SYSTEMATIC REVIEW

SILVER NANO-PARTICULATE COATING ON IMPLANTABLE TITANIUM DEVICES: CAN WE TEACH AN OLD DOG A NEW TRICK? —A SYSTEMATIC REVIEW

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Implant materials are one of the most investigated topics in modern medicine. This review is focused only on addressing silver as coating substance on top of titanium based implantable devices, and focused on the last five years of silver coated titanium implants on human cell population. This study was conducted on Medline, PubMed, Science Direct, Scopus and Google Scholar. A time window of the previous five years was selected up to May of 2021. The study was done at HBS Dental College, Islamabad and the Higher Education Commission Library, Islamabad. The multi-location reviewing and gathering of articles assured lack of bias in the article selection. The search for articles was done using prescribed keywords and then the sieving of articles further using systemic review methodology via PRISMA flowchart. There was excessive evidence to suggest that the surface modification with silver is effective to eliminate surface microbes which might interfere in good quality healing of bone around the titanium implant material. Silver has great antimicrobial activity however it does not show simultaneously just as good compatibility. This study points towards evidence of establishing the 'sweet spot' between the most favourable cytotoxic concentrations and most effective antimicrobial concentrations.

Keywords: Silver, Ag, Nanoparticle, titanium, implantable devices, implant, dental, MTT assay

Pak J Pysiol 2023;19(3):51–5

INTRODUCTION

Although Titanium is a very good material to be used as an implant material in the dental prosthesis in restorative department, it is still understood that titanium itself has poor inherent antimicrobial properties. Therefore, to bridge this gap in Titanium's ability to ward off infections coating is done in a variety of metal oxides in order to give titanium a favourable antimicrobial profile. Use of Zinc, Copper, Cerium and Silver has always been a popular choice for antimicrobial activity.[1] The pleasantness of these compounds is determined by their ability to appear more tooth like or bone like. Zinc and silver in this matter win over the others by having closer tooth like colours such as silver or white and strong antimicrobial potentials.[2–5]

Silver has been used in medicine ever since middle ages and now with nano-technology we're teaching this old dog new tricks. When aimed at making silver an implantable material as a part of our silver coated implants, silver can be coated as an oxide or nitride.[6]

The main advantage of focusing on nano-particle is, the fact that they can provide a very high surface area in case of oxides that are capable of having antimicrobial activity on the contact surfaces.[7] At the same time these materials do not cause a lot of toxicity because the overall quantity is way below the lethal toxic dose.[8] They are used as delivery vehicles to intercellular deposition of growth factors. They behave like biological proteins and can pass through Lingard gates. Helping medicate regions of the body or the cell that are otherwise unapproachable by bigger molecules.[9] The use of silver as an antimicrobial material is as old as time itself, and yet its potential in functionality delivers its way forward with the number of researches published in the year 2021 alone is overwhelming. The number of publications crossing over 35,000 as per Google Scholar, and this review is written only halfway into 2021.

As the use of silver is one of the most popular one in the current biomedical world right now, the aim of this review is to study and quantify the degree of success that is achieved by its quoting on the titanium implants, be it orthodontic implant or prosthodontic implant. This review will highlight trends and upcoming advancements in the world of silver coatings in implantable devices.

MATERIAL AND METHODS

This study was conducted using databases of Medline, PubMed, Science Direct, Scopus, and Google Scholar. A time window of the previous five years was selected, leading up to May 2021, at HBS Dental College, Islamabad and the Higher Education Library, HEC, Islamabad. A multi-location reviewing and gathering of

articles assured the lack of bias in the article selection procedure. Search for articles was done with the prescribed keywords and then the sieving of articles was further done by the systemic review methodology via PRISMA flowchart. The keywords used were Ag, Silver, Nanoparticle, Titanium, Implantable devices, Dental implant, MTT assay. Studies with calcium compound and hydroxyapatite were excluded because they can cause increase cell adhesion in osteogenic cells and fibroblasts and were confounding to the study.

Inclusion criteria:

- *In vitro* studies
- Studies with cell studies
- Studies with cells with human origin
- Studies done after 2016
- Studies on titanium implant
- Studies with rat/mice cell assays
- Studies on commercially pure titanium implants
- Study conducted on titanium foils, sheets or rods
- Studies on titanium aluminium vanadium implants

Exclusion criteria

- Human trials due to lack of histological evidence
- Animal trials
- Studies with hydroxyapatite
- Studies with calcium compounds
- All in vivo studies
- Studies done prior to 2016

RESULTS

Thirteen (13) articles were selected from January 2016 to May 2021. The selection process of these articles was as shown in the PRISMA flowchart below. Calculation of biases was done via ROBINS tool.

