

# The use of silver coating in hip megaprostheses: a systematic review

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HIP International  
1–14  
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DOI: 10.1177/1120700018811070  
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## Abstract

Retrospective studies of silver-coated hip implants have demonstrated promising results and safety profile, however, the potential benefits are so far unproven in prospective studies. Silver-coated implants may have a role in patients undergoing revision or primary surgery with a high risk of infection but as yet there are no human studies investigating silver in primary hip arthroplasty. Adequately powered robust prospective studies are needed in this area to determine if silver-coated implants would be efficacious and cost-effective. The purpose of this systematic review article is to review the current literature regarding the use of silver in hip arthroplasty. Our review showed that there is some encouraging evidence that silver coatings can reduce infection.

## Keywords

Hip replacement, infection, prevention, silver

Date received: 5 February 2018; accepted 16 July 2018

## Introduction

### Background

Silver is a chemical element discovered in approximately 3000BC with an atomic number of 47. Its chemical symbol, Ag, is derived from the Latin word *argentum*. Silver has a plethora of uses: from jewelry to being woven into gloves, making them compatible with touchscreen phones. Its use in medicine is a function of its antimicrobial properties and in this context, it was first used in the 18th century to treat ulcers.<sup>1</sup>

### Mechanism of action of silver

Silver has activity against bacteria, fungi and viruses.<sup>2</sup> It has been described as “oligodynamic” due to being toxic to bacteria at very low concentrations.<sup>3</sup> The mechanism of action is complex and multifaceted. Silver ions are biologically active and facilitate the bactericidal effect. Silver ions interact with 3 specific bacterial cell structures.<sup>4</sup> At the peptidoglycan cell wall and plasma membrane they cause destruction and cell lysis.<sup>5,6</sup> They interact with bacterial DNA preventing DNA replication and thereby reproduction via binary fission. They also interact with bacterial

proteins, denaturing ribosomes, disabling protein synthesis and causing degradation of the plasma membrane.<sup>7–10</sup> An additional mechanism of toxicity to bacteria is through formation of reactive oxygen species (ROS) by silver ions. Park et al.<sup>11</sup> have demonstrated ROS-mediated silver toxicity with an increased antimicrobial activity in aerobic compared to anaerobic conditions.

The multifaceted mechanism reduces the opportunity for the development of bacterial resistance in comparison to traditional antibiotics. Current literature suggests resistance to silver is rare and sporadic although it is known that silver-resistance genes exist in certain types of bacteria.

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Randall et al.<sup>12</sup> have discussed and try to further elucidate the endogenous (mutational) and exogenous (horizontally acquired) mechanisms through which silver resistance has developed. As observed by Percival et al.,<sup>13</sup> bacterial resistance to antibiotics has occurred in the last 70 years but on the contrary, no widespread resistance to silver has developed in over 4 billion years of exposure.

### Medical application of silver

Clement and Jarrett<sup>3</sup> comment that the use of silver has been documented since the time of the King of Persia using water storage in flagons of silver when going to war. Since then, silver has become widespread in different medical applications. These include silver-coated catheters,<sup>14</sup> municipal water systems,<sup>15</sup> hospital surfaces disinfection and wound dressings particularly in the care of burns.<sup>16,17</sup>

Silver has been used in both compound forms such as silver nitrate and more recently as nanosilver following advancement in manufacturing processes. Furthermore, the antimicrobial efficacy of silver has been shown to be related to its structural make up, with nanosilver proving more effective than silver chloride and silver nitrate.<sup>18</sup> Nanoparticles can be used in coating medical devices, with the aim of preventing biofilm formation and technology has developed to enable silver to adhere to the surface of a device.<sup>19</sup> This development is of potentially huge significance as it allows silver to be used to potentially reduce the risk of prosthetic joint infection (PJI) – a complication seen in 1.5–2.5% of all primary hip and knee arthroplasty.<sup>20</sup>

Antibiotic prophylaxis therapy is common practice after surgery, but it is difficult to demonstrate a clear supremacy of a particular antibiotic over another.<sup>21</sup> The most common pathogens associated with postoperative infection are *Staphylococci* yet gram negative organisms such as *Pseudomonas aeruginosa* can often be very challenging to eradicate given the biofilms produced.<sup>22</sup> By introducing prostheses, pathogenic microbes have a surface on which they can develop biofilms. Bacteria grow in aggregates that become encased in an extracellular matrix produced by the bacteria, where the matrix is often rich in polysaccharides, proteins and DNA.<sup>23</sup> They are associated with increased rates of infection on human surfaces such as teeth, skin, and the urinary tract, as well as medical devices such as catheters, heart valves, and orthopaedic implants.<sup>23,24</sup> The biofilm forms a haven for safe growth, making them more difficult to be destroyed by the immune system and more resistant to antibiotics.<sup>25,26</sup>

