures of the marginal bone level, only in humans, patients subjected to tooth replacement with a single unit implant, the number of implants and patients ≥ 15 and a mean observation period of at least 12 months. To reach a higher level of evidence, it was the option to only include studies with a prospective design (RCTs and prospective clinical trial). Furthermore, eligible data considered were patients' mean age, implant design (1 or 2 pieces), type of loading and time of implant placement.

Exclusion criteria to the focused question were in vitro studies, titanium alloys and alumina-toughened zirconia implants, retrospective studies, pilot studies, case series studies, and other languages than english, spanish, portuguese or french.

Information sources and search strategy

A detailed search strategy was developed for the identification of all the prospectively designed human studies reporting on implant therapy with zirconia implants in online electronic databases (PubMed, Embase and Cochrane).

This search was complemented by hand searches and expert recommendations. For possible additional studies, all reference lists of selected papers were scanned. No further search was performed after the last executed update, which was on 30 of April, 2018.

The search strategy was designed and established by the review author (SD). The review author realized the searches based on the identified medical subject headings (MeSH) search terms. To perform the search in the databases, the terms were applied using the appropriate Boolean operators, "OR" and "AND". The complete set of search terms used on MEDLINE/PubMed, Cochrane and Embase are described on figure 1.

MEDLINE/PubMed

(dental implantation, osseointegrated[MeSH Terms]) OR implantation, osseointegrated dental[MeSH Terms] OR osseointegrated dental implantation[MeSH Terms] OR osseointegration[MeSH Terms] AND (zirconium[MeSH Terms] AND titanium[MeSH Terms]) AND (dental implants[MeSH Terms] OR dental implants, single tooth[MeSH Terms] OR single tooth dental implants[MeSH Terms]) AND (dental implantation, endosseous[MeSH Terms])

Cochrane Library

["Dental Implantation, Endosseous" (MeSH descriptor) OR "Osseointegration" (MeSH descriptor)] AND "Zirconium" (MeSH descriptor) AND ["Dental Implants" (MeSH descriptor) OR "Dental Implants, Single-Tooth" (MeSH descriptor)]

Embase

'osseointegration'/exp AND ('zirconium oxide'/exp OR 'titanium'/exp) AND ('tooth implantation'/exp OR 'tooth implant'/exp OR 'single tooth implant'/exp)

Figure 1. Complete set of terms used on MEDLINE/PubMed, Cochrane and Embase, respectively.

Study selection

Restrictions were applied relating to the type of studies included, which included all studies with a prospective design (randomized controlled trials - RCTs, prospective cohort studies, prospective case-control studies, and prospective case series). All the others were automatically excluded from the review. After the removal of the duplicate records and reading titles and abstracts, one shortlisted studies were included for a full-text analysis. The author extracted data from the studies meeting the inclusion criteria.

Data extraction and management

The review author extracted data using Microsoft Excel spreadsheets for cataloging the extracted information. When in doubt, concerning the extracted data, the second review author (JPT) was contacted by email or personally.

Risk of bias and quality assessment of the included studies

The methodological quality of the included RCTs was evaluated using the Cochrane Collaboration's tool for assessing the risk of bias. Data was extract regarding sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective outcome reporting and risk of other potential sources of bias. Studies were classified as low risk (all domains with low risk), moderate risk (unclear risk of bias for one or more key domains) and high risk (one or more key domains with high risk of bias).

As part of the data extraction process, the qualitative assessment of the included prospective clinical trials was analyzed with the Newcastle-Ottawa Scale, regarding the selection, comparability, and outcome.

Summary measures and synthesis of results

To be able to answer the PICO question, the primary outcome measure set was the implant survival rate. Our secondary outcome measure was the marginal bone level (MBL, millimeters). The review author (SD) also extracted information necessary according to the inclusion criteria: number of patients, number of implants, and observation period (months). Then, others measures were extracted to complement the review: mean age (years), type of the implant, pieces, loading, bone regeneration and placement of the implant.

A meta-analysis was performed for our first and second outcome, only at 12 months of follow-up. For the survival rate, the first outcome, 7 included studies were used. Two studies^(15, 16) were excluded from this meta-analysis because they did not made reference to 12 months survival rate. For the MBL, the second outcome, all studies were included because they reported the same outcome measures at 12 months. Also a statistical sub-analysis was performed to verify if there was statistically significant influence regarding MBL, the type of loading and bone regeneration. Forest plot were used for graphic presentation of the results for main parameters.

Study selection

In the PRISMA flow diagram (figure 2) are described the details of the original search. The systematic database search retrieved a total of 1465 records. More specifically, the electronic search in MEDLINE/PubMed, Embase and Cochrane yielded 1373, 73 and 19, respectively. After removing duplicates, a total of 1390 articles were screened for title and abstract. After exclusion of articles irrelevant for this systematic review, 24 were selected for full-text analysis. Of these, 15 records could not be included in this review and reasons could be found on appendix A.

The articles for this systematic review consisted of nine publications: two RCTs (Cannizaro et al, 2010; Payer et al, 2015), three prospective cohort study (Kohal et al, 2012; Gahlert et al, 2015; Grassi et al, 2015), two prospective case series (Kohal et al, 2013; Payer et al, 2013), one prospective cohort investigation (Spies et al, 2018) and one prospective cohort clinical trial (Jung et al, 2015). The results of the included and analysed articles can be found on the table 1.

