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REVIEW ARTICLE

Influence of surface electric charge of Ti implants on osteoblastic interaction: A systematic review

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KEYWORDS

Titanium;
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Dental implant;
Electrical charge;
Zeta potential;
Osseointegration

Abstract *Objective:* A critical analysis of the existing literature to answer "What is the influence of electrical charge of titanium alloys in the electrical interaction with osteoblastic cells for osseointegration?".

Design: This systematic review followed PRISMA. The personalized search strategy was applied in PubMed, Science Direct, Embase, and Scopus databases, furthermore, in the grey literature in the Google Scholar and ProQuest. The selection process was carried out in two stages independently by two reviewers according to the eligibility criteria. The risk of bias was also analyzed.

Results: When applying the search strategy, 306 articles were found, after removing duplicates 277 were analyzed by title and abstract, of which 33 were selected for full reading, of which 10 met the eligibility criteria. And one was included from the additional literature search. Of these, all had a low risk of bias.

Conclusions: 1. The phenomenon of osseointegration is complex and, independent of the superficial electrical charge of the implant, it may occur. To understand osseointegration, attention must be paid to the synergistic action of the electrical potential; chemical composition, intrinsic to the alloy and from surface treatment; and topography, which will determine the speed of adhesion, proliferation, and osteoblast differentiation. 2. The presence of $Ca2+$ deposited on the surface acts as a driving force for biomineralization that induces osteoblastic attraction and differentiation; 3. For a better understanding of the current literature, more studies are needed to describe the osteogenic regulation process through protein mediation; 4. Topography and chemical composition act as decisive parameters for cell viability independent of the attractive electrical charge.

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Contents

1. Introduction

Titanium alloys are mostly indicated for biomedical rehabilitation because they present, a high strength/weight ratio, corrosion resistance, and certain biocompatibility, chemical inertness, which makes stable integration with bone tissue difficult (Bandyopadhyay et al., 2019; Dai et al., 2019; Ferraris et al., 2019; Tovani et al., 2019; Wei et al., 2019; Raja et al., 2020; Zhang et al., 2020). The layer of TiO_2 formed automatically when exposed to the environment is dielectric and capacitive, capable of accumulating electrical charge, therefore, studies aim to understand the influence of charge storage on osteoblastic interaction to promote a stable *peri*-implant integration in the short term (Salari et al., 2011, 2012; Bandyopadhyay et al., 2019; Singh et al., 2021).

The osteoblastic interaction is dependent on the topography, chemical composition, and charge, thus, superficial treatments are proposed to promote bioactivity to the implants (Jin et al., 2014; Dai et al., 2019; Ferraris et al., 2019; Raja et al., 2020; Dias Corpa Tardelli et al., 2020b). Through modifications in the electrical system through physical and chemical methods that change the charge and its polarity, and thus directly interfere with adhesion, proliferation, and osteoblast differentiation, nevertheless, the literature presents few studies focused on the electronic influence of the oxide layer on bioactivity (MacDonald et al., 2011; Ghimire et al., 2014; Löberg et al., 2014; Vandrovcova et al., 2021).

Controlling and understanding the phenomenon of osseointegration at the material cell interface is crucial for the development of pro-osteogenic surfaces (Ceylan et al., 2014; Dias Corpa Tardelli et al., 2020a, 2020b; Krenek et al., 2021). Studies infer those positive marks promote greater attraction since osteoblast cells have a negative electrical charge due to their content of hyaluronic acid in its pericellular lining, however, it is necessary to elucidate this process (Finke et al., 2007; Patil et al., 2007; Guo et al., 2012; Jin et al., 2014; Rebl et al., 2016; Krenek et al., 2021).

In addition to electrostatic interaction, the cell flattening and spreading is dependent on protein adhesion points stimulated by Ca^{+2}, osteoconductive (Bodhak et al., 2010; Dai et al., 2019; Lin et al., 2020; Krenek et al., 2021), which may or may not be present and are dependent on the amount of ions present. And in this case, the negative charge of the implant surface induces biomineralization by stimulating Ca^{+2} precipitation on the surface (Zhu et al., 2004; Bodhak et al., 2009; Tovani et al., 2019).

Such factors are related, in addition to osteogenic induction, to antibacterial activity dependent on negative electrical potential and its lower susceptibility to adhesion since most bacteria have negative cell walls (van Loosdrecht et al., 1990; Hamouda and Baker, 2000; Rabea et al., 2003; Hu et al., 2012; Ghimire et al., 2014; Yang et al., 2016; Ferraris et al., 2019; Kreve and Reis, 2021). Therefore, this systematic review aimed to promote the knowledge of pro-osteogenic surfaces by verifying the factors involved in this process and if only positive surfaces are favorable to osseointegration through a critical analysis of the existing literature through the question "What is the influence of the electrical charge of titanium alloys on the electrical interaction with osteoblastic cells for osseointegration?".

