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A systematic review on improving the biocompatibility of titanium implants using nanoparticles

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Abstract. An ideal biomaterial should be biointegratable with minimum adverse immune response. Titanium (Ti) and its alloys are widely used biomaterials for manufacturing clinical implants because of their innate biocompatibility. However, the bioinert property of Ti may hinder tissue–implant integration and its biocompatibility nature allows for attachment of bacterial cells on implant surfaces. Nanoparticles (NPs) have been proposed as a possible intervention to overcome these biological shortcomings of Ti-based implants. The aim of the current systematic review was to identify literature that demonstrates enhanced biocompatibility of Ti-based implants by incorporating NPs. Electronic searches were conducted through the PubMed/MEDLINE, ScienceDirect, Web of Science and EBSCOhost databases. Studies published in English were extracted, without restrictions on the year of publication, using the following keywords: 'biocompatibility', 'nanoparticles', 'titanium' and 'implant'. The guidelines stipulated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement were followed. A total of 630 articles were identified in the initial search and upon reviewing, 21 articles were selected according to the eligibility criteria. The selected literature showed robust evidence to support the hypothesis that the inclusion of NPs improves biocompatibility of Ti implants. The studies further indicated a close correlation between biocompatibility and antibacterial properties, of which NPs have been proven to characteristically achieve both.

Keywords: Antibacterial / biocompatibility / cytotoxicity / nanoparticles / titanium-based implants

1 Introduction

Biomaterial are typically expected to be integratable with the biological system and stimulate minimum adverse tissue response [1,2]. Titanium (Ti) and its alloys are widely used in medicine and dentistry because they exhibit minimal immunogenic potential in vivo and display superior biostability and biocompatibility in comparison to allogenic grafts and other biomaterial [3–5]. In contrast, Ti is a bioinert metal and thus does not initiate the initial cellular responses required to achieve biocompatibility [6]. This may subsequently interfere with bone repair at the tissue–implant interface and result in implantation failure. Incorporating nanoparticles (NPs) has emerged as an effective intervention towards improving the biological principles of Ti-based implants.

The synergy of biointegration without triggering an immune response is achievable through the use of foreign material whose properties resemble those of the innate tissue [5]. Nano-sized particles are structurally similar to various body proteins, ligands receptors and deoxyribonucleic acid (DNA) [1] Moreover, nanobiomaterials have been established as able to absorb living cells and, therefore, may be utilized to transport nucleic acids and conjugate with organic material, which contributes significantly to biointegration [7]. NPs include ultrafine structures with nano-range dimensions in diameter and are composed of any type of biocompatible substance [8,9]. It is well documented that incorporating nano-sized particles increases the biocompatibility and bioactivity of implant materials more efficiently as compared to similar bulk material [6,9,10].

The probability of implant success may be further enhanced by coating the Ti-based implants with material that exhibits both biocompatibility and antimicrobial activity; particularly since Ti surfaces not only promote

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cell adhesion followed by osseointegration, but also promote bacterial adhesion resulting in infection and inflammatory processes [4,6,9]. Inorganic NPs are hydrophilic, biocompatible, highly stable, have a low toxicity profile and are not readily susceptible to microbial attack [7]. Enriching Ti implants with NPs, such as copper, silver and zinc, allows for antimicrobial efficacy and non-cytotoxicity against human cells [5,11]. The superior antibacterial properties of metal NPs hinder bacterial attachment and present further beneficial clinical treatments since these assembling NPs may prevent infection during the bone healing process [4,9].

Technologies involving nanoparticle-based methods for delivery of bioactive molecules and enhancing biocompatibility and cellular survival continue to evolve with the intended use being for the clinical environment [10]. The prescribed sequence of biological research requires for the implant material to first undergo in vitro cytotoxicity testing procedures, followed by in vivo testing to describe the interaction with soft tissue and assess the biocompatibility of these devices [5,12]. However, the detailed cellular mechanisms at the bone–implant interface during osteogenesis and the actual mechanism of interaction of NPs with different cells in a biological medium are still largely unknown [13]. Furthermore, the extent to which modifying Ti implants to include NPs enhances the biocompatibility of these implants is not well documented. Therefore, the aim of the current systematic review was to establish evidence which support the hypothesis that NPs improve the biocompatibility properties of Ti-based implants while prolonging the antibacterical effects.

