

G55: Are there modified implant surfaces proven to reduce the incidence of clinical infection following major orthopedic procedures?

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Response/Recommendations: Systematic reviews of numerous *in vitro* and *in vivo* animal basic science studies, have shown the combined positive anti-bacterial and osteogenic effect of novel surface modifications and nanostructured orthopaedic implants. However, the preclinical positive effects have not yet been translated into meaningful positive clinical outcomes.

Level of Evidence: Strong

Prosthetic joint infection (PJI) represents one of the most devastating complications in joint arthroplasty, with a prevalence of 1-2% after primary joint replacement and 4% after revision.^{1,2} It is also the most common reason for early revision.³ PJI has a severe impact on morbidity and mortality rates, and quality of life is severely affected in these patients.¹

Various strategies have been developed to eliminate the effect of infection risk factors, such as patient optimisation, ultra clean surgical operation rooms, pre-operative preventive antibiotics, improved surgical techniques and implants with modified surfaces.^{4,5}

The aim of this systematic review is to evaluate the efficacy and safety of nanotechnology modified implants (other than silver, iodine povidone and hydrogel surface modified surfaces) in reducing the incidence of clinical infection in major orthopedic procedures.

Research Strategy. A systematic computer based literature review search with predefined criteria was performed according to the preferred reporting items for Systematic Review and Meta-analyses (PRISMA) guidelines in the Scopus and Pubmed databases. Research Methodology used a combination of mesh terms developed by librarians and intended to capture any relevant publications. All electronic literature searches were conducted by four authors (TK, AK, SC, PC) and an experienced librarian. The above authors independently screened the titles and the abstracts to identify relevant studies. In cases of disagreement, a final decision was made by the liaison author. Only full text articles were eligible for our study. There were no publication date limitations set. Additional inclusion criteria included: a) studies written in the English language, b) studies on nanotechnology modified implant surfaces, c) experimental *in vitro* or *in vivo* studies, d) clinical studies using nanotechnology modified implants, e) relevant review papers and f) relevant systematic review and meta-analysis studies.

Exclusion criteria included: a) silver coated implants, b) povidone iodine coated implants, and c) hydrogel coated implants.

From the initial search, 3,999 studies (2,946 PubMed, 1,053 Scopus) were identified and imported for screening. Covidence identified and removed 122 duplicates. The titles and abstracts of 3,877 studies were screened by the authors and 3,450 studies were considered as irrelevant (applying additional inclusion and exclusion criteria). Subsequently, the full text of 425 studies was accessed by the authors and a further 87 studies were excluded (not meeting inclusion and exclusion criteria). At the end 338 studies were included in this systematic review. Of these 338 relevant studies, 198 were *in vitro* experimental studies, while 14 were *in vivo* animal studies relevant to nanotechnology modified implant surfaces. 117 papers were basic science reviews relevant to antimicrobial coatings and nanotechnology modified implant surfaces. Nine systematic reviews and meta-analyses relevant to modified implant surfaces were also found. It has to be stressed that no human clinical study relevant to the reduction of the incidence of clinical infection in major orthopedic procedures was found.

The application of nanotechnology novel surfaces and coatings was reported in 198 studies using a variety of experimental settings. Anti-microbial efficacy was studied using different bacterial strains (mainly *Staphylococcus aureus*). Osseointegration and biocompatibility were studied in eukaryotic cells. A variable antimicrobial spectrum of reduced bacterial growth and inhibition of biofilm formation, and an unaffected or enhanced interface bone ingrowth were reported.

The application of nanotechnology novel surfaces and coatings was also evaluated in animals and reported in 14 studies. Antimicrobial efficacy was studied using different bacterial strains (mainly *Staphylococcus aureus*). Osseointegration and biocompatibility were studied in various animal models (mainly rats). A variable antimicrobial spectrum of reduced bacterial growth and inhibition of biofilm formation, and an unaffected or enhanced implant osseointegration were also reported.

In the recent years, several attempts have been made, by scientists and engineers, to develop antibacterial strategies related to materials and surfaces with antibacterial properties.^{6,7} These strategies include anti-adhesion polymer coatings, superhydrophilic, superhydrophobic, liquid-infused surface coatings and bacteria killing coatings.^{6,7} Nanomodification of implants is a good option and has the potential to induce different types and degrees of anti-bacterial effects in clinical setting. At the same time, implant nanostructures should not adversely affect

osteogenic activity and osseointegration. Mechanical, chemical and physical methods are used for the nanomodification of titanium alloy surfaces.^{8,9} Nanomodification of titanium implant materials differs widely by means of nanostructure formation procedures, formation of nanomaterial coatings and nanomorphology. Nanomaterials are classified by structure form; clusters (made of solid nanoparticles), nanorods (made of nanowires), coatings (made of films) and nanotubes (made of pillars). Nanomaterials are also classified by the existence of antibacterial active ingredients; metal ion antibacterial active ingredients and oxide photocatalytic antimicrobial materials. All of these nanostructures can inhibit or kill bacterial micro-organisms.^{8,9}

Systematic reviews have already shown the combined positive anti-bacterial and osteogenic effect of novel surface modifications and nanostructured orthopaedic implants in *in vitro* and *in vivo* studies.^{4,5,10,11} However, despite the enormous effort that basic scientists, engineers and orthopedic surgeons have put into the development and evaluation of anti-bacterial nanostructured orthopaedic implants, the preclinical positive effects have not yet been translated into meaningful positive clinical outcomes related to major orthopaedic procedures.¹¹⁻¹⁹

Moreover, the possible toxic effects of these nanomodified implant surfaces on other cellular lineages surrounding orthopaedic have been already addressed *in vitro* studies_ and should be further investigated.²⁰

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