This provides the rationale for research into orthopaedic applications of silver, such as in tumour prostheses, external fixator pins, bone cement and coating of implants.<sup>19</sup> PJI can have devastating effects on a patient's quality of life.<sup>27</sup> Reducing the incidence of PJI would lead to a

reduction in the number of revision procedures, improved outcomes for patients and reduce the cost to society. In bone cement the addition of nanosilver has shown promising *in vitro* results and low levels of toxicity.<sup>28</sup> Similarly, *in vitro* results of silver-coated trauma implants have shown promise but with mixed *in vivo* results.<sup>29,30</sup> Silver has been demonstrated to cause toxicity to human tissue, particularly renal, hepatic and neural tissues. Additionally, local argyria, a blue/purple discoloration of the skin, around implants has also been reported. However clinical studies have so far not elucidated any malignant toxicity. The number of silver implants currently used are low and sporadic at present.

The purpose of this article is to review the current literature regarding the use of silver in hip arthroplasty.

### Materials and methods

Our review team used a rigorous and systematic approach conforming to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the critical evaluation of studies relating to the use of silver in total hip replacement surgery.

#### Protocol

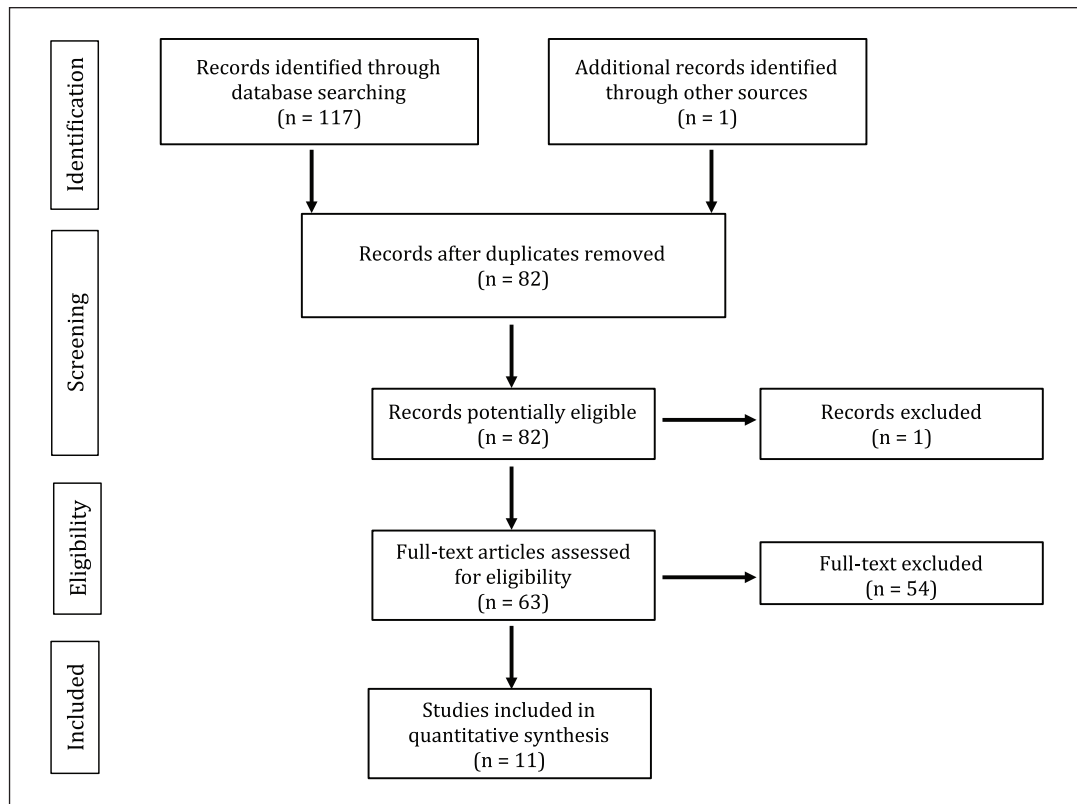
A protocol was registered online before commencing the study with PROSPERO (International prospective register of systematic reviews, CRD42017082680) as recommended by the Quality of Reporting of Meta-analyses (QUOROM) statement.<sup>31</sup>

#### Search strategy

We searched all studies indexed in OVID MEDLINE, EMBASE, ACM, ADS, arXiv, CERN DS, Crossref DOI, DBLP, Espacenet, Google Scholar, Gutenberg, Highwire, IEEEExplore, Inspire, JSTOR, OALster, Open Content, Pubget, PubMed, Web of Science for the last 10 years using the search strategy shown in Figure 1. The search strategy was not limited by language or patient age. We also evaluated the grey literature with hand searches of 6 major orthopaedic journals over the last 5 years. The bibliographies of the relevant articles were then cross-checked to search for articles not identified in the search. The initial screening of studies was performed by 2 independent assessors with any disagreements meaning that the study in question was included. An electronic spreadsheet was constructed to summarise the findings of relevant studies.