2 Materials and methods

2.1 Review question

The addressed focus question was 'Does the inclusion of nanoparticles in manufacturing titanium-based implants enhance biocompatibility of the implants?' and developed according to the Participant, Intervention, Control, Outcome (PICO) principle as follows [14]:

(P) Participants: The test samples were intended for human implantation treatment and should be Ti-based.

(I) Types of interventions: The interventions of interest were those demonstrating enhancement of biocompatibility by using NPs.

(C) Control intervention: Ti implant material without NPs.

(O) Outcome measures: Improved biocompatibility and reduced bacterial infection in samples with NPs.

2.2 Procedure

The present systematic review was conducted according to the guidelines set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [15]. The studies were selected according to the eligibility criteria described in the proceeding subsection.

2.3 Eligibility criteria

The extracted articles contained data indicating the extend to which NPs affect biocompatibility of Ti implants. In vitro and in vivo studies were considered with the implant material intended for human use. Furthermore, the inclusion criteria consisted of studies published in English and without restrictions on the date range of publication. The studies that were excluded were those that did not use Ti as the base biomaterial, attributed biocompatibility to the use of micro/macro particles or nano-forms other than NPs and those that assumed biocompatibility without evaluations thereof.

2.4 Information sources

Information was retrieved from the following electronic databases that contain articles published in journals relating to biomedical sciences: PubMed/MEDLINE, ScienceDirect, Web of Science and EBSCOhost. Additional sources were used to supplement the data obtained.

2.5 Search strategy

The selected electronic databases were searched using the keywords 'biocompatibility', 'nanoparticles', 'titanium' and 'implant'. These keywords were applied to the databases as follows:

- For PubMed/MEDLINE, the keywords were entered as (biocompatibility AND nanoparticles AND titanium AND implant).
- For ScienceDirect, the keywords were entered as ('biocompatibility' AND 'titanium' AND 'implant' AND 'nanoparticles').
- For Web of Science, the topic searches were entered as (biocompatibility* AND titanium AND implant* AND (nanoparticle* OR nano particle*)).
- For EBSCOHost, the Boolean search phrase was (biocompatibility AND titanium AND implant AND nanoparticles).

The full-texts were downloaded either directly via the links provided on the databases or via ResearchGate and Google Scholar profiles for the articles identified using additional sources.

2.6 Criteria for studies selection

Data selection began with analysing the titles followed by carefully evaluating the abstracts of the titles indicating inclusion. Thereafter, the articles that were considered eligible for review were selected for reading of the full-texts. Two reviewers to ascertain whether the studies fulfilled the inclusion criteria thus independently reviewed the obtained full-texts of the studies. Inconclusive decisions among the researchers were resolved by consulting the third reviewer. Studies that were unanimously selected as fulfilling the inclusion criteria were processed for data extraction.

