Nano Modification of Titanium Dental Implants- A Meta-Analysis

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Abstract

This meta-analysis presents the comparison of nanostructured/nanoparticles as Ti-based implant materials to control and improve the implant success rate with a focus on enhanced osseointegration.

Materials and Methods: A literature review of articles was conducted by using MEDLINE PubMed database and google scholar restricted to 2000 – 2019.

Results: Source: PubMed and Google scholar

Independent screenings of the abstracts were done to identify the articles related to the question in focus 97 studies were selected out of which 10 articles were further excluded.Finally 11 articles were included.

Conclusion: Based on the results, it was found that there is a significant difference between the uncoated and nano-coated titanium dental implants, concluded that the nano-coated titanium implant surface increases bone-implant contact thereby enhances osseointegration.

Keywords; *"Dental Implants" [Mesh terms] Titanium surface, Implants and surface modifications, Titanium surface with Nanostructure, Osteoblast proliferation, Nano-coated implants, Osseointegration.*

Introduction

An important parameter for achieving successful osseointegration is the establishment of direct contact between the surface of the implant and the surrounding bone. The implant surface roughness affects the rate of osseointegration. Classification of the surface roughness of implants can be divided into macro, micro, and nano. The implant surface modifications can be achieved by additive or subtractive methods[1].

Bone is a natural nano rough surface that consists of nano-sized collagen and HA crystals as a result, nano rough surface implant is more favorable for osteoblast growth. Surface which replicates natural bone structures provide an environment that is more suitable for osteoblast growth. Better osteoblast adhesion on the nano rough regions of the patterned titanium substrates is because of their optimal interactions with proteins, proteins are mediating osteoblast adhesion such as fibronectin, and therefore protein response on the titanium surface is responsible for optimal osteoblast behavior. Early functions of osteoblast are affected by the size of the aligned pattern. There are some optimal patterned dimensions of nano features in which osteoblast prefers to function, in other words, a threshold exists in which osteoblast does not attach and spread properly.

The bone constituents are organic matrix 90% Type 1 collagen 10% in an organic matrix which is composed of HA. Type 1 collagen synthesized by osteoblast and contains linear fibrils 30nm in length and 0.5 nm in width, HA is 25 nm thick and 20 – 80 nm long.

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The nanometer-sized roughness and also the chemistry have a key role in the interactions of surfaces with proteins and cells. The micromechanical features which influence the process of secondary integration are bone growth, turnover, and remodelling. At the nanoscale, more textured surface topography increases the surface energy which in turn increases the wettability of the surface to blood, adhesion of cells to the surface, and facilitates binding of fibrin, matrix proteins, growth, and differentiation factors[2, 3,4].

Many studies were conducted to investigate various implant surface nanostructures and their influence on cell behaviour as proliferation. This meta-analysis presents the comparison of nanostructured/nanoparticles as Ti-based implant materials to control and improve the implant success rate with a focus on enhanced osseointegration.

Aim

· To evaluate through systematic review and meta-analysis of the articles published, related to the nano surface modification of dental implant surface.

· The aim is to compare, based on the recently available evidence, the influence of various nanostructure surface modifications of titanium implants, on osteoblasts proliferation and osseointegration.

Objective

· To collect reliable journal articles reporting comparison of osseointegration of untreated and nano modified surface with additive process made over dental implant surface.

· To compare the parameters across the articles.

· To address the limitations in data.

· To compare nanostructured and nanoparticles as Ti-based implant materials to control and improve the implant success rate with a focus on enhanced osseointegration.

Material and Methods

MATERIALS

1. MEDCALC software version 19.1
2. Acer E 11 laptop
3. Rorito B max pen
4. Natraj pencil
5. Jumbo note book
6. Apple 6 Iphone
7. Jio broadband
8. Rox printers

Methodology

The PubMed library, Google scholar databases was searched for articles in English language from 2000 to 2019 using the MeSH terms the review included are laboratory research studies, in vitro studies that used cells from human or animals and in vivo studies on animals.

Electronic search was performed independently following MeSH terms. Detailed search strategies were developed for each database searched.

SEARCH TERMS

The following keywords are used;

· Titanium dental implant surface

· Implants and surface modifications

· Titanium surface with Nanostructure

· Osteoblast proliferation

· Nano-coated implants

· Osseointegration.

Inclusion Criteria

· In vitro and/or in vivo studies.

· Nanostructured implant surface + control sample.

· At least one Ti sample with nanostructure must be included in the study.

· Studies about osseointegration rate on nanostructured implant surface.

· Studies providing quantitative results.

Exclusion Criteria

· No osseointegration rate described.