#### Eligibility criteria

We included all studies that related to silver implants in hip surgery.



**Figure 1.** PRISMA flow diagram.

### Screening

A total of 117 records were identified from the searches described above. The titles and abstracts were screened to identify articles for inclusion in this systematic review. After screening, 63 articles were assessed for eligibility against criteria and from these 11 articles were reviewed formally. A flow diagram of the progression of studies through this systematic review is provided in Figure 1.

### Data extraction

2 of the authors worked independently to extract the data using standardised forms. We extracted data on participants, joint involved, survivorship of implants, prevention of infection and toxicity.

### Results

There were 63 articles reporting a mix of laboratory studies, animal studies, review articles and 11 studies using silver-coated implants in patients providing level III evidence. Study characteristics are summarised in Table 1.

### Endoprosthesis

Much of the source material gathered around silver-coated prostheses was centred on megaendoprosthesis.

Endoprosthesis are used to address large bone defects when conventional prostheses may not suffice. Examples include: major osteolysis causing implant loosening, tumours, periprosthetic fractures, or periprosthetic infection. Megaendoprosthesis are commonly modular, allowing intra-operative flexibility, but in contrast to regular prostheses have a larger surface area, typically require larger surgical exposures, are used in operations of long duration due to the complexity of the indications, and have higher blood loss;<sup>52</sup> all factors associated with an increased risk of PJI.

Revision surgery for tumour endoprosthesis has been shown to carry a reinfection rate of up to 43%. Often the bacterial biofilm proves too difficult to remove and the prosthesis must be removed.<sup>34</sup> Commonly, oncological patients are immunologically deficient due to chemotherapy, or may be weakened by simultaneous disease in other organs, or the malignancy itself, and are at higher risk of infection.<sup>21</sup>

### In vitro

Silver-coated nanotubes have been shown to be effective in preventing biofilm formation and lowering bacteria numbers in the early postoperative period.<sup>45</sup> *In vitro* and *in vivo* evaluations show that nanotubes on titanium surfaces encourage osseointegration, cell differentiation, mineralisation, and anti-microbial properties (including reducing the initial

Table 1. Characteristics of included studies.

Author	Journal/year	Study type/ Level of evidence	Number of patients	Implant	Indication/context	Evidence of infection prevention	Risk/safety
Ando et al. <sup>32</sup> Calcium phosphate coating containing silver shows high antibacterial activity and low cytotoxicity and inhibits bacterial adhesion.	Materials Science and Engineering: C 2010	Laboratory study	-	Novel coating technology of calcium phosphate containing silver, using thermal spraying technique.	Evaluated antibacterial efficacy and biological safety of coating.	<i>In vitro</i> antibacterial activity showed growth of bacteria to be completely suppressed.	Animal cells were found to grow on the coating in a cytotoxicity test.
Chen et al. <sup>33</sup> Silver release from silver- containing hydroxyapatite coating.	Surface and Coatings Technology 2010	Laboratory study	-	Silver- containing hydroxyapatite coatings were prepared by coprecipitation or plasma spraying.	Behaviour of silver release from composite coating in buffering fluid and simulated body fluid monitored.	Rate of release of silver particles was higher for coprecipitation method compared to plasma spraying. Phase composition and surface morphology of coatings may affect their bioactive properties.	
Hardes et al. <sup>34</sup> Reduction of periprosthetic infection with silver-coated megaprosthesis in patients with bone sarcoma.	Journal of Surgical Oncology 2010	Prospective cohort (silver group). Retrospective cohort (titanium group)	125 (silver = 51 titanium = 74)	MUTARS proximal femur and proximal tibia replacement.	Proximal femur/tibia sarcoma requiring replacement.	Incidence of periprosthetic infection reduced from 17.6% to 5.9% ( $p = 0.062$ ).	1 case of suspected local argyrosis 50 months postoperativ ely.
Mondanelli et al. <sup>35</sup> Modular prosthesis with a silver coating for periarticular reconstruction in septic prosthetic and post- traumatic failures.	Journal of Orthopaedic Traumatolog y (In-depth oral presentations and oral communications) 2012	Case series	10	MegasystemC with a silver coating.	Septic arthroplasty (4), septic meta- epiphyseal post- traumatic deformity of non-union (5), epithelioid hemangio- endothelioma (1).	Preliminary results demonstrate resolution of infection in all cases.	No comment.
Trujillo et al. <sup>36</sup> Antibacterial effects of silver-doped hydroxyapatite thin films sputter deposited on Titanium.	Materials Science and Engineering: C 2012	Laboratory study	-	Plain titanium, titanium coated with Hydroxyapatite, titanium coated with silver-doped hydroxyapatite.	Bacterial adhesion study.	Less bacteria adhere to surfaces containing hydroxyapatite and Silver.	-