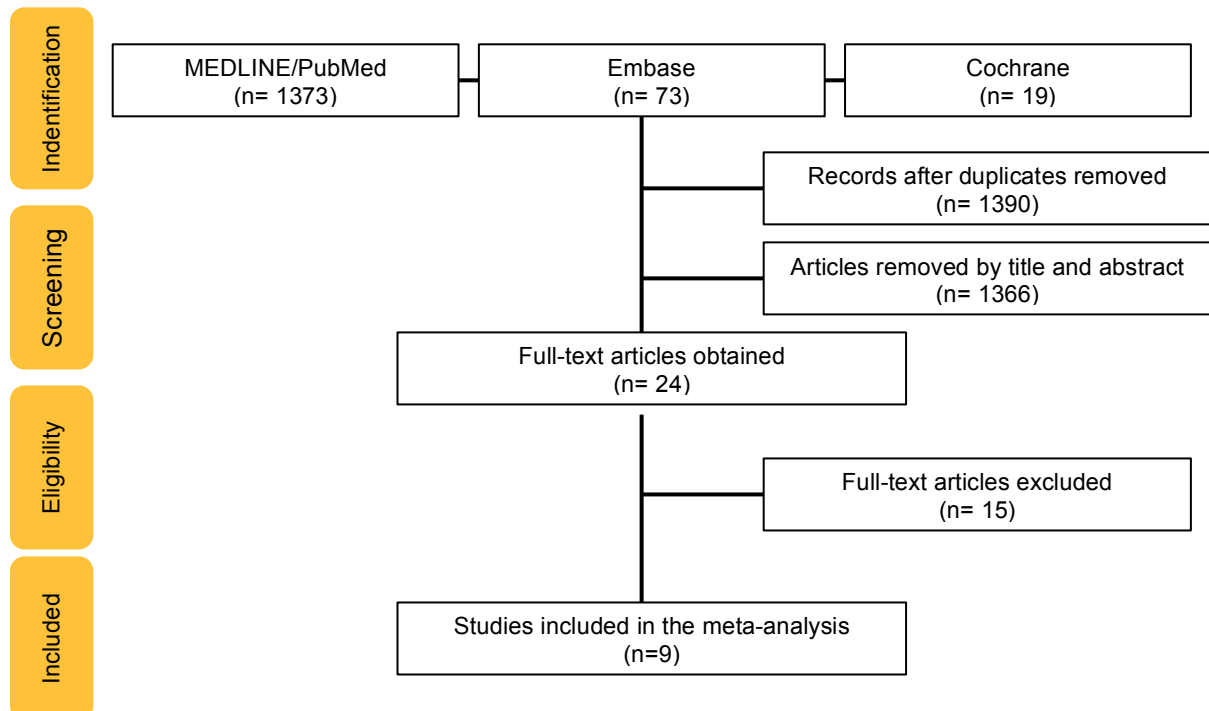


Figure 2. Flow diagram showing the entire identification and inclusion process, by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).

Table 1: Results of the Included and Analyzed Articles.

Author/Year	Patients, n	Mean age, y	Implants, n	Observation Period, m	Survival, %	Success, %	Mean \pm MBL, mm	Pieces	Type	Loading	Placement	Bone Regeneration
Spies et al, 2018 (Prospective cohort investigation)	54	48,1 \pm 13	71	12m (67 evaluated)	98,60%	-	0,60 (\pm 0,57)	One	ceramic implant; vitaclical, VITA Zahnfabrik, Bad Säckingen, Germany	Immediate	71 in healed sites	Guided bone regeneration procedures
				42,73m \pm 4,19 (65 evaluated)	98,50%		0,70 (\pm 0,72)					
				12m			0,67 (\pm 0,61)					
				42,73m \pm 4,19			0,73 (\pm 0,77)					
				12m			0,44 (\pm 0,43)					
42,73m \pm 4,19		0,64 (\pm 0,62)										
Cahlert et al, 2015; (prospective clinical study)	44	48	44	12 (\pm 4 weeks)	97,60%	97,60%	6 m: 0,88 (\pm 0,86) 12 m: 1,02 (\pm 0,90)	One	PURE Ceramic Implant; Institut Straumann AG, Basel, Switzerland	No immediate (Single-tooth)	44 in healed sites	Major bone augmentation (3m after surgery) and minor bone augmentation
Jung et al, 2015 (prospective cohort clinical trial)	58	-	71	12	98,30%	-	12m: 0,78 (\pm 0,79)	One	Ceramic implant, vitaclical, VITA Zahnfabrik, Bad Säckingen, Germany	Immediate	71 in healed sites	Guided bone regeneration procedures
							0,66 (\pm 0,61)					
							0,44 (\pm 0,42)					
Payer et al, 2015 (randomized controlled clinical trial)	22	46	31 (16 zirconia)	24	93,3 (mean survival of 16,2 m)	93,3	12m: 1,2 (\pm 1,01) 24 m: 1,48 (\pm 1,05) (only 7 zirconia implants to follow up at 24m)	Two	Ziterion vario z, Ziterion GmbH, Uffenheim, Germany	No immediate (Single-tooth)	16 in healed sites	-
Grassi et al, 2015 (prospective clinical cohort study)	17	52,3 \pm 4,8	32	12m and 60 (Mean obs 5,1y)	12m: 96,9% 60m: 96,8%	Optimal success was observed for all implants (96,9%); of 30 surviving implants, 29 showed success grade I and 1 success grade II.	12m: 0,83 \pm 0,24 60m: 1,23 \pm 0,29	One	White-SKY® Bredent Medical, Germany	Immediate (Single-tooth)	16 immediately and 16 in healed sites	Minor bone augmentation

Continuation of the table 1.

Author/Year	Patients, n	Mean age, y	Implants, n	Observation Period, m	Survival, %	Success, %	Mean \pm MBL, mm	Pieces	Type	Loading	Placement	Bone Regeneration
Kohal et al, 2013; (prospective case series)	28	53,6	56	12	98,20%	At the 1-year follow-up, 60% of the patients were success grade I and 72% success grade II.	1,95mm (\pm 1,71mm)	One	Nobel Biocare, Gothenburg, Sweden	Immediate (3-unit FDPs)	5 implants immediately after extraction and 51 in healed sites	Guided bone regeneration procedures
Payer et al, 2013 (prospective case series)	20	44,4	20	24	95% (22,9 m)	-	12m: 2,27 (\pm 1,0) 24m: 1,29	One	White-SKY® Bredent, Senden Germany	Immediate (Single-tooth)	20 implants immediately after extraction	-
Kohal et al, 2012 (prospective cohort study)	65	39,3	66	12	95,40%	At the 1-year follow-up, 66% of the patients were success grade I and 86% success grade II.	1,31mm (\pm 1,49mm)	One	Nobel Biocare, Gothenburg, Sweden	Immediate (Single-tooth)	5 implants immediately after extraction and 61 in healed sites	Guided bone regeneration procedures
Cannizaro et al, 2010 (RCT)	20	39	20	12	90%	-	0,72 (\pm 0,59)	One	Z-Systems, Oensingen, Switzerland	No immediate (Single-tooth)	5 implants immediately after extraction and 15 in healed sites	Minor bone augmentation
	20	38	20	12	85%	-	0,90 (\pm 0,48)	One	Z-Systems, Oensingen, Switzerland	Immediate (Single-tooth)	5 implants immediately after extraction and 15 in healed sites	Minor bone augmentation

Risk of bias/quality assessment of the included studies

The representation of the risk of bias is described in the figure 3.