2. Material and methods

2.1. Elaboration

This systematic review followed the guidelines of the Preferred Reporting Items for Systematic Review and Meta Analyzes Protocols (PRISMA 2020) (Page et al., 2021) and was registered in the Open Science Framework (osf.io/ud8t7). The acronym PICOS was structured according to the research question "What is the influence of the electrical charge of titanium alloys on the electrical interaction with osteoblastic cells aiming at osseointegration?" P = surface of titanium alloys; I = electrical charge; C = control group; O = interaction with osteoblastic cells; S = in vitro experimental studies. The personalized search strategy was applied to the Embase, PubMed, Scopus, and Science Direct databases on August 31st, 2021, without the restriction of time, furthermore, the

search in the grey literature was applied to Google Scholar and ProQuest (Table A.1).

2.2. Eligibility criteria

For the selection process of the articles to be included in this systematic review, in vitro experimental articles that evaluated the electrical charge of titanium alloy surfaces for implants and their interaction with osteoblasts were defined as inclusion criteria. Exclusion (1) Did not evaluate electrical charge of the surface, (2) Did not evaluate osteoblastic cell; (3) Polarized by application of an external field, (4) systematic reviews, book chapters, conference abstracts, (5) articles with no full text available, (6) Did not have a control group.

2.3. Selection process

The article selection process was carried out in two stages. In the first step, reviewers J.D.C.T and A.C.R evaluated the title and abstract of the articles found after applying the search strategy in the Rayyan web application according to the eligibility criteria, to select the articles to be read in full. In the second step, J.D.C.T and A.C.R independently assessed the articles selected for full reading according to the eligibility criteria. Doubts regarding the inclusion or not of the article were resolved by the coordinator of the A.C.R.

2.4. Data extraction

Data tabulation was performed in an Excel spreadsheet according to the criteria (a) Author, year; (b) Chemical composition/Surface treatment; (c) Groups; (d) Electric potential evaluation method; (e) Results; (f) Osteoblastic viability assessment method; (g) Cell; (h) Results (Table 1).

2.5. Risk of bias

Since there is no specific tool for experimental in vitro studies in the literature, the Joanna Briggs Institute checklist for quasi-experimental studies (Tufanaru et al., 2017) as was used in the study by Nagendrababu et al., 2018. The risk of bias classification was performed in the RevMan 5.3 software (The Nordic Cochrane Center) according to the criteria (1) if all answers were considered positively, low risk of bias (high methodological quality), (2) if more than 65 % of responses positively moderate risk of bias (moderate methodological quality), (3) if less than 65 % of responses are considered positively, high risk of bias (low methodological quality).

3. Results

When applying the personalized search strategy in Embase, PubMed, Scopus, Science Direct databases, 306 articles were found, after removing duplicates, 277 articles were screened by title and abstract, of which 33 were selected for a full reading of and, these 10 (Hu et al., 2012; Zhang et al., 2012; Ghimire et al., 2014; Jin et al., 2014; Yang et al., 2016; Dai et al., 2019; Ferraris et al., 2019; Tovani et al., 2019; Wei et al., 2019; Krenek et al., 2021) met the eligibility criteria and were included in this review and 22 excluded (Table A.2). The additional search in the reference list of included articles resulted in the inclusion of the article by Li et al., 2020. Fig. 1 demonstrates the selection process.

In the studies by Hu et al., 2012, Tovani et al., 2019, Wei et al., 2019, Yang et al., 2016, and Zhang et al.2012 the surface treatment applied to Ti surfaces by immobilization of vascular endothelial growth factor on Ti by either covalent binding or heparin-VEGF (Hu et al., 2012), immobilization of Col and CaCO3 by LbL immobilization of Col and $CaCO_3$ by LbL (Tovani et al., 2019), silicon-doped hydroxyapatite (Si-HA) deposited by Plasma electrolytic oxidation (PEO) and microwave hydrothermal (MH) (Wei et al., 2019), immobilization of gold nanoparticles onto TiO2 nanotubes by 3-aminopropyltrimethoxysilane (APS) (Yang et al., 2016), and immersion in 5 mL of 30 wt% H2O2 80 ℃ for 6 or 24 h followed by calcined at 450 ℃ (Zhang et al., 2012) promoted a negatively charged surface that provided improved adhesion and osteoblast proliferation.