Table 1. (Continued)

Author	Journal/year	Study type/ Level of evidence	Number of patients	Implant	Indication/context	Evidence of infection prevention	Risk/safety
Swieczko-Zurek <sup>26</sup> The influence of biological environment on the appearance of silver-coated implants.	Advances in Materials Science 2012	Laboratory study	-	Polymer vein implant covered with silver and stainless steel intramedullary nail covered with silver.	<i>In vitro</i> study.	Strong protection against biofilm production in polymer and metallic implants.	-
Kose et al. <sup>37</sup> A silver ion-doped calcium phosphate-based ceramic nanopowder-coated prosthesis increased infection resistance.	Clinical Orthopaedics and Related Research 2013	Animal study	27 (9 uncoated 9 hydroxapatite coated 9 silver coated)	Titanium implants	-	Silver ion-doped ceramic nanopowder coating of titanium implants led to an increase in resistance to bacterial colonisation compared to uncoated implants.	No cellular inflammation of foreign-body granuloma was observed around the silver-coated prostheses.
Zimmerli <sup>38</sup> Clinical presentation and treatment of orthopaedic implant-associated infection.	Journal of Internal Medicine 2014	Review	-	-	-	Antimicrobial agents have limited efficacy against biofilm infections: novel preventative options are needed. Prevention may be achieved in the future by implant coating with novel substances.	-
Brennan et al. <sup>19</sup> Silver nanoparticles and their orthopaedic applications.	The Bone and Joint Journal 2015	Review	-	-	-	Silver nanoparticle technology in orthopaedic devices has great potential to reduce implant infection.	Further research warranted, particularly to elucidate potential harmful effects.
Wafa et al. <sup>39</sup> Retrospective evaluation of the incidence of early periprosthetic infection with silver-treated endoprostheses in high risk patients: case-control study.	The Bone and Joint Journal 2015	Retrospective case-control	170 (silver = 85 titanium = 85)	Aglyma-treated tumour implants versus uncoated implants.	50 primary reconstructions, 79 one-stage revisions and 41 2-stage revisions.	Overall post-op infection rate 11.8% in silver group versus 22.4% in control group ( $p = 0.033$ )	No comment

(Continued)

Table 1. (Continued)

Author	Journal/year	Study type/ Level of evidence	Number of patients	Implant	Indication/context	Evidence of infection prevention	Risk/safety
Donati et al. <sup>40</sup> Silver coated prosthesis in oncological limb salvage surgery reduce the infection rate.	Journal of Biological Regulators and Homeostatic Agents 2015	Retrospective case-control	158	Silver coated versus non-silver coated.	Primary or metastatic bone tumours treated with excision and tumour implant reconstruction.	Early infection: 2.2% with silver implant versus 10.7% with standard.	No evidence of silver toxicity.
Donati et al. <sup>41</sup> Silver-coated hip prosthesis reduce the infection rate in oncological limb salvage surgery.	Abstracts from International Combined Meeting BHS- SIdA 26–27 November 2015	Retrospective cohort	68	Silver coated versus non-silver coated.	Primary or metastatic proximal femur bone tumours treated with excision and tumour implant reconstruction.	Early infection: 2.2% with silver implant versus 10.7% with standard. Similar rate of infection at 6 months.	No evidence of silver toxicity.
Eto et al. <sup>42</sup> First clinical experience with thermal-sprayed silver oxide- containing hydroxyapatite- coating implant.	Primary Arthroplasty 2015	Prospective case series	20	AMS HA Cup and 910 PerFix Fullcoat D stem thermal sprayed with silver.	Inclusion criteria: age ≥65 years and an indication for THA.	Harris Hip Scores were improved after surgery in line with traditional implants.	1 hip dislocation at 6 weeks. 4 cases showed detectable spot welds at 1-year x-ray. No argyria or neurologic symptoms. No infections.
Furko et al. <sup>43</sup> Complex electrochemical studies on silver-coated metallic implants for orthopaedic application.	Journal of Solid State Electrochemi- stry 2015	Laboratory study	-	Silver grains deposited onto different implant materials commonly used in orthopaedic Surgery.	Electrochemical behaviour of the coating and silver ion release rate were investigated.	-	-
Furko et al. <sup>44</sup> Comparative corrosion study on silver coated metallic implants.	Material Science Forum 2015	Laboratory study	-	Nanostructure d silver layer was deposited. onto different implant materials commonly used in orthopaedic surgery.	Electrochemical behaviour of the coatings investigated.	-	-



