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Silver-coated megaprostheses: review of the literature

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Abstract Periprosthetic infection remains one of the most serious complications following megaendoprostheses. Despite a large number of preventive measures that have been introduced in recent years, it has not been possible to further reduce the rate of periprosthetic infection. With regard to metallic modification of implants, silver in particular has been regarded as highly promising, since silver particles combine a high degree of antimicrobial activity with a low level of human toxicity. This review provides an overview of the history of the use of silver as an antimicrobial agent, its mechanism of action, and its clinical application in the field of megaendoprosthetics. The benefits of silver-coated prostheses could not be confirmed until now. However, a large number of retrospective studies suggest that the rate of periprosthetic infections could be reduced by using silver-coated megaprostheses.

Keywords Silver · Megaprosthesis · Periprosthetic infection · Infection prevention

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Introduction

In tumor orthopedics, the majority of bony metadiaphyseal defects following resection of a bone sarcoma are currently treated using tumor prostheses [1]. These modular prosthetic systems are now increasingly also being used in revision surgery in non-oncology patients, and the prostheses are therefore nowadays also termed "megaendoprostheses." When megaendoprostheses are used, periprosthetic infection is the most serious complication, alongside local recurrence. In the great majority of cases, infection in the form of exogenic infection becomes manifest within the first two postoperative years [2, 3]. The main pathogens involved are staphylococci, but gram-negative organisms such as *Pseudomonas aeruginosa* are also found.

The incidence of infection varies, particularly depending on the location in which the prosthesis is implanted [4]. Whereas periprosthetic infections are a rarity in proximal humerus replacements [1, 4, 5], they occur in up to 19% of cases in proximal femur replacements [1, 6], up to 11% of cases in distal femur replacements [1, 4], and up to 23% of cases in proximal tibia replacements. However, these infections are certainly only partly due to the implant (particularly with the large area of contact with a foreign body). Other risk factors for infection mainly consist on the one hand of patient-associated risk factors (cancer, chemotherapy-induced immunosuppression, poor soft-tissue situations due to radiotherapy), the often prolonged operating times required, and—particularly with proximal tibia replacement—the difficulty of achieving muscle coverage of the prosthesis [3, 4, 7].

Despite a large number of preventive measures that have been introduced (e.g., enhanced soft-tissue reduction techniques, use of laminar airflow, use of skin film,

intraoperative irrigation, shorter operating times, perioperative antibiotic treatment), it has not been possible to further reduce the rate of periprosthetic infection in recent years. A recent review of antibiotic prophylaxis when megaprostheses are used in the lower extremity showed, with a mean infection rate of 10%, that administering postoperative antibiotics for a period of more than 24 h led to a lower infection rate than a period of less than 24 h [8]. However, the optimal duration of postoperative antibiotic prophylaxis is still as yet unclear and is the subject of continuing research.

Attempts have therefore been made for several years to reduce the rate of periprosthetic infections by modifying the implant surface [9]. The latest options for antimicrobial surfaces include antibiotic-based coatings, chitosan coatings, antiseptic coatings, photoactive-based coatings, and silver coatings [10]. All of these different types of coating have their own pros and cons [11]. Antibiotic coatings have been widely studied and are easy to obtain, but they have several limitations, such as limited duration of drug elution and the risk of resistance [12]. Antiseptic coatings include chlorhexidine and chloroxylenol. Several studies have shown that these are effective in vivo and in vitro, but general toxicity has also been reported [13–15].

With regard to metallic modification of implants, silver in particular has been regarded as highly promising, since silver particles combine a high degree of antimicrobial activity with a low level of human toxicity. In addition, the efficacy of the silver ions is long-lasting, since they should only be released into solution from the implant surface in relevant amounts in the presence of a negative pH value [16].

This article provides an overview of the history of the use of silver as an antimicrobial agent, its mechanism of action, and its clinical application in the field of megaendoprosthetics.