While in the studies by Ghimire et al., 2014, Jin et al., 2014, and Dai et al., 2019 the surface treatment applied to Ti surfaces by acid etching followed by immobilization of chitosan (Ghimire et al., 2014), Zn/Ag co-implantation by arc plasm (Jin et al., 2014), and immobilization of rhBMP-2 by electrostatic interaction (Dai et al., 2019) promoted a positively charged surface in which there was improved adhesion and osteoblast proliferation. While in the study by Li et al., 2020 the decrease in zeta potential by hydrothermal treatment favored osteoblastic adhesion and mineralization.

Unlike the study by Krenek et al., 2021, in which the surface treatment applied by laser surface texturing (LST) followed by chemical treatment with NaOH–$CaCl_2$-heat-water treatment on titanium was biocompatible to a certain extent, in addition to making the surface more negative compared to those without treatment, inhibited to some extent the metabolic activity of osteoblastic cells and changed their shapes. In the study by Ferraris et al., 2019 the superficial treatment of etching in dilution hydrofluoric acid followed by controlled oxidation in hydrogen peroxide in Ti-6Al-4 V turned the surface more negative and, did not significantly interfere with osteoblastic cell adhesion and viability when compared to control.

Regarding the risk of bias, all studies presented a low risk. (Figs. 2 and 3). Because the studies show heterogeneity in titanium alloy, surface treatment, electrical potential assessment, osteoblastic activity assessment, and cell assessment, statistical analysis, meta-analysis, is not possible.

4. Discussion

It is the osteoblastic cell biomaterial interaction that motivates the development of pro-osteogenic implants to speed up this initial step and promote osseointegration in the short term. One of the properties of the biomaterial that directly interferes is electronics, so this systematic review, the first in the literature, allowed to answer the research question and infer that regardless of the surface charge is positive, it will occur. Because it is the result of the synergistic action of the electric potential; chemical composition, intrinsic to the alloy and from the surface treatment; and topography; which will determine the speed of osteoblastic adhesion, proliferation, and differentiation.

Table 1 Characteristics of included studies.

Author, year	Chemical composition/ surface treatment	Groups	Electric potential evaluation method	Results	Osteoblastic viability assessment method	Cell	Results
Dai et al. 2019	Ti Surface treatment: immobilization of rhBMP-2 by electrostatic interaction.	Ti^A TA^B TA/BPP^C $TA/BPP/BMP\text{-}2^D$	Surface potentials by Solid Surface Zeta Potential Analyzer	$31,2^C < 0^A < +7,76^B < +9,3^D$	CCK-8	MC3T3-E1	Group D was the best for cell adhesion and viability.
Ferraris et al. 2019	Ti-6Al-4 V discs Chemically-treated: association of etching in hydrofluoric acid and oxidation in hydrogen peroxide	$Ti6Al4V–MP^A$; $Ti6Al4V–CT^B$;	Zeta potential	The negative electrical charge in descendent order B > A	Alamar Blue	hFOB 1.19	There were no statistically significant differences in cell adhesion and viability.
Ghimire et al. 2014	Ti Surface treatment: association of acid etching and chitosan immobilization.	$UN\text{-}Ti^A$ $SA\text{-}Ti^B$ $SA\text{-}CS\text{-}Ti^C$	Zeta potential by particle analyzer.	$0,81^A < 4,15^C < 5,56^B$	MTT and SEM	SaOS-2	Viability and cell adhesion was significantly higher on treated surfaces B and C compared to A. The highest for C.
Hu et al. 2012	Ti Surface treatment: immobilization of VEGF or heparin-VEGF by covalent binding.	Ti^A $Ti\text{-}HAC^B$ $Ti\text{-}HepC^C$ $Ti\text{-}HAC\text{-}VEGF^D$ $Ti\text{-}HepC\text{-}VEGF^E$	Zeta potential by SurPass electrokinetic analyser	$78,6^C < -57,5^E < 32,5^B < 23,1^D < -10,4^A$	Alizarin Red staining	hOBs	The osteoblastic mineralization of A, B and C were similar. Whereas, that of E was the highest and different from that of D.
Jin et al. 2014	Ti Surface treatment: Zn/Ag co-implantation by arc plasm	Ti^A $Zn\text{-}PIII^B$ $Ag\text{-}PIII^C$ $Zn/Ag\text{-}PIII^D$	Zeta potential by Surpass electrokinetic analyzer	The negative electrical charge in descendent order A > C > D > B	Alamar Blue	rBMSCs	The ion-treated samples are more favorable for cell adhesion and proliferation, the best being D.
Krenek et al., 2021	Ti-grade 2 Structured by LST Chemical treatment: NaOH–CaCl2-heat-water treatment	Pristine $flat^A$; Chemical treated $flat^B$; pristine $structured^C$; Chemical treated $structured^D$.	Zeta potential by SurPASS Instrument	$-68mV^B < -65mV^A < -51mV^D < -39mV^C$.	Alizarin staining and quantification	hMSCs	It is inferred that surface D showed less viability due to surface treatment, electrical potential, and topography.
Li et al. 2020	Ti Surface treatment: hydrothermal.	Ti^A; $NW\text{-}Ti^B$; $NN\text{-}Ti^C$; $NF\text{-}Ti^D$.	Zeta potential by Surpass electrokinetic analyzer	The negative electrical charge in descendent order A > D > C > B	Extracellular Matrix Mineralization Assay and Immunofluorescence	BMSCs	Group B showed the highest adhesion and mineralization of BMSCs.
Tovani	Ti	$Ti^ATi\text{-}$	Zeta potential	$19^C < -2,7^A < -0,8^B$	MTT	osteoblast	The viability of osteoblastic cells in B and C were