Table 1. (Continued)

Author	Journal/year	Study type/ Level of evidence	Number of patients	Implant	Indication/context	Evidence of infection prevention	Risk/safety
Amin Yavari et al. <sup>45</sup> Antibacterial behaviour of additively manufactured porous titanium with nanotubular surfaces releasing silver ions.	ACS Applied Materials and Interfaces 2016	Laboratory study	-	Titanium nanotubes loaded with silver.	Antimicrobial activity and cell viability of developed material were assessed.	Silver loaded nanotubes extremely effective in preventing biofilm formation.	Specimens with highest concentrations of silver adversely affected cell viability.
Funao et al. <sup>24</sup> A novel hydroxyapatite film coated with ionic silver via inositol hexaphosphate chelation prevents implant-associated infection.	Scientific Reports 2016	Animal trial.	10 (silver = 5 titanium = 5)	Hydroxyapatite film coated ionic silver versus titanium implant.	In vivo study; antibacterial effects of ionic-silver coating in a murine model of implant- associated osteomyelitis.	No bacteria detectable after inoculation. Serum IL-6 reduced. CRP reduced.	No comment
Donati et al. <sup>21</sup> Silver-coated hip megaprosthesis in oncological limb salvage surgery.	BioMed Research International 2016	Retrospective cohort	68	Silver-coated hemiarthroplasty (MUTARS) versus uncoated megaprosthesis.	Primary or metastatic bone tumour proximal femur.	Early infection 2.6% versus 10% (not statistically significant).	No evidence of silver toxicity.
Scoccianti et al. <sup>46</sup> Levels of silver ions in body fluids and clinical results in silver-coated megaprosthesis after tumour, trauma or failed arthroplasty.	Injury 2016	Retrospective case series	33	MegasystemC with a silver coating.	A silver-coated prosthesis was chosen for the following causes: septic failure of previous megaprosthesis: 8 patients. Septic complication after fracture: 7 patients. Septic failure of previous standard joint arthroplasty: 6 patients. Oncological resection with patient at particular risk of infection complication: 8 patients. Non- oncological resection with patient at particular risk of infection complication: 4 patients.	There was no infection during the first 2 years after surgery in the 12 patients who received a silver-coated megaprosthesis and had no previous history of infection. Infection recurred in 2 out of 21 patients who had received the implant because of previous septic complications.	No evidence of silver toxicity.
Besinis et al. <sup>25</sup> Antibacterial activity and biofilm inhibition by surface modified titanium alloy medical implants following application of silver, titanium dioxide and hydroxyapatite nanocoatings.	Nanotoxicology 2017	Laboratory study	-	Titanium alloy implants modified to create silver, titanium oxide and hydroxyapatite coatings.	In vitro study. Antibacterial performance assessed.	Silver coating inhibited bacterial growth in surrounding media and bacterial biofilm production reduced by 97.5%.	-

(Continued)

Table 1. (Continued)

Author	Journal/year	Study type/ Level of evidence	Number of patients	Implant	Indication/context	Evidence of infection prevention	Risk/safety
Devlin-Mullin et al. <sup>47</sup> Atomic layer deposition of a silver nanolayer on advanced titanium orthopaedic implants inhibits bacterial colonisation and supports vascularised de novo bone Ingrowth.	Advanced Healthcare Materials 2017	Laboratory study	-	-	<i>In vitro</i> and <i>in vivo</i> study.	Bacterial growth slower on silver coated titanium scaffolds. Also reduced bacterial recovery and biofilm formation.	Strong adherence and growth of human bone or endothelial cells in titanium and silver coated implants.
Nandi et al. <sup>48</sup> Silver nanoparticle deposited implants to treat osteomyelitis.	Journal of Biomedical Materials Research Part B 2017	Animal study	15 (rabbits)	Silver coated pins	Osteomyelitis rabbit model	Silver coated pins offered result in terms of eradication of infection in rabbit osteomyelitis model.	No toxicity to major organs.
Schmidt-Braekling et al. <sup>22</sup> Silver-coated megaprosthesis: review of the literature.	European Journal of Orthopaedic Surgery and Traumatology 2017	Review	-	-	-	Evidence of potential benefit of silver coated megaprosthesis so far not been confirmed in prospective and randomized studies alone. Reduced infection rate seen in retrospective studies.	Several side effects reported in earlier studies but most recent studies have confirmed lack of systemic toxicity to silver.
Schmolders et al. <sup>49</sup> The role of a modular universal tumour and revision system (MUTARS) in lower limb endoprosthetic revision surgery – outcome analysis of 25 patients.	Fur Orthopaedie Und Unfallchirurgie 2017	Retrospective case series	25	MUTARS	Patients undergoing revision surgery for failed endoprosthetic replacement or failed trauma surgery, using MUTARS.	Good clinical and functional results. High rates of infection.	-