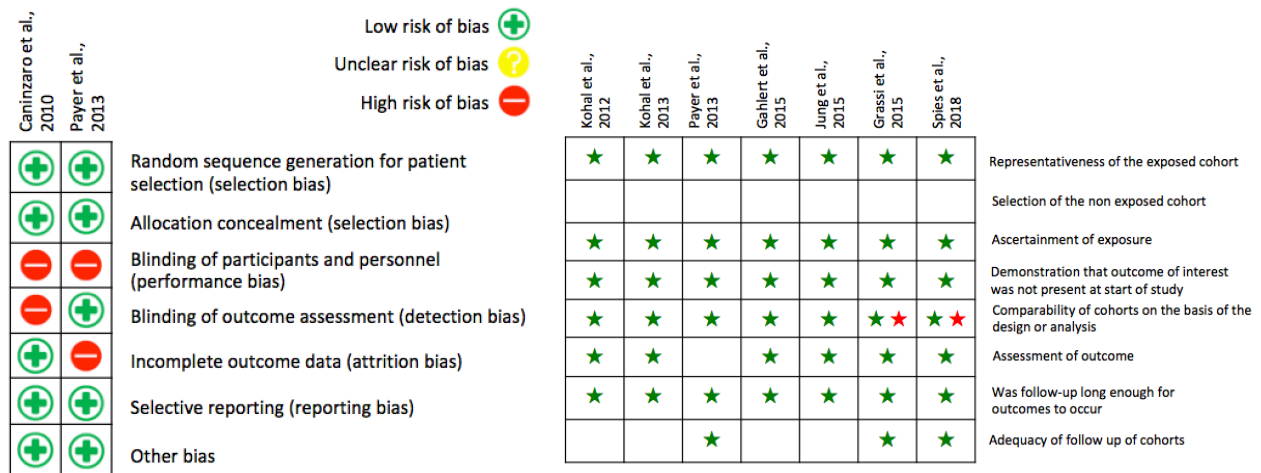


Figure 3: Representation of the risk of bias: RCT evaluated through the Cochrane Collaboration Tools and the Newcastle-Ottawa Scale to evaluated the prospective clinical trials.

The two randomized controlled trials ^(16, 17) were classified as high risk of bias because they both had a high risk of bias for one or more key domains, according with the Cochrane Collaboration Tools. So, it is important to have in attention when evaluating statistically both studies because they present a high risk of bias.

A star system was used to judged a study on three broad perspectives (the selection of the study groups, the comparability between the groups and the ascertainment of either the exposure or outcome of interest.) For the risk of bias analyzed with the Newcastle-Ottawa Scale most of the cases, the evaluation resulted in 6 stars. Two studies were classified with 8 stars. ^(20, 22) According to that scale, all the included studies presented with a low risk of bias.

Study characteristics

The 9 articles included a total of 348 patients with a mean age ranging from 38 ⁽¹⁷⁾ to 53,6 years ⁽²¹⁾ The follow-up was between 12 months ^(18, 19, 21, 23) and 60 months. ⁽²⁰⁾ One study presented a 3 years follow-up period. ⁽²²⁾

After analyzed the studies, two types of implants could be identified: an implant design as a single-piece and a two-piece implant that was used only in one study. ⁽¹⁵⁾ Studies also included different loading concepts (immediate/no immediate) with provisional restorations being or not out of occlusion, and different type of restorations (single-tooth restored with single-crowns or fixed dental prostheses). There were also two types of implant placement: immediately after extraction (type 1) or in healed sites (type 4).

Implant Survival

A total of 416 implants were at the data baseline but only 399 implants completed the 12 months of follow-up of the nine studies. The survival rate ranged between 85% ⁽¹⁷⁾ and 100%. ⁽²⁰⁾ Based on the authors, the early period after implant placement was when they identified most implant failure. ^(16-18, 20, 23)

Our meta-analysis resulted on a 12 months survival rate of 98% (95% confidence interval [95% CI]: 96% to 99%). There was no heterogeneity between the outcomes evaluated [Test for Heterogeneity: $Q(df = 7) = 5.5405$, $p\text{-val} = 0.5943$; $I^2 = 0.09\%$]. The forest-plot of the survival rates at 12 months of follow-up is represented on figure 4.

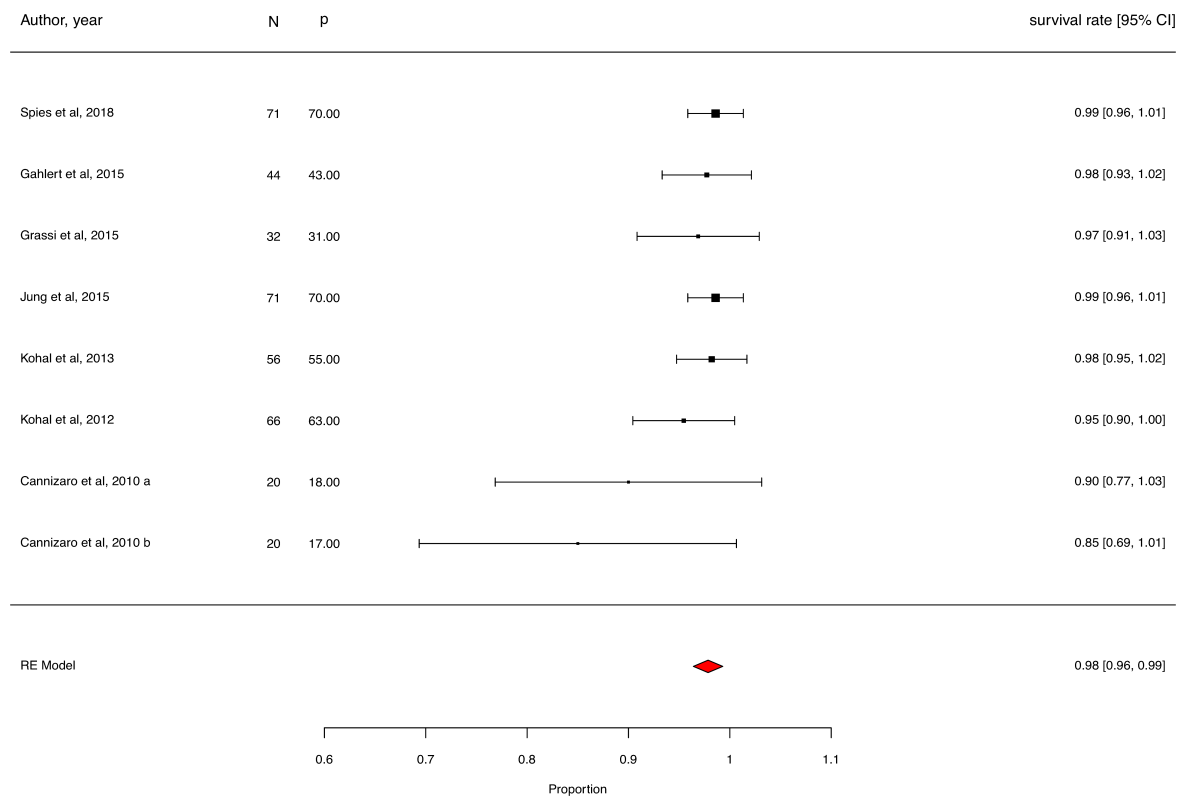


Figure 4: Forest-plot of the survival rates at 12 months of follow-up. 95% CI, 95% Confidence Interval

Marginal Bone Level

The MBL was evaluated at follow-ups and measured on standardized intraoral digital radiographs. The authors referred that the distance was measured from "the implant shoulder to the crestal bone margin". The values at 12 months ranged from 0,60 mm (SD: 0,57 mm)⁽²²⁾ to 2,27 mm (SD: 1,00 mm).⁽¹⁶⁾

The meta-analysis for the second outcome resulted in a MBL of -1.13mm (95% confidence interval [95% CI]: -1.45 to -0.80). The test for heterogeneity revealed heterogeneity between the 9 included studies [Test for Heterogeneity: $Q(df = 9) = 90.6093$, $p\text{-val} < .0001$; $I^2 = 95,82\%$]. As it is a loss of bone, in other words the bone decrease, the values were expressed in negative in the meta-analysis. The forest-plot of the MBL measures at 12 months of follow-up is represented on figure 5.