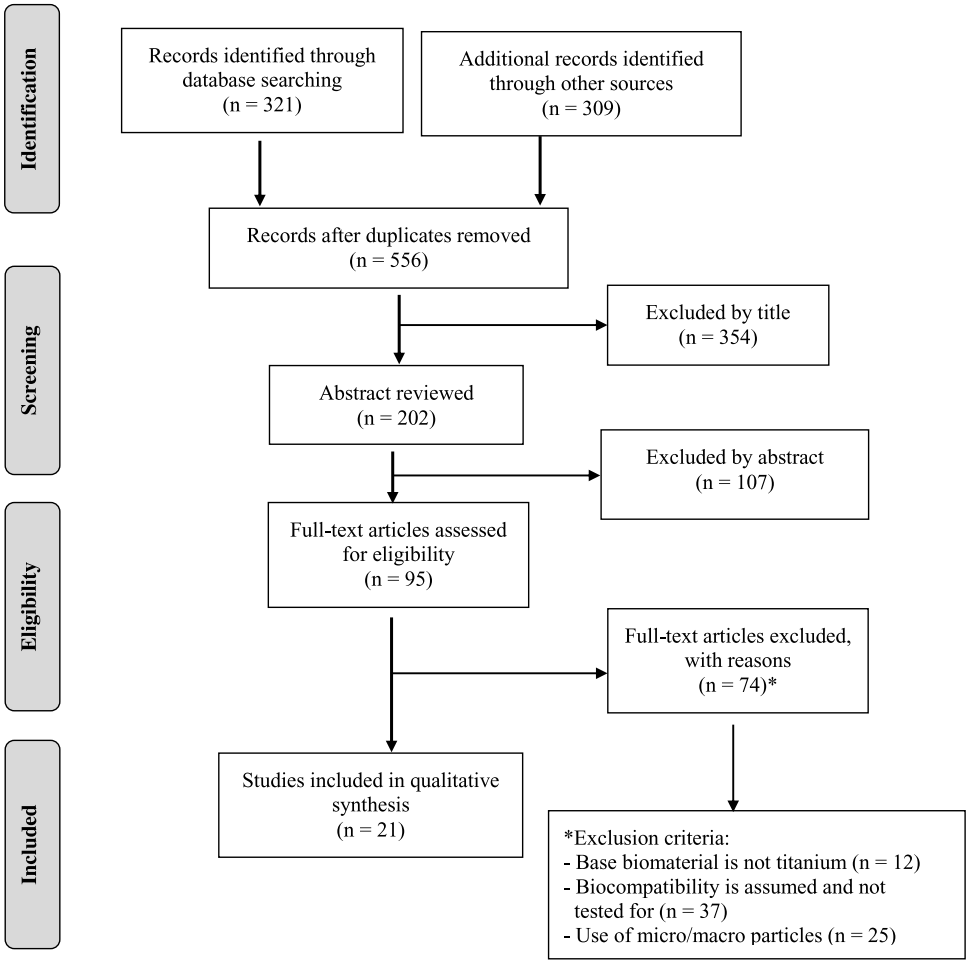

Fig. 1. The PRISMA flow chart for search strategy and selection criteria for eligible articles.

2.7 Risk of bias assessment

The Cochrane Collaboration's tool for assessing risk of bias was used to assess the individual studies [16]. The risk of bias assessment parameters were as following:
– Random sequence generation (√/×/?);
– Allocation concealment (√/×/?);
– Blinding of participant's and personnel (√/×/?);
– Blinding of outcomes assessment (√/×/?);
– Incomplete outcome data (√/×/?);
– Selective reporting (√/×/?);
– Other sources of bias (√/×/?).

2.8 Additional analyses

Antibacterial examinations were considered since Ti significantly lacks in antibacterial properties and exhibits susceptibility to bacterial colonisation, which may negatively affect the biocompatibility functions of Ti implant. Additionally, nanoparticles are renowned antibacterial agents.

3 Results

3.1 Study selection

The flowchart of the systematic review is depicted according to the PRISMA flow diagram in Figure 1. Searches of the selected databases retrieved 321 articles and were supplemented with 309 articles from additional sources, which resulted in a total of 630 titles identified in the initial search. After the duplicate records were removed, 556 articles remained. A further 354 and 107 articles were excluded after screening the titles and the abstracts, respectively. Eligibility of the full-texts of the articles was assessed from which 74 article were found to not fulfil the inclusion criteria. Finally, 21 articles were included in the present systematic review and processed for data extraction in the following order (Tab. 1): substrate material, type of nanoparticles (diameter in nm), type of study, type of cell/organism, type of laboratorial analysis, type of biocompatibility test, experimental/incubation period, was antibacterial effect tested for? and references.

Table 1. Summary of relevant data extracted from the selected articles.