Table 1. (Continued)

Author	Journal/year	Study type/ Level of evidence	Number of patients	Implant	Indication/context	Evidence of infection prevention	Risk/safety
Schmolders et al. <sup>50</sup> Lower limb reconstruction in tumour patients using modular silver-coated megaprosthesis with regard to perimegaprosthesis joint infection: a case series, including 100 patients and review of the literature.	Archives of Orthopaedic and Trauma Surgery 2017	Case series	100		Tumour-related lower limb salvage surgery.	10% suffered periprosthetic infection.	No evidence of silver toxicity.
Alt <sup>51</sup> Antimicrobial coated implants in trauma and orthopaedics-A clinical review and risk-benefit analysis.	Injury 2017	Review	-	-	-	Low amount silver Agluna technologies have shown the "proof of concept" for antimicrobial coatings of implants with good risk benefit ratio.	High amount silver coating associated with local argyria. Further data from randomised controlled trials desirable. No comment.
Zajonz et al. <sup>52</sup> Silver-coated modular Megaendoprostheses in salvage revision arthroplasty after periprosthetic infection with extensive bone loss – a pilot study of 34 patients. Origin-One and Logical- One Clinical Evidence Evaluation Report.	BMC Musculoskele tal Disorders 2017	Retrospective cohort	34 (14 non- silver coated group 20 silver- coated group).	MML Munchen- Lubeck modular endoprosthesis system versus MUTARS.	All patients fitted with modular endoprosthesis of lower extremity after a cured bone infection.	Reinfection rate after healed reinfection in silver group was 40% compared to 57% in non-silver group. Not statistically significant. These devices are safe and effective for their intended use. Warrant further clinical research to establish their effectiveness in a total hip replacement procedure and in reducing periprosthetic infection.	

adhesion and colonisation of *Staphylococcus epidermidis*). Nanotube surface treatment can be applied to existing macro and micro porous titanium implants. Nanotubes have been shown to improve bone bonding nine-fold and mineralisation by 3 times that of non-treated titanium surfaces.<sup>53</sup>

Thermal sprayed coatings of calcium phosphate containing silver showed significant decrease in the adherence of *Escherichia Coli*, *Staphylococcus aureus* and Methicillin-resistant *Staphylococcus aureus* (MRSA).<sup>32</sup> In megaendo-prostheses, silver coating may be accomplished by galvanic deposition of elementary silver. This 1st layer is additionally coated with another layer of gold (the cathode) to enable continuous release of silver ions (the anode).<sup>22,51</sup>

Albers et al.<sup>54</sup> investigated silver ion, and nanoparticle, induced cytotoxicity in primary osteoblasts (OB) and osteoclasts (OC). They found that the treatment of OBs and OCs with silver particles lowered the cell differentiation and number of viable cells, OBs more so than OCs; OBs viability being reduced at 128 µg/ml silver nanoparticles and differentiation being reduced at 64 µg/ml, with OCs viability and differentiation being reduced at 256 µg/ml and 128 µg/ml respectively. Dose and size also played a key part with nanoparticles (average size 50 nm) being more damaging than microparticles (3 µm). The bactericidal effects of silver occurred at 2–4 times the levels that induced cytotoxic effects.<sup>54</sup>

Ando et al.<sup>36</sup> found that hamster lung cells grew on the silver calcium phosphate coating in a cytotoxicity test. In the presence of hydroxyapatite, silver has a much higher photocatalytic activity than titanium oxide-silver mixtures alone, due to the generation of free radicals. These free radicals may lead to oxidative stress and cell death.<sup>25</sup>

Fielding et al.<sup>55</sup> found that the antibacterial properties of the silver coatings, tested against *Pseudomonas aeruginosa*, were highly effective. They then tested cell-material interactions using human foetal osteoblasts *in vitro*. Cells grown on silver-hydroxyapatite surfaces demonstrated dysfunctional features such as premature apoptosis, delayed differentiation and cell death, with nearly complete impediment of functional alkaline phosphate activity.