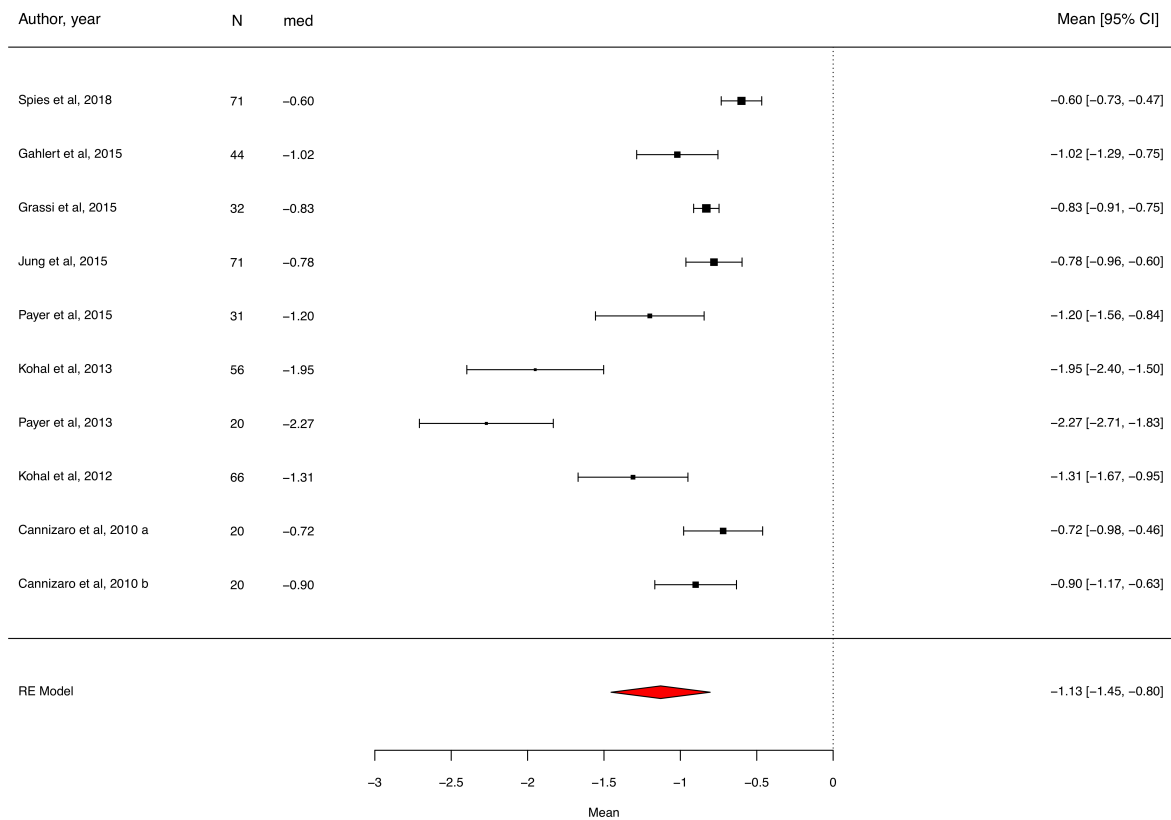


Figure 5: Forest-plot of the MBL measures at 12 months of follow-up. 95% CI, 95% Confidence Interval

Type of restorations

The nine studies mentioned different type of restorations. Six of these studies addressed single-tooth replacements all with cemented all-ceramic crowns ⁽¹⁵⁻²⁰⁾ one study considered 3-unit FDPs and all-ceramic three-unit bridges were cemented ⁽²¹⁾ and two studies included both types, also with cemented all-ceramic crowns and FDPs. ^(22, 23)

Implant Temporization and Loading

There were two types of implant temporization: seven studies performed immediate temporization ^(16-18, 20-23) and two performed no immediate temporization. ^(15, 19) Provisional

acrylic restorations were used in six of the studies performing immediate temporization of the implants. ^(17, 18, 20-23) Payer et al. ⁽¹⁶⁾ preferred to restore the implants with all-ceramic CAD/CAM provisionals crowns. The two studies which option was a non immediate temporization, made the definitive restoration in a delayed load concept after 11 to 13 weeks ⁽¹⁹⁾ and in a late load concept after 4 to 6 months after implant placement. ⁽¹⁵⁾

Concerning the implant loading, only one study referred to an immediately or non immediately loaded prosthesis. ⁽¹⁷⁾ Grassi et al. ⁽¹⁹⁾ applied an immediate loading concept. The others studies opted for leaving off the provisionals out of occlusion. The authors state that all "centric and eccentric contact points were removed to avoid any excessive forces on the implant". However, Jung et al. ⁽²³⁾ even if he tried to prevent the excessive occlusal and lateral loads, he opted for slight occlusal contacts.

A sub-analysis was performed to verified if there was statistically significant influence regarding MBL and the type of loading. The statistical analysis resulted in a MBL of -1.18 mm and -0.94 mm (95% confidence interval [95% CI]: -1.58 to -0.78 and -1.41 to -0.47), to immediate and no immediate loading, respectively. The test for heterogeneity revealed heterogeneity between the 8 included studies which have an immediate loading and the 2 with no immediate loading [Test for Heterogeneity (immediate): $Q(df = 7) = 85.9317$, $p\text{-val} < .0001$; $I^2 = 96.92\%$ and Test for Heterogeneity (no immediate): $Q(df = 1) = 4.5795$, $p\text{-val} = 0.0324$; $I^2 = 78.16\%$]. The forest-plot of the sub-analysis to verified if there was statistically significant influence regarding immediate loading or no immediate loading and MBL at 12 months of follow-up are represented on figure 6 and 7, respectively.