The antibacterial effect of silver since antiquity

It has been known for millennia that silver is an anti-infective agent; one of the earliest mentions of it dates back to 4000 BC [17]. Herodotus also reported that King Cyrus had water transported in silver vessels for his troops. In Sanskrit writings, it is also mentioned that silver improves the quality of water. In ancient Egypt, silver foil was used to dress wounds.

Today, silver is used as an antimicrobial agent in a large number of products (e.g., plastics or other metals). Special manufacturing processes are used in which ions are bound to the surface using various processes. Many applications for silver salts have been described in the literature, and

silver sulfadiazine (AgSD) was widely used particularly for burns [18]. Due to the underlying disease, however, sometimes very large amounts of the silver sulfonamide antibiotic were absorbed over longer periods, so that this treatment is now obsolete.

Vaporized ions can be applied in and onto almost any surface using the ion beam-assisted deposition (IBAD) technique in a vacuum. This process is particularly suitable for applying silver ions to polymers [19]. The same also applies to the plasma spraying procedure. Electroplating application is particularly suitable for solid bodies. Release takes place via the active surface, which corresponds to the surface of the solid body. Procedures such as roughening using corundum blasting can substantially enlarge the surface area. Almost any rates of release desired can be achieved through the various physical and chemical applications, so that the target concentration of active silver ions in the surroundings can be established very precisely. This explains the large number of sometimes widely divergent effects and side effects reported in the literature. In the medical field (and particularly for oncology patients), silver is used to prevent colonization by bacteria from materials that remain on or in the body for longer periods: vascular catheters (particularly central venous catheters), urinary catheters, dressing materials, vascular prostheses, bone cement, suture material, skin dressings, contact lenses, heart valves, pins for external fixators, etc. [20].

How does it work?

In the nineteenth century, the Swiss botanist Carl Wilhelm Nägeli noticed that water that has come into contact with metals causes microorganisms to die [21]. The damaging effect of metal cations is reported to be oligodynamic. Some metals have a damaging effect on bacteria, viruses, and fungi, and this effect has been confirmed in particular for mercury, silver, and copper. The oligodynamic effect is today used to stabilize drinking water and is used in several disinfectants. Silver is regarded for these purposes as the second most potent metal after mercury.

In contrast to most antibiotics, the effects of silver are not limited only to a single mechanism of effect, but comprise various local points of attack. The cell's respiratory chain is blocked by the affinity of silver to the sulfhydryl and thiol groups (SH), thus affecting the cell's energy supply. A similar mechanism also disrupts cell transport systems. In addition, silver binds to the nucleosides and nucleotides of DNA and RNA and can thus limit the cell's internal translation and transcription processes [21]. Although resistances to silver have been reported, they are of no clinical significance [22, 23].

Toxicity

The advantage of using silver lies in the wide therapeutic window it provides. Although a therapeutic bactericidal effect is already seen at very low concentrations (starting from 35 ppb) [6, 20], toxic effects for human cells can only be expected at much higher concentrations (300–1200 ppb) [21]. A low degree of tolerance for silver in osteoblasts must be mentioned here as a limiting aspect (see below).

Several side effects have been reported in earlier studies, including argyria, kidney and liver damage, leukopenia, and toxicity in neural tissues [19, 24, 25]. These effects have been described at blood concentrations exceeding 300 ppb, but even concentrations below this value have been shown to cause cytotoxic side effects [26].

Hardes et al. carried out a prospective study including 20 patients, in whom no signs of toxic side effects were noted after the implantation of silver-coated megaprostheses. Silver levels in blood samples did not exceed 56 ppb and were considered non-toxic. Changes in liver and kidney function were also excluded on the basis of laboratory values. The authors concluded that silver coatings on megaprostheses are not associated with any local or systemic side effects [27]. However, a report was recently published by Glehr et al. describing asymptomatic local argyria in 23% of patients with silver-coated megaprostheses [28]. One limitation of the study that must be noted here is that the majority of the patients included had the silver-coated prostheses implanted during revision procedures, so that increased release of Ag+ ions must be suspected due to a negative pH value. The study confirmed the lack of systemic toxicity of silver [28].