Substrate material	Type of nanoparticles (diameter in nm)	Type of study	Type of cell/ organism	Type of laboratorial analysis	Type of biocompatibility test	Experimental/ incubation period	Was antibacterial effect tested for?	References
Titanium	Silver nanoparticles (AgNPs) (~58)	In vitro	Dental pulp stem cells (DPSCs)	Alamar Blue assay® and SEM	Cell viability	14 days	yes	[17]
Ti13Zr13Nb	AgNPs (~50)	In vitro	MC3T3-E1	MTS assay	Cell proliferation	3 and 7 days	yes	[18]
Nickel–titanium (NiTi)	AgNPs (~230)	In vitro	Human bone mesenchymal stem cells (hBMSCs)	CCK-8 assay	Cytotoxicity	1, 2, and 3 days	yes	[19]
Ti6Al4V and Ti6Al4V/TNT5 alloys	AgNPs (18–115)	In vitro	Murine fibroblast cell line L929, Human osteoblast-like MG63 cells	MTT assay SEM	Cell adhesion and proliferation	24, 72 and 120 hr	yes	[11]
Commercially pure titanium (cp-Ti)	Silica-gentamycin (~298)	In vitro	Human skin fibroblasts	CCK-8 assay SEM	Cytotoxicity Cell adhesion and proliferation	2 hr 24 hr	yes	[20]
Ti	AgNPs (10–30)	In vitro	Human osteoblast-like cells MG63	MTT assay	Osteoblasts adhesion and proliferation Cytotoxicity	24, 48, 120 hr, and 7 days	yes	[21]
Medically pure Ti	AgNPs (10–40)	In vitro	Rat bone marrow mesenchymal stem cells (rBMMSCs)	CellTiter-Blue® cell viability assay PicoGreen dsDNA assay kit CLSM	Cell viability Normalized alkaline phosphatase activity Intracellular reactive oxygen species (ROS) quantity	1, 4, and 7 days 3 days	yes	[22]
cp-Ti	TiO_2 (100–360)	In vitro	Simulated body fluid (SBF) Human foetal osteoblastic cell lines	Biomineralisation studies MTT assay SEM analysis	Apatite-forming ability Cell adhesion and proliferation, cytotoxicity Cell adhesion and proliferation	21 days 1 and 3 days ~5 days	yes	[23]
cp-Ti	AgNPs (~10)	In vitro	MC3T3-E1	WST-1 SEM ALP test Filamentous actin (F-actin) staining	Cell proliferation and cytotoxicity Morphology of cells on substrate ALP activity Cytoskeleton organization of cells grown	1, 3, 5, and 7 days 10 days 1 hr	yes	[24]

Table 1. (continued).

Substrate material	Type of nanoparticles (diameter in nm)	Type of study	Type of cell/ organism	Type of laboratorial analysis	Type of biocompatibility test	Experimental/ incubation period	Was antibacterial effect tested for?	References
Ti	AgNPs (∼100)	In vitro	Human gingival fibroblasts (hGFs)	MTT assay FL SEM	Cell viability Cell morphology and cytoskeletal architecture Cell attachment and proliferation	1, 2, 4, 6, and 8 days 24 hr 3 and 12 hr	yes	[25]
cp-Ti and Ti6Al4V alloy	AgNPs (20– 200)	In vitro	Human osteosarcoma cells (MG63)	MTT assay	Cells viability	4 hr	yes	[26]
TiAI6V4 alloy	AgNPs (25)	In vitro	MC3T3-E1	FL	Cells viability	2 and 4 days	yes	[27]
cp-Ti	AgNPs (<100)	In vitro	human mesenchymal stromal cells (hMSCs)	MTT assay SEM analysis FL Matrix formation analysis qRT-PCR analysis	Cells viability: metabolic activity of cells Morphology of cells on substrate Cells attachment, spreading, and morphology Collagenous and noncollagenous contents of extracellular matrix Levels of osteogenic genes on substrate	1, 3, and 6 days 2 and 4 days 3 h, 1 and 6 days 10 and 17 days 14 days	no	[28]
cp-Ti	TiO_2 (20)	In vitro	L929 murine fibroblasts	SEM	Cell attachment and growth	48 hr	no	[29]
Ti	AgNPs (∼5)	In vitro	MC3T3-E1	CLSM FL ALP test	Cell proliferation, cytotoxicity Cell morphology Osteoblastic differentiation	1, 3 and 5 days 5 days 7, 14 and 21 days	yes	[30]
cp-Ti	AgNPs (100–150)	In vitro	Human gingival fibroblasts HGF-1, human osteoblast U-2 OS	FL MTT assay Cell cycle evaluation	Cell growth on substrate Cytotoxicity Cell proliferative activity	96 hr 72 and 96 hr 72 and 96 hr	no	[31]
Ti	AgNPs (∼30)	In vitro	MC3T3-E1	FL and FE-SEM CCK-8 assay	Cell adhesion and morphology Cytotoxicity	1 day $1-4$ hr	yes	[32]
cp-Ti	AgNPs	In vitro	Human foetal osteoblast cells (hFOB)	MTT assay SEM	Cell proliferation early cell adhesion Cytotoxicity	4 and 7 days ∼24 hr	no	[33]