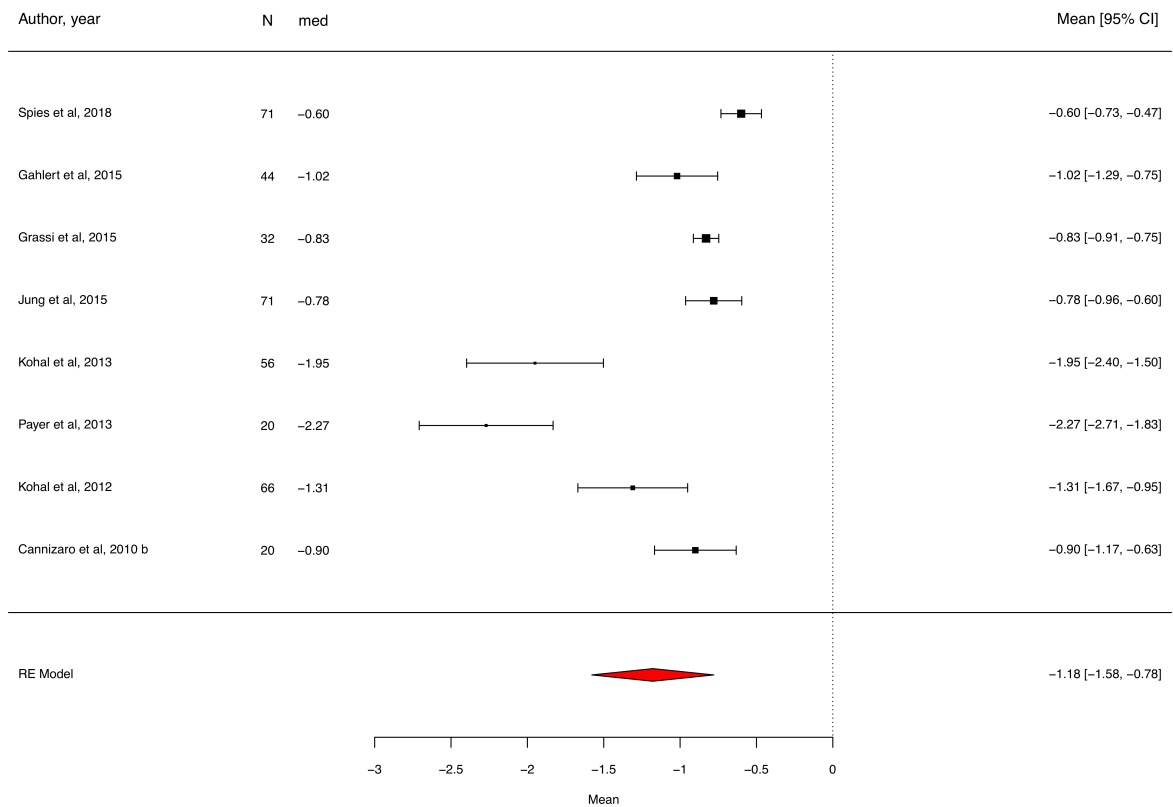


Figure 6: Forest-plot of the sub-analysis to verify if there was statistically significant influence regarding immediate loading and MBL. 95% CI, 95% Confidence Interval.

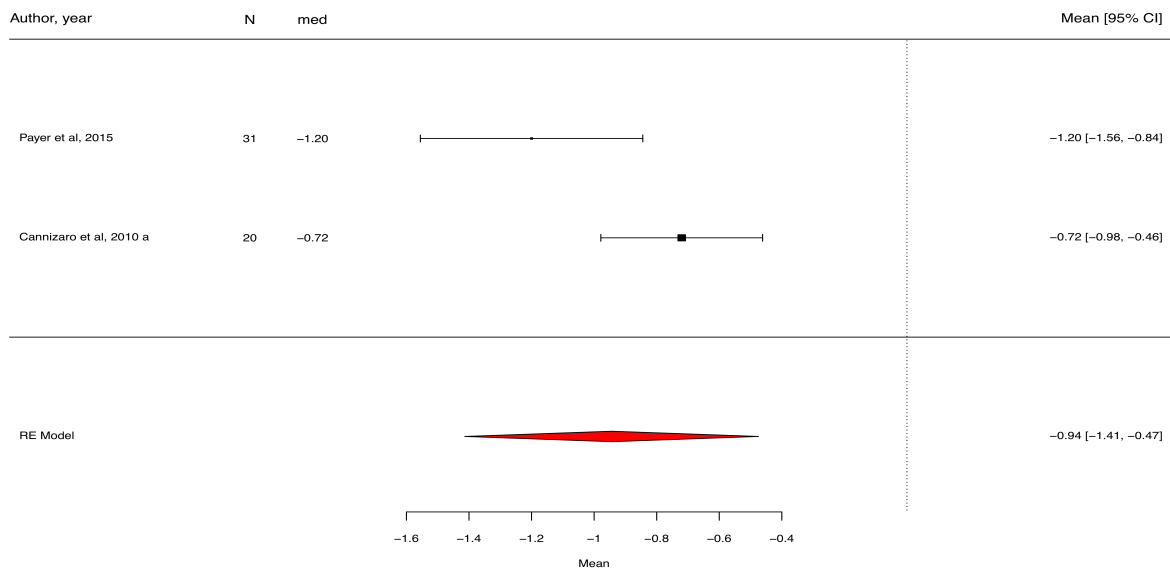


Figure 7: Forest-plot of the sub-analysis to verify if there was statistically significant influence regarding no immediate loading and MBL. 95% CI, 95% Confidence Interval.

Implant Placement

Only one study inserted the implant immediately after extraction (type 1 implant placement).⁽¹⁶⁾ In this study, a total of 20 implants were inserted in single-tooth gaps, which 11 were in the maxilla and 9 in the mandible. Four studies inserted implants in healed sites (type 3 or 4 implant placement) only.^(15, 19, 22, 23) Gahlert et al.⁽¹⁹⁾ referred a time of at least 8 weeks after tooth extraction (type 3 implant placement); the others four studies used all the techniques (type 1, 3 or 4 implant placement).^(17, 18, 20, 21) So, a total of 56 implants were placed immediately after extraction (type 1) and 360 implants were inserted in partial or completely healed sites. Grassi et al.⁽²⁰⁾ used both techniques (type 1 or 4 implant placement) and referred that in healed sites the survival rate was 100% and in immediately after extraction the rate decrease to 93,75%. Placement in healed sites can be a promising parameter because of the enhancing of a better primary stability that can translate in a better initial osseointegration.

A sub-analysis was not performed because a forest-plot could not be performed with the results of the placement type. This is because different studies use both techniques (type 1, 3 or 4 implant placement) and with a different number of implants depending on the technique. It would not be a reliable comparison.