A recent study by Scoccianti et al. reported promising results with silver-coated megaprostheses (PorAg®; Link International, Hamburg, Germany). The silver coatings used consist of two layers: a deep basic layer of silver (1 μm thick) and a hard top layer of TiAg20 N (0.1 μm thick). The coating is called PorAg® (porous argentum). The study included 33 patients who underwent revision surgery with a megaprosthesis after tumor, trauma, or failed arthroplasty. No side effects were detected, including argyria or peripheral neuropathies. Fluids from wound drains were also analyzed and showed a tenfold higher concentration of silver in comparison with the blood concentration [29]. The authors suspect that this is similar to the silver concentration on the silver prosthesis. In this area, there is therefore such a high concentration that bacterial growth can very likely be inhibited.

Early use of antimicrobial silver coating in megaendoprosthetics

The potential benefits of silver-coated orthopedic hardware have still not yet been confirmed [20]. The application of silver coating through galvanic deposition of elementary silver (with a percentage purity of 99.7%) onto the surface of orthopedic megaprostheses was first reported by our own group in an animal trial [16]. Since a noble metal is needed for the silver ions to dissolve, gold was initially applied to the titanium using vapor deposition. The gold serves as the cathode, allowing the silver ions to be released as the anode. In the trial, the femoral diaphysis in 30 rabbits was replaced either with a titanium prosthesis or with a silver-coated prosthesis. The prostheses were then artificially contaminated with *Staphylococcus aureus*. A significantly ($P < 0.05$) reduced infection rate was noted in the group with silver-coated prostheses in comparison with the group with titanium-coated prostheses (with infection rates of 7% vs. 47%) [16]. Silver-coated endoprostheses were later implanted in 20 patients in order to exclude toxic side effects [27].

Silver in infection prevention

There have to date been only very few studies investigating the role of silver in infection prevention. The first study to address the topic was by our own research group and was published in 2010. The rate of postoperative infections among 125 patients who received megaendoprostheses in the proximal femur or proximal tibia was compared. Fifty-one patients received a silver-coated prosthesis, and 74 were treated with titanium prostheses [9].

Periprosthetic infection was noted in three of the 51 patients (5.9%) with silver-coated megaprostheses. By contrast, 13 periprosthetic infections (17.6%) occurred among the patients who received titanium prostheses ($P = 0.062$). The highest infection rates were observed in the proximal femurs. Six (of 33) patients with titanium prostheses developed infections (18.2%), in comparison with only one infection (among 22 patients) with silver-coated prostheses (4.5%; $P = 0.222$). The picture was similar in the proximal tibiae, with infection rates of 17.1% with the titanium prostheses and 6.9% with the silver-coated prostheses ($P = 0.289$). The median period up to the development of periprosthetic infection was 11 months (range 1–70 months).

Another recent study retrospectively investigated 68 oncology patients, 30 of whom received a titanium proximal femoral replacement and 38 of whom received a silver-coated proximal femur replacement [30]. A marked

reduction in the rate of early infections (within the first 6 months) was noted with the silver-coated prostheses (2.6%, in comparison with 10% in the titanium group). However, the difference was not significant due to the small numbers of patients included. A clear difference was not seen among the late-onset infections (later than 6 months; 5.3% in the silver group and 6.6% in the titanium group). However, the study did not make any distinction between primary bone tumors and metastases.

Silver in revision cases

Most recent studies on silver-coated megaprostheses have used them in revision cases [28, 31]. Glehr et al. reported a reinfection rate of 12.5% among 32 patients who had been treated with MUTARS silver-coated prostheses [28]. Wafa et al. compared 85 patients who were treated with silver-coated tumor prostheses (Agluna; Stanmore Implants, Elstree, UK) with a control group of 85 patients with uncoated prostheses (Stanmore Implants) [31]. In the Agluna coating process, ionic silver is "stitched" into the surface of the titanium alloy using a patented method. This is achieved by anodization of the titanium alloy, followed by absorption of silver from an aqueous solution. The engineered surface modification is integrated into the substrate and loaded with silver through an ion exchange reaction. This results in the formation of circular features with a diameter of 5 μm on the surface of the implant, containing amorphous titania species within which the bulk of the ionic silver is stored [31]. This retrospective study reported an overall postoperative infection rate of 11.8% in the silver-coated group, compared with 22.4% in the uncoated group ($P = 0.033$). The research group also noted a reduced reinfection rate after periprosthetic joint infection in two-stage revision procedures with silver-coated implants (with a success rate of 85% in the silver group compared with 57.1% in the uncoated group).