Table 1. (continued).

Substrate material	Type of nanoparticles (diameter in nm)	Type of study	Type of cell/ organism	Type of laboratorial analysis	Type of biocompatibility test	Experimental/ incubation period	Was antibacterial effect tested for?	References
cp-Ti	AgNPs	In vitro	Rat bone marrow stem cells (rBMSCs)	SEM analysis Alamar Blue assay	Cells attachment and spreading Proliferation rate	1, 3 or 7 days 3 and 7 days	yes	[34]
Ti	AgNPs (20–30)	In vitro In vivo	MC3T3-E1 Rabbits	Cell counting kit-8 ALP test Alizarin red staining Radiographic evaluation Histological evaluation	Cytotoxicity Cell differentiation Degree of mineralization New bone formation	3, 5, and 7 days 7 and 14 days 15 and 21 days 8 weeks	yes	[35]
cp-Ti	AgNPs (20–50)	In vitro	MC3T3-E1	FL MTT assay ALP assay	Cell attachment and proliferation Cell differentiation	12 h, 24 h and 5 days 4, 7 and 10 days	yes	[36]

AgNPs = silver nanoparticles; ALP= alkaline phosphatase; CCK-8 = Cell Counting Kit-8; CLSM = confocal laser scanning microscopy; cp-Ti = commercial pure titanium; DNA = deoxyribonucleic acid; FL = fluorescence microscopy; MC3T3-E1= mouse osteoblast precursor cell line; MTS = (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium); MTT= 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide; PCR = polymerase chain reaction; rBMSCs = rat bone marrow stem cells; SEM = scanning electron microscope; TiO_2 = titanium dioxide; WST-1 = 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4- disulfophenyl)-2H-tetrazolium, monosodium salt.

Table 2. Risk of bias assessment summary of the seleceted studies.

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcomes assessment	Incomplete outcome data	Selective reporting	Other sources of bias
[17]	×	×	?	√	√	√	?
[18]	×	×	?	√	√	√	?
[19]	×	×	?	√	×	√	?
[11]	×	×	?	√	√	√	?
[20]	×	×	?	√	√	√	?
[21]	×	×	?	√	√	√	×
[22]	×	×	?	√	√	√	√
[23]	×	×	?	√	×	×	×
[24]	×	×	?	√	√	√	√
[25]	×	×	?	√	√	√	?
[26]	×	×	?	√	√	√	?
[27]	×	×	?	√	×	×	×
[28]	×	×	?	√	√	√	√
[29]	×	×	?	√	×	×	×
[30]	×	×	?	√	√	√	×
[31]	√	√	√	√	√	√	×
[32]	×	×	?	√	√	√	?
[33]	×	×	?	√	√	√	?
[34]	√	√	√	√	√	√	?
[35]	×	×	?	√	√	√	?
[36]	×	×	?	√	√	×	?

√ = low risk; ? = unclear risk; × = high risk.

3.2 Risk of bias assessment

The results from the risk of bias assessment are summarised in Table 2. The results showed that 16 studies were considered to have a low risk of bias while three were considered to have high risk of bias since the authors had opted not to include all the initially prepared test samples in all the analyses. The remaining two were considered to be of moderate risk.