Table 1 (*continued*)

Author, year	Chemical composition/ surface treatment	Groups	Electric potential evaluation method	Results	Osteoblastic viability assessment method	Cell	Results
et al. 2019	Surface treatment: immobilization of Col and $CaCO_3$ by LbL.	$(PAA/Col)_6^B$Ti-$(PAA/Col)_6NT^C$	by Zetasizer Nano ZS instrument				similar and 1.4 times higher than in A.
Wei et al. 2019	Ti sheets Surface treatment: Si-HA, PEO, and MH.	Ti^A; $TiPEO^B$; $TiPEO\text{-}MH^C$	Zeta potential	$46{,}61^B < -28{,}68^C < -11{,}14^A$	SEM	MC3T3-E1	All samples were viable for cell migration and adhesion. It is emphasized that the micro/nanostructure of C was better than that of A and B which showed no significant differences.
Yang et al. 2016	Ti Surface treatment: immobilization of gold nanoparticles onto TiO2 nanotubes by APS	TNT^A $GNP\text{-}1^B$ $GNP\text{-}3^C$	Zeta potential by Surpass electroki-netic analyzer	The negative electrical charge in descendent order C > B > A	Alamar Blue and fluorescence microscopy	rBMSCs	Surface C promoted greater cell adhesion and viability followed by B and A respectively.
Zhang et al. 2012	Ti Surface treatment: immersed in 5 mL of 30 wt% H2O2 80 ° C for 6 or 24 h followed by calcined at 450 ℃	Ti^A $Ti\text{-}6^B$ $Ti\text{-}24^C$	Zeta potential by Surpass electrokinetic analyzer	$8^C < -7^B < -5^A$	Adhesion assay	rBMMSCs	Cell adhesion was highest in C followed by B and A.

Ag-PIII, Ti treated by plasma immersion Ag implantation according to parameters III; APS, 3-aminopropyltrimethoxysilane; AS-CS-Ti, Ti immersed in 48 % H_2SO_4 + 5 mg/mL dopamine hydrochloride in 10 % 0.1 M Tris–HCl + immersion in 3 % glutaraldehyde at 0.5 % chitosan solution (in 1 % acetic acid aqueous solution); BMSCs, mouse bone marrow mesenchymal stem cells; BPP, Butylamin-*b*-poly(2-(2-pyridinyldithio)ethylamineaspartate-*co*-(butylenediamine aconitic acid) amineaspartate; CCK-8, cell counting kit-8 (KeyGEN Biotech, China); Col, collagen; D1 stem cells, bone marrow mesenchymal stem cells, line cloned from Balb/C mice, ATCC; GNP-1, heat treated TiO2 nanotubes followed by APS during 1 h; GNP-3, heat treated TiO2 nanotubes followed by APS during 3 h; hFOB 1.19, Cells Human osteoblasts progenitor cells; hMSCs, human Mesenchymal stem cells; hOBs, Human osteoblasts; LbL, layer-by-layer technique; LST, laser surface texturing; MH, Microwave hydrothermal; MTT, tetrazolium salt, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium; MW, microwave-assisted hydrothermal; NF-Ti, nanoflakes titanium; NN-Ti, nanonests titanium; NW-Ti, nanowires titanium; PAA, poly acrylic acid; PEO, Plasma electrolytic oxidation; rBMMSCs, rat bone marrow mesenchymal stem cells (BMMSCs); rhBMP-2, Bone morphogenetic protein 2; SaOS-2, Osteoblast-like cells; SA-Ti, Ti immersed in 48 % H_2SO_4; SEM, scanning electron microscope; Si-HA, silicon-doped hydroxyapatite; TA, Ti coated with gold nanoparticles by magnetron sputtering; TA/BPP, Ti coated with gold nanoparticles by magnetron sputtering followed by decoration with BPP; TA/BPP/BMP-2, Ti coated with gold nanoparticles by magnetron sputtering followed by decoration with BPP and rhBMP-2; Ti, titanium; Ti-$(PAA/Col)_6$,Ti with col and PAA; Ti-$(PAA/Col)_6$NT, Ti with col, PAA and CaCO3; Ti-24, Ti immersed in 5 mL of 30 wt% H2O2 80 ℃ for 24 h; Ti-6,Ti immersed in 5 mL of 30 wt% H2O2 80 ℃ for 6 h; Ti6Al4V–CT, Ti6Al4V chemically-treated;Ti6Al4V–MP, Ti6Al4V mirror polished; Ti-HAC, Ti with hyaluronic acid-catechol (HAC); Ti-HAC-VEGF, Ti-HAC with vascular endothelial growth factor (VEGF); Ti-HepC, Ti with heparin-catechol (HepC); Ti-HepC-VEGF, Ti-Hepc-VEGF with vascular endothelial growth factor (VEGF); TNT, heat treated TiO2 nanotubes without APS; UN-Ti, untreated Ti;VEGF, vascular endothelial growth fator; WST-8, cell counting kit containing WST-8 (CCK-8 kit, Dojindo); Zn/Ag-PIII, Ti treated by plasma immersion Zn/Ag implantation according to parameters III; Zn-PIII, Ti treated by plasma immersion Zn implantation according to parameters III.