· Studies describing Ablative implant surfaces.

· Nanostructure and morphology has not been described.

STUDY SELECTION AND DATA COLLECTION:

The search results were carefully refined to those articles that explicitly mention variables considered for the study. In addition bibliography of these selected articles were also scanned to obtain the maximum number of results possible The search yielded 544 potentially relevant articles in PubMed, 300 in Google search. After screening the abstracts of the articles, 97 articles were selected for full text screening from PubMed and Google scholar .After elimination of duplicate articles, a total of 87 were selected for full text screening. Out of that 11 articles were selected based on eligibility criteria.

A total of 11 articles were shortlisted as mentioned and the following parameters were retrieved, (table 1)

· Mean bone-implant contact of uncoated and coated titanium implant surface.

· Standard deviation (SD) of uncoated and coated titanium implant surface.

STUDY PERIOD - This study was carried out for a period of one year from august 2018 to august 2019.

STUDY SAMPLE -Sample size was 600 – 850 articles

STUDY DESIGN - SEARCH RESULTS FOR META ANALYSIS

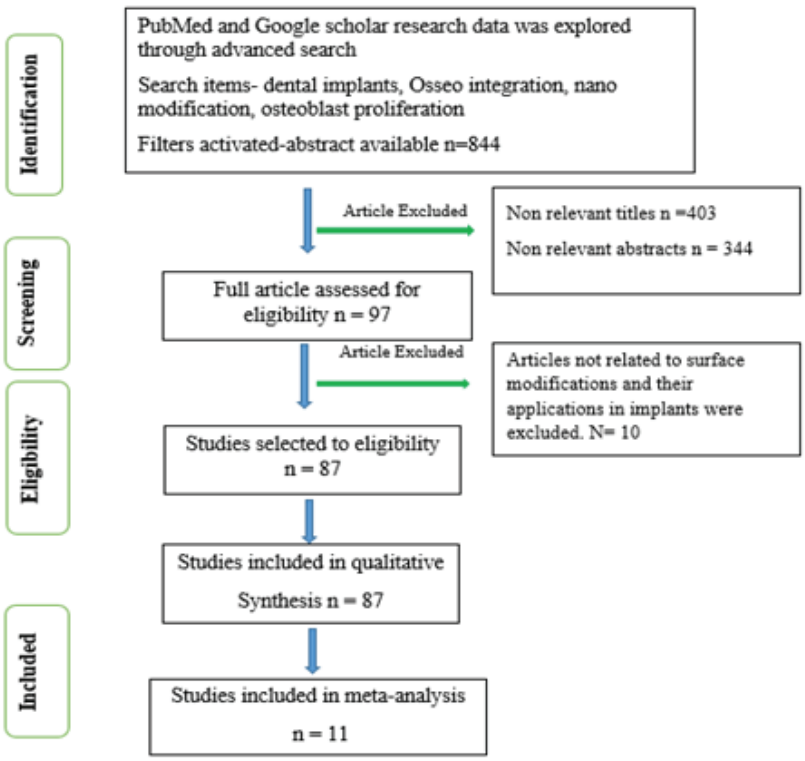

Fig .1, Flow diagram of studies selection according PRISMA guidelines

Results

Characteristics of the studies included and comparison of bone implant contact area with an observation period

Table 1

Bone Implant Contact (Time Interval Of 1month To 3 Months After Implant Placement)	**Control Surface** **Uncoated/Micro Coated**		**Test** **Nano Surface**	
Laetitia Salou Et Al N= 6	45.1± 9.1	(N=3)	65.1±20.7	(N=3)
Jack Wan Lee Et Al N=20	11.1±17.0	(N=10)	16.3±11.9	(N=10)
Ellingsen Je Et Al N=30	39±11	(N= 15)	31±6	(N= 15)
Lars M Bjursten Et Al N= 13	21.7±24.7	(N= 6)	21.7±24.7	(N=7)
Von Wilmowsky Et Al N=50	18.33±16.45	(N=25)	18.14±14.87	(N=25)
Ingmer Et Al N=34	53.2±10.8	(N=16)	56.2±6.6	(N=16)
Orisini G Et Al N=20	19±14.2	(N=10)	32.2±15	(N=10)
Yves Et Al N=24	62.46±6.37	(N=12)	75.54±5.93	(N=12)
Ballo Et Al N=40	42±27	(N= 20)	76±16	(N= 20)
Luiz Merelles Et Al N=20	Sd 14 % (0-41)	(N=10)	Sd 9 % (0 – 29)	(N=10)
Jimbo Et Al N=20	32.1%(9.9)	(N=10)	35.7% (80)	(N=10)

Meta Analysis

· Mean difference of the mean bone implant contact was calculated for uncoated and coated titanium implant surface and compared using student T test at the confidence interval of 95%.