3.3 Study characteristics

From Table 1, it may be observed that of the 21 studies included in this systematic review, 18 (86%) made use of silver nanoparticles (AgNPs) with the diameters ranging between 10 and 230 nm. Other nanoparticle materials used were titanium dioxide (TiO_2) and silica-gentamycin with particle diameters of between 20 and 360 nm. The NPs were added to the substrates by means of surface modification techniques that include depositing the particles onto the surface or incorporating the NPs in a coating solution.

Common methods of analyses were 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay, Cell Counting Kit-8 (CCK-8) assay, alkaline phosphatase (ALP) test and surface morphology characterisation using a scanning electron microscope (SEM) and a fluorescence microscope. These techniques were mainly applied to determine biocompatibility of the NPs in terms of adhesion and proliferation of cells on the surfaces of the substrates (MMT assay and microscopic observations), cytotoxicity of the nanoparticle (MMT and CCK-8 assays) and cell differentiation (ALP test).

Majority of the studies (95%) were conducted in vitro and mainly against cultured human osteoblast and fibroblast cell lines (48%) as well as cultured mouse osteoblast cell line (MC3T3-E1) (33%). [35] conducted in vivo analyses to qualify biocompatibility and biocidal aspects using rabbits while [32] performed in vivo antibacterial assay using male rats. A total of 17 (81%) studies examined the antimicrobial ability of NPs along with the biocompatibility evaluations. Most of the antibacterial testing was carried out on the common Gram-positive *Staphylococcus aureus* (*S. aureus*) and Gram-negative *Escherichia coli* (*E. coli*) bacteria.

4 Discussion

Nanomaterials have been deemed as the 'material of the 21st century' because of their unique designs and wider combination of properties as compared with conventional materials [37]. In addition, there is growing interest in the application of nanoparticles to control various infections because of their biocidal properties and anti-adhesive

capabilities against biofilms, particularly since biofilm formation on the surface of implant devices may cause peri-implantitis and lead to bone loss [25,38]. However, the extensive use of NPs, especially in medicine, incites the consideration of the potential toxicity to the human body. Therefore, along with cell adhesion and proliferation, cytotoxic potential of NPs is one of the most common features investigated during in vitro studies to determine biocompatibility [39]. These biocompatibility features were included in the studies selected in the present systematic review.

The results of the cell viability assay conducted by [17] illustrated that AgNPs implanted titanium surface favoured biocompatibility for long-term use whereby the surface treated with NPs showed unchanged cell viability as compared to the surface control. The authors also evaluated the antibacterial properties of the prepared surfaces against *S. aureus* and AgNPs containing surfaces exhibited a distinct inhibition of bacterial growth, while the nanoparticle deficient surfaces showed minimal effect on bacterial growth. These results are in agreement with those observed by [18] and [19] which showed that modifying Ti specimen surfaces with nanosilver does not deteriorate the overall biocompatibility of the material construct while allowing for adequate antibacterial protection.

During the study of [11], the lowest addition of NPs revealed optimal biointegration properties and high biocidal properties. The MTT assay and SEM micrographs of the tested samples showed an increase in the fibroblast and osteoblast proliferation over time. The viability of the cells after 120 hours of incubation was 85% or more as compared to reference specimens and thus demonstrated reasonable biocompatibility of the tested nanomaterials. The MTT test of [21] showed that on AgNP-modified coating, there was an initial reduction in human osteoblast cell-like MG63 cell viability at 24 hours followed by an increase after seven days of culture and reached a mean value higher than 60% over the control culture. An antimicrobial effect was demonstrated and ascribed to the presence of NPs.