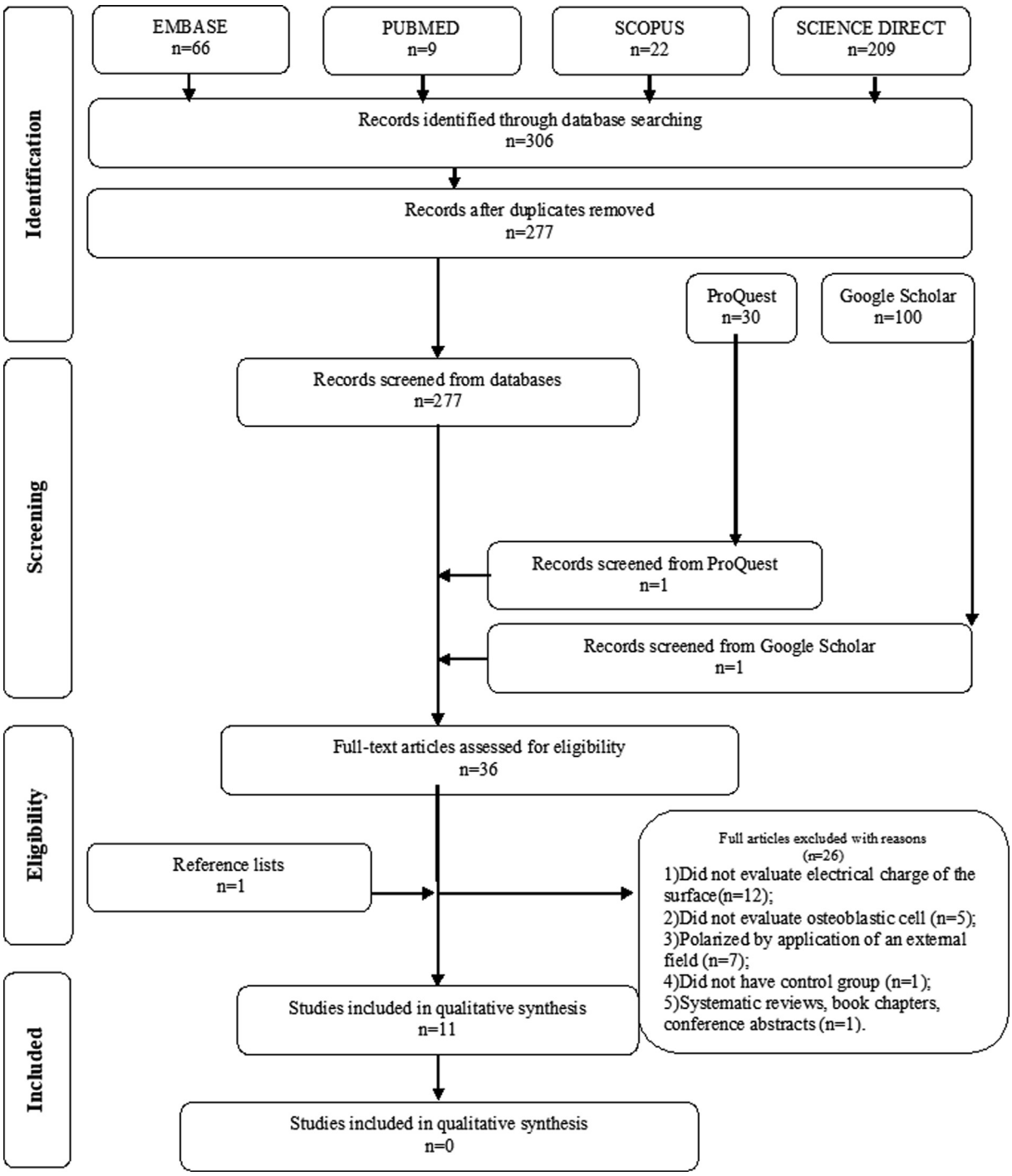

Fig. 1 Flow diagram of literature search and selection criteria.

The 11 heterogeneous in vitro studies included 11 (Hu et al., 2012; Zhang et al., 2012; Ghimire et al., 2014; Jin et al., 2014; Yang et al., 2016; Dai et al., 2019; Ferraris et al., 2019; Tovani et al., 2019; Wei et al., 2019; Li et al., 2020; Krenek et al., 2021) in this systematic review allowed a qualitative analysis of the osseointegration process and, demonstrated the synergistic influence of electrical potential, chemical composition, intrinsic to the alloy and resulting from surface treatment, and topography on osteoblast adhesion, proliferation, and differentiation. Thus, this systematic review contests the scientific literature that only positive surfaces (Finke et al., 2007; Patil et al., 2007; Chen et al., 2012; Guo et al., 2012; Jin et al., 2014; Bahl et al., 2015; Rebl et al., 2016; Camargo et al., 2020; Krenek et al., 2021) are favorable to osteoblastic attraction through the elucidation of complex dependent factors, (1) mineralization; (2) protein adsorption; (3) osteoblastic adhesion, proliferation, and differentiation; to contemplate osseointegration.

Thus, the critical analysis of the studies included in this systematic review allows us to infer that codependent and simul-

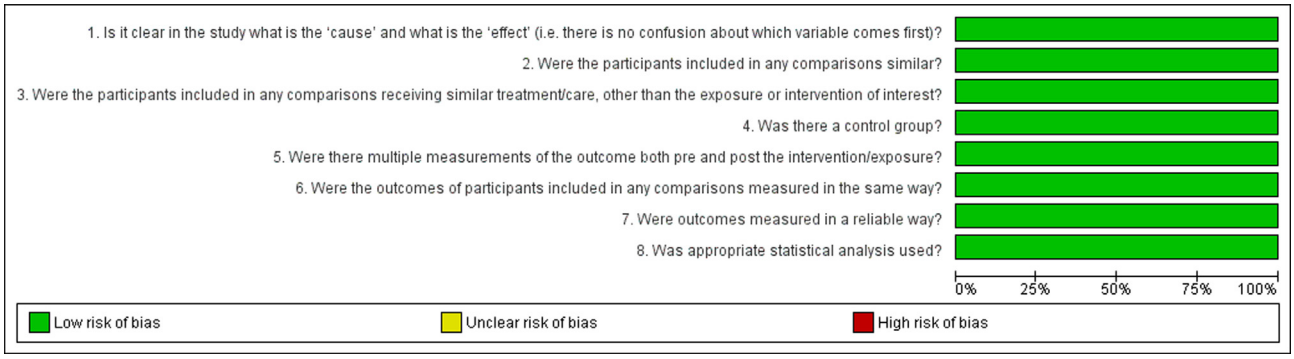