Bone Regeneration

Of the nine studies, only two did not apply any type of bone regeneration.^(15, 16) Both studies state that patients with the need for bone augmentation were an exclusion criteria. Gahlert et al.⁽¹⁹⁾ was the only study to mention that a major augmentation with autogenous bone was necessary at least 3 months before implant surgery, in 31,8% of the cases and in addition, it was also performed a minor bone augmentation (synthetic bone grafts). Minor bone augmentation were necessary in two others studies^(17, 20), with Grassi et al.⁽²⁰⁾ performing that bone regeneration at seven implant sites and three in the study of Cannizzaro et al.⁽¹⁷⁾ The others studies referred to guided bone regeneration procedures with bovine bone or autogenous bone covered with a resorbable membrane.^(18, 21-23)

A sub-analysis was also performed here to verified if there was statistically significant influence regarding MBL and procedures of bone regeneration. The statistical analysis resulted in a MBL of -0.98mm and -1.73mm (95% confidence interval [95% CI]: -1.24 to -0.71 and -2.78 to -0.68), to the use of bone regeneration or not, respectively. The test for heterogeneity revealed heterogeneity between the 8 included studies which have bone regeneration procedures and no immediate loading [Test for Heterogeneity (bone regeneration): $Q(\text{df} = 7) = 45.4958$, $p\text{-val} < .0001$; $I^2 = 93.35\%$ and Test for Heterogeneity (no bone regeneration): $Q(\text{df} = 1) = 13.8095$, $p\text{-val} = 0.0002$ $I^2 = 92.76\%$]. The forest-plot of the sub-analysis to verified if there was statistically significant influence regarding bone regeneration procedures or no bone regeneration procedures and MBL at 12 months of follow-up are represented on figure 8 and 9, respectively.

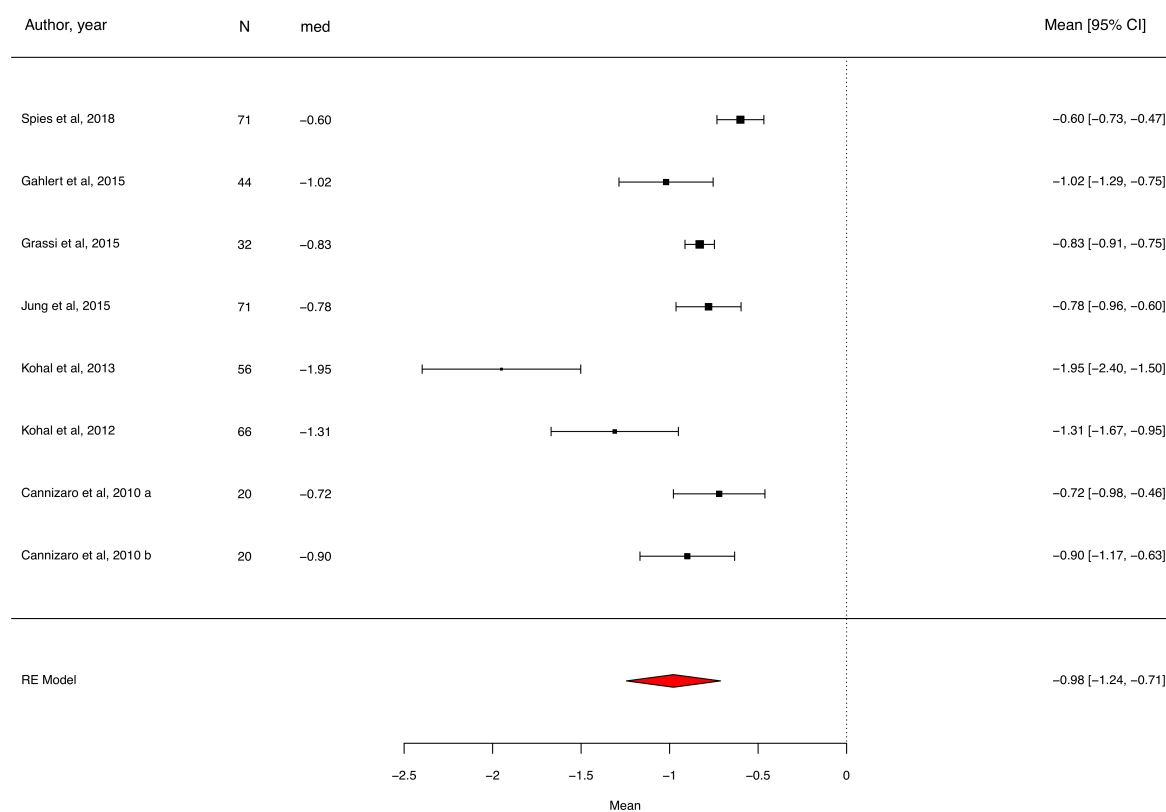


Figure 8: Forest-plot of the sub-analysis to verify if there was statistically significant influence regarding bone regeneration procedures and MBL. 95% CI, 95% Confidence Interval.

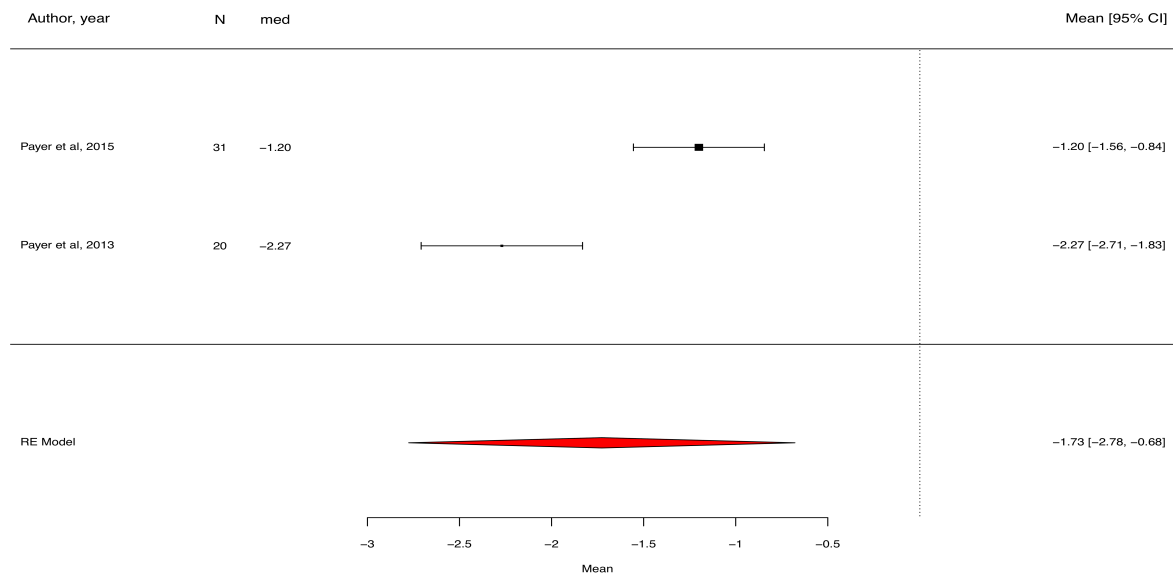


Figure 9: Forest-plot of the sub-analysis to verify if there was statistically significant influence regarding no bone regeneration procedures and MBL. 95% CI, 95% Confidence Interval.