[23] and [24] revealed that low concentrations of NPs are favourable for preosteoblast spreading and cytotoxicity prevention. [23] further showed through the MTT assay that the addition of TiO_2 NPs at low concentration (2 and 5 wt.%) to polymetric scaffolds advanced the proliferation of human foetal osteoblast cells (hFOB) cells. SEM analysis showed higher proliferation of hFOB cells on the scaffolds containing TiO_2 NPs after only three days of culture. The added TiO_2 NPs increase the surface area and surface hydrophilicity, thus supporting cell adhesion on the first day and cell proliferation on the third day. Optimized nanoparticle concentration (~5 wt.%) may be applied to engineering scaffolds favouring new tissue formation [23].

[24] discovered that at extended incubation periods, cell extensively spread and secreted abundant extracellular matrix to benefit cell proliferation for AgNP concentrations of 0.01, 0.001, and 0.0001 M. Furthermore, low concentrations of AgNPs exhibited no obvious negative effects on the osteogenic differentiation of the MC3T3-E1 after 10 days of culture during the ALP assay. The ALP activity was measured as an early marker for osteogenic differentiation potential of preosteoblasts. Also, substrate groups coated with AgNPs showed significant antibacterial effects against *S. aureus* and *E. coli*. The antimicrobial activities were positively correlated with the nanoparticle dosage loaded on surfaces of substrates. In support of these findings, the microscopic analysis and CCK-8 test conducted by [20] revealed good biocompatibility properties of all tested specimens where the released silica-gentamycin NPs was biocompatible with human fibroblasts. In addition, after incorporating NPs, an effective antibacterial coating on the Ti substrate was achieved.

The unambiguous biocompatibility and antibacterial effects of NPs was further demonstrated by [35] during their in vitro and in vivo investigations. In vitro, the nanosilver-coated Ti samples promoted the ALP activity of MC3T3-E1 cells more effectively with a significant increase observed for extended incubation periods. Moreover, matrix mineralisation of cells (which was observed after 21 days culture in osteogenic medium) on the NPs sample was 2.15 times greater than that on the uncoated Ti control and the CCK-8 assay showed that the NPs did not reduce MC3T3-E1 cell growth, but improved cell proliferation more effectively. The in vitro antibacterial experiments indicated that the uncoated Ti control did not inhibit bacterial adhesion or proliferation, while nanosilver-concentration-dependent animicrobial behaviour was observed in all nanoparticle-embedded surfaces. These results indicating cell–substrate compatibility and biocidal impact of nanoparticle coated samples were supported by the in vivo studies of [35] in the tibial canals of rabbits. During these studies, specimens with AgNPs accelerated the formation of new bone while suppressing survival of methicillin-resistant *S. aureus* and the *Pseudomonas aeruginosa*. Therefore, implants impregnated with NPs have simultaneous antibacterial and osteoinductive activities in vitro and in vivo proportional to the concentration of NPs [35]. The in vivo antibacterial assay of [32] showed similar results of the long-term antibacterial ability of Ti substrates coated with AgNPs.

Applications of NPs in the selected research papers was mainly in the form of embedding the ultrafine structures into a coating material such as nanosilver-loaded bone cement coatings [18], nanosilver-loaded dopamine coatings [36], AgNP-filled hydrogen titanate nanotube layer [30], Ag nanoparticle-loaded TiO_2 nanorods (NRDs) coatings [32], hydroxyapatite (HA) coatings [34], thin mussel adhesive protein (Mefp-1)/AgNP composite film [24] and cross-linked gelatin/SG composite coating [20]. The incorporation of NPs into such surface modification coatings facilitates the slow release of ions from NPs and the subsequent reduction of toxicity and prolonged antibacterial effects.

5 Conclusion

A resounding agreement occurred amount the reviewed studies that the inclusion of NPs in the manufacturing of titanium implants enhanced biocompatibility of the implants. Furthermore, majority of the studies showed

that evaluating biocompatibility without exploring antimicrobial interventions might result in the benefits of NPs not being fully exploited. Thus, the combination of antibacterial ability and biocompatibility, as well as non-cytotoxicity, studied mainly in vitro indicates that the optimal nanoparticle enriching method could provide a promising strategy for the fabrication of long-term tissue–implant integration. As recommended by majority the authors included in this systematic review, future work on long-term implantation in vivo should be reported in future publications and a variety of nanoparticle materials should be explored.

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