Fig. 2 General analysis of the risk of bias of the studies.

taneous biomineralization and osteogenesis events are indeed influenced by the electrical charge, but not dependent on a positive biomaterial for the attraction of osteoblastic cells, due to the driving force of biomineralization induced by Ca^{+2} to induce osteoblastic attraction and differentiation.

Since in the studies by Hu et al., 2012 and Tovani et al., 2019, the more negative surface of the biomaterial from surface treatment applied immobilization of VEGF on Ti via either covalent binding of heparin-VEGF (Hu et al., 2012) or immobilization of Col and $CaCO_3$ by LbL3 (Tovani et al., 2019), allowed greater mineralization and osteoblastic viability, respectively, a fact that can be explained by the electrical attraction between the negative surface and the Ca^{+2} ion, providing the formation of an electrostatic bridge between the Ca^{+2} ions deposited on the surface with the negatively charged bone cells (Sul, 2007; Bodhak et al., 2010; Hu et al., 2012; Saffarian Tousi et al., 2013; Anitua et al., 2017; Ansar et al., 2019; Dai et al., 2019; Tovani et al., 2019; Canepa et al., 2020; Lin et al., 2020; Krenek et al., 2021). This corroborates with the study of Sunarso et al., 2016, who reported that the presence of Ca^{+2} induces osteoblastic differentiation.