VI - Discussion

Due to the aggressive marketing that exists today, it becomes necessary to know how we can improve our clinical results. Successful clinical results depend on different parameters in the treatment. So, clinicians and patients should have the opportunity to choose which type of implant to use to assure patient satisfaction and successful clinical outcomes, with an implant in function without complications and with good aesthetics. Titanium implants have been considered the gold standard. However, due to some disadvantages, like the color and the allergic reactions in some patients, new alternatives have arisen, as the zirconia implants.

The primary outcome measure set was the implant survival rate. The meaning of survival is the implant being *in situ* independently of the modifications that can occur during the observation period. It is therefore necessary to be judicious when referring to this parameter and its values, regarding its implications in our clinical practice. Branemark et al. reported the first retrospective clinical studies, which included the rates of osseointegrated implants. In completely edentulous arches, the authors referred survival rates of 78% and 86% in the maxilla and mandible after 15 years of function, respectively. ⁽²⁴⁾

In this systematic review the rates range between 85% ⁽¹⁷⁾ and 98,6% ⁽²²⁾, in a follow-up of 12 months. Cannizzaro and co-authors ⁽¹⁷⁾ obtained this survival rate when they placed the provisional crown in immediate occlusion with the opposite dentition. They also referred that 80% of failed implants were placed immediately after tooth extraction (four out of the five). This type of failures is considered as biological failure, which could be divided on early (failure to establish osseointegration, like in case of immediate loading) or late (failure to maintain the established osseointegration). Kohal et al. placed 5 implants immediately after extraction and 61 in healed sites ⁽¹⁸⁾ and 5 implants immediately after extraction and 51 in healed sites. ⁽²¹⁾ However, the authors did not discriminate in the 2012 publication ⁽¹⁸⁾ what the type of implant placement of the 3 that were lost. In the 2013 paper ⁽²¹⁾, they referred that one implant, which was placed immediately, failed after 21 days. Grassi et al. ⁽²⁰⁾ placed 16 immediately and 16 in healed sites. In this prospective clinical cohort study, one immediate implant was lost after 3 months, making a survival rate of 93,75% and 100% in immediately and in healed sites, respectively. Not many studies evaluated both type of placement (immediately after extraction or in healed sites) with zirconia implants, making more difficult to compare the two types. Spies et al. ⁽²²⁾ obtained the higher survival rate of 98,5%, after 3

years in function. One implant was lost 5 weeks after implantation due to a loss of osseointegration. Payer et al. ⁽¹⁵⁾, in a randomized controlled clinical trial, was the only one to evaluate two-piece zirconia implants compared to titanium implants. The survival rate was 93,3%, showing no significant difference in the clinical outcome between zirconia and titanium implants. Clinically and radiologically all implants were osseointegrated. To our knowledge, it is the only study that placed two-pieces zirconia implants; the values showed no difference between titanium and zirconia implants but comparing to one piece zirconia implants the survival rate was lower. Nevertheless, this two-pieces systems, can afford some advantages like the sub-gingival placement (submerged implant) that can afford lower initial forces on the implant and, consequently, translate a better initial osseointegration. More data are necessary to draw final conclusions about this two-pieces zirconia implants, which can be very promising.

Our goal was to have as a primary outcome the implant success rate, which is a more reliable parameter for clinical practice, but the different studies did not refer it or used different classification criteria to set the implant success. Despite the use of different classifications, there is no clinical implication, because the major criterion that is to keep the implant in the mouth within well established parameters is covered by all classifications. However, it was not possible to extract data appropriately and to compare between them all the studies about the success rates. Success is classified differently among authors. Ostman et al. ⁽²⁶⁾ classified as success grade I (bone loss ≥ 2 mm) and success grade II (bone loss ≥ 3 mm) and Albrektsson et al. ⁽²⁷⁾ classified as grade I when there are no clinical and radiographic signs of pathology and ≤ 2 mm MBL at the first year of follow-up and grade II if it had no clinical and radiographic signs of pathology and > 2 mm MBL during the first year of follow-up.

Four studies did not mention the success rates of the zirconia implants. ^(16, 17, 22, 23) Grassi et al. ⁽²⁰⁾ referred an optimal success was observed for all implants (96,9%) of 30 surviving implants (29 showed success grade I and 1 success grade II). Others two studies ^(15, 19) also referred that the implant success was the same as implant survival rates (97,6% and 93,3%, respectively). Kohal et al. make reference to the success rates and despite the high survival rates of 95,4% ⁽¹⁸⁾ and 98,2% ⁽²¹⁾, when they consider the MBL as a success criteria, 66% of the patients were success grade I and 86% success grade II ⁽¹⁸⁾ and 60% of the patients were success grade I and 72% success grade II, at the 1-year follow-up. ⁽²¹⁾

The MBL, which was our secondary outcome measure, is an important criteria to classify an excellent clinical result and the maintenance of periodontal health, being a translation of an effective osseointegration. The goal is to have a minimal long-term loss of marginal perimplant bone levels. According to Buser et al.⁽²⁾, during the first five years, it is well accepted that crestal bone loss is an inevitable phenomenon. For successful osteointegrated implants, in the first year, a marginal bone loss is between 1-1.5 mm after placement and a bone loss of 0.2 mm annually can be expected. However presently, advance in vitro and clinical research guided us to a new world of new implants designs and materials, so these values tend to decrease.

To evaluate the MBL a radiographic analysis is required. To make sure that all radiographs were taken in the same position, two techniques were used and all studies referred an paralleling technique used to radiograph. Of the 9 included studies, 8 studies referred or the use of an holder beam aiming device^(15, 19, 20) or a customized radiographic stents attached to the cone of the radiographic source.^(18, 21, 23, 25) One study did not make reference to the technique used to ensure the same position.⁽¹⁷⁾ The MBL was measured using different softwares. A critical aspect is that different techniques and software used may lead to discrepancies in the measures of the MBL, between the different studies. In the same study, imperceptible errors can always occur. Also the three-dimensional aspect is not evaluated in a periapical radiography. The validity of this radiographic analysis in these cases is therefore insufficient for a completely reliable evaluation.

Despite the cause of crestal bone loss is an unanswered question, it is generally pointed as an adaptive response to loading and surgical trauma. This bone loss can compromise the results and lead to implant failure, with a risk of implant loss, making necessary to identify the type of implants (implant material, implant design, etc.) that better avoid or minimize this crestal bone loss.