· The data was presented as funnel plot and forest plot.

· Meta-analysis was done using 'MEDCALC software version 19.1'

META-ANALYSIS: CONTINUOUS MEASURE

Variable for studies	**Study**
	1. Intervention groups
Variable for number of cases	N1
Variable for mean	mean1
Variable for SD	sd1
	2. Control groups
Variable for number of cases	N
Variable for mean	Mean
Variable for SD	Sd

Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%)	
									Fixed	Random
laetitasalou	3	3	6	0.998	0.712	-0.980 to 2.976			2.99	6.62
jack wan	10	10	20	0.339	0.432	-0.567 to 1.246			8.16	9.22
ellingsen je	15	15	30	-0.878	0.373	-1.642 to -0.115			10.93	9.78
lars m bjursten	7	6	13	0.000	0.517	-1.139 to 1.139			5.68	8.39
von wilmowsky	25	25	50	-0.0119	0.278	-0.572 to 0.548			19.61	10.63
ingmer et al	16	16	32	0.327	0.347	-0.382 to 1.035			12.62	10.03
orisinisg et al	10	10	20	0.865	0.450	-0.0791 to 1.810			7.52	9.05
yves et al	12	12	24	2.052	0.493	1.030 to 3.075			6.25	8.62
ballo et al	20	20	40	1.502	0.352	0.788 to 2.215			12.23	9.98
luizmerelles et al	10	10	20	-0.319	0.431	-1.224 to 0.587			8.17	9.22
jimbo et al	10	10	20	1.751	0.510	0.680 to 2.822			5.84	8.46
Total (fixed effects)	138	137	275	0.454	0.123	0.211 to 0.696	3.681	<0.001	100.00	100.00
Total (random effects)	138	137	275	0.567	0.275	0.0257 to 1.108	2.062	0.040	100.00	100.00

Test for heterogeneity

Q	46.9803
DF	10
Significance level	P < 0.0001
I2 (inconsistency)	78.71%
95% CI for I2	62.42 to 87.94