The kinetics of adsorption of proteins on the implant, when considering the electrostatic condition, is complex, as they are attracted to highly charged surfaces even when their charges are of the same polarity, as suggested by Lin et al., 2020, in addition to being able to reorganize and change their charges at different pH (Yoshinari et al., 2002; Lin et al., 2014; Lorenzetti et al., 2015; Dai et al., 2019; Lin et al., 2020). This fact was validated in the study by Yang et al., 2016 in which the surface obtained by immobilization of gold nanoparticles onto TiO_2 nanotubes by APS promoted a more negative surface with greater adhesion and osteoblastic viability due to gold nanoparticles accelerating protein adsorption and thus favoring cell adhesion and cytocompatibility. Thus, this systematic review highlights that, although proteins act as mediators of osteoblast adhesion, studies that elucidate how they influence the osteogenic regulation process are needed (Dai et al., 2019; Lin et al., 2020, 2014; Lorenzetti et al., 2015; Parisi et al., 2020, 2019; Park et al., 2021; Toffoli et al., 2020; Yoshinari et al., 2002).

Nanotopography provides focal points with high surface energy which regulate osteoblast adhesion by affecting cytoskeletal tension and differentiation by modulating the integrin/-catenin-linked kinase pathway (Diener et al., 2005; Lüthen et al., 2005; Zhang et al., 2012; Zhang et al., 2013; Wei et al., 2019; Lin et al., 2020). Lin et al., 2020 emphasized that nanotopography influences cellular events much more than surface chemical stimulation, a fact that may justify the better adhesion of osteoblastic cells in the studies by Li et al. 2020, Wei et al., 2019, and Zhang et al., 2012 despite the negative surface electrical charge and greater adhesion when on a positive surface (Lin et al., 2020). Thus, the articles in this review highlighted the importance of nanotopography, as it increases the surface area and potentiates osteoblastic cell adhesion and spreading regardless of whether the surface charge is positive or negative.

According to the literature, osteoblastic cell attraction is favored in positive microenvironments (Finke et al., 2007; Patil et al., 2007; Chen et al., 2012; Guo et al., 2012; Jin et al., 2014; Bahl et al., 2015; Rebl et al., 2016; Camargo et al., 2020; Krenek et al., 2021) because the cells have a negative electrical charge (Diener et al., 2005; Finke et al., 2007; Patil et al., 2007; Guo et al., 2012; Jin et al., 2014; Rebl et al, 2016; Krenek et al., 2021). Thus, the studies by Dai et al., 2019, Ghimire et al., 2014, and Jin et al., 2014 corroborate with the literature by demonstrating greater adhesion and cell viability in samples with more positive surfaces after the application of surface treatments immobilization of rhBMP-2 by electrostatic interaction (Dai et al., 2019), acid etching followed by immobilization of chitosan (Ghimire et al., 2014), and Zn/Ag co-implantation by arc plasm (Jin et al., 2014).

On the contrary, Ferraris et al., 2019 after the application of surface conditioning in dilute hydrofluoric acid followed by controlled oxidation in hydrogen peroxide, characterized the surface as nanometric and positive, however, despite these beneficial characteristics, the adhesion of osteoblasts did not differ from the group to control. Whereas, in the study by Krenek et al., 2021, laser surface texturing (LST) treatment followed by chemical treatment with NaOH-$CaCl^2$-heat-water treatment was biocompatible to some extent, as it inhibited the metabolic activity and altered the shape of the cells more significantly than the surface of the biomaterial is negative.

Thus, a critical analysis of the studies by Dai et al., 2019, Ghimire et al., 2014, Jin et al., 2014, Ferraris et al., 2019, Krenek et al.,2021 allows inferring that, regardless of the