To combat these effects of silver, strontium was added as a coating mixture acting as a binary dopant. The strontium acts to stimulate bone formation, while inhibiting bone resorption. By adding strontium oxide to the silver-hydroxyapatite mixture they effectively offset the damaging effects and enhanced the performance when compared to pure hydroxyapatite coated samples.<sup>55</sup>

### *In vivo*

Silver reduces infection in medical devices such as external fixation pins, heart valves, endotracheal tubes, and cardiac and urinary catheters.<sup>34</sup> Unlike the majority of antibiotics, silver is not limited to a single mechanism but can use

several: blocking the cells respiratory chain, disrupting cell transport, and binding to nucleotides and nucleosides of RNA and DNA to limit transcription and translation without significant reports of resistance.<sup>22</sup>

Kose et al.<sup>37</sup> used a silver ion-doped calcium phosphate-based ceramic nanopowder to look at resistance of bacterial colonisation in knee prostheses in rabbits. They inoculated the femoral canals of 27 rabbits with MRSA and replaced the joints after 6 weeks with titanium implants (9 uncoated, 9 hydroxyapatite-coated (HA), and 9 silver-coated). 8 of 9 uncoated prostheses showed positive cultures, 5 of 9 HA were positive, and only 1 of 9 silver-coated prostheses was positive.<sup>37</sup>

Gosheger et al.<sup>56</sup> demonstrated in rabbit models that silver levels were elevated in silver prostheses but were within their pre-defined safety parameters with no histological change to the organs of the animal. Alongside Hauschild,<sup>57</sup> they later demonstrated silver levels in canines. Mean values of silver trace elemental concentrations in serum samples ranged from 0.20–1.82 ppb with baseline data representing normal values ranged from 0.20–1.38 ppb.<sup>57</sup> Therapeutic bactericidal effect can be seen at low concentrations (starting at 35 ppb) whereas toxic effects for human cells are expected at much higher concentrations (300–1200 ppb).<sup>22</sup>

In dentistry, implants have been trialed with antimicrobial coatings such as antibiotics and chlorhexidine but have not been viable due to short-term efficacy or cytotoxicity respectively. In addition to silver, strontium, gallium, gold/palladium, and zinc alloyed with magnesium have also been found to have antimicrobial effects whilst demonstrating biocompatibility.<sup>25,47</sup> Other methods of coating include chitosan coating, photoactive-based coatings, resorbable antibiotic loaded hydrogels, and silver coatings.<sup>22</sup>

33 patients who received Porag (Porous Argentum) megaprotheses between 2010 and 2014 were followed up by Scoccianti et al.<sup>46</sup> The implants were used for a variety of reasons including oncological disease, arthroplasty, and trauma. In such prostheses the shaft is silver-coated whilst the bone-implant interface in general is not. The megaprotheses included proximal, distal and total femurs as well as knee arthrodesis prostheses. 3 of the 33 patients developed post-operative infections; 1 that had had no previous infection and 2 patients developed recurrent infections. Scoccianti displayed no local or systemic side effects.<sup>46</sup>

Donati et al.<sup>40</sup> followed up 68 patients with primary or metastatic proximal femur bone tumours. Of the 18% that required further surgery, 13% were due to infection. Patients that had been given silver-coated prostheses developed early infection (under 6 months after surgery) in 2% of cases, whereas standard tumour prostheses developed early infection in 11% of cases. Late infection (occurring after 6 months) occurred at similar rates in both groups. 2 silver-coated prostheses removed at 27 and 82 months after surgery showed near total absence of silver.

Bloods taken at various times after surgery showed serum silver levels to be significantly below the toxic threshold, and no patients exhibited any symptoms of silver toxicity. Donati reported no local or systemic side effects.<sup>40</sup>

Over a 10-year period, Wafa et al.<sup>39</sup> matched 85 patients with Agluna-treated tumour implants (silver-coated megaendoprosthesis) with 85 identical, but uncoated, tumour prostheses. The infection rate in uncoated prostheses was almost double, with Agluna infection rates at 11% and the control at 22% ( $p = 0.033$ ). 7 of the infected 10 Agluna prostheses were treated with debridement and implant retention and antibiotics, versus 6 of the 19 control implants; 70% versus 32% respectively. Chronic infection rates were found to be 4% in the silver group, and 15% in the control group. Wafa reported no local or systemic side effects and commented that the Agluna prosthetic uses less silver in its coating than traditional prostheses (less than 2% of the lowest estimate of Harges' prosthesis).<sup>39</sup>

In 2010, Harges et al.<sup>58</sup> compared the infection rate between silver-coated and titanium megaprotheses. The silver group consisted of 51 patients (22 proximal femur, 29 proximal tibia) and the titanium group 74 patients (33 proximal femur, 41 proximal tibia). 6% of those that received silver implants developed periprosthetic infection, compared to 18% of those that received titanium implants. Infection rates were decreased in the silver prostheses. 5 patients ultimately underwent amputation due to infected proximal tibia prostheses, whereas none to that received a silver implant had undergone amputation. 1 patient of Harges (a silver-coated prostheses patient) presented 50 months postoperatively with a blue-grey discoloration of the skin over the area operated on. The differential diagnoses were known varicosis with venous insufficiency and suspected local argyrosis.<sup>34</sup> In an analysis of 56 patients who received silver implants for proximal tibia replacement in sarcoma; 4 were alive with disease (7%), and 5 dead of disease (9%), and of the 42 that received titanium 2 were alive with disease (5%), and 9 were dead of disease (21%).<sup>58</sup>