TABLE 2

FUNNEL PLOT

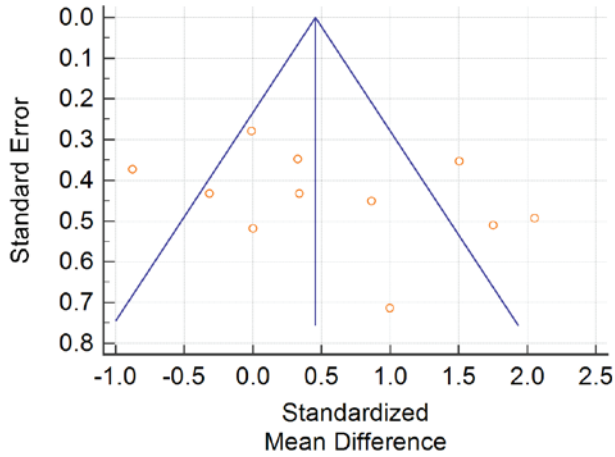

FIGURE 2, FUNNEL PLOT FOR DETECTION OF PUBLICATION BIAS

FOREST PLOT

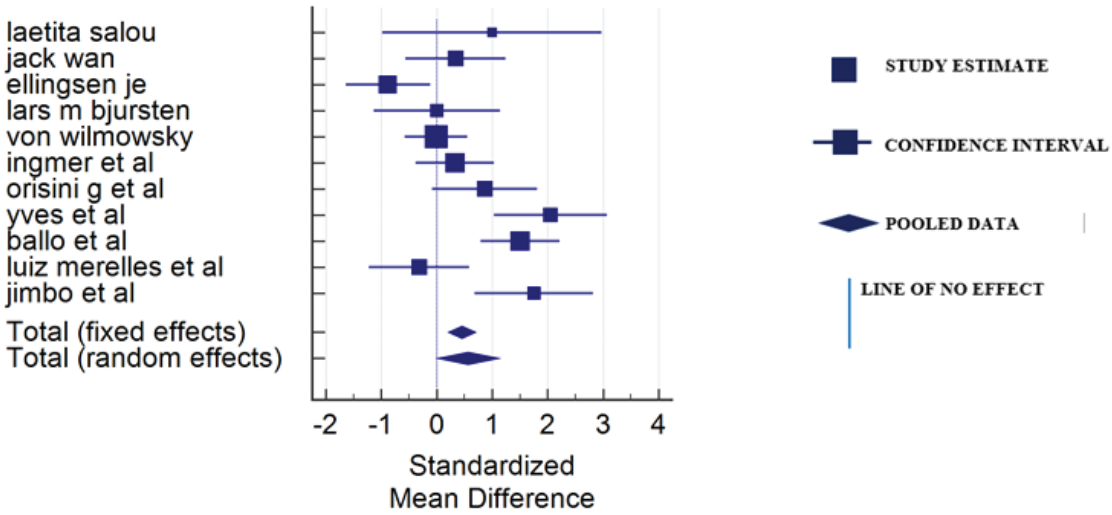

FIGURE 3, FOREST PLOT DEPICTS THE MEAN DIFFERENCE OF BONE IMPLANT CONTACT OF UN COATED AND COATED DENTAL IMPLANTS. _

META-ANALYSIS INTERPRETATION:

· Initial electronic and manual search identified 87 articles. After the subsequent search at the title, abstract and full-text reading level, 11 studies were finally selected for meta-analysis.

· The funnel plot was used to determine the possibility of publication bias of the selected studies. (Figure 2,)

· The forest plot was used to determine the pooled bone-implant contact rate of the selected studies. (Figure 3,)

· Heterogeneity of the data was analyzed to determine if the data from the selected studies can be analyzed and if the data random effects model can be used in meta-analysis. (Table 2,)

· Of the 11 studies selected, 11studies are evaluated for the bone-implant contact area of uncoated and coated bone titanium dental implant surfaces. The included studies all used similar criteria for evaluating the bone-implant contact area of titanium implants.

· The bone-implant contact was based on osteoblast proliferation, alkaline phosphatase activity, the time interval was between 1 to 4 months after implant placement.

· The systematic analysis of the selected 11 studies is shown in the funnel plot which is analyzed for publication bias.

· The forest plot showed a pooled effect of the bone-implant contact area.

FUNNEL PLOT

In this analysis, Few studies (4 out of 11) was scattered out of the funnel plot it shows that there was a possible error in the studies, which may due to poor standardization, , heterogeneity (size of effect differs according to study size) and sampling variation.

FOREST PLOT

The main outcome of meta-analysis is a forest plot, graphical display as in figure 1,

· Some confidences interval are entirely on the positive side of zero, in other words, these studies show a statistically significant positive effect.

· Some confidences interval are entirely on the negative side of zero, in other words, these studies show a statistically significant negative effect.

· Study done by Von wilmowsky et al is the only study that contributes maximum to the analysis because of its minimum (-0.567 to 0.548) of confidence interval (bigger the study, the smaller the horizontal line and bigger the black box representing the point estimate) and study estimate.

The diamond at the bottom of the forest plot shows the results when all the individual studies are combined and averaged. The horizontal points of the diamond are the limits of the 95% confidence interval and are subject to the same interpretation as any of the other individual studies on the plot.

Though 11 studies are included in the analysis, not all studies are equally contributing to the analysis.

In this analysis, diamond-shaped 'Pooled Data' is found on the left of the line of no effect (total fixed effect 95% of CI - 0.211 to 0.696) it's mainly because of most of the studies supports the comparison group rather than control group, which means 'Nano coated titanium implant surface increase the bone-implant contact' thereby it enhances the osseointegration.

TEST OF HETEROGENEITY

I2 (inconsistency) 78.71%

$P < 0.0001$

Total fixed effect – 95% of CI - 0.211 to 0.696

Discussion

The implant surface is an active research topic, because nano features could offer some advantages over untreated titanium dental implants it increase surface area, improves cell attachment, improve biomechanical interaction of implant with bone. Though many studies reveals the superiority of nano modified dental implants, we are dealing with negative reports as follows. Ross et al in 2013 reported superiority of microstructure surface over nanostructured samples.Yu et al in 2013 described a lower proliferation rate on 80 nm nano-foveolae structure compared to a smooth control sample. Controversial results were noticed about incorporation of HA within nanotubes Due to difference in opinions and results from different studies, a need was felt to analyze the non-treated/uncoated and nano-coated dental implant surface by undertaking a meta-analysis approach[5, 6].

The PubMed and Google scholar search resulted in more than 800 articles matching the search terminologies. Initial electronic and manual search identified 87 articles as per the inclusion criteria. After the subsequent search at the title abstract and full-text reading level, 11 studies were finally selected for meta-analysis. In vivo and in vitro studies that investigated the bone-implant contact of non-coated vs. nano-coated titanium dental implant surface were included.