In this systematic review, the values at 12 months ranged from 0,60 mm (SD: 0,57 mm)⁽²²⁾ to 1,95 mm (SD: 1,71 mm)⁽²¹⁾. Spies et al.⁽²²⁾, who evaluated the mean marginal bone loss at 3 years of follow-up after the final prosthetic restoration, referred a value of 0.70 mm (SD: 0,72 mm). The authors also reported that between the implant surgery and the insertion of the final restoration they observed the largest marginal bone loss.⁽²²⁾ Forty eight implants

received a single-crown and eleven a fixed dental prosthesis, reporting marginal bone loss of 0,67 mm (SD: 0,61 mm) and 0,44 mm (SD: 0,43 mm) at 12 months and 0,73 mm (SD: 0,77 mm) and 0,64 mm (SD: 0,62 mm) at 3 years of follow-up. Also in this prospective cohort study, 13% and 56% of the implants gained marginal bone and lost less than 1 mm, respectively. Jung et al. ⁽²³⁾ in a prospective cohort clinical trial made the same comparison and reported on 49 implants who received a single-crown a value of 0,66 mm (SD: 0,61 mm) and on 22 implants who received a fixed dental prosthesis a value of 0,44 mm (SD: 0,42 mm), at 12 months of follow-up. Kohal et al. ⁽²¹⁾, in a prospective case series, stated the higher value of the MBL, from implant insertion to 12 months of follow-up on the 25 patients evaluated. They referred that 2% of the patients gained some bone; however, in 40%, 28% and 12% of the patients lost more than 2 mm, 3 mm and 4 mm of bone, respectively. They found a correlation between the flap design and bone loss ⁽¹⁷⁾, where implants placed with no flap (4.52 mm; SD=1.5 mm) or with the punch technique (4.13 mm; SD= 3.5 mm) showed more bone loss comparatively with a flapped approach (1.66 mm; SD= 1.8 mm). Grassi et al. ⁽²⁰⁾ showed values for the MBL at 12 months and 60 months (5 years) with statistically significant difference ($p < 0.0001$), which were 0,83 mm (SD= 0,24 mm) and 1,23 mm (SD= 0,29 mm), respectively. At 12 months of follow-up, 5 implants lost 1.1 to 2.0 mm of bone; this number increased to 12 implants having lost this amount of bone at 60 months. In this prospective study, no significant difference was found between the intervention timing at 12 and 60 months of follow-up ((immediate: 0,88 mm (SD= 0,22 mm) and 1,29 mm (SD= 0,25 mm); healed sites: 0,78mm (SD= 0,26 mm) and 1,17 mm (SD= 0,33 mm)). Payer et al. ^(15,16) also referred values of MBL at 24 months; in the prospective case series of 2013 publication ⁽¹⁶⁾, the mean bone loss after 24 months was 1.29 mm on 20 zirconia implants, not reaching further significant differences compared to initial implant insertion ($p > 0.05$). In the study of 2015 ⁽¹⁵⁾, the value was 0.19 mm higher (SD= 1,05 mm), but only 7 zirconia implants were evaluated at 24 months.

Our goal was also to try to evaluate with a sub-analysis if there was statistically significant influence regarding MBL and the type of loading and bone regeneration procedures. The heterogeneity was too bigger to allow a reliable conclusion. However, it was possible to verified that the values of MBL were lower when bone regeneration procedures and no immediate loading were evaluated. Despite this, it is important to pay attention that only two studies were analysed to the no immediate loading. A sub-analysis regarding the survival rate was also thought out. However, we would obtain results with also a huge heterogeneity and the focus of the meta-analysis would be lost. So, we only opted to make a sub-analysis

regarding the MBL, an important criteria to translate an effective osseointegration

Some values should be taken as goals for zirconia implants. To our clinical practice, it is important to guide us according to the success rates. Titanium alloys have success rates of 92-98% after 10 years, which could be a promising goal to zirconia implants too. Survival rate, that was our first outcome, is also an important clinical factor. Promising rates ranging from 85% to 100% were reported in this systematic review, so we could be ambitious and point to values around 98% on a 12 months follow-up. However, it is necessary to take into account all the conditions and parameters that can change these rates and the question of clinical survival and its clinical implications. The MBL, our second outcome, is also an important factor to translate an effective osseointegration. The values at 12 months ranged from 0,60 mm to 2,27 mm in this review, with a statistical analysis referring an MBL of 1,13 mm, values that are among those considered to have successful osseointegrated implants.

VII - Conclusion

It is important to emphasize that the strategy showed could result in a loss of relevant data. An inadvertent exclusion of relevant articles may be provided by the conjugation of MeSH terms and the boolean connectors. So, a combination of MeSH terms and text words should be used in different databases to ensure the best search quality

Recently, the option for zirconia implants has increased exponentially due to the characteristics offered by the material. Survival and success rates along with marginal bone level (MBL), which translates into an effective osseointegration, present values very similar to titanium implants. Although these rates are promising to 1 year and comparable to 2 years of follow-up, more studies with a longer follow-up are required, which present not only the survival rates of zirconia implants but also their success rates.

The conclusion values for the survival rate and for the MBL are 98% and 1,13 mm at the 12-month follow-up, respectively. Maintaining these values in the coming years and consequent data makes zirconia implants very promising for clinical application.

VIII - Implications for Clinical Practice

Despite this systematic review was guided by the recommended guidelines, a lack of higher scientific evidence and a short follow-up of the included studies must be taken into account. A high level of evidence can provide results that will later be more reliable in clinical practice. Also, a larger follow-up will allow us to have a more correct long-term notion of clinical outcomes.

All included studies only made a reference for single-tooth gaps or/and 3-unit fixed dental prostheses. The showed outcomes are similar to those of titanium implants making zirconia

implants a valuable option in particular clinical cases. More studies with different kind of rehabilitations and a considerable longer follow-up period are necessary to expand the clinical practice with zirconia implants.

A point to have in consideration is that outcomes could be modified by each patient individual biology. The experience of the dentist and the patient compliance are crucial to ensure a good prognosis. It is, also, important to highlight that each patient has a different need and a good planning should always be taken into account, in order to obtain the best and more reliable clinical result.

This systematic review does not make reference on surface modifications that aimed to improve osseointegration. Subtle changes on the surface implant, as etching, sintering, coating or sandblasting, can have a high impact on bone apposition, so particular attention has to be paid to this in future reviews.

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XI - Appendix

Article	Reason for exclusion
Blaschke and Volz et al., 2006	Retrospective design; No mbl measurements
Pirker and Kocher et al., 2009	No mbl measurements; <15 patients
Oliva et al., 2010	No mbl measurements
Borgonovo et al., 2012	<15 patients
Borgonovo et al., 2013	<15 patients
Turk et al., 2013	No survival values
Gahlert et al., 2013	Retrospective design
Osman et al., 2013	Pilot study design; <15 patients
Brull et al., 2014	Retrospective design
Cionca et al., 2015	No mbl measurements
Roehling et al., 2015	Retrospective design
Siddiqi et al., 2015	No survival values
Spies et al., 2015	No zirconia implants (ATZ)
Jank et al., 2016	Retrospective design
Kohal et al., 2016	Clinical cohort design

Appendix A: Reasons for exclusion when 24 articles were screened.

XII - Index

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