### Toxicity

Given the known problems with metal ion toxicity following metal-on-metal arthroplasty, there is concern about potential toxicity of silver. Silver nanoparticles can cause toxic effects to human tissues and there is evidence of an immunosuppressive effect.<sup>59,60</sup> Silver nanoparticle-mediated cytotoxicity to mesenchymal stem cells and osteoblasts has been shown to occur at higher concentrations, with the inference that a therapeutic window is likely to exist.<sup>61</sup> Necula et al.<sup>62</sup> looked at the cytotoxicity of different concentrations of silver nanoparticles on an implant surface against a human osteoblastic cell line and found an optimum cell growth combined with antibacterial effect at certain concentrations. However, it has been demonstrated

that antibacterial effects of silver occur at levels higher than those which induce cytotoxic effects, and indeed the authors commented that their study provides evidence of potential problems associated with orthopaedic implants.<sup>54</sup> In their review, Brennan et al.<sup>19</sup> comment that further research is required to find a method of controlling release of nanoparticles from an implant so that it is compatible with the host as well as providing antibacterial activity. Silver toxicity may occur at serum levels as low as 0.3 mg/mL and present as argyria and leukopenia, as well as causing alterations in renal, hepatic, and neural tissues.<sup>21</sup> The minimum doses mentioned in the literature to cause argyria are approximately 4–6 g.<sup>63</sup>

Glehr et al.<sup>64</sup> followed up 31 patients that underwent megaendoprotheses for infection or resection of malignant tumours between 2004 and 2011. Levels of silver locally in drains and seromas were measured. 7 patients (23%) developed local argyria (median 25 months). No malignant symptoms of silver poisoning (neurological/ renal/ hepatic) were found. They stated that local argyria is generally benign, although fairly irreversible. The size of the implant was not associated with argyria. Patients with and without argyria, both had similar levels of serum silver.<sup>64</sup>

### Discussion

Silver has established antimicrobial properties. By interacting with the cell wall, plasma membrane, DNA and RNA silver ions can cause cell lysis. Its widespread effects and low resistance rates make it a good candidate for use in hip arthroplasty. Silver is a versatile material and is relatively easy to apply to implants, where the risk of biofilm formation is high, it can help to reduce the risk of prosthetic joint infection.

*In vitro* cases demonstrate promise. The antimicrobial effects of silver are reproduced in cell cultures and are effective against *Staphylococcus epidermis* (the most common bacteria to colonise prostheses), *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*. However, silver demonstrates cytotoxic effects at the cellular level, inhibiting osteoblast and osteoclast performance. This osteoblastic cytotoxicity presents concerns about the longevity of implant fixation and, secondarily, revision for loosening. This effect could potentially be reduced with the addition of other elements such as strontium that act to stimulate osteoblast and osteoclast cells. Alternatively, the silver coating could be localised away from the implant-bone interface such as adjacent to the hip articulation itself.

Silver is used to reduce the risk of infection in implants and devices such as catheters and stents. The majority of the data published in relation to silver-coated orthopaedic implants involves megaendoprotheses used in tumour surgery. Silver's antibacterial properties are attractive in patients that may be immunocompromised due to disease

or chemotherapy. The included studies indicate that infection rates in the postoperative period were lower in those that had received silver-coated implants over controls. It is difficult to pinpoint the level at which silver may cause serious local or systemic damage. Most of the cases had no significant side effects from silver, though trace elements of silver in the blood were often raised but below the toxic threshold. Local argyria occurred in a small number of cases but did not seem to cause any systemic upset.

## Conclusion

Silver has antimicrobial properties. It is easily applied to implants and has shown efficacy in smaller devices or implants. In vitro studies of silver have shown signs of cell toxicity, but it does not seem to cause systemic upset in *in vivo* studies. The available literature is predominated by silver-coated megaendoprostheses used in malignancy or recurrent infection; in this context, it has proved effective in reducing infection rates. There is no randomised trial evidence of its use in primary hip arthroplasty. Furthermore, silver coated primary implants would need to be monitored closely via the National Joint Registries.

The potential benefits of silver-coated hip implants are so far unproven in prospective studies. Retrospective studies have demonstrated promising results and safety profile. Silver-coated hip implants may have a role in patients undergoing revision or primary surgery with a high risk of infection. Prospective robust studies are needed in this area to determine if silver-coated implants would be efficacious and cost-effective in this setting.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the NIHR Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

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