The meta-analysis was done using MEDCALC software version 19.1. Meta-analysis was conducted for differences in mean values of non-coated and nano-coated titanium dental implant surfaces. Mean differences were included in the meta-analysis, 11 studies were finally selected for meta-analysis. Out of 11 studies 4 studies does not contribute to the analysis.

As surface characteristics modulate the outcome of cells behavior to the presence of a dental implant and subsequently the osseointegration level, the development of an implant surface that aims to attract osteoblasts that produce a bone extracellular matrix to ensure a high bone-implant contact. For this purpose, numerous surface engineering methods have been developed to create featured implant surfaces to improve the clinical performance of implants and to get a stable mechanical bone-implant interface. Also, persistent efforts have been made to improve the surface properties of dental implants to meet the increasing demands of implant treatments such as improving the success rate, expanding the applicability, and shortening the healing time required for sufficient bone-implant integration[7].

The osseointegration performance of a surface is influenced by its topography at the nanoscale, following different biological mechanisms than on the micro-scale. The nano topography is supposed to influence the surface energy and therefore the surface/protein interactions. A significant surface energy allows to improve the surface wettability to blood and the adhesion and spreading of fibrin fibers and matrix proteins on the surface, and therefore to improve cell attachment and tissue healing, particularly during the early healing phases on the implant interface[8].

A specific nanopattern surfaces promotes cell proliferation and differentiation, through the direct modulation of cell behavior[9]. Among the many forms of nanostructures (nano roughness, nano patterning, nanotubes, nanoparticles), it remains however difficult to determine which nano feature is the most efficient for the bone-implant interface and is practically usable with adequate clinical results in dental implant surfaces[10,11].

Studies demonstrate that the use of nanostructure enhance bone formation and growth because nanophase metal mimic the characteristic dimensions of bone constituents. Creating nanostructure of bone reduces infection, inflammation and promote osseointegration (Webster 2007) collagen spontaneously forms fibrils of aligned nanoscale protein helices (laton 2001). These fibers serve as a template for the nucleation and growth of hydroxyapatite crystals thereby creating a highly organized nanostructured surface that extends in a parallel orientation to the physiological loading of bone, the orientation of HA is dependent on the organization of collagen fibril helices. Several investigators have revealed that nanoscale topography influences cell adhesion and osteoblastic differentiation (Dalby et al., 2008, Webster et al., 1999). These findings reiterate observations demonstrating that nano topography may directly influence adherent cell behavior (Webster et al., 2000). Nanotechnology can alter the implant surface at an atomic level (Oh et al., 2005) and also influence the chemical composition of these surfaces.

A systematic analysis of the results gleaned from the chosen articles revealed that in fewer studies both types of implant surfaces reported having poor osseointegration. The results of the meta-analysis show that 1. Statistically, there is a difference between uncoated and coated implant surfaces in terms of bone-implant contact. 2. The rate of osseointegration of nano-coated was slightly more than that of a non-coated implant surface. Irrespective of the direction that dental implant biomaterials research takes in the future, it is clear that the most significant developments in this space will be at the cutting edge interface of material science and will be informed by innovations in substrate-surface differentiation and ability to easily "custom-create" surface properties, aided by the mainstreaming of nanotechnology.

Limitation

The main limitation is that the samples group types, the culture techniques and evaluation methods are not the same across studies and difficult to compare.

Summary and Conclusion

To analyze the osseointegration rate of non-coated and nano-coated titanium implant dental surface concerning bone-implant contact, a meta-analysis was conducted by searching the PubMed database for articles published in between 2000-2019. The articles were selected based on specific inclusion criteria to throw light on comparative features.

The search resulted in more than 800 articles of which most of them were reviews and works that did not give a clear idea about osseointegration rate was excluded from the analysis. Eleven articles were selected to achieve the objectives. The chosen parameter

were applied, data collected and the results statistically analysed and interpreted.

Although the advantages associated with the use of nanoscale titanium are supported by a large body of experimental observations, the potential risks and risk-benefit balance of nano titanium have yet to be evaluated, especially in long-term studies. Research priorities should also include detailed studies to demonstrate the superiority and real clinical advantages of nanoscale titanium as a cost-effective tool compared with traditional materials

Based on the results, it was found that there is a significant difference between the uncoated and nano-coated titanium dental implants, concluded that the nano-coated titanium implant surface increases bone-implant contact thereby enhances osseointegration.

Ethical Clearance – Institutional Ethics Committee, Sree Balaji Dental College and Hospital, Committee registered with DCGI. (Registration no: SBDCH/IEC/04/2019/21)

Source of Funding – Nil

Conflict of Interest – Nil

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