The result of the articles selected is summarised in a tabulated form in this review. All studies were done *in vitro* settings and were non-clinical random sequencing and concealment of the test specimen was not required in these studies. The specimens were to hold identical properties and were tested against identical mediums. Personnel blinding or incomplete outcome reporting was also not prevalent. Only three of the following eleven studies were considered to have higher risk of bias because the authors do not initially opt to include the sample preparation methodology in their text. This being pointed out altogether, the risk of bias was very low in the *in vitro* studies.

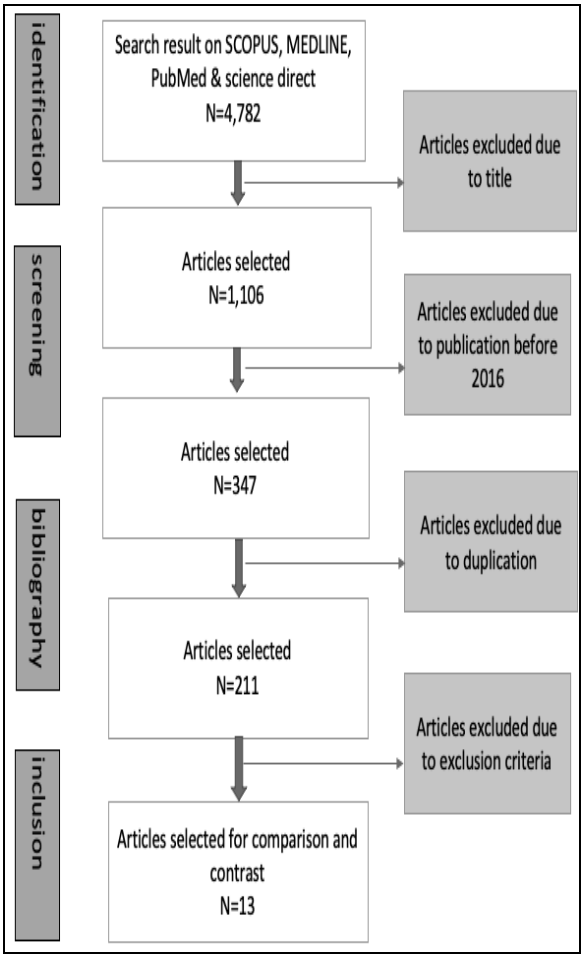

Figure-1: PRISMA flowchart applied to article selection process

Table-1: Evaluation of risk of biases based on ROBINS tool

Study	Random sequencing	Allocation blinding	Personal blinding	Outcome assessment blinding	Incomplete outcome assessment	Selective reporting
10	H	H	U	L	L	L
11	H	H	U	L	L	L
12	H	H	U	L	L	L
13	H	H	U	L	L	L
14	H	H	U	L	H	H
15	H	H	U	L	L	L
16	L	L	U	L	L	L
17	H	H	U	L	L	L
18	L	L	U	L	L	L
19	H	H	U	L	L	L
20	H	H	U	L	L	L
21	H	H	U	L	L	L
22	H	H	U	L	L	L

L=low risk, U=unclear risk, H=high risk

Table-2: Summary of results from selected articles

Study	Substrate	Particle size nm	Cells	Testing	Duration hours	Conclusion
Radtke *et al*[10]	Ti6Al4V	18–115	Human osteoblast-like MG63 cells	MTT assay	24, 72, 120	85% cell viability at 120 hrs
Zhang *et al*[11]	Medically pure Ti	10–40	Rat bone marrow derived mesenchymal cells	CellTiter-Blue® cell viability assay	24, 96, 168	Biocompatibility by suppressing intercellular ROS production
Yang *et al*[12]	Commercially pure Ti	1–10	Mice osteoblast	WST-1 cell proliferation assay kit	24, 72, 120, 168	Normal morphology of cells with full vitality
Kranz *et al*[13]	Ti6Al4V	25	Mice osteoblast	Florescent microscopy	48, 96	High initial biocompatibility
Marques *et al*[14]	Commercially pure Ti	<100	Adult human bone marrow cell	Florescent microscopy	3, 24, 144	Early attachment and proliferation
				MTT assay	3, 24, 144	Increased cell population progressively
Kaczmarek *et al*[15]	Commercially pure Ti	100–150	Human osteoblast	MTT assay	72, 96	Increased cell count
Guan *et al*[16]	Ti foils & rods	1–30	Mice osteoblast	Florescent microscopy	24	Normal cell morphology
Shivaram *et al*[17]	Commercially pure Ti	Unidentified	Human foetal osteoblast cells	MTT assay	96, 168	Increased cell density
Zeng *et al*[18]	Commercially pure Ti	20–30	Mice osteoblast	Cell counting kit-8	72, 120, 168	Proliferation increase by increasing nano particle concentration, new bone formation in proximity to 2% implant
Zhang *et al*[19]	Commercially pure Ti	20–50	Mice osteoblast	Florescent microscopy	12, 24, 120	Good vitality and cell differentiation
				MTT assay	96 168, 240	Favourable vitality and proliferation rate
Ulfah *et al*[20]	Ti6Al4V	134 diameters of nanotubular deposits	Human osteoblast	MTT assay	168, 336	cell viability 107=115% of control
Torres *et al*[21]	Ti6Al4V	52.5–95 diameters of nanotubular deposits	Human foetal osteoblasts	MTT assay	72, 168, 336	140–329% greater vitality than control
Sun *et al*[22]	Ti6Al4V	900	Mice osteoblast	MTT assay	24-168	100% cytocompatibility