Wilding et al. [32] recently carried out a retrospective study including eight patients who underwent arthrodesis using silver-coated MUTARS devices.

What happens when silver-coated megaprostheses become infected?

If a silver-coated prosthesis becomes infected again, the way in which the periprosthetic infection can be treated is also important. In their recent study, Hardes et al. showed that in cases of reinfection, the surgical measures needed with silver-coated prostheses may also be more minor—for example, rinsing and debridement or one-stage revision were often sufficient [9]. In their case–control study, Wafa

et al. reported that silver-coated prostheses are associated with a reinfection rate of 5.1% after single-stage revisions [31]. By contrast, the reinfection rate in the titanium control group was 12.5%.

Hardes et al. also reported on amputations in cases of periprosthetic infection. Amputations were necessary in only 14.3% of patients in the group with silver-coated prostheses, in comparison with 37.5% of those with titanium prostheses.

What should be silver coated?

In vivo studies to date have always included patients who only had the prosthesis body coated with silver. It has been shown in vitro that osteoblasts have reduced tolerance to silver [33]. Our own group has shown in vivo in a dog model that silver-coated hip endoprostheses grow in suboptimally [34]. The use of silver-coated shafts in humans has therefore, to the best of our knowledge, been restricted to individual cases.

Conclusions

The potential benefits of silver-coated orthopedic megaprostheses have so far still not yet been confirmed [20] using evidence from prospective and randomized studies alone. However, a large number of retrospective studies—including admittedly smaller numbers of patients—have shown that silver coating leads to a reduced rate of infections (Table 1). However, only one study has reported a preventive effect in the absence of prior infection and without statistical significance [9]. Fortunately, however, other studies with different implants have confirmed a reduced rate of infection as a result of silver coating, usually in revision cases, in both oncology and non-oncology patients [28, 29, 31, 32].

The question now arises, however, of why the difference between infection and reinfection with silver-coated megaendoprostheses is not clearer in the studies mentioned. From our viewpoint, this might be explained by silver's mechanism of action. If a hematoma or wound healing disturbance occurs postoperatively, the active free silver binds to these proteins and is in the process inactivated [35]. This can lead to increased bacterial colonization of the soft tissue, and at these points the silver will not provide sufficient protection against infections. As we see it, silver can prevent bacteria in the direct vicinity of the prosthesis from colonizing it and can kill them, but due to inactivation of the silver in the periprosthetic tissue, this is no longer possible at greater distances from it. Although gram-negative bacteria can develop resistance to silver

Table 1 Major findings and conclusions in the literature on silver-coated megaendoprostheses