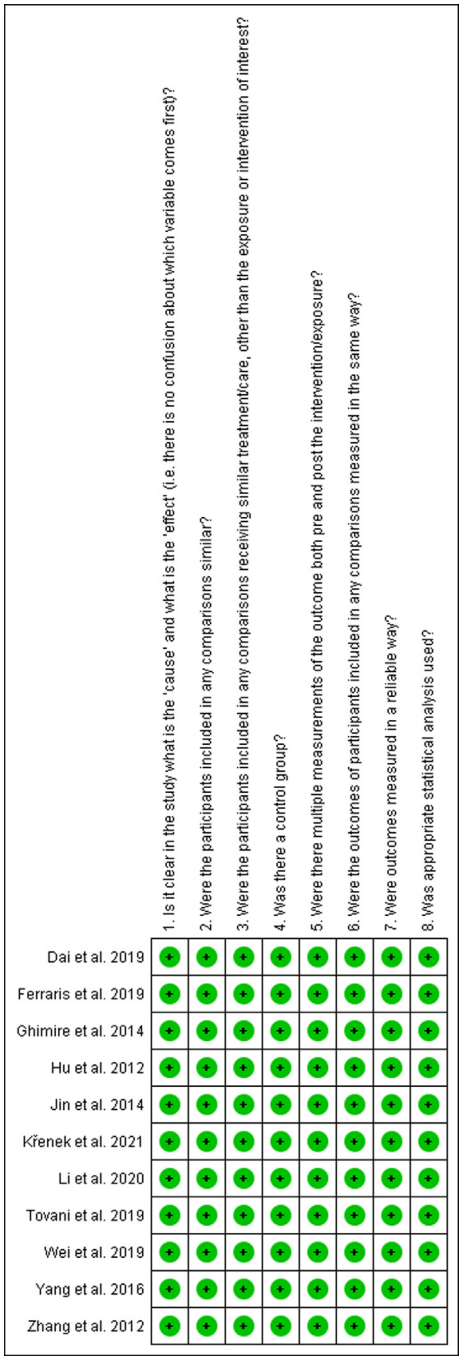

Fig. 3 Analysis of the risk of bias per study.

polarity of the surface charge, thus, is highlighted that the chemical composition of the applied surface treatment, as this is a plausible justification for the non-difference (Ferraris et al., 2019) and even cell inhibition (Krenek et al., 2021) corroborating a previous systematic review (Dias Corpa Tardelli et al., 2020b) that demonstrated that the chemical cytotoxicity of surface treatments is dependent on cell type, dose, nanoparticle size, temperature, and exposure time.

Thus, the 11 studies (Hu et al., 2012; Zhang et al., 2012; Ghimire et al., 2014; Jin et al., 2014; Yang et al., 2016; Dai et al., 2019; Ferraris et al., 2019; Tovani et al., 2019; Wei et al., 2019; Li et al., 2020; Krenek et al., 2021) included in this systematic review demonstrated that the osseointegration process is a multifactorial phenomenon that, depending on the methodology used, demonstrates independence from the positive surface electrical charge for its occurrence (Finke et al., 2007; Patil et al., 2007; Guo et al., 2012; Jin et al., 2014; Rebl et al., 2016; Krenek et al., 2021). Hence, it is noteworthy that qualitative data analyses in this systematic review should be interpreted with caution due to the heterogeneity of titanium alloy, surface treatment, method of determining electrical potential, method of determining osteoblastic activity, and evaluated cell types prevent the exact correlation of factors (electric charge, deposition of calcium, protein adsorption, cell attraction, topography, and chemical composition).

Therefore, to solve the stated problem for the realization of this systematic review, it is suggested to encourage the development of studies that jointly assess the correlation of composition and structure with the properties of each surface to understand the osteoblastic mineralization process, protein adsorption, and osteoblastic attraction, adhesion, and differentiation, since the variation of one interferes with the expression of the other so that a detailed look at biomolecular events and their influence on the development of pro-osteogenic bioactive surfaces that favors short-term osseointegration.

Osseointegration is a complex phenomenon dependent on in vivo conditions, bone quantity and quality, systemic conditions of the patient, design and surface treatment of the implant, and surgical technique (Kittur et al., 2020; Li et al., 2020; Amengual-Peñafiel et al., 2021; Tardelli et al., 2021), so this systematic review presents as a limitation the evaluation of only in vitro studies that allowed a critical analysis at the cellular level. Thus, the data presented should be evaluated with caution, because in vivo local and systemic conditions directly interfere in this phenomenon.".

5. Conclusions

According to the literature evaluated, it can be inferred:

1. The phenomenon of osseointegration is complex and independent of the superficial electrical charge of the implant, it may occur. To understand osseointegration, attention must be paid to the synergistic action of the electrical potential; chemical composition, intrinsic to the alloy and from surface treatment; and topography, which will determine the speed of adhesion, proliferation, and osteoblast differentiation.
2. The presence of Ca^{+2} deposited on the surface acts as a driving force for biomineralization that induces osteoblastic attraction and differentiation;
3. Studies describing the osteogenic regulation process through protein mediation are needed for a better understanding of the current literature;
4. Topography and chemical composition act as decisive parameters for cell viability independent of the attractive electrical charge.

Ethical statement

This systematic review was performed through a critical analysis of the studies present in the literature. So it was not necessary Ethical statement for animals or people.

CRediT authorship contribution statement

Juliana Dias Corpa Tardelli: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Andréa Cândido dos Reis:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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