DISCUSSION

The oral cavity is known to have a poly-microbial flora, which presents both pathological and probiotic microbial species.[23] Although antimicrobial properties in implants can be produced, but to choose between the perfect cytotoxicity is the real challenge.[24] Quite often, implant associated infections may be induced by Methicillin resistant Staphylococcus aureus.[25]

These infections can cause a great deal of delay, especially in orthodontic implant assisted treatments. This often occurs because children do not tend to their oral health who are prime candidate for orthodontic treatments.[26] In prosthodontic treatment, the implant surfaces are prone to infection because they are often given to individuals who are partially edentulous and are subject to old age or systemic disease.[27]

According to one of the earliest studies[28] conducted in 1998 a 0.3% concentration of silver in either sulfadiazine or nitrate form can lower the amount of Staphylococcus formed on the biofilm surface up to 3,000 times. The incubation period used for these experiments was 16 hours. The study showed that silver shows similar antimicrobial potency as levofloxacin or povidone-iodine.[28] Following years, numerous studies were done in order to evaluate and identify the antimicrobial properties of silver.[29,30] Soon after the idea of having nano-particulate materials that offer a greater surface area to volume ratio came about.[31]

Timorous quoted through a variety of methodologies, either it was sprayed over, electroplated, dip galvanised and quite recently anodised.[20,21,32,33] The anodization methodology, which is recently used has the advantage that it causes formation of nano-tubular structures which leads to an improvement in the hydrophilicity of the implant surface against the bone matter.[34,35] Hydrophilicity in implants is associated with reduction of implant rejection through the body's immune system. This increases its integration strength, reduces osteointegration time.[35,36] The improved intimacy of contact between bone and implant reduces the availability of pocket for infection formation as well.[37]

The studies that are being highlighted in this review are simply selected in order to ascertain if Nanoparticulate silver can be a resolve in choosing between silver's very established antimicrobial activity

versus its ability to be cytotoxic. Using silver in Nanoparticulate solution coming from control release methodology, such as that formed by anodization can lead to a perfect balance of antimicrobial activity, increased hydrophilicity, and increased osseointegration. Even though silver itself can be cytotoxic at certain doses, but the presence of silver nano-particles on titanium has caused increased cell growth with proper cell differentiation. Cell growth has been increased up to 170% in certain studies and over 340% in others.[21]

Interestingly enough, an unexpected output of this systematic review was that the silver nano-particles are more effective in sustaining cell differentiation and growth of cell count in human cells rather than that in mice cell populations.[21] The study shows that a controlled drug release methodology is the best way to reduce the amount of silver in circulation while giving it its maximum antimicrobial properties.[38]

CONCLUSION

According to these *in vitro* studies, it may be suggested that variable techniques of coating silver ions on top of any form of implantable titanium, commercially pure, medical grade titanium, or titanium vanadium aluminium alloy implants may serve as an effective methodology of improving cell integration. Silver ions have improved antimicrobial activity against the osteomyelitis causing organisms. Concentration, rate of release and times exposure are pivotal factor in determining the balance between title toxicity, an antimicrobial effects of silver.

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Received: 30 Sep 2022 **Reviewed:** 24 Aug 2023 **Accepted:** 24 Aug 2023

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AI: Concept, initial selection of articles, designing of study
ZA: Refining of article and writing of discussion
SA: Bias calculation, article refining and conclusion writing
STF: Categorical assortment of data, refining of article writing
FB: Writing of material and methods section, proof reading
TS: Basic draft writing and proof reading to retain information

Conflict of Interest: None to be declared
Funding: None