Authors, reference	Journal, year	Study design	Patients (n)	Results	Conclusion
Gosheger et al. [16] Silver-coated megaendoprostheses in a rabbit model: analysis of infection rate and toxicological side effects	Biomaterials 2004	Animal trial	30 (silver n = 15, titanium n = 15)	The silver group showed significantly (P < 0.05) lower infection rates (7% vs. 47%) in comparison with the titanium group after artificial contamination with S. aureus	The new silver-coated MUTARS megaprosthesis resulted in reduced infection rates in an animal trial
Hardes et al. [27] Lack of toxicological side effects in silver-coated megaprostheses in humans	Biomaterials 2007	Prospective	20	No signs of toxic side effects after implantation of silver-coated megaprostheses. The silver levels in blood were considered non-toxic. No changes in liver or kidney function	Silver coatings on megaprostheses show no local or systemic side effects
Hardes et al. [9] Reduction of periprosthetic infection with silver-coated megaprostheses in patients with bone sarcoma	Journal of surgical oncology 2010	Prospective (silver group); retrospective (titanium group)	125 (silver n = 51, titanium n = 74)	The infection rate was substantially, but not significantly, reduced from 17.6% in the titanium group to 5.9% in the silver group. Included were patients with a proximal femur or proximal tibia replacement	Using silver-coated prostheses reduced the infection rate over the medium term
Glehr et al. [28] Argyria following the use of silver-coated megaprostheses: no association between development of local argyria and elevated silver levels	Bone and joint journal 2013	Retrospective	32	Asymptomatic local argyria in 23% of patients with silver-coated megaprostheses. No systemic toxicity due to silver	However, the majority of the patients received silver-coated prostheses in revision cases after infection, so that due to a negative pH value, increased release of Ag+ ions may be suspected
Wafa et al. [31] Retrospective evaluation of the incidence of early periprosthetic infection with silver-treated endoprostheses in high-risk patients: case–control study	Bone and joint journal 2015	Retrospective	170 (silver n = 85, titanium n = 85)	This retrospective study showed a postoperative infection rate of 11.8% in the group with silver-coated prostheses versus 22.4% in group with uncoated prostheses (P = 0.033)	Silver-coated implants showed a reduced reinfection rate after periprosthetic joint infection in two-stage revisions (success rates of 85% in silver group compared to 57.1% in uncoated group, P = 0.05)
Politano et al. [20] Use of silver in prevention and treatment of infections: silver review	Surgical infections 2013	Review	–	Benefits of silver-coated orthopedic prostheses are still unproved	
Wilding et al. [32] Can a silver-coated arthrodesis implant provide a viable alternative to above-knee amputation in the unsalvageable, infected total knee arthroplasty?	Journal of arthroplasty 2016	Retrospective	8	With a mean follow-up period of 16 months (5–35 months), only one patient had recurrent infection, but prosthesis-preserving treatment was possible	The silver-coated arthrodesis is a good alternative to amputation, particularly in infected knee prostheses

Table 1 continued

Authors, reference	Journal, year	Study design	Patients (*n*)	Results	Conclusion
Scoccianti et al. [29] Levels of silver ions in body fluids and clinical results in silver-coated megaprostheses after tumor, trauma, or failed arthroplasty	Injury 2016	Retrospective	33	There were no infections during the first two years after surgery in the 12 patients who received a silver-coated megaprosthesis and had no previous history of infection. An infection developed in one of the following two further surgical procedures. Infection recurred in two out of the 21 patients (9.5%) who had received the implant because of previous septic complications	Lower incidence of infection with silver-coated megaprostheses, mainly patients with previous infection. No local (argyria) or systemic side effects
Donati et al. [30] Silver-coated hip megaprostheses in oncological limb salvage surgery	BioMed research international 2016	Retrospective	68	Clear reduction in early infections (within the first 6 months) with silver-coated prostheses (2.6%) versus the titanium group (10%), but difference not significant. No evidence of toxic side effects	Recommendation to use silver-coated prostheses as primary implants for limb salvage surgery, in primary or metastatic bone tumors affecting the proximal femur, in view of the absence of signs of toxicity and lower rate of early infection

[36], we believe that the above-mentioned mechanisms of action play a more important role here through protein-related inactivation of silver.

In conclusion, future research in larger numbers of patients will be needed in order to obtain definitive evidence for the effectiveness of silver. Silver will certainly only be able to prevent or reduce biofilm formation, but will not prevent infection of the periprosthetic tissue.

Compliance with ethical standards

Conflict of interest G. Gosheger has patent silver with royalties paid. F. Boettner is a consultant for Smith and Nephew, OrthoDevelopement and DePuy. The other authors (T.S.B., A.S., M.N., H.A., R.D., W.G., D.A., G.H., B.M., W.W., and J.H.) declare that there is no conflict of interest regarding the publication of this paper.

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